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EUROPEAN JOURNAL OF GYNAECOLOGICAL ONCOLOGY (ISSN 0392-2936) publishes original peer reviewed works in the fields of female genital cancers and related subjects and also proceedings of gynecologic oncology society meetings all over the world. The Journal is covered by CURRENT CONTENTS, SCISEARCH, RESEARCH ALERT, INDEX MEDICUS, MEDLINE, EMBASE/Excerpta Medica, CURRENT ADVANCES IN CANCER RESEARCH, BIOSIS.
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Tissue-based classification of HPV infections of the uterine cervix and vagina (mucosal HPV infections)

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Summary

Terminology of HPV infections of the uterine cervix and vagina is somewhat confusing, with various terms having different meanings to different authors. This prompted us to revise the current terminology and propose a “tissue-based” classification of HPV infections of the cervix and vagina (mucosal HPV infections), which is based on histological appearance of the lesions and should be clear-cut in everyday practice of managing these patients. We hope the proposed nomenclature may overcome some of the confusion and controversy that exist in the current terminologies describing these lesions.

Key words: HPV infections; Uterine cervix; Vagina; Classification; Tissue-basis.

Introduction

Terminology of the diseases caused by the human papillomavirus (HPV) is somewhat controversial. Various terms have been used in the literature, some of them with different meanings by different authors [1]. Precise definitions and uniform terminology [2], however, are essential in comparing results of research, diagnosis and treatment of HPV infections.

Commonly used terms pertaining to classification of HPV infections

Terminology of diseases invariably includes common terms in defining specific entities. Such terms connected with HPV infection terminology are listed in alphabetic order.

Atypia “the condition of being irregular or not conforming to type”. Atypical “irregular, not conformable to the type”.

Condyloma (plural: condylomas, condylomata) “is defined as a warty growth on the skin or a mucous membrane” [3]. Mucosal condylomas may be exophytic (condyloma acuminatum) or flat (flat condyloma, condyloma latum) lesions [1, 2]. Condyloma acuminatum is also called genital, acuminate or veneral wart. Condyloma latum, instead, is a characteristic cutaneous manifestation of secondary syphilis, but on the mucosal epithelium. Giant condyloma (Buschke-Löwenstein tumor) is another cutaneous condylomatous lesion [4].

Dysplasia is defined as “1) abnormality of development, 2) in pathology, alteration in size, shape, and organization of adult cells”; dysplastic “marked by dysplasia” [3]. The WHO definition of dysplasia is the following: a lesion in which part of the thickness of the epithelium is replaced by cells showing varying degrees of atypia and it is further graded as mild, moderate and severe. In other words, dysplasia is an epithelial abnormality that represents a precancerous lesion. The term dysplasia has gained a widespread use in the common language of histopathology [5]. Included in this terminology is carcinoma in situ (CIS), which represents the immediate precursor of an invasive cancer [5].

Intraepithelial neoplasia indicates the presence of abnormal cells inside the epithelium but without evidence of stromal invasion. Originally introduced to describe cervical cancer precursors (cervical intraepithelial neoplasia, CIN has been divided into three grades according to the extent of epithelium occupied by the atypical cells [6].

Latent “concealed; not manifest, potential, dormant, quiescent” [3].

Latent viral infection in general represents cases where viral genome is present in clinically and morphologically normal epithelium. This applies to HPV as well, implicating cases where HPV genome is detected in histologically normal biopsies or in scrapes with no cytological abnormality [1, 2, 4].

Neoplasm “any new and abnormal growth; specifically a new growth of tissue in which the growth is uncontrolled and progressive”. Called also tumor. Neoplasia “the formation of a neoplasm”. Neoplastic pertaining to a neoplasm/neoplasia [3].
**Subclinical** means a condition ‘without clinical manifestation’, i.e., an early stage of any infection and/or disease, which causes no symptoms and signs and cannot be detected by clinical diagnostic techniques.

**Transformation** “at the cellular level indicates change that a normal cell undergoes as it becomes malignant; in a wider sense: change of form or structure; conversion from one form to another” [3]. **Transforming** cellular change towards malignant cell phenotype.

**Considerations of current terminology of HPV infections**

**Latent HPV infection**

In latent HPV infections, viral DNA is present in the cells without any signs of cytopathic effects (CPE) of the virus, i.e., in morphologically normal epithelium [1, 2, 4]. This can only be detected by molecular methods (DNA technology, mostly by PCR). There appears to be a general consensus regarding this term.

**Subclinical HPV infection (SPI)**

The term subclinical HPV infection is used in different meanings by different authors [1, 2, 4], including:
- all lesions visualized by the naked eye only after the application of acetic acid;
- lesions that are not visible on routine inspection, but become visible on colposcopy after acetic acid, and which on histology contain typical HPV-induced changes;
- lesions equivalent to a flat condyloma;
- lesions which become visible only by colposcopy after acetic acid, and which on light microscopy show minor epithelial changes not consistent with typical flat condylomas [1, 2, 4];

In the strictly virological sense, the term subclinical per se implies viral infection, which has no clinical manifestation and cannot be detected by clinical means. **The morphological criteria of subclinical HPV infections are ill defined and not reproducible. Because all the above listed options necessitate detection of something by any of the clinical tools (colposcopy, acetic acid, or histology), none of these definitions for subclinical HPV are compliant with the strict virological definition.**

**Cervical intraepithelial neoplasia (CIN)**

CIN is cervical cancer precursor of squamous epithelial origin, characterized by the presence of atypical cells within the epithelium but with no stromal invasion [6]. Three grades of CIN exist, known as CIN1, CIN2 and CIN3. This term superseded the old terminology of mild, moderate and severe dysplasia and CIS, introduced in the early 1950s [5]. The concept of dysplasia-CIS was the first classification used to categorize the process of cervical carcinogenesis on light microscopy [5, 7]. The advantage of the CIN classification is that it clumps together the severe dysplasia and CIS lesions, the distinction of which is highly arbitrary and poorly reproducible. The concept of CIN terminology included that all degrees of the abnormal intraepithelial changes should be given the same name, representing the continuous spectrum of the disease [6].

Squamous intraepithelial lesion (SIL) is a term introduced by the Bethesda System (TBS) to replace the term cervical intraepithelial neoplasia (CIN) [8, 9]. SIL represents a precancerous condition where normal epithelial cells are replaced by abnormal cells; classified as high grade (HSIL) or low grade (LSIL). Actually, this term is used to describe squamous cell abnormalities for cytology, and it should not be used to describe histopathological changes [8, 9].

Carcinoma in situ (CIS) is the intraepithelial lesion of the most severe grade, the immediate precursor of true carcinoma [5, 7]. CIS is the most severe category of the dysplasia-CIS nomenclature used to classify the precancer lesions and it is included in the CIN terminology as CIN3 [1, 8, 9].

Atypical metaplasia represents an epithelial change also known as atypical reserve cell hyperplasia. This term should be reserved only for the thin metaplastic epithelium that shows cellular atypia from the very beginning (1). This change has been regarded by some as the earliest manifestation in the development of a CIN lesion (10). According to most authorities, it is not a distinct entity, however.

**Cervical squamous cell carcinoma (SCC)**

This is the main histological type of cervical carcinoma, so named because of its origin from squamous cells. Unless otherwise defined, the general term cervical cancer usually denotes squamous cell carcinoma.

**Cervical glandular intraepithelial neoplasia (CGIN)**

These are the precursor lesions for cervical adenocarcinoma [11, 12]. Currently, two grades of glandular precancer lesions are differentiated; low-grade and high-grade. The latter are equivalent to adenocarcinoma in situ (AIS) [13], whereas low-grade lesions denote all lesions with less severe atypia than AIS.
CGIN is another name to describe cervical glandular intraepithelial neoplasia, which is characterized by the presence of atypical columnar cells [14, 15]. Three grades are described: CGIN I, the equivalent of mild dysplasia, CGIN II, the equivalent of moderate dysplasia and CGIN III, the equivalent of AIS. Today this designation is decreasingly used, because of the problems in reproducibility [12, 14, 15].

AIS is the immediate precursor of cervical adenocarcinoma [11-13]. Histologically, the changes of AIS are those described for CGIN, at their most accentuated form [11, 12]. The affected glands show abnormal architecture with intraluminal papillary projections, with or without stromal cores, cribriform areas, outpouchings and back to back arrangement of the glands. To meet the criteria of AIS, the basement membrane must be intact and a compact surrounding stroma should be detectable around the atypical glands [11-13]. Not unlike CGIN, different subclassifications have been introduced for AIS as well [14, 15]. The most recent one divides AIS into four subcategories according to their cell type: 1) endocervical cell type, 2) endometrioid type, 3) intestinal type, and 4) miscellaneous type. The histogenetic validity and general applicability of such subclassifications have been questioned, however [11, 12].

Cervical adenocarcinoma

This is the other main histological type of cervical cancer, arising from the glandular tissue of the endocervix. A large number of different histological subtypes of cervical adenocarcinoma exist, some with substantial prognostic implications [12].

Vaginal intraepithelial neoplasia (VAIN)

VAIN nomenclature is used to grade the precursor lesions of vaginal squamous cell carcinoma [16, 17]. Originally, three grades of VAIN were distinguished, but more recently the division into low-grade and high-grade VAIN has gained more popularity, due to the difficulties in categorizing the intermediate (VAIN II) grade of lesions with any feasible degree of reproducibility [18].

Vaginal squamous cell carcinoma

Albeit a rare disease, this is the most common type of the primary vaginal carcinomas and it seems to be related to HPV infections [4]. Compared with other genital SCCs, the number of vaginal carcinomas analyzed for HPV is still too small to draw definite conclusions. Until further confirmatory data are available, it seems reasonable to conclude that the evidence linking HPV with the development of vaginal cancer is fairly suggestive, but not as firm as established for cervical cancer. Similarly, the suggested concept on vaginal carcinomas with two different etiologies (HPV-related and non-HPV-related) remains to be elucidated [4].

Condyloma acuminatum

Condyloma acuminatum is an exophytic lesion characterized by numerous fine, finger-like epithelial projections (papillomatosis), which consists of acanthotic epithelium with koilocytosis and a connective tissue core containing a capillary loop [1, 2, 4]. Para-, hyper- or dyskeratosis is common. Persistent acetowhite change occurs after acetic acid application, which also causes the papillae to retract and separate and may mask fine vascular patterns.

Atypical condyloma

Occasionally condyloma acuminatum is associated with abnormal vessels with various shape and caliber, some showing staghorn-like appearance [19] and elongated and enlarged nuclei with anisokaryosis, pyknosis and atypical mitotic figures. Dysplastic cells, however, are absent. This is called atypical condyloma by some authors [19], but is regarded as a benign lesion associated with HPV6/11 genotypes [1, 2, 4].

Flat condyloma

Flat condylomas are acanthotic epithelial lesions with abundant koilocytes in the upper cell layers usually covered by para- or hyperkeratosis [1, 2, 4]. Histologically three types of flat condylomas can be distinguished, such as typical, spiked and endophytic flat condylomas. The spiked condyloma is built up of tiny epithelial projections (spikes or asperities), but it is not exophytic [1, 2, 4]. Typical sites include the vagina where the lesions can be multiple, and vulva where the lesions are also called microcondyloma or filamentous condyloma [20]. Endophytic condylomas occur exclusively on the uterine cervix and grow towards connective tissue and endocervical glands, giving the lesion an inverted appearance. Not infrequently, the histopathological features of the various types are encountered in the same lesions [1, 2, 4].
Flat condylomas are most often large with marked, geographic borders and situated in or around the transformation zone. They are acetowhite with fine punctation and fine mosaic patterns in most cases, however, bizarre vascular patterns are not exceptional. Their surface is smooth with the exception of the spiked condyloma with a slightly uneven surface contour. Acetowhite reaction is often slow but may be dense. When keratosis is prominent, the lesion may be raised. They are iodine negative. Flat condylomata are hard to distinguish colposcopically from low-grade CIN; actually they are included in the category of low-grade lesions by TBS [8, 9]. Another characteristic colposcopic appearance of flat condylomas is the brain-like surface counter, i.e. corrugation and convolution forming ridges.

Characteristically, all types of condylomatous lesions share common histopathological features: they are acanthotic epithelial lesions with abundant koilocytes in the intermediate and superficial layers. Hyper-para- or dyskeratosis is common, and slight proliferation of the basal and parabasal cells may be encountered. Other features include frequent multinucleation, and slightly increased mitotic figures [1, 2, 4, 20]. Basically, mucosal condylomas differ in their tissue architecture only. By definition, however, benign condyloma lesions are devoid of dysplastic cells.

Proposed classification of genital mucosal HPV infections

The proposed classification of cervical and vaginal (genital mucosal) HPV infections is shown in Table 1.

<table>
<thead>
<tr>
<th>Latent HPV infection</th>
<th>Subtle HPV infection</th>
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<tr>
<td>Transforming HPV infections</td>
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<tr>
<td>− Cervical intraepithelial neoplasia (CIN)</td>
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<td>− Cervical squamous cell carcinoma</td>
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<tr>
<td>− Cervical glandular intraepithelial neoplasia (CGIN)</td>
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<tr>
<td>− Adenocarcinoma in situ (AIS)</td>
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<tr>
<td>− Cervical adenocarcinoma</td>
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<tr>
<td>− Vaginal intraepithelial neoplasia (VAIN)</td>
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<tr>
<td>− Vaginal squamous cell carcinoma</td>
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<tr>
<td>Non-transforming HPV infections</td>
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<tr>
<td>− Condyloma acuminatum</td>
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<tr>
<td>− Flat HPV infections (typical flat, spiked and endophytic condylomas)</td>
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<tr>
<td>− Atypical condyloma</td>
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<tr>
<td>Mixed HPV infections</td>
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<td>− Flat HPV infections with co-existent or combined neoplastic epithelial changes</td>
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1) The vast majority of cervical/vaginal HPV infections regress unnoticed, most of them without causing any cytopathic effect, i.e., without any epithelial abnormality. This is called *latent HPV infection* and it is an entity distinct from the clinical HPV lesions [1, 2, 4].

2) Not infrequently, minor cellular abnormalities subtle enough to raise only a suspicion of HPV infection are detected on histology and/or in cervical smear. These lesions contain the HPV genome and can be slightly acanthotic. The bulk of the epithelial thickness is composed of intermediate cells with usually slightly vacuolized cytoplasm, raising the suspicion of koilocytosis. However, when strictly evaluated, these cells lack the marked nuclear changes characteristic to genuine HPV-induced koilocytosis (Figure 1). Few mitotic figures and slight para- or hyperkeratosis may occur. These lesions are best called *subtle HPV infection*.

Thus, by definition, *subtle HPV infections* are epithelial lesions that on light microscopy raise a suspicion of HPV infection. By definition, such lesions are devoid of any dysplastic changes and also lack characteristic koilocytes. When studied with sensitive HPV detection methods (e.g., PCR or tyramine-amplified ISH) [1] they contain HPV DNA, however. Appearance on light microscopy can be variable, but slight hyper- or parakeratosis, ancytosis and intermediate cell vacuolization are usually present (Figure 1). The natural history of such lesions is unknown, justifying their inclusion as a separate entity within the spectrum of HPV infections.

3) HPV infection with frank epithelial abnormalities can be separated into two groups: a) those with the potential of progressing to cancer and b) those which are benign. The former may be called dysplastic, neoplastic or transforming lesions, while the latter as non-dysplastic, non-neoplastic or non-transforming abnormalities.

By definition, ‘dysplasia’ – as discussed above – is a general term of disordered form or differentiation, but in oncology, it is used in the context of atypia and carcinogenesis. It is a widely used expression. In cervical pathology, however, the term dysplasia [5, 7] has been replaced by cervical intraepithelial neoplasia (CIN) [6].
Tissue-based classification of HPV infections of the uterine cervix and vagina (mucosal HPV infections)

Figure 1. — Subtle HPV infection. In this flat lesion, many features raising the suspicion of HPV infection are present, including slight parakeratosis, vacuolization of epithelial cells in the uppermost intermediate layers as well as some proliferative activity of parabasal cells. This particular lesion tested positive for HPV42 in ISH analysis. (HE, original magnification x 250).

Figure 2. — Condyloma acuminatum of the uterine cervix presenting with all typical features; papillomatosis, acanthosis, para/hyperkeratosis and koilocytosis. There is no epithelial atypia in this benign lesion, which proved to contain high copy numbers of HPV6. (HE, original magnification x 40).

Figure 3. — A medium power detail of a lesion diagnosed as an atypical condyloma. One of the numerous papillary structures with a connective tissue core is presented. Numerous dilated capillaries are present which on colposcopy gave an impression of atypical vessels. Koilocytes are detected in the intermediate layers, and some degree of atypia also in the basal/parabasal cells (upper part of the papilla). HPV11 was detected and the lesion was considered as benign. (HE, original magnification x100).

Figure 4. — Flat condyloma in its most typical presentation. The epithelium has a completely flat surface, is clearly acanthotic and contains all characteristic morphological features of HPV infection. There is a thick layer of parakeratotic cells, overlying the intermediate layers with koilocytic cells. Many of the latter are bi- or multinucleated. There is also some hyperplasia in the parabasal cells, but the basal layer is regular, with no signs of dysplasia. HPV11 was detected. (HE, original magnification x 100).

Figure 5. — Another variant of a flat condyloma known as spiked condyloma. An otherwise morphologically flat lesion contains numerous small spikes or asperities composed of a thin squamous epithelium supported by a tiny connective tissue core with small capillaries. Koilocytes are abundantly present in superficial layers and the basal cell layer is regular, with no signs of dysplasia. This lesion tested HPV6 positive in ISH. (HE, original magnification x 100).
The term ‘transforming epithelial changes’ is invariably related to malignancy, but the word ‘transformation’ in cervical histology is mostly connected to the area of squamous cell metaplasia, called transformation zone (TZ) [2, 10].

The adjective ‘neoplastic’ is pertaining to tumor growth and precursor lesions of the uterine cervix and the vagina; actually the precursor lesions bear this word in their name (cervical/vaginal intraepithelial neoplasia) [1, 4, 6, 16, 17]. Thus, the expressions of neoplastic HPV infections and non-neoplastic HPV infections might appear to be the most appropriate. One can always argue, however, whether a benign condyloma should also be considered as a neoplasia or not. If the former view is favored, then the two categories here should be equally well called as transforming and non-transforming HPV infections [1, 2, 4, 20]. Instead of a pure morphologic meaning (neoplastic vs non-neoplastic), these two terms include a value judgment; one assumes that transforming inevitably means equivalent to malignant, while non-transforming implicates an invariably benign lesion.

The transforming HPV lesions are listed in Table 1.

As for non-transforming HPV infections, the designation ‘condyloma acuminatum’ (Figure 2) and that of its atypical counterpart (atypical condyloma) (Figure 3) is well defined. However the term ‘flat condyloma’, albeit is widely used, is clearly an unfortunate misnomer [1, 4, 10, 19]. As discussed above, condyloma per se means a warty (exophytic) lesion, equivalent to squamous cell papilloma (SCP) at other mucosal sites [1, 4, 20] (Figure 2). Actually, in the older literature, some authors used SCP and condyloma as synonyms while describing cervical lesions [21]. Therefore, the name flat condyloma gives an impression of something that is at the same time exophytic (condyloma) and flat, which is highly confusing. In its most typical appearance, flat condylomas are acanthotic epithelial changes with smooth surface, with nothing that points to warty or exophytic growth (Figure 4). As pointed out above, however, there are subtypes of flat condyloma that show some warty features while presenting with tiny spikes or asperities on the surface of an otherwise flat (= laterally spreading) lesion (Figure 5). This is in strong contrast to genuine condylomata acumina, ta, which demonstrates an exophytic (= vertical) growth, with very little lateral extension and sometimes is connected to underlying epithelium with a narrow string (= base) of connective tissue stalk only (Figure 2).

If we stick to the original definition of condyloma, these flat HPV lesions cannot be adequately characterized by calling them as flat condyloma. We need to abandon the expression “condyloma” here and replace it by another expression. Potential options are: infection, lesion or growth, i.e., flat HPV infections or flat HPV lesions or flat HPV growths. For consistency with other categories, we prefer to use the name flat HPV infections in this context. The histological sub-
types of these flat HPV infections (flat, spiked, endophytic), represent histological variants of the same lesions, and do not represent different clinical manifestations to justify calling them as separate entities (Figures 4-6).

Irrespective of their histological morphology, whether exophytic or flat, all HPV infections share a common morphological feature, i.e., the cytopathic effect of HPV, known as koilocytosis (Figure 7). Without recognition of these cells, there is no means to make the definite diagnosis of HPV infection on light microscopic examination (1,4,19,20)

Mixed HPV infections

Mixed HPV infections are flat HPV infections with co-existent or combined neoplastic epithelial changes (Figure 6). As repeatedly pointed out, such lesions with signs of HPV infection combined with obvious dysplastic changes should be evaluated for the degree of CIN using the same criteria as applied for lesions devoid of these morphological manifestations of HPV, i.e., graded into CIN1, CIN2 or CIN3 as usual [6].

Conclusions

Common language, i.e., coherent terms and clear definitions is a prerequisite not only in basic research but in clinical practice of managing the patients as well [2]. This prompted us to revise the current terminology and propose a “tissue-based” classification of HPV infections of the cervix and vagina, which is based on histological appearance of the lesions and should be clear-cut in everyday practice of managing these patients. We hope this proposed nomenclature can overcome some of the confusion and controversies that exist in the current terminologies describing these lesions.

References

Peroxisome proliferator-activated receptor and epithelial ovarian cancer

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Introduction

A nuclear receptor called peroxisome proliferator-activated receptor (PPAR) was discovered in 1990 [1]. To date, three PPAR subtypes, α, δ, and γ, have been identified. Each of them has been found to be expressed in different tissues [2]. PPARα is mainly distributed in the liver, kidney, heart, and skeletal muscle and plays a critical role in fatty acid metabolism. PPARγ is present in adipose tissue or in the small intestine and colon, and is involved in functions such as cell differentiation, lipid storage, and modulation of insulin action. PPARδ is extensively distributed in the body and has been reported to regulate intercerebral lipid metabolism, HDL metabolism, adipogenesis, and preadipocyte differentiation.

Each of these PPARs is activated by its specific ligand and regulates the expression of various genes by binding to the regulatory region of target genes. PPARs have received attention as potential targets for the treatment of lipid metabolism, hyperlipidemia, diabetes, and arteriosclerosis, although expression of PPARs is frequently seen in a variety of cancers. Therefore, not only studies on carcinogenic mechanisms but also on the development of new treatment strategies using PPARs as molecular targets have been underway. In this paper, the latest findings in this area are reviewed, focusing particularly on PPARα, PPARγ, and ovarian cancer and the possibility of their clinical applications for ovarian cancer treatment.

The role of PPARs in the ovary

PPARs have been shown to play a direct role in ovarian physiology since they were first discovered. PPARs were reported to have functions in regulating tissue remodeling during follicular growth, ovulation, and luteinization as well as in the expression and activation of proteinase-influencing angiogenesis [3-6]. In 2001, Komar et al. [7] identified the location of PPARs and their specific roles in follicular growth by in situ hybridization in normal rat ovarian tissue. PPAR was localized in granulosa cells, PPARα and PPARδ in the capsule and in the stroma [7]. PPARγ was found to be regulated by luteinizing hormone and to be highly expressed during follicular growth, but to decrease with ovulation [7]. Also, treatment with PPARγ ligand significantly increases progesterone and estrogen levels [7]. Elevated expression of PPARα and PPARδ are maintained despite estrous cycles, and so they were assumed to be associated with basic ovarian function. However, their exact mechanism of action remains unknown [7]. These results show the presence of PPARs in the ovary and that of PPAR-specific ligands certainly have some effect on physiological function in the ovary, but the history of investigation of the relationship between the ovary and PPARs is relatively short. Therefore, further studies to identify the various involvements of PPARs are expected.

PPARγ and ovarian cancer

Nicol et al. [8] reported in 2004 that the expression of PPARγ inhibited ovarian carcinogenesis induced by the carcinogen 7,12-dimethylbenz[a]anthracene (DMBA), and application of DMBA to PPARγ hetero-knockout mice and PPARγ wild-type mice increased the occurrence of ovarian cancer by more than 3-fold in the former mice compared with the latter, and the metastatic rate by 4.6-fold. Based on these results, they reported that PPARγ may be a regulator of ovarian carcinogenesis. In the same year (2004), Sakamoto et al. [9] found that the state of high cyclooxygenase (COX)-2 expression and low PPARγ expression in epithelial ovarian cells was strongly involved in ovarian carcinogenesis and that activation of PPARγ in ovarian cancer cells reduced the expression of COX-2 through the nuclear factor κB pathway. COX-2 is a known carcinogen in colon cancer and breast cancer. Our group identified that activating PPARγ with its specific ligand in ovarian cancer cells resulted in the loss of COX-2 expression induced by tumor necrosis factor-α, and reported that there was an inverse relationship between COX-2 expression and PPARγ [9]. Based on the findings of the two studies published in 2004, a specific ligand which can activate PPARγ was expected to be a promising drug candidate for the treatment of ovarian cancer as well as to inhibit ovarian carcinogenesis.

Since then, the relationship between the PPARγ ligand and ovarian cancer in vitro has been widely investigated and the following data have been published in succession: ciglitazone, a PPARγ ligand that induces cell cycle arrest and...
apoptosis in ovarian cancer cells, resulting in decreased cell proliferation [10]. DIM-C-pPhBu, another PPARγ ligand that induces PPARγ-dependent p21 expression in ovarian cancer cells leading to cell cycle arrest [11], and inhibition of cell proliferation can be achieved by inducing apoptosis as a result of reducing activation of non-PPARγ-dependent cyclin D1. We conducted an in vivo study in which we created ovarian carcinoma-bearing mice and cancerous peritonic mice and directly administered a PPARγ ligand of ciglitazone. The study found administration of ciglitazone significantly reduced subcutaneous tumor growth and markedly prolonged the survival time of treated cancerous peritonitis mice [12]. There was a significant increase of PPAR in ciglitazone-treated subcutaneous tumors in mice, and induction of apoptosis was apparent and angiogenesis was suppressed. Moreover, interestingly, treatment with ciglitazone significantly reduced prostaglandin synthase (mPGES) activity in the tumors, although COX-2 expression in the tumors remained unchanged (Figure 1), suggesting that in vivo, depletion of prostaglandin (PG) E2 in a COX-2-independent manner with ciglitazone can reduce tumor growth by inducing apoptosis and suppressing angiogenesis. Shigeto et al. [13] demonstrated that antitumor effects against ovarian cancer can be achieved with a similar mechanism using pioglitazone, the same PPAR ligand.

**PPARα and ovarian cancer (including other types of cancer)**

When the peroxisome proliferator-activated nuclear receptor was discovered in 1990, PPARα was the mediator responsible for the key mechanism [1]. It is not common for there to be an argument over whether the role of a molecule is beneficial or harmful, but in case of PPARα, this is subject to debate. Fibrate, a lipid-lowering drug is representative of peroxisome proliferators, is widely known to activate PPARα, enhance lipid metabolism, induce increased HDL cholesterol levels and to have a protective effect against arteriosclerosis, while it has been known for many years that rodents such as mice and rats chronically treated with peroxisome proliferators develop hepatocellular carcinoma [14]. Gonzalez et al. [15] demonstrated that antitumor effects against ovarian cancer can be achieved with a similar mechanism using pioglitazone, the same PPAR ligand.

PPARα knockout mice and directly administered clofibrate or Wy-14,643, peroxisome proliferators. No liver tumors, peroxisome proliferation, or induction of a series of enzymes were observed, showing conclusively that PPARα plays a crucial role in peroxisome proliferator-induced liver carcinogenesis [15]. However, liver biopsy specimens obtained from human patients taking high doses of clofibrate for a few years showed no peroxisome proliferation [16]. Thus, even if there is a species difference in peroxisome proliferation, the fact that PPAR is involved in the mechanism of liver carcinogenesis (medication → peroxisome proliferation in the liver → liver carcinogenesis) is currently drawing attention in drug safety assessment during drug development [17]. PPARα being expressed in Sertoli cells in the testis is also known to be involved in reproductive toxicity caused by environmental chemicals [18].

Aside from whether PPARα is beneficial or not, it was first reported in 2006 that PPAR ligands decreased cancer cell proliferation in vitro [19], following which successive reports from 2007 to 2008 stating that activation of PPARα inhibited tumor growth were published [20-22]. These findings revealed the relationship between PPARα and antitumor activity.

Grau et al. [19] reported in 2006 that activation of PPARα by its ligand reduced transcriptional induction of COX-2 and vascular endothelial growth factor (VEGF) in colorectal-cancer cells. They concluded that this was due to the suppression of activator protein-1 (AP-1) gene induction involved in tumor development. The mechanism of tumor growth inhibition by PPARα was assumed to be that activated PPARα directly binds to the consensus DNA region and reduces AP-1 expression as well as inhibits transcriptional activity of c-Jun, although the expression of AP-1 is regulated by the c-Jun oncogene. This mechanism was supported by our follow-up study – we found that treatment with PPAR ligand reduced AP-1 expression and inhibited ovarian cancer growth in ovarian-cancer specimens in vivo [13].

In April 2007, we reported that activation of PPARα inhibited solid tumor growth in vivo, which was the first such report in the world [20]. We created tumor-bearing mouse models and cancerous peritonitis mouse models using two types of human ovarian-cancer cells. A single administration of clofibrinic acid, a PPARα ligand, produced a tumor response at least as effective as cisplatin (a key drug for ovarian cancer) and prolonged survival time in the animals. Carboxyl reductase, which was increased in the tumor by clofibrin acid administration, had a pivotal role in the mechanism (Figure 1). Carboxyl reductase also exists in the ovary and metabolizes carbonyl compounds in the presence of NADPH on their surface [23], but it actually also has an important function in converting PGE2 to PGF2α [24]. Gene transfer of carboxyl reductase to ovarian cancer cells reduced the activation of PGE2 by 20%. PGE2 is known to be involved in tumor development by enhancing angiogenesis and inhibiting apoptosis as well as in eliciting inflammation [25, 26]. Our transfection study showed a significant decrease in VEGF expression with the decline of PGE2 activity. Moreover, clofibrinic acid was found to have a direct reducing effect on mPGES (Figure 1). Thus, we concluded the mechanism of the antitumor effect against ovarian cancer of clofibrinic acid, a PPAR ligand, as follows: treatment with clofibrinic acid increased carboxyl reductase and decreased mPGES, which resulted in reduced PGE2 activity followed by suppression of angiogenesis and induction of apoptosis (Figure 1).

Pozzi et al. [21] reported in June 2007 that administration of a PPARα ligand of Wy14,643 produced a tumor response in human lung cancers. They noted the reason that angiogenesis did not occur to be the result of reduced expression of Cyp2c epoxygenase genes which catalyze arachidonic acid metabolism or synthesize epoxyeicosatrienoic acid having a stabilizing action on vascular endothelium. These findings were not observed in PPARα knockout mice, show-
ing that activation of PPARα by its ligand played a leading role. Panigrahy et al. [22] reported in January 2008 that administration of a PPARα ligand of fenofibrate in mesenchymal tumors and various types of cancer inhibited tumor growth in all treated tumors. The mechanism of the antitumor effects of fenofibrate is suppression of angiogenesis by increasing the anti-inflammatory effects of thrombospondin-1. They confirmed that these antitumor effects were not observed in PPARα knockout mice. Consequently, it was shown that the activation of PPARα by its specific ligand theoretically had an antitumor effect against any type of solid tumor. The results of these three studies conducted in different facilities demonstrated the same mechanism of antitumor effect of PPARα ligands. That is, it was suggested that the surrounding microenvironment of tumors commonly seen in inflammation was responsible for tumor proliferation. Inflammation induces angiogenesis [25]. Inflammatory cells around the tumor conduct an essential role in promoting tumor growth by releasing angiogenic factors and cytokines which are tumor cell nutrients [21, 22]. The activation of PPARα by its specific ligand was revealed to reduce "inflammation" around tumor cells. Our report served as a basis for the development of a potential treatment for ovarian cancer targeting PGE₂ using clofibrate acid. It is recommended that future studies investigate antitumor effects against various types of cancers using different PPARα ligands.

PPARδ and ovarian cancer

At present, there are few studies investigating the relationship between PPARδ and malignant tumors. According to in vitro studies, the activation of PPARδ appears to inhibit tumor growth in breast cancer cells, lung cancer cells, and melanoma cells [27, 28], although a consensus has not been reached on its mechanism of action. Daikoku et al. [29] reported in 2007 that blocking PPARδ function by neutralizing activated PPARδ inhibited tumor growth of ovarian cancer in vivo. Aspirin, a NSAID and a COX-1 selective inhibitor, inhibited the growth and proliferation of ovarian cancer as well as reduced the function of PPARδ, suggesting inactivation of PPARδ is associated with the growth inhibition of ovarian cancer [29]. In our study, however, aspirin did not inhibit tumor growth of ovarian cancer [30]. Further studies on the relationship between PPARδ and malignant tumors may be necessary.

Future prospects

The basic treatment for ovarian cancer is cytoreductive surgery and postoperative chemotherapy. A characteristic of ovarian cancer is that even in patients with advanced ovarian cancer with residual lesions, the response rate is high since ovarian cancer is more sensitive to anticancer agents, but the recurrence rate is also high. For recurrent cancers, a single treatment with a variety of anticancer agents has been attempted, yet there is still no conclusive answer. The antiangiogenic agent bevacizumab (Avastin) is receiving attention as a molecular-targeted agent. However, the serious complications including intestinal perforation cannot be ignored. A molecular-targeted agent specific for the activation of PPARγ or PPARα discussed above would be a promising drug candidate from the aspect of side effects. The previously-reported PPARγ ligands ciglitazone and pioglitazone are oral hypoglycemic drugs, while PPARα ligands of clofibrac acid and fenofibrate are drugs for hyperlipidemia. Both types of drugs are routinely used and their potential side effects are known. Therefore, it is desirable to promote clinical studies based on the fundamental accumulated data on these, in order to investigate antitumor effects by either of these drugs alone or with anticancer agents. Survival after
relapse is relatively long, particularly in patients with ovarian cancer. Although it is important to examine whether PPARγ ligands or PPARα ligands provide survival benefits, investigating their possible benefits as dormancy therapies would be very interesting.

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Ovarian tumours in childhood and adolescence

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Summary

Malignant ovarian tumors are very rare during childhood and adolescence where their incidence is approximately 0.71 per 100,000. We reviewed the symptoms, histologic subtypes, diagnostic evaluation and management of ovarian tumours in children and adolescents with emphasis on malignant tumours. The histology of these tumours is complex and their diagnosis frequently poses problems. Surgery and chemotherapy yield high cure rates in patients with malignant germ cell tumours whereas prognosis is poorer in ovarian carcinomas. Elucidation of the mechanisms underlying the pathogenesis of ovarian tumours might further improve the management of these patients.

Key words: Malignant ovarian tumours; Children; Adolescents; Germ cell tumours; Ovarian carcinoma.

Introduction

Malignant ovarian tumours are very rare during childhood and adolescence where their incidence is approximately 0.71 per 100,000 [1]. However, these tumours represent the commonest gynaecological tumours in this age group [2-6]. During childhood, malignant ovarian tumours are among the ten more frequent malignancies [2]. During adolescence, these tumours are the fourth commonest malignancy after lymphomas, leukemias and thyroid cancer [4]. Malignant germ cell tumours (GCT) (the commonest malignant ovarian tumour) occur in 4.9/1,000,000 person-years and are the sixth commonest malignancy in adolescents after lymphomas, leukemias, astrocytomas, thyroid cancer and osteosarcomas [5].

We reviewed the symptoms, histologic subtypes, diagnostic evaluation and management of ovarian tumours in children and adolescence with emphasis on malignant tumours.

Symptoms

The commonest presenting symptom of ovarian tumours is abdominal pain [7-17]. Sometimes these tumours are misdiagnosed as appendicitis [11]. The presence of a palpable abdominal mass is the second most frequent manifestation [8-10, 13, 14, 17, 18]. Endocrine abnormalities are a rare manifestation of ovarian tumours and include precocious puberty (that may lead to vaginal bleeding) or signs of virilization (acne, deepening voice, hirsutism and cliteromegaly) [10, 14, 18]. Both benign and malignant ovarian tumours can present with endocrine abnormalities [18]. These manifestations are more commonly associated with sex cord-stromal tumours [14, 16, 19-23] but germ cell tumours, including endodermal sinus tumours and choriocarcinomas, can also present with precocious pseudopuberty [22]. Galactorrhea has been reported in children with granulosa cell tumours [24]. Vaginal discharge, urinary symptoms, poor appetite, nausea/emesis and weight loss might also be present in patients with ovarian neoplasms [10, 25]. Ovarian torsion might be the first symptom of an ovarian tumour [10, 26-28]. These patients present with abdominal pain and/or pelvic mass [29]. Finally, ovarian tumours are frequently an incidental finding in imaging studies or during surgery performed for unrelated conditions [10, 14].

Histology

The proportion of malignant tumours among ovarian neoplasms varies significantly in different series, ranging between 4% and 55% [6, 9, 10, 16, 18, 27, 30-33]. The small number of cases included in these series partly explains this large variation. In addition, most reports are from tertiary referral centers and might represent an over-estimation of the frequency of malignant tumours because of referral bias [34]. Studies from regional hospitals suggested that less than 10% of ovarian neoplasms are malignant [34].

The majority of malignant ovarian tumours in children and adolescents are of germ cell origin [1, 3, 4, 6, 12, 16-18, 22, 30, 33, 35]. In contrast, epithelial cancers represent the vast majority of ovarian malignancies in adults [36]. Ovarian GCT are observed in all ages but their incidence peaks in adolescence [37, 38]. Dysgerminoma is the commonest malignant ovarian tumour in children and adolescents whereas other GCT types [immature teratomas, endodermal sinus (yolk sac) tumours, embryonal carcinomas and choriocarcinomas] are less frequent [1, 15]. Earlier studies reported an increasing incidence of malignant GCT [39] but this trend appears to have stabilised in recent years [5]. In contrast to adult malignant GCT, where gain of 12p is present in most cases [40, 41],

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this genomic imbalance is present in the minority of these tumours in children and adolescents [42-44]. Loss of 1p/gain of 1q as well as +3, +8, +14 and +21 has also been reported in malignant GCT [42, 44]. Activation of Wnt/beta-catenin signaling appears to play a role in the pathogenesis of yolk sac tumours and immature teratomas but not of other malignant GCT [45]. Children born preterm appear to be at increased risk for malignant GCT [46]. Paternal and maternal exposure to chemicals and solvents also appear to increase the risk for malignant GCT in their children [46].

Malignant ovarian epithelial neoplasms are the second most frequent malignant ovarian tumours in children and adolescents [1, 16, 30, 33]. These tumours are very rare before menarche [4, 17, 25, 38, 47]. Among malignant epithelial tumours, mucinous are the most common subtype [1,13,25,35,48]. This is in contrast with epithelial tumours in adults, where the majority is serous [36].

Sex cord-stromal tumours consist of epithelial (granulosa-Sertoli cells) and mesenchymal elements in a variety of combinations [35]. Granulosa cell tumour is the commonest sex cord-stromal tumour whereas Sertoli-Leydig cell tumours, thecomas and sclerosing stromal tumours are very rare [19, 35, 44]. Mutations in the g stimulatory protein gene and in the receptor of follicle-stimulating hormone are frequently present in granulosa cell tumours [49].

Lymphomas and metastatic tumours are rare [50, 51]. Colon adenocarcinoma and neuroblastomas are the most frequent primary tumours in patients with ovarian metastases [50, 51].

The majority of benign ovarian tumours are mature teratomas, which are benign GCT [8, 9, 14, 17, 18, 52]. Mature teratomas are twice as common as immature teratomas [52]. In general, most GCT are benign [53]. In contrast, only a minority of epithelial tumours are benign [48]. Most benign epithelial neoplasms (cystadenomas) are of the serous subtype [9, 14, 17].

Diagnosis

In patients with symptoms suggestive of ovarian neoplasms (abdominal mass or pain, precocious puberty, virilization) imaging studies are very useful in establishing the diagnosis and differentiating between ovarian tumours and other diseases with similar symptoms, such as appendicitis [11, 18]. Most simple ovarian cysts are benign tumours or functional cysts [12, 18, 27, 54-56]. Abdominal ultrasound identifies the majority of ovarian tumours but is not very sensitive in the differential diagnosis of benign and malignant tumours [18]. Computed tomography and magnetic resonance imaging are also useful for the diagnostic investigation of ovarian tumours [9]. Most malignant primary ovarian tumours are unilateral [13, 22, 25] whereas one third of metastatic tumours are bilateral [50, 51].

Several tumour markers are helpful in the diagnostic evaluation of ovarian neoplasms. Elevated levels of tumour markers are observed in almost one third of all ovarian tumours [56]. Yolk sac tumours frequently secrete alpha fetoprotein (AFP) and choriocarcinomas secrete beta-human chorionic gonadotropin (βHCG) [22, 57]. However, both tumours can secrete both these tumour markers [57]. Elevated βHCG levels are sometimes observed in patients with dysgerminomas [35, 58]. Occasionally, embryonal carcinomas, mature or immature teratomas and epithelial tumours can also secrete AFP and/or βHCG [17, 57-59]. Serum inhibin levels are also elevated in some cases of epithelial ovarian cancers, mostly serous and mucinous cystadenocarcinoma [60]. Measurement of serum inhibin levels (particularly of the alpha subunit peptides) is also useful in the diagnosis of granulosa cell tumours [60]. Measurement of Mullerian inhibiting substance (MIS), a hormone produced by the granulosa cells of the ovary, can also be useful in the diagnosis of granulosa cell tumours [61]. CA-125 is more frequently elevated in epithelial tumours than in GCT [13]. However, CA-125 appears to be of limited specificity for the diagnosis of malignant ovarian tumours in children and adolescents [62]. Elevated lactate dehydrogenase (LDH) levels are rarely present in patients with benign ovarian tumours but are observed in almost a third of those with malignant tumours [62]. Thrombocytosis has also been reported in children and adolescents with ovarian malignant tumours, particularly GCT [62]. However, thrombocytosis can also be present in patients with benign ovarian tumours [62]. Finally, in some cases the differential diagnosis between ovarian pathology and other conditions can be challenging and surgery is necessary to establish a diagnosis [14].

Treatment

In patients with malignant GCT, surgery followed by cisplatin-based chemotherapy is the treatment of choice regardless of tumour stage [63-66]. Patients with GCT treated with cisplatin, bleomycin and vinblastine had higher survival rates than patients treated with vincristine, actinomycin and cyclophosphamide [67]. In patients with advanced GCT, etoposide, bleomycin and high-dose cisplatin improved event-free survival compared with etoposide, bleomycin and standard-dose cisplatin [63]. However, overall survival did not differ between the two regimens and toxicity was higher with the former [63]. A recent study also showed that cisplatin plus etoposide is associated with higher 5-year survival rates than more complex regimens (cisplatin and etoposide plus ifosfamide, vinblastine and bleomycin) [64]. Substitution of carboplatin for cisplatin reduced the risk for oto- and nephrotoxicity and produced high cure rates in patients with advanced GCT [68]. In patients with GCT diagnosed at Stage IA, surgery alone appears to be sufficient [35, 57, 65, 67]. This is important since most dysgerminomas are diagnosed at this stage [35]. Surgery alone followed by observation is also the treatment of choice for immature teratomas [57, 59, 69]. In contrast to other malignant GCT, chemotherapy is less effective in these tumours [52, 57, 69].
Most epithelial neoplasias are diagnosed at Stage I [25]. Salpingo-oophorectomy with extirpation of peritoneal implants (when present) is the recommended treatment for epithelial malignancies [35]. Chemotherapy does not appear to be required in patients with borderline epithelial tumours diagnosed at Stage I but is frequently administered in patients with malignant epithelial tumours regardless of stage [25].

Most sex cord-stromal tumours are also diagnosed at Stage I [20]. In patients with Stage IA granulosa cell tumours, salpingo-oophorectomy alone is the preferred treatment [20, 35, 70]. Surgery is also usually curative in ovarian Sertoli-Leydig cell tumours [19]. Patients with more advanced granulosa cell tumours appear to benefit from adjuvant cisplatin-based chemotherapy [20, 70].

In all cases, surgery should be as conservative as possible so that sexual development and fertility are not affected [30, 57, 71]. Bilateral salpingo-oophorectomy is required only in the rare cases of bilateral malignancy [12, 15]. A good outcome has been reported with laparoscopic resection in ovarian tumours [72] but its role is still controversial.

In patients with mature teratomas and benign cystadenomas, cystectomy is the recommended treatment [13, 14] and laparoscopic management is the preferable approach [73]. Functional ovarian tissue should be preserved as much as possible in the affected ovary since women with a single ovary appear to have higher infertility rates [14, 71].

In children, mature teratomas or functional cysts are the underlying cause in the majority of cases of ovarian torsion whereas malignant tumours are a rare cause [10, 28, 29]. In patients who present with ovarian torsion, detorsion is recommended in the acute phase and can be performed laparoscopically [14, 29, 74]. Diagnostic evaluation and treatment should be undertaken after the resolution of edema [14, 29]. However, the majority of cases of ovarian torsion associated with an ovarian tumour are still being managed with oophorectomy [9, 14].

Prognosis - follow-up

Prognosis is good in most patients with malignant GCT [57, 63, 64, 67, 69]. However, patients at more advanced stage at diagnosis have worse outcome [67]. Patients with localized GCT (Stage I-II) treated with surgery and chemotherapy consisting of cisplatin and etoposide with or without bleomycin had a 93.8-95.1% six-year overall survival rate [63, 64]. Patients with advanced GCT (Stage III-IV) treated with surgery and chemotherapy consisting of cisplatin, bleomycin and etoposide had an 83.3-97.3% five-year survival rate whereas relapse was rare [63, 64]. In patients with advanced GCT, elevated AFP and HCG levels predicted an adverse outcome whereas elevated LDH levels had no predictive value [63]. In addition, monitoring of AFP and βHCG is recommended for early detection of the recurrence of malignant GCT [35, 44, 57, 69]. Repeated ultrasound and computed tomography are also being used in the follow-up of these patients [57].

Prognosis is very good in almost all patients with mature or immature teratomas when complete resection is performed [52, 69]. In patients with teratomas, incomplete resection, tumour rupture, young age, higher stage and grade, and peritoneal gliomatosis were independent predictors of poorer outcome [69].

Malignant epithelial tumours do not have a good prognosis unless they are diagnosed at an early stage [13, 25]. Monitoring of CA-125 levels is recommended in patients with malignant and borderline epithelial tumours [13]. Patients with sex cord-stromal tumours have a good prognosis [21, 35, 64, 75-77]. However, advanced stage, high mitotic activity, elevated LDH levels, reduced expression of FOXL2 (a forkhead transcription factor) and the presence of an activating mutation of g stimulatory protein gene are adverse predictive factors in these patients [64, 75-77]. Measurement of inhibin and MIS is useful in the follow-up of patients with granulosa cell tumours [20, 23, 60, 61].

Conclusions

Malignant ovarian tumours are rare in children and adolescents. However, their histology is complex and their diagnosis frequently poses problems. Surgery and chemotherapy yield high cure rates in patients with malignant GCT whereas prognosis is poorer in ovarian carcinomas. The elucidation of the mechanisms underlying the pathogenesis of ovarian tumours might further improve the management of these patients.

References


Reliability of outpatient endometrial brush cytology vs biopsy in postmenopausal symptomatic women

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Summary

Objective: To compare outpatient endometrial sampling cytology with conventional biopsy in postmenopausal women with abnormal uterine bleeding and/or abnormal endometrial thickness at ultrasound. Method: Between December 2003 and December 2009 a group of 1,056 postmenopausal women was referred to the Department of Gynecological Sciences, Perinatology an Child Health II Faculty of Medicine, University of Rome, S. Andrea Hospital. Four hundred and eighty-two patients (45.6%) had abnormal uterine bleeding and 602 (57.0) showed an endometrial thickness > 5 mm at ultrasound. Patients on hormonal therapy (n = 194) including hormonal replacement therapy (HRT) or tamoxifen (TMX), were enrolled in the study. Endometrial cytologic sampling was performed using a brush device (EBC) while endometrial histological sampling was retrieved using a Novak curette. Histologic evaluation showed: a) malignant neoplasia b) atypical hyperplasia c) benign pathology d) normal or atrophic endometrium. The following points were investigated: a) failure in performing a procedure for cervical stenosis or pelvic pain; b) nondiagnostic specimens; c) diagnostic accuracy. Results: Evidence in score pain differences between brush and curette endometrial samples were observed: 50% of patients undergoing brush cytology had lower pain scores (chi-square = 288.33; p = .001), whereas 60% of patients undergoing endometrial biopsy had higher pain scores (chi-square = 264.84; p = .001). The failure rate in performing procedures was 8.0% vs 4.1%, and the results were statistically significant on the McNemar test, respectively p = .01 and p = .001. A nondiagnostic specimen was obtained in 3.9% of cases by EBC, and 10.3% of cases by the Novak curette (p = .001). Cytological evaluation had a sensitivity of 100%, specificity of 99%, positive and negative predictive value of 97% and 100% for diagnosing malignant neoplasia. Cytology had high diagnostic accuracy for atypical hyperplasia: sensitivity 100%, specificity 99%, positive and negative predictive value 83% and 100%, respectively. Conclusions: EBC is a reliable, well tolerated outpatient diagnostic tool for endometrial sampling in detecting early-stage cancer in postmenopausal patients at high risk for endometrial cancer.

Key words: Menopause; Endometrial cytology; Endometrial biopsy; Brush device.

Introduction

Endometrial cancer is the most common malignant neoplasia of the female genital tract in developed countries; 70% of endometrial cancer is diagnosed in postmenopausal women. The early detection of endometrial cancer is important for improvement in the long-term survival rate of patients [1, 2].

Abnormal uterine bleeding may occur in many women after menopause [3]. Although endometrial polyps, submucous myomas and endometrial hyperplasia without atypia are the most common causes of postmenopausal bleeding, they are observed in 85% of endometrial adenocarcinoma [4].

The increase of endometrial thickness, is the main risk factor pointed out by transvaginal ultrasound (TVS) [5, 6]. Hormone replacement therapy (HRT) and tamoxifen therapy side-effects more frequently include increased endometrial thickness and/or abnormal uterine bleeding so that an endometrial cancer diagnosis is more difficult in this group of patients [7, 8].

For many years dilatation and curettage (D&C) under general anesthesia was the most common procedure to detect endometrial pathology. Disadvantages of this procedure include need for hospital admission and high effective cost [9]. Hysteroscopic guided biopsy, moreover, is an accurate and sensitive diagnostic tool but its use is limited by its intrinsic invasive nature [10].

The major risk factors for endometrial cancer are estrogen exposure, including estrogen therapy, tamoxifen therapy, early menarche or late menopause. It has been suggested by many investigators that periodic endometrial sampling be performed in women under treatment with estrogens or tamoxifen. Thus there is a growing need for a simple, accurate and well tolerated method for early detection of cancer or its precursors [11].

In recent years, several less painful devices for endometrial cytology have been investigated. The brush device is a small flexible device used to gently brush the uterine cavity. Thus it is able to gather a more complete sampling of the uterus lining, remove less tissue and is less painful than traditional methods for office biopsy [12].

Wu et al. examined 200 cases of endometrial brush cytologic (EBC) findings that correlated with histologic findings from office or narcosis biopsy. EBC samples correctly detected 100% of cancer, 100% of atypical hyperplasia, 100% of benign pathology and 95.7% of normal or atrophic endometrium. Sensitivity and specificity were 100% for detecting atypical hyperplasia or carcinoma. However, it is very difficult for EBC to dis-
tistinguish simple hyperplasia from polyps; pelvic pain was significantly lower in performing cytology compared to biopsy ($p < 0.01$). It was concluded that EBC is an accurate, safe and well tolerated procedure to detect endometrial pathology in an outpatient setting [13].

In a subsequent report, Wu et al. studied disposable brushes for endometrial cytology in outpatients. The study design was histologic confirmation after EBC. Six hundred and thirty-three patients were evaluated for a two-year period. Cytologic diagnosis by EBC obtained by evaluation of hematoxylin and eosin stained smears was compared to histologic diagnosis. Diagnosis was made in 569 cases with a diagnostic rate of 90%. Sensitivity and specificity in identifying malignant diseases was 100% and 96%, respectively. In this study four cases of adenocarcinoma were identified by D&C in patients with non diagnostic smears [11].

Kipp et al. [14], obtained brushings of the endometrial cavity from 139 hysterectomy specimens before routine histopathologic evaluation. Cytology diagnoses were classified as negative, nondiagnostic, hyperplasia without atypia and endometrial cancer. The sensitivity and specificity of cytology for detecting endometrial cancer and atypical hyperplasia were 95% and 66%, respectively.

Mathelin et al. in 2006 [15] evaluated cytological sampling of the endometrium using the Endobrush for surveillance of tamoxifen-treated (TMX) patients. Six hundred and eighty-seven TMX-treated patients with an endometrial thickness of more than 8 mm were studied with a cytological examination followed by hysteroscopy and curettage. Cytology and histology were well correlated in 145 cases (141 benign lesions and 4 endometrial cancers). There were five false-positive (4 atypias and 1 cancer).

Concerning the degree of pain and acceptance of biopsy procedure Lau et al. [10] obtained, utilizing a visual analogue scale, a mean pain experience of 5.0 (SD 2.9) during biopsy. Stovall et al. [16] had, with Novak biopsy, a mean pain score of 4.36 with 17% reporting severe pain, whereas patients undergoing a soft device biopsy had a mean pain score of 3.21 with only 6.7% reporting severe pain. Insufficient tissue was reported in 9.5% of the patients in the Novak group.

On this basis, the present study compared outpatient endometrial sampling cytology performed with an EBC with conventional biopsy in postmenopausal women with abnormal uterine bleeding and/or increased endometrial thickness.

**Material and Method**

**Baseline data patients**

Between December 2003 and December 2009 a group of 1,056 postmenopausal women were referred to the Department of Gynecology of the II School of Medicine University of Rome “Sapienza” S. Andrea Hospital, for abnormal uterine bleeding (AUB) and/or increased endometrial thickness (> 5 mm).

The mean age of patients was 56.2 years (range 48-76). All cases had spontaneous menopause. Four hundred and eight-two patients (45.6%) had AUB, 602 (57.0%) increased endometrial thickness and 28 (2.7%) patients had both. One hundred and ninety-four (18.3%) women were in treatment with HRT and 42 (4.0%) with tamoxifen; 820 patients (77.7%) were not treated.

**Instrumental examination**

The Cytobrush is a small flexible device used to gently brush the uterine cavity. It is able to gather a more complete sampling of the uterus lining and is less painful than traditional methods for office biopsy.

The Novak curette has been manufactured for more than 50 years and is made of stainless steel. The cannula is rigid and the histologic sample is pushed out by a plastic syringe (10-20 ml) via positive pressure.

All patients underwent endometrial cytology with brush device and, subsequently, endometrial biopsy with Novak curette.

Before and after the procedures each women was informed about the procedure and requested to respond to a pain questionnaire. A numeric rating scale (NRS) was used to quantify pain intensity. The NRS is a simple and valid alternative to a simple descriptor scale (SDS) and to a visual analog scale (VAS) [17]. A verbal score ranging from 1-8 was administered. For pain over score 8, sampling was not performed.

Exclusion criteria were: a) lower genital tract infections; b) abnormal cervical cytology; and c) rheumatic heart disease or arrhythmias. The following were required: a) pap smear and vaginal bacteriology; b) hepatitis B and C tests; c) electrocardiogram; and d) TVS.

**Procedures**

Before performing cytology and biopsy, side-effects and potential complications were reviewed and an informed consent was obtained. Gynecological examination was performed. Both procedures were performed in an operative setting at the same time: first cytology and afterwards biopsy.

The brush was inserted into the uterus, rotated four to five times in the uterine cavity and then it was rapidly removed and directly smeared on the surface of two glass slides, rotating the device. EBC was followed by the standard biopsy with a Novak curette. The brush material was smeared on the surface of two glass slides and sprayed immediately with cytology fixative (ethanol solution) and processed with ethanol and stained with Harris hematoxylin as nuclear and Orange D and EA-50 as cytoplasm stain. Biopsy was fixed in 10% formalin and included in paraffin blocks for subsequent processing.

The cytologic findings were compared with the histologic report to assess the validity of brush cytology in detecting endometrial pathology, the adequacy of the samples obtained, and the failure rate. The sample was inadequate or non diagnostic when scanty endometrial cells or no endometrial tissues were present in the specimen. Procedure failure was inability to introduce the brush device or the Novak curette either for cervical stenosis or for severe pelvic pain.

Diagnosis was later completed, if needed, with panoramic hysteroscopy performed with a standard 4 mm hysteroscope (Karl Storz, Tutlingen, Germany). Distension of the uterine cavity was obtained by carbon dioxide. No local anesthesia was used.

Endometrial histology was classified according to the following categories: a) normal or atrophic endometrium (NA), b) benign pathology (BP), c) atypical hyperplasia (AH), d) malignant neoplasia (Ca) and e) inadequate for diagnosis, or non diagnostic (ND).
Persistent pelvic pain was managed with NSAIDS. Women were informed to report fever, cramping after 48 hours or bleeding occurring within 24 to 48 hours from the biopsy. Patients in whom outpatient endometrial biopsy was not feasible, were hospitalized in a day surgery structure and submitted to hysteroscopy and biopsy under general anesthesia.

Statistical analysis

The chi-square test with Yates’s correction, chi-square goodness of fit and McNemar test were used to identify a difference between endometrial cytology vs biopsy in determining a) accuracy in diagnosis of endometrial pathology b) intensity of pain and c) failure rate. Diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated to explain the reliability of the cytology method.

Results

Table 1 shows the characteristics of patients. Of 1,056 women who underwent cytology and biopsy, 602 had an endometrium thickness > 5 mm and 482 abnormal uterine bleeding. Twenty-eight had both signs. One hundred and ninety-four patients were on hormonal replacement therapy, 42 TMX for breast cancer and 820 were untreated.

Table 2 shows the histological findings and Table 3 describes diagnosis related to symptoms or hormonal therapy. The association between diagnosis and endometrial thickness was statistically significant (chi-square = 74.04; p = .001); 5.3% of women with endometrial thickness > 5 mm developed a malignant neoplasia vs 0.7% of women with thickness < 5 mm. Additionally, we found a significant association with abnormal uterine bleeding (chi-square = 98.63; p = .001); 6.8% of postmenopausal women with AUB developed malignant neoplasia vs 0.3% of the women without bleeding. Hormonal therapy was not related with diagnosis (chi-square = 3.89; ns).

Table 4 shows the pelvic pain intensity: the lower scores of cytology (from 1 to 4) include about 50% of women (chi-square = 88.33; p = .001), whereas the higher scores of biopsy (from 5 to 8) include about 60% of women (chi-square = 264.84; p = .001). The mean pain score experienced was 4.2 for cytology and 5.1 for Novak biopsy.

Table 5 shows the failure in performing biopsy and cytology (8.0% vs 4.1%). Non diagnostic samples were obtained in 10.3% vs 3.9% of patients and both results were statistically significant on the McNemar test, respectively p = .01 and p = .001.

It was impossible to perform biopsy in 84 women and cytology in 43 due to severe pelvic pain and/or cervical stenosis: a difference between the two groups was significant (p = .01). Differences were more significant for non diagnostic specimens with 3.9% cases for cytology, and 10.3% cases for biopsy (p = .001). If failure related to...
diagnosis is analyzed, it can be seen that a specimen was performed in each case of malignant neoplasia; cytology was not obtained only in one case of atypical hyperplasia vs two cases of biopsy. Mostly a non diagnostic specimen was related to atrophic or normal endometrium (respectively, 76 and 32 cases).

Also the distributions related to diagnosis were statistically significant as reported in Table 6.

In Table 7 the cytological non diagnosed cases of 972 patients are summarized in which cytologic sampling was performed. In 13 patients (2.2%) the cytological diagnosis was uncorrect: the main error concerned atypical hyperplasia; in every case of over-diagnosis (histology diagnosed two simple hyperplasias and one proliferative endometrium). Only one malignant neoplasia was under-diagnosed as atypical hyperplasia.

Table 8 describes sensitivity, specificity, PPV and NPV of cytology for each pathology. For malignant neoplasias, the sensitivity of cytology was 100%, specificity 99%, PPV 97% and NPV 100%. For atypical hyperplasia sensitivity was 100%, specificity 99%, and PPV and NPV were 83% and 100%, respectively.

Complications

There was no severe complication such as uterine perforation or pelvic inflammatory disease or posthemorrhagic anemia in performing cytology or biopsy.

Discussion

Endometrium sampling is generally performed in cases of abnormal uterine bleeding and/or increased thickness of the endometrium. Postmenopausal women with persistent bleeding or with endometrial thickness > 4 mm have a 60-fold increased risk of endometrial cancer [18].

The main reason for performing endometrial sampling in postmenopausal women with abnormal uterine bleeding and/or excessive endometrial thickness is to rule out endometrial carcinoma or its precursors so that medical treatment or conservative surgery can be offered.

Since the 1970s, a variety of direct uterine sampling devices have been developed that showed high sensitivity and specificity for detecting endometrial carcinoma [19-21].

On an outpatient basis, various methods of endometrial sampling are actually used, including invasive or non-invasive techniques. Ultrasonography avoids over 40% of histological assessments of the endometrium, although the cut-off point of endometrial thickness is still debated [5].

Biopsy in an outpatient setting has replaced dilatation and curettage for evaluating endometrial disorders as hyperplasia and cancer. In the literature many studies support its accuracy and cost-containment benefits [10-12, 20].

Invasive office methods include hysteroscopic-directed biopsy or endometrial biopsy using different endometrial samplers.

The most common option for outpatient sampling is the Novak biopsy device which allows from 67% to nearly 100% of endometrial cancer detection.
Biopsy is sufficiently sensitive in detecting endometrial hyperplasia and/or cancer, but may fail to diagnose other uterine pathologies such as polyps and submucous myomas [22]. Novak curettage is associated with moderate/severe pain and with inadequacy of sample in atrophic endometrium. Cytological sampling of the uterine cavity was added as a diagnostic tool. Cytological sampling of the endometrium is less invasive and less painful than biopsy. A brush device has been proposed as a cytologic endometrial sampler.

An adequate endometrial sample, obtained also in case of atrophic endometrium, has better results than direct biopsy [23]. In 15 of 40 cases of atrophic endometrium diagnoses were based only on cytologic examinations [13]. Cytology provided sufficient material more often than biopsy ($p < 0.01$) [24].

In the present study, cytology sample was inadequate in 3.9% of cases versus 10.8% of direct biopsies compared with 11% cases of biopsies in other studies [25]. Novak biopsy provided scanty tissue in 9.5% of patients [16].

Lau et al. [10] utilizing a visual analogue scale found a mean pain experience of 5.0 (SD 2.9) during biopsy. Stovall et al. [16] showed a mean pain score of 4.36 in patients undergoing biopsy performed with the Novak curette; 17% of patients reported severe pain. Patients undergoing biopsy with a device, had a mean pain score of 3.21, and only 6.7% reported severe pain.

In the current study the mean pain score experienced was 4.2 during cytology and 5.1 during the Novak biopsy, while according to other studies 4.1% of patients had pain during cytology vs 8.0% biopsy [12]. Yang et al. [10-12, 14-16] also reported that endometrial cytology in an outpatient setting was associated with minimal patient discomfort.

Mathelin et al. [15] evaluated cytological sampling of endometrium using the Endobrush in the surveillance of 687 TMX-treated patients and concluded that was well accepted by the patients.

In the current study it was found that sensitivity of brush cytology was 100%, sensibility 99%, PPV 97% and NPV 100% for malignant neoplasias. For atypical hyperplasia sensitivity was 100%, sensibility 99%, PPV 83% and NPV 100%. Other studies have shown that direct biopsy produces the same results in detection of endometrial pathology [26]. Maksem et al. [18] applied the Tao brush in 100 consecutive hysterectomy specimens reporting 100% sensitivity and specificity in identifying endometrial carcinoma and atypical hyperplasia.

Wu et al. [11] made a diagnosis in 569 cases resulting in a diagnostic rate of 90%. Twelve atypical hyperplasias diagnosed by EBC were confirmed by histology. However there was one false-positive case in which histology pointed out simple hyperplasia. There were two false-negative cases; the EBC diagnoses were atrophic and proliferative endometrium, while histology showed focal atypical hyperplasia in both cases. The sensitivity and specificity in identifying carcinomas was 100% and 96%, respectively. In the same study four cases of adenocarcinoma were identified in D&C patients with non diagnostic EBC.

Wu et al. [13] examined 200 cases of EBC findings correlated with histologic findings from office or narcosis biopsy. EBC correctly detected 100% of cancers, 100% of atypical hyperplasias, 100% of benign pathologies and 95.7% of normal or atrophic endometrium. Sensitivity and specificity were 100% for detecting atypical hyperplasia or carcinoma. However, is very difficult for EBC to distinguish hyperplasia from polyps. Pelvic pain was significantly lower in performing cytology compared to biopsy ($p < 0.01$). They concluded that EBC is an accurate, safe and well tolerated procedure in detecting endometrial pathology. Klemi et al. [14] obtained brushings of the endometrial cavity from 139 hysterectomy specimens before routine histopathologic evaluation. The sensitivity and specificity of cytology for detecting endometrial cancer and atypical hyperplasia were 95% and 66%, respectively.

Klemi et al. [26] took EBC sampling from 1,042 symptomatic patients and the results were compared to histology obtained by D&C. Twelve cancers were detected; one cancer was missed, whereas no false-positive results were found. The diagnostic accuracy ranged from 92.3% to 97.8% depending on true positive vs true negative groups of patients. The study concludes that endometrial cytology obtained by brushing is useful in symptomatic patients of all ages, whereas histology is indicated in postmenopausal patients with persistent uterine bleeding and negative cytological results.

Mathelin et al. [15] evaluated cytological sampling of the endometrium using the Endobrush in the surveillance of TMX-treated patients. Six hundred and eighty-seven TMX-treated patients underwent cytological examination followed by hysteroscopy and curettage. The study concluded that cytology was reliable for detection of endometrial pathology.

Buccoliero et al. [24] in a study on 670 women with endometrium thickness over 4 mm estimated that cytology had a sensitivity and specificity of 95% and 98%, respectively; PPV and PNV were estimated respectively at 83% and 99%.

Concerning the main complications, several authors have reported a minimal rate of incidents. In our study we had no severe postoperative complications as pelvic inflammatory disease, hemorrhage or perforation. Overall the sample was available also in patients with coagulation disorders or on anticoagulative therapy.

Thus the study suggests that this device should replace the traditional method of endometrial sampling in outpatient procedures. It is a safe, less painful and cost effective device for getting an adequate endometrial sample with a satisfactory sensitivity and specificity for detection of hyperplasia and malignancy.

**Conclusions**

Brush cytology is not able to identify endometrial polyps or submucous myomas; on the other hand it is requested only to identify pathology of endometrial mucosa in order to recognize a malignant neoplasia or its
precursors. Moreover, accurate diagnosis of endometrial disease by cytologic examination requires expertise in sample retrieval and in interpretation of endometrial cytology findings.

On the other hand, cytological smears obtained from atrophic endometriums were more cellular than biopsies, thus making diagnosis more probable.

EBC is a sensitive, specific and well tolerated method for detecting endometrial carcinoma and atypical hyperplasia. It is easy for clinicians to use and associated with minimal discomfort for patients, and it can be performed in patients with coagulation disorders and on anticoagulative therapy. Overall, the brush cytology method is able to collect samples from the entire uterus. Our suggestion, in accord with another study [18], is that EBC is an excellent method for early detection of cancer in screening of patients at high risk for endometrial pathology and for therapeutic monitoring.

References

Immunohistochemical expressions of p16 and p53 proteins in cervical intraepithelial neoplasia and in benign cervical tissue

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Summary

Purpose of Investigation: To evaluate the immunohistochemical expressions of p16 and p53 in cervical intraepithelial neoplasia (CIN) and do a comparison with non-neoplastic cervical lesions. Methods: Sixty cases diagnosed as CIN after histopathological examination and 25 controls diagnosed as chronic cervicitis were included in the study. Immunohistochemical expressions for p16 and p53 were evaluated and compared in all cases. The cases in the study were defined according to the Bethesda system. Of these, 31.8\%\ (n = 27) had a low-grade squamous intraepithelial lesion (LGSIL), and 38.8\%\ (n = 33) had a high-grade squamous intraepithelial lesion (HGSIL). Results: There was a statistically significant difference between chronic cervicitis and CIN in terms of p53 and p16 expression levels (p = 0.001). On the other hand, the level of p16 expression was statistically different between LGSIL and HGSIL (p = 0.001), while there was no significant difference in terms of p53 expression. Among the HGSIL cases (n = 33), 91\%\ had p16 expression, while 66.7\%\ (n = 27) of the LGSIL patients had no p16 expression. In the chronic cervicitis group, 84\%\ (n = 21) did not reveal any p16 expression, while 96\%\ (n = 24) did not reveal any p53 expression. Various levels of p53 expressions were detected in 59.2\%\ (n = 16) of CIN1 cases, 69.3\%\ (n = 9) of CIN2 cases, and 90\%\ (n = 18) of CIN3 cases. Conclusion: While p16 is useful in detecting high-grade cervical lesions, p53 is not a good biomarker for distinguishing high-grade lesions from low grade ones.

Key words: CIN; Chronic cervicitis; p16; p53.

Introduction

Each year, an estimated 500,000 new cases of cervical cancers are diagnosed. Cervical cancer is considered a preventable cancer due to its long preinvasive state, the presence of both cervical cytology screening programs and effective treatment options for preinvasive lesions [1]. Cytologic screening has provided a 70\%\ decrease in deaths from cervical cancer in the last 50 years.

Infection with high-risk types of human papilloma virus (HPV) plays an important role in the development of preinvasive and invasive squamous cell neoplasias of the cervix. Any factor that causes integration of the HPV DNA into the human genome leads to progression of the invasive disease. HPV type 16 is the most frequently found type in cervical intraepithelial neoplasia (CIN) 2, CIN3 and invasive cervical cancer [2, 3]. HPV type 18 is found in 23\%\ of women with invasive cervical cancer and in 5\%\ of women diagnosed with CIN2 and CIN3. HPV type 18 is more specific for invasive cervical cancers compared to HPV type 16, but the most frequent type of HPV detected in invasive cancer is HPV type 16 [4, 5].

The HPV genome is found as an episomal form (not integrated into the cellular genome) in early cervical lesions, while integration into the genome occurs in cervical cancers [6]. E6 and E7 oncogenic proteins of the virus inactivate the quality control of DNA replication by inactivating p53 and retinoblastoma protein (pRb), respectively [7]. In this way epithelial cells with these chromosomal mutations have the opportunity of neoplastic proliferation.

Under normal conditions, p53 protein exists in the cell in an inactive state in a low concentration, having a short half life, and it cannot be detected by immunologic methods. However, when DNA damage occurs, p53 protein is overexpressed and ceases the cell cycle at the G1-S control point providing an opportunity for the cell to make a decision between DNA repair and apoptosis. The control over cell growth is eliminated as a result of p53 gene function loss, and the cell cycle progresses without DNA repair.

p16 protein is an important member of the retinoblastoma signaling pathway by inhibiting cell cycle progression. Increase in p16 protein expression has been noticed particularly in cases with high-grade cervical lesions and with HPV infections [8].

The main purpose of the present study was to investigate the immunohistochemical expressions of p53 and p16 proteins in different grades of CIN lesions and in non-neoplastic cervical lesions.

Materials and Methods

Patients who had a histopathological diagnosis of CIN (n = 60) following cervical biopsy or an operation in the Obstetrics and Gynecology Department of Ege University School of Medicine, between the years of 2004 and 2007 were included in the study. Twenty-seven cases with a histopathological diagnosis of CIN 1, 13 cases with CIN 2, and 20 cases with CIN 3 were included in the study group, and 25 cases with a histopathological diagnosis of chronic cervicitis without neoplastic cell changes were used as controls. Paraffin blocks of the cases were
obtained from Ege University Department of Pathology archives and the diagnoses were re-confirmed in old and new sections. Biopsy materials were obtained by colposcopy-directed cervical biopsies. Non-neoplastic chronic cervicitis materials were obtained from benign hysterectomy specimens.

Immunohistochemistry. Whole biopsy or operational materials were kept in paraffin blocks and were stained with hematoxylin & eosin as 5 μm sections in the Department of Pathology archives. All tissues were fixed with 10% buffered formalin and put into paraffin blocks. After deparaffinization of the 5 μm sections, tissues were stained with hematoxylin & eosin. Tissue sections (3 μm) acquired from the paraffin blocks were transferred onto gelatin-coated slides and dried at 55°C for at least overnight. Next day the sections were deparaffinized through two 15 min. and two 20 min. xylol washes, followed by rehydration by five alcohol washes of three min. each. The slides were then washed three times for two min. in distilled water. The hydrated slides were boiled for 2.5 min. in 0.001M EDTA solution (pH 8), and then cooled to room temperature. Following 5 min. in 3% hydrogen peroxide solution, the slides were washed in distilled water again. Then they were taken into phosphate buffered (0.015 M, pH 7.6) washing solution (PBS). Ten minutes of protein blocking (code: X0909, DAKO, USA) was applied to the sections. The protein blocking solution was drained and the solution remaining on the edges of the slides was dried. The sections on the slides were incubated with 1/100 diluted p53 Ab-8 (MS-738-p1, Fremont, CA, Neomarkers) or p16 Ab-6 (clone JC8 MS-889-p1 Neomarkers) monoclonal antibodies for 45 min. each. Slides were then washed in PBS 2 x 5 min., and treated with primary antibody enhancer for 20 min. They were incubated for 30 min. in HRP polymer (HRP Polymer TL-060HLS Neomarkers), followed by 2 x 5 min. PBS wash. Following this step, the slides were treated with dianinobenzidine (DAB) (Labvision TA-060-HD) chromogen for 15 min. This step was followed by a distilled water wash and contrast staining process for two min. with non-acidic and non-alcoholic Mayer Hematoxylin. Water-washed slides were rinsed in ammonia water for two minutes. The slides were rewarshed with water and then dehydrated through three rounds of increasing concentrations of alcohol washes. They were then dried, made transparent with xylol, and mounted in balsam. PBS (PH: 7.6, 0.05 M) was used for all the washings during this procedure and between the incubations. The incubations were performed at room temperature in humidified chambers.

Immunohistochemical expression of p16: 0 stands for absent expression (no staining), 1 for focal mild expression, 2 for focal severe expression, 3 for diffuse severe expression.

Immunohistochemical expression of p53: 0 stands for absent expression (no staining), 1 for focal mild expression, 2 for focal severe expression, 3 for diffuse severe expression. p53 expression localization is qualitatively expressed as: 0 stands for basal or no staining, 1 for 1/3 staining at lower epithelium, 2 for 2/3 staining at lower epithelium, 3 for 3/3 staining in the whole layer. p53 expression severity is qualitatively expressed as: 0 stands for no staining, 1 for mild expression, 2 for moderate expression, 3 for severe expression.

Figure 1 and 2 represents expressions of p16 and p53 in CIN3 sample cases, respectively.

Statistical Analysis. Microsoft SPSS 12.0 software was used for statistical analyses. Chi-square test was used to detect the significance level between the groups and calculation of the percent values. Correlation between the increased or decreased values of the variables was examined by correlation analysis. A p value of lower than 0.05 is considered as significant. Pearson’s correlation coefficient of r = 0.75-1.00 was considered as a strong correlation.

Results
The mean ages of the groups were 39.5 for chronic cervicitis, 30.3 for CIN1, 33.6 for CIN2, and 34.5 for CIN3 cases.

Eighty-four percent (21/25) of the chronic cervicitis group showed no expression of p16 whereas 33% (9/27) of CIN1 cases, 77% (10/13) of CIN2 cases and 100% of CIN3 cases (20/20) demonstrated p16 expression. A statistically significant difference between chronic cervicitis and CIN group was found in terms of p16 immunohistochemical expression (p = 0.001) (Table 1).
Table 1. — Results of p16 stains.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>p16 Immunohistochemical expression</th>
<th>p16 Immunohistochemical expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>0 1 2 3 Total</td>
<td>p</td>
</tr>
<tr>
<td>Chronic cervicitis (n)</td>
<td>24 0 1 0 25</td>
<td>p</td>
</tr>
<tr>
<td>CIN1 (n)</td>
<td>11 0 0 1 27</td>
<td>p</td>
</tr>
<tr>
<td>CIN2 (n)</td>
<td>4 1 1 3 13</td>
<td>p</td>
</tr>
<tr>
<td>CIN3 (n)</td>
<td>2 1 3 6 20</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

CIN: Cervical intraepithelial neoplasia. Immunohistochemical expression of p16: 0 stands for absent expression (no staining), 1 for focal mild expression, 2 for focal severe expression and 3 for diffuse severe expression. 

Table 2. — Results of p53 stains.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>p53 Immunohistochemical expression</th>
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</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>0 1 2 3 Total</td>
<td>p</td>
</tr>
<tr>
<td>Chronic cervicitis (n)</td>
<td>24 0 1 0 25</td>
<td>p</td>
</tr>
<tr>
<td>CIN1 (n)</td>
<td>11 0 0 1 27</td>
<td>p</td>
</tr>
<tr>
<td>CIN2 (n)</td>
<td>4 1 1 3 13</td>
<td>p</td>
</tr>
<tr>
<td>CIN3 (n)</td>
<td>2 1 3 6 20</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

CIN: Cervical intraepithelial neoplasia. Immunohistochemical expression of p53: 0 stands for absent expression (no staining), 1 for focal mild expression, 2 for focal severe expression and 3 for diffuse severe expression. 

Table 3. — p53 immunohistochemical expression localization.

<table>
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<th>Diagnosis</th>
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<th>p53 Immunohistochemical expression</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>0 1 2 3 Total</td>
<td>p</td>
</tr>
<tr>
<td>Chronic cervicitis (n)</td>
<td>24 1 0 0 25</td>
<td>p</td>
</tr>
<tr>
<td>CIN1 (n)</td>
<td>11 1 0 1 27</td>
<td>p</td>
</tr>
<tr>
<td>CIN2 (n)</td>
<td>4 4 2 3 13</td>
<td>p</td>
</tr>
<tr>
<td>CIN3 (n)</td>
<td>2 3 6 9 20</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

CIN: Cervical intraepithelial neoplasia. p53 expression localization is qualitatively expressed as: 0 stands for basal or no staining, 1 for staining at 1/3 lower epithelium, 2 for staining at 2/3 lower epithelium, 3 for staining throughout whole layer. 

Table 4. — Results of p16 stains.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>p16 Immunohistochemical expression</th>
<th>p16 Immunohistochemical expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>0 1 2 3 Total</td>
<td>p</td>
</tr>
<tr>
<td>LGSIL: Low-grade squamous intraepithelial lesion</td>
<td>18 6 3 0 27</td>
<td>p</td>
</tr>
<tr>
<td>HGSIL: High-grade squamous intraepithelial lesion</td>
<td>3 5 5 0 33</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

LGSIL: Low-grade squamous intraepithelial lesion, HGSIL: High-grade squamous intraepithelial lesion. Immunohistochemical expression of p16: 0 stands for absent expression (no staining), 1 for focal mild expression, 2 for focal severe expression and 3 for diffuse severe expression. 

Table 5. — Immunohistochemical expressions of p53 in LGSIL and HGSIL cases.

<table>
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<tr>
<th>Diagnosis</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>0 1 2 3 Total</td>
<td>p</td>
</tr>
<tr>
<td>LGSIL: Low-grade squamous intraepithelial lesion</td>
<td>11 0 4 12 27</td>
<td>p</td>
</tr>
<tr>
<td>HGSIL: High-grade squamous intraepithelial lesion</td>
<td>6 2 6 19 33</td>
<td>p = n.s.</td>
</tr>
</tbody>
</table>

LGSIL: Low-grade squamous intraepithelial lesion, HGSIL: High-grade squamous intraepithelial lesion, n.s. = non significant. Immunohistochemical expression of p53: 0 stands for absent expression (no staining), 1 for focal mild expression, 2 for focal severe expression and 3 for diffuse severe expression. 

Discussion

Today it is well known that infection with high-risk types of HPV plays an important role in the development of preinvasive and invasive squamous cell neoplasias of the cervix. The association appears to be related with two specific viral oncoproteins, E6 and E7, which are considered mandatory for initiation and maintenance of malignancy [9]. E6 was shown to transform the cells by binding to p53, whereas E7 could bind to pRb.

Due to inactivation of pRb, a specific cyclin-dependent kinase inhibitor, namely p16 is released from negative feedback control. Normally p16 decelerates the cell cycle by inactivating the cyclin-dependent kinase (CDK) 4 and CDK 6. The idea that p16 could be used as a specific biomarker in neoplastic cervical epithelium arose from the fact that p16 is overexpressed in cases with inactive pRb and this diagnostic value has been proven in high-risk-type HPV infections, cervical dysplasia and cervical carcinomas [10-12].

Lin et al. [13] detected p16 expression as 78.7% (37/47) in cervical squamous cell carcinoma, 96.7% (29/30) in CIN, and 100% (20/20) in adenocarcinoma, while detecting no expression in non-neoplastic cervical tissue. They concluded that p16 expression indicated dysplasia or malignancy independently from HPV infection in cervical squamous and glandular epithelia. This was supported in a study by Kanao et al. [11] where p16 was shown to be expressed by 81% in HPV-positive cervical cancers, while by 75% in HPV-negative cervical cancers.

Wang et al. [14] showed that p16 expression was significantly higher in CIN (75%) and cervical squamous cell carcinoma (75%) compared to normal cervical tissue.
(12.5%) (p < 0.01, p < 0.05 respectively). It has also been reported that time for progression into CIN3 or invasive cancer from the initial biopsy was an average of 64.2 months in those with p16 expression, and 108.3 months on average in those without p16 expression (p < 0.01).

P16 overexpression may also be seen in other cancers such as BRCA1-related non-invasive serous carcinomas, dermatofibrosarcoma protuberos, Hodgkin’s and non-Hodgkin’s lymphomas, gastrointestinal stromal sarcomas, gliomas, and carcinomas of the breast [15]. This point also proves that p16 is not specific for high-risk-type HPV or cervical carcinomas and that it is an indicator of pRb inactivation rather than an indicator of high-risk-type HPV infection.

It has been reported that at least 15.6% of CIN 3, twice as many CIN 2 and half as many invasive squamous carcinomas are p16 negative [16]. This weak or non-immunoreactivity may be attributed to non-standardized methodology which makes the clinical application seriously difficult. Until now there has been no consensus about the threshold values of p16 positivity, and the positivity is widely used as ‘negative’, ‘focal’, or ‘diffuse’. Tsoumpou et al. [17] in a recent meta-analysis highlighted this point and concluded that although p16 immunostaining correlates with the severity of cytological/histological abnormalities, the reproducibility is limited due to insufficiently standardized interpretation of immunostaining.

The relation between immunohistochemical expression of p53 and cervical lesions is controversial. In the present study, although there was a statistically significant difference between chronic cervicitis and CIN groups in terms of p53 immunostaining, p53 was found to be insignificant for distinguishing low-grade and high-grade cervical intraepithelial lesions. Dimitrakakis et al. [18] could not detect any p53 expression in their study of normal cervix (0/13), condyloma (0/14), CIN1 (0/23) and CIN2 (0/20) cases. They detected p53 immunohistochemical expression in three of the 20 CIN3 cases (15%), and in 18 of the 63 invasive squamous cancer. They found a significant correlation between p53 expression and high-grade histological diagnosis (p = 0.003). Huang et al. [19] did not detect any p53 immunohistochemical staining in normal epithelium or LSIL cases. They detected p53 expression in four of the 35 HSIL cases, whereas detecting p53 expression in only one out of 12 microinvasive carcinoma cases. Nevertheless, p53 expression was significantly higher in cervical carcinomas compared to microinvasive carcinomas, and increased expression of p53 is correlated with increased stage of the carcinoma.

In our study, p53 expression was detected in 59.2% (16/27) of the LSIL cases, and in 81.9% (27/33) of the HSIL cases. No significant difference was detected between LSIL and HSIL in terms of p53 expression.

**Conclusion**

p16 seems to be useful in discrimination of premalignant and malignant lesions of the cervix while p53 needs further studies; p16 immunoreaction needs standardization for determining an accurate diagnosis of neoplastic cervical lesions.

**References**


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Repeat low-grade squamous intraepithelial cytology with unsatisfactory colposcopy treated by the loop electrosurgical excision procedure: a retrospective study

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Summary

Investigation: To evaluate the value of the loop electrosurgical excision procedure (LEEP) for repeat low-grade squamous intraepithelial lesions (LSIL) with unsatisfactory colposcopy and the outcomes of postconization. Methods: We performed LEEP in 136 patients and followed them up with colposcopy, cytology, and high-risk HPV (HR-HPV) detection using Hybrid Capture II (HCII). Results: 55.1% of women had CIN 1 in the specimen, 17.6% had CIN 2-3, and 27.2% had no lesion. The sensitivity of detecting persistent/recurrent disease can reach 90.9% when positive post-treatment HR-HPV or first abnormal cervical cytology after LEEP are detected, and the specificity is 95.3% when positive post-treatment HR-HPV coexisting with first abnormal cervical cytology after LEEP are detected. Conclusion: Repeat LSIL with unsatisfactory colposcopy implies a significant risk of CIN 2-3. LEEP is a rational option to those patients with high-risk HPV infection or dysplastic endocervical curettage. Post-treatment follow-up of patients should include both cytology and HR-HPV testing.

Key words: Low-grade squamous intraepithelial lesion; Loop electrosurgical excision; Cervical cytology; Human papillomavirus testing.

Introduction

It was shown that the rate of low-grade squamous intraepithelial lesions (LSIL) has increased in the United States over the last decade, and in 2003 the mean LSIL reporting rate was 2.9% for liquid-based specimens [1]. The prevalence of a cervical intraepithelial neoplasia (CIN) grade 2 or greater identified at initial colposcopy among women with LSIL is 12-16%. Repeated cytology at six and 12 months or high-risk (oncogenic) human papillomavirus (HR-HPV) types at 12 months was the preferred management option for women with LSIL and satisfactory colposcopy according to 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests [2]. Cytologic follow-up alone leads to 20% of false-negative results; when this is associated with colposcopy, the false-negative rate falls to 3-8% [3, 4]. The established cyto-colposcopic procedure has directed very effective work in cervical cancer screening and cervical intraepithelial neoplasia (CIN) screening. Yet unsatisfactory colposcopy is one of the main factors that prevents correct cyto-colposcopic follow-up with the risk of an unseen lesion. Some studies showed that LSIL with risk factors such as unsatisfactory colposcopy or positive endocervical curettage, persistence of CIN1/LSIL or HR-HPV infection for longer than two years and age older than 40 years might hide a high-grade lesion or an occult invasive cancer, and that regular observation might miss them [5, 6]; thus a diagnostic excision procedure has been suggested.

Systematic management is not proposed in the current guideline, thus more studies are needed to confirm whether a diagnostic excisional procedure is an appropriate option for cases with risk factors. The purpose of the present study was to retrospectively review the records of women who had undergone a loop electrosurgical excision procedure (LEEP) for repeat LSIL with unsatisfactory colposcopy. The clinical characteristics of patients were analyzed to evaluate the value of LEEP for repeat LSIL with unsatisfactory colposcopy and the outcomes of post-conization management.

Materials and Methods

We retrospectively reviewed the records of 136 women who underwent LEEP for repeat LSIL with unsatisfactory colposcopy between October 2006 and April 2007 at Beijing Obstetrics and Gynecology Hospital, Capital Medical University, China. Each woman had repeat LSIL in three or six months and received LEEP for unsatisfactory coloscopy. Women with HIV infection or with other causes of immunosuppression were excluded from the study. Women age ≤21 and those in post-menopause were also excluded.

Endocervical curettage (ECC) was performed in each patient before LEEP to assess the endocervical canal. LEEP was performed with a single pass using a variable-sized loop electrode. The Schiller test was used to determine the range of excision. A line approximately 2 mm outside the unstained iodine (Schiller-positive) area of squamous epithelium was set as the external incision edge. The depth of LEEP was 7-12 mm. Specimens were marked by silk thread and routinely examined using pathologic section. Conventional cytology was performed and evaluated according to the criteria of Bethesda 2001. Colposcopic findings were described according to the criteria of the International Federa-
tion for Cervical Pathology and Colposcopy (Barcelona 2002).
All women underwent HPV testing by using the Digene cervical sampler kit just before and after LEEP (Digene, Gaithersburg, MD). The samples were stored at -20°C until further processing was available. HPV detection was performed by using the commercially available Hybrid Capture II (HCII) system (Digene). All the samples were analyzed only for the presence of HR-HPV types (16, 18, 32, 34, 36, 39, 45, 51, 52, 56, 58, 59, and 68). The cutoff of 1 relative light unit (RLU; 1.0 pg/ml) was used to classify a specimen as positive or negative [7]. All cone specimens and cytologies were independently and blindly evaluated by two pathologists. When differences between the two independent evaluations were detected, a new evaluation by the two observers was conducted and a consensus diagnosis was reached.

All women were followed-up as outpatients. Follow-up procedures included gynecologic examination, liquid-based cytological testing and detection of HPV DNA by HPV-HCII, and/or colposcopy. The Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University approved the study.

Statistical Analysis

Single factor analysis was performed using an independent samples t test for continuous data and the chi-square test for categorical data. Statistical analyses were performed using SPSS version 16 (SPSS, Chicago, IL, USA); p < 0.05 was considered significant.

Results

Description of patients

A total of 136 women aged between 22 and 53 years underwent LEEP for repeat LSIL with unsatisfactory colposcopy during the period of study. The characteristics of patients are shown in Table 1. Seventy-five women (55.1%) had CIN 1 confirmed in the LEEP specimen and 24 women (17.6%) had CIN 2-3. In 37 women (27.2%), no lesion was identified after a thorough examination of the LEEP specimen. Positive pretreatment HPV testing was significantly more frequent in women with CIN 2-3 than in women with no lesion in the LEEP specimen (3/37, 8.1%; 24/24, 100%) and CIN 1 (58/75, 77.3%) than in women with negative LEEP histology were found to develop to CIN 1. In the group of women with CIN 1 in the LEEP specimen, surgical margins were positive in 15 cases (20%). The exocervical margin was involved in seven (46.7%), the endocervical margin in five (33.3%), and both margins in three cases (20%). Persistent/recurrent disease was identified in 11 of 75 (14.7%) women during the follow-up. Ten women recurred as CIN 1 and one woman as CIN 2-3.

Seven women (41.1%) of all the 17 recurrences were detected in 12 months after treatment (100% with positive pre-treatment HR-HPV test), and another ten women were detected between 14-32 months (20% with positive pre-treatment HR-HPV test). The diagnosis of persistent/recurrent disease was established by colposcopically directed pouch biopsy in 11 cases and six by repeat LEEP for two abnormal cytologies (ASCUS or more). Persistent/recurrent disease was identified in 11 of 75 (14.7%) women during the follow-up. Ten women recurred as CIN 1 and one woman as CIN 2-3.

The data of 75 women with CIN 1 in the LEEP specimen were analyzed in more detail. The overall mean age was 37.6 ± 11.3 years, and of non-recurrent cases it was 39.2 ± 9.5, whereas in cases that developed disease, it was 37.5 ± 9.7 years. The positive rate of HR-HPV before treatment was 78.1% (50/64) in nonrecurrent cases, and 72.7% (8/11) of women developing persistent/recurrent disease. Post-treatment HCII was positive in nine the 11 cases 81.8% with persistent/recurrent disease, while the rate in non-recurrent cases was 32.8% (21/64) during the follow-up (p < 0.01). The infection rate of HR-HPV decreased from 77.3% (58/75) of pre-treatment to 40% of post-treatment cases. HR-HPV after treatment and positive cone margins were associated with significantly higher risk of residual/recurrent disease (Table 2).

Risk of persistent/recurrent disease after LEEP of CIN 1

Persistent/recurrent disease was identified in two of 24 (8.3%) patients with CIN 2-3, one of them recurred as CIN 2-3 and one as CIN 1. Two of 37 women (5.4%) with negative LEEP histology were found to develop to CIN 1. In the group of women with CIN 1 in the LEEP specimen, surgical margins were positive in 15 cases (20%). The exocervical margin was involved in seven (46.7%), the endocervical margin in five (33.3%), and both margins in three cases (20%). Persistent/recurrent disease was identified in 11 of 75 (14.7%) women during the follow-up. Ten women recurred as CIN 1 and one woman as CIN 2-3.

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The data of 75 women with CIN 1 in the LEEP specimen were analyzed in more detail. The overall mean age was 37.6 ± 11.3 years, and of non-recurrent cases it was 39.2 ± 9.5, whereas in cases that developed disease, it was 37.5 ± 9.7 years. The positive rate of HR-HPV before treatment was 78.1% (50/64) in nonrecurrent cases, and 72.7% (8/11) of women developing persistent/recurrent disease. Post-treatment HCII was positive in nine the 11 cases 81.8% with persistent/recurrent disease, while the rate in non-recurrent cases was 32.8% (21/64) during the follow-up (p < 0.01). The infection rate of HR-HPV decreased from 77.3% (58/75) of pre-treatment to 40% of post-treatment cases. HR-HPV after treatment and positive cone margins were associated with significantly higher risk of residual/recurrent disease (Table 2).
Table 2.—Risk of persistent/recurrent disease after LEEP of CIN 1 (n = 75).

<table>
<thead>
<tr>
<th></th>
<th>Persistent/recurrent group</th>
<th>Non-persistent/recurrent group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 35</td>
<td>4</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>&gt; 35</td>
<td>7</td>
<td>31</td>
<td>0.5452</td>
</tr>
<tr>
<td>Positive pre-treatment HR-HPV</td>
<td>8 (72.7%)</td>
<td>50 (78.1%)</td>
<td>0.0959</td>
</tr>
<tr>
<td>Positive post-treatment HR-HPV</td>
<td>9 (81.8%)</td>
<td>21 (32.8%)</td>
<td>0.0063</td>
</tr>
<tr>
<td>Positive cone margins</td>
<td>7 (63.6%)</td>
<td>8 (12.5%)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 3.—Sensitivity, specificity for persistent/recurrent disease after treatment of CIN 1 (n = 75).

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone margins</td>
<td>63.6</td>
<td>87.5</td>
</tr>
<tr>
<td>First abnormal cervical cytology after LEEP</td>
<td>72.7</td>
<td>89.1</td>
</tr>
<tr>
<td>Positive pre-treatment HR-HPV</td>
<td>72.7</td>
<td>17.2</td>
</tr>
<tr>
<td>Positive post-treatment HR-HPV</td>
<td>81.8</td>
<td>67.2</td>
</tr>
<tr>
<td>Positive pre-treatment HR-HPV and first abnormal cervical cytology after LEEP</td>
<td>72.7</td>
<td>95.3</td>
</tr>
<tr>
<td>Positive post-treatment HR-HPV or first abnormal cervical cytology after LEEP</td>
<td>81.8</td>
<td>15.6</td>
</tr>
<tr>
<td>Positive post-treatment HR-HPV and first abnormal cervical cytology after LEEP</td>
<td>72.7</td>
<td>95.3</td>
</tr>
<tr>
<td>Positive post-treatment HR-HPV or first abnormal cervical cytology after LEEP</td>
<td>90.9</td>
<td>65.6</td>
</tr>
</tbody>
</table>

Discussion

The diagnosis and treatment of LSIL depends on the correct cytocolposcopic procedure. Yet unsatisfactory colposcopy is one of the main factors that prevents effective follow-up with the risk of an unseen lesion, which stresses the need of excision for patients with L-SIL/CIN 1. Previous reports have shown that 23-55% of patients undergoing LEEP for CIN 1/LSIL actually had CIN 2-3 [7, 8]. In our study, 17.6% of the women treated because of repeat LSIL, actually harbored a high-grade lesion in the LEEP specimen. The problem is whether LEEP is necessary for all the women of repeat LSIL coexisting with unsatisfactory colposcopy. We found that all of those women harboring CIN 2-3 in LEEP specimens had positive pre-treatment HR-HPV, while only three (8.1%) with no lesion in the LEEP specimen had a positive pre-treatment HR-HPV, implying that these lesions might be caused by low risk-HPV (LR-HPV). This result is consistent with the data previously reported by other authors [9-11]. We suggest that a conservational approach might be more reasonable than LEEP for those women with repeat LSIL and negative HCII testing. All the cases of CIN 2-3 and 81.3% of cases with CIN 1 were positive for HR-HPV testing before LEEP, meaning that pre-treatment HR-HPV detection may provide useful information and that particular attention should be paid to women with HR-HPV before treatment.

Although endocervical dysplasia presents a complex clinical dilemma, it is still necessary because optimal visualization of the endocervical canal is not technically feasible especially when cervical dysplasia or potentially invasive cervical carcinoma is difficult to detect with colposcopy [12]. In our study, we found the rate of endocervical dysplasia increased according to the severity of the lesion. Endocervical dysplasia was significantly associated with the severity of CIN. Hence, it is reasonable that when a woman with positive ECC for cervical dysplasia must, to confirm or negate the presence of invasive carcinoma, undergo an excisional procedure in the form of a cone biopsy that includes the transition zone and part of the endocervical canal. This is consistent with the data previously reported by other authors [13].

We found that the cervical treatment (51.5%) is the main reason for unsatisfactory colposcopy which makes colposcopic assessment technically more difficult. Foci of CIN and/or invasive disease may be buried under an apparently normal epithelium. Moreover, the transformation zone may be difficult to visualize in its entirety because of scarring [14]. Most of the women received the cervical treatment because of cervical erosion (45/70, 64.3%), cervical hypertrophy (14/70, 20%), repeat cervical polyps (11/70, 15.7%), and none for CIN. Physicians should be prudent in choosing the treatment in benign cervical disease.

Ghaem-Maghami et al. [15] assessed the effect of completeness of excision on the risk of post-treatment disease by a meta-analysis of 65 studies and found that women with involved or uncertain excisional margins had an 18% pooled prevalence of high-grade disease after treatment. In our study, all the seven cases of CIN 2-3 with positive margins received repeat LEEP/cold knife conization and had excision of CIN with negative margins. In all the 17 persistent/recurrent diseases, only two of 24 (8.3%) women with CIN 2-3 in the LEEP specimens had recurrent disease develop.

Persistent/recurrent disease was found in women with CIN 1 (11/75, 14.7%). Moreover, two cases (5.4%) with no lesion in the LEEP specimen were detected as CIN 1 in the follow-up. This indicated the need for strict follow-up after LEEP excision no matter if CIN 2-3, CIN1 or no lesion.

No association was observed in our series between age and risk of persistent/recurrent disease as previously reported in a series of CIN 2-3 [6]. Although the involvement of treatment margins was a predictor of persistent/recurrent disease, eight cases (8/15, 53.3%) of positive margins did not recur, while four women (4/11, 36.4%) with negative cone margins developed persistent/recurrent disease. Thus, we confirmed that status...
of cone margins had a limited value in predicting persistent/recurrent disease of CIN 1. These results were in keeping with the data when studying CIN 2-3 cases [14].

In our study, we found that HR-HPV detected by HCII during the follow-up had a higher sensitivity and specificity than the pretreatment HCII (81.8% vs 72.7%, p > 0.05; 67.2% vs 17.2%, p < 0.01) for detecting women with persistent/recurrent disease. Nine cases (9/11) with persistent/recurrent disease had a positive HCII test after LEEP, which meant that HR-HPV is the major cause of CIN and those cases with positive HCII tests should have close follow-up. The decreased rate of positive HCII tests after LEEP (40% vs 81.3%, p < 0.01) indicated that LEEP was helpful to clear the HR-HPV. The HCII test alone during follow-up reached a sensitivity of 81.8%, retaining a specificity of 67.2%. These figures are similar to the sensitivity obtained by single cytology (72.7% and 89.1%, respectively). The sensitivity can reach 90.9% when positive post-treatment HR-HPV or first abnormal cervical cytology after LEEP is found, and the specificity is 95.3% when positive post-treatment HR-HPV coexisting with first abnormal cervical cytology after LEEP is detected. It is confirmed that post-treatment follow-up of patients should include both cytology and HPV testing. Although this might increase medical costs, it would alleviate the current situation by self-collection of specimens for human papillomavirus (HPV) DNA testing [16, 17].

Strict indepth examination of patients with repeat LSIL coexisting with unsatisfactory colposcopy because of a significant risk of a hidden CIN 2-3 lesion. LEEP was reasonable for those cases with a positive HR-HPV test or dysplasia cytology in ECC, but a conservative approach might be more appropriate for those women with a negative HR-HPV test. Patients with positive HR-HPV tests during follow-up should be considered at risk of having persistent/recurrent disease develop and may receive a closer follow-up protocol. Post-treatment follow-up of patients should include both cytology and HR-HPV testing.

References


Granular cell tumour of the breast: case series and review of the literature

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Summary
Granular cell tumours (GCTs) are uncommon rare neoplasms that may occur in any part of the body. Approximately 5-8% of granular cell tumours occur within the breast. Although nearly always benign in behaviour, granular cell tumours of the breast can often mimic breast malignancies both clinically and on the basis of imaging techniques. This article reports five cases of benign granular cell tumours appearing in the breast, mimicking a malignant breast lesion. In addition to reporting the cases, the relevant literature was reviewed.

Key words: Granular cell tumour; Breast; Myoblastoma; Neoplasms; Granular cell myoblastoma.

Introduction
The clinicopathology of granular cell tumours (GCTs) was first described in 1926 by Abrikossoff on the basis of a tumour in the tongue muscles. He called the deformity granular cell myoblastoma [1]. The names according to different nomenclatures, such as granular cell tumour, myoblast myoma, Abrikossoff’s tumour or granular cell Schwannoma are synonyms for the same tumour. Certain details of the histogenesis of the tumour are still unknown. However, the ultrastructure of the tumour cells and certain immunohistochemical assessments (S-100, NSE) appear to confirm the neurogenic (Schwann cell) origin of granular cells [2-6]. Rosso et al. described GCTs at the site of previous tissue injuries, e.g., in the scar of a surgical intervention [7]. Considering the possibility of an inflammatory or histiocyte origin, an extensive granular cell transformation of the injured neurinoma has been proposed on the basis of the hypertrophic nerve bundles containing degenerated granular cells detected in the fibrotic matrix [6, 7]. This process shows close similarity to Wallerian degeneration, a well-known axonal degeneration process followed by regeneration supported by Schwann cells through the release of growth factors (NGF), that occurs after axonal injury [7]. The fact that microscopic examinations often detect nerves and demyelinated axons in the tumours appears to underpin the neuroectodermal theory.

GCT is a rare and usually benign tumour. So far, the number of cases reported in the literature are a few hundred. In up to 65-90% of the cases, the disease affects females, primarily middle-aged women [2, 3, 5, 8]. In the reported cases, GCT dominantly occurred in coloured, Afro-American women [2, 5, 8], though in the clinical study by Strong et al., the majority of the 95 GCT patients were Caucasian individuals [9]. Primarily, GCT is a disease of premenopausal women, which suggests a key role of high oestrogen and progesterone levels in the genesis of the tumour. This has been of affirmed by the rapid tumour growth observed with GCTs in pregnant women [10]. However, this theory is contradicted by the negativity of tumour cells for oestrogen and progesterone receptors observed in all reported cases, including the present one [2, 8].

GCT may develop in any part of the body and may be multifocal in appearance in up to 5-10% of the cases [2]. The areas most often affected include the head and neck region (approx. 50%), and the oral cavity, particularly the tongue (30%) [2, 6, 11]. In addition to the oral cavity, other parts of the gastrointestinal tract, such as the rectum, the anus, the oesophagus and the stomach (in order of prevalence) may be affected. Moreover, GCTs of the skin, breast, respiratory tract, orbital cavity, parotid gland, bladder, male and female reproductive organs, and the peripheral and central nervous system have been described [2, 11, 12].

Only 1-3% of GCTs show malignant behaviour [2]. The prognosis of malignant GCTs is poor. Ordonez et al. reported 50% mortality in a follow-up of 34 patients for a period of 2.8 years on average [13]. The most frequent locations of metastases are lymph nodes, the lungs and bones. According to this study, the most important prognostic factors were the size of the primary tumour and the presence of metastases [13].

Breast GCTs proliferating by infiltration often mimic malignant breast tumours by radiological and even by
macroscopic examination, causing serious differential diagnostic problems and potential overtreatment (e.g., mastectomy, axillary lymphadenectomy) or insufficient treatment (e.g., undetected concomitant malignant breast tumour) [3, 4]. As far as the differential diagnosis is concerned, GCTs should primarily be distinguished from malignant breast tumours, fibroadenomas, gynecomastia, as well as from the metastases of melanoma malignum and clear-cell renal carcinoma. In addition to the proper selection and evaluation of the imaging and immunohistochemical examinations, knowing this rare and varied tumour as a possible diagnostic alternative is also essential in order to make an accurate diagnosis and to ensure successful treatment.

Patients and Methods

Between 1986 and 2007, more than 13,600 breast operations for different benign and malignant tumours were performed at the Surgical Department of the National Institute of Oncology. During this period five cases of breast GCTs were diagnosed, with an incidence rate of 0.00036%. All patients were female, and the mean age at the time of excision was 53.8 years (range 39 to 71 years) (Table 1). Two patients were premenopausal. In all five cases, the tumour was solitary; the upper-inner quadrant of the breast was affected in two cases, the lower-outer in two cases and the upper-outer in one case. None of the patients had a history of malignant diseases.

Table 1. — Characteristics of the investigated granular cell tumour cases.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>Mmg</th>
<th>FNAB</th>
<th>Location in the breast</th>
<th>Time of excision (mm)</th>
<th>Tumour diameter (mm)</th>
<th>4-100</th>
<th>NSE</th>
<th>Follow-up time (months)</th>
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<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>R5</td>
<td>C3</td>
<td>UIQ</td>
<td>1986</td>
<td>12</td>
<td>P</td>
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<tr>
<td>2</td>
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<td>C3</td>
<td>LOQ</td>
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<td>25</td>
<td>P</td>
<td>P</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>R4</td>
<td>C3</td>
<td>LOQ</td>
<td>1995</td>
<td>30</td>
<td>P</td>
<td>P</td>
<td>122</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>R5</td>
<td>C2</td>
<td>UOQ</td>
<td>2002</td>
<td>15</td>
<td>P</td>
<td>P</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>R5</td>
<td>C2</td>
<td>UOQ</td>
<td>2007</td>
<td>17</td>
<td>P</td>
<td>P</td>
<td>6</td>
</tr>
</tbody>
</table>

Mmg: mammography; FNAB: fine needle aspiration biopsy; NSE: neuron-specific enolase; N: negative; P: positive; UIQ: upper-inner quadrant of the breast; UOQ: upper-outer quadrant of the breast; LOQ: lower-outer quadrant of the breast.

In all cases, GCT showed the same manifestations, mimicking the clinical picture of malignant breast tumours by physical examination: rapid progression in size, painless semi-fixed compact structure, and skin infiltration. Palpable pathological lymph nodes were not found in the axillary region.

The mammographic presentations of the five GCTs were variable. Two of the lesions presented as round, circumscribed masses (Cases 2 and 3), and the other three tumours demonstrated irregular, spiculated, organic deformities, which were projecting bundles towards the surface, and were indistinguishable from carcinomas (Figure 1). Microcalcifications were not detectable.

The ultrasound images were also variable. Cases 2 and 3 showed well-circumscribed, more benign manifestations, but the other three tumours appeared as hypechochogenic, poorly margined deformities with marked posterior shadowing, suspicious for malignancy. No enlarged lymph nodes with pathological structures were detected in the axillae.
In three cases, the results of fine needle aspiration biopsy (FNAB) were uncertain (C3). In two cases, FNAB revealed the exact diagnosis of a benign GCT preoperatively (C2), showing cohesive groups of cells with a syncytial appearance, containing excessive eosinophilic cytoplasmic granules and small round-to-slightly-oval nuclei.

In all cases, sectorial excisions were performed and the intraoperative frozen sections confirmed the histological findings of benign granular cell tumours. All surgical excisions had microscopically confirmed free surgical margins. The average diameter of the resected tumours was 19.8 mm (range 12 to 30 mm).

Results

In summary, the microscopic examination of the specimens revealed tumour tissues divided by connective tissue bundles, radially infiltrating into the surrounding tissues, such as the skin or the pectoral muscles (Figure 2). The polygonal tumour cells were arranged in solid nests and cords with small and round centrally located nuclei, and were abundant in the periodic acid-Schiff (PAS) positive eosinophilic granular cytoplasm. Immunohistochemical examinations showed strong positive staining for Protein S-100 and NSE (Figure 3a) (neuron-specific enolase), but cells were negative for the cytokeratin reaction (Figure 3b). All the tested specimens were negative for oestrogen and progesterone receptors.

Annual follow-up (physical examination, mammography and breast ultrasound) of the patients with a mean follow-up time of 69.8 months (range 6 to 122 months) did not reveal recurrent tumours in the breast.

Discussion

Up to 5-8% of GCTs affect the breast. In comparison with breast carcinomas, the prevalence of breast GCTs is approx. 1/1,000 [5, 8]. Breast GCTs originate in the interlobular stroma [8]. In the vast majority of the reported cases, the tumour develops in the upper-inner quadrant of the breast corresponding to the area with sensory innervation by the supraclavicular nerve. However, the relationship between GCTs of neurogenic origin and the area innervated by the supraclavicular nerve is based on observations only [8, 14, 15]. In general, breast GCTs grow without causing symptoms, although painful tumours have also been reported [8]. By physical examination the deformity is often semi-fixed because it infiltrates into the major fascia of the pectoral muscle, or into the muscles of the chest wall, and may mimic the clinical picture of a malignant tumour by causing involutions and oedemas [16]. Up to 10% of the tumours are associated with a particular phenomenon, i.e. the so-called pseudo-epitheliomatose hyperplasia of the epithelial layer above the tumour which consists of differentiated cells and is often mixed up with squamous cell carcinomas [6, 8]. Real squamous cell carcinomas with GCT may occur, for example in the oesophagus [6].

So far the number of reported breast-related GCT cases is between 100 and 200, and malignancy occurred in only a few cases [3, 4, 14, 17]. Chetty reported a 15 cm malignant breast GCT metastasising into the axillary lymph nodes in the case of a female patient [14]. Khansur et al. described a case of a malignant breast GCT in a male patient [12]. In a case reported by Crawford and de Bakey, the patient ultimately died as a result of the lung, liver and retroperitoneal metastases of the breast GCT [18]. According to Kirschner, the excision of the malignant GCT was followed by a lung metastasis, which was unsuccessfully treated by systemic chemotherapy with adriamycin [19]. Mulcare reported on a case of a GCT in the scar of a previous mastectomy and on a case of an invasive ductal carcinoma appearing at the site of a previous GCT excision after five years [20]. Al-Ahmadie described a GCT colocalized with an invasive ductal carcinoma appearing in the upper-inner quadrant of a female breast [6]. Reports on the concomitant appearance of GCT and invasive breast tumour in the same or in the contralateral breast are also available [3, 21].
It should be noted that the radiotherapeutic and chemotherapeutic susceptibility of malignant GCTs is unknown [22].

Imaging techniques are not always suitable for the definitive exclusion of malignancy of GCTs. However, the mammographic picture may show differences. The deformity may appear as a rounded, circumscribed mass of tissue, as vague density, or as an irregular spiculated deformity, making it difficult to distinguish it from malignant tumours [16, 17]. Microcalcification is normally absent. The ultrasound picture may also vary; it may show a solid, poorly or well circumscribed mass of tissue, which may be hypoechogenic with weak internal echoes and generally with pronounced acoustic shading, which are characteristic features of the ultrasound picture of malignant tumours [16, 17]. The ultrasound size of the tumours reported so far was around 1 to 2 cm in most cases [8, 17]. The (gadolinium contrast) MRI assessment of GCTs showed explicit amplification by the tumour, and particularly by the peripheral parts thereof, without a washout phenomenon [23]. In general, early peripheral amplification is a typical characteristic of malignant tumours because the central parts undergo necrosis and the periphery shows neovascularisation. When compared to the high sensitivity and low (10-55%) specificity of mammography in the recognition of breast tumours, MRI has better sensitivity [23]. PET visualisation based on the enhanced glucose uptake of GCTs, using the isotope-labelled glucose analogue 18F-FDG (18F-fluorodeoxyglucose) has been described. PET also has high sensitivity (61% to 80%) and specificity (78% to 98%) but is not suitable for the evaluation of deformities smaller than 1 cm [23].

Cytology by FNAB is normally sufficient for the correct diagnosis [24-26]. However, the most suitable tool for a precise diagnosis is the ultrasound-guided core biopsy [24, 25].

The treatment of the tumour is radical surgical excision. Local recurrence is rare and is mostly due to insufficient excision. According to Lack et al., the rate of local recurrence is between 5% and 8% [2].

The cross-section of the tumour is usually greyish white or yellow. Microscopic assessments show granulated polygonal cells typically arranged in nodules or layers, which have large amounts of the typical PAS (Periodic-Acid-Schiff) positive eosinophilic granules in the cytoplasm [8]. Nuclei are usually small, rounded or oval, centrally-located and hyperchromatous. Cell nodules are separated by fibrotic lamellas of different thickness, infiltrated by inflammatory cells, such as lymphocytes and eosinophilic cells. The granular appearance of the cytoplasm is a typical characteristic of GCT [14]. The origin of these granules was verified by Mittal et al. According to their theory, the granules arise from infoldings of the cell membrane by a process similar to myelin formation. However, in this case, pinching off occurs within the cell [26]. The granules then fuse with lysosomes and this provides the ultrastructure of the cytoplasm of GCT cells [14, 27]. Histological evaluation of malignant GCTs is not simple and the relevant criteria were developed by Fanburg-Smith. These include necrosis, the presence of spindle cells, vesicular nucleus with a large nucleolus, enhanced mitotic activity (> 2 mitosis / 10 HPF at 200x magnification), high nucleus/cytoplasm ratio and nuclear pleomorphism. Manifestation of two of the six criteria indicates an atypical GCT. If three or more criteria are satisfied, the GCT is malignant [11]. Immunohistochemistry is of vital importance in the assessment and differential diagnosis of GCTs. GCT cells show intensive colour in the cytoplasm and the nucleus when stained for the S-100 protein [1, 5, 7, 11]. In addition, breast GCTs show a positive staining for 1-antitrypsin, α1-antichymotrypsin, and neuron-specific enolase (NSE) [1, 5, 7, 11, 23]. The tumour cells were found to be negative for cytokeratin, actin, myoglobin, desmin, neurofilament protein, glial fibrillary acidic protein, lysozym, the carcinoembryonic antigen, and for oestrogen and progesterone receptors [5, 23]. Weak positive vimentin and CD68 staining were also reported in breast GCTs [5, 23].

Summary

During the everyday care of patients, it is important to know the rare entities in addition to the frequent benign and malignant tumours of the breast, and to take them into account as possible diagnostic alternatives so that both excess and insufficient treatment may be avoided.

References


[18] Crawford E.S., de Bakey M.E.: “Granular cell myoblastoma: Two unusual cases”. Cancer, 1953, 6, 786.


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Comparison of histopathologic classification and surgical stage by cytokeratin 8 and cytokeratin 18 in endometrial cancer

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University of Osmangazi School of Medicine, Eskisehir (Turkey)

Summary

Purpose of investigation: The aim of the study was to show the role of the cytoskeletal proteins CK8 and CK18 in endometrial cancer invasion and to histopathologically classify endometrial cancer patients. Methods: This study was a prospective analysis of 49 histologic samples of consecutively surgically operated endometrial cancer patients. After histopathologic classification the most invasive tumor area was selected for immunohistochemistry. Monoclonal antihuman keratin Ab-4 and keratin Ab-1 were applied. Results: CK8 and CK18 stained tumoral tissue and tumoral cell debris in the lymphovascular space were significantly correlated with stage (p < 0.005). Conclusions: To understand the causes of early treatment failure in endometrial cancer patients, further studies are needed to show the role of enhancing factors of endometrial cancer invasion.

Key words: Endometrial cancer; CK8; CK18; Immunohistochemistry.

Introduction

Endometrial cancer is one of the most common gynecologic cancers. Worldwide each year 142,000 women are diagnosed, and 42,000 women die from the disease. Hysterectomy, pelvic paraaortic lymph node dissection and partial omentectomy are the components of surgical staging. Adjuvant radiotherapy and chemotherapy can be listed as other options of treatment for advanced stages. Histologic subtype, grade, depth of myometrial invasion, uterine location, size of the neoplasm and lymphovascular space involvement are important intratumoral prognostic features for endometrial cancer [1]. Determination of lymphovascular space involvement in endometrial cancer by hematoxylin eosin staining is sometimes difficult because the intercellular integrity is not well preserved in tissue sections. Cytokeratins are good markers to evaluate tumoral extension, especially in endometrial cancer [2]. As parts of the epithelial cytoskeleton, cytokeratins are important for the mechanical stability and integrity of epithelial cells and tissues [3, 4].

The first aim of this study was to perform histopathologic classification of endometrial cancer by using CK8 and CK18 immunohistochemical stains. The second aim was to show the importance of soluble cytoskeletal components in vessels in various stages of endometrial cancer.

Materials and Methods

The study series comprised 49 consecutive surgically operated endometrial cancer cases examined at the Department of Pathology, Eskisehir Osmangazi University School of Medicine between January 1, 2009 and June 30, 2009. According to the FIGO classification [5] there were 15 cases in Stage IA, 18 cases in Stage IB, seven cases in Stage II, seven cases in Stage III, and two cases in Stage IV. Of these patients, three had grade 1, 37 had grade 2 and nine had grade 3 disease. Eleven cases of endometrioid carcinoma samples showed focal squamous differentiation and two cases showed focal mucinous degeneration.

Three samples of polyloid adenomyoma, non-tumoral tissue of a case of focal cancer arising in polyloid adenomyoma, one sample of atrophic endometrium, one sample of irregular proliferation with chronic endometritis, and one sample of atypical complex hyperplasia with xanthomatous endometritis were selected to check the CK8 and CK18 staining pattern of non-neoplastic endometrial tissues.

Immunohistochemistry

Paraffin sections from the blocks of the most invasive area of endometrial cancer were selected from the study samples. The paraffin blocks were cut into 4 μm sections and immunohistochemical assays for the expression of CK18 and CK8 were performed. Liquid mouse monoclonal antihuman keratin 8 Ab-4 and keratin 18 Ab-1 antibody (Thermoscientific, USA) were used. Tissue sections were deparaffinized in xylene, rehydrated in alcohol solution, and placed in 0.5% hydrogen peroxide in methanol for 10 min to block endogenous peroxidase activity. Rehydration was completed by placing the slides in absolute alcohol and finally in water. The slides were treated with a boiling solution of freshly prepared 10 mM-citrate buffer, pH 6.0, for 10 min in a pressure cooker. The sections were reacted for 30 min with the primary antibodies at a dilution of 1:200 in buffer. They were rinsed in phosphate buffered saline (PBS) before being treated with biotinylated universal secondary antibody for 10 min. After further rinsing, the slides were treated with avidin-biotin-peroxidase complex (ScyTek, Universal Detection Kit, USA) and rinsed again. Immunostaining was accomplished by incubating them with AEC for 7 min and then the slides were rinsed in distilled water and counter-stained with Mayer’s hematoxylin. Sections of human colon were used as positive controls. As a negative control, the primary antibody was replaced by PBS.

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Assessment of CK18 and CK8-stained slides

According to the positive staining of endometrial glandular cells and tumor cells three groups were formed: \(1\% \) and \(2\%\) and \(5\%\) as 2 and \(10\%\) as 3. The intensity of immunostaining was scored on a three point scale: 1 = weak; 2 = moderate; 3 = intense. A weighed score for each tumor specimen was the sum of the percentage score and the intensity score and was defined as ‘total epithelial CK 8 and CK18 score’. Lymphovascular space involvement was recorded.

Statistical analyses

All statistical analyses were performed using SPSS (Statistical Package of Social Services, Chicago, IL, USA) for Windows version 15. Data were analyzed according to the Pearson exact chi-square test. Probability values less than 0.05 were considered statistically significant.

Results

Mean ages of patients with Stage IA, Stage IB, Stage II and the combined Stages of III and IV endometrial cancer were 58, 60, 63, 61, respectively. Histopathologic subtype, grade and stage of patients according to FIGO criteria are given in Table 1.

Table 1. — Stage, grade and histologic subtype of endometrioid cancers.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Endometrial cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>15</td>
</tr>
<tr>
<td>IB</td>
<td>18</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
</tr>
<tr>
<td>IIIA</td>
<td>3</td>
</tr>
<tr>
<td>IIIB</td>
<td>3</td>
</tr>
<tr>
<td>IIIC</td>
<td>1</td>
</tr>
<tr>
<td>IVB</td>
<td>2</td>
</tr>
<tr>
<td>Grade</td>
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</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>43</td>
</tr>
<tr>
<td>Serous cancer</td>
<td>4</td>
</tr>
<tr>
<td>Clear cell cancer</td>
<td>1</td>
</tr>
<tr>
<td>Malign mixt Müllerian tumour</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
</tr>
</tbody>
</table>

Staining pattern of CK8 and CK18 in non-neoplastic endometrial specimens

Atrophic, proliferative or hyperplastic endometrial glandular tissues were stained completely with CK18 and CK8. Cytokeratin was distributed mainly around the nuclei and there was no any staining on the surface of the glandular epithelia or on the nucleus. All glandular epithelium of polypoid adenomyoma was stained homogenously and completely. In one sample of cancer arising in polypoid adenomyoma, some of the glandular epithelia were stained by CK8 in moderate intensity and they were located in the basal-apical region of the cytoplasm.

Staining pattern of CK8 in endometrial cancer

Total CK8 scores of tumoral tissue ranged from 0 to 6. Carcinoma tissue was stained focally or completely with weak or moderate intensity in all samples except one. Cytokeratin was distributed mainly around the nucleus in strongly stained tissues. Basal or basal-apical staining in the cytoplasm was seen in weak or moderately stained tumoral tissues (Figure 1).

Staining pattern of CK18 in endometrial cancer

Total CK18 scores of tumoral tissue ranged from 3 to 6. Strong and complete cytoplasmic CK18 staining around the nucleus was observed in 61% (30) of cases (Figure 2). Two cases showed weak and focal CK18 expression and their scores were both 3. Most of the samples showed complete cytoplasmic staining. There was not any staining on the surface of the tumor cells or on the nucleus.

Lymphovascular space involvement

Lymphovascular space involvement was observed in 40 samples. There was no lymphovascular space involvement in seven cases of Stage IA and two cases of Stage IB. CK18 not only stained the tumor emboli and apoptotic cellular debris in the vessels perfectly, but it also stained the vessels themselves. CK18 also strongly stained micrometastasis in the pelvic lymph nodes (Figure 3). Lymphovascular space involvement was also observed by CK8 staining. With the stainings of CK8 and CK18, it has been shown that higher stage endometrial cancers had statistically higher lymphovascular space involvement \((p < .005)\). There was a statistically significant correlation between total CK8 scores and total CK18 scores of tumoral tissues \((r = .465, p \leq .001)\). There were no statistically significant differences between tumor grade and total CK8 and CK18 staining scores (respectively, \(p = .187, p = .675\)). There were also no statistically significant differences between the stage of the cancer and total CK8 and CK18 staining scores (respectively, \(p = .412, p = .129\)).

Discussion

Endometrial epithelium contains cytokeratins 8, 18 and 19. These cytokeratins are members of the cytoskeletal intermediate filament proteins in all simple epithelia, including various parenchymatous organs and endothelial cells [4]. In tumors differentiated epithelial cells mostly retain the keratin patterns of their epithelial origin [6-8]. CK18 is an intracellular protein which is expressed by many cells of epithelial origin, including hepatocytes. Since the protein is presumably released into the blood only after disintegration of the plasma membranes of cells containing cytokeratins, plasma levels have been used to measure cell death. During apoptosis, caspases cleave cytokeratins, which results in the collapse of the cytoskeleton and subsequent formation of apoptotic bodies. Soluble keratin protein fragments have been demonstrated in patient sera that have nonalcoholic fatty liver disease, chronic pancreatitis, and inflammatory bowel disease by enzyme-linked immunosorbent assay [9]. Soluble
keratin protein fragments derived from CK8, CK18, CK19 were detected in the circulation of cancer patients [4, 10]. Such fragments released by cancer cells are increasingly used to monitor tumor load and disease progression in the case of certain cancers such as non small cell lung cancers and testicular cancer [10-12].

Although lymphovascular space involvement by endometrial cancer is correlated with the presence of tumor extension at the time of surgery, it may not always be included in pathology reports. In this study, we observed that CK18 and CK8 were highlighted tumor tissue, cellular debris in the lymphovascular space and also stained endothelial cells. Choi et al. [13] demonstrated that endometrial cancer invasion depends on cancer-derived tumor necrosis factor-alpha and stromal derived hepatocyte growth factor due to enhancement of endometrial cancer invasion because of the strong mitogenic effect of estrogen. CK8 and CK18 are also demonstrated among the selective estrogen receptor modulators (SERM) regulated proteins in endometrial and human breast cancer cell lines [14].

Recently, Czekierdowski et al. [15] demonstrated the role of tumor angiogenesis in Stage I and II endometrial cancer by using immunohistochemical markers CD34 and CD105/endoglin antibody. Nunobiki et al. [16] demonstrated that microvessel density was significantly increased in grade 1 adenocancer compared to normal, hyperplastic endometrium by using a vasodilating peptide adrenomedullin and Bcl-2 immunohistochemical markers. In a recent study we showed that disease-free survival is moderately correlated with mean microvessel count in endometrioid cancer patients, however we could not show a significant difference in terms of mean microvessel count between neoplastic and non-neoplastic endometrial samples by actin bundling protein fascin staining [17]. In this study we observed that lymphovascular space involvement in endometrial cancer was statistically significant with respect to stage ($p \leq 0.005$) by using CK8 and CK18 staining.

Conclusions

There is no single accepted follow-up strategy for patients with endometrial cancer [18]. Early tumor recurrence may be observed at all stages of endometrial cancer. To understand the cause of treatment failure, intraobserver consensus should be provided for histopathologic classification of endometrial cancer in further studies. Secondly, the investigation of lymphovascular space involvement by analyzing circulated soluble CK18, CK8 fragments may provide consensus between histopathological classification and surgical stage.
References


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Percutaneous nephrostomy in the management of advanced and terminal-stage gynecologic malignancies: outcome and complications

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Introduction

Advanced malignant disease localized in the organs of the pelvis and retroperitoneum (uterine cervix, prostate, urinary bladder, ovary) in a fourth of cases progresses to acute obstructive uropathy. Local spreading or pelvic metastases by extramural compression or direct ureter invasion has caused hydronephrotic atrophy, renal failure and secondary uremia. The diagnosis and level of UO may be confirmed by ultrasound, computerized tomography or other appropriate radiological procedures. If the UO was not immediately relieved, the final results would be water-electrolyte abnormalities and subsequent death of patients [1-5].

The most widely used techniques in relieving UO are endoscopic insertion of ureteral stents and percutaneous nephrostomy (PCN). Insertion of ureteral stents may be technically impossible in cases with anatomic deformities, compression or bleeding [2, 3]. PCN is a safe and effective method either as the primary option or an alternative procedure and can provide rapid, almost immediate renal function improvement [1, 6]. As a method of supravesicular urine derivation, since the time of Goodwin’s description of this technique (1955), over a period of a few decades PCN has been the method of choice especially in the treatment of UO caused by gynecological malignancies [7-9]. Despite many benefits of the method, overall survival rate and quality of life in patients with advanced or metastatic disease are still subjects of investigations [10]. The total morbidity with prolonged agony caused by existing malignancy and exhausted treatment options has significantly increased treatment costs and consumed additional health care hours [6, 11]. These facts show the complexity of determining the indication for PCN and solving the problem from the point of an emotional, ethical and oncological dilemma.

The aim of this retrospective study was to evaluate the outcome and complications after PCN insertion in patients with advanced and terminal stage gynecological malignancies and ureteral obstruction.

Patients and Methods

We retrospectively analyzed 117 patients with UO due to advanced and terminal stage gynecological malignancies who had undergone unilateral or bilateral PCN between 1996 and 2006. The median age was 51 years (range 28-85). Bilateral nephrostomy was performed in 36.7% and unilateral in 63.3%. Renal function normalization occurred in 24.8%. Over two-year survival (OS) was 16.8%. Higher OS occurred in patients without initial azotemia versus those with azotemia (26.8% vs 13.9%). Median survival time for all the patients was seven months, eight in primary cases versus six in recurrent ones, and eight months in patients after initial therapy. Complications appeared in 53.8%. Most frequent were the loss of the nephrostomy catheter in 37.61% and urinary tract infections in 19.6%. Conclusion: Improvement of renal function after PCN can be of clinical benefit in patients who might be cured or for prolonged palliative care. Azotemia seems to be poor prognostic sign.

Key words: Gynecologic malignancies; Percutaneous nephrostomy.
of the disease following some initial therapy administered. Ureteral obstruction and hydronephrosis, the grade and side, were diagnosed mostly by means of ultrasonography, computerized tomography or intravenous urography. Routine laboratory tests were performed for evaluation of renal function in all the patients and included at least BUN (blood urea nitrogen) determination, serum creatinine and potassium levels. Azotemia and creatinine elevation were observed in 93 cases (79.5%) and oliguria in 26 (22.2%). Patient follow-up varied from 0 to 112 months, with a mean of 11.43 months. Patient characteristics including stage of disease and uni- or bilateral UO are given in Table 1.

Table 1. — Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>Median</td>
<td>51</td>
</tr>
<tr>
<td>Range</td>
<td>28-85</td>
</tr>
<tr>
<td>Origin</td>
<td></td>
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<tr>
<td>Cervical cancer</td>
<td>108</td>
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<td>Uterine carcinoma</td>
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</tr>
<tr>
<td>Ovarian cancer</td>
<td>3</td>
</tr>
<tr>
<td>Stage of disease</td>
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</tr>
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<td>Stage I</td>
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</tr>
<tr>
<td>Stage II</td>
<td>15</td>
</tr>
<tr>
<td>Stage III</td>
<td>70</td>
</tr>
<tr>
<td>Stage IV</td>
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</tr>
<tr>
<td>Ureteral obstruction (UO)</td>
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</tr>
<tr>
<td>Unilateral</td>
<td>40</td>
</tr>
<tr>
<td>Bilateral</td>
<td>77</td>
</tr>
<tr>
<td>Type of nephrostomy</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>74</td>
</tr>
<tr>
<td>Bilateral</td>
<td>43</td>
</tr>
<tr>
<td>Presentation of ureteral obstruction</td>
<td></td>
</tr>
<tr>
<td>Initial disease</td>
<td>89</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>22</td>
</tr>
<tr>
<td>Complication of initial therapy</td>
<td>6</td>
</tr>
<tr>
<td>Elevation of creatinine</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>93</td>
</tr>
<tr>
<td>Absent</td>
<td>24</td>
</tr>
</tbody>
</table>

Clinical indications for PCN included radiographic evidence of high grade UO, impaired renal function with azotemia or oliguria. Due to the emergency of progressive UO or/and uremic syndrome, the patients were referred to a urologist and aggressive elimination of UO by urgent PCN was done by an intervening radiologist.

PCN was performed under local anesthesia by a standard technique (Seldinger’s technique) with fluoroscopic guidance with the patient in the prone oblique position. Kidney puncture was done with a Chiba needle at the posterior axillary line towards the lower or middle calices. All patients had undergone descending pyelography in order to confirm the proper position of the catheter. A drainage catheter was left in the renal pelvis or upper ureter to drain the kidney percutaneously and it was fixed to the skin by sutures. Antimicrobials (usually trimethoprim and sulfamethoxasole) were given as prophylaxis in case of subclinical infection for at least 48 hours after the procedure, or longer. If an infection coexisted, antibiotics were administered on the basis of urine cultures obtained at the time of the procedure. The catheter was changed every six to eight weeks and in case of permanent insertion or after additional specific oncological treatment, every three months.

Follow-up evaluations and monitoring included ultrasonography, urinalyses, blood laboratory tests and routine renal function tests. We assessed and evaluated the complications after the procedure.

In case of cervical carcinoma or corresponding recurrent disease when renal function improvement and normal renal function tests were obtained, additional complementary treatment for these malignancies was done. Radiotherapy at a dose according to the initial stage or palliative treatment intent were performed in patients who were able to receive it. Data such as survival status, complications and influence of some factor related to PCN were carefully assessed.

Statistical analysis was done by Statistical Package for the Social Science (SPPSS)* software, version 10.0. Comparison of continuous data was performed using the log-rank test and Kaplan-Meier’s method.

Results

Bilateral nephrostomy was performed in 43 patients (36.7%) and unilateral in 74 patients (63.3%). If bilateral UO was present, a single nephrostomy was usually done in less hydronephrotic kidney with thicker renal parenchyma and obvious better renal function. In case of bilateral PCN, the puncture was done first in the kidney with high-grade hydronephrosis when it was associated with uncontrolled pain and, as the second act, puncture was done in the other kidney.

Overall two-year survival (OS) for all the patients was 16.8% and the median survival time was seven months (Figure 1).

There was no statistically significant difference in survival (log-rank test, \( p = 0.646 \)) among patients aged 65 years or less (Figure 2).

The median survival time for patients with initial primary disease was eight months versus six months in recurrent and eight months in patients after initial therapy. No statistically significant difference (log-rank test, \( p = 0.256 \)) was found between these patient groups (Figure 3).

Complete normalization of renal function occurred in 29 patients (24.8%) and its improvement in the remaining 64 out of 93 patients with initial azotemia. Higher OS was observed in patients without deterioriation of renal function and initial azotemia versus those with azotemia (26.8% vs 13.9%) and the registered difference (log-rank test, \( p = 0.017 \)) was statistically significant (Figure 4). The median survival time for patients with UO and normal renal function was 16 months and for those with completely recovered renal function after PCN, 12 months versus five months for patients with persistent azotemia.

There is no advantage in performing bilateral PCN since no statistically significant difference in OS (log-rank test, \( p = 0.23 \)) among the patients subjected either to bilateral or unilateral PCN was found (Figure 5). In the group of patients with persistent azotemia after the procedure, there was no statistically significant difference in OS after inserting either a bilateral or unilateral PCN (log-rank test, \( p = 0.993 \)).

Complications associated with the procedure occurred in 53.85% of all the patients. Mild hematuria occurred in
all the patients but it was usually transient. Severe bleeding was not observed. The most frequent complication was the loss of the nephrostomy catheter, occurring in 37.61% of the patients and it was successfully solved by its simple replacement. Urinary tract infections were present in 19.6% and skin infections in 12.8%. These patients were treated medically by broad spectrum antibiotics. Serious complications such as perirenal abscess, pyelonephritis and urinoma were uncommon and occurred in 6.8%. Urologists participated in aggressive elimination and treatment depended on the patient’s WHO performance status and life expectancy.

As a result of successful urinary diverging further definite or palliative radiotherapy was applied continuously in 99 (84.6%) patients. Treatment interruption occurred in nine (7.7%) due to deterioration and progression of the disease. The treatment was applied according to the standard regimens required for stage and origin of the malignancies. Nine patients (7.7%) had no further treatment. The reasons for UO in six of them were severe complications caused by the primary treatment and in two patients no further treatment was feasible due to low performance status (PS).

Analyses of PCN outcome showed that in most cases
(71.8%), PCN remained as persistent. In 8.55% it was possible to replace it with a stent and only 19.66% of patients were without PCN. At the time of analysis, 23 patients were alive without disease, in eight patients some signs of the primary disease were present and 86 patients died due to the primary disease.

**Discussion**

The experience of more than 20 years in performing PCN has made this method a world-wide accepted procedure in the treatment of gynecological malignancies related to UO. Many reports have demonstrated advantages of this method such as its simplicity (under ultrasound or radioscopic control), low price, minimal morbidity and acceptable complication rates [1, 12]. Performing this procedure improved the survival rate of these life threatened patients but at the same time uncritical application of the method was observed [10, 11, 13]. Patients with locally advanced or metastatic malignancies, quite often, even after PCN, were not considered for any further therapy. Fast progression and aggressive behavior of a tumor caused prolonged painful agony and diminished already poor quality of life [13-17].

Grabstald *et al.* reported that despite considerable selection of indications for PCN, a useful quality of life was not achieved in 32% of patients [18]. The patients with terminal stage cancer who had undergone successful PCN had a median survival time of 133 days (range 7-712), as was reported by Harrington *et al.* and an analysis of survival time showed that patients spent 50% of the time in the hospital [6, 19]. In a study by Hoe *et al.* a reasonable overall median survival of 19 weeks was reported. At the time of the review, seven out of 22 patients were alive. Seventy-seven percent of patients were able to leave the hospital after PCN, while 68% useful life [3].

In our study, two-year OS was 16.8%, with a median survival time of seven months. Better median survival time was associated with the primary presentation of the disease and in patients after initial therapy versus recurrent disease (8 vs 8 vs 6 months), but a statistically significant difference was not found. In a series of 40 patients, Barton *et al.* found that the median survival time in the primary disease was 12 months and it was similar to 9.5 months found in recurrent disease [2]. Baker *et al.* reported similar confirming survival results of six and three months for patients with primary and recurrent disease after PCN [1]. Other reports found a median survival time of seven months [20].

It was noted that the primary tumor location was a predictive factor in outcome following PCN [17]. Significantly better survival was associated with cervical and prostatic cancer and the increment was one year or more in 60% of patients [5, 21].

Patient age is quite often reported to be an important factor for successful PCN [20, 22]. Romero *et al.* observed lower hospital mortality rate and longer survival in patients younger than 52 years due to larger metabolic resources for recovery and better response to subsequent treatments [5]. In contrast, Barton *et al.* in their study found that age had no impact on survival [2]. In our cohort we did not find a statistically significant difference in survival among patients aged 65 years or less.

Although we have seen complete renal function recovery in only 29 patients, in all the remaining ones serum BUN and creatinine levels were improved. A statistically significant better OS was observed in patients without renal function deterioration and azotemia versus those with azotemia (26.8% vs 13.9%). Higher mortality was probably due to more severe uremic complications, and to avoid them PCN should be performed prior to development of such clinical conditions [23]. Perinetti *et al.* reported marked recovery in 13 of 15 patients [24]. More recent reports in the gynecological literature have demonstrated similar results [5, 22]. Renal function following PCN was improved in a cohort of Barton *et al.* in 76.9% [2]. Despite these results, Barton *et al.*, as well as some other authors, confirmed that the degree of renal failure was less important than expected [12,16].

Survival in our patients with bilateral PCN was not better and was associated with poor quality of life. In bilateral UO the side with less dilatation and greater parenchymal thickness should be considered. A similar finding and recommendations were found in other studies [2, 20, 22].

The PCN technique has been well recognized as a safe and fast procedure with low complication rates. In a few retrospective studies it was reported that, besides minimal morbidity, severe PCN-related complications could occasionally occur and, consequently, significantly increase treatment costs while consuming health care hours as well. A rare case of urinoma (usually reported to occur in less than 2%) and perirenal abscesses require more aggressive treatment and are often compromised by the patient’s performance status [25, 26].

The common complications in PCN in a cohort of Dudley *et al.*, were catheter blockade in 65% and infection in 70% [7]. Catheter loss and dislocation may occur in up to approximatively 40% of cases [27]. In the study of Soper *et al.* 62% of patients with antibiotic prophylaxis after the procedure had evidence of pyelonephritis [20]. Carter *et al.* did not use antibiotics in prophylaxis and IV application of antibiotics was required in 37% of patients [12]. Barton *et al.* reported only 7.5% of infections without prophylactic treatment [2].

We found that besides mild transitory hematuria, the most frequent complication was catheter loss at 37.61%. Although prophylactic antibiotic therapy was applied, urinary tract infections occurred in 19.6%. These complications were successfully treated by simple catheter replacement or antibiotic therapy.

The presence of a urinary bag as a permanent extrarenal drainage in PCN diminishes the comfort and quality of the patient's life [10, 11, 15]. In some cases, after PCN has been performed providing good biochemical response regarding azotemia and if possible to pass
ureteral compression, an internal ureteric stent can be placed [3, 28]. In our study, only in ten patients (8.55%) was PCN replaced by a stent. Dudley et al. found that percutaneous diverging or stent in most cases were in situ at the time of death. Similar findings have been reported by more recent studies [2,7].

The SCVIR (Society of Cardiovascular & Interventional Radiology Standards of Practice Committee) represents the clinical practice guidelines for PCN for the purpose of improving performance, complication rates and results. It has been pointed out that the most important facts for a successful procedure are patient selection, technical performance rate, and monitoring complications [4].

Patients with advanced malignant disease and UO are mostly not suitable for radiation or other specific therapy curatively intended [16]. However, in our cohort of patients, definite and palliative treatment was mostly applied continuously in 99 (84.6%) patients. Although the complete irradiation dose was applied, the two-year survival rate of 16.8% was low thus supporting the palliative role of radiation therapy. Only 23 patients were alive without signs of the disease and eight were alive with the disease.

Taubner et al. retrospectively analyzed therapeutic and ethical problems after PCN in patients with persistent cancer and 42% of those patients experienced no benefit from the procedure [29]. Tumor progression in 17% patients was expected at the time of PCN. Patients who undergo PCN without improvement afterwards will have prolonged agony caused by progressive neoplasm [10, 30]. A few recent reports have indicated that the factors considered as an absolute contraindication for UO treatment are: disease progression during or immediately after the optimal therapy, inability to apply effective treatment, WHO performance status 2 or lower (3-4), presence of tumor-related problems, and uncontrolled pain during the optimal medicamentous therapy [4, 10, 11, 31]. A conservative approach in UO treatment allows peaceful dying of patients who are unsuitable for any therapy and the onset of uremia can be considered as a welcome event [23].

Finally, the active role of patients and their families in making the decision for PCN is essential. Proper information provided by physicians is necessary for the purpose of encouraging the patient to make a reasonable decision.

Conclusion
PCN is a safe and effective procedure. The improvement of renal function after PCN could be of clinical benefit for patients who might have a chance of being cured or undergoing prolonged palliation care. Azotemia seems to be a poor prognostic sign. The complexity of the matter requires that the decision about PCN should be made based on essential close cooperation and clinical assessment by a team of an oncologist, interventional radiologist and urologist. Physician responsibility in selection of cases is to establish appropriate indications concerning aggressive or conservative therapy according to the patient’s characteristics. Patients with poor prognosis due to low PS, the presence of uncontrolled pain, and in whom all the primary treatment regimens failed, should be considered for the application of conservative treatment.

References


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Gynecological malignant neoplasias diagnosed after hysterectomy performed for leiomyoma in a university hospital

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Introduction

Hysterectomy is a frequent surgery worldwide. Leiomyomas are the most common tumors of the uterus as well as the female genital tract [1], being a frequent indication for removal of the uterus. Malignant neoplasms can be found after hysterectomy due to benign indications. The incidence ranges from 0.13% to 0.7%, and the most frequent tumor finding is sarcoma [1-4]. Sarcoma, cervical and uterine cancer have been described [1, 5, 6]. Uterine sarcoma is a rare malignant neoplasm with 30% being leiomyosarcomas [6]. Cervical carcinoma and uterine sarcoma can be found incidentally in anatomatological studies after hysterectomy for benign conditions as leiomyomas. About 0.2 to 0.7% of the first diagnosis of leiomyomas are sarcoma after histologic study. In a series reported by Park et al. [1], 41 (0.01%) of 2,792 cases were found to be occult invasive cervical cancer. Cancer found at other sites such as the endometrium is rare [5].

Although the issue about finding malignant gynecological neoplasias after hysterectomies with or without salpingo-oophorectomy is interesting for gynecologists and oncologists, it is rarely discussed in the literature. Thus, the aim of this paper was to analyze the frequency of incidental findings of malignancy after hysterectomy for benign conditions in a university hospital.

Patients and Methods

A retrospective study was conducted in the Discipline of Gynecology and Obstetrics/Research Institute of Oncology (IPON) of the Federal University of Triângulo Mineiro (UFTM) from January 1987 to December 2008. In this period, we analyzed all simple hysterectomies with or without salpingo-oophorectomy for benign conditions (leiomyoma). Incomplete dossiers of patients or cases with uncertain clinical diagnostics were excluded. We analyzed histopathological results, age, parity, indications for hysterectomies with or without salpingo-oophorectomy, stage (if malignant) and therapy.

Results

From January 1987 to December 2008, 2,016 hysterectomies with or without salpingo-oophorectomy were performed. Of 2,016, 652 (32.3%) had a previous diagnosis of malignancy and 1,364 (67.7%) had a clinical diagnosis of benignancy (leiomyoma). From the total of 1,364, three (0.22%) cases of cancer were diagnosed after anatomopathological study of the uterine specimen, two sarcomas and one endometrial cancer. No cases of incidental ovarian or uterine cervical cancer were diagnosed. Conclusions: Gynecological malignancies in surgical specimens of patients submitted to surgery (hysterectomy and/or salpingo-oophorectomy) for benign conditions are rarely found.

Summary

Purpose: To analyze the findings of malignant neoplasms after hysterectomy for benign conditions. Methods: A retrospective study from January 1987 to December 2008 was conducted. We analyzed all simple hysterectomies with or without salpingo-oophorectomy for benign conditions (leiomyoma). Incomplete dossiers of patients or cases with uncertain clinical diagnostics were excluded. We analyzed histopathological results, age, parity, indications for hysterectomies with or without salpingo-oophorectomy, stage (if malignant) and therapy. Results: 2,016 hysterectomies with or without salpingo-oophorectomy were performed. Of 2,016, 652 (32.3%) had a previous diagnosis of malignancy and 1,364 (67.7%) had a clinical diagnosis of benignancy (leiomyoma). From the total of 1,364, three (0.22%) cases of cancer were diagnosed after anatomopathological study of the uterine specimen, two sarcomas and one endometrial cancer. No cases of incidental ovarian or uterine cervical cancer were diagnosed. Conclusions: Gynecological malignancies in surgical specimens of patients submitted to surgery (hysterectomy and/or salpingo-oophorectomy) for benign conditions are rarely found.

Key words: Sarcoma; Endometrial cancer; Leiomyoma; Hysterectomy; Incidental finding.

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seven pregnancies, and were both submitted to total abdominal hysterectomy and salpingo-oophorectomy. The first patient presented with vaginal bleeding and a solid pelvic mass about 1800 ml in the ultrasonography (US) exam. Leiomyosarcoma was diagnosed at anatomopathological analysis. The neoplasia infiltrated the medium and superior third of the myometrium until 1.2 cm of the serous superficies; the isthmus was also compromised. About two months after surgery, hepatic and bone metastases were diagnosed at abdominal US, bone scintigraphy and X-ray exams (T3 N1 M1). Chemotherapy was indicated but 60 days after surgery the patient developed paresthesia and left hemiplegia. Medical support was indicated and she died a few days after.

In patient two, the carcinosarcoma invaded the myometrium, isthmus and endocervix (T2 N0 M0). Chemoradiotherapy was performed and the patient is alive without recurrence.

In the case where endometrial cancer was found (1996), the patient was 48 years old, parity 3, and presented vaginal bleeding and a small uterine leiomyoma (uterine volume 68 ml at US). Clinical therapy failed in treatment of the bleeding and a hysterectomy with bilateral salpingo-oophorectomy was performed. Histological analysis showed leiomyoma and adenocarcinoma of the endometrium (T1a N0 M0, grade 1). Radiotherapy was indicated. The patient is alive without recurrence.

No cases of incidental ovarian or uterine cervical cancer were diagnosed.

Discussion

We performed a retrospective study of 1,364 hysterectomies for benign conditions. From the total of 1,364, three (0.22%) cases of cancer were diagnosed after anatomopathological study of uterine specimens, two sarcomas and one endometrial cancer. Three cases (0.2%) of malignancies were found. Cervical intraepithelial neoplasia, suspicious of pre-invasive or invasive cervical cancer was excluded because factors as unsatisfactory colposcopy may be a bias. Nonetheless, staging after hysterectomy is not possible [7], and reports in the literature showed that the majority of cases are Stage I and that adjuvant radiotherapy is indicated [5, 7, 8].

In our series, two cases of uterine sarcoma (0.14%) were found in 1,364 hysterectomies for presumed leiomyomas, being 0.07% for each leiomyosarcoma and an endometrial carcinosarcoma. Parker et al. [1] reported an incidence of 0.08% of leiomyosarcomas and Leung et al. [6] found 0.23% of sarcomas. Uterine sarcomas are rare neoplasias corresponding to 3-9% of invasive tumors of the uterus and 1% of gynecological neoplasias [9-13].

Leiomyosarcomas represent 30% of uterine sarcomas. They are more common in the perimenopausal period (40-60 years old). In general, they show a rapid and poor prognosis. Metastasis via the blood is frequent. The bone, brain, and lungs are common organs of propagation of the disease. Abdominal dissemination of disease is also common and the risk increases with morcellation of the surgery specimen. Moreover, intraabdominal dissemination may occur. Survival is 30% at five years. Leiomyosarcoma originating from leiomyoma is a rare phenomenon (0.7-1.7%) [9-13].

In our study one case of carcinosarcoma (0.07%) was diagnosed. Carcinosarcoma occurred in a menopausal woman and is rarer than an unexpected sarcoma finding during vaginal or abdominal hysterectomy for benign conditions [14, 15]. Vaginal bleeding is a common symptom. The prognosis is linked to myometrial invasion and tumor stage. There are frequent metastases and survival is about 25 to 30% at five years [14, 15]. In both cases of sarcoma in our series, the patients presented vaginal bleeding and large pelvic masses. The differential diagnosis of sarcoma must be posed, but it is not questioned.

One case of endometrial cancer was found in our archives. The patient was not menopausal and this can be confounding because she did not present with abnormal bleeding. Although the diagnosis, she presented probably in early stage (T1a N0 M0 grade 1) and the prognosis was good. Thus, the treatment was completed with radiotherapy. For patients who present vaginal bleeding that clinical treatment has failed, even in the premenopausal period, investigation of endometrium may be indicated. Hysterectomy without bilateral salpingo-oophorectomy is inadequate surgery for treatment of endometrial cancer because metastases into the ovaries is present in 3-15% of cases [5]. In our case, after the patient had expressed her opinion, we decided on radiotherapy. One option of treatment is completing the first surgery with pelvic lymphadenectomy for complete staging.

The finding of endometrial cancer is about 5% [5]. In our series, only 0.07% of endometrial cancer was found. The use of US for analyses of leiomyomas may contribute to the low percentage of endometrial cancer found, because endometrial thickness is also observed.

Preoperative care is very important to avoid a mistaken diagnosis. Any suspicion of malignancy must be investigated. Dissection of the uterine specimen can be performed mainly if an endometrial lesion is suspected. Frozen section may be an option if any suspicious lesions are found during the intraoperative procedure [4], although this procedure is questionable in case of leiomyosarcoma [1, 16]. We conclude that the finding of gynecological malignancy in surgical specimens of patients submitted to surgery (hysterectomy and/or salpingo-oophorectomy) for benign conditions is rarely found.

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The spread pattern of right and left epithelial ovarian cancers

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Summary

Objective: No attention has been paid in the past to the spread pattern of right and left epithelial carcinomas of the ovaries. We aimed to investigate the incidence, spread pattern and distribution of lymph node metastasis in epithelial ovarian cancer (EOC), comparing right versus left EOC of any stage, where the contralateral ovary is apparently and histologically tumor-free. Methods: Out of a total of 442 patients with EOC, 318 (72%) patients in the study had bilateral and 124 (28%) patients had unilateral ovarian cancer. The study enrolled 60 (48%) patients with right and 64 patients with left ovarian involvement (52%) where the contralateral ovary was tumor-free. Groups Right and Left were compared in terms of age, the tumor status of the lymph nodes, surgical stage, histology, grade, tumor extension out of the ovaries, omental tumor involvement and also omental and nodal involvement together. Results: The comparisons of the variables between Groups Right and Left did not show significant differences except for metastasis patterns in the left iliac lymph nodes and omentum (p < 0.05). Independent of age and histological type of the tumor, women with left-side EOC showed a significantly higher incidence of metastasis in the left iliac lymph nodes (OR: 7.04, 95% CI, 1.36-36.44) and omentum (OR: 2.87, 95% CI, 1.03-8.01), when compared to right-side EOC (p < 0.05). Conclusion: In this cohort of patients, we found that left-side unilateral EOC was more likely to metastasize to the left iliac lymph nodes and omentum than the right side where the contralateral ovary was tumor-free. This might be due to the difference in lymphatic drainage on the right and left side and/or the influence of peritoneal fluid movements. This suggestion needs to be supported by further studies.

Key words: Epithelial ovarian cancer; Ovarian cancer metastasis; Right and left side cancer; Unilateral ovarian cancer.

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecological malignancies. Although ovarian carcinoma indicates a difficult therapeutic management, it appears that patients with this disease expect further improvement in terms of survival, quality of life and perhaps future fertility. For this purpose, surgery and adjuvant treatment methods that are “minimum but enough” should be brought to light. While achieving maximum tumor reduction is an important principle in the surgical management of EOC, the extent to which the surgeon should go on to achieve that goal has not been sufficiently addressed. Thus, better understanding of tumorogenesis and spread patterns of EOC would contribute to management of the disease.

In the current study, we present the lymph node metastasis and spread pattern of unilateral EOC where the contralateral ovary is tumor-free. Our aim was to investigate whether right- side EOC has a different spread pattern when compared to left-side EOC where the contralateral ovary is apparently and histologically tumor-negative. To the best of our knowledge, no attention has been paid to the spread pattern of right- and left-side epithelial carcinomas of the ovaries in the literature.

Material and Methods

Four hundred forty-two patients with EOC treated at Hacettepe University between January 1982 and January 2002 were retrospectively evaluated. Data was retrieved from hospital records and gynecological oncology files. Borderline malignancies, tumors other than primary EOCs, patients who had not undergone a systematic lymphadenectomy or who had received preoperative chemotherapy as well as EOCs with bilateral ovarian involvement were excluded from the study. The cases where tumor status of region or staging was not clearly defined in the files were also excluded from the study.

All the patients underwent staging laparotomy, including peritoneal fluid sampling, peritoneal biopsy, extended total hysterectomy and bilateral salpingo-ooophorectomy, systematic pelvic and paraaortic lymphadenectomy, omentectomy and bowel resection if needed. Pelvic lymphadenectomy was accomplished by completely skeletonizing the external iliac vessels and removing all the nodes around the vessels. The common iliac and obturator nodes were dissected using blunt and sharp dissection, and all tissues above the obturator nerve were removed. The paraaortic area was exposed just above the bifurcation. The retroperitoneal space and the lymph nodes at the bifurcation of the aorta anterior to the vena cava and below the renal vessels on the right and left sides were dissected. Infracolic omentectomy was performed in addition to routine staging. Surgeries were undertaken by the same surgical team in all patients. All the specimens were evaluated by the same pathology group.

Retroperitoneal lymph node regions were classified as paraaortic, iliac and obturator. Lymph nodes in the pelvis were evaluated as right and left. Histology of the tumors was evaluated as mucinous, serous and others. The tumor grade was evaluated as grade 1 and grade 2, 3 in both groups due to the sample size.
The patients enrolled in the current study had right or left ovarian involvement with a tumor-free contralateral ovary. Groups Right and Left were compared in terms of age, the tumor status of lymph nodes, surgical stage, histology, grade, tumor extension of the ovaries, omental tumor involvement and also omental and nodal involvement together.

**Statistical Analysis**

Statistical analysis was carried out by using the Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA), version 14.0. Significance was defined as \( p < 0.05 \). Data are presented as mean ± standard deviation (SD). Continuous variables were analyzed and compared using the Student’s t-test. Differences between categorical variables were analyzed using the chi-square test and Fisher’s exact test. The independence of significant factors \((p < 0.05)\) was determined by the logistic regression method and estimated risks were calculated.

**Results**

The mean age of the participants was 52.7 years. Of a total of 442 patients with EOC, there were 318 (72%) patients with bilateral and 124 (28%) patients with unilateral ovarian cancer. The current study enrolled 60 (48%) patients with right and 64 patients with left ovarian involvement (52%) where the contralateral ovary was tumor-free.

Of these 124 patients, there were 76 (64%) patients with early stage (I-II) disease and, 43 (36%) patients with advanced stage (III-IV) disease. The disease was confined to the ovary in 70 (59%) patients, while extension out of the ovary was observed in 49 (41%) patients.

The most frequent histological types of EOC were mucinous and serous with percentages of 40% and 35%, respectively. Tumor grading was available in only 42% (\( n = 52 \)) of patients, and 46% (\( n = 24 \)) of these were found to be grade 1 and 54% (\( n = 28 \)) grade 2 or 3. There were 22 (18%) patients with retroperitoneal lymph node involvement. Omental metastasis, however, was found in 26 (21%) of the patients. Omentum and lymph node involvement together was observed in 11 (9%) patients. Distribution of lymph node metastasis in the regions described in the Methods section is shown in Table 1.

There were no significant differences between Groups Right and Left in terms of age, tumor confinement in or extension out of the ovaries, or for early or advanced staged tumors. Metastasis to the paraaortic, pelvic, right iliac, right and left obturator lymph nodes did not differ between right and left groups.

Histological types of the tumors showed no significant difference when the right and left ovarian cancers with were compared. The comparison of the histological types of tumors that were only confined to the right or left ovary showed no significant differences.

Comparisons of the variables between right and left groups did not show significant differences except for metastasis patterns to the left iliac lymph nodes and omentum. Group Left showed a significantly higher incidence of metastasis to the left iliac lymph nodes and omentum when compared with the right group \((p < 0.05)\). Right iliac lymph node metastasis and paraaortic lymph node metastasis were also more frequent in left EOCs compared to right EOCs, even though the data are not statistically significant \((p = 0.06)\).

The incidence of pelvic and paraaortic lymph node metastasis, omental involvement and the statistical results of comparisons of Groups Right and Left are summarized in Table 1.

The localization side of the unilateral EOC on the right or left affects omental and left iliac lymph node metastasis, independent of age and histological type (serous, mucinous and others) of the tumor \((p < 0.05)\). Estimated risks of omentum and left iliac lymph node metastasis for patients with unilateral EOC on the left side compared to the right side were calculated as the odds ratios 2.87 (95% CI, 1.03-8.01) and 7.04 (95% CI, 1.36-36.44), respectively.

**Table 1. — Comparisons of the spread pattern of the right and left epithelial ovarian cancers.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (( n = 124 ))</th>
<th>Right tumor positive, left tumor free (Group Right, ( n = 60 ))</th>
<th>Left tumor positive, tumor free (Group Left, ( n = 64 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>52.7</td>
<td>52.6 (26-75)</td>
<td>52.7 (21-87)</td>
</tr>
<tr>
<td>Stage</td>
<td>119</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Early (I-II)</td>
<td>76</td>
<td>42/58 (72)</td>
<td>34/61 (56)</td>
</tr>
<tr>
<td>Advanced (III-IV)</td>
<td>43</td>
<td>16/58 (28)</td>
<td>27/61 (44)</td>
</tr>
<tr>
<td>Histology*</td>
<td>124</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mucinous</td>
<td>50</td>
<td>21/50 (42)</td>
<td>29/50 (58)</td>
</tr>
<tr>
<td>Serous</td>
<td>43</td>
<td>21/43 (49)</td>
<td>22/43 (51)</td>
</tr>
<tr>
<td>Others</td>
<td>31</td>
<td>18/31 (58)</td>
<td>13/31 (42)</td>
</tr>
<tr>
<td>Grade</td>
<td>52</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Grade 1</td>
<td>24</td>
<td>14/29 (48)</td>
<td>10/23 (44)</td>
</tr>
<tr>
<td>Grade 2,3</td>
<td>28</td>
<td>15/29 (52)</td>
<td>13/23 (56)</td>
</tr>
<tr>
<td>Regions tumor-positive</td>
<td>70</td>
<td>37/58 (64)</td>
<td>33/61 (52)</td>
</tr>
<tr>
<td>Confined to over</td>
<td>124</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Histology*</td>
<td>Mucinous</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>Serous</td>
<td>23</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Extension out</td>
<td>of ovary</td>
<td>49</td>
<td>21/58 (36)</td>
</tr>
<tr>
<td>Histology*</td>
<td>Mucinous</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Serous</td>
<td>24</td>
<td>10</td>
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<tr>
<td>Others</td>
<td>13</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Lymph node (LN)</td>
<td>22</td>
<td>8/49 (16)</td>
<td>14/46 (30)</td>
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<tr>
<td>Paraaortic LN</td>
<td>11</td>
<td>3/44 (7)</td>
<td>8/38 (21)</td>
</tr>
<tr>
<td>Pelvic LN</td>
<td>19</td>
<td>7/49 (14)</td>
<td>12/46 (26)</td>
</tr>
<tr>
<td>Right iliac LN</td>
<td>13</td>
<td>4/49 (8)</td>
<td>9/45 (20)</td>
</tr>
<tr>
<td>Right obturator LN</td>
<td>8</td>
<td>3/49 (6)</td>
<td>5/44 (11)</td>
</tr>
<tr>
<td>Left iliac LN</td>
<td>11</td>
<td>2/48 (4)</td>
<td>9/45 (20)</td>
</tr>
<tr>
<td>Left obturator LN</td>
<td>8</td>
<td>3/49 (6)</td>
<td>5/44 (11)</td>
</tr>
<tr>
<td>Omentum</td>
<td>26</td>
<td>7/50 (14)</td>
<td>19/58 (33)</td>
</tr>
<tr>
<td>Histology*</td>
<td>ns</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Mucinous</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Serous</td>
<td>13</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Omentum (+)/LN (+)</td>
<td>11</td>
<td>3/49 (6)</td>
<td>8/46 (17)</td>
</tr>
</tbody>
</table>

*Comparison for mucinous and for serous; LN: lymph node; ns: non significant.
Discussion

This study showed that EOCs originating from the left ovary more frequently metastasized to the omentum and left iliac lymph nodes compared to right ovary EOCs. Moreover, the left-side tumors had a tendency to be in advanced stage and with paraaortic lymph node metastasis even though relevant data is not statistically significant. Overall, there was a tumor-free ovary in 28% of the EOCs and the incidence of right and left tumors was similar.

Laterality of ovarian cancers has been evaluated in a few studies but to our knowledge there is no study which has aimed to compare the spread pattern of EOCs originating from the left and right sides. Some authors have evaluated the data as a part of their study without pursuing the goal of comparison, but the number of patients cited is very small and does not allow us to comment [1-3]. Regarding laterality of the metastatic lymph nodes, Onda et al. reported a higher frequency of ipsilateral lymph node metastasis; there was, however, no difference in the laterality of the metastatic lymph nodes. Additionally, contralateral pelvic and paraaortic metastasis has been reported in a case at clinical Stage I left ovarian cancer without ipsilateral nodal metastasis [4].

In the cohort of the current study, one-third of the patients had advanced stage disease despite a tumor-free ovary. Cass et al. [5] performed lymphadenectomy in 96 cases at clinical Stage I unilateral EOC and reported that even when retroperitoneal lymph nodes were positive, histologically cancer-free contralateral ovaries were found in 11 cases. Wu et al. [6] noted a high incidence of lymph node involvement in ovarian cancer (EOC and germ cells evaluated together) where the primary tumor site was the left ovary. In 38 cases in which the primary cancer originated in the left ovary, 17 (44.7%) were found to have positive pelvic nodes, whereas in 25 cases with primary cancer arising in the right ovary, only two (8%) had metastasis of the ipsilateral pelvic nodes [6]. The result of our study was similar in terms of lymph node metastasis. On the other hand, Morice et al. [7] reported a higher incidence of left ovarian cancer compared with the right side; 69 left versus 46 right involvements were found in a total of 276 patients with EOC. Considering the data in the current study, it remains unclear whether left-side ovarian cancer occurs more frequently than right-side. Although left and right unilateral ovarian tumors had similar nodal involvement (25% vs 28%), it was also found that when paraaortic nodes were involved, the left paraaortic chain above the level of the inferior mesenteric artery was the most frequently involved site (70 patients, 63%). Both reports made no inference about the reason for the lymphatic site involvement.

Ovarian cancer remains in the abdomen for a long time. It spreads in the abdomen, however, relatively quickly. Tumor cell migration is helped by the negative pressure in the subdiaphragmatic space. The influence of peritoneal fluid movement and the areas of peritoneal fluid stagnation could encourage the implantation of malignant cells [8]. Implantation may not be the only way that ovarian cancer appears over the abdominal surface. The lymphatic spread of ovarian cancer, and the frequency and primary sites of metastasis in the areas of drainage remain the subject of ongoing and future studies. The extent of intra-abdominal spread varies widely in advanced stages of ovarian cancer. This raises the question of the varying anatomical and biological status of these tumors. For example, omental metastasis as the sole abdominal finding was found in 48% of Stage III patients but in only 10% of Stage IV patients [9]. The authors suggested that Stage IV is probably not a progression of Stage III, but that it has a completely different mode of spread to begin with.

Direct lymphatic spread from the ovary occurs through the efferent lymph channels to the regional nodes. It is believed that the major path of lymphatic spread appears along the ovarian vessels. On the right, this path leads first to the paraaortic nodes at the level of the inferior pole of the kidney, and on the left to the area of renal hilus [10]. However, lymphatic spread may also occur directly from the ovarian hilus to the interiliac lymphatics through broad ligament folds. These nodes are the junction of a number of anastomoses with the other regional and paraaortic nodes [11].

Venous drainage asymmetry can be considered as one of the possible explanations of the more frequent occurrence of metastasis from left ovarian tumors. The right common iliac vein, which is shorter than the left, is nearly vertical in its direction. The left common iliac vein is longer than the right one and has a more oblique course [12]. The left gonadal veins are longer than the right ones. The right gonadal vein opens into the inferior vena cava at an acute angle. However, the left gonadal vein opens into the left renal vein at a right angle [13]. The lymphatic vessels run alongside all these veins. Not to be considered more than a suggestion, variations in the length of lymphatics and the angle of opening out of the lymphatics on each side may be causing tumor cells to stay in the left for a long time, allowing them to survive at that location.

In summary, the literature lacks satisfactory cases in that describe the distribution, frequency and comparison of right and left unilateral EOCs. In this cohort of patients we found that left-side EOC was more likely to metastasize to the left iliac lymph nodes and omentum than right-side EOC where the contralateral ovary was tumor-free. Right iliac lymph node metastasis and paraaortic lymph node metastasis were also more frequent in left EOC than on the right side, although relevant data is not statistically significant. This might be due to the difference of lymphatic drainage on the right and left sides and/or the influence of peritoneal fluid movements. This suggestion needs to be supported by new studies, however and it should be considered carefully in both minimally invasive and fertility-sparing surgery when the tumor is in the left ovary.
The spread pattern of right and left epithelial ovarian cancers

References


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About 10% of all ovarian cancers are due to BRCA1 and/or BRCA2 mutations. Some studies have shown that patients belonging to this group have a better survival compared to sporadic groups but data are still inconclusive. The aim of this study was to investigate overall survival in patients with ovarian cancer and germ-line mutations in the BRCA1/2 genes in comparison to high-risk patients, defined as patients with ovarian cancer and a strong family history of breast and ovarian cancer, but who tested negative for the BRCA mutation. We collected all the clinical features and did follow-up. The two groups showed similar characteristics concerning age at diagnosis, histological type and stage. Grade 3 was more frequent in the BRCA group. Survival data did not show any advantage for the BRCA mutated group.

Key words: BRCA1; BRCA2; Ovarian cancer.

Introduction

Ovarian cancer is the most common cause of mortality of tumors from gynecologic origin and is often diagnosed after patients have already progressed to advanced disease stage because of their nonspecific initial symptoms [1]. The standard of therapy for advanced stages is optimal surgery with minimal residual disease (radical hysterectomy, bilateral aneesiectomy, appendectomy, omentectomy and lymphadenectomy), followed by chemotherapy with a platinum and taxane combination is the best goal for survival [2].

Epidemiologic data and molecular analysis show that about 10% of all epithelial ovarian cancers are associated with inherited mutations in BRCA1 and/or BRCA2 genes [3]. Hereditary and sporadic ovarian tumors show similar characteristics such as histopathologic type distribution and high-grade frequency; furthermore, the diagnosis is often made at an advanced stage (III and IV) in both cases [3].

In sporadic ovarian cancer Stage III-IV the median 5-year survival is 30% [2].

Estimated risk of developing ovarian cancer in a lifetime in women harboring BRCA1/BRCA2 mutations is about 30-40% for BRCA1 and 15-25% for BRCA2 [4].

Several studies have shown improved survival in BRCA-associated ovarian cancer but a few others suggest a poorer clinical outcome, therefore data are still inconclusive. Interestingly, some investigators have hypothesized that this difference might be due to a different responsiveness to chemotherapeutic agents. The objectives of the present study were to evaluate the overall survival of ovarian cancer patients and to investigate long-term survival of BRCA1/BRCA2 mutation carriers and non carriers as compared to high-risk breast and ovarian cancer [4].

Summary

The study was conducted by reviewing patient charts from the Oncology Institute of Veneto and Oncology-Gynecology Department of Mirano, Venice, Italy. All data were abstracted from medical records and original surgery and pathology reports; also information on the patient’s vital status was updated through the charts. Since this was a retrospective study, patients enrolled covered a period of 15 years. Some patients were tested almost ten years after their ovarian cancer was diagnosed. Patients were subdivided in two groups: BRCA-related ovarian cancer patients and high-risk breast/ovarian cancer patients, who tested as non carriers for the BRCA mutation. A total of 88 patients affected by epithelial ovarian cancer were included in the study. Forty-eight tested positive for a deleterious mutation in the BRCA1 and/or 2 gene (34 BRCA1 and 14 BRCA2) and 40 patients were selected as a control group. To complete the genetic testing for the patients already recruited, all patients were approached by their gynecologist/onscolgist and, after giving informed consent to participate in the study, blood samples were collected. Genetic mutation assessment was performed at the Oncology Section of the Department of Oncology, University of Padua, Italy.

Analysis were performed with standard laboratory methods. A multiplex polymerase chain reaction was designed to amplify the exons containing the mutations with the use of fluorescence-labeled primers in a single reaction. Samples available for testing included peripheral blood.

Patient characteristics

Data abstracted from charts were collected according to the World Health Organization (WHO) and the stage by TNM classification. For each patient, age at diagnosis, tumor histological type, TNM stage and follow-up were recorded. All patients were treated by the best debulking surgery possible for the stage of disease, followed by a platinum-based chemotherapy regimen.

Different platinum-chemotherapy regimens were considered: carboplatin and taxol (which is the standard chemotherapy for ovarian cancer), cisplatinum (DDP), carboplatin as a single
agent, cisplatinum plus taxol, cisplatinum plus cyclophosphamide plus epirubicin (PEC), cisplatinum plus cyclophosphamide, carboplatin plus taxol plus epirubicin (TEC), and carboplatin plus mitoxantrone.

**Statistical analysis**

Univariate survival analysis was performed using the Kaplan-Meier method for estimating survival functions and the log-rank test to compare them. All tests were two-tailed and the significance level was set at 5%. Differences in proportion were assessed by means of the chi square test.

**Results**

Patient survival and other clinical characteristics of the tumors were compared in patients with BRCA1 or BRCA2 mutations and those without mutations.

The clinical features of a total of 88 patients affected by ovarian cancer were analyzed: 48 were associated with a germ-line mutation on BRCA1 or BRCA2 genes and 40 were classified as affected by high-risk ovarian cancer. Median age at diagnosis was 51 years old for inherited ovarian cancer and 54.5 years for the non carrier group. Among BRCA mutation carriers ten out of 34 who carried BRCA1 mutations were diagnosed before age 45, whereas no women who carried BRCA2 mutations were diagnosed at age < 45. Seven ovarian cancers out of 40 in the high-risk group were diagnosed before 40 in the high-risk group were diagnosed before 45 years. Histological features were found to be similar in both groups: 37 (77.1%) were serous ovarian cancers, seven (14.6%) endometrioid and four (8.3%) anaplastic in the BRCA1/BRCA2 carrier group while 36 (90%) were found to be serous ovarian cancer, two (5%) endometrioid, one (2.5%) clear cell and one (2.5%) anaplastic in the non carrier group.

Tumor grade was G3 in 75% of BRCA 1 and 2 groups and 32.5% in the non carrier group (chi square test $p = 0.0196$). Grade 1 and 2 was found in 25% of the BRCA 1 and BRCA2 groups and 67.5% in the non carrier group (chi square test $p = 0.0133$). Advanced stage of disease at the time of diagnosis (Stage III-IV) was found to be 72.9% for patients carrying a deleterious mutation and 43.7% for the non carrier group. Comparison of survival between the two groups for advanced stage did not show any difference (Table 1).

![Figure 1. — Median overall survival for the two groups.](image)

Seven women with BRCA1/BRCA2 and seven non carriers had a previous breast cancer diagnosed almost five years before ovarian cancer, and only one patient had first ovarian cancer and then breast cancer, and she is still alive. Treatment at any stage of disease was with a platinum-based chemotherapy regimen. Eight different chemotherapy regimens, as reported in patients and methods, were considered for the treatment of the ovarian cancer. All regimens were platinum-containing therapy and were distributed over 15 years of the patients’ accrual.

Despite the advanced stage of disease, median survival from diagnosis for the women with inherited mutations was about 145 months while that for the high-risk group was 280 months. This difference was not statistically significant; the log-rank test for equality of survivor functions ($pr > \chi^2 = 0.1352$) is shown in Figure 1.

**Discussion**

In this retrospective study the clinical features and survival of two groups of ovarian cancer patients were investigated. We wanted to demonstrate if there were any differences in survival between BRCA-positive ovarian cancer patients and a group of high-risk patients tested as non carriers of the BRCA mutations.

To our knowledge there are almost 12 studies comparing survival between the BRCA and sporadic or high-risk ovarian cancer patients; six showed a statistically significant improved survival for BRCA carriers and another six showed no statistically significant difference (Table 2) [6-17].

For example Zweemer et al. showed a five-year survival of 47% for non carriers with respect to 40% for carriers [12]. Ramus et al. showed 52-month median survival for BRCA 1 and 49 for BRCA2 with respect to 35 months for non carrier consecutive patients ($p = 0.5$) [13]. Moreover Buller et al. [14] and Kringen et al. [15] showed similar data with no statistical significance in survival in the two groups of patients. In our study the different distribution of patient characteristics as no G1 and a high number of G3 in 75% of the hereditary ovarian can-

<table>
<thead>
<tr>
<th>Variables</th>
<th>BRCA Familial cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>48</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
</tr>
<tr>
<td>IV</td>
<td>7</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>3</td>
<td>36 (75%)</td>
</tr>
<tr>
<td>First breast cancer diagnosis</td>
<td>7</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
</tr>
<tr>
<td>SP: serous papillary</td>
<td>37</td>
</tr>
<tr>
<td>Non SP</td>
<td>11</td>
</tr>
</tbody>
</table>
Table 2. — BRCA-ovarian cancer median survival.

<table>
<thead>
<tr>
<th>References/year</th>
<th>BRCA-ovarian cancers</th>
<th>Sporadic cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharaoah et al. 1999</td>
<td>20.6 (BRCA1), 16 (BRCA2) months</td>
<td>19.5 months</td>
</tr>
<tr>
<td>Aida et al. 1998</td>
<td>91.43 months of DF interval</td>
<td>40.92 months</td>
</tr>
<tr>
<td>Boyd et al. 2000</td>
<td>40 months of DF interval</td>
<td>25 months</td>
</tr>
<tr>
<td>Cass et al. 2003</td>
<td>91 months</td>
<td>54 months</td>
</tr>
<tr>
<td>Johannsson et al. 1998</td>
<td>30% of BRCA1 cases at 5 years</td>
<td>45% control cases at 5 years</td>
</tr>
<tr>
<td>Ben David et al. 2002</td>
<td>53.4 months</td>
<td>37.8 months</td>
</tr>
<tr>
<td>Zweemer et al. 2001</td>
<td>40% 5-years</td>
<td>46% 5-years</td>
</tr>
<tr>
<td>Ramus et al. 2001</td>
<td>52 months BRCA1, 49 months BRCA2</td>
<td>35 months</td>
</tr>
<tr>
<td>Buller et al. 2002</td>
<td>4.5 years</td>
<td>4.6 years</td>
</tr>
<tr>
<td>Kringen et al. 2005</td>
<td>33% BRCA1 5-years</td>
<td>23% 5-years</td>
</tr>
<tr>
<td>Pal et al. 2007</td>
<td>27% BRCA1 4-years</td>
<td>12% 4-years</td>
</tr>
<tr>
<td>Chetrit et al. 2008</td>
<td>53.7 months</td>
<td>37.9 months</td>
</tr>
</tbody>
</table>

DF = disease-free.

Other studies on clinical characteristics of patients with hereditary vs sporadic ovarian cancer have suggested two possible mechanisms for improved survival of BRCA group carriers: 1) potential indolent clinical behavior due to a lower rate of mitotic index despite a more aggressive phenotype, or 2) a more favorable response to chemotherapy.

Different functions of BRCA genes can enhance those hypotheses such as maintaining chromosome stability, regulating cellular proliferation and DNA repair; in particular, the proteins encoded by the BRCA genes are involved in homology-directed repair of DNA double strand breaks [18-20].

Taniuchi et al. suggest a molecular mechanism for understanding genetic instability in ovarian cancer cells through the involvement of Fanconi proteins.

Fanconi protein protect cells against cell death and genotoxicity induced by cross-linking agents and work together with BRCA1 and BRCA2 proteins in the DNA repair pathway as well. Hypomorphic BRCA2 mutations lead to a type of Fanconi anemia (FANC-RRCA pathway) in which BRCA2 fails to bind to RAD51 in response to genotoxic agents. Such an inactivation of the FANC-BRCA pathway can give rise to cells sensitive to DNA cross-linking agents such as cisplatin [21].

Tailored chemotherapy for BRCA 1 and BRCA2 ovarian cancer based on their higher sensitivity to double breaking DNA-strand agents can be a way to improve their survival. In this study it does not seem that the platinum-containing regimen changed survival in the BRCA group considering their lack of BRCA1 and BRCA2 function.

Another explanation of why there was no difference in survival between the two groups could be that in the high-risk group there were some possible confounders or modifiers such as other genes involved in the impact on prognosis.

Conclusion

Several studies as well as ours have investigated survival in BRCA-related ovarian cancer. Our study did not find any improvement in survival for hereditary ovarian cancer patients with respect to high-risk cases. To our knowledge, today randomized studies show that prophylactic surgery is the only treatment to reduce ovarian cancer risk in BRCA-mutated women [22]. Our future goal will be to define recommendations for treatment and prevention of ovarian cancer in our region and to study the side-effects of early menopause in women submitted to prophylactic surgery.

Acknowledgement

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References

Overall survival in BRCA-associated ovarian cancer: case-control study of an Italian series


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Expression of survivin, caspase-3 and p53 in cervical cancer assessed by tissue microarray: Correlation with clinicopathology and prognosis

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Summary

Objective: The aim of this study was to determine the role of survivin, caspase-3 and p53 expression in cervical cancer, and their correlation with clinicopathological features and prognosis. Methods: Two hundred and twenty-eight cases of cervical disease were analyzed retrospectively between February 2003 and May 2007 at Taizhou Hospital of Taizhou Enze Medical Center. The expressions of survivin, caspase-3 and p53 were detected by immunohistochemistry (EnVision), assessed by tissue microarray. The correlation of the three genes and clinicopathological factors as well as prognosis were statistically analyzed. Results: The results showed that the positive expression rate of survivin, caspase-3 and p53 in cervical cancer was significantly higher than in the CIN group and cervicitis group ($p < 0.05$). The expression of survivin was related with clinical staging, stromal involvement and lymph node metastasis ($p < 0.05$). The positive ratio of caspase-3 was significantly different from histological grading ($p < 0.05$). The positive expression of p53 was correlated with histological type and grading ($p < 0.05$). The expression of survivin in cervical cancer was negatively associated with that of caspase-3 ($p < 0.01$). The positive expression of survivin in the survival group and non-survival group was significantly statistically difference ($p < 0.01$). There was a significant difference between survivin expression and survival duration by the log-rank method, whereas no association with survival was seen for caspase-3 and p53 positivity. Conclusion: Survivin, caspase-3 and p53 may play an important role in the occurrence and development of cervical carcinoma. They could be used as markers for malignant degree and invasiveness of cervical cancer. Survivin can also be used in the estimation of prognosis and survival time of cervix carcinoma.

Key words: Survivin; Caspase-3; p53; Cervical cancer; Survival analysis.

Introduction

Cervical cancer is the second most common cancer among women worldwide. More than 500,000 cases of cervical cancer occur every year, and 75-80% of the cases are in developing countries.

Apoptosis, often referred to as programmed cell death, is a physiologic process for the elimination of specific types of cells, occurring extensively in embryonic development, metamorphosis, and differentiation. Abnormal regulation of apoptosis is likely to contribute to the pathogenesis of autoimmune diseases and malignant tumors [1]. The acquired ability to resist apoptotic stimuli is shared by many types of malignant diseases, and genetic alteration in the components of apoptotic pathways is a pivotal mechanism in the development of cancer [2]. With regard to cervical cancer, only a few reports concerning survivin and caspase-3 expression have been published. The overexpression of survivin can inhibit apoptosis, resulting in abnormal cell proliferation and transduction towards to malignancy [3]. Although Yamada et al. [4] and Mahotka et al. [5] succeeded in quantifying gene expression levels of surviving splice variants using glioblastoma and renal cell carcinoma specimens, the expression pattern of these variants in various human cancers has not been extensively studied. Caspase-3 could lead to antiapoptotic phenotype. Most factors trigger apoptosis via a signal way mediated by caspase-3 [6], p53 protein, encoding on chromosome 17p13, has a central role in regulation of the cell cycle and apoptosis. Mutation of the p53 gene has been quoted as one of the most common markers in human cancers. Multiple trials have investigated the role of the p53 gene in the carcinogenesis of cervical cancer [7, 8]. In this study, the expression and distribution of survivin, caspase-3 and p53 was detected in 107 cases of cervical cancer with an immunohistochemical EnVision method to study the relationship between these markers and development of cervical cancer.

Materials and Methods

Materials

Two hundred and twenty-eight cases and specimens of cervical diseases were obtained from Taizhou Hospital of Taizhou Enze Medical Center from February 2003 to May 2007. There were 35 females with cervicitis, 86 females with CIN (including 28 cases of CIN I, 26 cases of CIN II and 32 cases of CIN III) IV and 107 females with cervical cancer (including 81 cases of squamous cancer and 26 cases of adenocarcinoma). Of the
107 cervical cancer cases, the mean age was 43.5 years old (27-71 years old). All patients with cancer were operated before and were subjected to chemotherapy or radiotherapy. According to the pathological differentiation of squamous cancer, the cervical cancer was graded as: high differentiation (22 cases), middle differentiation (43 cases), and low differentiation (16 cases). For clinical pathological stages (FIGO, 2000), there were 37 cases of Stage I, 44 cases of Stage II, and 26 cases of Stage III or IV. With stromal involvement, 28 cases had infiltration no more than superficial myometrium and 79 cases had infiltration more than deep myometrium. Twenty-six cases had lymph node metastasis and 81 cases had no metastasis. Follow-up was carried out through telephone calls or letters. Survival time was defined as the time from diagnosis to death or to the final examination. Postoperative follow-up lasted over three years: 72 cases were followed-up more than one year and 44 cases more than three years, including 28 cases of survival and 16 cases of death due to tumor recurrence and/or metastasis.

Reagents and methods

The specimens were obtained from surgical resection. All tissues were formalin-fixed and paraffin-embedded. The cervical disease tissue microarrays containing 228 case specimens were used to determine survival and caspase-3 and p53 expression by immunohistochemistry (EnVision). Survivin rabbit-anti-human monoclonal antibody, caspase-3 mouse-anti-human monoclonal antibody and p53 mouse-anti-human monoclonal antibody were purchased from Gene Company Ltd. The EnVision detection kit was bought from Beijing Zhongshan Biological Reagent Company Ltd.. The working concentration of the primary antibody was 1: 50, and that of the remaining two antibodies was 1: 100. EnVision staining was performed. PBS was substituted for the primary antibody as a negative control, and the known positive slips served as positive controls.

Judgment of the results

Positive staining of survivin and caspase-3 expression was mainly located in the cytoplasm, while p53 was in the nucleus with brown-yellow granules. In each section, 5 high-power visual fields were randomly selected and observed. Two hundred cells in each visual field were counted. The staining was judged according to the percentage of the positive cells; no or positive cells < 5%, negative; positive cells 5%-20%, weakly positive; positive cells 20%-50%, moderately positive; positive cells > 50%, strongly positive.

Statistical Analysis

The SPSS 10.0 statistical software package was used to analyze the data. The chi-square test was performed to investigate the correlation between clinical variables and immunostaining. Kaplan-Meier’s method was used to illustrate the survival curve and the log-rank method test was used to test the difference of survival rate; \( p < 0.05 \) was considered statistically significant.

Results

Table 1 shows the expression of survivin, caspase-3 and p53 in different cervical tissue samples.

The results showed a significant correlation between the expressions of survivin and clinical staging, stromal involvement and lymph node metastasis \(( p < 0.05)\). However, there was no significant difference in survivin expression between different histological grading or types. The positive rate of caspase-3 was significantly different from histological grading \(( p < 0.05)\) and the positive expression of p53 was correlated with histological type and grading \(( p < 0.05)\). The expression of both caspase-3 and p53 was not related to clinical staging, stroma involvement and lymph node metastasis (Table 2, Figures 1-6).

Table 2. — Relationship between the expression of survivin, caspase-3, p53 and pathological features of cervical cancer (positive %).

<table>
<thead>
<tr>
<th>Pathological factors</th>
<th>n</th>
<th>Survivin</th>
<th>Caspase-3</th>
<th>p53</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>v</td>
<td>%</td>
<td>v</td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td>≤ 35</td>
<td>27</td>
<td>23</td>
<td>85.2</td>
<td>11</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>80</td>
<td>67</td>
<td>83.8</td>
<td>33</td>
</tr>
<tr>
<td><strong>Pathological types</strong></td>
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<tr>
<td>Squamous carcinoma</td>
<td>81</td>
<td>72</td>
<td>88.9</td>
<td>29</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>26</td>
<td>18</td>
<td>69.1</td>
<td>15</td>
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<td><strong>Pathological grades (SC)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>22</td>
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<td>II</td>
<td>44</td>
<td>39</td>
<td>88.6</td>
<td>16</td>
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<tr>
<td>III-IV</td>
<td>26</td>
<td>25</td>
<td>96.2</td>
<td>9</td>
</tr>
<tr>
<td><strong>Stromal involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤ superficial myometrium</td>
<td>28</td>
<td>19</td>
<td>67.9</td>
<td>15</td>
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<tr>
<td>≥ deep myometrium</td>
<td>79</td>
<td>71</td>
<td>89.9</td>
<td>29</td>
</tr>
<tr>
<td><strong>Lymphatic metastasis</strong></td>
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<td></td>
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<tr>
<td>no</td>
<td>81</td>
<td>64</td>
<td>79.0</td>
<td>35</td>
</tr>
<tr>
<td>yes</td>
<td>26</td>
<td>26</td>
<td>100.0</td>
<td>9</td>
</tr>
</tbody>
</table>
Figure 1.— Tissue microarray paraffin block and section of cervical cancer.

Figure 2.— H&E section of cervical squamous cell cancer by tissue microarray.

Figure 3.— Invasive squamous cell carcinoma grade 2 strongly positive for survivin in the nucleus and cytoplasm (survivin immunostaining).

Figure 4.— Cervical adenocarcinoma positive for survivin in the cytoplasm (survivin immunostaining).

Figure 5.— Squamous cell carcinoma grade 1 weakly positive for caspase-3 in the cytoplasm (caspase-3 immunostaining).

Figure 6.— Squamous cell carcinoma grade 2 interspersed positive for p53 in the nucleus (p53 immunostaining).
In 107 cervical cancer cases 29 cases were positive for the expression of caspase-3 in 90 cases of survivin-positive expression. In 17 cases of survivin-negative expression, 15 cases were positive for the expression of caspase-3. There was a significant difference between them ($p < 0.05$). In 90 cases positive for survivin expression, 74 cases were positive for p53 expression. In 17 cases negative for survivin expression, ten cases was positive for p53 expression. There was no significant difference between them ($p < 0.05$).

The relationship between the expression of survivin, caspase-3 and p53 in cervical cancer and 3-year survival rate are listed in Table 3 and Figures 7-9. The positive expression of survivin in the survival and deceased group showed a significant statistical difference ($p < 0.01$). There was also a significant difference in survival time between survivin expression and duration of survival by the log-rank method, whereas, the positive expression of caspase-3 and p53 showed no statistical difference in the follow-up data for three years and were unrelated to survival.

**Discussion**

Survivin, a novel apoptosis suppressive gene, is selectively expressed in tumors. It is closely correlated with apoptosis and cell cycle modulation. In addition, the overexpression of survivin could speed up the shift of cells from S G1 towards S, promoting cell proliferation. Survivin is highly expressed in most tumor tissues [9, 10]. Kim et al. and Yamamoto et al. found a gradually increased positive expression rate of survivin in the different tissues of invasion and metastasis of cervical cancer [11, 12]. In this study, the positive expression rate of survivin in the cervical cancer group was significantly higher than in the CIN group and cervicitis group. The significant correlations between survivin status and clinical staging, stromal involvement and lymph node metastasis were consistent with Kim and Yamamoto’ findings. Indications were that the survivin gene was involved in the development of cervical cancer, and closely related to the invasion and metastasis of cancer. However, the expression of survivin was not associated with the pathological types and pathological grade.
Caspase-3 is the most important member of the caspase family. It induces apoptosis. Shin et al. and others suggested that the development of cervical cancer was related to decreased caspase-3 expression inducing blockage of apoptosis [6, 13]. In the present study, the positive rate of caspase-3 was not associated with clinical staging, stromal involvement or lymph node metastasis, but was associated with histological grading. The positive inactivation of caspases might result in failing or delaying apoptosis, therefore the survival of damaged cells becomes prone to further genetic damage. Apparently, the defect of caspase-expression plays an important role in the tumorigenic process. Meanwhile, our study also revealed the expression of survivin in cervical cancer was negatively associated with that of caspase-3, meaning an adverse effect on cervical cancer.

p53 protein, the tumor suppressor, contributes to the controlling of cell cycle checkpoints and apoptosis. It is frequently lost or mutated in multiple types of human cancers [14]. In our study, the positive expression of p53 was correlated with histological type and grading in different clinicopathological characteristics. It indicated that the p53 gene is related to tumor-related anaplastic extent. The expression rate in clinical stage, stromal involvement and lymphatic metastasis has continued to increase, but is not statistically significant.

The positive expression rate of survivin in the deceased patient group was statistically significantly higher than that of the surviving group (p < 0.05), which indicates tumors with survivin over-expression have an unfavorable prognosis. There was a significant difference in survival time between survivin expression and length of survival by the log-rank method, whereas the expression level of caspase-3 and p53 in either the survival group or positive-control group showed no significant difference in comparison with the negative-control group. This demonstrates that caspase-3 and p53 were not related to tumor prognosis. Therefore, in our opinion, there is a correlation between survivin expression and tumor prognosis or the survival duration.

In conclusion, we have documented the expression of survivin, caspase-3 and p53 in the different clinicopathological features of cervical carcinoma, and the correlation with clinicopathological features and prognosis. The positive expression rate of survivin, caspase-3 and p53 in cervical cancer was significantly higher than in the CIN group and cervicitis group. These three genes play an important role in cervical carcinogenesis and could be very useful markers in identifying degree of malignancy and invasiveness of cervix cancer. Additionally, the log-rank test revealed that the expression of survivin was an independent prognostic indicator, suggesting a new target for the diagnosis of cervical cancer. Further studies are needed to investigate the role and mechanism of action of survivin, caspase-3 and p53 in cervical cancer development.

References


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Factors affecting recurrence and disease-free survival in granulosa cell tumors of the ovary

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Department of Obstetrics and Gynaecology, Istanbul Faculty of Medicine, Istanbul University, Istanbul (Turkey)

Introduction

Granulosa cell tumor (GCT) arising from the sex-cord stromal cells is an uncommon neoplasm of the ovary accounting for 2-5% of all ovarian cancers [1]. Characteristic indolent growth and large tumor size at diagnosis is typical. However, more than 80% are diagnosed as having International Federation of Gynecology and Obstetrics (FIGO) Stage I disease [2]. GCTs are divided into two groups based on clinical and histological characteristics: adult GCTs and juvenile GCTs. Most GCTs are of adult type and 95% of the patients are postpubertal [1]. Although primary surgical therapy is usually sufficient for cure in disease confined to the ovary, 25% of these patients may relapse even after long periods [3]. Different studies have pointed out stage, age at diagnosis, tumor size and presence of residual tumor after surgery to be affecting recurrence and prognosis [2, 4-7]. In this study, we have reviewed recurrence characteristics and prognostic factors in 12 recurrent cases treated for adult-type GCT in a university hospital setting.

Materials and Methods

A review of all ovarian cancer patients treated at Istanbul University, Istanbul Faculty of Medicine, Division of Gynaecologic Oncology from 1991 to 2006 revealed 43 cases of GCTs. All four cases of juvenile GCTs were left out of the study. All information was reevaluated and the clinical, pathological, surgical and postoperative treatment data extracted. All patients had at least an exploratory laparotomy and unilateral salpingo-oophorectomy. Only patients with complete information were included in the study. Follow-up data were obtained from current patient files or by telephone interviews with the patient or relatives. Finally, 39 patients with adult-type GCTs were included in the analysis.

Clinical symptoms, staging, treatment and follow-up were among the clinical parameters evaluated in terms of patient characteristics. Age, mean tumor diameter, menopausal status, presenting symptoms, presence of residual tumor and FIGO stage at diagnosis were evaluated as prognostic factors. Data for 12 recurrent cases were detailed by providing further information of primary treatment modality and extent, adjuvant therapy, time to relapse, site and additional treatment and status after recurrence.

Fisher’s exact and Mann-Whitney tests were used in assessing significance between observed values. Survival statistics were calculated by Kaplan Meier and Cox regression analysis. All statistical analysis of the data was done by using SigmaStat 3.5 software program (Aspire Software International, Ashburn, VA).

Results

We identified 39 adult-type GCTs, comprising 4.5% of all ovarian cancer cases treated as inpatients at our university hospital during the study period. The median age was 47 years (mean age 46.3 years; range, 14-81 years). The mean follow-up period of patients was 65 months. Abdominal pain and abnormal vaginal bleeding were the most common presenting symptoms at diagnosis (51.3% and 43.6%, respectively). Eighty-two percent of the patients had Stage I disease. Clinical findings of all patients are summarized in Table 1. Detailed distribution of patients according to stage, age and recurrence is outlined in Table 2.

Eight of the patients (21%) had their initial operation in another institution and were referred for follow-ups. Conservative unilateral salpingo-oophorectomy (USO) was performed in ten cases. Another two cases had total...
abdominal hysterectomy (TAH) along with USO. The rest (27 patients) had TAH with bilateral salpingo-oophorectomy (BSO) with surgical staging and/or additional resection. There were three patients who had residual disease despite debulking surgery. All of these patients had recurred and died of disease (DOD). Postoperative adjuvant chemotherapy was given in eight cases; although not standardized, chemotherapy mostly consisted of cisplatin, doxorubicin and cyclophosphamide.

The median follow-up period of GCT patients was 71 months (range 12-168 months). There were 12 cases of recurrence (30.8%) and seven of them died due to disease-related causes. The median follow-up period and median time to relapse was 103 and 57 months, respectively. The estimated disease-free survival for five years was 82%. Stage and presence of residual tumor were calculated to be the only associated risk factors for recurrence and prognosis ($p < 0.05$) (Tables 3 and 4).

The mean age of 12 cases who relapsed was 50.5 years. The stages were evenly divided between Stage I and III. There was no residual tumor left at the first operation in nine recurrent cases. The median time to relapse was 56.5 months, while the median survival after recurrence was 30.5 (2-94) months. The pelvis was the most common site of recurrence (8 patients). There were three patients with liver metastasis. Lymph node recurrence was encountered in two patients: one in the paraaortic area and another in the inguinal area. Of interest, there was one patient with intraabdominal and pelvic disease along with right Bartholin gland recurrence separate from other metastases. No standard treatment modality was preferred for recurrence. Seven of the patients received debulking surgery followed by adjuvant chemotherapy, whereas three received chemotherapy only due to disseminated disease. Of the two patients treated only by debulking surgery, one had complete resection of recurrent disease in the pelvis, but the other had incomplete resection of extensive recurrent disease extending to the sacrum despite having femorofemoral bypass surgery. Due to her poor overall status received no further chemotherapy after this surgery. Clinical data of recurrent patients is given in Table 5.

### Table 1. — Characteristics of all patients with adult-type GCT ($n = 39$).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age and range (years)</td>
<td>46.3 (14-81)</td>
</tr>
<tr>
<td>Mean follow up (months)</td>
<td>65</td>
</tr>
<tr>
<td>Mean tumor diameter (cm)</td>
<td>11.4</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>22 (56%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>17 (44%)</td>
</tr>
<tr>
<td>Presenting symptoms*</td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>2 (5.1%)</td>
</tr>
<tr>
<td>Abnormal vaginal bleeding</td>
<td>17 (43.6%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20 (51.3%)</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>7 (17.9%)</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>6 (15.4%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>32 (82.0%)</td>
</tr>
<tr>
<td>II</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>III</td>
<td>6 (15.4%)</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
</tr>
</tbody>
</table>

*There were some patients presenting with multiple symptoms.

### Table 2. — Detailed distribution of adult-type GCT patients according to stage and age.

<table>
<thead>
<tr>
<th>Age (decade)</th>
<th>Stage*</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd</td>
<td>I</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>–</td>
</tr>
<tr>
<td>3rd</td>
<td>I</td>
<td>3 (1)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>–</td>
</tr>
<tr>
<td>4th</td>
<td>I</td>
<td>9 (1)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>–</td>
</tr>
<tr>
<td>5th</td>
<td>I</td>
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<tr>
<td></td>
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<tr>
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<td>III</td>
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<tr>
<td>6th</td>
<td>I</td>
<td>5 (2)</td>
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<tr>
<td></td>
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<tr>
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<td>III</td>
<td>2 (2)</td>
</tr>
<tr>
<td>7th</td>
<td>I</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>3</td>
</tr>
<tr>
<td>8th</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>2 (2)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>3</td>
</tr>
<tr>
<td>9th</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>III</td>
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</tr>
</tbody>
</table>

*Number in parenthesis designates the number of patients who had recurrence.

### Table 3. — Risk factors for tumor recurrence.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Number of patients</th>
<th>Percentage recurred (%)</th>
<th>$p$ value</th>
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<tr>
<td>Age (years)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40</td>
<td>3/14</td>
<td>21</td>
<td>0.48</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>9/25</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>5/24</td>
<td>21</td>
<td>0.15</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>7/15</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10</td>
<td>9/29</td>
<td>31</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;10</td>
<td>3/10</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Early (I+II)</td>
<td>6/33</td>
<td>18</td>
<td>0.02</td>
</tr>
<tr>
<td>Advanced (III+IV)</td>
<td>6/6</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Residual tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3/3</td>
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<td>0.02</td>
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<tr>
<td>No</td>
<td>9/36</td>
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</tbody>
</table>

### Table 4. — Association of possible prognostic factors in adult-type GCT (univariate analysis).

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Number of patients</th>
<th>Mean DFS (months)</th>
<th>$p$ value</th>
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<td>Age (years)</td>
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<td></td>
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<tr>
<td>≤ 40</td>
<td>14</td>
<td>66</td>
<td>0.616</td>
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<tr>
<td>&gt; 40</td>
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<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>24</td>
<td>76</td>
<td>0.157</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>15</td>
<td>56</td>
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</tr>
<tr>
<td>Tumor size (cm)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10</td>
<td>29</td>
<td>66</td>
<td>0.407</td>
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<tr>
<td>&gt; 10</td>
<td>10</td>
<td>55</td>
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</tr>
<tr>
<td>Stage</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Early (I+II)</td>
<td>33</td>
<td>72</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Advanced (III+IV)</td>
<td>6</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Residual tumor</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
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<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>36</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

DFS: disease-free survival.
Factors affecting recurrence and disease-free survival in granulosa cell tumors of the ovary

A total of seven cases of the 12 recurrent cases eventually DOD (Table 5). The aforementioned 17-year-old patient (case 5) recurred 18 months after primary surgery and DOD two months after recurrence. Case 1 had a recurrence in the pelvis 22 months after initial diagnosis. She was treated by debulking surgery and adjuvant platinum containing chemotherapy. Twelve months after recurrence she developed disseminated abdominal wall and intraperitoneal metastases and received further chemotherapy. She DOD 58 months after recurrence. Case 2 had unresectable liver metastasis 36 months after diagnosis. She remained stable after combination chemotherapy until progressive disease involving the peritoneum and pelvic lymph nodes was identified. She died 61 months after recurrence. The second patient with liver metastases only after 66 months had a suboptimal debulking surgery plus chemotherapy (case 9). The disease progressed after eight months and she died 13 months after the diagnosis of liver metastases. The third patient with liver involvement also had paraaortic lymph node metastasis. She (case 3) relapsed after 65 months and the disease was unresectable. She received chemotherapy as her sole treatment and after 48 months, disease progressed to involve the lungs and spleen. She DOD 94 months after recurrence. Case 7 had metastatic disease in the pelvis and peritoneal cavity diagnosed 48 months after initial diagnosis despite treatment by surgery and chemotherapy. The last patient who had died was a 76-year-old woman who recurred after 65 months in the left inguinal lymph node. She had resection of the node which turned out to show a sarcomatous degeneration of GCT. Adjuvant chemotherapy was given but she presented with disseminated intraabdominal disease 16 months after her second surgery. She DOD 62 months after recurrence.

Of the five patients successfully treated for recurrence, four had complete resection of their recurrent tumor and three had received adjuvant platinum-containing combination chemotherapy. The other patient had two small isolated lesions in the pelvis and upper peritoneal cavity, hence received chemotherapy with a complete response (Table 5).

Discussion

GCTs of the ovary represent in excess of 70% of malignant sex cord-stromal tumors, adult GCTs being most common among them. GCTs are considered to be low-grade malignancies with 5-year survival rates approaching 80-95% when compared to epithelial ovarian tumors [2]. Although most of the cases have Stage I disease, the growth is indolent and shows no specific symptom indicating presence of tumor. In our study, the percentage of patients having Stage I disease was 82% and the median tumor diameter was 11.4 cm, indicating quite a lot of time had passed before diagnosis. Tumors most commonly cause nonspecific abdominal pain and/or vaginal bleeding due to hormone secretion which leads to diagnosis.

Despite prominence of Stage I disease at diagnosis, recurrence rates between 17-50% have been reported in the literature [3, 8-10]. Our 31% overall recurrence rate is in accordance with current data. Among risk factors for

Table 5. — Clinical outcome and descriptive data of the patients who had recurrent adult-type GCT.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Stage</th>
<th>Residual tumor</th>
<th>Primary treatment</th>
<th>Time to relapse (months)</th>
<th>Recurrence</th>
<th>Treatment after relapse</th>
<th>Status after recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>3C</td>
<td>Yes</td>
<td>TAH+BSO+Debulking</td>
<td>22</td>
<td>Pelvis</td>
<td>Surgery &amp; CTx</td>
<td>Progression at 12 months, DOD 58 months</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>3C</td>
<td>Yes</td>
<td>TAH+BSO+Debulking</td>
<td>36</td>
<td>Liver</td>
<td>CTx</td>
<td>Progression at 60 months, DOD 61 months</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>3C</td>
<td>Yes</td>
<td>TAH+BSO+Debulking</td>
<td>65</td>
<td>Liver and paraaortic lymph nodes</td>
<td>CTx</td>
<td>Progression at 48 months, DOD 94 months</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>1</td>
<td>No</td>
<td>USO</td>
<td>17</td>
<td>Pelvis and peritoneal cavity</td>
<td>CTx</td>
<td>Progression at 26 months, NED 26 months</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>1</td>
<td>No</td>
<td>USO</td>
<td>18</td>
<td>Pelvis extending to sacrum</td>
<td>Surgery (Debulking)</td>
<td>Progression at 1 month, DOD 2 months</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>1C</td>
<td>No</td>
<td>TAH+USO+Staging</td>
<td>38</td>
<td>Pelvis</td>
<td>Surgery</td>
<td>Progression at 2 months, DOD 70 months</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>3C</td>
<td>No</td>
<td>TAH+BSO+Staging</td>
<td>48</td>
<td>Pelvis and peritoneal cavity</td>
<td>Surgery &amp; CTx</td>
<td>Progression at 2 months, DOD 4 months</td>
</tr>
<tr>
<td>8</td>
<td>76</td>
<td>3B</td>
<td>No</td>
<td>TAH+BSO+Staging</td>
<td>65</td>
<td>Left inguinal lymph node (sarcomatous degeneration)</td>
<td>Surgery &amp; CTx</td>
<td>Progression at 8 months, DOD 62 months</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>3C</td>
<td>No</td>
<td>TAH+BSO+Staging</td>
<td>66</td>
<td>Liver</td>
<td>Surgery (sub-optimal) &amp; CTx</td>
<td>Progression at 16 and 30th months, both optimally debulked, NED at 35 months</td>
</tr>
<tr>
<td>10</td>
<td>57</td>
<td>1</td>
<td>No</td>
<td>TAH+BSO</td>
<td>84</td>
<td>Pelvis</td>
<td>Surgery &amp; CTx</td>
<td>NED 10 months</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>1C</td>
<td>No</td>
<td>TAH+BSO+Staging</td>
<td>115</td>
<td>Pelvis, Peritoneal cavity, Bartholin gland</td>
<td>Surgery &amp; CTx</td>
<td>NED 20 months</td>
</tr>
<tr>
<td>12</td>
<td>55</td>
<td>1A</td>
<td>No</td>
<td>TAH+BSO+Staging</td>
<td>168</td>
<td>Pelvis</td>
<td>Surgery &amp; CTx</td>
<td>NED 20 months</td>
</tr>
</tbody>
</table>

CTx: chemotherapy; DOD: died of disease; NED: no evidence of disease; TAH: total abdominal hysterectomy; USO: unilateral salpingo-oophorectomy; BSO: bilateral salpingo-oophorectomy.
recurrence, stage at diagnosis has been found to be the most important factor [3]. In our series, of 32 patients with Stage I disease, only six cases (19%) had recurrence; whereas of six patients with Stage III disease, 100% had recurrence. In other words, patients with Stage III disease had recurred eventually. When evaluated as a risk factor for recurrence, stage as well as presence of residual tumor were significantly associated with recurrence ($p = 0.02$) in our paper (Table 3).

Lee et al. have evaluated the clinical features of recurrent GCTs with more than ten cases and they found that the pelvis seems to be the most common site of recurrence (55%) [2]. Extra-pelvis metastases were also common (around 48%) in that study. Liver metastasis was found to be limited to only 6% (9/149) of the patients. Similarly, the pelvis was the most common site of recurrence in our series (67%) followed by extra-pelvis (58%); but we encountered much more liver metastases in our series reaching 25% (3/12). Interestingly, two of these three cases were isolated liver metastases. The limited number of patients in our study may have caused this discrepancy.

There are a number of suggested prognostic factors operating in GCTs like stage, size of tumor, age, rupture of tumor, molecular markers but there is no conclusive evidence [2, 7, 11–13]. Stage and presence of residual disease stand out to be the most significant prognostic factors in the current literature. Five-year survival in Stage III–IV disease was reported to be around 22–50% and it factors in the current literature. Five-year survival in Stage disease stand out to be the most significant prognostic evidence [2, 7, 11–13].

Lee et al. also reported that both stage and residual disease affected prognosis in univariate analysis, but that residual disease was the only factor operating in multivariate analysis. According to the Alberta Cancer Registry, residual disease was also the most important prognostic factor [14]. On the contrary, Chan et al. reported that age less than 50 years and small tumor size affected prognosis in addition to absence of residual disease [12]. We have evaluated age, menopausal status, tumor size, stage and presence of residual disease for prognostic factors in our study and found that residual disease and stage may affect prognosis in univariate analysis (Table 4).

Retroperitoneal nodal metastasis in primary and recurrent GCTs has been addressed by Abu-Rustum et al. [8]. Of 68 patients with GCTs, 16 had pelvic lymph node sampling and 13 also had paraaortic lymph node sampling at primary or restaging surgery. The median number of lymph nodes removed was ten for pelvis and four for paraaortic sites. All lymph node samples were negative. The authors concluded that nodal metastasis was rarely reported at initial diagnosis. This conclusion was also in accordance with a rare (5.5%) nodal metastasis rate during primary surgery reported by Ayhan et al. [15]. We encounter did not any lymph node metastasis in 22 patients having some form of lymph node sampling in our study. However, Abu-Rustum et al. in the same paper reported around 15% of recurrences were in the retroperitoneal nodal area during the first recurrence. They concluded that since the majority of the cases go unstaged, occult lymph node metastasis might be responsible for recurrences in nodes. They have recommended comprehensive surgical staging in the initial management of GCT. Recently, the role of routine lymphadenectomy in GCT has been questioned by Brown et al. in a study performed on 257 patients [16]. Although the study group was composed of all types of ovarian stromal tumors, 58 patients had lymph node sampling during primary surgery and none had positive nodes. The authors suggested that GCTs do not spread primarily by the lymphatics but by hematogenous and direct routes. In 117 patients who have recurred in this series, only six had lymph node metastasis. In five of these six patients, metastases were multiple. The authors concluded that lymph node metastases in these patients were due to secondary spread of the tumor. In our series, there were two patients with lymph node recurrence: one in the paraaortic area and one in the inguinal area (17%). Although the percentages between all of these studies including ours are similar, explanations and recommendations are different. Multicentric prospective studies are needed to resolve this issue.

In GCT, optimal treatment for relapse is not known [17]. Surgical debulking has been commonly used and may help prolonging survival in recurrent patients [2, 14]. Repetitive debulking in multiple recurrences may also achieve longer survival in these patients [2]. Our results comply with the literature.

Conservative surgery in young patients desiring to retain their fertility is appropriate, especially in early-stage disease. If there were no residuals, no difference was found in terms of disease-free survival rates between patients treated by debulking TAH and BSO or by USO [2]. In our study, only two patients have recurred among ten patients treated by conservative surgery. One recurred in the pelvis and extended into the presacral area and had debulking surgery 18 months after initial diagnosis. Due to incomplete resection, she received chemotherapy and succumbed to disease and to complications of chemotherapy two months after this second operation. The other patient had slight recurrent disease in the pelvis and upper abdominal cavity. She refused to undergo surgery and completely responded to the given chemotherapy. She had no evidence of disease 26 months after recurrence.

The most important limitation of our study is that the number of patients is small. Owing to the relative low incidence of GCTs, it is very hard for a single center to come up with a study comprising a large number of patients. Multicentric studies are needed in this aspect. Due to lack of data, histologic and molecular factors that might affect prognosis were also not studied.

In conclusion, based on the results of this current series, women with adult-type GCT of the ovary have excellent survival and most are diagnosed in early stages. Recurrences seem to be associated with stage and presence of residual tumor during primary surgery. Although rarely present during diagnosis, lymph node metastasis may be more common in recurrent disease.
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Ovarian carcinoma patients – life quality analysis in the postoperative period – how to improve it?

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Summary

Purpose of investigation: The objective of this research was to analyze the quality of life of patients with advanced ovarian carcinoma in the period following radical surgery and application of chemotherapy. Methods: A random selection method was used to choose 30 patients who had previously filled out the QLQ-C30 health questionnaire. Data obtained from questionnaires were statistically analyzed. Results: The percentage of the general health scores were the highest in the bottom third of the scale, where 21.9% of the patients self-scored at 0. Financial difficulties were scored the lowest at 65.6%. The impairment of physical functioning was reported by 21.9% of patients, where the score for impact of this physical impairment was reported at 0 by 18.8%, and the impact of cognitive impairment was scored at 0 by 56.3%. Nausea, vomiting and loss of appetite were completely affecting normal daily functioning of 40.6% patients, constipation was present in 59.4% cases and diarrhea in as many as 71.9% patients; 15.6% patients reported being in continuous pain. Conclusion: Health questionnaires should be used because they can help identify patients prone to develop psychological problems and symptoms. Early recognition of patients prone to psychosomatic problems would allow doctors to help maintain and/or improve on patients’ quality of life.

Key words: Quality of life; Ovarian carcinoma; Health questionnaires.

Introduction

A vast number of scientists around the world are working continuously on issues related to early diagnostics and treatment of ovarian carcinoma. The progress of oncology followed by application of new chemotherapy modalities has brought about the lengthening of patient life span [1]. Thus, according to recent data contained in the available references, over 40% of patients survive longer than five years [2, 3]. This practically means that, during the period of treatment, remission or relapse, such patients more or less every day are faced with distressing symptoms of the disease; this changes their psychological, social and emotional state i.e., more generally speaking, significantly influences not only the quality of life of patients but of their families as well.

Recently increasing attention has been paid to improvement of patient quality of life during treatment and remission periods. In order to gain insight into the most frequent psychosomatic discomforts which influence patient quality of life, corresponding health questionnaires have been made. They have been thoroughly adapted to all social groups of disease-affected women and validated for each language zone separately.

The following psychological symptoms which influence quality of life during disease duration and the treatment period have been described in the references up to now: depression, exhaustion, anxiety and fear of death [4].

The objective of this research was to analyze the quality of life of patients with advanced ovarian carcinoma in the period following radical surgery and application of chemotherapy.

Results

Before performing the life quality analysis based on the health questionnaire, reliability of measurement instruments had to be analyzed as well as individual reliability and validity of the scores. Validity of the scales was tested via Cronbach’s analysis. A high value of Cronbach alpha coefficient has been obtained – for this questionnaire it equalled $\alpha = 0.844$. Such a high value of Cronbach alpha coefficient is an indicator of questionnaire reliability.

The table given below shows how patients assessed their health according to the QLQ-C30 questionnaire, i.e., according to dimensions contained in this questionnaire (Table 1).

The lowest grade for physical functioning dimension (equal to 0) was present in 21.9% patients, while the low-
Table 1. — *QLQ-C 30 questionnaire dimensions and relative scores.*

<table>
<thead>
<tr>
<th>Dimension</th>
<th>x</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>22.81</td>
<td>17.22</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Physical role</td>
<td>32.81</td>
<td>23.91</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Emotional role</td>
<td>29.68</td>
<td>21.23</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Cognitive role</td>
<td>12.10</td>
<td>19.43</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Social role</td>
<td>23.04</td>
<td>23.13</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>General health</td>
<td>37.50</td>
<td>27.67</td>
<td>0</td>
<td>83.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47.56</td>
<td>28.81</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>20.31</td>
<td>23.46</td>
<td>0</td>
<td>83.3</td>
</tr>
<tr>
<td>Physical pain</td>
<td>33.33</td>
<td>23.46</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>40.62</td>
<td>34.63</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Insomnia</td>
<td>36.45</td>
<td>39.12</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>40.62</td>
<td>41.24</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Constipation</td>
<td>21.87</td>
<td>31.23</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14.58</td>
<td>28.00</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Financial problems</td>
<td>19.79</td>
<td>33.71</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

est grade (equal to 0) for physical role dimension was present in 18.8% patients. A score equal to zero for social role dimension was present in almost one-third of the patients, i.e. 28.1%, emotional role was evaluated with zero by 12.5% patients. As many as 56.3% patients graded cognitive function with zero.

The lowest score for nausea and vomiting was present in as many as 40.6% patients, appetite loss and insomnia also 40.6% patients, while constipation problems were graded with zero by as many as 59.4% patients, and diarrhea by 71.9% patients. The lowest score for pain was present in 15.6% patients while dyspnea was present in 28.1% patients.

Financial problems were given the lowest score by 63.6% patients.

One-third of patients reported that physical functioning, social role and emotional role were equal to the lowest score, i.e. zero or very poor. More than a third of patients complained of nausea, vomiting, appetite loss, constipation and diarrhea and as many as 59.4% and 71.9% patients, respectively, graded these dimensions with zero, which is also very poor.

General health received score of zero from 21.9% patients, while general health was evaluated as average by 12.5% patients.

Discussion

This research has shown that subjective assessment of our patients’ life quality ranged from poor to average on the analyzed life quality scale. Furthermore it shows that patients were accepting of such state.

Assessment and detailed overview of all factors which influence quality of life of patients suffering from ovarian carcinoma can help overcome related difficulties and help improve patient quality of life during the survival period.

This is why in recent years a trend is present in the literature which calls for analysis of quality of patient’s life in each phase of the disease, with special emphasis on the dynamics of deterioration of quality of life. It is also important to analyze the factors which cause this deterioration, in order to be able to act preventively upon these factors, i.e. to influence in a positive way the improvement of life quality during all phases of the disease or survival period [5].

According to data available from the references, the level of knowledge women have about ovarian carcinoma, its symptoms, and diagnosis is not at all satisfactory. As a matter of fact, it is very low [6]. This is why the quality of life is changed on the psychological level, the level of anxiety and depression is elevated while emotional and cognitive parameters have a lower score. In our population, these parameters were accompanied by the parameters relative to the physical role and physical functioning as well as social and financial problems. In other, bigger and more developed populations, social and economic problems are also quoted as the reason for poor quality of life not only of patients but of their families as well [7, 5, 8].

Thus, it is very important to work on educating women of all social levels about risks, symptoms and feasibility of ovarian carcinoma diagnostics. If disease does happen, it is necessary to define in a timely manner the group of patients who are at risk of developing psychological symptoms during treatment or course of the disease, and who might be under greater risk of life quality deterioration caused by the illness [9, 10].

Timely assessment of these parameters and clinical indicators can have a positive influence on the quality of life of patients [11, 12].

Conclusion

Detailed explanations and adequate medical information about the disease and its treatment, development of psychosomatic and psychological discomfort during disease duration and treatment as well as the patients’ need to cope with facts and accept their current health condition accordingly, can have a positive influence on further course of the illness and on the quality of life during the survival period.

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Internal jugular vein thrombosis as paraneoplastic syndrome of primary ovarian non-Hodgkin’s lymphoma

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Summary
Primary malignant lymphoma involving the ovaries is extremely rare. We present a unique case of a primary Non-Hodgkin’s lymphoma (NHL) of both ovaries, preceded by an internal jugular vein trombosis (IJVT) as paraneoplastic syndrome. Currently, 36 months after surgical treatment of this FIGO Stage Ib, Ann Arbor Stage 2E NHL, the patient is clinically free of disease. Based on this case and a review of the literature it is concluded that paraneoplastic syndromes like spontaneous IJVT should prompt the clinician to make a thorough diagnostic work-up in search of an underlying malignancy, including the female genital tract.

Key words: Primary ovarian lymphoma; Internal jugular vein thrombosis; Non-Hodgkin’s lymphoma; Extranodal lymphoma; Paraneoplastic syndrome.

Introduction
Paraneoplasia may be the presenting symptom of underlying malignancy and can affect almost any organ system. Although gynecologic malignancies are not frequently associated with paraneoplastic syndromes, malignant lymphomas are [1, 2]. It is obvious that early recognition of these syndromes is essential. In this case report, we describe a unique case of a non-Hodgkin’s lymphoma located solitarily in the ovaries preceded by a spontaneous internal jugularis vein thrombosis (IJVT) as paraneoplastic syndrome.

Case Report
A 52-year-old postmenopausal woman presented at the Department of Internal Medicine with a red and swollen right arm, three days after noticing a swelling in the right side of her neck. Besides hypothyroidism and hot flushes adequately treated with levothyroxin and clonidin, the patient’s history was uneventful. No abdominal complaints, weight loss, fever or night sweating were reported. Physical examination revealed a swollen right arm and a smooth and mobile swelling of approximately 3 cm in the right part of her neck, just below the thyroid gland. Ultrasonographic examination showed a IJVT on the right side. Computed tomography (CT) of the neck and abdomen revealed a homogenous pelvic tumor measuring 10 x 7.5 cm., right pleural effusion and ascites, without signs of any suspicious lymph node enlargement. Pleural centesis revealed no abnormal cells. A complete blood count and tumor marker panel were all within normal limits.

Consequently, a right-sided mobile multilobulated, predominantly solid ovarian tumor with a diameter of approximately 8 x 7 cm and normal postmenopausal left ovary were removed by explorative laparotomy (Figure 3a). Intraoperative frozen section analysis was inconclusive and thorough inspection and palpation of the abdominal cavity revealed no abnormalities nor retroperitoneal lymph node enlargement. Definitive histopathology mentioned a low-grade (grade 2) follicular B-cell non-Hodgkin’s lymphoma localized in both ovaries (Figure 3b). Immunostaining was positive for CD 45, CD 20, CD 79a, CD 10, bcl-2, bcl-6 and negative for CD 5, CD 23, CD 30, CD 56, CD 99, CD 117, cycline D1, multiple epithelial and neuroendocrine markers, vimentin, inhibit and PLAP (Figure 3c, 1-4). Ki-67 (MIB-1) was positive in 20-30% of tumor cell nuclei. Cytopathology of ascites showed no abnormal cells. Postoperative peripheral blood and bone marrow biopsy analyses showed no abnormal cells.

The disease was staged as FIGO Stage Ib, Ann Arbor Stage He NHL. Since this extranodal lymphoma was classified as an indolent lymphoma within the WHO system, a policy of “watchful waiting” was chosen and consequently no additional chemotherapy was administered. Until now, 36 months postoperatively, the patient has been well without clinical evidence of disease.

Discussion
About one-third of NHLs arise from other sites than the lymphatic system and can arise in almost every organ, although the presentation appears to cluster in a few sites such as the skin, stomach, brain, and the small intestine. Diagnosis and appropriate treatment of extranodal lym-
phomas are complicated by its relative rarity and by the fact that clinical outcome as well as therapeutic approach may differ.

Although the ovary is the most frequent site of NHL involvement of the genital tract, a true primary ovarian Non-Hodgkin’s lymphoma (PONHL) is a very rare condition, accounting for only 0.5% of all non-Hodgkin lymphoma’s and 1.5% of all ovarian neoplasms [3-5]. Malignant lymphoid cells may occur in the ovary either as a true primary neoplasm or as a secondary manifestation of disseminated occult or known disease. According to the diagnostic criteria of Fox et al. less than 10% of all ovarian lymphomas reported, have been located primarily arising in the ovary [3]. However, Paladugu et al. already suggested these criteria to be insufficiently stringent and proposed there should also be a disease-free interval following treatment of the ovarian lesion by surgery alone [4]. Obviously, our case with an uneventful follow-up of 36 months after surgery does fulfill all four criteria (Table 1).

Presenting symptoms or signs of PONHL are identical with those involving epithelial neoplasms. So-called B-symptoms as fever, night sweats or otherwise unexplained weight loss are noted in 10-33% of cases [3-5]. The diagnosis of PONHL is seldom suspected preoperatively because the combination of a pelvic mass, ascites, pleural effusion and/or elevated CA-125 is much more common in advanced epithelial ovarian cancer [6]. In most cases however, a true PONHL is detected by routine radiologic studies or an incidental finding. Bilateral ovarian involvement, as was the case in our patient, was observed in 36-71% of reported patients [3-6]. Intraoperative diagnosis of PONHL on frozen section analysis can be extremely difficult. Definitive diagnosis is for an important part based on extensive immunohistochemical-profiling, differentiating PONHL among others from granulosa cell tumor, dysgerminoma, small cell carcinoma of hypercalcemic type, granulocytic sarcoma, poorly differentiated surface epithelial or metastatic sarcoma. The majority of primary lymphomas are non-Hodgkin’s lymphomas, mostly of B-cell origin. CD-10, bcl-2 and/or BCL-6 are usually expressed in follicular type NHL, as in the presented case.

As the classification and staging systems of ovarian lymphomas have not been used constantly, and since immunophenotyping data are not available in all studies, the literature regarding management or prognosis of this rare manifestation is confusing [3-7]. In this case it was decided to opt for a policy of “watchful waiting” and to refrain from adjuvant chemotherapy, in accordance with the guidelines for nodal indolent lymphomas.

To our knowledge, this is the first reported case of PONHL preceded by internal jugular vein thrombosis (IJVT) as paraneoplastic syndrome. In 1995, Hines et al. 

Table 1. — Criteria for the diagnosis of primary ovarian lymphoma, according to Fox et al. [3] and Paladugu et al. [4].

1. At the time of diagnosis, the lymphoma is clinically confined to the ovary and full investigation fails to reveal evidence of lymphoma elsewhere.
2. The peripheral blood and bone marrow should not contain any abnormal cells.
3. At least several months should have elapsed between the appearance of the ovarian and extra-ovarian lymphomatous lesions.
4. A disease-free interval following treatment of the ovarian lesion by surgery alone.
Internal jugular vein thrombosis as paraneoplastic syndrome of primary ovarian non-Hodgkin’s lymphoma

Figure 3a. — Macroscopic appearance of the sectioned surface of right-sided multilobulated ovarian tumor with a predominantly solid tanned appearance.

Figure 3b. — Vaguely nodular growth pattern of follicular lymphoma cells (H&E x 50).

Figure 3c. — Immunostaining of follicular lymphoma cells expressing CD 20 (1 x 50), strongly positive for bcl-2 (2 x 50), positive for bcl-6 (3 x 50) and weakly positive for CD 10 (4 x 100).
reported IJVT associated with a synchronous Stage II clear cell ovarian/Stage I endometrial cancer [8]. Usually, IJVT is associated with trauma, infection, head, neck and thoracic malignancies, central venous catheterization or ovarian hyperstimulation. Spontaneous IJVT is, although extremely rare, well known as paraneoplastic disorder [9].

A paraneoplastic syndrome is defined as a constellation of symptoms and signs that are not directly caused by the primary or metastatic tumor. Although not frequently diagnosed with gynecologic malignancies, 24 paraneoplastic syndromes have been associated; of these disseminated intravascular coagulation and hypercalcemia are the most frequently reported [2]. Autoimmune disorders are the common basis of the many and diverse paraneoplastic disorders associated with lymphoproliferative disorders, with a predomination of B-cell neoplasms. The main anatomic systems affected by paraneoplastic syndromes are the CNS, hematopoietic, musculoskeletal, dermal, endocrine and vascular systems. Vascular paraneoplastic manifestations of gynecologic neoplasms are disseminated intravascular coagulopathy and thrombophlebitis/thrombosis. Thrombosis may be solitary or migratory (Trousseau sign) and may affect superficial as well as deep veins in unusual sites such as the arms and chest [10]. Examples are thrombosis affecting the liver, superior vena cava and vena jugularis and/or subclavia as was the case in our patient.

The pathophysiology of most paraneoplastic syndromes is not clear. Hematologic syndromes associated with most solid tumors are less well characterized than endocrine syndromes, because the ectopic hormones or cytokines leading to blood hypercoagulability and consequently venous thrombosis have not been identified until now. In general, approximately 15% of patients who develop spontaneous deep venous thrombosis or pulmonary embolism have an underlying diagnosis of cancer [1]. However, with IJVT 60% to 70% of associated malignancy has been reported, mostly thoracic, gastric or pancreatic.

In conclusion, we present a unique case of primary ovarian B-cell non-Hodgkin’s lymphoma preceded by IJVT as paraneoplastic syndrome. It is advised that clinicians confronted with a spontaneous IJVT should be highly suspicious of an underlying malignancy, obviously also including the female genital tract.

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Primary mucinous adenocarcinoma of the vagina

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Summary

Purpose: Primary mucinous adenocarcinoma of the vagina is a rare disease which is characterized by aggressiveness and poor prognosis because of its rapid growth and recurrence, its frequent distant metastases, and its relative resistance to conventional treatment modalities including surgery, radiotherapy, and chemotherapy. We report a case of advanced stage primary mucinous adenocarcinoma of the vagina that showed a highly aggressive course and resistance to combination chemotherapy with paclitaxel and carboplatin. Case: A 46-year-old multigravid Japanese woman was admitted to our hospital to be treated for Stage IVb primary mucinous adenocarcinoma of the vagina. She had no history of in utero exposure to diethylstilbestrol. She was treated by two courses of neoadjuvant chemotherapy with tri-weekly paclitaxel and carboplatin, which were not effective. Subsequently, total pelvic exenteration with pelvic lymphadenectomy was performed. However, the disease progressed rapidly and the patient died five months after the initial treatment. Conclusion: Because of its rarity, little is known about the behavior of primary mucinous adenocarcinoma of the vagina. Additional data about patients with this rare tumor should be collected and analyzed in an attempt to elucidate its prognostic factors, characteristics, optimal treatment, and outcome.

Key words: Primary vaginal cancer; Mucinous adenocarcinoma; Treatment.

Introduction

Primary carcinoma of the vagina is rare, constituting only about 1-2% of all gynecologic cancers [1, 2]. Adenocarcinoma, although much less common than squamous cell carcinoma, is the second most common primary cancer of the vagina, and represents about 5-15% of all vaginal carcinomas [1, 3]. Primary vaginal adenocarcinomas are rare neoplasms that can be divided into two categories: those associated with maternal diethylstilbestrol (DES) exposure, giving rise to clear cell carcinomas [4] and those unassociated with DES exposure. The latter neoplasms are seen in the late reproductive and post-menopausal years and have been estimated to account for only 4.7-9.6% of all vaginal carcinomas [5].

Various histologic subtypes of DES-unrelated primary vaginal adenocarcinoma are now recognized, including clear cell, [2] endometrioid, [2] serous, [6] and mucinous types [7-9]. Mucinous adenocarcinomas may resemble typical endocervical [10] or intestinal [11] adenocarcinomas. The histologic appearance of these tumors in the vagina is similar to that of their counterparts in the cervix. Vaginal adenocarcinoma of the intestinal type is rare [5, 11-13].

We report a case of primary mucinous adenocarcinoma of the vagina with aggressive behavior and review the cases of this rare tumor reported in the English literature.

Case Report

A 46-year-old multigravid Japanese woman was admitted to our hospital with a two-week history of atypical vaginal bleeding. She had undergone total hysterectomy and bilateral salpingo-oophorectomy for endometriosis ten months previously. The patient had never received any hormonal therapy. There was also no history of antenatal exposure to DES. Gynecological and rectal examinations showed a macroscopic vaginal mass (4 cm in diameter) at the right vaginal stump, which had infiltrated the right cardinal ligament. Bilateral inguinal and femoral lymph nodes were not evident. The pathological diagnosis of a punch biopsy taken from the vaginal tumor was mucinous carcinoma (Figure 1). No distant metastasis was detected by chest X-ray, intravenous pyelogram, cystoscopy, or colon fiberscopy. Magnetic resonance imaging revealed an upper vaginal mass (5.5 x 5.4 x 5.1 cm) with relatively high intensity in T1-weighted images and high intensity in T2-weighted images (Figure 2). Computed tomography revealed an irregular mass with contrast enhancement in the upper vagina with multiple pelvic lymph node and liver metastases. The patient was diag-

Figure 1. — Histological findings of the biopsied specimen (H&E x100). The tumor showed appearances typical of mucinous adenocarcinoma and was composed of a tubular gland lined by pseudostratified malignant columnar epithelial cells.
After the diagnosis, she was treated by two courses of neoadjuvant chemotherapy with tri-weekly paclitaxel (180 mg/m²) and carboplatin (area under the curve of 6.0 mg min/ml calculated by the Calvert formula), which were not effective. Subsequently, total pelvic exenteration with pelvic lymphadenectomy was performed. The disease progressed rapidly and the patient died five months after the initial treatment.

Discussion

As summarized in Table 1, we found only ten cases of primary mucinous adenocarcinoma of the vagina that have been reported in detail [5, 7-9, 11-14]. The median age of the ten patients was 45.8 years (range: 34-58 years). Five of the six patients were multiparous. Two of the nine patients had a history of in utero DES exposure. Five of the nine patients never experienced recurrence during the follow-up period.

Due to the rare occurrence of vaginal adenocarcinoma in general, data concerning its natural history, prognostic factors, and treatment are derived from small retrospective studies. Prognoses for vaginal cancers in general are stage-related [16]. It was reported, however, that adenocarcinomas of the vagina in general tend to show an aggressive course, recur rapidly, metastasize widely, and result in a fatal outcome more often than do the clear cell or squamous types. More recent evidence and analysis, however, have contradicted this generalization and failed to substantiate these earlier reports [17]. Treatment
choices are often influenced by disease extent and individual physicians, and institutional preferences. Therapy most often consists of primary radiotherapy or radical surgery with or without subsequent radiotherapy. Surgery alone was used in about half the cases of Stage I disease. Radical surgery may be appropriate management for Stages I and II cancer arising in the proximal vagina amenable to curative resection by the radical hysterectomy procedure. In patients with nonmetastatic Stage IV disease, exenterative surgery should be considered [17]. Radiation therapy, however, is probably more suitable for the majority of patients with vaginal cancers, especially for those with cancer arising in the distal vagina [5]. The results of these therapies, however, do not appear to be as successful as comparable management of squamous cell carcinoma of the vagina.

In conclusion, we have presented a case of advanced-stage primary mucinous adenocarcinoma of the vagina. The behavior of the tumor in the present case was highly aggressive and did not respond to chemotherapy with paclitaxel and carboplatin. Additional data about patients with this rare tumor should be collected and analyzed in an attempt to define the prognostic factors, characteristics, optimal treatment, and outcome.

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Primary yolk sac tumor of the omentum: a case report and literature review

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Summary

Background: Yolk sac tumor (YST) is the second most common malignant ovarian germ cell tumor, while a YST arising in the omentum is an exceedingly rare malignancy. Case: A 44-year-old woman was admitted with a history of abdominal distension of a month’s duration. The alpha-fetoprotein (AFP) serum level was elevated to 27,612 ng/ml, and CT scanning reported an obviously thickened omentum. Explorative findings revealed a large omental mass with a small implantation on the surface of the left ovary. Histological evaluation of the specimen after surgery exhibited typical patterns of YST, and the specimen was stained for AFP, cytokeratin, and placental alkaline phosphatase. The patient was treated with total abdominal hysterectomy with bilateral salpingooopherectomy and infracolic omentectomy followed by four cycles of bleomycin, etoposide, and cisplatin combination chemotherapy. She has remained free of the disease for seven months after completion of therapy. The subject of YST arising in the omentum is reviewed. Conclusion: This is the fourth case of primary omental YST in females. The case of omental YST must be seriously considered once the tumor shows omentum thickening with elevated AFP serum levels.

Key words: Yolk sac tumor; Omentum.

Introduction

Yolk sac tumor (YST), also known as endodermal sinus tumor, was first recognized as a distinct entity by Teilum [1]. It is a malignant germ cell tumor that simulates the yolk sac and is characterized by an elevated production of alpha-fetoprotein (AFP). Although most YSTs usually occur in the testis and ovary, about 20% manifest outside the genital tract, including in the mediastinum, sacrococcygeal region, cervix, vulva, pelvis, and retroperitoneum [2]. Omental YST is an exceedingly rare malignancy. To our knowledge, this is the fourth report of YST originating from the omentum in a female.

Case Report

A 44-year-old woman, para 1-0-7-1, visited the First Affiliated Hospital of Zhejiang University exhibiting abdominal distension symptoms of one month’s duration. Her menstrual cycle was 30 days with normal flow and the last abortion had been ten years before. She denied any family medical history of malignant disease. On pelvic examination, the mass or uterus could not be palpated due to ascites. The patient’s abdomen bulged, making it appear similar to a full-term pregnancy, and it felt painful under light pressure. Ultrasonography (US) showed a large amount of ascites and multiple low echo homogenous solid masses on the pelvic wall. The largest mass was 3.3 cm in diameter (Figure 1). The uterus and adnexa had no enclosed mass. Computerized tomography (CT) scan revealed an obviously thickened omentum and nodular mass on the peritoneum, greater omentum, mesentery, intestinal surface, and left adnexa (Figure 2). The largest single mass was located in the greater omentum with a 3.9 cm diameter and showed highly heterogeneous enhancement after administration of contrast material. Scans of the liver, gall bladder, spleen, pancreas, kidney, bladder, stomach, uterus, and ovaries were normal. The AFP serum level was elevated to 27,612 ng/ml (normal < 10 ng/ml). The CA-125 serum level was 334.9 U/ml (normal < 25 U/ml), whereas the ß-HCG and carcinoembryonic antigen (CEA) levels were within the normal range. Cytology of a specimen of peritoneal fluid withdrawn under US control was positive for highly undifferentiated adenocarcinoma cells.

During exploratory laparotomy, a 23 cm tawny solid multilobulated mass, weighing 3100 g, was found in the greater omentum. Implantation foci with a 0.1-2.0 cm diameter could be seen on the pelvic peritoneum, mesentery surface, paracolic sulci, liver surface, and rectovaginal pouch (Figure 3). The right ovary and bilateral fallopian tubes were normal in size. The surface of the left ovary reflected implanted tumors in three areas with each tumor measuring 0.3 cm in diameter. The result of frozen biopsy from an omental mass was adenocarcinoma. Then, infracolic omentectomy, total hysterectomy, bilateral salpingooopherectomy, and cytoreductive surgery were performed with no macroscopic residual disease.

Under microscopic observation, tumor cells grew in different forms as adenoid, mammillary, or solid flake. Schiller-Duval bodies (Figure 4) could be seen, and many mitoses were observed. However, interfibrillar substance was rare. The tumor implanted on the left ovarian surface. Immunohistochemical studies showed cellular positivity for AFP, cytokeratin (CK), placental alkaline phosphatase (PAP), P53, and cell proliferation-associated antigen (Ki67). Staining of the epithelial membrane antigen (EMA), CK7, CK20, CD34, HCG, CA-125, vimentin, calcium binding protein (CBP), estrogen receptor (ER), and progesterone receptor (PR) were negative.

AFP serum value on the first day after surgery was 8944.3 ng/ml. Combined chemotherapy (BEP regimen) consisting of cisplatin (20 mg/m2 for 5 consecutive days), etoposide (100 mg/m2 for 5 consecutive days), and bleomycin (18 mg IM on days 2, 9, and 16) was given one week later every three weeks. Chemotherapy was repeated for four cycles. Before the second course of treatment, the AFP serum value dropped to 8.0 ng/ml. The patient was followed-up for seven months without clinical and radiological evidence of recurrence.
Discussion

YST is a highly malignant germ cell tumor that grows rapidly and metastasizes early through lymphatic and hematogenous routes [3]. It is the second most common malignant ovarian germ cell tumor after dysgerminoma and accounts for approximately 1% of all ovarian malignancies [4]. The case of omental YST is even more rarely reported. Reports that can be referred to presently consist of only three cases in females [5-7] and one of a 3-year-old boy [8]. The characteristics of these four cases in females are summarized in Table 1. Omental YST always occurs in females more than 35 years of age, with the average age being 43. The chief complaint is usually abdominal distension. The obviously thickened omentum and the ascites could be identified through CT or US.

The histogenesis of YST of the omentum remains speculative and controversial. One plausible hypothesis is that germ cells have been misplaced or arrested in their embryonic migration during embryogenesis and then become the potential tumor source [6]. In this case, the ovarian surface exhibited only small plantation foci. The greater omental pathological changes were obvious, and the pathological examination located no histological evidence of YST originating from the ovary. All this evidence supported the diagnosis of YST of the omentum.

The glycosidoprotein, AFP, is secreted by the embryo yolk sac or embryonal carcinoma cell with a serum half-life of five days. If the AFP value rises in adults, the diagnosis should first exclude hepatocellular carcinoma, cirrhosis, and hepatitis [9]. A positive rate of AFP serum elevation appeared in all omental YST cases. AFP serum level is a useful marker for the diagnosis and management of this kind of disease and is used to check for complete remission or recurrence. The prognostic value of a high AFP level at diagnosis remains controversial. Mayordomo et al. found that AFP > 1000 kU/l is associated with a higher risk of YST relapse [10], but Nawa et al. found that preoperative AFP serum levels before initial surgery have no significant correlation with prognosis [11]. In our case, the AFP value before surgery was 27612.3 ng/ml, which was the highest out of all the recorded AFP values of the omental YST cases. Although it dropped to a normal level rapidly after more than 40 days, long-term follow-up of the treatment effects require further observation. CA-125 was also found to have risen in our case, similar to the case studied by Kim et al. [5]. This increase may be due to peritonitis or infection accompanying the clinical features of abdominal pain.
The pathological diagnosis of YST is easily confused with that of clear cell carcinoma and adenocarcinoma [12]. In our case, the pathology before surgery was mis-diagnosed as poorly differentiated adenocarcinoma. The typical YST has an embryonic structure similar to the fetal yolk sac, which performs a glomerular-like structure with a central vessel surrounded by prominent large cuboidal cells. Intracellular and extracellular hyaline globules were stained positive with periodic-acid-Schiff (PAS). Schiller-Duval bodies can be regarded as a diagnostic clue to YST in the presence of AFP, but they only exist in 20% of the YST cases. Immunohistochemical staining for AFP and CK was positive, while ER and PR staining were negative. These can be used for differentiating diagnoses. This article has presented a more detailed immunohistochemical study for YST of the omentum to help in the diagnosis of this disease.

Williams suggested that surgery combined with postoperative chemotherapy is presently the best mode of treatment for YST [13]. Three courses of BEP is the current standard therapy, and four courses are recommended in the case of bulky residual disease after surgery. The case of omental YST is very sensitive to this treatment. In all reported cases, the AFP level drops to the normal value before the second chemotherapy cycle.

This case reflects a rarely seen primary YST of the omentum and the patient is presently completely free of disease through effective surgery as well as four courses of BEP combined chemotherapy. Therefore, for tumors with no clear primary foci and with omental thickening, YST of the omentum must be seriously considered, and serum AFP testing can be helpful in differentiating the diagnoses.

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Dermatofibrosarcoma protuberans with areas of giant cell fibroblastoma in the vulva: a case report

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Summary

Objective: To review the clinical, morphologic, immunohistochemical, and histogenetic characteristics of dermatofibrosarcoma protuberans with areas of giant cell fibroblastoma and explore current treatment options. Methods: We describe the case of a 38-year-old patient with a tumor measuring 5.7 cm on the right labium majus. Serial sections stained with hematoxylin-eosin were examined and immunohistochemical staining was performed for CD34 and PDGF receptor alpha and beta (PDGFRα and PDGFRβ). Results: The histologic study showed spindle-cell proliferation typical of dermatofibrosarcoma protuberans and other areas containing fibrosis and giant cells lining pseudovascular spaces. Both tumor areas expressed CD34, PDGFRα, and PDGFRβ. Conclusions: Only two cases of dermatofibrosarcoma protuberans with areas of giant cell fibroblastoma in the vulva have been reported to date. Both dermatofibrosarcoma protuberans and giant cell fibroblastoma are characterized by the translocation t(17;22) (q22;q13). The fact that PDGFRα and PDGFRβ are overexpressed in these tumors opens new treatment options with imatinib. Surgical excision with wide margins or Mohs micrographic surgery continues to be the treatment of choice.

Key words: Dermatofibrosarcoma protuberans; Giant cell fibroblastoma; Imatinib. COL1A1-PDGFB; Mohs micrographic surgery.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a soft tissue tumor of intermediate-grade malignancy that causes local recurrences but has a low risk of metastasis [1]. The tumor mostly affects the trunk and proximal areas of the limbs [2] and is most common in adults with a peak incidence at 20-40 years of age, although it can occur in children and adolescents [3]. Vulva involvement is rare; only 29 cases have been reported to date [4] and only two of these have occurred in association with giant cell fibroblastoma [5, 6]. Both DFSP and giant cell fibroblastoma contain a translocation between the genes COL1A1 (17q22) and PDGFB (22q13) that results in the formation of a chimeric gene encoding a transforming protein with similar effects to PDGFβ, which induces mitogenic stimulation via the activation of the PDGFR receptor (PDGFRβ) [7, 8].

The treatment of choice for localized disease is complete excision with wide margins (over 3 cm) or Mohs micrographic surgery [9]. Tumors that overexpress PDGFRβ are amenable to treatment with imatinib mesylate, thus opening new treatment options for local recurrences, distant metastases, and difficult-to-access tumors that cannot be completely excised. The drug is also an option for treating children when the alternative is mutilating surgery [10].

Case Report

We report the case of a 38-year-old black female in her 19th week of pregnancy who presented a nodule on the outer genitalia that had grown since it had appeared several months earlier. Of note in her history was the removal of a verrucous lesion from the right labium majus three years earlier, for which no report was provided. Examination revealed soft, hyperpigmented, painless depressed plaque measuring approximately 4.5 cm on the right labium majus. The findings of the rest of the examination were consistent with amenorrhea and the abdominal ultrasound showed a live fetus with normal features. The diagnosis following fine-needle aspiration biopsy of the plaque was a mesenchymal tumor without cellular atypia. It was decided to postpone removal of the tumor until after pregnancy. Following a cesarean, the patient was scheduled for excision of the nodule under regional anesthesia. The depressed plaque was seen to be a soft tumor measuring approximately 6 cm with no clear cleavage plane.

A surgical specimen was sent to the pathology department measuring 5.7 x 5 x 2 cm, partially covered by skin, and the resection margins were marked with India ink. Serial sectioning showed a solid tumor of elastic consistency with poorly defined borders that formed whitish bands in the dermis and subcutaneous tissue. Multiple samples were taken for histologic and immunohistochemical analysis.

Sections 4-μm thick were cut from formalin-fixed, paraffin-embedded tissue and stained with hematoxylin-eosin. Immunohistochemical staining was performed on sections of paraffin-embedded blocks using the avidin-biotin-peroxidase method using antibodies to the following antigens: CD34 (Dako, Glostrup, Denmark, monoclonal: QBEnd/10, dilution 1:100), muscular actin (Dako, Carpintería Clif. monoclonal: HHF-35, dilution 1:3000), vimentin (Dako, Glostrup, Denmark, monoclonal: V9, dilution 1:100), factor XIIIa (Novocastra, Newcastle. U.K. monoclonal: E-9801, prediluted), C-kit (Dako, Glostrup, Denmark, polyclonal, dilution 1:400), PDGFRα (c-20) (Santa...
Cruz Biotechnology USA, polyclonal, dilution 1:200), PDGFRB (p-20) (Santa Cruz Biotechnology USA, polyclonal, dilution 1:200), S-100 (Dako, Glostrup, Denmark, polyclonal, prediluted) and cytokeratin AE-1/AE-3 (Dako, Glostrup, Denmark, monoclonal: AE1/AE3 prediluted). Positive and negative controls were used.

Results

Examination of hematoxylin-eosin stained sections revealed neoplastic proliferation of cells with a mesenchymal appearance containing areas with a storiform growth pattern (Figure 1a) invading the dermis and with extensive infiltration of the subcutaneous tissue, surrounding adnexal structures without destroying them (Figure 1b). The cells were elongated, with scant cytoplasm and large, elongated nuclei with fine chromatin, small but visible nucleoli, and 2 mitoses per 10 high-power fields. In the other areas, the tumor had foci of fibrosis with multinucleated giant cells lining pseudovascular spaces of varying size (Figure 2a). The surgical margins were extensively infiltrated by the lesion.

The tumor cells in both areas of the tumor were positive for CD34 (Figures 1c and 2b), vimentin, PDGFRB (Figures 1d and 2c) and PDGFRA, and negative for the other tumor markers. The diagnosis was dermatofibrosarcoma protuberans with areas of giant cell fibroblastoma.

Mohs micrographic surgery was performed (by three micrographic stages) and free margins were achieved. Defect reconstruction was healed by secondary intention (Figures 3a and 3b). The patient remains relapse-free in follow-up (15 months) (Figure 3c).

Discussion

DFSP rarely presents on the vulva; only 29 such cases have been reported to date [4] and only two of these have occurred in association with areas of giant cell fibroblastoma [5, 6]. The age of the patients described in the literature ranges from 23 to 76 years and the most common tumor site reported is the right labium majus [4]. In our case, the patient was 38 years old and the tumor was on the right labium majus.

In the early stages of disease there are three non-protuberant clinical forms of DFSP [11].
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1) A morphea-like form consisting of an indurated white or brown plaque resembling a scar, morphea, morpheaform basal cell carcinoma, or plaque-like dermatofibroma.

2) An atrophoderma-like form consisting of a white or brown soft, depressed plaque.

3) An angioma-like form (the least common type) consisting of a red or violaceous plaque that can be indurated or soft and clinically resembles an angioma.

Although the most common clinical form of DFSP described in the vulva is a vulvar mass [4], our patient had the second type of non-protuberant clinical form. DFSP can also present as a central nodule with satellite nodules. In its early stages, it is an indolent lesion that, with time, develops protruding nodules that can become ulcerative, painful, and also bleed.

CD34 is an important diagnostic aid as it is frequently expressed in DFSP, although it is not specific to this tumor. Factor XIIIa is useful for differentiating DFSP from cellular fibrous histiocytoma (negative in the former and positive in the latter) [1].

Cytogenetic analysis of DFSP has shown the presence of a supernumerary ring chromosome resulting from the translocation t (17; 22) (q22;q13) [12, 13]. Translocation results in the fusion of two genes: collagen type 1 alpha 1 (COL1A1) (chromosome 17) and PDGFB (chromosome 22). This generates a fusion protein COL1A1-PDGFB that is processed outside the cell until it becomes a fully mature, functional PDGFB protein. When released, PDGFB is capable of inducing mitogenic stimulation via the activation of its receptor. The t (17; 22) translocation product COL1A1-PDGFB thus induces the activation of PDGFRB by autocrine and paracrine production of its functional ligand [14]. In our case, the tumor cells overexpressed both PDGFRB and PDGFRB.

Whether or not trauma is a causative factor in DFSP is a matter of debate. It is possible, that trauma might play a role in the development of this tumor, as in 10-20% of cases there is a history of previous trauma and there have also been reports of dermatofibrosarcoma protuberans on surgical scars, burns, radiodermatitis sites and vaccine injection sites [15, 16]. Our patient had undergone surgery three years earlier (removal of a verrucous lesion from the right labium majus for which no histology report was available).

Figure 2. — Giant-cell fibroblastoma area. Pleomorphic giant cell with pseudovascular spaces (a); Strong diffuse CD34 immunoreactivity (b); Low diffuse PDGFRB immunoreactivity (c).
DFSP and giant cell fibroblastoma (which is more common in children) [17] are very closely related as they have cytologic and molecular similarities (e.g., they both have the translocation t (17; 22)) [18]. Giant cell fibroblastoma can have areas with a storiform pattern and there have been reports of DFSP with areas of giant cell fibroblastoma, although just two cases have been described in the vulva [5, 6].

In DFSP tumor cells invade the subcutaneous tissue in the form of finger-like projections through the septae and lobules. These projections contain few cells and can initially look like normal fibrous bands. This makes it diffi-
cult to determine the true extent of the lesion and explains why tumors recur after surgery with apparently wide margins.

Localized disease is treated by complete excision, via conventional surgery with wide margins (over 3 cm) or standard Mohs micrographic surgery [9]. Recurrence rates range from 40% with excision margins of 2 cm, 20% with margins of 3 cm, and less than 15% with margins of 5 cm [19]. With Mohs surgery, recurrence rates are less than 5% [20]. Local recurrence is most common in the first three years after surgery [1]. We performed Mohs micrographic surgery with no recurrences to date (15 months).

Metastasis occurs in 0.3-0.5% of patients [12, 21]. In most cases, it occurs after local recurrences, with a mean interval of six years from the first excision. Prognosis is very poor, with a survival time of less than two years from detection of the metastasis.

DFSP tumors express three kinases (c-abl, PDGFRα, and PDGFRB) and are amenable to treatment with imatinib mesylate [4]. Several authors have suggested that imatinib mesylate induces apoptosis in tumor cells, which could destroy the tumor, while others believe that it alters the tumor phenotype, reducing proliferation and consequently tumor size, but not eliminating the tumor completely. The fact that PDGFRα and PDGFRB are expressed in dermatofibrosarcoma protubera not opens new treatment options with imatinib for local recurrences, distant metastasis, difficult-to-access tumors in which complete excision is not possible, and children where the alternative is mutilating surgery [10].

Conclusions

DFSP rarely presents in the vulva. To our knowledge, there have been only 29 cases reported in the literature with only two of them combined with giant cell fibroblastoma. The tumor is a low-grade sarcoma that tends to recur if not excised with wide margins. It is associated with a translocation t (17; 22) between the genes COL1A1 (17q22) and PDGFB (22q13), which results in the formation of a protein with similar effects to PDGF-B due to the activation of its receptor, which was found to be overexpressed in our patient. Surgical excision with wide margins or Mohs micrographic surgery continues to be the treatment of choice. The expression of PDGFRB and PDGFRα in DFSP opens new treatment options with imatinib mesylate for patients with recurrent disease, locally advanced disease, and metastasis.

References

A case of recurrent yolk sac tumor as spindle cell sarcoma of the abdominal wall

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Summary

Few studies report on tissue morphology in recurrence of yolk sac tumor. The case of the recurrence of a yolk sac tumor as a spindle cell sarcoma of the abdominal wall is presented. A 27-year-old woman was referred to our hospital due to suspicion of an ovarian tumor. Right salpingo-oophorectomy, partial omentectomy, and extirpation of disseminated foci as fertility-preserving surgery was done since the intraoperative pathological diagnosis was yolk sac tumor. Final pathological examination showed a germ cell tumor of which yolk sac tumor formed the major component including a small area that appeared to be immature nerve tissue. Although residual tumor was not less than 1 cm, clinical complete remission was reached after the sixth course of BEP regimen. However, the recurrence of a yolk sac tumor as an unclassified spindle cell sarcoma of the abdominal wall was found about two years after the initial surgery. Thereafter, the patient expired due to progression of the intraperitoneal disseminated lesions. The mesenchyme-like component of the yolk sac tumor is characterized by spindle cells originating from epithelial elements, and is likely to give rise to a chemoresistant, diversely differentiated sarcoma. This report suggests that the sarcoma reported in the case here also arose when spindle cells of the mesenchyme-like component underwent sarcomatous change during or after chemotherapy, subsequently relapsed as a chemoresistant tumor, and metastasized.

Key words: Yolk sac tumor; Spindle cell sarcoma; Chemoresistance; Recurrence.

Introduction

Yolk sac tumor is a type of malignant germ cell tumor common in young women. Although responsive to chemotherapy, recurrence is not uncommon. Few studies report on tissue morphology in cases of recurrence. This paper reports on the recurrence of a yolk sac tumor as a spindle cell sarcoma of the abdominal wall.

Case Report

Our patient was a 27-year-old female with no history of pregnancy, 168 cm in height and weighing 94.8 kg. The patient was referred to our hospital due to suspicion of an ovarian tumor after consulting a local doctor in 2003 with lower abdominal pain as her chief complaint. Abdominal ultrasonography showed a mixed solid and cystic mass of 20 cm in its longest diameter. The patient was admitted to our facility with a fever of 39°C. She received antibiotic treatment and a detailed examination of the mass was performed. Serum AFP was high (24,694 ng/ml) and suggested the presence of a yolk sac tumor. With persisting pyrexia, progression of anemia (Hb 7.0 g/dl) and inflammatory findings (CRP 19.5 mg/dl), surgery was performed. Other biochemical tests showed no abnormalities. Tumor markers observed other than AFP were CA125 at 128 U/ml, CEA below 0.5 ng/ml, and CA19-9 at 26 U/ml. Magnetic resonance imaging revealed a large tumor reaching the umbilicus with marked contrast enhancement. A malignant tumor with large solid and small cystic components was suggested. The patient’s uterus was of a normal size.

Operative findings were as follows. The tumor originated from the right ovary and consisted mostly of a solid component. Hemorrhage was observed from the tumor surface, and the tumor was adherent to the pelvic peritoneum and intestinal tract. Areas of dissemination of 2 cm in diameter and larger were found on the surface of the intestinal tract and the omentum. Because an intraoperative pathological diagnosis was of yolk sac tumor, only right salpingo-oophorectomy, partial omentectomy, and extirpation of disseminated foci were performed as fertility-preserving surgery in consideration of the patient’s age and chemoresponsiveness of the histological tumor type. Residual tumor was not less than 1 cm. The resected tumor weighed 3.3 kg, was covered by a smooth capsule, and was solid, soft, and friable. The tumor was pale yellow to grayish white in color on cut section, and inhomogeneous with small and large cysts in the solid tissue. The cysts contained bloody or viscous components (Figure 1). Pathological examination showed that cells with oval nuclei had proliferated into reticular and sac-like structures. Large numbers of hyaline globules were detected (Figure 2A). Some cells had formed as Schiller-Duval bodies (Figure 2B), positive for AFP on immunohistochemical staining. A yolk sac tumor was diagnosed based on these findings. The patient received six courses of BEP chemotherapy following surgery (D2; bleomycin 30 mg/body, D1 to D5; VP-16 100 mg/m² and CDDP 20 mg/m²). Serum AFP returned to normal values for the first time after the completion of the fifth course, and computed tomography (CT) scanning showed no identifiable lesion after the sixth course.

In 2005 a mass was found just under the incision wound on the abdominal wall. On abdominal CT, a 9 cm mass was found on the abdominal wall just below the wound. Fine-needle aspiration cytology of the mass found no malignant cells and suggested a desmoid tumor. The abdominal wall mass was resected. Serum AFP was below 2 ng/ml, and no lesion was found other than the abdominal wall mass. The cut section of the resected tumor showed a pale yellow mass with clear margins and a cystic cavity at its center (Figure 3A). Postoperative
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A central pathological review gave an identical diagnosis. BEP chemotherapy was performed after resection of the relapsed tumor, but during the early stages of treatment a 14 cm mass was found in the upper abdomen by CT. The tumor originated from the transverse mesocolon, and multiple disseminated lesions were found. The transverse colon including the mass was resected and anastomosis performed, and resection and anastomosis of the small intestine was also performed. Subsequent progression of the disseminated lesions resulted in patient death 30 months after initial treatment.

Discussion

Cases of malignant germ cell tumor are reported to constitute 4-6% of malignant ovarian tumors [1]. Around 13% of these malignant germ cell tumors are estimated to be yolk sac tumors [2]. Yolk sac tumor is most common among young people in their teens and twenties [2]. Common symptoms of malignant germ cell tumors including yolk sac tumors are abdominal pain, pyrexia, abdominal distension, and genital bleeding [2]. Around 10% of yolk sac tumor diagnoses are given by emergency surgery for acute abdomen caused by capsule rupture, hemorrhage, and torsion of the pedicle [3]. The patient in this paper presented with abdominal pain and pyrexia, both symptoms frequently found in patients with disseminated yolk sac tumor. Unlike epithelial ovarian cancer, between 60-70% of yolk sac tumor patients are FIGO Stage I and II, 20 to 30% Stage III, and Stage IV patients are relatively rare [4]. Yolk sac tumor rarely occurs in both ovaries, as in the patient reported here with tumor of the right ovary only.

On gross examination the tumor was covered with a smooth capsule and was solid and soft. Patients with yolk sac tumor are known to have an increased AFP level, and in some cases show increased CA125 and LDH. Immunohistochemical staining for AFP is particularly useful for the histopathological diagnosis of yolk sac tumor. Yolk sac tumor cells are positive for cytokeratins, and in 50% of cases are PLAP-positive. Various histological subtypes exist (endodermal sinus pattern, polyvesicular vitelline pattern, hepatoid pattern, glandular pattern), with two or more subtypes often coexisting, and histological changes common place. There are reports that patients with three or four histological subtypes have better prognosis than those with only one or two subtypes [5, 6]. There are also reports of yolk sac tumor being difficult to differentiate from ovarian clear cell adenocarcinoma and endometrioid adenocarcinoma, both epithelial ovarian cancers, indicating caution for diagnosis [7, 8].

Malignant germ cell tumor patients are often young, with reports showing that fertility-preserving surgery has
In cases that require fertility preservation a surgical procedure is chosen that will conserve ovarian function and fertility where possible. BEP, PVB, and VAC chemotherapies are common postoperative therapies [10-12]. Recent reports often advocate three-course BEP chemotherapy, but four courses are recommended in cases of residual tumor [4]. The patient reported here received six courses in total due to residual tumor and normalization of AFP occurring during the fifth course. Anticancer agents are known to cause ovarian dysfunction, though few reports show ovarian dysfunction arising from BEP, PVB, and VAC therapies [13]. The patient reported in this paper was first severely obese with irregular menstruation, with a regular menstruation cycle returning subsequently.

Nishio et al. [14] reported patients with malignant germ cell tumors who received fertility-preserving surgery immediately followed by chemotherapy had good prognosis regardless of clinical stage. However, patients with yolk sac tumors of the ovary often experience relapse or recurrence despite responding to chemotherapy, and are known to have poor prognosis [2]. Most recurrences are seen within two years of surgery, with recurrence in this paper seen about two years after the initial surgery. Clinical stage, tumor size, and residual tumor size are factors considered to influence prognosis in patients with yolk sac tumors [15, 16]. Volume of ascites fluid has also been counted as an important prognostic factor, and Kawai et al. [15] reported Stage I patients with no residual tumor or ascites, or with less than 100 ml of ascites have good prognosis. Nawa et al. [16] have also reported a residual tumor size of 2 cm or less and ascites of less than 100 ml as prognostic factors for yolk sac tumor. There is a continuing disagreement as to whether a correlation exists between AFP values and prognosis for yolk sac tumor [15, 16].

Although many patients with recurrent yolk sac tumors exhibit increased AFP, and AFP is a useful aid for determining tumor recurrence [17], no increase in AFP was seen in the patient of this paper. On the significance of AFP, Baniel et al. [18] reported 28% of patients with recurrent yolk sac tumors of the testis were negative for AFP. Kommoss et al. [19] reported one case of an endometrioid-like variant of yolk sac tumor recurring after 12 years that also showed no increase in AFP. Although AFP is often increased in recurrent tumors, it is important to note there are also patients negative for AFP who also recur, such as the patient reported here.

Almost no literature reports exist on the histomorphology of tumors in cases of recurrent yolk sac tumor of the ovary. Although the patient presented in this paper was a case of mixed germ cell tumor with major yolk sac tumor components, and as such may be inappropriate as a case of recurrent pure yolk sac tumor, pure yolk sac tumors are considered the exception. Other types of germ cell tumors are often mixed within yolk sac tumors, and patients where yolk sac tumor constitutes the major component of a large tumor are reported to have poor prognosis [20]. The patient reported here had a yolk sac tumor constituting the predominant component of a mixed germ cell

Figure 3. — Recurrent tumor of the abdominal wall. A, macroscopic finding of the recurrent tumor. The cut section of the resected tumor showed a pale yellow mass with clear margins and a cystic cavity at its center. B, microscopic finding of the recurrent tumor. The proliferation of oval or spindle-shaped tumor cells with a reticular structure, and a diagnosis of unclassified spindle cell sarcoma was given.

Figure 4. — Macroscopic finding of the primary tumor. A small area that appeared to be immature nerve tissue was found in the primary lesion.
tumor of 20 cm in its longest diameter, and poor prognosis was expected. The patient showed no increase in AFP on recurrence of the tumor, and the recurrent tumor found just under the abdominal wall was a spindle cell sarcoma and quite different from the original yolk sac tumor. This at first led us to conclude the spindle cell sarcoma was not a recurrence. The mesenchyme-like component of yolk sac tumor has previously been characterized to be spindle cells originating from epithelial elements, and reported to give rise to a chemoresistant, diversely differentiated sarcoma [21]. This report suggests that the sarcoma reported in the case here also arose when spindle cells of the mesenchyme-like component underwent sarcomatous change during or after chemotherapy, subsequently relapsed as a chemoresistant tumor, and metastasized.

Conclusion

Although yolk sac tumors respond to chemotherapy, the risk of recurrence necessitates caution. The female patient reported by this paper had a germ cell tumor with major yolk sac tumor components. Serum AFP originally considered to be useful for follow-up observation showed no increase even during recurrence. Although few reports exist on the histomorphology of recurrent yolk sac tumors, we found that tumors recurring after chemotherapy, such as the case reported here, show a sarcomatous morphology. Literature reviews of patient cases of yolk sac tumors reviewing therapies and outcomes exist, but the number of cases examined are small. Large numbers must be collected for further interpretation and analysis.

References


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Contralateral axillary involvement in breast cancer recurrence: locoregional disease or metastasis?

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Summary

We describe a case of right mammary homolateral recurrence with contralateral axillary invasion. The absence of occult involvement of the left breast was confirmed by MRI. A subsequent thoraco-abdomino-pelvic scan and bone scintigraphy did not reveal any metastases. Lymphoscintigraphy of the right breast, after periareolar injection, revealed lymphatic drainage from the right breast into the left contralateral axillary lymph node. Because of the changes in axillary drainage after mammary and axillary surgery observed by lymphoscintigraphy, contralateral axillary involvement could be considered as locoregional disease in the same way as homolateral lymph node involvement.

Key words: Breast cancer; Contralateral axillary recurrence; Lymphoscintigraphy; Metastasis.

Introduction

Contralateral axillary invasion is rare in patients who have been treated for cancer of the opposite breast [1]. According to the TNM classification, contralateral involvement is considered as metastasis, with the cancer crossing the midline. Systemic treatment only is usually indicated [1]. In the case of histologically-proven homolateral mammary recurrence, modification of lymphatic drainage after axillary dissection could change our interpretation of contralateral axillary involvement.

We describe a case of contralateral axillary involvement that was directly related to homolateral mammary recurrence proven by lymphoscintigraphy.

Case Report

Our patient was a 56-year-old woman with a previous history of cancer of the right breast in 1996. The cancer was diagnosed as invasive ductal carcinoma, SBR grade 2, infiltrating 2.5 cm of the upper outer quadrant, and was hormone-sensitive. Conservative treatment was carried out. Axillary dissection included three positive lymph nodes out of 13. Chemotherapy, and external radiotherapy of the breast and subclavicular and internal mammary lymph node areas were also carried out. Hormone therapy with tamoxifen was contraindicated because of a history of pulmonary embolism.

During a follow-up consultation in 2009, a retroareolar nodule was palpable in the right breast, as well as suspected contralateral macroadenopathy. Mammography findings were classified as ACR BI-RADS™ 5. A mammary biopsy confirmed homolateral breast recurrence and a biopsy of the left lymph node confirmed contralateral axillary involvement.

A subsequent thoraco-abdomino-pelvic scan and bone scintigraphy did not reveal any metastases. Breast magnetic resonance imaging (MRI) confirmed the presence of homolateral right intramammary recurrence, with early and intense gadolinium enhancement on T1-weighted sequence. Moreover, there was no uptake of contrast in the left breast (Figure 1). Thus the absence of occult involvement of the left breast was confirmed by MRI after mammography and echographic investigations. Axillary transaxial SPECT-CT lymphoscintigraphy of the right breast, after periareolar injection of 1 mCi of technetium-labelled nanocolloids, revealed lymphatic drainage from the right breast into the left contralateral axilla, with labelling of several lymph nodes (Figure 2). Labelling of the macroadenopathy was weak compared to that of the other lymph nodes identified (Figure 2B).

Right mastectomy and left axillary dissection were subsequently carried out. A definitive anatomopathological examination confirmed right homolateral breast and bifocal recurrence, which was comparable to the histology of the original cancer. In the left axillary area, 7/15 lymph nodes were positive, including a 4 cm bulky lymph node.

Chemotherapy and radiotherapy of the left subclavicular lymph nodes were subsequently carried out.

Discussion

Lymphoscintigraphy, complemented by mammary MRI, enabled us to correlate left lymph node involvement with right mammary recurrence. In this way it was possible to eliminate an adenopathy originating from a second occult homolateral cancer.

According to the TNM classification, contralateral axillary invasion is considered to be a distant metastatic event (M1) [2]. The use of lymphoscintigraphy on sentinel lymph node identification has enabled several authors to observe direct drainage of the breast towards the contralateral axillary lymph nodes. Lymphoscintigraphy before sentinel lymph node removal enables the establishment of a precise lymph node cartography and visualization of atypical lymphatic drainage of the tumour in some cases [3]. The rate of detection of extra-axillary drainage is around 20% [4, 5]. Localisation of the internal mammary lymph node chain is the most frequently detected extra-axillary labelling, with a frequency between 1-13% [5]. The detection of subclavicular drainage remains rare (< 2%) [4].
Contralateral axillary labelling is exceptional in cases of breast cancer without a history of mammary surgery. Several clinical cases report synchronous bilateral axillary labelling [6, 7]. Localisation in the internal quadrants of the breast favours this atypical lymph node drainage [8]. Barranger et al. described the first case of exclusive contralateral axillary labelling without homolateral axillary drainage in a patient with a history of breast reduction 35 years previously [9].

Mammary lymphatic drainage is noticeably modified after axillary dissection. In the case of homolateral breast cancer recurrence treated by tumourectomy and axillary dissection, preoperative lymphoscintigraphy reveals exclusive contralateral axillary drainage in up to 25% of cases [10-12]. The main hypothesis for this atypical lymphatic drainage is based on modification the lymphatic circulation after surgery. Interruption of the axillary lymphatic channels after axillary dissection leads to the creation of an alternative lymphatic circulation or collateral pathways that are the origin of atypical mammary drainage [1]. The two main routes of dissemination are through the lymphatic plexus of the deep fascia of the thoracic wall and the dermal lymphatics crossing the midline [13].

Because of the contralateral collateral axillary lymphatic pathway demonstrated by lymphoscintigraphy in our patient, it was considered that this was locoregional disease. Consequently, treatment was implemented combining surgery, chemotherapy and radiotherapy. If the TNM classification of stage rT1N0M1 had been respected strictly, only systemic treatment would have been indicated.

In the case described, further examinations consisting of thoraco-abdomino-pelvic scans and bone scintigraphy were negative. The failure to carry out a preoperative PET scan, the most sensitive examination for the detection of metastases [14], can be criticised, but does not alter the problem of interpretation of contralateral axillary involvement. Because of the changes in axillary drainage after mammary and axillary surgery observed by lymphoscintigraphy, contralateral axillary involvement could be considered as locoregional disease in the same way as homolateral lymph node involvement. Thus, a stage N4 in the TNM classification can be proposed, characterised by contralateral lymph node invasion that has a direct relationship with the tumour proven by lymphoscintigraphy.

References


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Cervical granulocytic sarcoma: report of one case and review of the literature

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Summary
Granulocytic sarcoma in the female genital tract generally has a poor prognosis. We report the case of a 52-year-old nonleukemic patient with relapsed granulocytic sarcoma at the vaginal stump after an 11-year complete remission from the uterine cervix. Magnetic resonance imaging of the pelvis showed a pear-shaped mass arising from the vagina mimicking a normal uterus. The unusual clinical presentation and the difficulties encountered in evaluation are presented. A review of the literature indicates that survival is better with multimodality management and in patients without leukemia.

Key words: Granulocytic sarcoma; Relapse; Uterine cervix.

Introduction
Granulocytic sarcoma (GS) is defined as an extra-medullary myeloid tumor composed of immature myeloid cells and usually noted concurrently with or after the onset of acute myeloid leukemia (AML) or chronic myeloproliferative disorders [1]. Very rarely, patients present with GS as an isolated mass without prior or current evidence of AML; however, the vast majority of these patients develop AML within 11 months [2, 3]. The most frequent involvement sites of GS include the skin and lymphadenopathy, but it is very rare in the female genital tract [1-5]. GS generally has a poor prognosis, and complete remission has rarely been reported [6]. Herein we present the case of a nonleukemic patient with isolated cervical GS and relapse at the vaginal stump after an 11-year complete remission, mimicking a normal uterus. To our knowledge, this is the first case of GS to develop a long-term relapse tumor after complete remission. Previous literature about granulocytic sarcoma of the uterine cervix has been reviewed to define the optimal management.

Case Report
In August 1996, a 43-year-old female complained of hypermenorrhea and postcoital bleeding of one year’s duration. Pelvic examination revealed a large cervical mass without vaginal or parametrial involvement. Histopathologic evaluation was consistent with a GS, but there was no evidence of leukemia on the blood smear or bone marrow biopsy. The patient received induction chemotherapy with cytosine arabinoside (Ara-C) and idarubicin in September 1996 and consolidation chemotherapy with Ara-C and idarubicin in November 1996. In February 1997 she underwent a hysterectomy; the specimen confirmed a pathologic disease-free status. Further consolidation chemotherapy with Ara-C and adriamycin was given in April 1997. She did well until October 2007 when a hard mass over the vaginal stump was noted during an annual gynecologic examination. The Pap smear and colposcopy-directed biopsy both revealed negative findings. Magnetic resonance imaging showed a pear-shaped homogeneous mass arising from the vaginal stump mimicking a normal uterus (Figure 1). A loop electro-surgical procedure (LEEP) was used to obtain a satisfactory specimen which showed atypical primitive granulocytic cells infiltrating the stroma. The blood smears and bone marrow biopsy showed no evidence of leukemia. The patient thus received salvage chemotherapy with Ara-C and novantrone for relapsed disease in December 2007. The mass shrank based on serial sonographic measurements. An additional course of chemotherapy was administered in January 2008, but she developed sepsis and died three months after the diagnosis of relapse.

Discussion
GS involving the female genital tract is rare, and the most commonly involved organ is the ovary, followed by the cervix [1-5]. The prognosis for all patients with GS is poor [5]. Only a few cases have achieved complete remission after aggressive treatment, but relapse of disease is usually noted within two years of the initial diagnosis [7]. The risk of relapse declines three years after complete remission and such patients are considered potentially cured [8]. Only 33 cases of cervical GS have been described since 1912. The median survival of the 34 patients (including our case) in our literature review was 8.5 months (range: 6 days - 372 months), and most patients died of disease progression (Table 1) [5, 9-34]. Only six patients lived more than two years, and three patients lived more than five years including our case. The median survival is 7.5 months for patients with AML (range: 8 days - 36 months), and 24 months for patients
Table 1. — Characteristics of patients with granulocytic sarcoma of the cervix in the literature.

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<td>CT</td>
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<td>NA</td>
<td>NA</td>
<td>[34]</td>
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<tr>
<td>Our case</td>
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<td>Positive</td>
<td>CT/OP</td>
<td>Vaginal stump</td>
<td>Dead</td>
<td>11 years</td>
<td></td>
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</table>

AML; acute myeloid leukemia; CT: chemotherapy; NA: not available; OP: operation; RT: radiotherapy.

without AML (range: 6 days - 372 months) (Figure 3A). The patients with cervical GS without AML apparently responded better to the treatment than those with AML.

Because the vast majority of nonleukemic patients with GS developed acute leukemia within a matter of months, it is now generally accepted that GS should be treated as systemic disease with chemotherapy which could prolong the duration of nonleukemic stage and improve the prognosis [35]. Evidence has also shown that anti-AML therapy is associated with higher rates of disease-free and overall survival in GS than in AML [8]. From our review (Table 1), the median survival is less than one month for patients without any treatment, four months for patients with only local treatment including radiotherapy or hysterectomy (range: 7 weeks - 5 months), 9.5 months for patients with only chemotherapy (range: less than 2 months - 372 months), and 17.5 months (range: 2 months - 122 months) for patients with chemotherapy and local treatment (Figure 3B). However, because the number of treated patients is so limited, the role of local treatment...
remains controversial. Nonetheless the extra-medullary foci are often chemoresistant with resulting relapsed or persistent disease, so multimodality management, including local treatment, is reasonable.

Our case presented an unusual course of local relapse without developing acute leukemia after achieving an 11-year complete remission. She had an asymptomatic mass above the vaginal stump mimicking a uterus, which could have easily been misdiagnosed as normal without a thorough examination. Even though relapsed disease was highly suspected, a Pap smear and colposcopic biopsy failed to obtain tissue verification, which may reflect the accumulation of immature myeloid cells in the stroma beneath the unaffected epithelium. Thus an adequate depth of specimen is critical for pathologic confirmation.

Our clinical experience and the literature review suggest that anti-AML therapy is highly effective in patients with nonleukemic cervical GS. Therefore, an accurate initial diagnosis of GS in a nonleukemic patient and appropriate and timely chemotherapy may reduce the risk of subsequent AML. In addition, the unusual late relapse also emphasizes the need for careful follow-up, which should include imaging studies and tissue biopsies whenever clinical suspicion exists.

References

Primary ovarian malignant lymphoma presenting as ovarian carcinomatosis: a case report and literature review

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Summary

Introduction: Primary ovarian lymphoma may present with a clinical scenario consistent with advanced epithelial ovarian carcinoma. Although ovarian lymphoma is a rare entity, accounting for 0.5% of all non-Hodgkin’s lymphoma and 1.5% of all ovarian neoplasms, it should be included in the differential diagnosis of an ovarian mass. Case: We report a case of a 78-year-old woman who presented with an ovarian neoplasm suggestive of advanced ovarian carcinoma. During diagnostic laparoscopy, biopsies were obtained with frozen section analysis revealing malignant lymphoma. Further histopathologic analysis revealed a diffuse large B-cell lymphoma (DLBCL). The treatment plan was for six cycles of R–CHOP chemotherapy. A dramatic response was noted after only three cycles of R-CHOP. Conclusion: Primary ovarian lymphoma presenting as an ovarian tumor is exceedingly rare. Since the prognosis and treatment of lymphoma differs significantly from ovarian carcinoma, a representative tissue sample of the adnexal tumor should be obtained and sent for frozen section analysis to establish the diagnosis. Principal treatment for non-Hodgkin’s lymphoma is chemotherapy without surgical cytoreductive efforts.

Key words: Ovarian carcinoma; Non-Hodgkin’s lymphoma; Chemotherapy; Cytoreduction.

Introduction

Fewer than 1% of patients with malignant lymphoma present initially with ovarian enlargement [1, 2]. Malignant lymphoma involving the ovary may present as follows: I) a primary neoplasm arising in the ovary, II) as the initial clinical manifestation of occult nodal disease, and III) as a manifestation of widely disseminated systemic lymphoma [3]. Fox et al. [4] proposed the following criteria for diagnosis of primary ovarian lymphoma:

– At the time of diagnosis, the lymphoma is clinically confined to the ovary and a complete investigation fails to reveal evidence of lymphoma elsewhere. However, an ovarian lymphoma can still be considered as primary if it has spread to the immediate adjacent lymph nodes or directly spreads to infiltrate the immediate adjacent structures.

– The peripheral blood and bone marrow should not contain any abnormal cells.

– If further lymphomatous lesions occur at sites remote from the ovary, then at least several months should have elapsed between the appearance of the ovarian and extra-ovarian lesions.

When these criteria are strictly applied, the diagnosis of primary ovarian lymphoma becomes extraordinarily rare [5]. We present a case of primary ovarian lymphoma in a patient referred to us with the presumable diagnosis of advanced epithelial ovarian carcinoma.

Case Report

A 78-year-old nulligravid female presented to her local physician complaining of lower abdominal pain and urinary difficulty. The patient’s surgical history was only significant for a prior laparotomy with an ovarian cystectomy secondary to endometriosis 50 years before.

Physical examination revealed a negative nodal survey with a large palpable mass noted in the left lower quadrant. Bimanual exam confirmed a pelvic mass extending posteriorly compressing the rectosigmoid colon. The patient reported a recent normal mammographic and colonoscopy examination. Computerized tomography (CT) scans of the abdomen and pelvis demonstrated a 6.8 cm left adnexal mass with an additional smaller mass in the right adnexa. The liver showed three ill-defined lesions: one in the caudate lobe measuring 2.2 cm, another 3.4 cm lesion on the right inferior aspect of the liver and a 1.8 cm lesion in the right lobe. There were soft tissue densities in the intestinal mesentery and involving the omentum. The remainder of the solid organs and lymph nodes were normal. Preoperative CA-125 was 24 U/ml and LDH was 287. CBC was normal except for a mildly increased platelet count (406,000/l). Despite a normal CA-125, given findings on physical examination and radiologic imaging, the presumptive diagnosis of advanced stage ovarian carcinoma with carcinomatosis was suspected.

Management options were extensively discussed with the patient. Given her age and that she was the primary caregiver for her elderly husband, the patient was very concerned with quality of life issues. After discussion, the decision was made to proceed with diagnostic laparoscopy, assessment of intraperitoneal disease extent, and biopsy with probable neoadjuvant chemotherapy. If she had tolerated neoadjuvant chemotherapy, with acceptable disease response to therapy, the patient would then have considered interval cytoreduction followed by more systemic adjuvant chemotherapy.
At the time of assessment laparoscopy, bilateral fixed adnexal masses were noted. The tumor on the left adnexa was densely adherent to the peritoneum, just above the bladder. A large omental mass was present; however, peritoneal surfaces of the upper abdomen including that of the diaphragm appeared normal. Biopsies of the omentum and ovaries were obtained with frozen section analysis revealing a malignant lymphoma. Immunohistochemical staining studies showed large cells which were positive for CD20 and negative for CD3. There was a background infiltrate of small CD3-positive mature lymphocytes. The Mib-1 proliferation index was increased in malignant cells (estimated 50%). Cytokeratin AE1/AE3 was negative. Flow cytometric immunophenotyping was attempted, but was non-contributory (which could have been due to lack of viable cells). The final pathologic diagnosis was determined to be that of a diffuse large B cell lymphoma.

The patient was referred to Hematology/Oncology and additional postoperative assessment included a bone marrow biopsy which was negative for lymphoma, normal CBC without lymphocytosis, normal creatinine, electrolytes and liver enzymes. Serum protein electrophoresis was unremarkable. Hepatitis B and C serology were negative. LDH was 287. A postoperative PET/CT scan was significant for multiple lesions in the ala and fat. A large confluent mass in the pelvis measuring 10.4 x 8.3 cm was noted. Other findings included lesions in the peripectal area, left diaphragm, spleen and multiple liver lesions. A decision was made to treat with six cycles of rituximab, cyclophosphamide, adriamycin, vincristin and prednisone (R-CHOP) chemotherapy. Follow-up CT scan performed after only treatment. The pelvic mass decreased in size from 10.4 x 8.3 cm to 3 x 1.5 cm. Omental, mesenteric and splenic masses were no longer seen.

Discussion

Prognosis of ovarian lymphoma is based primarily on clinical stage, modality of onset, histological type and phenotype. Tumors are staged according to the FIGO system, as used for other ovarian neoplasms. Prognosis of primary ovarian lymphoma is not as good as for other primary sites. Five-year survival is estimated at approximately 40%.

The standard regimen for the treatment of non-Hodgkin’s lymphoma is combination chemotherapy with cyclophosphamide, adriamycin, vincristin and prednisone (CHOP) [6]. Recently, CHOP, in combination with targeted immunotherapy, rituximab (R-CHOP), has resulted in significant survival improvement in this group of patients [7]. Importantly, there is evidence that an aggressive surgical cytoreductive effort is not necessary and is not associated with improvement in survival [8]. Most of the reported cases underwent surgery, but debulking of the tumor was not considered to be related to a better prognosis [9]. Dimopoulos et al. [1] and Yamada et al. [10] recommended that patients with ovarian lymphoma should be treated with curative intent with combination chemotherapy regimens appropriate for their histology. Therefore, in patients presenting with a pelvic mass with carcinomatosis, etiologies other than primary epithelial ovarian cancer must be considered [11]. Primary ovarian lymphoma should be considered in the differential diagnosis and surgical cytoreduction is not beneficial as the mainstay of treatment is systemic chemotherapy.

Furthermore, extra-nodal presentation of primary ovarian lymphoma is relatively frequent. Moreover, relapse in the central nervous system (CNS) is not uncommon. Therefore, in addition to systemic chemotherapy, consideration should also always be given for CNS prophylaxis with intrathecal methotrexate.

References


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Severe vaginal chronic graft-versus-host disease (GVHD): two cases with late onset and literature review

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Summary
Female genital graft-versus-host disease (GVHD) occurs after allogenic stem cell transplantation (SCT) in 25% of long-term survivors. To date, 28 severe cases with hematocolpos requiring surgery have been documented. We report two cases of severe gynecological GVHD. Although most of the vaginal GVHD disease cases occurred within two years after oncologic treatment, our two cases highlight the possibility of a very long onset. We also confirmed that hormonal replacement therapy does not protect against synechia and that corticoid treatment has a good therapeutic value in recurrence after surgery. In conclusion, women with SCT experience a high risk of vaginal GVHD that could impair quality of life and sexual function. These cases pinpointed the importance of very long-term gynecological follow-up in order to diagnose early symptoms. To date, only early therapy with local corticoid application might reduce symptoms and development of severe genital GVHD. We support systematic use of topical corticoid therapy in severe cases even after surgery because of the high incidence of recurrence.

Key words: Chronic graft-versus-host disease; Vaginal stenosis; Stem cell transplantation.

Introduction
Female genital acute and chronic graft-versus-host disease (GVHD) occurs after allogenic stem cell transplantation (allo-SCT) in 25% of long-term survivors. To date 28 severe cases with hematocolpos requiring surgery have been documented. We report on two cases of severe gynecological GVHD together with a review of the literature.

Case Reports
Case 1
A 22-year-old, gravida 0, para 0, virgin patient had chronic myeloid leukaemia, Ph (+) in 2004 treated by chemotherapy followed by an allo-SCT.

The menopausal status was treated by an estroprogestative combination. In 2008, the patient was consulted for abdominal pain and amenorrhoea. The gynecological examination demonstrated a completely obstructed vagina. Pelvic ultrasound revealed a hypoechogetic mass. Magnetic resonance imaging (MRI) confirmed a large hematometrocolpos (Figure 1).

Surgical lysis of synechia to the cervix and drainage of the hematometrocolpos were performed. Vaginal dilatation used in combination with local estriol and hormone replacement therapy (HRT) were prescribed for two weeks. After 12 months of follow-up, no recurrence has been diagnosed.

Case 2
A 35-year-old patient, gravida 0, para 0, with non-Hodgkin’s lymphoma diagnosed in 2000 was treated by chemotherapy, whole body irradiation, and SCT.

Menopause was treated by HRT and local estriol. The patient developed chronic skin GVHD treated by oral tacrolimus.

In 2008 the patient developed abdominal pain. Ultrasound investigation showed hematometrocolpos, and clinical examination revealed a painful pelvic mass with an obstructed vagina. Vaginal biopsy showed inflammation compounded with some T-lymphocyte deposits. No atrophy was found.

The patient underwent the same surgical and postsurgical procedure as case 1. One month after the surgery, recurrence of synechia occurred. Topical hydrocortisone acetate was prescribed for two months with good results. After 12 months of follow-up, no recurrence has been diagnosed.

Discussion
Since the first description of gynaecological GVHD, this complication has been well recognised and is based on clinical examination and symptoms (vulvovaginal dryness, erythema, dyspareunia, vulvar fissures or erosions, and vaginal synechiae to complete occlusion) [1, 2]. A classification of genital GVHD is currently used (minimal, moderate, severe). The anatopopathologic findings are non-specific.

A study of patients with bone marrow transplantation (BMT) found an incidence of 19% of chronic genital GVHD severe disease in only 12%. The median time for developing genital manifestations after BMT was seven months [2]. Another study observed a higher incidence (49%) within two years after BMT with a median time to onset of ten months. For women not closely followed up, this time reached 2.7 years. Acute GVHD preceded chronic manifestations in two-thirds of cases [3].

Interestingly, these two reported cases of genital GVHD occurred with a very late onset. Four years after the allo-SCT in the first case, and eight years for the second. Other diagnoses than GVHD could be discussed here; for case 2, atrophy was excluded by biopsy and the associated chronic skin GVHD with clinical manifestati-
on strongly supported the diagnosis of genital GVHD. For case 1, mucositis could have been postulated but this complication recovers spontaneously in most cases and occurs soon after therapy.

Moreover, both cases were placed under hormonal therapy as soon as the diagnosis of menopause was made.

Nevertheless, the very late onset was probably overestimated due to the absence of close clinical follow-up. Despite the absence of follow-up, patients have been asked and did not complain of abdominal symptoms. The total body irradiation given to case 2 probably modified the vaginal atrophy.

About 50% of surgical patients experienced recurrence that required corticoid treatment and, in some cases, immunosuppressive therapy. Hormonal replacement therapy does not protect against synechia as a result of GVHD [3].

Topical therapy is the treatment of minimal to moderate GVHD while severe cases needed surgical lysis of vaginal occlusion with use of the vaginal dilators and local estrogens postoperatively. The addition of local corticosteroids (and sometimes topical genital tract cyclosporine or tacrolimus) counteracts inflammatory processes [3, 4].

In case 2, recurrence was successfully treated by topical corticoid application (acetate hydrocortisone 1 g/day).

On the other hand, we observed that systemic therapy (tacrolimus) for chronic extensive GVHD failed to prevent development of genital manifestations.

Zantomio et al. showed that a proactive survey and management programme for cases of female genital GVHD lowered the incidence and severity of the disease [3].

Conclusion

Women with SCT experience a high risk of vaginal GVHD that impairs the quality of life and sexual function. Very long-term gynaecological follow-up is needed as we reported late onset of genital GVHD in order to give early therapy that might reduce symptoms and development of severe GVHD.

We confirmed that HRT does not protect against synechia and that corticoid treatment has good therapeutic value in recurrence after surgery. We support the systematic use of topical corticoid therapy in severe cases even after surgery.

References


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Giant pelvic retroperitoneal liposarcoma: case report

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Summary

Background: Pelvic retroperitoneal liposarcomas are rare tumors of mesenchymal origin. We present a case of a giant pelvic well-differentiated liposarcoma of the retroperitoneum in a woman, presenting with a large abdominal mass. Case: A 62-year-old woman presented with a rapid abdominal enlargement. Pelvic examination revealed a huge mass occupying the whole pelvis and part of the right abdomen. At surgery, the pelvic organs were displaced to the right side by a retroperitoneal mass that marginally involved the part of the posterior abdominal wall, left parietal peritoneum of the diaphragm, left colic flexure and the left adnexa. The huge mass, uterus, and both adnexa were removed; hemicolectomy and latero-lateral anastomosis were carried out. No adjuvant irradiation was given. The patient is alive and free of disease five years after the operation. Conclusion: The gynecologist should consider retroperitoneal liposarcoma in the differential diagnosis of large pelvic or abdominal masses.

Key words: Giant; Retroperitoneal liposarcoma.

Introduction

Liposarcoma is defined as an adipocytic soft tissue tumor (STT) [1, 2]. It is a rare tumor of mesenchymal origin representing 15-20% of non osseous sarcomas but accounting for only 0.1-0.2% of adult solid tumors. Most commonly it occurs in soft tissues of the extremities, but other sites may also be involved; one fifth of liposarcomas originate in the retroperitoneum [1-3]. Retroperitoneal liposarcomas often have a slow and constant growth in the deeply hidden and clinically silent retroperitoneal space and thus achieve a considerable size before diagnosis. They can also be misdiagnosed as a huge adnexal mass, e.g. ovarian tumor, therefore the gynecologist should be aware of the possibility of having to deal with this rare and unexpected pathology [4].

The treatment of retroperitoneal liposarcomas is exclusively surgical; due to their location in a dangerous and complicated anatomic site, it represents a challenge requiring highly skilled hands [5].

However, local recurrence is a well known risk following even the most expert surgical resection, and the outcome is influenced by site, dimension, histologic subtype and tumor grade [6, 7].

Case Report

A 62-year-old woman presented with a six-month history of lower abdominal discomfort and sense of fullness, and she had 6 kg weight loss during this period. Her family medical history was unremarkable. She had hypercholesterolemia. Pelvic examination revealed a huge, smooth-walled pelvic mass that occupied the pelvis and apparently part of the abdominal cavity. The uterus seemed normal.

Ultrasonography showed a large, apparently circumscribed, non homogeneous hypoechogenic tumor that occupied the pelvis and part of the right abdomen.

At exploratory laparotomy through a longitudinal supraumbilico-pubic midline incision, a large tumor was observed that arose from the left retroperitoneal space and displaced the abdominal viscera to the right side of the abdominal cavity. An apparently well-delimited, lobulated neoplasm occupied the abdomen and the whole pelvis (Figure 1).

A surgical oncologist specialized in retroperitoneal tumors performed the complete surgical excision. It was necessary to remove part of the posterior abdominal wall including portions of the quadratus lumborum muscle and psoas minor muscle, and also the left parietal peritoneum of the diaphragm. The left colic flexure was involved and surrounded by the tumor, therefore a hemicolectomy and latero-lateral anastomosis were performed. The left kidney and spleen were not macroscopically infiltrated by the cancer but only stretched to the right not requiring excision. With the huge mass we removed the left adnexa as well, since it was involved in the neoplasm; the gynecologist performed a total hysterectomy and right salpingo-oophorectomy.

The tumor weighed 11.6 kg and measured 60 cm in the greatest diameter. On macroscopic examination the mass was well-circumscribed, encapsulated and lobulated. On section one half of the tumor appeared yellow and pale grey and was firm, while another half was intensely yellow to bright orange and very soft in consistency. No hemorrhage or necrosis were noted.

At histological examination the tumor was classified as a well-differentiated sclerosing type liposarcoma, consisting of atypical cells with hyperchromatic nuclei and lipoblasts within the matrix of the lipomatous portion that alternated with areas of dense fibrosis.

The colon excised en bloc with the mass did not prove to be microscopically infiltrated by the tumor. The uterus and adnexa were negative. After first 24 hours of intensive care and infusion of blood and plasma, the postoperative course was uneventful, and the woman was discharged after 11 days. No adjuvant irradiation was given. Five years after the treatment she is well and free of disease.

Discussion

Liposarcoma is the most common histological type of soft tissue sarcomas (STS) which represent less than 1%
of all human neoplasms [1-3]. It is frequently located in the upper or lower extremity or in the retroperitoneum. The peak incidence of this neoplasm is in the fifth and sixth decades, being more common in males [3, 4, 7].

Pathologists classify liposarcomas in different subtypes: well-differentiated (atypical lipomatous tumor), de-differentiated, mixoid, pleomorphic, and a mixed type liposarcoma showing a combination of two or three components representing 5-10% of cases [2, 3].

If this rare tumor develops in the retroperitoneal space it may remain clinically silent for years, growing and achieving a huge size as in our patient. The organs and structures are generally squizzed and slowly dislocated, while the tumor can occupy the whole abdominal cavity and the pelvis. A liposarcoma is to be considered in the differential diagnosis when both abdominal and pelvic mass are present. In most cases the symptoms are non specific (painless abdominal distension, weight gain/loss, vague sense of abdominal fullness), therefore an early diagnosis is highly unlikely [8-10].

In contrast with liposarcomas of the extremity, retroperitoneal liposarcomas are frequently recognized as large abdominal/pelvic tumors that represent a true management challenge.

Many authors have described sonographic findings of liposarcomas and tried to show a correlation between ultrasound (US) features and histology of retroperitoneal neoplasms [11, 12]. Ishida et al. [11] described a US pattern related to the well-differentiated type of retroperitoneal liposarcoma consisting of evenly distributed, multiple, fine echogenic lines corresponding to well-differentiated fatty components within the tumor. However, the evaluation of echogenity is sometimes difficult or impossible when the tumor is very large or has a complex internal structure. We performed transvaginal and abdominal scan and found a mass that seemed to be a large ovarian mucinous cystadenoma, with a sonographic pattern characterized by hypo/hyperechogenic spots filling up the huge cyst that seemed to be thin-walled. It should be stressed that it is impossible to fully explore a huge abdominal mass with US due to the limits of technology in scanning the deepest structures in the retroperitoneum behind the tumor.

Complete excision of the mass was performed due to the skill and experience of an oncologist specialized in operations for retroperitoneal neoplasms. Total removal of the mass is the most effective treatment modality, and an essential requisite for potential long-term survival and local control [5, 13-15]. The viscera excised with the tumor were not microscopically infiltrated, which is in agreement with reports in literature [15], but major organ resection is frequently performed to facilitate dissection. Given that the intention of the first operation is to attain cure, contiguous organ resection is justifiable when involved by the tumor, and this is in accord with the basic principle of en bloc resection to maximize the chance of cure [5, 15].

Nevertheless, the histological diagnosis is most important for predicting the clinical course of disease. Low-grade lesions show a high incidence of local recurrence but little to no propensity for metastasis, in contrast with high-grade or poorly differentiated tumors which often show aggressive clinical behavior with a high incidence of local recurrence and distant metastasis [7, 16, 17]. After the analysis of data collected during more than 15 years at Sloan-Kettering Cancer Center, Linehan et al. [7] observed that microscopic margin status is not as good a predictor of local recurrence as in other types of cancer, and that the assessment of microscopic margins for retroperitoneal liposarcomas is often difficult because of dimensions which are frequently very large [16].

Since there are cases with existing difficulties that need to be surgically microscopically sufficiently radical, it could be reasonable to think of introducing adjuvant therapy. The use of adjuvant radiotherapy, however, remains controversial: favorable results were observed after extended resection followed by postoperative radiation therapy, but in localized forms of liposarcomas radiotherapy was not given [18]. Namely, radiation therapy of the retroperitoneal space has the risk of generating increased fibrosis, scarring and making future resections more difficult. Any potential benefit must be weighed against the potential of these techniques to generate iatrogenic obstacles for surgical treatment for patients who will probably need more than a single intervention in this region in their lifetime [19]. Moreover, the volume to be irradiated has not been clearly established. A large retroperitoneal mass could need a wide radiation target including almost the whole abdominal/pelvic cavity and this is hard to achieve even if using new 3D ultrasound systems [18, 19].

There are data suggesting that adjuvant chemotherapy would be useful to shorten the time for the occurrence of local and distant recurrence, but for well localized resectable soft tissue sarcomas it is not applicable [20]. However, these studies cannot provide guidance on particular drug regimens due to the rarity of these tumors. Moreover, the rarity and complexity of these tumors have made the recruitment of sufficient numbers of patients...
into randomized trials very difficult, if not impossible, therefore the routine use of adjuvant chemotherapy for retroperitoneal liposarcoma cannot be considered the current standard of care that is required for all patients [20].

We used the standard pathological classification of well-differentiated liposarcoma. Currently, morphological features to classify the types of tumors are being used, yet the scientific community is already facing a new challenge, i.e., the molecular classification of tumors [21].

Segal et al. [21] have proposed a genomic-based classification of STS. The molecular classification of STS includes two major categories on the basis of 1) a single recurrent genetic alteration, such as chromosomal translocation (synovial sarcoma, myxoid/round cell liposarcoma, clear-cell sarcoma) or activating mutation, or 2) non-recurrent genetic aberrations, which form part of a complex abnormal karyotype.

The molecular classification of cancer has been prompted by the sequencing and annotation of the human genome and technical advancement in gene transcription profiling [21, 22]. This identification of subsets of STS with a particular expression profile could potentially facilitate an objective diagnosis of the tumor type and assist in subsequent therapeutic studies.

The combined approach of biological-based and morphological classification of rare neoplasms could lead to specific therapies for each subclass, if not therapy tailored for single patient’s tumor [15].

An example of the application of these researches is given by the demonstration of PPAR-γ expression in liposarcoma tumor cells. PPAR-γ is a critical regulator in the process of normal adipocyte differentiation but is also expressed in each of the major histological subtypes of liposarcoma including well-differentiated, de-differentiated, myxoid, round cell and pleomorphic liposarcomas [23, 24].

Antidiabetic drugs of the thiazolidinedione class are agonist ligands for PPAR- and ex-vivo stimulation has induced terminal differentiation in primary cultures of human liposarcoma cells, with a reduction in cellular proliferation [23, 24].

This could be used to prevent a typical long-term complication of well-differentiated liposarcomas, which is the development of pathologically and clinically higher grade non-lipogenic tumor arising within the fatty well-differentiated tumor.

Conclusions

The management of patients with retroperitoneal liposarcoma that presents as gynecological pathology remains a challenge. Even if rare, gynecologists should consider retroperitoneal liposarcoma as a differential diagnosis in patients presenting with a large ovarian tumor. We think that this should be treated by a multidisciplinary team led by a surgical oncologist with experience in techniques of en bloc resection considering the prognostic value of radical surgery in these cases.

In the near future molecular techniques of diagnosis and biologic-based tailored therapies could give us a chance to complete surgical treatment to improve patient quality of life and long-term survival.

References


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Retroperitoneal mass with ischiorectal fossa extension: diagnosis, clinical features and surgical approach. A literature review starting from a rare clinical case of primary retroperitoneal dermoid cyst

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Summary

Background: Primary retroperitoneal teratomas are rare and occur mostly in the sacrococcygeal area of children. They constitute less than 4% of all extragonadal teratomas with less than 120 cases having been reported, and only partly described in the retroperitoneum of adults. We describe an unusual case of a paravesical teratoma with ischio-rectal extension and its successful surgical management. Clinical case: A 24-year-old female was referred to our hospital with a history of pelvic pain, pressure and evidence of a pelvic-perineal tumor. Serial work-up disclosed a mass in the left paravesical fossa that bulged out through the levator-ani muscle, in the left ischial-rectal fossa, altering the symmetry of the gluteal/perineal region. At surgery a cystic tumor, consistent with a dermoid, was completely excised from the left paravesical fossa by means of a laparotomic approach. Pathological examination revealed a mature cystic teratoma. The postoperative course was smooth and the patient was doing well at two-year follow-up. Conclusion: This is the second reported case of paravesical dermoid cyst with ischio-rectal extension through the levator-ani muscle. Retroperitoneal teratomas are rare and difficult to early diagnose because of non specific signs and symptoms and should be considered in the differential diagnosis of a pelvic mass in adults. Solid and cystic morphology, fat signal and areas of calcification are some of the helpful features in diagnosing this neoplasia. Once the diagnosis is made, surgical removal is indispensable because of the indeterminate course of the disease. Prognosis depends on the histologic nature of teratoma. Patients with complete resection of benign teratoma have an excellent prognosis. Malignant teratomas, either with germ cell elements or with somatic elements, have a poor outcome.

Key words: Dermoid cyst; Mature/immature cystic teratoma; Retroperitoneal neoplasms; Paravesical fossa tumors; Ischiorectal fossa.

Introduction

Dermoid cyst, also defined as benign cystic teratoma, is a tumor comprised of a variety of parenchymal cell types representative, usually, of more than a single germ layer. Both terms are used as synonymous, although some authors continue to make a distinction, referring to dermoid cysts when indicating well arranged tumors with well-differentiated ectodermal and mesodermal derivatives surrounding endodermal tissues, and to teratoma when considering disorganized solid structures with immature components. They derive from a totipotential germ cell that can produce virtually any adult tissue (mature teratoma) and fetal tissue (immature teratoma), including abortive organs, limbs, hair, bones, and teeth.

The majority of teratomas are present in the sacrococcygeal region of infants, within the ovaries of adolescent females and within the testes of young males, but they have been identified in midline or paraxial structures such as mediastinum, retroperitoneum, pineal gland (and other intracranial and intraspinal sites) [1]. Sites for dermoid cysts also include the skin of the face, scalp and neck, and the floor of the mouth as well (Table 1).

Primary retroperitoneal teratomas are rare and occur mostly in the sacrococcygeal area of children [2] (presumably due to a concentration of rich pluripotent cells at the end of the coccyx). They constitute less than 4% of all extragonadal teratomas [3] with less than 120 cases having been reported, and only partly described in the retroperitoneum of adults [1-7]. We describe an unusual case of a paravesical teratoma with ischio-rectal extension and its successful surgical management.

Case Report

In March 2003, a 24-year-old nulliparous was sent to the Department of Obstetrics and Gynecology, University Medical Centre, Ljubljana, because of mild pelvic pain, pelvic pressure, hesitancy of micturition and constipation on and off, with a bulging lower gluteal region on the left side. Her anamnesis was unremarkable and symptoms had been going on for ten months. On physical examination, a mass 10 x 10 cm in size filled the left side of the small pelvis; the tumor was slightly mobile, had well defined margins and bulged out in the left ischial-rectal fossa, making the appearance of the perineal and gluteal regions asymmetric.

The value of serum tumoral markers (AFP, p-hCG, CEA, CA 19.9, CA 125) were within the normal range as well other hematological and biochemical investigations. Sonography, either transabdominal either transperineal, showed an hypecho
Table 1. — Anatomic location of dermoid cysts.

<table>
<thead>
<tr>
<th>Anatomical sites</th>
<th>Gonadal</th>
<th>Extragonadal</th>
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<tr>
<td>Ovaries</td>
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<td>Testes</td>
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<tr>
<td>Skin</td>
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<tr>
<td>Trunk, penile, sacrococcygeal region</td>
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<td>–</td>
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<tr>
<td>Mucous membrane</td>
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<td>Floor of the mouth, tongue, hard palate, nasopharynx, vaginal wall</td>
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<td>–</td>
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<tr>
<td>Intracranial</td>
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<tr>
<td>Pineal gland, eustachian tube, orbit, lateral ventricle</td>
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<td>Intraspinal</td>
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<td>Filum terminalis, conus medullaris or perinatal sites</td>
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<td>Mediastinum, chest</td>
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<tr>
<td>Mediastinum anterior (mainly) and posterior, lung, thyroid, pericardium</td>
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<tr>
<td>Abdominal viscera other than gonads</td>
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<tr>
<td>Omentum, mesentery, bile ducts, stomach, large bowel, liver, pouch of Douglas, bladder, placenta, fallopian tube, uterus, round ligament of the uterus</td>
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<tr>
<td>Retroperitoneal sites</td>
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<tr>
<td>Kidney, diaphragm, iliac fossa, sacrocccygeal area (in adults mainly in the aortic retroperitoneum)</td>
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</table>

Table 2. — Differential diagnosis of solid/cystic masses located in the small pelvis.

<table>
<thead>
<tr>
<th>Anatomical sites</th>
<th>Extramedullary hematopoesis</th>
<th>Granuloma after inguinal herniorrhaphy</th>
<th>Paravesical extension of psoas abscess</th>
<th>Aggressive angiomyxoma</th>
<th>Leiomyosarcoma</th>
<th>Schwannoma of the obturator nerve</th>
<th>Lipoma</th>
<th>Liposarcoma</th>
<th>Lymphangioma</th>
<th>Ectopic adrenal gland tissue</th>
<th>Hemangiopericytoma</th>
<th>Angiofollicular hyperplasia of the lymph nodes (Castleman tumor)</th>
<th>Myelolipoma</th>
</tr>
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</table>

The discussion begins with a detailed account of the clinical presentation of the patient, including the findings from physical examination, imaging studies, and laboratory tests. The differential diagnosis is critically examined, with a focus on distinguishing between solid and cystic masses, extragonadal and gonadal tumors, and other potential causes of pelvic masses. The differential diagnosis includes a wide range of conditions, such as lipomas, leiomyosarcomas, schwannomas, granulomas, and myelolipomas, among others.

The surgical approach is described in detail, highlighting the importance of careful dissection and tumor resection. The procedure includes a thorough exploration of the pelvic cavity, with a focus on the identification and delineation of the tumor boundaries. The surgical technique is tailored to the specific features of the mass, with a particular emphasis on minimizing iatrogenic trauma and preserving surrounding structures.

The postoperative course is reported, including the surgical outcomes and any complications that occurred. The patient's recovery is described, with a focus on the functional and cosmetic results of the procedure. The long-term follow-up is also mentioned, with a discussion of the potential for recurrence and the need for regular surveillance.

In conclusion, the case highlights the importance of a multidisciplinary approach to the diagnosis and management of pelvic masses, emphasizing the value of a thorough clinical history, physical examination, and imaging studies. The surgical technique employed is tailored to the specific features of the tumor, with a focus on minimizing iatrogenic trauma and preserving surrounding structures. The long-term follow-up is essential to monitor for recurrence and to ensure optimal outcomes for the patient.
Gonadal teratomas appear to arise from reproductive cells that are the haploid descendants of embryonic germ cells, through some kind of parthenogenesis [9]. This theory (germ cell theory) is reinforced by chromosomal analysis demonstrating that the gonadal teratomas, although diploid, contain pairs of identical chromosomes rather than the normal pairs of maternal and paternal.

On the contrary, Wagner et al. [10] demonstrated that extragonadal teratomas arise from cells with a diploid chromosome; from this ascertainment they suggested that these teratomas arise from either premeiotic germ cells or pluripotent ectopic embryonal or extraembryonal cells. Since every somatic cell contains the full genetic code, theoretically, without being a “germ” cell, it could produce any other type of cell (embryonic cell theory). Although this is one of the principles of cloning, it allows an alternate theory of teratoma formation from ordinary somatic cells rather than from pluripotent germ cells.

A macroscopic classification of terATOMa distinguishes two variants: cystic masses that are composed of mature elements and solid neoplasms that are more likely to contain immature tissues (mainly immature neuroepithelium whose amount is graduated by the grading scheme by Norris et al. [11]). The teratomas are also classified into three histopathologic categories: mature, made of well differentiated structures and tissues, immature, containing areas of primitive mesoderm, ectoderm or endoderm elements, and malignant containing frankly malignant tissues of germ cell origin (germinoma, yolk sac carcinoma, choriocarcinoma, endodermal sinus tumor). To these, pathologists add the “teratoma with malignant transformation” that include teratomas containing malignant non-germ-cell elements (squamous carcinoma, adenocarcinoma, melanoma, sarcomas) presumably derived from somatic tissue within the teratoma. A detailed teratoma classification system has been introduced by Olsen and Gonzales-Crussi in 1982 [8]; it allows, on the basis of the nature of tissues, their proportions and their characteristics, a better correlation of histologic findings and prognosis. According to this classification, a teratoma could be considered as mature if it contains up to 10% of undifferentiated tissue.

Figure 1. — MRI: oval formation with fluid, soft tissue and lipid densities, and with clear margins filling the left ischio-rectal fossa. 1st) coronal view, T1 weighted; 2nd) coronal view, T2 weighted; 3rd) axial view. In MRI the mass can be clearly seen [1]; the alteration of pelvic-perineal anatomy [2].

Primary retroperitoneal teratomas are rare and represent 1-11% of all retroperitoneal tumors [1], ranking third behind neuroblastoma and nephroblastoma in the pediatric population. The incidence has two peaks, in the first six months of life and in early adulthood [12] and is from two to three times more frequent in female than in males [13, 14]. In adults their prevalent locations include the lombo-aortic retroperitoneum (with a left suprarenal predominance [15]), whereas pelvic retroperitoneal locations (sacroccygeal area) are more frequent in children. It has been reported that 2% of dermoids undergo malignant transformation, mainly squamous cell carcinoma; this percentage seems to be higher for teratoma located retroperitoneally. Some authors have suggested considering mature teratomas as premalignant lesions and to carefully analyze and detect small areas of malignant change which indicate a high risk of recurrence [16]. Malignant change of teratoma is higher in adults than in children [14], with an incidence of 25.8% and 6.8%, respectively [15, 17]. However, Augè et al. [18] found a similar malignant rate (23.5%) among 34 retroperitoneal teratoma discovered during the first postnatal month. Until 1995 ten of the 40 reported cases in adults were malignant [19]. Retroperitoneal teratomas are usually asymptomatic. The most common presenting manifestation is a very large space-occupying lesion responsible for compression of neighboring organs with consequent pain, discomfort, abdominal distension, gastrointestinal and genitourinary symptoms. While benign teratomas are usually diagnosed as an incidental finding, malignant ones are usually symptomatic because of rapid growth and progression. Rarely infection or acute abdomen due to a traumatic rupture of retroperitoneal teratoma, has been described [20-22]. The workup for dermoid cysts is largely radiographic; X-rays, sonography, CT and MRI are useful for the differential diagnosis in cases of space-occupying lesions of the retroperitoneum.

Plain radiographs are useful for the preoperative diagnosis, demonstrating suggestive calcifications resembling teeth or bone in up to 74% of cases or the calcific rim of the cyst (calcifications cannot be considered a sign of
benignity since 12.5-25% of calcified tumors are malignant [17]). If calcifications are absent, an opacity or radiolucent mass causing displacement of adjacent structures could be detected.

Ultrasound may show a solid, cystic, or mixed solid and cystic mass (echocomplex appearance) occasionally with a fat-fluid level; sonographic features that suggest the specific diagnosis of dermoid cyst are the presence of echogenic spots with acoustic shadows (teeth or bone fragments) or dermoid plugs (rounded polyoid soft tissue masses projecting into the lumen made of tufts of hair or of tissue overgrowth from the inner surface of the cyst). However, sonography has limited sensitivity because of poorly identified fat and calcifications which both suggest the diagnosis of teratoma. CT scan gives more specific information and usually shows a well marginated, multilobulated mass with both cystic and solid components with fluid, fat, soft tissue and bone densities; the presence of a fatty portion, which represents sebum, is virtually pathognomonic of these tumors.

MRI has advantages over CT as its better tissue contrast enables delineation of the internal components of the tumor more accurately, as well as determination of the relations of the mass to adjacent organs [23]. MRI better delineates the five portions that usually compose a dermoid: adipose tissue, bone, hair, sebum, and loose edematous fibrofatty tissue with skin. Fat is suggested by high-intensity signals on T1-weighted images.

Angiography is an adjunctive tool useful in detecting the blood supply and presence of hypervascularity suggesting malignancy. Sometimes retroperitoneal teratomas may show abnormally high AFP [24], CEA [25], CA 19-9 [26] and CA 125 levels. Elevated serum markers are seen more often in patients with malignancy than in patients with immature or benign lesions. Postoperative rise in serum marker levels is a good indicator of recurrence only when they were also elevated preoperatively. Tumor masses of pelvic retroperitoneum should include every type of tumor arising from pelvic organs and developing extraperitoneally or from extraperitoneal structures, enlarged lymph nodes as well as non-neoplastic lesions including lymphoceles, abscess and hematoma. The differential diagnosis of cystic/solid tumors filling the lateral pelvic space should consider extramedullary hematopoiesis [27], granuloma after inguinal herniorrhaphy [28, 29], paravesical extension of psoas abscess [30], aggressive angiomyxoma [31], leiomyosarcoma [32], schwannoma of the obturator nerve [33], lipoma [34], liposarcoma [35], lymphangioma [36], ectopic adrenal gland tissue [37], hemangiopericytoma [38, 39], angiofibrolaricular hyperplasia of the lymph nodes (Castleman tumor) [40], and myelolipoma [41]. It should be emphasized that teratoma is a surgical disease, with chemotherapy and radiotherapy having a relatively small role. The treatment of choice for retroperitoneal tumors is complete surgical excision, since definitive diagnosis is only achieved following histologic evaluation of the specimen. Other reasons are worsening symptoms and life threatening complications associated with the increasing mass effect as the tumor continues to grow, acute complications related to cystic rupture, or infection and malignant changes. Squamous carcinoma or malignant melanoma may develop from the skin components though this is rare; adenocarcinoma [42] and carcinoid [43] have recently been reported. The prognosis is excellent if complete surgical resection can be accomplished. When possible, the laparoscopic route potentially allows for a rapid recovery and minimal morbidity but requires laparoscopic skills and thorough preoperative planning.

Prognosis depends on the histologic nature of the teratoma. Patients with complete resection of benign teratomas have an excellent prognosis. Malignant teratomas, either with germ cell elements or somatic elements, have a poor outcome.

Conclusion

This is the second reported case [44] of a paravesical dermoid cyst with ischio-rectal extension through the levator-ani muscle. Retroperitoneal teratomas are rare and difficult to diagnose early because of non specific signs and symptoms, and should be considered in the differential diagnosis of a pelvic mass in adults. Solid and cystic morphology, fat signal and areas of calcification are some of the helpful features in the diagnosis of this neoplasm. Once the diagnosis is made, surgical removal is indispensable because of the indeterminate course of the disease.

References

Retroperitoneal mass with ischiorectal fossa extension: diagnosis, clinical features and surgical approach. A literature review.


**Mullerian adenosarcoma of the uterus: a rare neoplasm with a need for onco-fertility**

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**Summary**

A 23-year-old nulliparous woman re-presented with menorrhagia and intermenstrual bleeding two years after her first presentation with a similar history. Her initial symptoms were thought to be due to a removed fibroid polyp with histological confirmation. However, at the second presentation, following a polypectomy, a diagnosis of low-grade mullerian adenocarcinoma of the uterine body was made. She had total abdominal hysterectomy and pelvic lymph node dissection. Peritoneal fluid was collected for cytology to conserve her fertility. No residual tumour was found and lymph nodes were negative. She remains well under clinical surveillance in a multidisciplinary team setting. Different management options that have been used in past reports have been examined and also fertility sparing surgical techniques available for use in successful management of gynaecological cancer are also being explored to shed more light on potential surgical techniques that may be used in treating such rare tumours, particularly in women wishing to retain their fertility.

**Key words:** Fertility; Mullerian adenocarcinoma; Fertility-sparing surgical techniques.

**Introduction**

Mullerian adenosarcoma of the uterus is a rare occurrence, particularly in premenopausal women. It comprises benign mullerian epithelium and sarcomatous stroma. There is little data on the ideal management of the condition.

Due to improved cancer treatment, cancer survivors are living longer. Women wish to have children with the hope of improving their quality of life. In a scenario where the patient in question is keen to retain her fertility, the fertility-sparing surgical options available have to be considered.

**Case Report**

A 23-year-old nulliparous woman presented for the second time with menorrhagia and intermenstrual bleeding two years after her first presentation with a similar history. The initial presentation was attributed to a fibroid polyp confirmed on histology. However, at the second presentation, following a polypectomy, a diagnosis of low-grade mullerian adenocarcinoma of the uterine body was made. She had total abdominal hysterectomy and pelvic lymph node dissection. Peritoneal fluid was collected for cytology with conservation of ovaries to preserve her fertility. No residual tumour was found and lymph nodes were negative. She remains well under clinical surveillance in a multidisciplinary team setting.

**Discussion**

Uterine mullerian sarcoma is a rare subtype of uterine cancer and few cases have been reported in the literature. It is composed of benign mullerian epithelium and sarcomatous stroma [1]. The incidence is unknown and occurs largely in postmenopausal women [2]. The survival rate is unknown but poor prognostic factors have been suggested to include depth of invasion, sarcomatous overgrowth, high-grade malignant features in the stromal component and extra-uterine genital lesions [1]. It presents typically as vaginal bleeding, polyps (recurrent) or simply as a pelvic mass. Management of the condition has been varied as reported in several studies [1-3] and includes hysterectomy plus or minus bilateral salpingo-oophorectomy plus or minus chemotherapy and radiotherapy. Therapy has been individually tailored. As recurrences may occur locally or after long periods of remission following initial conservative treatments (cone biopsy/ trachelectomy), long-term follow-up has been suggested [1].

With sparse available literature, management of these patients in a multi-disciplinary setting could be at best tricky.

Management of this patient was limited to a total abdominal hysterectomy and long-term surveillance in order to preserve her fertility. This management plan was arrived at by taking into account the low-grade nature of the lesion, lack of invasion and extra-genital lesions, and the patients wish to retain her fertility. The procedure was carried out after due counseling, particularly regarding risks of recurrent disease, need for long-term surveillance.
and need for hysterectomy in the future once having completed her family. A radical trachelectomy or cone biopsy could not be offered as the original polyp had been at the level of the upper third of the uterine body. This option could avail a young nulliparous woman the opportunity of having her ‘genetic’ children through the use of a surrogate mother.

Fertility preservation in oncology is becoming an increasing concern. Due to improved cancer treatment, cancer survivors are living longer with the women nursing the hope of becoming parents in order to improve their quality of life. As it is not uncommon for women in Western society to delay child-bearing, the risks of developing illnesses before having children increase. A dilemma exists as it is widely known that traditional treatment of gynaecological cancers result in loss of fertility. Recent surgical advances such as laparoscopic approaches and robotic surgery have been made primarily to reduce treatment-related morbidity but have also been seen to be fertility sparing.

An overview of fertility-sparing surgical techniques used in the management of common gynaecological cancers is discussed below. These techniques may be considered for use in managing a patient keen on retaining her fertility. The type and stage of tumour, degree of differentiation, presence of hormonal pathophysiology and the presence of other prognostic factors will play an important role in determining type of technique, if indicated, to be used. It goes without saying that decisions are made after adequate counseling of the patient in a multidisciplinary setting regarding inadequate staging, recurrence or metastases of disease, her chances of fertility, need for assisted reproductive techniques, the obstetric risks of miscarriages, and preterm labour with attendant risks of long-term fetal impairment.

Cone biopsy for FIGO Stage 1A1 cervical cancer has been advocated. Heat artifact as a result of diathermy leading to difficulty in staging the disease precludes the use of large loop excision of the transformation zone (LLETZ), hence it is not recommended. For Stage 1A2 disease, pelvic node dissection is needed in addition to large cone biopsy [4]. Laparoscopic pelvic node dissection with radical trachelectomy is advocated for FIGO Stage 1B1 disease [5]. Ovarian transposition into the paracolic gutters for Stage 1B2 and above in combination with radical trachelectomy is recommended with or without oocyte retrieval [6, 7]. This protects patients from radiotherapy but not from the cytotoxic effects of chemotherapy [8].

As there is a 6% incidence of endometrial cancer under the age of 50, fertility will be of concern to some of these women [9]. The use of progestogens in the successful conservative management of these women with Stage 1A disease has been reported [10]. However the disease has to be accurately staged to avoid progression of a disease that could have been cured by hysterectomy to an advanced incurable stage. Risks of under-treatment is a concern as some 10-29% of young women with endometrial cancer may have co-existing ovarian cancer [11, 12].

A study by Ushijima et al. [13] reported recurrence rates as high as 47% of women between seven and 36 months with 12 pregnancies and seven deliveries in a cohort of 28 women over a 3-year follow-up period. The women have to be adequately counseled as to the risks.

Ovarian cancer is the most common female gynaecological cancer in the U.K. with 10% occurring in women of reproductive age [14]. The most common ovarian tumours in young women are germ cell tumours hence the need for oncofertility. Conservative unilateral salpingo-oophorectomy for Stage 1 germ cell tumours has been advocated by Zanetta et al. [15] following a low recurrence rate of disease and a subsequent high rate of conception and delivery.

As most borderline epithelial ovarian tumours are confined to the ovaries, preservation of the uterus and contralateral ovary may be offered, otherwise bilateral ovarian cystectomies can be performed [4]. Though recurrence rates are reported to be higher in women who have had fertility sparing surgery, survival rates are similar to women who have had hysterectomy and bilateral salpingo-oophorectomy within this subgroup of tumours [16]. Full surgical staging including peritoneal washings, omentectomy and ipsilateral paraaortic lymph node dissection is needed before unilateral salpingo-oophorectomy is offered. Endometrial biopsy should be advised as there is a 10-29% incidence of co-existing endometrial cancer.

Other fertility preservation techniques which are not widely available include oocyte retrieval (this option is sometimes used in Stage 1B2 cervical cancer and above. The risk of disease progression during delay of commencing treatment needs to be discussed with the woman) [6, 7]. In vitro fertilization is carried out with later transfer of embryos into the patient herself or a surrogate mother. Embryo cryopreservation is the only recognized method of fertility preservation according to the Ethics Committee of the American Society for Reproductive Medicine (2005), but this requires the woman be of pubertal age, have a partner or use donor sperm, and be able to undergo a cycle of ovarian stimulation (if this is not contraindicated by type of cancer). As this option may not be available for single or virgin women or even possible prepubertal girls, transplantation of human ovarian tissue is another option which is under development with limited success. Of almost 30 cases in the literature, six live births have been reported [17].

For choriocarcinomas, chemotherapy has proven to be a successful treatment intervention. For cases limited to the uterus total cure has been recorded, while cure for those with metastases has been over 90%. Though rare, its incidence is higher in certain ethnicities hence its discussion.

When considering oncofertility, careful staging with histological grading of the disease is needed with cautious patient selection. Adequate counseling regarding the risk of incomplete excision due to inadequate staging, recurrence, or metastases of disease is needed. This is necessary as the safety of certain procedures has been...
questioned. Due to the risk of ovarian metastases following ovarian transposition in women with bulky disease or lymphovascular space involvement, its safety is questionable [18-20].

Secondly, chances of fertility have to be discussed (some series have reported up to a 70% pregnancy rate following radical trachelectomy [21]). Pregnancies have also been reported in women who had undergone ovarian transposition [22]. There is little information regarding the background fecundity. Therefore an assessment of background fecundity and presence of comorbidities must be made as these will be confounding factors.

Thirdly, the risks of obstetric complications such as miscarriages, preterm labour and its sequelae in the fetus delivered before 34 weeks should be discussed with the woman. As there is a significant risk of preterm labour following certain treatments (incidence of preterm deliv-
eries in women who have undergone radical trachelectomy has been reported by Shepherd et al. to be about 25% [23], adequate counselling has to be put in place.

Conclusion

Mullerian adenosarcoma is a fairly rare tumour which can present at anytime during a woman’s reproductive period. In those women still keen to retain their fertility, fertility-sparing techniques or management need to be considered. Oncofertility is an emerging subspecialty which affords women who have survived their malignancies to achieve their dreams of becoming mothers in order to improve their quality of life. Difficult decisions may have to be made following adequate counseling in a particularly rare tumour such as this.

However it is imperative that surgeons are aware of fertility-sparing surgical techniques currently available, indications and limitations according to tumour type, degree of differentiation and treatment, and also possess the ability of relaying these to the patient in an unbiased manner while providing care in a multi-disciplinary setting of adequate expertise.

References


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Primary mixed epithelial and germ cell tumors of the ovary.
Two case reports and literature review

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Summary

Two cases of mixed germ cell and epithelial primary ovarian tumors which developed in women 47 and 57 years of age are reported. In both cases, large teratomas measuring 20 and 21 cm were observed in combination with carcinoids and malignant mucinous neoplasms. A possible common oncogenic mechanism is discussed and a literature review is presented.

Key words: Mucinous adenocarcinoma; Dermoid cyst; Carcinoid; Degeneration.

Introduction

Mature cystic teratomas are common benign ovarian tumors (10-20% of all ovarian neoplasms) [1, 2]. They could occur at any age, however the peak incidence is reported between 20 and 40 years old [3]. They are composed of mesodermal, endodermal and ectodermal elements such as hair follicles and teeth [4]. Malignant transformation of mature cystic teratoma is an uncommon complication [5, 6]. Most cases of malignant transformation are detected between age 30 and 70 years [7, 8]. Primary goblet cell/mucinous carcinoids of the ovaries are frequently found in association with mucinous tumors and rarely with mucinous cystadenocarcinomas arising from mature cystic teratomas [9, 10]. This report describes two cases of an ovarian borderline mucinous adenocarcinoma and an ovarian borderline mucinous cystadenoma with characteristics of insular carcinoid tumor arising in a cystic teratoma of the right ovary, respectively. These cases were selected among 87 cases of ovarian teratomas studied from 1996-2005 in our Department.

Case Reports

Case 1

A 45-year-old non-smoking woman, gravida 2, para 2, was referred to our hospital due to a 6-month history of palpable mass and complaints of dysuria. There was no previous history of routine gynecologic examinations. The physical examination revealed a 20 cm in size cystic mass in the right adnexa and a 10 cm in size cystic mass in the left adnexa. CA-125 levels preoperatively were 65 IU/ml, whereas CA19-9 levels were 98 IU/ml. Ultrasound (US) showed a huge cystic ovarian mass with no ascites. Computed tomography (CT) scanning revealed two cystic masses measuring 21 x 12 x 10 cm and 11 x 6 x 5 cm in the right and left adnexa, respectively, with characteristics of dermoid cysts (mucus, teeth). Laparotomy revealed a huge cystic mass in the right ovary and a smaller cystic mass in the left ovary. Hysterectomy with bilateral salpingo-oophorectomy was performed. The postoperative period was uneventful. Pathologic findings were as follows:

a) Right adnexa measuring 24 x 14 x 10 cm and weighing 4750 g which was composed of a multilocular cyst with solid nodules of soft, yellowish tissue and a tooth;

b) Left adnexa measuring 11 x 5.5 x 5 cm with hair follicles and a tooth.

c) Normal size of the uterus (8 x 7 x 3 cm) with six fibroids measuring 2.5-0.3 cm.

On microscopic examination, the right cyst with elements of mature teratoma was found to be borderline mucinous cystadenocarcinoma with production of signet ring and mucus. The morphological characteristics were of a goblet cell/mucinous carcinoid. Immunohistochemically, the carcinoid part was positive for chromogranin, synaptophysin, AE3 and CEA. The microscopic examination of the left ovary revealed a cystic mature teratoma.

Case 2

A 57-year-old woman presented in our department complaining of abdominal swelling for six months. CT scan revealed bilateral ovarian cysts measuring 20 x 16 x 13 cm and 7 x 5 x 4 cm in the right and left ovary, respectively. Laparotomy confirmed the diagnosis and the patient underwent bilateral salpingo-oophorectomy and hysterectomy. The pathologic findings were as follows: a 23 x 17 x 13 cm right ovary was composed of a multilocular cyst with solid nodules of soft, yellowish tissue. The left ovary measured 7 x 5.5 x 4 cm. Microscopic examination revealed a cyst with elements of mature teratoma, lined by mucinous epithelium, showing slight to moderate cellular atypia and moderate nuclear stratification of borderline mucinous cystadenoma. The solid neoplasm was composed of nests of atypical cells with the appearance of an insular carcinoid. Immunohistochemistry showed that the carcinoid part was positive for neuron-specific enolase, chromogranin and synaptophysin. The microscopic examination of the left ovary revealed a cystic mature teratoma.

Discussion

The frequency of malignant transformation of mature cystic teratomas is 6.8% [4]. Carcinoma could arise from any of the epithelial elements [4], whereas the most frequent transformation is squamous cell carcinoma [11].
The first case of a borderline mucinous adenocarcinoma in a mature cystic teratoma was presented by Hunter et al. in 1988 [12]. Other neoplasms arising in mature cystic teratomas are basal cell carcinoma, adenosquamous carcinoma, thyroid carcinoma, malignant melanoma, sarcoma, neuroectodermal tumor and carcinoid tumor [13].

Teratomas with a malignant transformation have a more aggressive course [4]. Cyst wall invasion, rupture, tumor dissemination, ascites, adhesions and tumor types different than squamous cell carcinomas are poor prognostic factors of the tumor [14]. Mucinous cysts and/or mucinous cystadenomas are complicated with ovarian carcinoids [9, 10].

The hypothesis that ovarian borderline mucinous cystadenocarcinomas and carcinoids arise from argentaffin cells could be proposed as an explanation of our findings [15]. According to Okada et al. if a cystic teratoma during CT or US scanning is accompanied with a multiseptated cyst and if that cyst contains fatty foci, the potential of the coexistence of ovarian tumors should be suspected [16].

References


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Grade 2 endometrioid adenocarcinoma arising from adenomyosis of the uterus: report of a case

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Introduction

Adenomyosis is a frequent disorder in women and endometrial carcinoma cases have had coexistent adenomyosis in 16-60% [1, 2]. However, adenocarcinoma arising from uterine adenomyosis with a normal endometrium is a very rare situation. We report the case of a 59-year-old woman with a pelvic mass diagnosed as endometrioid carcinoma arising from adenomyosis of the uterus.

Case Report

The patient, a 59-year-old woman, was admitted to the gynecology clinic of Ege University Hospital with the complaint of pelvic pain. She had been in the postmenopausal period for nine years. Her surgical history included a cholecystectomy for gallstone disease and an umbilical hernia repair afterwards. Pelvic examination revealed a solid mass, 15 x 10 cm in diameter, located in the pelvis. Transvaginal sonography (TVS) showed a heteroechogenous pelvic mass involving the uterus, 15 cm in size. Pelvic computed tomography (CT) revealed a pelvic mass like a leiomyoma nodule filling the left lower quadrant of the pelvis. Preoperative tumor markers were as follows: CA125: 489 U/ml, CA19.9: 854 U/ml, CA15.3: 141 U/ml. Colonoscopy and mammography were both within normal limits. Laparatomic exploration revealed a solid mass originating from the fundus of the uterus adherent to the sigmoid colon 15 x 9 cm in diameter. Both ovaries were atrophic. The fragile mass was extirpated in pieces from the serosa of the sigmoid colon and the serosal defect was sutured. After extirpation of the mass, the remaining isthmic part of the uterus and both adnexa were removed. Three units of erythrocyte suspension were transfused during the operation. The postoperative period was uneventful except for a wound dehiscence.

Pathological findings showed solid mass pieces and the cut surfaces were coarsely trabecular in pattern. Microscopically, grade 2 endometrioid adenocarcinoma was discovered. Lymphovascular invasion was present. There was no tumor involvement of the endometrial cavity (Figures 1, 2, 3).

Discussion

The diagnostic criteria for carcinoma arising from adenomyosis are: 1) The carcinoma must not be situated in the endometrium or elsewhere in the pelvic area; 2) The carcinoma must demonstrate a direct transition from benign to malignant, and stroma with epithelial elements must be found; 3) Endometrial stromal cells must be present to support a diagnosis of adenocarcinoma arising from adenomyosis [3-5].

Hsu et al. [6] reported a grade 1 endometrioid adenocarcinoma in a focus of adenomyosis with normal proliferative phase endometrium. From a pathological point of view, distinguishing an adenocarcinoma that invades the myometrium and that of carcinoma exhibiting intramural extension into foci of adenomyosis is very important for accurate surgical staging [7]. For example women with endometrial adenocarcinoma extending directly (without myometrial invasion) into foci of adenomyosis have an excellent prognosis and need no further treatment [8, 9]. On the other hand myometrial invasion adjacent to foci of adenomyosis may require further therapy depending on the depth of myometrial invasion. Although radiologic modalities such as TVS, intraoperative sonography and magnetic resonance imaging may be used to predict myometrial invasion for endometrial cancer and thus the extent of surgical staging [10], ideally the pathologist is requested peroperatively to assess the depth of myometrial invasion. This is important to select patients for lymphadenectomy.

The prognostic features of adenocarcinomas arising from adenomyosis are not well described because of the rarity of the situation. Immunohistochemical studies have demonstrated that endometrial carcinomas with p53 overexpression and lack of estrogen or progesterone receptor had poor prognosis [11]. Taskin and colleagues [12] studied 94 patients with endometrial adenocarcinoma, including those with adenomyosis and a control group with adenomyosis cases but without endometrial cancer. They failed to find p53 positivity by immunohistochem-

Summary

Adenomyosis is defined by the presence of endometrial tissue (glands and stroma) within the myometrium and malignant transformation of adenomyosis in premenopausal women with normal endometrium is extremely rare. Adenocarcinomas arising within adenomyosis need to be distinguished from endometrial carcinomas which arise from the eutopic endometrium, then extend into preexisting adenomyosis of the uterine wall. We report a case of grade 2 endometrioid adenocarcinoma arising from an adenomyotic focus in the uterus.

Key words: Endometrioid adenocarcinoma; Adenomyosis.
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istry in foci of adenomyosis without endometrial carcinoma; however, p53 was present in 7/28 (25%) cases of adenomyosis with co-existent endometrioid adenocarcinoma. It is therefore possible that a defect in the p53 tumor suppressor gene may play an important role in the de novo neoplastic transformation of adenomyosis. Also studies have shown that endometrial adenocarcinoma arising from adenomyosis had a weak expression of hormone receptors compared with adenomyotic lesions that were strongly positive for estrogen receptors and progesterone receptors in all cases [3, 13]. This may indicate non-hormonal-dependent growth.

In summary we have reported a case of endometrioid adenocarcinoma arising in adenomyosis. The clinical importance of the present case is the grade 2 endometrioid adenocarcinoma with lymphovascular invasion originating from adenomyosis.

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