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Surveillance of endometrial pathologies, especially for endometrial cancer, of breast cancer patients under tamoxifen treatment

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Summary
Tamoxifen is the antihormonal treatment of choice for postmenopausal breast cancer patients with positive estrogen receptors. One of the most significant and deleterious side-effects of TAM treatment appears to be a proliferative effect on the endometrium, including endometrial cancer. Today no active screening for patients treated with tamoxifen other than routine annual gynecologic surveillance is recommended, however many investigators have recommended that those women should warrant closer gynecological surveillance for endometrial cancer during treatment, especially those with high-risk factors. This article evaluates the diagnostic flow chart for the surveillance of endometrial pathologies in tamoxifen-treated breast cancer patients, according to the literature and to the Committee Opinion of the Triveneto Directors of Gynecological and Obstetrical Departments (North-east Italy).

Key words: Endometrial cancer; Breast cancer; Tamoxifen.

Introduction
Tamoxifen, a selective estrogen receptor modulator, is one of the most commonly prescribed antineoplastic drugs in the world. Tamoxifen has a complex mechanism of action including anti-estrogenic activity in the breast and estrogenic effects in other tissues, including the endometrium. It is widely used for the treatment of breast cancer and for chemoprevention in high risk pre- and postmenopausal women [1-4]. Tamoxifen has been shown to cause adverse effects at the uterine level, of which endometrial carcinoma and uterine sarcoma are the most significant [1-4].

Controversy exists regarding appropriate surveillance for endometrial cancer in these patients, and surveys have indicated that some physicians favor surveillance of asymptomatic breast cancer patients treated with tamoxifen [1, 5, 6].

Currently the American College of Obstetricians and Gynecologists (ACOG) does not recommend screening by endometrial biopsy or transvaginal ultrasound (TVS) for asymptomatic women treated with tamoxifen. The ACOG does recommend a baseline gynecologic evaluation prior to the initiation of tamoxifen followed by routine annual gynecologic evaluation [7, 8].

Women should be informed about the risk of endometrial hyperplasia, endometrial cancer, and uterine sarcoma and should promptly report any abnormal vaginal symptoms, and any abnormal vaginal bleeding should be investigated [7-9].

Endometrial hyperplasia without atypia diagnosed before endocrine therapy for breast cancer in menopausal women shows an early and high progression-rate to atypical lesions under tamoxifen influence [10].

Tamoxifen (TAM) treatment of breast cancer is associated with an increased risk of endometrial cancer, but tamoxifen-related risks of endometrial cancer are unclear in premenopausal women, in long-term users of TAM, and in women for whom several years have passed since ending treatment [11-15].

There is an increasing risk of endometrial cancer associated with longer TAM treatment, extending well beyond five years. The increased risk of endometrial cancer associated with TAM treatment should be considered clinically for both premenopausal and postmenopausal women during treatment and for at least five years after the last treatment [12-16].

Tamoxifen-treated patients develop endometrial malignancies with a higher incidence of poor prognostic malignancies [11, 12]. TAM increases the risk of uterine corpus cancer, and long-term TAM users have shown a higher proportion of non-endometrioid tumors than non-users (32.7% vs 17.4%), especially serous adenocarcinomas and carcinosarcomas. An increased proportion of FIGO Stage III and IV tumors was also observed in several studies (20% vs 11.3%). Tamoxifen-associated tumors have less favorable histological features and worse survival [11-15].

Currently no active screening for patients treated with TAM other than routine annual gynecologic surveillance is recommended [8].

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Overview

Different types of endometrial pathologies are reported in association with postmenopausal TAM treatment, including endometrial cancer and sarcoma [11, 12]. However, the ACOG Committee Opinion on TAM and endometrial cancer found the prospective trials on proper follow-up of asymptomatic postmenopausal breast cancer TAM-treated patients as insufficient to give definitive guidelines. As screening tests have not been effective in increasing the early detection of endometrial cancer in women using TAM, they are not recommended. Investigations should be performed only in case of any abnormal vaginal bleeding, bloody vaginal discharge, staining or spotting [1, 3, 10, 15].

However, many investigators have recommended that postmenopausal women who receive TAM for breast cancer should warrant closer gynecological surveillance during treatment, especially those with positive estrogen replacement therapy (ERT) histories, those obese, as well as long-term TAM users [9, 17]. Their close supervision is of importance, especially if the patients experience any gynecological symptoms including pelvic pain or pressure.

The prevalence of thickened endometrium in postmenopausal breast cancer patients taking tamoxifen is extraordinarily high [9, 17]. There is however a discrepancy between the value and the endometrial abnormalities detected histologically [6, 7, 15, 18, 19]. Therefore radiologists need to be familiar with the effects of tamoxifen on the genital tract, and the strengths and weakness of the imaging modalities [20, 21]. To aid in that process, we offer an imaging algorithm based on results in published reports [21, 22]. TVS should be the first-line imaging modality for evaluation of the uterus in asymptomatic women undergoing tamoxifen treatment.

Although there is nonconsensus, we conservatively use 8 mm as the upper limit for endometrial thickness. Asymptomatic women can be screened annually with TVS from one to two years after starting TAM. The strength of TVS is the normal finding. In cases where the TVS image is non-diagnostic or is suggestive of abnormality, sonohysterography can be used to image polyps and endometrial-myometrial/subendometrial cysts with confidence, and can help direct sampling procedures when necessary.

Saline infusion sonohysterography (SIS) has been reported to enhance the accuracy of TVS in detecting endometrial pathologies, in asymptomatic, postmenopausal TAM-treated women with abnormal endometrial thickness. SIS improves the accuracy of diagnosis of an intrauterine mass in asymptomatic women. Assessing the size of an intrauterine mass with SIS generates more information and improves the accuracy of examinations; size of the intrauterine mass correlates with severity of the endometrial pathology [20-26].

The increased risk of endometrial cancer developing in polyps in this iatrogenic context is estimated between 2.5% and 10% in the literature [25].

Polyps containing proliferative endometrium have a diameter of 5.4-5.1 mm, while those containing simple hyperplasia have a diameter of 24.8 ± 13.8 mm. Moreover, a single polyp containing malignancy has a diameter of 43 mm. Any additional millimeter in the diameter of the intrauterine mass detected by SIS increases the risk of developing new endometrial pathology by 1.37-fold [16-23].

Magnetic resonance imaging (MRI) may be appropriate in patients with an equivocal or abnormal endovaginal TVS scan who are unable to undergo SIS due to cervical stenosis and centers that do not offer SIS [17, 19-25].

Operative hysteroscopy should be performed when an intrauterine echogenic mass has been identified. All other cases must be followed with diagnostic hysteroscopy and endometrial sampling [17, 19-25].

DIAGNOSTIC FLOW CHART for women under TAM treatment (premenopausal and post-menopausal women) proposed by “COLLEGIO TRIVENETO” (Directors of Gynecological and Obstetrical Departments, North-east Italy).

BEFORE STARTING TAM treatment

• Gynecological visit
• Pap test
• TVS
  – Menopausal women with endometrial thickness < 4 mm: No biopsy before starting required [27-29].
  – Menopausal women with endometrial thickness > 4 mm: SIS to detect endocavitary lesions. Diagnostic hysteroscopy with endometrial biopsy if endometrial thickness is confirmed without lesions. Operative hysteroscopy if lesions with histological sampling.
  – Premenopausal women - morphological study of the endometrium: SIS to detect endocavitary lesions if there are endometrial profile irregularities. Diagnostic hysteroscopy with endometrial biopsy if endometrial irregularities are confirmed without endocavitary lesions; Operative hysteroscopy if lesions, followed by histological sampling [27-29].

DURING TAM treatment

• Gynecological visit yearly
• Repeat TVS in both premenopausal and postmenopausal women after two and five years of treatment
• EVERY AUB or vaginal bleeding or spotting should be investigated with biopsy (dilatation and curettage, operative hysteroscopy, diagnostic hysteroscopy with visual-guided biopsy)
• If atypical hyperplasia occurs TAM treatment should be interrupted and the endometrium should be investigated with biopsy (dilatation and curettage, operative hysteroscopy, diagnostic hysteroscopy with visually guided biopsy). If atypical hyperplasia is confirmed total hysterectomy should be performed to avoid progression to endometrial cancer (EIN).

• Restarting TAM treatment after hysterectomy is possible according to the oncologic end-point.

Conclusions

Tamoxifen is the antihormonal treatment of choice for postmenopausal breast cancer patients with positive estrogen receptors. One of the most significant and deleterious side-effects of postmenopausal TAM treatment appears to be its proliferative effect on the endometrium. Overall endometrial pathologies, including hyperplasia, polyps, carcinoma and sarcoma have been identified in up to 36.0% of postmenopausal breast cancer TAM-treated patients [1, 2, 5, 15-24].

Different types of endometrial pathologies have been reported in association with postmenopausal TAM treatment, including endometrial cancer and sarcoma [11, 12]. However, the last ACOG Committee Opinion on TAM and endometrial cancer found the prospective trials on proper follow-up of asymptomatic postmenopausal breast cancer TAM-treated patients as insufficient to give definitive guidelines. As screening tests have not been effective in increasing the early detection of endometrial cancer in women using TAM, they are not recommended. Investigation should be performed only in case of any abnormal vaginal bleeding, bloody vaginal discharge, staining or spotting [3, 4, 6-9, 16].

However, many investigators recommended that postmenopausal women who receive TAM for breast cancer should warrant closer gynecological surveillance for endometrial cancer during treatment, especially those with positive ERT histories, those obese when prescribed TAM as well as long-term TAM users [2, 3, 14, 17, 24].

Moreover, in view of the latest findings - that two-thirds of endometrial cancers diagnosed in postmenopausal breast cancer TAM-treated patients are poorly differentiated and progeses poorer than endometrial cancers found in non-treated patients, clinicians should be alerted to these pathologies, especially EIN and MMT, which may, in some cases, potentially increase the mortality rate of these patients [3, 11, 12, 16]. Consequently, it has been suggested that close supervision is important, especially if the patients experience any gynecological symptoms, including pelvic pain or pressure [19, 21].

In asymptomatic postmenopausal breast cancer TAM-treated patients, the use of wider ultrasonographic endometrial cutoff values could be associated not only with the performance of fewer endometrial samplings, but also with a higher possibility of endometrial pathologies, including endometrial cancers being left undiagnosed [6, 20-24].

Vaginal sonography monitoring could be proposed to premenopausal women treated with TAM among whom endometrial pathology is usual. TVS alone is useful in asymptomatic patients because it selects patients with increased endometrial thickness who should undergo hysterectomy. Hysteroscopy is more accurate in detecting polyps, hyperplastic and neoplastic changes. Asymptomatic TAM-treated women should be evaluated as symptomatic patients.

References


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Patterns of care in the initial management of women with ovarian cancer in Ontario

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Summary

Background: To facilitate the planning of future resources for cancer services in Ontario, Cancer Care Ontario commissioned an evaluation of operative services delivered for ovarian cancers. The affected population was characterized in terms of age, location of residence, and SES. Operative care delivery was described in terms of inpatient versus outpatient access, LHIN of treatment, surgical specialist providing treatment, and specific operative procedures. The investigations and consults around the time of diagnosis are described. Methods: Women with an incident diagnosis of an ovarian malignancy were identified from 1 April 2003 to 31 March 2004 using the Ontario Cancer Registry. Record linkages were created to other provincial health databases such as the Ontario Health Insurance Plan. Results: We report on 963 women with ovarian cancer. The incidence of disease was related to increasing age. Access to surgery correlated with the highest income quintile, urban residence and LHIN. Twenty-seven percent of women did not have surgery for their ovarian cancer. Women of younger age were more likely to receive surgery for ovarian cancer. Use of a laparotomy for biopsy was most common in community hospital (40%). Lymphadenectomy rates were low overall; rates for gynecologic oncologists were 13.2%. All women were assessed by CXR. CT scan of abdomen and pelvis occurred in 77% of women. MRIs were done infrequently. Medical oncology were involved in 26.6% of the patients. Conclusions: These pilot data would be enhanced with further information such as comorbidity, treatment intent (palliative/curative), histology, grade and stage. However, there are clear referral patterns to academic centres which means a need for manpower and hospital resources to deal with this population.

Key words: Ovarian cancer, Health services.

Introduction

Canadians are concerned about timely access to cancer surgery [1]. To validate this concern, a formal provincial assessment of surgical waiting times has shown that there is geographic variation in access to care. Formulating health care policy around surgical waiting times and geographic variations in access to care begins with understanding what services are currently being accessed. The objective of this report is to provide information on operative services for ovarian cancers in Ontario. We will: 1. Characterize the patients; 2. Inventory the components of the operative procedure; and 3. Describe the health services women receive peri-operatively.

Methods

Ethics approval for this study was obtained from the Research Ethics Board at Sunnybrook and Women’s College Hospital. This was a population-based study of all women with an incident ovarian cancer from 1 April 2003 to 31 March 2004. The International Classification for Disease codes (ICD-9) for ovarian cancer used was 183. The cohort was identified using the Ontario Cancer Registry (OCR). There was record linkage to other provincial health databases such as Ontario Health Insurance Plan (OHIP), Canadian Institute for Health Information (CIHI) discharge abstract database (DAD) and same day surgery (SDS), and National Ambulatory Care Reporting System (NACRS) to within one year of diagnosis. To be included the patient required a valid OHIP number and was 18 years or older at the time of diagnosis. Patient age and postal code at time of surgery were obtained from the Ministry of Health and Long-Term Care Registered Persons Database (RPDB). Patients’ postal codes were used to obtain ecologic income quintiles and conversion to Local Health Integration Networks (LHIN) using Statistics Canada conversion files. There are 14 Local Health Integrated Networks (LHIN) in Ontario. These are non-for-profit corporations that work with local health care providers and community members to determine health care priorities for their region. Vital statistics information (Socio-economic status, urban/rural residence) was available through RPDB. Spot checks on the procedure data by cancer site showed congruence between the CCI procedure codes and the OHIP billed procedure to within 5%. The top 20 CCI therapeutic and diagnostic procedure codes associated with the disease were identified to within 1% of the count for a period of 2002-2005.

Statistical analysis was performed using SAS 9.1. Age was stratified into four cohorts (20-35, 36-49, 50-69, 70 years and over). All numbers reported here are age standardized per 100,000 women 20 years and older (ASR). Socioeconomic status was measured by the median household income in the neighborhood where the women lived. This was distributed into five quintiles. Rural versus urban residence was classified by one of three community population sizes (< 100,000, 100,000-1,249,000 and over 1,249,000). Physician specialty was identified manually crosschecked using Scott’s Medical Database. Surgeon type was gynecologic oncologist, gynecologist, general surgeon and other.
Results

Demographics: Incidence and Treatment

From April 1, 2003 to March 31, 2004, 963 women in Ontario developed epithelial ovarian cancer (EOC). Surgery was part of the treatment in 72.7%.

Age and incidence: Risk of developing EOC was increased when women became menopausal, with the highest rate in those women over 70 years (57.5/100,000 women compared to 33.9/100,000 women 50-69 years old).

Age and surgery: Use of surgery appeared to be related to age. Of those over 70 years, 47.9% had surgery and 52.1% did not. Of those under 70 years, 87.8% had surgery and 12.2% did not.

SES: A woman's income quintile did not appear to be related to the likelihood of developing disease. There was a slight trend for women of higher income quintile to receive surgery (69/100,00 in the lowest income quintile versus 74.4/100,000 in the highest income quintile).

Geography: Urban/rural residence did not appear to be related to the likelihood of developing disease. Women in rural settings had a slightly lower rate of surgery compared to women in urban settings (71/100,000 vs 74/100,000).

LHIN: There was a variation in incidence of ovarian cancer by LHIN (14.3/100,000 in Waterloo Wellington compared to 22.5/100,000 in North Simcoe Muskoka). There was a significant variation in access to surgery with more than an 80% difference from the mean in Erie St. Clair and South West.

Definitive Treatment

1. Hospitalization

Among the 700 women who had surgery for ovarian cancer, there were a total of 766 hospital-based surgical encounters (1.1 per woman) of which 3.9% were ambulatory and 96.1% were overnight hospitalizations. Most women (64.0%) received surgery in the same LHIN where they lived.

2. Operative therapy

Surgery in ovarian cancer can be performed for several reasons: to make a histologic diagnosis (i.e., a biopsy type procedure; i.e., unilateral or bilateral salpingo-oophorectomy) (completed in 34.2%); to determine the extent of disease (i.e., lymphatic spread of disease (USO/BSO with pelvic or pelvic and paraaortic node dissection) (completed in 8.1%) or an assessment of the intraabdominal contents (i.e., USO/ BSO and omentectomy) (completed in 57.6%); or to remove as much disease as possible with a goal to microscopic residual disease. Given the data sources available, we were not able to assess the quality of debulking surgery in Ontario. Histologic assessment of the nodes occurred in only 8.1% of the women who received surgery.

Age: Removal of only one or both ovaries at the initial operation is more common in premenopausal women (36%). (In the circumstance of invasive epithelial ovarian cancer, these women should receive a second operation to complete the surgical staging. A less desirable option is the use of 4-6 cycles of adjuvant chemotherapy.)

SES: The type of surgery does not appear to vary by income quintile.

Geography: Forty percent of ovarian cancer operations occurred in community hospitals. There was a trend to “biopsy only” as the initial operation in rural communities (39.8% ASR vs 32.7% ASR). Rates of USO/BSO with omentectomy were lower in rural settings (52.9% ASR for rural vs 60.4% ASR for urban dwellers).

3. Surgical discipline involved

The 17 gynecologic oncologists in Ontario completed 53.3% of the operative procedures of women with ovarian cancer. The 175 gynecologists in Ontario completed 41% of the procedures (1.5 procedures per gynecologist) and 48 general surgeons were involved in 5.7% of the primary procedures. Approximately 9.4% of women received extensive staging with node dissection, 57.3% had omentectomy as part of the surgery. A patient was more likely to get an omentectomy if the primary surgery was in an urban/rural setting compared to women in rural settings (57.3% vs 47.9%).

Perioperative workup

Pelvic ultrasound by the intravaginal or abdominal route was the most common diagnostic test in the 12 months around the time of diagnosis and was done at least once in all women. Pelvic magnetic resonance imaging was used very infrequently. Preoperative paracentesis occurred in one-third of patients. Abdominal computed tomography scans (2 scans/patient) were more common than abdominal ultrasounds (1.2 scans/patient) in this period. Colonoscopy occurred in 20% of patients.

In the 12 months before or after surgery, a gynecology visit occurred in 71% of patients, a gynecologic oncology visit in 66.7%, a general surgery visit in 42%, a medical oncology visit in 26.6% with 61.3% of all patients receiving chemotherapy. The discrepancy between medical oncology visits and the rate of chemotherapy delivered is related to the role gynecologic oncologists have in delivering chemotherapy.

In the women who did not receive surgery, the investigational profile was similar to that of women who did receive surgery. A visit with a gynecologist occurred in 34.2%, a visit with a gynecologic oncologist in 26.6%, a visit with the general surgeon in 49.4% and a visit with a medical oncologist in 26.6%. The rates of chemotherapy for women who did not receive surgery were low (33.1%).

(Further details from which this report is derived are available from reference [20]).
Discussion

This is the third detailed provincial review of perioperative and operative care of women with ovarian cancer in Ontario women. It appears that the incidence of ovarian cancer increases with age and is not affected by SES or location of residence. This is in contrast to the report from Ontario in 1996-1999 which showed a direct relationship of rate of disease to size of community [2]. This is also in contrast with the USA, where higher rates of ovarian cancer were seen in the highest SES [3]. These later two reports [2, 3] appear not to be age standardized.

In our socialized health care environment, access to an operation was slightly influenced by SES or geography. Young woman were more likely to have an operation. It is not clear if this decision is based on severity of the disease, other comorbidities or patient choice.

Almost all patients required a hospital stay. Sixty-four percent received care in their LHIN but that means the others travelled outside of their region for surgical care. How the LHIN mechanism addresses planning for this resource and what fiscal responsibility the LHIN of residence has toward the LHIN of service is not clearly defined.

In ovarian cancers, it appears that younger women are receiving operations that are conservative, likely aimed at preserving fertility. The type of operation was not influenced by SES; it was influenced by where the woman lived. Those women residing in rural communities were more likely to have only a biopsy at the initial operation. This is in keeping with prior reports [4]. The most appropriate operation in ovarian cancer is extensive surgical staging for early disease and aggressive surgical debulking to less than 1 cm of residual disease when the disease is advanced. Both scenarios require a clinician who has a high degree of suspicion of the diagnosis, access to intraoperative frozen pathology, subspecialty trained surgical involvement and allied health services to manage the perioperative issues like massive fluid shifts. Unfortunately one of the limitations of this paper is the lack of information on confounders like stage and residual disease. Thus correction of surgical procedure by confounders was not possible. Suffice it to say that an open biopsy alone is not an adequate surgical procedure for ovarian cancer. Such a procedure delays the woman’s access to the most appropriate care.

Gynecologists conducted 41% of the operations for women with ovarian cancers in Ontario. This is a drop from 49.5% in 1996-1998 [2]. Lymphadenectomy was an uncommon procedure when gynecologists were involved in a patient’s care (5.6%). However, even when gynecologic oncologists performed the surgery, lymphadenectomy was only performed in 13.3% of cases. This rate appears consistent with the rate of 13.2% from 1996 [2, 4]. The reason for the low lymphadenectomy rates cannot be discerned from the available data. Other information such as stage, histology, ovarian rupture, and grade would be required to determine whether patients received an appropriate operation [5].

The high rate of general surgery involvement in women with ovarian cancer who did not undergo surgery was interesting. This may reflect the difficulty in making the initial diagnosis, the high rates of bowel compromise at diagnosis or the difficulty women have in accessing gynecologic oncologists. This finding suggests that any quality initiatives or educational endeavors around ovarian cancer should also involve general surgeons.

Unlike other surgical oncology services, gynecologic oncologists often are involved in the delivery of chemotherapy to patients [6]. It is difficult to illicit from the data whether the low rates of medical oncology involvement reflect this role being shared by both disciplines. What is concerning is the low rate of chemotherapy (33%) in patients who did not undergo surgery; it is lower than previously reported in 1996-2002 (58%) [6]. One would hypothesize a higher rate of chemotherapy given it would be the only treatment modality available to this group of women. It is not clear if the non-surgical population is diagnosed post-mortem or if they are too ill by the time of diagnosis to get access to chemotherapy or if this is related to patient preference.

There is significant literature dealing with the impact of race on incidence and mortality of ovarian cancer [3, 7-10]. There is also literature on the impact of income status on access to care for ovarian cancer in the context of a privately funded health system like that found in the United States [11]. This report adds to the literature about the interplay between age, socio-economic and geographic factors on the incidence and delivery of ovarian cancer care in the context of a socially funded medical system.

Conclusion

There is significant literature on ovarian cancer outcomes by region from countries in the developed world [13]; much of this work is augmented by the massive undertaking of retrospective data collection. Information corrected for confounders and cofactors is available for Ontario women with ovarian cancer [4, 5, 14]. In this publication, we describe the relationships between age, SES and location of residence on the incidence and surgical management of ovarian cancers in Ontario. Certainly the rates of gynecologic oncologist involvement have improved from 35% in 1996-1998 to 49% in 2003-2004. Unfortunately the current report is limited by the lack of information on confounders (i.e., stage), cofactors (i.e., smoking) and pathologic details (grade, histology).

Cancer Care Ontario and the Program in Evidence Based Medicine are moving toward better defining the surgical care of women with ovarian cancer through practice guidelines and practice standards [15-17]. The Canadian Partnership against Cancer (CPAC) is looking at standardized operative reporting [19] as a means of prospectively collecting the details of the surgery and major confounders like body mass index and FIGO stage. Quality indicators for ovarian cancer have been identified in Ontario [18]. As further population based data is col-
lected and corrected for these confounders, we can move into the future being better able to discern the gap between the recommended care and the care delivered. Opportunities to narrow this gap will require focused interventions.

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An attempt at conservative treatment in selected cases of type I endometrial carcinoma (Stage I A/G1) in young women

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Summary

**Purpose:** The aim of the study was to evaluate an attempt of conservative treatment in selected cases of endometrial carcinoma Stage I A/type I in young women. **Materials and Methods:** The study comprised five young nulliparous women aged 24-38 (30.8 ± 4.2) with well-defined type I endometrial carcinoma Stage I A/G1. Diagnostic dilatation and curettage (D&C) in these women was performed. Biochemical hormonal studies comprised the assessment of estrone, estradiol, progesterone, prolactin in basal conditions, prolactin after a metoclopramide test and total testosterone. In the treatment phase estriol was given intravaginally. Additionally progesterone was applied for 12 days in the second phase of therapeutic cycles. Moreover the women were given ergocryptine and metformin. **Results:** After six months of therapy and during two years of follow-up histopathological examinations of material obtained from D&C the endometrial pattern was normal and free of cancer cells. **Conclusions:** 1) In selected cases the conservative treatment of young women diagnosed with type I endometrial carcinoma Stage I A/G1 could be indicated. 2) Conservative pharmacological treatment of young women with well-defined endometrial carcinoma Stage I A/G1 type I should be monitored with follow-up histopathological examinations of material obtained from D&C of the endometrium and assessment of concentrations of sex hormones in the serum. 3) This kind of therapy requires frequent and thorough gynecological and clinical follow-up.

**Key words:** Sex hormones; Mucous membrane; Uterus; Endometrial carcinoma; Bromocriptine; Metformin.

Introduction

Endometrial carcinoma is the most common gynecological cancer in the United States, with approximately 40,000 cases diagnosed annually. Most of the women with endometrial carcinoma have Stage I disease at diagnosis. Endometrial carcinoma occurs most frequently in perimenopausal and postmenopausal women. The mean age at diagnosis of women with endometrial carcinoma is 61 years; less than 5% of cases occur in women younger than age 40. Twenty-five percent of cancers occur in premenopausal women and the disease has been reported in women aged 20-30 years. In recent years there has been an increased tendency for occurrence of this type of neoplasia in young women. Classically, endometrial carcinoma affects obese, nulliparous, infertile, hypertensive and diabetic white women, but it can occur in the absence of all these factors [1-3].

It has been suggested that there are two types of endometrial carcinoma, type I and II. Type I, carcinomas are estrogen-induced, well-differentiated, superficially invasive tumors. They frequently coexist with endometrial hyperplasia, respond to treatment with progestins, and are associated with a good prognosis. This type of endometrial carcinoma is connected with the proto-oncogene Ras mutation and mutations in suppressor genes [4, 5]. More than 75% of endometrial carcinomas are type I. Type II endometrial carcinoma may not be associated with unopposed estrogen stimulation of the endometrium. It occurs in women older than those who develop type I. It is characterized by poorly differentiated tumors (i.e., grade 3) or aggressive histologic types (e.g., papillary serous, clear cell) that deeply invade the myometrium. Type II endometrial carcinoma is associated with a poorer prognosis than type I, and in type II mutations occur in the suppressor gene for p 53 protein [4, 5].

Stage I A/G1-3 (according to FIGO surgical staging of carcinoma of the uterine corpus, 1988) confines tumors limited to the endometrium. The grade of the tumors refers to the architecture and nuclear atypia. The architecture of the tumor is judged by the percentage of differentiated (glandular) versus nondifferentiated (solid) elements within the tumor specimen. Grade 1 tumors consist of at least 95% of glandular tissue and have less than 5% of a nonquamous solid growth pattern. Areas of squamous differentiation are not considered to be solid tumor growth.

Hysteroscopy does not offer any better sensitivity for detecting endometrial hyperplasia or adenocarcinoma than endometrial biopsy. However if the endometrial biopsy is negative or inconclusive and the patient continues to experience vaginal bleeding, hysteroscopy should be considered.

Transvaginal ultrasonography (TVS) is of value. At a threshold of 5 mm for endometrial thickness the negative predictive value of TVS is 99%.

The hormones regulate proliferation, differentiation and apoptosis of cells. The higher the proliferation index in the endometrium, the greater the risk is that endometrial carcinoma may occur [6]. Treatment with progestins can prevent the development of endometrial adenocarcinoma.
The reason to attempt undertaking conservative therapy in selected cases of endometrial carcinoma, Stage IA/G1, type I in young women was a retrospective study of histopathological examinations obtained during dilation and curettage (D&C) with histopathological material from hysterectomy. These two examinations were in complete agreement only in 15%. However, in 85% of women there were discrepancies between the above-mentioned histopathological results [7]. This might suggest that the primary endometrial carcinoma was totally removed in the cases of D&C. These discrepancies have brought about an attempt at more conservative therapy in selected cases of endometrial carcinoma (Stage IA, G1) in young, childless women. This goal can be achieved by means of appropriate hormonal and metabolic treatment of women and follow-up with repeated fractional D&C. Hormone profiles of these patients were monitored with biochemical methods.

**Materials and Methods**

The study comprised five young nulliparous women aged 24-38 (30.8 ± 4.2) with a mean body mass index (BMI) of 23.2 ± 1.4. These patients had irregular, excessive menstrual bleeding lasting from three to five years and infertility in the history.

After clinical and gynecological examination and after taking blood for hormonal assays from the antebrahial vein, gynecological TVS was performed (Siemens, 7 MHz, Adar). Diagnostic D&C was performed on the first day of irregular menstrual bleeding.

Biochemical hormonal studies comprised the assessment of estrone, estradiol, progesterone, prolactin in basal conditions, prolactin after a metoclopramide test and total testosterone.

In the treatment procedure estriol was given intravaginally in globules over 22 days of therapeutic cycles. The dose of estriol was 0.03 mg/24 h. Additionally progesterone (Polfa), was applied in the form of sublingual tablets at the dose of 50 mg/24 h for 12 days in the second phase of the therapeutic cycle. Moreover in the continuous mode of administration ergocriptine (bromocriptine, Polfa) was given at the dose of 5 mg/24 h and metformin (Polfa) at the dose of 1 g/24 h.

The time of pharmacological treatment was dependent on the results of follow-up studies of D&C, TVS and the concentration of sex hormones in the serum.

Most endometrial carcinoma recurrences occur within the first two years after therapy. Follow-up studies were carried out after three months, and then at 6-month intervals for two years. The total time of observation of the patients was 15 years. Dilation and abrasion of the canal of the uterine cervix and D&C were performed two days before expected menstrual bleeding. The obtained material from the uterine cervix was described as #1 and from the uterine isthmus as #2. The material from the

![Fig. 1](image1.png)  ![Fig. 2](image2.png)  ![Fig. 3](image3.png)

Figure 1. — Hyperplasia of the endometrium with well-differen-
tiated cancer cells before treatment (magnification 200x, H&E).

Figure 2. — A few cancer foci (at the bottom of the figure) with scarce stroma after 3 months of treatment (magnification 200x, H&E).

Figure 3. — Secretory endometrium without cancer cells after 6 months of treatment (magnification 200x, H&E).
right uterine cornu was described as #3A and from the left #3B. The D&C material from the anterior uterine wall as # 4A and from the posterior uterine wall as #4B. The presence of cancer cells in the biopsy material from #1 or #2 signifies the primary localization of the neoplasm in the uterine cervix. However, the occurrence of cancer cells in the biopsy material described as #3A, 3B and 4A and 4B shows endometrial cancer.

The specimens obtained from D&C were stained routinely by hematoxylin-eosin. Pictures were taken under an AxiosImager microscope (Zeiss) with the use of a Nikon digital camera. Numerical elaboration microscopically was performed by using Axiolmager AxioVision LE (Zeiss).

Assessment of histopathologic D&C material was performed at the Pathomorphology and Genetics Department of Pomeranian Medical University. The protocol was approved by the Bioethical Committee of the Pomeranian Medical University in Szczecin.

Statistical analyses were performed using the statistical analysis package (Statistica PL, vers. 5, StatSoft, US). Patient characteristics and laboratory findings were analyzed using the Student’s t-test and by the Mann-Whitney U test. Differences associated with a p value of < 0.05 were considered statistically significant.

Results
The results are shown in Table 1 and Figures 1-3. The preliminary gynecological ultrasound studies showed enlargement of the uterine corpus (mean 8.5 ± 1.4 cm), increase of the endometrial thickness (in three women - 12.1 ± 1.8 mm and in two 16.2 ± 2.4 mm) and irregularities of the endometrial lining. The mean size of the ovaries was 4.0 ± 0.6 x 1.9 ± 0.3 x 0.95 ± 0.3 cm and the mean mass was 6.5 ± 1.1 g.

At the beginning of the treatment the preliminary histopathological examination from diagnostic D&C in all five women showed endometrial hyperplasia with presence of foci for well-differentiated endometrial carcinoma (Figure 1). Material obtained from the endocervix was without histopathological changes. Follow-up histopathological examination material obtained from the endocervix after three months of hormonal therapy also revealed no changes. However the histopathological examination material received from curettage of the endometrium found carcinoma cells only in a few endometrial glands (Figure 2). Nonetheless after six months of therapy and over two years of follow-up histopathological examinations of material obtained from D&C, the endometrial pattern was normal with secretion changes free of cancer cells (Figure 3).

Menstrual cycles in the studied women after six months of hormonal therapy were regular with a two-phase course. The serum concentrations of gonadotrophins, estrogen, progesterone, prolactin in the basal condition and after a metoclopramide test and total testosterone taken in the luteal phase of menstrual cycles are presented in Table 1. In the above-mentioned women the concentrations of gonadotrophins in the preliminary study were low with a tendency to increase during the observation time (p < 0.001) after six months of treatment. However the concentrations of estrone, estradiol and progesterone after six months of treatment were significantly lower than in the preliminary study (p < 0.001). The concentrations of prolactin in the basal condition and after the metoclopramide test were significantly lower (p < 0.05) after three months of hormonal therapy. A normal concentration of prolactin was achieved after 12 months of therapy. The concentration of total testosterone was significantly lower after 12 months of therapy in comparison to the preliminary results (p < 0.01) (Table 1).

During the long-term observation (15 years) and numerous follow-up studies we found that the women were in good gynecological and general condition. Four of these women became pregnant.

Discussion
Estrogens and progesterone are the two main hormones that influence the metabolic and proliferative state of the endometrium. In general, estrogens stimulate the endometrium, unlike progesterone, which has an antiproliferative effect. Estrogen induces mitotic activity of the endometrial epithelial and stromal cells. Under an estrogenic influence endometrium proliferation and glandular epithelium becomes pseudostratified. Long-term exposure to estrogens can lead to endometrial hyperplasia and,
subsequently, to hormone-driven atypical endometrial hyperplasia and endometrial cancer. Progesterone has an antiproliferative effect on the endometrium and can induce apoptosis of endometrial cells.

Preliminary biochemical data have shown that in young women with type I endometrial cancer Stage I A/G1 hypogonadotropism, relative hyperestrogenism, hyperprolactinemia, and hyperandrogenism were found. The serum concentration of prolactin and testosterone above normal range causes disorders of the menstrual cycle and progesterone synthesis in the ovaries. Progesterone and progestagens have a protective influence against endometrial carcinoma [8]. Low estriol/estrone + estradiol index (6.1 ± 1.3) in the preliminary study of women with this disease was connected with disturbances of estrogen metabolism leading to decreased activity of estradiol 17β-hydroxysteroid dehydrogenase. This enzyme converts estradiol to estrone and estrone/estradiol to estriol. Moreover decreased enzyme activity of estrogen sulfotransferase which catalyzes estrogen esterification diminishes the conjugation of estrogens with glucuronic acid [4, 9, 10].

The application of intravaginal estriol in selected infertile young women diagnosed with endometrial carcinoma Stage I A/G1 type I as an antiestrogen suppresses the proliferative activity of estrone and estradiol in the endometrium. Estriol increases the expression of progestrone receptors in cancer cells and increases their sensitivity to progestrone/progestagens [10]. Progestrone/progestagens cause the increase of conversion estrone and estradiol to estriol and inhibit DNA and RNA synthesis. Moreover these agents in the first stage of atypia influence the maturation of endometrium cells and enhance their secretory function [11-13]. Increased levels of overt prolactin in the preliminary study indicated application of an antiprolactin agent - bromocriptine until 18 months of follow-up studies.

Bromocriptine diminishes the secretion of GnRH, gonadotrophins and other hormones. Bromocriptine enhances the occurrence of regular menstrual cycles [14, 15]. The application of metformin in young, infertile women diagnosed with endometrial carcinoma brings about normalization of hormonal and metabolic disturbances, increased progesterone and decreased testosterone concentrations in serum.

The obtained results suggest the possibility of conventional treatment of young, especially infertile, women diagnosed with endometrial carcinoma Stage I A/G1, type I based on repeated follow-up histopathological examinations of the endometrium as well as thorough gynecological TVS and clinical observation. This mode of therapy favorably influenced the histopathology of endometrial carcinoma causing endometrial changes to recede. These results are a milestone and permit changes of the up to now surgical procedure of endometrial carcinoma Stage I A/G1, type I in young women to a conventional one. The indications for conventional treatment of endometrial carcinoma should be established upon follow-up of histopathological examinations of specimens in the course of pharmacological proceedings. This kind of diagnosis since 1878, the year in which Wilhelm Freund performed removal of the whole uterus, was the indication for surgery with all negative consequences.

Conclusions

In selected cases conservative treatment of young women diagnosed with endometrial carcinoma Stage I A/G1, type I could be indicated. This treatment should be monitored by using follow-up histopathological examinations of material obtained from D&C of the endometrium and the assessment of concentrations of sex hormones in the serum. Frequent and thorough gynecological and clinical follow-up are essential.

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Clinicopathological implications of inactivation of RASSF1A in serous epithelial ovarian cancers

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Summary

Objective: To investigate the frequency of promoter hypermethylation of RASSF1A gene in ovarian cancers and its correlations to gene expression and clinicopathological characters in the Chinese population. Methods: In this study, we detected the frequency of promoter hypermethylation of the RASSF1A gene in 60 patients with primary serous epithelial ovarian carcinomas (SEOCs) using Methylation-Specific PCR (MSP). The gene expression of mRNA and protein was examined by RT-PCR and Western blot. Results: The frequency of promoter hypermethylation of RASSF1A in Chinese primary SEOCs was 53.3%, whereas promoter hypermethylation was not found in normal ovarian tissues and benign ovarian tissues. The expression of both mRNA and protein of RASSF1A was significantly down-regulated or lost in the methylated group than in nonmethylated group (p < 0.05, respectively). SEOCs with Stage III, IV exhibited a higher frequency of RASSF1A promoter hypermethylation (70.4%, 81.8%) than those with Stage I or Stage II (16.7%, 20.0%, p < 0.05, respectively). Hypermethylation patterns in RASSF1A were more frequently detected in poorly differentiated SEOCs (78.6%) than in well-differentiated SEOCs (27.3%, p < 0.05, respectively). Conclusions: The high frequency of promoter hypermethylation of RASSF1A contributes to the gene expression in Chinese primary SEOCs. The inactivation of the RASSF1A gene due to hypermethylation in the promoter region might play a critical role in the pathogenesis of ovarian cancers.

Key words: RASSF1A; Hypermethylation; Inactivation; Ovarian cancer.

Introduction

Ovarian cancer is the second most commonly diagnosed reproductive malignancy in women worldwide, accounting for 4.4% of female cancers and the leading cause of death from gynecological malignancy [1, 2]. The highly lethal nature of ovarian cancer is related to the absence of symptoms in the majority of women with early stages of the disease. It is difficult to diagnose ovarian cancer in its early stages (I/II) until it spreads and advances to later stages (III/IV). Three quarters of patients are diagnosed at the late stages (III/IV) and 5-year survival for patients with advanced disease is less than 20% [3].

It is now clear that the biological features of cancer are determined by underlying genetic and epigenetic alterations that may occur in the very early stage of carcinogenesis or precede clinically obvious cancer and can be useful in the diagnosis of cancer. It is well documented that genetic changes, such as mutations and deletions, play a functional role in silencing tumor suppressor genes (TSGs) [3]. However, these genetic changes do not seem to be the main mechanism of inactivation of TSGs [4].

The methylation of CpG islands in several TSGs has been found in virtually every type of human neoplasm including ovarian cancer. Methylation of the DNA occurs most frequently on the 5’ cytosine residues within 5’-CpG-3’ di-nucleotides, which often cluster together in CpG islands that can stretch for several kilobases [5]. In actively transcribed genes, CpG islands within regulatory regions are often unmethylated. In contrast, methylation at these sites represses transcription by altering chromatin structure so that the transcriptional machinery does not have proper access to functionally important regions of the promoter [5].

The RASSF1 gene, cloned by Dammann et al., is located at chromosome 3p21.3, a region that frequently exhibits loss of heterozygosity in human tumors [6]. The C-terminus of RASSF1 shows high homology to the mammalian Ras-effector protein Nore1, and therefore, the gene has been named Ras-association domain family 1 gene. RASSF1A is one of the major isoforms of the RASSF1 gene which is generated by alternative splicing and has been proposed as a TSG [7]. The tumor-suppressor function of RASSF1A was indicated by reduced colony formation, suppressed anchorage independent growth, and inhibited tumor formation in nude mice [8]. RASSF1A is frequently inactivated in a variety of primary human cancers, but inactivating mutations of this is very rare. It has been suggested that promoter hypermethylation of the CpG island is a major mechanism in the inactivation of the RASSF1A gene [9]. Promoter hypermethylation of RASSF1A has frequently been detected in various primary tumors including the lung, breast, pancreas, kidney, liver, cervix, nasopharyngeal, prostate, thyroid and other cancer. Inactivation of RASSF1A was found associated with an advanced tumor stage and poor prognosis [10]. Therefore, detection of aberrant RASSF1A hypermethylation may serve as a diagnostic and prognostic marker.
However, whether the inactivation of the RASSF1A gene by promoter hypermethylation occurs in Chinese serous epithelial ovarian cancer (SEOC) patients has not been well addressed, which promotes us to examine the frequency of RASSF1A hypermethylation in this type of cancer, and the relationship between its methylation status and expression levels. In addition, the potential clinical implication of promoter hypermethylation of the RASSF1A gene was also evaluated.

Materials and Methods

Patients and Samples

Available fresh tumor tissues were collected from 60 SEOC patients, aged 18 to 81 years, operated on for gynecological cancers between 1999 and 2003 at the Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University (Shenyang, China). Tumor samples and clinical data were obtained with the consent from all patients. The specimens were frozen immediately after resection and stored at -80°C, for subsequent laser capture microdissection (LCM), DNA and RNA isolation and protein extraction. Surgical specimens were examined for histological type and grade based on World Health Organization criteria. Of 60 patients, 11 were grade 1 (well differentiated), 21 grade 2, and 28 grade 3 (poorly differentiated). Ten specimens of histologically normal ovarian tissue were collected from the unaffected ovary. Ten patients with benign ovarian cyst were also included.

LCM

Over 90% of tumor cells were obtained from ovarian cancer tissue samples using the LCM system (Arcturus, Mountain View, CA) to select cancer cells on slides according to the manufacturer’s protocols. On average, about 30,000 tumor cells from one specimen were yielded by LCM shots.

DNA isolation

Genomic DNA from frozen tissue after LCM was extracted by digestion in a buffer containing 50 mmol/l Tris-Cl (pH 8.0), 10% SDS, and 0.5 mg/ml proteinase K at 37°C overnight. The digested products were purified with phenol-chloroform twice. DNA was then precipitated using the EtOH precipitation method and re-suspended in distilled DNase-free water.

RNA extraction

Total RNA was prepared from frozen preserved tissues after LCM by acid phenol/chloroform extraction Trizol (Invitrogen, Carlsbad, CA) followed by purification with RNeasy Mini Kit (Qiagen, Valencia, CA) according to the manufacturer’s instructions. RNA was quantified at 260 nm by a spectrophotometer and quality was assessed by visualization of 18S and 28S RNA bands after electrophoresis through agarose gels.

RT-PCR

A 2 μg of total RNA was used for each reverse transcription reaction. First-strand synthesis of cDNA was performed by using an oligodeoxythymidylic acid primer and Superscript II reverse transcriptase according to the manufacturer’s instructions (Invitrogen, Carlsbad, CA). GAPDH amplification was used for normalization. 1 μl of cDNA was used for PCR amplification with RASSF1A specific primers (forward primer, 5'-CGACCTCTGGCGACTTCTGGA-3'; reverse primer, 5' AGGTAGGTTGTCTCCACTCCACAG-3'). PCR was performed for 40 cycles: 95°C for 30 sec and 68°C for 3 min. PCR products were separated on 2% agarose gels, stained with ethidium bromide, and visualized under UV illumination.

Bisulfite modification

One μg of the genomic DNA was denatured by 2M NaOH and then incubated in 3M sodium bisulfite and 10 mM hydroquinone for 16 hours at 50°C. Bisulfate-treated DNA was then purified using the Wizard DNA Cleanup Kit (Promega, Madison, WI), and treated again with NaOH. After precipitation with ethanol, DNA was recovered in water.

Methylation-specific PCR (MSP)

After bisulfite treatment, all unmethylated cytosines were converted to uracils but methylated DNA is protected. Modified DNA was amplified by PCR using primers specific for either the methylated or unmethylated RASSF1A promoter. The primer sequences of RASSF1A for the unmethylated reaction were sense 5'-GGTTTTGCGAGAGTGTGTTTAG-3' and antisense 5'-CCTAACAACACACAAAACACC-3'. The primer sequences of RASSF1A for methylated reaction were sense 5'-GGTTTTGCGAGAGTGTGTTTAG-3' and antisense 5'-GCTAAAACACACAAACACC-3'.

PCR reactions were performed in a 25 μl reaction containing about 100 ng of modified DNA, 3% dimethyl sulfoxide, all four deoxynucleoside triphosphates (each at 200 μM), 1.5 mmol/l MgCl₂, 0.4 M PCR primers, and 1.25 units of HotStar Taq DNA polymerase (Qiagen, Valencia, CA). PCR amplification was hot-started at 95°C for 5 min, then followed by 35 cycles of 95°C for 30 sec, 65°C for 45 sec and 72°C for 45 sec, and concluded at 72°C for 5 min. Normal human lymphocyte DNA in vitro methylated with SssI methylase (New England Biolabs, Beverly, MA) was used as a positive control (M+). Normal lymphocyte DNA as a negative control (U-) and water replacing for DNA was used as blank control. After PCR, products were run on 2.5% agarose gels and visualized after staining with ethidium bromide. The hypermethylation status was determined by visualizing a 169 bp PCR product for the RASSF1A.

Western blot

Protein extraction from ovarian tumor tissues was done as described earlier [11]. The protein concentration was determined using the BCA protein assay reagent (Pierce, USA). Equal amounts of protein (20 μg) were denatured at 94°C for 10 min and subsequently separated on 10% SDS-PAGE, and finally transferred onto PVDF membranes (BioRad, Richmond, VA, USA). The membranes were blocked using 5% nonfat milk/TBS for 60 min and incubated overnight at 4°C with primary monoclonal anti-RASSF1A antibody (1:500) (eBiogenic, San Diego, CA). After washing, membranes were incubated for one hour with a horseradish peroxidase-labeled secondary antibody (1:500) (eBiogenic, San Diego, CA) at room temperature, and then followed by detection with enhanced chemiluminescence (Amersham Pharmacia Biotech, Piscataway, NJ). All experiments were repeated triplicate.

Statistical analysis

Statistical analysis was performed using the chi-square or Fisher’s exact test. A p value of less than 0.05 was considered statistically significant.
Results

Promoter hypermethylation status of the RASSF1A gene in Chinese SEOCs

We first carried out MSP analysis in 60 primary Chinese SEOCs to determine the frequency of RASSF1A promoter hypermethylation. We found that the promoter was hypermethylated in 53.3% (32/60) for the RASSF1A gene. In contrast, no RASSF1A promoter hypermethylation was found in ten normal ovarian tissues and ten benign ovarian cysts. Thus, the RASSF1A promoter hypermethylation exclusively occurs in SEOCs (SEOCs vs normal ovarian tissues and benign ovarian cysts, \( p < 0.05 \)) (Table 1) (Figure 1A).

RASSF1A mRNA expression in Chinese SEOCs

To determine whether the expression of RASSF1A mRNA is affected by promoter hypermethylation, we performed RT-PCR analysis. We found the absence of RASSF1A mRNA expression in 55% (33/60) of SEOCs. In contrast, mRNA was expressed in all the normal ovarian tissues (10/10), and in 90% of benign ovarian cysts (9/10). RASSF1A mRNA expression was significantly lower in SEOCs compared with that in normal ovarian tissues or benign ovarian cysts (\( p < 0.05 \)) (Table 2) (Figure 1B).

RASSF1A protein expression in Chinese SEOCs

To determine whether the expression of RASSF1A protein is altered by promoter hypermethylation, we performed Western blot analysis. We found reduced RASSF1A protein expression in 58.3% (35/60) of SEOCs. In contrast, RASSF1A protein was detectable in all the normal ovarian tissues (100%, 10/10) and benign ovarian cysts (100%, 10/10). RASSF1A protein expression was significantly lower in SEOCs compared with normal ovarian tissues or benign ovarian cysts (\( p < 0.05 \)) (Table 2) (Figure 1C).

Table 1. — Clinicopathological and hypermethylation analysis of RASSF1A in SEOCs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case numbers</th>
<th>Hypermethylation case numbers</th>
<th>Hypermethylation frequency (%)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEOCs</td>
<td>60</td>
<td>32</td>
<td>53.3</td>
<td></td>
</tr>
<tr>
<td>Normal ovary tissue</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Benign ovarian cyst</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>21</td>
<td>11</td>
<td>47.2</td>
<td></td>
</tr>
<tr>
<td>( \geq 50 )</td>
<td>39</td>
<td>21</td>
<td>53.8</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12</td>
<td>2</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>2</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>27</td>
<td>19</td>
<td>70.4</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>11</td>
<td>9</td>
<td>81.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (well)</td>
<td>11</td>
<td>3</td>
<td>27.3</td>
<td></td>
</tr>
<tr>
<td>2 (moderate)</td>
<td>21</td>
<td>5</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>3 (poorly)</td>
<td>28</td>
<td>22</td>
<td>78.6</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Table 2. — Correlation of RASSF1A hypermethylation and expression in SEOCs.

<table>
<thead>
<tr>
<th>RASSF1A expression</th>
<th>Case numbers</th>
<th>Hypermethylation status (+)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA</td>
<td></td>
<td>+</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>Protein</td>
<td></td>
<td>+</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>35</td>
</tr>
</tbody>
</table>
Clinicopathological implications of inactivation of RASSF1A in serous epithelial ovarian cancers

To determine whether the promoter hypermethylated status of the RASSF1A gene is associated with the clinicopathological characters of the SEOCs patients, we compared them in terms of patient age, clinicopathological stage and tumor differentiation. SEOCs with Stage III or Stage IV exhibited higher frequencies of RASSF1A promoter hypermethylation (70.4%, 81.8%) than those with Stage I or Stage II (16.7%, 20.0%, p < 0.05). In the meanwhile, hypermethylation patterns in RASSF1A were more frequently detected in poorly differentiated SEOCs (78.6%) than in moderately differentiated (23.8%) or in well-differentiated SEOCs (27.3%) (p < 0.05, respectively). The hypermethylation status of the RASSF1A promoter was not significantly correlated with patient age (Table 1).

Discussion

In the current study, we investigated the frequency of promoter hypermethylation of RASSF1A in 60 Chinese primary SEOCs. We found that the promoter hypermethylation rates of RASSF1A were 53.3% in SEOCs. Hypermethylation was not detected in normal ovarian tissues and benign ovarian cysts. We also examined the mRNA and protein expression of RASSF1A and found that 100% of the tumors with promoter hypermethylation had mRNA and protein expression reduction. Furthermore, hypermethylation of the RASSF1A gene was correlated statistically with late stage and poorly differentiated SEOCs.

The RASSF1 gene has several major isoforms due to alternative splicing and promoter usage, but epigenetic silencing of the longer isoform, RASSF1A, is specifically associated with cancer [12]. It has now been recognized that for some TSGs, such as RASSF1A, promoter hypermethylation is the major mechanism of transcription inactivation [6, 13, 14]. The frequent inactivation of RASSF1A due to promoter hypermethylation has been shown in a variety of tumors in spite of different occurrence in specific types of tumors [6, 9, 13-20].

The etiology of ovarian cancer is poorly understood. Studies on methylation of numbers of TSGs indicated that aberrant promoter methylation may be mechanistic alternatives to gene silence in the formation of ovarian tumors [21-25]. However, few studies on the promoter hypermethylation of RASSF1A have been published in ovarian tumors and the results are conflicting [13, 20, 26]. Ovarian cancer comprises tumors with different biological behavior. It has been shown that DNA methylation patterns are tumor-type specific [27]. However, in our previous studies, we did not find significant differences in promoter hypermethylation of RASSF1A among the serious adenocarcinomas, mucinous adenocarcinomas and endometrioid adenocarcinomas, the three major subtypes of ovarian epithelial malignant tumors. Consequently, we investigated the hypermethylation status of RASSF1A in Chinese ovarian cancer and focused on the most common subtype of ovarian cancer, SEOCs.

The promoter hypermethylation of RASSF1A was detected in 53.3% (32/60) of Chinese primary SEOC samples in this study. This result indicates that promoter hypermethylation of RASSF1A is a frequent genomic event in Chinese primary SEOCs. It has been reported that hypermethylation of RASSF1A is generally rare in normal, non-neoplastic tissues [6, 8, 13, 14, 16, 28]. We analyzed ten benign ovarian tissues and ten normal ovarian tissues in parallel with the tumors. No RASSF1A promoter hypermethylation was found in either benign ovarian tissues or normal ovarian tissues. This result clearly indicates that promoter hypermethylation of RASSF1A occurs specifically in ovarian cancer tissues. Thus, the frequent hypermethylation in the promoter region of the RASSF1A gene suggests that it might play an important role in ovarian tumorigenesis. The hypermethylation rate of RASSF1A observed in our studies was consistent with, but slightly higher than, that reported by others (30-40%) [20, 26]. This could be explained by the differences of the patient’s ethnicity and background.

The previous studies have shown that hypermethylation of a CpG island is usually associated with a lack of gene expression [29], but none of the studies has ever shown the correlation between promoter hypermethylation of RASSF1A and gene expression in the Chinese population. Therefore, we investigated hypermethylation of the RASSF1A gene; meanwhile RT-PCR and Western blot analysis were also performed to detect the mRNA and protein expression of RASSF1A in SEOCs. We found that RASSF1A hypermethylation was significantly associated with loss of mRNA and protein expression in SEOCs. Noticeably, no RASSF1A mRNA or protein expression was detected in all 32 tumors with RASSF1A hypermethylation, whereas the expression of RASSF1A mRNA and protein was detected in 27 of 28 and 25 of 28 nonmethylated tumors, respectively. These results demonstrate that inactivation of the expression of RASSF1A is highly correlated with the hypermethylation of its promoter.

Epigenetic inactivation of tumor suppressor genes through DNA methylation can lead to the development and progression of cancers [30-32]. In prostate cancer, aberrant methylation of CpG islands of the CD44 gene, E-cadherin gene and estrogen receptor gene has been reported to be associated with tumor progression [33-35]. Regarding RASSF1A related studies, high frequency of RASSF1A methylation was observed and correlated with advanced tumor stage and poor prognosis in bladder cancer. In lung cancer, it was found that the outcome of patients with hypermethylation of RASSF1A was poorer than those without. In this study, we analyzed the RASSF1A hypermethylation and its correlation with clinicopathological characters in SEOCs. Interestingly, the frequency of promoter hypermethylation was higher in advanced tumors compared with early-stage tumors, and it was more often identified in poorly differentiated tumors than well or moderately differentiated tumors. These results thus implicate that in addition to a role in tumorigenesis, RASSF1A hypermethylation may also regulate the progression and invasion of ovarian cancers.
In conclusion, our study showed that the high frequency of promoter hypermethylation of the RASSF1A gene contributes to the loss of gene expression in Chinese primary SEOCs. Furthermore, the results suggest that inactivation of the RASSF1A gene due to hypermethylation in the promoter region may play a critical role in tumorigenesis of ovarian cancers. Monitoring of RASSF1A promoter methylation can also provide useful information on the potential status of progression of ovarian cancer.

Acknowledgments

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References


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Ovarian carcinoma apparently confined to the ovaries - the accuracy of surgical staging in Israel

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Sheba Medical Center, Tel Hashomer (Israel)

Summary

Background: In order to allot an ovarian malignancy to FIGO Stage I, in addition to abdominal exploration and the basic operation, it is also necessary to do peritoneal washings for cytological examination, random peritoneal biopsies (including diaphragmatic assessment) and omental and retroperitoneal lymph node assessment. Objective: The aim of the study was to assess the accuracy of surgical staging of ovarian carcinoma classified as Stage I in Israel. Methods: Included were all patients with histologically confirmed epithelial ovarian carcinoma (EOC) classified as Stage I in a data base of a nationwide incidence case control epidemiological study of ovarian carcinoma conducted in Israeli Jewish women during the period 1994-1999. Surgical staging data of these patients were retrieved from pathological reports, and from clinical records when available. Results: A total of 182 EOC patients were classified as Stage I. About 86% of the patients underwent hysterectomy and bilateral salpingo-oophorectomy. The most commonly performed staging procedure was omental assessment (85.2%) while peritoneal biopsy was the least common one (34.1%). In 17 (9.3%) of the patients none of the staging procedures were done and only 34 (18.7%) had optimal staging. Conclusion: Although the data are from a decade ago, they seem to indicate the need for an increased awareness of the necessity for accurate surgical staging of tumors apparently confined to the ovaries since it can identify a group of patients who require surgical therapy alone and who can be spared the complications, inconvenience and cost of adjuvant chemotherapy.

Key words: Ovarian cancer, clinically confined to ovaries, surgical staging, accuracy, Israel.

Introduction

According to the 1986 FIGO surgical staging system of ovarian carcinoma [1], in addition to careful intraabdominal exploration and the basic operation, the following procedures are necessary to rule out extraovarian disease and in order to allot a tumor to Stage I: 1) peritoneal washings for cytologic examination, 2) assessment of the omentum, 3) random peritoneal biopsies (including biopsy or cytologic smear of the diaphragms) and 4) retroperitoneal pelvic and paraaortic lymph node sampling [1, 2]. Accurate surgical staging of ovarian carcinoma apparently confined to the ovaries is of clinical importance since it can identify a group of patients who require surgical therapy alone.

The aim of the present study was to assess the accuracy of surgical staging of ovarian carcinoma classified as Stage I in Israel.

Patients and Methods

All incident cases of histologically confirmed cancer of the ovary diagnosed in Israeli Jewish women between March 1994, and June 30 1999, were identified within the framework of a nationwide case-control epidemiological study of ovarian carcinoma. The study was approved by the Institutional Review Board and Ministry of Health. Specific details on the methodology of this study were given in a previous publication [3]. The present report includes all patients with epithelial ovarian carcinoma (EOC) classified as Stage I in this data base. The histological classification of the tumors was based on the original pathology report that was available for all patients. Data regarding the accuracy of surgical staging of these patients were retrieved from pathological reports, and from clinical records (i.e., discharge summaries and/or surgical notes), when available. When all four of the staging procedures namely peritoneal cytology, peritoneal, omental and lymph node assessment were done, the surgical staging was considered optimal.

Differences were calculated by chi square analysis.

Results

A total of 182 EOC patients in the data base were classified as Stage I. The mean age of the patients was 59.6 ± 12.4 ranging from 20 to 86 years. Thirty-four (18.7%) patients were younger than 45 years and 148 (81.3%) 45 years or older. Surgery of 163 (89.6%) patients was done in institutions that include a gynecologic oncology unit. Table 1 presents the distribution of the pathological type, grade of the tumors and the basic operative procedure performed. Serous and endometrioid carcinomas were the most common tumors (29.1% and 34.6%, respectively). Of the 42 grade 1 tumors, 22 where presumptive Stage IAG1 tumors. About 86% of the patients underwent TAH & BSO. Table 2 lists the distribution and number of staging procedures performed. Omental assessment was the most commonly performed staging procedure (85.2%) and peritoneal biopsy the least common staging procedure (34.1%).

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Table 1. — Histologic type, grade and basic procedure performed in the study group patients.

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>182</td>
<td>100.0</td>
</tr>
<tr>
<td>Serous carcinoma</td>
<td>53</td>
<td>29.1</td>
</tr>
<tr>
<td>Endometrioid carcinoma</td>
<td>63</td>
<td>34.6</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>38</td>
<td>20.9</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>13</td>
<td>7.1</td>
</tr>
<tr>
<td>Unspecified adenocarcinoma</td>
<td>7</td>
<td>3.9</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>6</td>
<td>3.3</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>No.</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>23.1</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>24.8</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>29.7</td>
</tr>
<tr>
<td>Not recorded</td>
<td>39</td>
<td>21.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basic procedure</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAH, BSO</td>
<td>154</td>
<td>84.6</td>
</tr>
<tr>
<td>TAH, USO</td>
<td>6</td>
<td>3.3</td>
</tr>
<tr>
<td>BSO</td>
<td>13</td>
<td>7.1</td>
</tr>
<tr>
<td>USO</td>
<td>8</td>
<td>4.4</td>
</tr>
<tr>
<td>Bilateral cystectomy</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>17</td>
<td>9.3</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>14.3</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>32.4</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>25.3</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>18.7</td>
</tr>
</tbody>
</table>

*139 patients had more than one staging procedure.

Discussion

Our data indicate that in Israel, during the study period, only 18.7% of EOCs apparently confined to the ovaries underwent optimal surgical staging. It has been shown that women managed by gynecologic oncology specialists are significantly more likely to be treated with recommended surgical procedures, and to have a better outcome with improved survival [4]. In one study 97% of 291 women operated on by gynecologic oncologists had complete surgical staging intraoperatively, but only 52% of cases operated on by general gynecologists were adequately evaluated [5]. The great majority of our patients (89.6%) had their surgery in institutions that include a gynecologic oncology unit headed by a trained gynecologic oncologist. However, whether the gynecologic oncologists were consulted or participated in the operation could not be ascertained. Some patients with tumors apparently confined to the ovaries may have been upstaged by subsequent relaparotomy and comprehensive staging. The proportion of optimally staged patients in the present report may therefore be an underestimation. A statistically significant lower percentage of patients < 45 years old underwent hysterectomy than in the older age group. In view of the current availability of assisted reproductive technology, when fertility preservation is of main concern in young women, the uterus and in some instances the uninvolved ovary may be retained in Stage I EOC [6-8]. Pregnancies and term deliveries have been reported in these cases but about 12% of recurrences have occurred as well [8, 9]. It should also be mentioned that comprehensive surgical staging can probably be omitted in mucinous tumors grossly confined to the ovaries [10]. We have no explanation for the significantly higher rate of adequate surgical staging of patients in the < 45 years age group. It can only be speculated that some patients in the older age group had comorbidities that did not allow a prolonged staging procedure.

Israel is not unique in the low proportion of accurately staged EOC patients [6, 11-15]. Of 785 women from the National Cancer Institute Surveillance, Epidemiology, and End Results program diagnosed with ovarian cancer in 1991, only about 10% with presumed Stage I and II underwent recommended staging. The absence of lymphadenectomy and assignment of histological grade were the primary reasons these women did not receive recommended staging and treatment [12]. Harlan et al. [13] examined patterns of care in a population-based sample of 601 ovarian cancer patients diagnosed in 1991, and a sample of 566 women diagnosed in 1996 to examine trends in care in the United States. They found that a significant number of the patients in both periods were not precisely staged. Thus, for example, 62 (41.3%) of 180 apparent Stage I patients had no lymph node sampling. Wolfe et al. [15] found that in 1991 of 25 patients with clinical Stage I tumors only seven (28%) had an omentectomy in South East England. Similarly, Zanetta et al. [6] from Italy reported that only 28% of such patients had optimal staging.

The necessity for accurate surgical staging has been repeatedly emphasized. Piver et al. [16] in 1978, prior to the introduction of the current FIGO staging system, reported that among 23 patients with ovarian tumors grossly confined to the ovaries diaphragmatic, aortic lymph node, pelvic lymph node and omental occult metastasis were found in 11.3%, 13.3%, 8.1% and 3.2%, respectively and malignant peritoneal washings in 32.9% of them. They also cite three previous publications that found occult metastasis in such cases. Since then many...
studies confirmed the importance of accurate staging of ovarian tumors macroscopically confined to the ovaries [6, 17-24] and the presence of occult metastasis in these instances. Le et al. [18] in a recent retrospective study reported that when no postoperative treatment was given to patients with tumor macroscopically confined to the ovary, a significant survival advantage was noted in an adequately staged group. Thus at a median follow-up of 58 months, of 60 patients with surgically proven Stage I patients treated expectantly, six (10%) recurred, whereas of 25 unstaged patients treated expectantly due to lack of risk factors seven (28%) recurred (p = 0.036). These findings demonstrate that some patients should undergo restaging laparotomy. Such a procedure can provide little benefit to those patients already requiring chemotherapy based on the original operative findings. However, patients with tumors apparently confined to the ovaries and lack of risk factors such as high grade should be considered for comprehensive restaging surgery prior to further treatment recommendations. The complication rate of relaparotomy for comprehensive surgical staging is about 30% and includes febrile morbidity, urinary and gastrointestinal tract complications, vascular injury and wound separation [23, 25]. Nevertheless, relaparotomy for comprehensive surgical staging can identify a group of patients who require surgical therapy alone [2, 25]. These patients can be spared the complications, inconvenience and cost of adjuvant chemotherapy.

The strength of our study is the relatively large number of consecutive clinical Stage I patients derived from a population data-base. The main weakness of the study is the lack of information regarding postoperative management and outcome.

Conclusions

The fact that a large proportion of EOC patients in the present study did not receive recommended surgical staging procedures for tumors apparently confined to the ovaries is of concern. Although the data are from a decade ago, they seem to indicate that the awareness to the importance of accurate comprehensive surgical staging should increase and prompt the frequent involvement of gynecologic oncologists in the initial surgery thus preventing the necessity of restaging laparotomies.

Appendix


References


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Perineural invasion in early-stage cervical carcinoma

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Summary

Purpose: Evaluation of the association between perineural invasion (PNI) and predictive and prognostic factors in early-stage cervical carcinoma patients treated with surgery. Methods: Fifteen PNI (+) and 21 PNI (-) early-stage cervical carcinoma patients, primarily treated by surgery, were evaluated retrospectively. Patients’ complete blood counts and biochemistry tests, tumor prognostic parameters, PNI status, postoperative treatment, recurrence and survival data were obtained from the records. Results: The percentage of mean depth of stromal invasion was significantly higher in the PNI (+) group (p ≤ 0.05). Vaginal (p ≤ 0.05) and uterine (p ≤ 0.01) invasion of the tumor were significantly more prevalent in the PNI (+) group. Lymphovascular space invasion, in particular lymphatic invasion (p ≤ 0.05), but not vascular invasion (p > 0.05) was significantly more prevalent in the PNI (+) group. Conclusion: PNI is closely related with stromal invasion in percentage, vaginal and uterine involvement and lymphatic invasion of the tumor.

Key words: Perineural; Cervix.

Introduction

Cervical cancer is the seventh most common cancer overall, but the second most common in women worldwide, with an estimated 493,000 new cases and 274,000 deaths in the year 2002 [1]. It has an overall 55% mortality rate, and shows great variations in age-adjusted survival rates; 70% in the USA to 21% in sub-Saharan Africa. Cervical cancer up to Stage IIA is usually treated by radical hysterectomy + bilateral salpingo-oophorectomy + bilateral pelvic and paraaortic lymph node dissection. Adjuvant treatment and patient management are decided according to prognostic criteria. Though perineural invasion (PNI) has been the matter of subject in many other carcinomas, the precise role of perineural spread in cervical carcinoma and the exact relationship between the PNI and other predictive and prognostic factors of the disease has not yet been well defined in the literature [2-16].

The purpose of this study was to evaluate the association between PNI and predictive and prognostic markers in early-stage cervical carcinoma patients treated with surgery.

Materials and Methods

Thirty-six women who had type III radical hysterectomy + bilateral salpingo-oophorectomy + bilateral pelvic and paraaortic lymph node dissection with the diagnosis of Stage IB1 or IB2 cervical carcinoma at Uludag University Medical Faculty Department of Obstetrics and Gynecology were evaluated retrospectively. The study was approved by the ethical committee of Uludag University Medical Faculty. Patient complaints at admission, demographic criteria, complete blood counts, renal and hepatic function tests, tumor size, histology, grade, invasion, spread pattern, surgical margin, lymphovascular and perineural invasion, postoperative treatment, recurrence and survival data were obtained from the records. Patients were categorized according to their status of PNI; PNI (+) (n = 15) and PNI (-) (n = 21).

Statistical analysis was performed using the statistical package for the Social Sciences (SPSS) v 13.0. Distribution patterns of the groups were analyzed using the Shapiro-Wilk test and Levene’s test for equality of variances. The t-test was used in the comparison of the two groups with normal distribution and the Mann-Whitney U test was used in the comparison of the two groups without normal distribution. The categorized data were analyzed using the continuity correction test and Fisher’s exact test. The two-sample Kolmogorov-Smirnov test was used to compare the distribution of the two groups with inadequate data. Statistical significance was defined at p ≤ 0.05.

Results

Seven (46.7%) patients in the PNI (+) group and ten (47.6%) patients in the PNI (-) group were postmenopausal and the remainder were regularly menstruating. Seven patients in both the PNI (+) (46.7%) and PNI (-) (33.3%) groups complained of postcoital bleeding while eight (53.3%) patients in the PNI (+) group and 14 (66.7%) patients in the PNI (-) group had the complaint of bloody vaginal discharge at admission. There was no statistically significant difference in means of age, reproductive history, complete blood counts and renal and hepatic function tests between the groups (p > 0.05) (Table 1). The histopathological subtypes, tumor stage and grade were evenly distributed among the groups (p > 0.05) (Table 2). The mean tumor size and cervical stromal invasion in millimeters were comparable between the groups (p > 0.05), but the mean depth of invasion in percentage of the stroma was significantly higher in the PNI (+) group (p ≤ 0.05). Vaginal (p ≤ 0.05) and uterine (p ≤ 0.01) invasion of the tumor were significantly more prevalent in the PNI (+) group while there was no significant difference between the frequencies of parametrial invasion, postoperative treatment, recurrence and survival data were obtained from the records. Patients were categorized according to their status of PNI; PNI (+) (n = 15) and PNI (-) (n = 21).

Seven (46.7%) patients in the PNI (+) group and ten (47.6%) patients in the PNI (-) group were postmenopausal and the remainder were regularly menstruating. Seven patients in both the PNI (+) (46.7%) and PNI (-) (33.3%) groups complained of postcoital bleeding while eight (53.3%) patients in the PNI (+) group and 14 (66.7%) patients in the PNI (-) group had the complaint of bloody vaginal discharge at admission. There was no statistically significant difference in means of age, reproductive history, complete blood counts and renal and hepatic function tests between the groups (p > 0.05) (Table 1). The histopathological subtypes, tumor stage and grade were evenly distributed among the groups (p > 0.05) (Table 2). The mean tumor size and cervical stromal invasion in millimeters were comparable between the groups (p > 0.05), but the mean depth of invasion in percentage of the stroma was significantly higher in the PNI (+) group (p ≤ 0.05). Vaginal (p ≤ 0.05) and uterine (p ≤ 0.01) invasion of the tumor were significantly more prevalent in the PNI (+) group while there was no significant difference between the frequencies of parametrial invasion, postoperative treatment, recurrence and survival data were obtained from the records. Patients were categorized according to their status of PNI; PNI (+) (n = 15) and PNI (-) (n = 21).

Statistical analysis was performed using the statistical package for the Social Sciences (SPSS) v 13.0. Distribution patterns of the groups were analyzed using the Shapiro-Wilk test and Levene’s test for equality of variances. The t-test was used in the comparison of the two groups with normal distribution and the Mann-Whitney U test was used in the comparison of the two groups without normal distribution. The categorized data were analyzed using the continuity correction test and Fisher’s exact test. The two-sample Kolmogorov-Smirnov test was used to compare the distribution of the two groups with inadequate data. Statistical significance was defined at p ≤ 0.05.
Table 1. — Demographic characteristics, complete blood counts, serum renal and hepatic function tests of the groups (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Perineural (+) (n = 15)</th>
<th>Perineural (-) (n = 21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>46.53 ± 10.10</td>
<td>47.67 ± 8.00</td>
<td>NS</td>
</tr>
<tr>
<td>Gravida</td>
<td>4.13 ± 1.60</td>
<td>4.24 ± 1.87</td>
<td>NS</td>
</tr>
<tr>
<td>Parity</td>
<td>2.53 ± 1.06</td>
<td>2.95 ± 0.86</td>
<td>NS</td>
</tr>
<tr>
<td>Abortion</td>
<td>1.60 ± 1.18</td>
<td>1.29 ± 1.38</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.38 ± 1.10</td>
<td>12.15 ± 1.27</td>
<td>NS</td>
</tr>
<tr>
<td>Leukocyte count (g/l)</td>
<td>5430.00 ± 2341.92</td>
<td>5838.57 ± 2433.96</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>93.07 ± 7.85</td>
<td>89.00 ± 11.08</td>
<td>NS</td>
</tr>
<tr>
<td>AST (u/l)</td>
<td>28.47 ± 9.30</td>
<td>26.29 ± 7.92</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (u/l)</td>
<td>26.67 ± 5.92</td>
<td>26.00 ± 6.71</td>
<td>NS</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>25.80 ± 5.05</td>
<td>28.29 ± 6.24</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.76 ± 0.10</td>
<td>0.80 ± 0.08</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: not significant.

Table 2. — Histopathology, stage, grade, tumor size and tumor invasion in millimeters and percentage of cervical stroma of the groups (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Perineural (+) (n = 15)</th>
<th>Perineural (-) (n = 21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>12 (80.0%)</td>
<td>15 (71.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>ASC</td>
<td>2 (13.3%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>1 (6.7%)</td>
<td>6 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IbI</td>
<td>10 (66.7%)</td>
<td>15 (71.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Iib</td>
<td>2 (13.3%)</td>
<td>6 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (6.7%)</td>
<td>4 (19.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>6 (40.0%)</td>
<td>6 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 (53.3%)</td>
<td>11 (52.4%)</td>
<td></td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>38.67 ± 9.63</td>
<td>33.71 ± 13.64</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor invasion (mm)</td>
<td>17.13 ± 6.05</td>
<td>13.52 ± 9.14</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor invasion (% of the stroma)</td>
<td>82.53 ± 20.44</td>
<td>60.90 ± 31.88</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3. — Parametrial, vaginal and uterine invasion, pelvic lymph node involvement and surgical margin positivity of the groups.

<table>
<thead>
<tr>
<th></th>
<th>Perineural (+) (n = 15)</th>
<th>Perineural (-) (n = 21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parametrial invasion (+)</td>
<td>4 (26.7%)</td>
<td>3 (14.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>(-)</td>
<td>11 (73.3%)</td>
<td>18 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>Vaginal invasion (+)</td>
<td>6 (40.0%)</td>
<td>2 (9.5%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(-)</td>
<td>9 (60.0%)</td>
<td>19 (90.5%)</td>
<td></td>
</tr>
<tr>
<td>Uterine invasion (+)</td>
<td>8 (53.3%)</td>
<td>2 (9.5%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>(-)</td>
<td>7 (46.7%)</td>
<td>19 (90.5%)</td>
<td></td>
</tr>
<tr>
<td>Pelvic lymph nodes (+)</td>
<td>8 (53.3%)</td>
<td>7 (33.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>(-)</td>
<td>7 (46.7%)</td>
<td>14 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Surgical margin (+)</td>
<td>5 (33.3%)</td>
<td>2 (9.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>(-)</td>
<td>10 (66.7%)</td>
<td>19 (90.5%)</td>
<td></td>
</tr>
</tbody>
</table>

NS: not significant.

Table 4. — Lymphatic and vascular invasion, recurrence and mortality rates of the groups.

<table>
<thead>
<tr>
<th></th>
<th>Perineural (+) (n = 15)</th>
<th>Perineural (-) (n = 21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic invasion (+)</td>
<td>9 (60.0%)</td>
<td>4 (19.0%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>(-)</td>
<td>6 (40.0%)</td>
<td>17 (81.0%)</td>
<td></td>
</tr>
<tr>
<td>Vascular invasion (+)</td>
<td>7 (46.7%)</td>
<td>5 (23.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>(-)</td>
<td>8 (53.3%)</td>
<td>16 (76.2%)</td>
<td></td>
</tr>
<tr>
<td>Lymphovascular space invasion (+)</td>
<td>12 (80.0%)</td>
<td>7 (33.3%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(-)</td>
<td>3 (20.0%)</td>
<td>14 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Recurrence (+)</td>
<td>4 (26.7%)</td>
<td>10 (47.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>(-)</td>
<td>11 (73.3%)</td>
<td>11 (52.4%)</td>
<td></td>
</tr>
<tr>
<td>Mortality (+)</td>
<td>3 (20.0%)</td>
<td>9 (42.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>(-)</td>
<td>12 (80.0%)</td>
<td>12 (57.1%)</td>
<td></td>
</tr>
</tbody>
</table>

NS: not significant.

Discussion

PNI is defined as carcinoma invading the nerve sheath surrounding the nerves that enter the tumoral mass; hence the neoplastic cells skip the confines of the tumoral mass by tracking the route of the nerves within the perineural space which is the tissue plane of least resistance. Ernst was the first to identify PNI in 1905 [17]. Magari et al., reported that the gates for cancer cells are the end points of the perineurium or the entrances of vascular structures to the perineurium [18]. However direct invasion of tumor cells have also been reported by some authors [8, 19]. In 1996, Yang et al., observed increased proliferation and decreased apoptosis of perineural cancer cells compared to cancer cells in other locations [20, 21]. In an effort to clarify the underlying molecular mechanism, Zhu et al., observed significantly higher nerve growth factor (NGF) and TrkA proto-oncogene mRNA expression in tumors with PNI compared to tumors without PNI; conversely, in tumors with high NGF and TrkA expression, PNI was more frequent [22]. In another study Bockman et al., reported an interaction between transforming growth factor-α (TGF-α) in nerves and epidermal growth factor receptor (EGFR) on cancer cells, which seemed to ease PNI in pancreatic cancer [23]. More recently Ayala et al., observed increased expression of NFkB, an apoptosis inhibitor, and its downstream effectors DAD-1 and PIM-2 in perineural prostatic cancer cells [21]. Moreover, nuclear translocation of NFkB was found to be associated with decreased biochemical recurrence-free survival.

Following invasion to the perineurum, tumor cells can travel within this conduit either cranially or caudally without evoking inflammation in the surrounding stroma and cause recurrence, even if surgical margins are free of tumor [24]. Therefore accurate detection of PNI is advocated in some tumors to decide on adjuvant and sometimes primary treatment. Otherwise there will be a delay in the diagnosis of perineural spread. PNI is clinically recognized by formication, dysesthesia, paresthesia, numbness, pain and even motor deficits [25]. Therefore a
high level of suspicion of the clinician is necessary not to overlook any spread of tumor.

PNI has been reported in skin, head and neck, oral cavity, tongue, salivary gland, stomach, pancreas, gall bladder, rectum, esophagus, ampullary and prostate carcinomas [2-16]. It was found to be predictive of depth of invasion, stage, grade, lymph node involvement, spread of disease, recurrence rate and survival in some carcinomas [26-34]. During the primary definitive surgery, some authors recommended the excision of the involved nerve up to the tumor-free level [35-37]. However other authors did not recommend such an approach, since they failed to find any significance of PNI in carcinomas [38-45].

PNI was observed in 17-50% of the prostate carcinoma needle biopsies [15, 26] up to 84% of radical prostatectomy specimens [30], and 53-90% of pancreatic carcinomas [19]. The College of American Pathologists (CAP) recommended that PNI status should be noted during reporting of the surgical specimens of prostate and pancreas carcinomas due to its potential value (http://www.cap.org/apps/cap.portal); however it was still not considered as a predictive factor by the Cancer Committee of the CAP [46, 47].

Cervical cancer up to Stage IIA is conventionally treated by radical hysterectomy + bilateral salpingo-oophorectomy + bilateral pelvic and paraaortic lymph node dissection [48]. Proposed prognostic factors are; stage, histological type, grade, tumor size, depth of cervical stromal invasion, parametrical invasion, LVI, lymph node metastases, surgical margin involvement [49, 50].

Cervical cancer up to Stage IIA are considered as early-stage disease, however up to 20% of the cases recur and the prognosis worsens with a mean survival time of ten months and a 5-year survival rate of 10% [51]. Because it is an important poor prognostic parameter, histopathological reports of the surgical specimen commonly note the tumoral invasion status of the parametrium [52, 53]. Though LVS1 is usually pointed out, PNI is often overlooked in those reports.

One of the explanations of highly prevalent perineural spread in pancreas carcinoma might be the position of the organ lying in a bed with abundant nerves. The prostate and cervix share the same feature as they are surrounded by the middle rectal plexus, the vesical plexus, and the prostatic or the uterine plexus. They also show some similarities in their innervations. Rami from the sacral portion of the sympathetic chain of the hypogastric plexus and the visceral branches of the second, third, and fourth sacral nerves form the pelvic plexus of the autonomic system and through the secondary plexuses it is distributed to all the pelvic viscera. The prostatic plexus, from the deeper ventral part of the pelvic plexus, is composed of larger nerves which are distributed to the prostate, seminal vesicles, and corpora cavernosa in males. On the other hand, the uterine plexus arises from the caudal portion of the pelvic plexus and approaches the uterus from its caudal and lateral aspect in the base of the broad ligament, beside the uterine artery. It is distributed to the uterine musculature including the cervix, supplies filaments to the uterine tube and communicates with the ovarian plexus which arises from the renal plexus, accompanies the ovarian artery and is distributed to the ovary, uterine tubes and the fundus of the uterus. Afferent fibers from the uterus enter the spinal cord solely through the 11th and 12th thoracic nerves [54]. Therefore the importance of PNI in prostate cancer might be extrapolated to cervical cancer. However there are only two studies in the literature evaluating the role of PNI in cervical cancer.

In 1997, Beitler et al., evaluated the role of intraoperative interstitial brachytherapy during pelvic exenteration in 26 recurrent cervical cancer patients retrospectively [55]. Of the ten treatment failures nine had ≤ 5 mm margins, LVS1 or PNI positivity; either of which or their combinations were significantly associated with disease-specific survival (p = 0.006) and local control (p = 0.013). Seven (27%) of the 26 patients had LVI or PNI with clear margins and three were with no evidence of disease following the therapy but four died of disease with local recurrence; revealing the adverse affect of either LVS1 and/or PNI on local control (p = 0.018). Among eight patients with local failure, seven had LSV1, four had PNI, three had ≤ 5 mm margins and two had microscopic nodal disease. Twelve of the 26 patients had LVS1 and/or PNI and eight of them died of disease, one was alive with disease and three did not recur. The authors concluded that patients with tumor-free nodes and margins, no LVS1 or PNI do not need further therapy as 11 of 12 patients in their study had no recurrence. In our study we found significantly deeper stromal invasion (percentage) and significantly more prevalent vaginal and uterine spread of the tumor in PNI (+) compared to PNI (-) patients. It was not surprising to see that the recurrence and mortality rates had a tendency to be lower in the PNI (+) group, because 13 (86.7%) patients in the PNI (+) but only nine (42.9%) patients in the PNI (-) group had postoperative chemoradiotherapy.

In 2003 Memarzadeh et al. observed that PNI was strongly associated with the presence of parametrical LVS1 in 90 early-stage cervical carcinoma cases [56]. There was 86% (6 cases) parametrical LVS1 in patients with PNI, but it was only 10% (86 cases) in those without PNI. Univariate analysis, considering recurrence or death due to disease as outcomes, showed that tumor size and parametrical PNI were significant independent predictors of poor outcome, each causing a 2.5-fold increase in risk of both recurrence and death. We confirmed the finding of Memarzadeh, and found LSV1 to be more prevalent in the PNI (+) compared to the PNI (-) group (p = 0.030) (Table 4). However when we individualized the components, the significance between the groups was higher in means of lymphatic invasion (p = 0.008) (Table 4).

This study had several limitations. As only patients who had type III radical hysterectomy + bilateral salpingo-oophorectomy + bilateral pelvic and paraaortic lymph node dissection with the diagnosis of Stage IB1 or IB2 cervical carcinoma followed-up regularly were included in the study, the sizes of the groups were small.
Therefore it was not possible to evaluate the predictivity of PNI positivity in patients with cervical cancer. The prognostic significance of PNI positivity was not able to be investigated either, since the follow-up period was not long enough and not all the patients completed their 5-year survival.

However, we concluded that PNI was closely related percentually with stromal invasion, vaginal and uterine involvement and lymphatic invasion of the tumor. Our findings provide a basis for further studies evaluating the predictive and prognostic role of PNI in cervical cancer.

References


Perineural invasion in early-stage cervical carcinoma


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Osmangazi 16010 Bursa (Turkey)
e-mail: hozan@superonline.com
Spleen involvement in women with ovarian cancer

G. Cormio, M.D., Ph.D.; V. Loizzi, M.D.; C. Carriero, G. Putignano, L. Selvaggi
Department of Obstetrics and Gynecology, Gynecologic Oncology Unit, University of Bari, Bari (Italy)

Summary

The aim of this study was to determine the prognostic factors of spleen metastases in ovarian cancer. A retrospective chart review was conducted and ten patients with spleen metastases were evaluated. Eight were Stage III, one Stage I and one Stage IV. One patient had a spleen metastasis at the time of ovarian cancer diagnosis, whereas, the remaining patients 23.4+12 months after ovarian cancer diagnosis. Spleen involvement is a late complication that rarely occurs in ovarian cancer and confers a poor prognosis. The interval time between ovarian cancer diagnosis and appearance of spleen involvement is the most important prognostic factor.

Key words: Spleen metastasis; Ovarian cancer.

Introduction

Ovarian carcinoma is the most common cause of death from gynecologic malignancy in Europe and the United States [1]. Although the intraperitoneal route of dissemination is considered the most common, ovarian cancer may also metastasize through the lymphatic channels and the hematogenous route [2]. Distant metastases may occur at the time of ovarian cancer diagnosis (Stage IV disease) or can arise during the evolution of the disease [3]. Involvement of the spleen from ovarian neoplasms is uncommon, and splenic metastases are reported to occur in about 3% of patients with ovarian carcinoma [3, 4].

Splenectomy has been predominantly reported as part of initial cytoreductive surgery in ovarian cancer [5-7]. Experience with splenectomy performed at secondary debulking is limited [6-9]. In most reports, the spleen was involved as part of a diffuse carcinomatosis and there are only a few cases of isolated parenchymal metastases [10-12].

The aim of this retrospective study was to investigate the incidence of parenchymal spleen metastases in ovarian cancer patients, to evaluate the risk factors for the development of splenic disease and to determine prognostic factors associated with survival.

Patients and Methods

A retrospective chart review was conducted on 240 ovarian carcinoma patients treated between 1991 and 2004 at the Gynecologic Oncology Unit of the Department of Obstetrics and Gynecology, University of Bari, Italy.

Course of ovarian carcinoma, pertinent clinical information and management of the spleen metastases were reviewed for each patient, as well as tumor histology and differentiation.

Clinical staging at the time of primary diagnosis was performed in all patients according to the International Federation of Gynecology and Obstetrics (FIGO) system [13]. All patients had undergone surgical procedures for their primary disease, usually consisting of total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy and had received platin-based chemotherapy for the treatment of ovarian cancer. Additionally, various other agents were used either in combination or alone for salvage therapy.

Parenchymal involvement was based on computed tomography (CT) scan and in some cases after pathologic examination following splenectomy. Only true parenchymal spleen metastases were recorded. In no case was autopsy permission granted.

Survival time was calculated from the time of diagnosis (usually the date of primary surgery) and from the time of diagnosis of spleen metastases. The median follow-up was 32 months (range 106-9). Survival curves were calculated using the standard actuarial life-table method of Kaplan-Meier [14]. Comparison of survival was made using the Mantel Haenszel [15] and the Wilcoxon tests [16].

Results

Among 240 patients with ovarian cancer ten (2%) were found to have spleen metastasis, and the clinicopathologic characteristics of these patients are summarized in Table 1.

The mean age of the patients at the time of ovarian cancer diagnosis was 55 years (range 40 to 61). Eight patients had FIGO Stage III C at the time of ovarian cancer diagnosis and one each had Stage IIA and Stage IV disease. Most patients had serous papillary cystoadenocarcinoma of the ovary (80%); one each had endometrioid and mucinous carcinomas (10%). Seven patients (70%) had poorly differentiated tumors. Due to poor general condition and massive abdominal disease, neoadjuvant chemotherapy was employed as primary treatment in one patient (case 1) following cytologic diagnosis obtained with paracentesis. The remaining nine patients had primary surgery performed through a primary laparotomic access. Most patients had large residual disease following surgery. All patients received platin-based first-line chemotherapy, and several chemotherapeutic regimes were used for second and third line.

Table 2 shows the clinicopathologic characteristics of the spleen metastases. Only one patient (case 2) had spleen involvement at the time of ovarian cancer diagnosis whereas, in the remaining patients the average time of...
appearance of spleen metastases after diagnosis was 45 months (range 1 to 124). Diagnosis of spleen involvement was made by ultrasound examination or CT scan of the abdomen. The diameter of the splenic lesions ranged between 1 and 5 cm. Eight patients had a single splenic nodule, while two had multiple spleen lesions. Metastatic splenic lesions were classified as parenchymal in five cases, subcapsular in four and hilar in one case. In four patients spleen involvement was the first site of recurrent disease. All but one patient (case 10) had concomitant disease in the abdomen and pelvis (mostly in the liver) at the time of spleen metastasis. One patient also had brain involvement.

Four patients had splenectomy through a laparotomic approach. Moreover all patients had intraperitoneal debulking with resection of bulky lymph nodes, partial omentectomy and resection of a superficial liver nodule. All patients received intravenous chemotherapy with different regimens. Of six patients with measurable disease two (33%) had a complete remission, while the remaining patients had partial response or stable disease.

Eight patients (80%) have died of disease and median survival after diagnosis of the splenic involvement was 16 months (range 6 to 27). Two patients are alive without tumor 22 and 45 months after diagnosis of the skin metastases. Overall survival after diagnosis of spleen metastasis from ovarian cancer was 18 months (range 6 to 45). Patients who had splenectomy had a median survival of 22 months (range 14 to 45) following the appearance of the spleen metastases compared to a median survival of 14 months (range 6 to 27) for patients treated with only chemotherapy. Due to the limited number of patients in our series an analysis of survival according the various clinicopathologic factors of the patients at ovarian cancer diagnosis (age, stage, histology, residual disease) or the clinical features of the spleen metastases (number, diameter and location) was not possible.

**Discussion**

The spleen was once considered to be relatively resistant to carcinomatous metastases. Reports of metastases were rare and various anatomic and physiologic theories regarding this resistance to metastasis had been reported [17]. More recent literature has shown that the incidence of splenic metastases is not as rare as was once reported [18]. Carcinoma of the breast and lung, and melanoma are most common, but metastases from other neoplasms do occur. Splenic metastases occur in a setting of widely disseminated disease, usually late in the disease course and are usually found at autopsy. Clinically evident splenic metastases, particularly in the absence of disseminated disease are extremely rare [17, 18].

Gynecological malignancies rarely metastasize to the spleen [6]. Unlike liver parenchymal involvement, splenic parenchymal involvement by epithelial ovarian cancer has not been incorporated into the FIGO staging system and it is generally thought that ovarian cancer grows around the spleen and not into it.

The purpose of the present study was to answer three main questions: what is the true incidence of spleen metastases in ovarian cancer; is it possible to predict those patients who might develop spleen dissemination
during the course of the disease and lastly, what is the prognosis in patients diagnosed with spleen metastases?

In the present series clinically detected spleen metastases were found in about 2% of ovarian cancer patients. Autopsy studies have revealed that spleen involvement occurs in 19 to 52% of epithelial ovarian cancers [2, 19]. On the other hand, in clinical studies the incidence of spleen metastases ranged between 1 and 15% [3-12].

In most cases spleen metastases tend to appear late in the course of the disease and usually are associated with poor prognosis [5-8]. In the present study median interval time between diagnosis of ovarian cancer and documentation of spleen metastasis was 45 months; this figure is similar to that reported in previous series [4].

There are several theories attempting to explain the pathogenesis of spleen metastases in ovarian cancer: direct invasion from the underlying growth, contiguous extension of tumor cells throughout the lymphatics, and accidental implantation of tumor cells during surgical procedures [5-7, 18].

When spleen metastases are present from ovarian or other gynecological malignant neoplasias, the disease is usually advanced and invariably accompanied by widespread intraperitoneal involvement [4, 7, 9]. In our series all but one patient had other sites of disease and the majority of them died of progressive abdominal disease. This indicates that control of the abdominal disease remains a major problem in the management of ovarian cancer patients.

Few guidelines are available to select the therapy for spleen metastases from ovarian cancer. Surgical resection is indicated in case of solitary spleen metastases, or when other sites of disease (liver, pelvis) can be resected. Indeed, in our series all patients submitted to splenectomy had no residual disease following surgery. Although most authors suggest polyvalent pneumococcal vaccine prior to splenectomy to prevent infectious complications [6, 9], no patient in our series experienced either sepsis, or severe thrombocytosis following splenectomy.

Spleen metastases often develop late in the course of disease, after administration of several chemotherapeutic regimens, which renders them rather resistant to further cytotoxic drugs. In our series some patients had objective response of spleen metastases to chemotherapy, however complete response of spleen involvement from an ovarian carcinoma with tamoxifen has been recently reported [11].

In our series median survival from diagnosis of the spleen metastases was four months, whereas Dauplat and colleagues reported a median survival of 12 months (range 1-41) [3]. Patients who had surgical excision followed by chemotherapy had a longer survival compared to those who had chemotherapy alone.

Prognosis of patients who develop spleen metastases is poor; however in selected cases integrated multimodality treatment may result in palliation of the symptomatology and even in a prolonged survival. Splenectomy may play an important role as a salvage treatment of isolated splenic metastasis of ovarian cancer, because the benefits of the procedure might outweigh the morbidity. The limited number of patients in our series does not allow the evaluation of other prognostic factors for survival after diagnosis of spleen involvement.

References


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The use of cod liver oil by patients receiving pegylated liposomal doxorubicin is associated with a lack of severe palmar-plantar erythrodysesthesia

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¹University at Buffalo School of Medicine, Buffalo, ²Division of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, NY (USA)

Summary

Pegylated liposomal doxorubicin (PLD) is an effective and tolerable agent in the treatment of recurrent and refractory ovarian carcinoma. One of the most common dose-limiting toxicities of PLD is palmar-plantar erythrodysesthesia (PPE). We report a retrospective review of patients who took cod liver oil (CLO) while being treated with PLD at Roswell Park Cancer Institute. None of the patients required dose reduction, treatment interruption or discontinuation secondary to skin toxicity. No patient experienced grade 2 or greater PPE. The mechanism for the development of PLD-induced PPE is unknown. CLO may possibly mitigate it via decreased extravasation of PLD and/or by a blunting of the local inflammatory response. The effects of CLO should be further evaluated in a prospective, randomized trial, and attempts to elucidate the mechanism by which CLO may exert its effects should be pursued.

Key words: Pegylated liposomal doxorubicin; Palmar-plantar erythrodysesthesia; Cod liver oil.

Introduction

Pegylated liposomal doxorubicin (PLD) is an effective and tolerable agent in the treatment of recurrent and refractory ovarian carcinoma [1, 2]. One of the most common dose-limiting toxicities of PLD is palmar-plantar erythrodysesthesia (PPE). In a randomized phase III study comparing PLD to topotecan, PPE occurred in 49% of patients in the PLD arm [3], PPE is characterized initially by dysesthesia of the hands and feet which progresses to edema with erythema with associated pain and subsequent fissure and ulcer development. These symptoms compromise the patient’s ability to perform activities of daily living secondary to pain associated with grasping objects and/or walking. The exact mechanism of PPE is unknown. PLD dose adjustments, oral pyridoxine, topical dimethylsulfoxide, steroids, and regional cooling have all been utilized in an attempt to prevent or treat PPE [4-8]. The aim of this study was to determine if cod liver oil (CLO) could prevent or mitigate PLD-induced PPE.

Materials and Methods

After obtaining institutional review board approval, a retrospective review of patients who took CLO while being treated with PLD at Roswell Park Cancer Institute was initiated. Eighteen patients met inclusion criteria. PLD was initiated at 40 mg/m² every 28 days when used as single-agent therapy or at 30 mg/m² every 28 days when used in combination with another agent. CLO was self administered. Patients had been instructed to take one capsule with meals, three times per day. Toxicities were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (Table 1). Patients were surveyed and examined at each clinic visit to assess their compliance with CLO, any associated side-effects as well as any PLD toxicity, including PPE.

Results

Eighteen patients had agreed to take CLO while on PLD. A total of 72 cycles of PLD were administered after initiation and continuation of CLO. The average number of cycles of PLD administered while on CLO was four (range: 2-8). No patients required dose reduction, treatment interruption or discontinuation secondary to skin toxicity. No patient experienced grade 2 or greater PPE. Of the 72 cycles administered, PPE was assessed as absent for 51 cycles and grade 1 for 21 cycles. Half of the patients (9) were assessed as having no evidence of PPE throughout their concurrent use of CLO and PLD.

Discussion

Here we report the association of the self-administration of oral CLO with a lack of significant PLD-associated PPE. This study is limited by its retrospective analysis, non-blinded nature and lack of a placebo-control group. However, even in this limited, exploratory analysis, the concurrent administration of CLO with PLD chemotherapy is impressive considering that with similar PLD dosages and scheduling in prior studies, a 21% incidence of PPE has been observed, including an 8% incidence of severe PPE [9].

Without knowing the mechanistic basis for the development of PLD-induced PPE, we can only speculate as to the exact mechanism by which CLO may mitigate it. One theory for the etiology of PPE involves extravasation...
Table 1. — *Hand-foot skin reaction grades*.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal skin changes or dermatitis (e.g., erythema) without pain.</td>
</tr>
<tr>
<td>2</td>
<td>Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function.</td>
</tr>
<tr>
<td>3</td>
<td>Ulcerative dermatitis or skin changes with pain interfering with function.</td>
</tr>
</tbody>
</table>

*According to NCI Common Terminology Criteria for Adverse Events (v 3.0).*

of PLD from the deeper capillaries of the hands and feet. CLO may decrease this leakage. Jensen et al. reported that dietary supplementation with CLO lowered the transcapillary escape rate of albumin in their study of diabetic patients [10]. The mechanism by which CLO normalizes the increased blood vessel permeability in diabetic patients may also play a role in the extravasation of PLD in cancer patients.

Another proposed mechanism for the development of PPE entails a local inflammatory reaction at the site of drug extravasation and accumulation in the stratum corneum. The active ingredients in fish oil include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DME) which are both omega-3-fatty acids. Consumption of EPA has been shown to decrease the production of inflammatory cytokines [11-13]. The decreased production of pro-inflammatory mediators by EPA in CLO may result in a decreased local inflammatory response and account for the lack of severe PPE seen in patients taking CLO supplementation while receiving PLD in our study. An inflammatory model is further corroborated by Drake et al.’s study demonstrating the attenuation of PLD-induced PPE with oral dexamethasone which may act to decrease the inflammation cascade [14].

PLD has proven activity in the recurrent ovarian cancer setting. Therapy which may mitigate PLD toxicity thus allowing for prolonged PLD treatment should be investigated. A common dose-limiting toxicity of PLD is PPE. Our finding of a lack of severe PLD-associated PPE with the concurrent use of CLO warrants further evaluation in a prospective, randomized trial, and further attempts are needed to elucidate the mechanism by which CLO may exert its effects.

References


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Clinicopathological features of primary fallopian tube carcinoma: a single institution experience

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Summary

Purpose of investigation: Primary fallopian tube carcinoma (PFTC) is a rare malignancy with only few data existing on the impact of prognostic factors. Methods: We retrospectively analyzed 26 patients. Tissue blocks were reviewed and sections were stained for vascular endothelial growth factor (VEGF), matrix metalloproteinases 2 and 9 (MMP-2, MMP-9), tissue inhibitors of metalloproteinases 1 and 2 (TIMP-1, TIMP-2), c-erbB-2, estrogen (ER), and progesterone receptors (PgR). Results: Reactivity for VEGF, ER, PgR, MMP-2, MMP-9, TIMP-1, TIMP-2 and c-erbB-2 was observed in 85%, 46%, 27%, 11.5%, 58%, 0%, 23% and 8% of specimens, respectively. None of the markers studied displayed prognostic significance. Regarding clinical prognostic factors, the hazard ratio (HR) for progression and death for patients with tumor residuum > 2 cm was 5.24 (p < 0.01) and 11.19 (p < 0.005), respectively. Patients with advanced stage disease had a HR of 12.55 (p < 0.05) for progression, while the HR for death was not found to be statistically significant. Conclusion: None of the biomarkers studied seems to influence survival. Early-stage disease and optimal debulking were associated with improved outcome.

Key words: Primary fallopian tube cancer; Immunohistochemistry; Prognostic factors; First-line chemotherapy.

Introduction

Primary fallopian tube carcinoma (PFTC) is a rare gynecologic tumor accounting for 0.3-1% of all female genital tract neoplasms [1]. The average annual incidence is 3.6/1,000,000 women per year. These rates were examined for epithelial malignant fallopian tube neoplasms diagnosed between 1973 and 1984 and reported to nine population-based cancer registries in the United States [2]. PFTC spreads in much the same manner as epithelial ovarian cancer (EOC), principally by exfoliation of cells that implant throughout the peritoneal cavity. Tumor spread can also occur by means of transmural migration, contiguous invasion, and hematogenous dissemination [3-5].

The diagnosis of PFTC is rarely considered preoperatively and is usually first established by the pathologist. Surgical staging and management as well as the use of chemotherapy follow the concepts used in EOC [6]. As with EOC, stage and residual tumor are the most important prognostic factors. Chemotherapy seems to have a strong rationale as adjuvant treatment even for patients with early-stage disease. Platinum-based combination chemotherapy is the most commonly used postoperative systemic therapy for PFTC patients [7-11]. Today the combination of paclitaxel with a platinum analogue is the preferred chemotherapy regimen for the treatment of newly diagnosed patients with EOC. In a recent analysis of 41 consecutive chemo-naïve patients with PFTC, who were referred to our department, postoperative platinum- and paclitaxel-based chemotherapy succeeded in high response rates and promising time to disease progression (TTP) and overall survival (OS). Early-stage disease and optimal debulking were related with improved survival outcome [12].

We conducted a retrospective analysis of 26 patients with PFTC who were treated in our department with first-line chemotherapy after initial staging laparotomy/cytoreductive surgery. The aim of the present study was to analyze some clinical and pathological prognostic factors, including the immunohistochemical expression of vascular endothelial growth factor (VEGF), matrix metalloproteinase 2 (MMP-2), matrix metalloproteinase 9 (MMP-9), tissue inhibitor of metalloproteinase 1 (TIMP-1), tissue inhibitor of metalloproteinase 2 (TIMP-2), c-erbB-2, estrogen, and progesterone receptors.

Materials and Methods

Patient selection

Twenty-six patients with PFTC who were referred to our department for postoperative chemotherapy were included in this analysis. All patients were operated on and surgically staged by a gynecologic oncologist who was the primary surgeon in all cases. Records of the patients were examined retrospectively. Data extracted from the records included information regarding demographic details, initial stage, grade, and histological type of the carcinoma. The type of surgery was defined and information about residual disease, adjuvant chemotherapy, recurrence and survival was collected as well. Uniform optimal surgical staging and treatment according to

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FIGO guidelines was performed in the majority of cases. This included total abdominal hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy, cautious inspection and palpation of intraperitoneal and retroperitoneal surfaces, biopsy sampling of suspicious macroscopic lesions and collection of peritoneal washings. The essential aim was the achievement of an optimal surgical debulking leaving residual disease no larger than > 1 cm in diameter during the primary cytoreduction.

Response Evaluation Criteria in Solid Tumors (RECIST) were used for the response evaluation [13]. Patients with solid tumors assessed by computed tomography (CT) scan (≥ 10 mm) or by ultrasonography (US) (≥ 20 mm) were categorized as measurable disease. Nonmeasurable disease was defined as lesions that measured < 10 mm on CT scan or < 20 mm on US. Nonmeasurable disease included cystic lesions and ascites. Patients with measurable disease after initial laparotomy were assessed for objective response. Imaging studies were routinely performed after the third and the sixth cycle of chemotherapy as well as in case of premature treatment discontinuation for any cause. Patients experiencing toxic death before an assessment of response would be rated as nonresponders. Patients with normalization of serum CA-125 levels and disappearance of all target lesions were considered to have a complete response (CR). A partial response (PR) was defined as a decrease ≥ 30% in the baseline sum of the greatest dimensions of the target lesions. Progressive disease was defined as an increase ≥ 20% in the sum of the longest diameter of target lesions with an increase of CA-125 levels ≥ 25%. All other cases were considered to have stable disease. In patients who had elevated levels of CA-125 only, a response was defined as a reduction ≥ 50% in the pretreatment CA-125 level.

Immunohistochemistry

Paraffin-embedded tissue blocks of the primary tumor were selected for immunohistochemical evaluation. Three-micrometer-thick paraffin sections were cut from these blocks, placed on charged slides, and dried at 56-58°C for one hour. Sections were then deparaffinized in xylene and rehydrated in a grade sequence of ethanol series. Further, they were washed in a citrate buffer at a pH 6.0 in a microwave oven for 15 min, and stained using the biotin-streptavidin–alkaline phosphatase conjugate method. Primary antibodies were applied to each section at the dilutions indicated in Table 1, and were incubated for 30 min or one hour. The following primary antibodies were used: (i) for VEGF, a mouse IgG2b monoclonal antibody (clone G153-694, BD Pharmingen, San Diego, CA, USA) that has been utilized to immunoprecipitate native human VEGF and to identify three isoforms of VEGF (165, 189, 206 aa) by Western blotting; (ii) for estrogen receptor α (ER) a mouse IgG1/k monoclonal antibody (clone 1D5, DAKO, Denmark); (iii) for progesterone receptor (PgR) a mouse IgG1/k monoclonal antibody (clone 636, DAKO, Denmark); (iv) for human matrix metalloproteinase 2 (MMP-2), also known as 72kDa collagenase IV or gelatinase A, a mouse IgG1 monoclonal antibody that recognizes pro (latent) and active forms of MMP 2 (clone A-Gel VC2, NeoMarkers, Fremont, CA, USA); (v) for human matrix metalloproteinase 9 (MMP-9), also known as 92kDa collagenease IV, a rabbit polyclonal epitope specific antibody (NeoMarkers, Fremont, CA, USA); (vi) for tissue inhibitor of metalloproteinase 1 (TIMP-1), a mouse IgG1 monoclonal antibody (clone 102D1, NeoMarkers, Fremont, CA, USA); (vii) for tissue inhibitor of metalloproteinase 2 (TIMP-2), a mouse IgG2a/k monoclonal antibody (clone 3A4, NeoMarkers, Fremont, CA, USA); and (viii) for c-erbB-2, a mouse IgG1 monoclonal antibody (clone CB11, Novocastra Laboratories Ltd, Newcastle upon Tyne, UK). Bound primary antibodies were then detected using proper biotinylated immunoglobulin (rabbit anti-mouse for all monoclonal antibodies and goat anti-rabbit for MMP-9) and a streptavidin–alkaline phosphatase reaction was developed using Fast Red as chromogen (alkaline phosphatase chromogen kit (Fast Red, GeneTex Inc., San Antonio, TX, USA). Finally, sections were counterstained with hematoxylin. Omitting the primary antibody from the immunohistochemical procedure and replacing it with antibody diluent or nonimmune rabbit serum acted as negative controls for monoclonal and polyclonal antibodies, respectively. Known positive control tissues were also stained. Immunoreactivity for each antigen was evaluated by examination of the sections by bright-field light microscopy by the same pathologist. All the markers were evaluated and sections were scored before obtaining outcome (survival) data for each case.

Staining intensity (weak, moderate, and strong) and proportion of tumor cells stained in each case were taken into consideration. The final score was the average from ten distinct high-power fields observed under X400 magnification. Initially, a four-level scoring system was used: expression was considered high (3+) when 50-100% of the neoplastic cells were strongly stained, moderate (2+) when 10-50% of the neoplastic cells were moderately or strongly stained, low (1+) when less than 10% of the neoplastic cells were weakly positive, and finally negative (0) when none were stained. However, for the purpose of clinical correlations, immunohistochemical staining was arbitrarily divided in two categories: negative (0) and positive (1+, 2+, 3+).

Table 1. — Details of the antibodies used in this study.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Type</th>
<th>Incubation (min)</th>
<th>Clone</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF&lt;sup&gt;v&lt;/sup&gt;</td>
<td>BD Pharmingen</td>
<td>M&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60</td>
<td>G153-694</td>
<td>1:30</td>
</tr>
<tr>
<td>ER&lt;sup&gt;v&lt;/sup&gt;</td>
<td>DAKO</td>
<td>M</td>
<td>30</td>
<td>1D5</td>
<td>1:50</td>
</tr>
<tr>
<td>PgR&lt;sup&gt;v&lt;/sup&gt;</td>
<td>DAKO</td>
<td>M</td>
<td>30</td>
<td>636</td>
<td>1:50</td>
</tr>
<tr>
<td>MMP-2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NeoMarkers</td>
<td>M</td>
<td>30</td>
<td>A-Gel VC2</td>
<td>1:100</td>
</tr>
<tr>
<td>MMP-9&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NeoMarkers</td>
<td>R&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30</td>
<td>3A4</td>
<td>1:80</td>
</tr>
<tr>
<td>TIMP-1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NeoMarkers</td>
<td>M</td>
<td>30</td>
<td>102D1</td>
<td>1:80</td>
</tr>
<tr>
<td>TIMP-2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NeoMarkers</td>
<td>M</td>
<td>30</td>
<td>3A4</td>
<td>1:100</td>
</tr>
<tr>
<td>c-erbB-2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Novocastra</td>
<td>M</td>
<td>60</td>
<td>CB11</td>
<td>1:40</td>
</tr>
</tbody>
</table>

<sup>v</sup>Vascular endothelial growth factor; <sup>e</sup>Estrogen receptors; <sup>c</sup>Progesterone receptors; <sup>m</sup>Matrix metalloproteinase 2; <sup>M</sup>Matrix metalloproteinase 9; <sup>T</sup>Tissue inhibitor of metalloproteinase 1; <sup>i</sup>Tissue inhibitor of metalloproteinase 2; <sup>1</sup>Monoclonal antibody; <sup>2</sup>Rabbit polyclonal antibody.

Statistical considerations

Exact binomial confidence intervals (CI) were used to determine the 95% upper and lower confidence limits of the response rate [14]. Overall survival (OS) was measured from the time of initiation of treatment until the date of last patient contact or death. Time to disease progression (TTP) was measured from the time of initiation of treatment until the time of documented relapse or to the date of death as a result of any cause. Survival curves were constructed using the Kaplan-Meier product limit method [15]. Differences in survival were compared with the log-rank statistical test. To evaluate the effect of various clinicopathological factors on survival and TTP Cox regression analysis was performed [16]. All analyses were performed with the use of SPSS statistical software (SPSS for Windows, version 11.0.1., SPSS, Chicago, IL, USA).
Results

Patient demographics

A total of 26 patients with PFTC who were referred to our department between 1996 and 2006 for postoperative chemotherapy were included in the study. Their main characteristics are summarized in Table 2. The median age was 65 years (range 42-78). Forty-three percent of patients had FIGO Stages I and II; 65% of patients had tumors with serous histology; and 62% of patients were suboptimally debulked, i.e., they had residual masses larger than 2 cm after staging laparotomy-initial cytoreductive surgery. Sixteen patients (62%) received paclitaxel, 175 mg/m², administered as an intravenous infusion in 500 ml of 0.9% saline over 3 h, and carboplatin targeted at AUC 6. Courses were administered every 21 days for a maximum of six cycles. Seven (27%) patients were treated with paclitaxel 175 mg/m², doxorubicin 50 mg/m², and cisplatin 75 mg/m², intravenously over 2 h [17]. Two (8%) additional patients were treated with six cycles of carboplatin targeted at AUC 6. Finally, one patient (4%) was treated with six cycles of paclitaxel and carboplatin followed by one cycle of high-dose melphalan (200 mg/m²) with autologous peripheral blood progenitor cell (PBPC) support. PBPC were mobilized with cyclophosphamide 4 g/m² and G-CSF [18]. All drug regimens were given on an outpatient basis, every three weeks, for a total of six cycles in case of response or disease stabilization.

Immunohistochemical findings and survival correlations

Analysis of individual markers is shown in Table 3. Reactivity for VEGF was observed in 22 (85%) tumor specimens, while all carcinomas were negative for TIMP-9. Although positive TIMP-2 expression was correlated with younger ages and positive MMP-2 expression with older ones these differences were not statistically significant. The results of survival analysis for each of the markers individually are shown in Table 4. None of the markers studied displayed prognostic significance in the whole cohort of patients. Regarding hormone receptor status, patients with positive estrogen receptor and negative progesterone receptor tumors had a 5-year survival rate of 87.5% (Table 5).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>26</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65</td>
</tr>
<tr>
<td>Range</td>
<td>42-78</td>
</tr>
<tr>
<td>Histology type</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>17 (65)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Adenocarcinoma NOSa</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Histology grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (4)</td>
</tr>
<tr>
<td>2</td>
<td>6 (23)</td>
</tr>
<tr>
<td>3</td>
<td>18 (69)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4)</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (12)</td>
</tr>
<tr>
<td>II</td>
<td>8 (31)</td>
</tr>
<tr>
<td>III</td>
<td>13 (50)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>TAH+BSO+omentectomy</td>
<td>13 (50)</td>
</tr>
<tr>
<td>TAH+BSO</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Biopsies only</td>
<td>3 (12)</td>
</tr>
<tr>
<td>TAH + BSO+omentectomy + LNS</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Debulking</td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>16 (62)</td>
</tr>
<tr>
<td>Suboptimal</td>
<td>10 (39)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel + Carboplatin</td>
<td>16 (62)</td>
</tr>
<tr>
<td>Paclitaxel + Doxorubicin + Cisplatin</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Paclitaxel + Carboplatin + HDM</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Table 2. — Selective patient and treatment characteristics.

Table 3. — Immunohistochemical analysis of individual markers.

<table>
<thead>
<tr>
<th>Reactivity</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>ER</td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>4 (77)</td>
</tr>
<tr>
<td>Positive</td>
<td>22 (85)</td>
</tr>
</tbody>
</table>

Table 4. — Univariate Cox regression analysis for overall and progression-free survival.

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
</tr>
<tr>
<td>I + II</td>
<td>1</td>
</tr>
<tr>
<td>III + IV</td>
<td>72.230.33-15889.320.120</td>
</tr>
<tr>
<td>Debulking</td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>1</td>
</tr>
<tr>
<td>Suboptimal</td>
<td>11.19 2.25-5.79</td>
</tr>
<tr>
<td>VEGF</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.51</td>
</tr>
<tr>
<td>Positive</td>
<td>1</td>
</tr>
<tr>
<td>ER</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0.99</td>
</tr>
<tr>
<td>Positive</td>
<td>2.73</td>
</tr>
<tr>
<td>PgR</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>0.88</td>
</tr>
<tr>
<td>MMP-2</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>0.78</td>
</tr>
<tr>
<td>MMP-9</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Notes: Hazard ratio; 95% confidence interval; n.s. = not significant.

Not otherwise specified; 1International Federation of Gynecology and Obstetrics; 2Total abdominal hysterectomy; 3Bilateral salpingo-oophorectomy; 4Lymph node sampling; 5High-dose melphalan.
Response, TTP and OS

Response was assessed in 14 women (54%) who entered the study with measurable disease. Twelve (85.7%) patients achieved an objective response, including ten CRs (71.4%) and two PRs (14.3%). At the time of the analysis 11 patients (42.3%) had relapsed and nine (34.6%) had died of disease. Fifteen patients (57.7%) were alive with no evidence of disease. The disease-related 5-year survival rate for the whole group was 77% with a progression-free 5-year survival rate of 65%. With a median follow-up exceeding eight years (105 months; range 59-149+ months) both median OS and median TTP for all patients have not yet been reached (Figure 1). In univariate analysis, the most important prognostic factors were residual disease status and initial FIGO stage. More specifically, the hazard ratio (HR) for progression and death for patients with tumor residuum > 2 cm was 5.24 (95% CI, 1.50-3.42, p < 0.01) and 11.19 (95% CI 2.25-67.59, p < 0.05), respectively. Patients with advanced stage disease (FIGO Stages III and IV) had a HR of 12.55 (95% CI, 2.5-133.4+, p < 0.05), respectively. Patients with Stage I disease, the depth of infiltration in the tubal wall and intraoperative tumor rupture are significant prognostic factors. Serum CA-125 level measurements in PFTC patients have the same significance as tumor and surrogate markers of response as in EOC patients [19]. The aim of the present study was to assess the value of the stage, histology, surgical cytoreduction and immunohistochemical expression of various gene products in a contemporary series of 26 chemo-naïve patients with PFTC who were treated over a 10-year period with paclitaxel- and platinum-based postoperative chemotherapy in a single institution. In all cases, paclitaxel was administered at a dose of 175 mg/m², over 3 h, with either carboplatin targeted at AUC 6 or cisplatin at a dose of 75 mg/m².

MMPs in humans are a family of 23 members that have classically been associated with remodeling of the extracellular matrix (ECM) [20]. Because of their involvement in processing of the ECM, MMPs were implicated in cancer invasion and metastasis. Consistent with this hypothesis, multiple data from model systems suggested that specific MMPs were causally involved in metastasis [21, 22]. When MMPs were first characterized [23], it was hypothesized that their major contribution to cancer development was merely to degrade ECM molecules, thereby facilitating cancer cell migration/invasion across tissue boundaries. More recent insights have, however, defined a more complex role for MMPs in cancer. They are now recognized as key regulators of various neoplastic processes by virtue of their ability to mediate differentiation, proliferation, and survival of neoplastic cells [24], release mitogenic growth factors from cell surfaces and from ECM reservoirs, and regulate tumor-associated angiogenesis [25, 26]. There are no data regarding the role of MMPs in PFTC. Since tubal carcinoma spreads in the same manner as epithelial ovarian cancer, some suggestions can be drawn from data already existing for the latter entity. Both MMP-2 and MMP-9 expression in human EOC tissue have been examined and it was found that essentially all invasive ovarian carcinomas, including early Stage I cancers as well as metastatic implants, over-express MMP-2 and MMP-9, while normal ovarian tissue exhibits significantly lower levels of expression, indicating that MMP-2 and MMP-9 are upregulated early in EOC progression [27, 28]. It has been shown that MMP-2 increased the adhesive capability of ovarian cancer cells by specific cleavage of fibronectin and vitronectin, allowing for enhanced attachment of malignant cells to fibronectin and vitronectin fragments through α5β1 and αvβ3 integrin. These findings implicate MMP-2 in EOC adhesion and indicate that therapeutic efficacy of MMP-
2-selective inhibitors will be best achieved clinically if applied prior to peritoneal dissemination [29]. In our study, reactivity for MMP-2 and MMP-9 was observed in three (11.5%) and 15 (58%) tumor specimens, respectively, but patients with expression of these metalloproteinases did not have a statistically significant shorter time to disease progression or overall survival than those without MMP expression. Of note, positive MMP-2 expression was marginally significantly correlated with older ages (p = 0.08), while positive TIMP-2 expression with younger ones (p = 0.06).

Expression by tumors of VEGF has been associated clinically with disease prognosis in many different types of malignancies. This expression is increased by diverse stimuli, including proto-oncogene activation and hypoxia, with the hypoxic state frequently arising in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature, thereby potentially contributing to tumor progression, because a leaky tumor endothelium enhances nutrient and catabolite exchange and lowers barriers to tumor cell migration and extravasation during metastasis. Indicators of enhanced angiogenesis, such as circulating levels of VEGF and tissue microvessel density, have been correlated with the presence of metastasis and survival in EOC [30]. The VEGF signalling pathway appears to contribute to growth and progression in 80% or more of all ovarian cancers [31], and PDGF and its receptor pathway have also been implicated in disease progression [32]. Clinical results from early studies in ovarian cancer and related diseases (PFTC and primary peritoneal carcinoma) have shown antitumor activity with the anti-VEGF monoclonal antibody bevacizumab when used either as a single agent in recurrent disease or in combination with low-dose metronomic chemotherapy [33-35]. In our study, 22 specimens (85%) demonstrated strong positive staining (2+ or 3+) for VEGF, but the patients did not have a shorter survival when compared with patients with weak (1+) or without VEGF expression.

The membrane receptor tyrosine kinase c-erbB-2 is overexpressed in several malignancies including breast, ovarian, gastric, and endometrial carcinomas. In a phase II study conducted by the Gynecologic Oncology Group (GOG), immunohistochemical overexpression of c-erbB-2 was observed in 95 (11.4%) EOC samples among 837 which were screened. Forty-five patients with c-erbB-2 overexpression who presented with persistent or recurrent disease were treated with the monoclonal antibody trastuzumab which resulted in an overall response rate of 7.3% including one complete and two partial responses [36]. Regarding PFTC, there are conflicting data for the overexpression of c-erbB-2. In a series of 73 women, none of the tissue samples investigated for c-erbB-2 oncogene amplification with a quantitative polymerase chain reaction method exhibited amplified this oncogene. Thus, the authors suggested that c-erbB-2 does not play a role in tumor transformation and progression in fallopian tube carcinomas [37]. On the other hand, Chung et al. [38] detected immunohistological overexpression of c-erbB-2 in 16 cases (89%) of PFTC, while in a more recent publication c-erbB-2 overexpression was present in 57% of patients with advanced stage PFTC. In the latter study, oncogene gain/amplification was found by array comparative genomic hybridization in 23% of analyzed PFTCs [39]. In our series, only two patients (8%) overexpressed c-erbB-2.

Steroid hormone receptors are important determinants of prognosis and predictive behavior in tumor tissues of several origins, especially in breast, uterine and prostate cancer. The determination of steroid hormone receptor status seems to offer additional prognostic information in EOC. In a German study, the expression of ER and PgR was assessed by immunohistochemistry in tumor specimens from 186 women with ovarian cancer who were treated over a 15-year period. Survival analyses supported the favorable prognostic value of PgR and its level of expression in ovarian carcinomas. Patients with ER-PgR+ tumors showed a significantly superior prognosis when compared with all other steroid hormone combinations and this expression was associated with early-stage disease, low quantity of ascitic fluid, and higher tumor differentiation [40]. In a recent and larger Danish study, estrogen receptors were expressed in 36% and progesterone receptors in 20% of patients with EOC, respectively. Tissue ER and PgR expression of 10% or higher was found to imply an independent significant advantageous course of patient disease-specific survival. The prognostic value of ER and PgR was found additive with a HR for patients with high ER and PgR expression of 0.48 compared to patients with < 10% expression for both receptors [41]. Regarding PFTC, a retrospective Austrian nationwide evaluation for a period of ten years revealed that 42% of the tumors were PgR positive and 26% were ER positive, while no correlation of steroid receptor expression with survival could be found [42]. In our study, 46% of the patients had ER positive and 27% PgR positive tumors. Although patients with positive estrogen receptor and negative progesterone receptor tumors had a 5-year survival rate of 87.5% compared with a corresponding rate of 77% for the whole cohort, this difference was not statistically significant.

TIMPs play key roles in maintaining homeostasis of ECM by controlling matrix metalloproteinases. In addition to their role in regulating MMPs, TIMPs have also been shown to have pluripotential effects on cell growth, apoptosis, and differentiation. The expression of TIMP-1 and -2, has also been shown to be associated with the clinical outcome in some cancers. However, the prognostic value of TIMPs seems to vary significantly in different malignant tumors [43]. An elevated preoperative serum concentration of TIMP-1 at diagnosis was found to correlate with the malignant phenotype of an ovarian tumor, while among patients with EOC high circulating TIMP-1 correlated with aggressive phenotype and unfavorable prognosis [44]. In another study, TIMP-2 immunostaining was found significantly more frequent in serous ovarian carcinomas. Furthermore, TIMP-2 overex-
pression by transfected ovarian cancer cell lines did not mediate proapoptosis, inhibited cisplatin-induced apoptosis, and induced MPM-2 expression, thus suggesting that TIMP-2 function may favor tumor growth in serious ovarian tumorigenesis [45]. In our series, all PFTCs were negative for TIMP-1. Positive TIMP-2 expression was observed in six (23%) cases but this finding did not correlate with a worse outcome.

Most of our patients' clinical characteristics were comparable to those reported in the literature. Among 14 patients with measurable disease, we observed a CR in ten (71.4%) women, and a PR in two women (14.3%) for an overall response rate of 85.7%. Several authors using cisplatin-based chemotherapy in patients with advanced PFTC reported overall response rates of 53–92% [46-50]. Our data also confirm the prognostic significance of stage and residual disease after initial surgical treatment [9].

In our study, the most common chemotherapy regimen was carboplatin and paclitaxel. Among 57 and 42 months for the PFTC and EOC groups, the 5-year OS rate differed at 95% and 76%, respectively (p < 0.05). Furthermore, 46 PFTC patients with Stage III and IV disease were matched with 92 EOC controls. The majority of them (88.5%) were optimally debulked, and the 3-year OS rate was 59% for both groups. In our study, the most important prognostic factors were residual disease status and initial FIGO stage. The HR for progression and death for patients with tumor residuum > 2 cm was 5.24 and initial FIGO stage. The HR for progression and death (FIGO Stages III and IV) had a HR of 12.55 for progression, while corresponding HR for death was not found to be statistically significant. The latter finding could be attributed to the limited number of patients included in the retrospective analysis. Rosen et al. [52] found 5-year survival rates of 50.8% for Stages I and II, but only 13.6% for Stages III and IV and Gadducci et al. [49] reported a 5-year survival rate of 55% if the residual tumor was < 1 cm in diameter compared with 21% for those with larger residual tumor.

Conclusion

Primary carcinoma of the fallopian tube is the rarest cancer of the female genital tract with an incidence of 0.5% among all gynecologic tumors. Hence, very little data exist on the impact of clinicopathological prognostic factors and on the activity of paclitaxel- and platinum-based first-line chemotherapy. We retrospectively analyzed patients who were treated with the above-mentioned combination and we staked sections from tissue blocks for VEGF, MMP-2, MMP-9, TIMP-1, TIMP-2, c-erbB-2, ER and PgR. Immunohistochemical findings as well as clinical characteristics were correlated with progression-free interval and overall survival. None of the biomarkers studied displayed prognostic significance. In any case, the results of the current study must be interpreted with caution. The study population was small and the design was neither prospective nor randomized. Regarding clinical parameters, early-stage disease (FIGO Stages I and II) and optimal debulking were associated with improved outcome.

References

Clinicopathological features of primary fallopian tube carcinoma: a single institution experience


Current management of endometrial hyperplasia and endometrial intraepithelial neoplasia (EIN)

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Summary

Endometrial hyperplasia is a commonly seen disorder in daily gynecology practice. The clinical importance of this pathological entity is the underlying risk of carrying a concomitant genital cancer or risk of progression to endometrial carcinoma during the follow-up. Despite recent advances in non-invasive techniques to define underlying endometrial cancer during the initial diagnosis of endometrial hyperplasia, none of these studies are conclusive yet. Today, in spite of intense discussions and related studies which aimed to define certain prognostic factors (WHO94 vs EIN) to predict cases that would progress to cancer, we still do not have a practical and accurate system available to use during daily practice. Treatment of endometrial hyperplasias depends on the patient’s age, fertility desire and the type of hyperplasia. Progestagens are still the most commonly used medical treatment modality in these patients. Response rates are higher for cases without atypia. In selected cases, hysterectomy may be performed as a definitive treatment modality. In this review article, the current management of endometrial hyperplasias is summarized in light of the associated literature. We also give a brief overview of the EIN classification and its clinical importance.

Key words: Endometrial intraepithelial neoplasia (EIN); Endometrial hyperplasia.

Introduction

Endometrial hyperplasia (EH) is a common disorder seen in gynecology clinics. Actual incidence is still unknown but it is estimated to be seen in about 1.5% of patients with abnormal uterine bleeding [1, 2]. The clinical significance of EH is the underlying genital malignancy which is around 5-10% [3-10], but the number of studies is still limited in the published literature. Therefore, there is an on-going debate about the diagnosis, classification and treatment options of endometrial hyperplasias. This review article analyzes the available published literature and summarizes the current management of endometrial hyperplasias.

Risk factors

Unopposed estrogen is the most well known risk factor for endometrial hyperplasia. Estrogen has both mutagenic and carcinogenic effects on endometrial glands and stromal cells. Excess estrogen results in hyperplastic lesions with the PTEN mutation, and depending on the total dose and time of estrogen exposure, hyperplasias convert into neoplastic lesions [1, 11]. Therefore, all hyperestrogenic conditions are risk factors for EH (chronic anovulation, obesity, tamoxifen usage, unopposed estrogen, etc.). Physicians should be alert for EH in the following risk groups:

1) Abnormal uterine bleeding in women > 40 years old
2) Abnormal uterine bleeding with the above-mentioned risk factors and < 40 years old
3) All abnormal bleeding refractory to medical treatment
4) Patients who received unopposed estrogen replacement therapy
5) Atypical glandular cells on cervical smears
6) Presence of endometrial cells in cervical smears of > 40-year-old patients
7) Patients with hereditary nonpolyposis colorectal cancer

Diagnosis

The most important step in the management of these patients is to collect sufficient tissue to make a definitive diagnosis of hyperplasia and differential diagnosis of hyperplasia and cancerous lesion. The gold standard for the diagnosis of EH is endometrial biopsy. However, new non-invasive technologies such as office hysteroscopy, etc. are also under review for the diagnosis of EH and its differentiation from endometrial cancers.

Non-invasive methods

Cervical cytology is rarely useful. Recently endometrial cytologic screenings (using endocyte samplers) were also analyzed but there is still not sufficient data in this respect [12]. Some clinical studies have focused on the role of transvaginal ultrasonography (TVS). Gray scale sonographies were not found to be helpful in EH diagnosis. Sensitivity and specificity values are particularly low in premenopausal patients. The median endometrial thickness was 16.2 mm (1.4-73) for EH while it was 18.7 mm (5-90) for endometrial cancer patients [13]. However, some other studies found a negative sonographic finding (endometrial thickness < 4.5 mm) to be more predictive than a negative office hysteroscopy [14-16]. Recent studies analyzing color Doppler and 3D-power angio-
sonography have had more promising results, however there are only a limited number of studies [13, 17, 18]. Intratumoral blood flow can differentiate endometrial cancers (median tumoral blood flow is 71.7%) from EH (median blood flow 5.6%) with a 97.4% success. However, neither the resistance nor the pulsatile indices and the peak systolic velocities were found to be significant [13, 17]. Another study also revealed endometrial and subendometrial flow indices found with 3D power Doppler angio to be potentially helpful in the differential diagnosis of cancer and EH [18]. However, we need more studies for a definitive conclusion.

Invasive methods

The gold standard for diagnosis of EH is endometrial biopsy. The optimal time for biopsy is just after the withdrawal bleeding since exogeneous progestagens may affect the pathological evaluation. What about the optimal sampling technique? Cost-effectiveness analysis reveals office biopsies to be better then classic dilatation and curettage biopsies [19]. Previous studies and meta-analyses revealed the Pipelle method to hasten the highest specificity and sensitivity in all age groups for the diagnosis of both EH and endometrial cancers [20-22]. Studies using the Pipelle and Yabra techniques found a 97-99% predictive value for endometrial cancer and 66.7-82.3% predictive value for EH [20-22]. In cases with insufficient material or in cases where the clinical suspicion continues, classic dilatation and curettage is indicated.

Starting with the new millenium, office hysteroscopy has been used more and more, similarly to sonography, for evaluation in out-patient clinics and has started to be used as a routine part of the gynecologic examination. EH may have a variety of gross appearances on hysteroscopic evaluation such as irregular regeneration areas, increased vascularity, bleeding, necrotic areas, asymetric thickening and polypoid structures [23-27]. Clark et al. reported a meta-analysis of 65 studies which evaluated the predictivity of these gross hysteroscopic findings to diagnose endometrial cancer [28]. They found a 71.8% cancer risk in patients with these gross abnormalities and the risk dropped to 0.6% in patients with a negative hysteroscopic finding. However, with respect to EH diagnoses there are a limited number of hysteroscopic studies. Office hysteroscopy was suggested to have a 48-71.4% positive predictivity and a 92-95.4% negative predictivity for EH.

As a conclusion, despite the good results of office hysteroscopy, there are still not adequate studies for a definite conclusion. Even hysteroscopic-guided endometrial biopsies may miss underlying endometrial cancer. Office hysteroscopy seems to be more effective in the diagnosis of polypoid lesions. Office hysteroscopy is insufficient for the differential diagnosis of cancer and EH. Moreover, despite the well known controversy on the prognostic role, there is a risk of peritoneal dissemination during office hysteroscopy in patients with endometrial cancer. Therefore, for patients suspicious for EH or cancer, the initial diagnostic attempt should be office biopsy and if hysteroscopy is needed, it should be performed using lower flow pressures.

Classifications

WHO94 System

EH was heterogeneously classified up to 1994 (mild, moderate and severe hyperplasias or cystic vs adenomalous hyperplasias). Later on, EH was classified with the classic WHO94 system depending on histopathological evaluation (Table 1) [29]. This system uses cellular atypias and structural patterns and EH subclasses correlated with the risk of cancer progression (Table 1) [6]. The most important criteria of WHO94 is the presence or absence of cellular atypia, and not the grade. With respect to structural pattern, EH is classified as simple in the presence of tubular glands without branching and as complex in the presence of branching tortuous and curvy glands. However the WHO94 system is now under debate for the following reasons [30-32]:

1) There is no consecutive progression between the EH classes. For example, a patient with simple EH without atypia may not have a progression to complex EH or complex EH with atypia but instead can directly progress into endometrial cancer.

2) WHO94 is excessively subjective. There is a high intra- and interobserver variation and the reproducibility is also low.

3) WHO94 can not clearly direct the management of EH patients.

4) Concomittant cancer lesions may be missed in this system. In some retrospective studies where the specimens were reevaluated, 45% of the patients with endometrial cancers were found to carry atypical EH and 17-62% of the patients with atypical EH were found to carry concomittant endometrial cancers. Of these concomittant cancers, 7.9-51% of the patients also had myometrial invasion [3-10].

5) Studies on endometrial carcinogenesis (clonality, PTEN, etc.) have also questioned the WHO94 system.

Table 1. — Classification systems of endometrial hyperplasias.

<table>
<thead>
<tr>
<th>Category</th>
<th>WHO94 System</th>
<th>Cancer progression risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) WHO94 System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple (adenomatous) hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without atypia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>With atypia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Complex hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without atypia</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>With atypia</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>b) EIN System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EIN terminology</td>
<td>Topography</td>
<td>Functional category</td>
</tr>
<tr>
<td>Endometrial (benign) hyperplasia</td>
<td>Focal</td>
<td>Estrogen effect</td>
</tr>
<tr>
<td>EIN</td>
<td>Focal, Diffuse</td>
<td>Precancer</td>
</tr>
<tr>
<td>Cancer</td>
<td>Focal, Diffuse</td>
<td>Cancer</td>
</tr>
</tbody>
</table>
Based on these findings and questions, in 2002 the Endometrial Collaborative Study Group developed a new classification system called endometrial intraepithelial neoplasia (EIN) [33-38].

**EIN System**

The EIN system was developed to have a better detection of the real cancer precursor lesions and also for a better direction of EH patients for further treatments (Table 1) [33-38]. This system classifies endometrial lesions into three classes:

1. Benign hyperplasia (benign structural changes due to unopposed estrogen)
2. EIN (a monoclonal and neoplastic lesion, initially local and then diffuse)
3. Carcinoma

EIN lesions may be diagnosed in two different ways (subjective vs objective criteria):

**Subjective EIN Criteria**

Volume percentage stroma (VPS) is the most important subjective criteria where the ratio of glandular areas versus stromal areas is checked. Lesions in which the stromal volume is less than <55% are classified as EIN. However, some believe that VPS evaluation may be even more subjective than the WHO94 system. Another subjective criteria is the diameter of the lesions which would be at least 1 mm for a correct VPS calculation, to perform reliable morphometry and clonal analysis and finally for making the differential diagnosis.

**Objective endometrial intraepithelial neoplasia (EIN) criteria**

The D-score (morphometric score) is the most important objective criteria. The D-score is evaluated by using three main pathological criteria:

- VPS (volume percentage stroma should be < 55%);
- OSD (outer surface area measuring the branching of glands);
- SDSNA (standard deviation of shorter nuclear axis – a scale for nuclear variation).

The D-score is a measure for clonality and precancerosis. D-scores vary between -4 and +4. If the D-score is < 1 there is a high propensity for progression. On the other hand, in patients with a D-score > 1, no progression was seen in 22 years of follow-up.

**WHO94 vs the EIN System**

The limited data available clearly point out the predictivity of D-scores for progression to cancer [39-41]. Overall the sensitivity and negative predictive value of the EIN system is around 100% while these figures are 89% and 94%, respectively, for the WHO 94 system [39-41].

EIN enables physicians to make more standardized diagnoses and therefore more algorithmic treatments. However we do not know the feasibility and cost-effectiveness of the EIN system for routine daily practice. Therefore there is still a debate on the routine use of the EIN system in daily practice.

In a study evaluating the concordance between WHO94 and EIN systems, in patients with EIN diagnoses, 63% had atypical hyperplasia, 27% harbored complex hyperplasia and 10% harbored simple hyperplasia. For WHO94, 79% of patients with atypical hyperplasia, 44% of patients with complex hyperplasia and 5% of patients with simple hyperplasia were found to have EIN lesions. As can be seen, there is actually not enough concordance between the two systems [42, 43].

**Treatment**

Treatment depends on the type and related malignant potential of EH, patient age and fertility desire, medical condition of the patient and also presence of other gynecologic disorders like ovarian tumors. Treatments are mainly divided into two groups; 1) Medical and 2) Surgical (Table 3) [43-65].

**Table 2. — EIN diagnostic criteria *.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Gland &gt; stroma area (VPS &lt; 55%)</td>
</tr>
<tr>
<td>Cytology</td>
<td>Cytologic discrepancy between the normal endometrium</td>
</tr>
<tr>
<td>Diameter</td>
<td>Maximal linear diameter &gt; 1 mm</td>
</tr>
<tr>
<td>Exclude the mimics</td>
<td>Secretory, polyps, repair</td>
</tr>
<tr>
<td>Exclude cancer</td>
<td>Solid areas, cribriform pattern</td>
</tr>
</tbody>
</table>

*VPS = volume percentage stroma; D-Score = +0.6229 + 0.0439xVPS-3.9934xln(SDSNA)-0.1592xOSD; SDSNA = standard deviation of short nuclear axis; OSD = outer surface area.

and and EIN systems, in patients with EIN diagnoses, 63% had atypical hyperplasia, 27% harbored complex hyperplasia and 10% harbored simple hyperplasia. For WHO94, 79% of patients with atypical hyperplasia, 44% of patients with complex hyperplasia and 5% of patients with simple hyperplasia were found to have EIN lesions. As can be seen, there is actually not enough concordance between the two systems [42, 43].

**Table 3. — Treatment of endometrial hyperplasia.**

A) **Medical treatments**

1) Progestins
   a) Low dose (12-14 days/month)
      - Medroxyprogesterone acetate (Provera®, Farlutal®): 10-20 mg/day
      - Norethindrone acetate: 5 mg/day
      - Micronized progesterone (Oral Progestan®, Vaginal Cyclogest®): 200 mg
      - Megestrol acetate (Megace®): 20-40 mg/day
   b) High dose (21 days/month)
      - Medroxyprogesterone acetate 40-100 mg/day
      - Micronized progesterone 300-400 mg/day
      - Megestrol acetate 80-160 mg/day
2) Oral contraceptives
3) Ovulation induction
4) Levanorgestrel containing intrauterine devices (Mirena®)
5) Danazol (400 mg/day, 3 months)
6) GnRH analogues (Triptorelin® 3.75 mg/days, 3-6 months)
7) Aromatase inhibitors
8) Danazol containing intrauterine devices
9) Mifepristone (RU486)

B) **Surgical treatments**

1) Dilatation and curettage
2) Endometrial ablation and resection
3) Hysterectomy
There are many studies which revealed successful outcomes with the use of progestins and GnRH analogues. Progestagens have been used for EH for more then 40 years. The side-effects of megestrol acetate are lower and also it is safer even in higher doses. A daily 160-320 mg dosage may cause a mild increase in total body weight, however it does not cause a significant change in serum glucose or lipid profile levels. Randall et al. followed 17 patients < 40 years old who had atypical hyperplasia or well differentiated carcinoma. They used 2 x 20 mg megestrol acetate or 10 mg medroxyprogesterone acetate and followed the patients with aspiration biopsies within three to six months. The doses were titrated depending on the biopsy results. Sixteen of the patients had a complete response. Median time for treatment was nine months (range 3-18) [49].

Cyclic medroxyprogesterone treatment was also successfully used in postmenopausal hyperplasia without atypia. Sixty-five patients were treated with cyclic 10 mg medroxy-progesterone acetate for 14 days/month. At the end of the first year of treatment, benign normal endometrium was observed in 92% of the patients. None of the patients had progressed to endometrial carcinoma [48].

Atypical EH can also be successfully treated by progestagens. However in postmenopausal patients hysterectomy should be preferred. Premenopausal patients under medical treatment, should be controlled by endometrial biopsies every three to six months and the doses should be titrated according to response.

GnRH analogues are also used for EH treatment. Forty-two patients (30 simple, 12 atypical EH) were treated with leuprolide or triptoreline acetate for six months. Except for the seven simple EH patients, all patients responded to the treatment [66]. Progestagens are also used successfully in atypical EH patients. In a report of 19 patients, 500 mg norethindrone acetate and six months of monthly 3.75 mg depot triptorelin were used. At five years of follow-up, complete regression was seen in 16 patients (53).

Some recent reports have focused on the use of topical progestagens. An 87% response rate was noted by the use of levonorgestrol containing intrauterine devices, irrespective of the type of EH. Also, 100 mg/day micronized progesterone cream usage in the 16-25 days of the cycle for three to six months was successful in 90% of patients with simple EH (52).

There are also some alternative medical treatments recently studied (danazole, mifepristone, aromatase inhibitors, and intrauterine devices with danazole). However the number of available studies and sample sizes are not adequate for a final conclusion.

The heterogenity of EH treatment is still ongoing (surgery vs medical vs combined medical, progestagens vs others, megestrol acetate vs others, dose and duration of medical treatments and follow-up, etc.). However there is still not any randomized prospective study which can resolve these problems. At least we can summarize the basic principles of treatment as follows:

• There is no data showing whether cyclic or continuous treatment is better.
• Low-dose progestagens are preferred as the first-line treatment in EH cases without atypia (Table 1).
• In cases with atypical EH, high-dose progestagens or surgical treatments are preferred if there is no fertility desire (Table 1).
• Medical treatments are also preferred in young patients with fertility desire or in patients whose medical conditions are not appropriate for surgery. In young patients with ovulation problems or infertility, we can also advise the use of combined oral contraceptives or controlled ovarian stimulation or pregnancy.
• In medical treatment options, endometrial biopsies are required every three to six months.
• Dilatation and curettage or endometrial resection/ablation is preferred in women < 40 years old with EH without atypia.
• Indications for hysterectomy are: 1) EH cases with recurrent atypia ≤ 40 years; 2) EH cases with or without atypia > 40 years.
• EH cases should be treated by a gynecologic oncologist due to the risk of concomitant endometrial or ovarian cancers. Moreover, for further management plans an experienced pathologist is also a crucial part of the treatment.
• Progestagen treatments are still the most effective and the most cost-effective treatment options.
• Response rates to low-dose progestagen treatments in EH cases without atypia are around 80%, persistant rates are 6%, recurrence rates 14% and cancer progression rates are 0%. Response rates are better in patients without atypia [48].
• Response rates of atypical EH cases to high-dose progestagens are variable. However there is no significant difference with respect to type of progestagens used. Overall response rates are reported to be 87-100% [50, 51].

Conclusion

There is no sufficiently reliable objective criteria showing the progression of EH to cancer. The EIN system is prognostic compared to WHO94, however the usefulness in daily practice is still controversial. EH without atypia responds better to medical treatments. Conservative medical treatments are also the first choice for young patients with atypia. Hysterectomy is the final endpoint of the disease but is indicated only in certain subgroups. These patients should be cautiously evaluated with the help of a gynecologic oncologist and an experienced gynecopathologist due the risk of concomitant endometrial and hormone-secreting ovarian tumors.

References

Current management of endometrial hyperplasia and endometrial intraepithelial neoplasia (EIN)


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The contribution of laparoscopy to the diagnosis of adnexal masses in young and premenopausal women

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Summary

The purpose of this retrospective study was to investigate the contribution of laparoscopy to the diagnosis of adnexal masses in young and premenopausal women, in whom surgery was deemed necessary, between the years 2002-2008. A total of 130 young and premenopausal women scheduled for surgery for an adnexal mass with a diameter of 5-10 cm underwent transvaginal ultrasound (US) examination prior to surgery. Laparoscopic management was successfully completed for 118 of the 130 patients in this study; however, 12 required conversion of laparoscopy to laparotomy due to endometriosis with extensive bowel adhesions, or suspected ovarian malignancy and peritoneal implants. One hundred and twenty-four patients (95.38%) had benign lesions, four (3.07%) had borderline tumors and two patients had malignant lesions (1.53%). We found a statistically significant association between laparoscopic and histological findings. Laparoscopic diagnosis of adnexal masses suspicious at US may help avoid many laparotomies for the treatment of benign ovarian disorders.

Key words: Ultrasonographic; Laparoscopic Laparotomy treatment of benign or suspicious adnexal masses.

Introduction

A pelvic mass may be gynecologic in origin or may arise from the urinary tract or bowel. The gynecologic causes of a pelvic mass may be uterine, or more likely ovarian [1]. Ovarian neoplasms are common in women of all ages. As many as 10% of women in the United States will undergo surgical removal of an adnexal mass at some point in their lifetime [2]. Adnexal masses are commonly (two-thirds) encountered during the reproductive years and most (80-85%) are benign [3]. Malignant neoplasms are uncommon in younger women but become more frequent with increasing age [4]. Most tumors produce few or only mild nonspecific symptoms and usually they are coincidental findings during a routine gynecologic and ultrasound (US) examination [5, 6]. However, they may manifest a great range of chronic or acute symptoms. The possibility of ovarian malignancy in younger women should always be considered. The role of US in differentiating benign from malignant adnexal masses is very helpful. Intracystic vegetations detected at preoperative US, among the different features of an ovarian cyst assessable before surgery, have been demonstrated to have the greatest importance in evaluation of the benign or malignant nature of the cyst [7-9]. Despite the fact that benign appearing adnexal masses may be observed expectantly, their persistence and significant size mandates surgical excision [10]. The laparoscopic management of adnexal masses provides the advantages of short hospitalization and less impact on fertility in the reproductive age group.

The aim of the present retrospective study was to evaluate the surgical management of adnexal masses in young and premenopausal women and describe the association of their histological diagnoses with the preoperative or intraoperative findings.

Materials and Methods

In the time period 1/2/2002 to 31/05/2008, 130 consecutive premenopausal patients with a preoperative tentative diagnosis of an ovarian mass were included in the present retrospective study. In the study patients, except those in whom US was suggestive of the presence of an adnexal cyst larger than 5 cm in diameter, a repeat US was performed four weeks after the first examination. Inclusion criteria included well-defined regular shape of the mass, which in the majority of cases was mobile during clinical examination in the transvaginal US; predominantly a cystic mass, without septations greater than 2 mm, with distinct borders and without excrescences and normal Doppler flow, whereas this third criterion was available in 39 cases (30.2%). In the majority of cases ineffective treatment with oral contraceptives had preceded.

The following laboratory evaluations were analyzed: white blood cell count (WBC), levels of beta human chorionic gonadotropin (β-HCG), carcino embryonic antigen (CEA), lactic dehydrogenase (LDH), CA-125 and alpha-fetoprotein (α FP), and the results of further endocrinologic workup such as gonadotropins, where appropriate.

The CA-125 levels were not considered in the selection of our patients due to inaccuracy in detecting malignancy, especially in premenopausal patients. Laparoscopy was performed under general anesthesia and pneumoperitoneum with CO₂ insufflation was established, and three to four port sites were used. At the beginning of the surgical procedure, a thorough evaluation of the pelvis, abdomen, and external surface of the cyst was performed to rule out any evidence of malignancy. Initially, peritoneal washings were obtained for rapid cytological examination and the pelvis and upper abdomen were carefully examined. This examination was then repeated between laparoscopy and laparotomy, expecting, the duct...
inspected. Determination for laparoscopic or laparotomic removal of the mass was made according to the macroscopic characteristics of the adnexal mass or existence of peritoneal implants, feasibility of removal (extensive bowel adhesions), results of the frozen section and the overall preoperative evaluation. Frozen sections were performed by a pathologist on the areas of suspicious tissue selected by histopathological examination at the time of operation. During follow-up after surgical treatment, we performed the following examinations on a three, six and 12-month basis: CA-125 level and hormone profile measurement, clinical examination transvaginal US.

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), version 15 (SPSS, Inc., Chicago, IL, USA). The normality of quantitative variables was tested with the Kolmogorov-Smirnov test. Normally distributed quantitative variables were expressed as the mean ± standard deviation, while non-normally distributed variables were expressed as the median and range. Qualitative variables were expressed as frequencies and percentages. The chi-square test was used to evaluate any potential association between qualitative variables. All tests were two-tailed and statistical significance was considered for p values less than 0.05.

Results

The mean age of the patients was 30.8 (min 15, max 46; range 31) years. Sixteen women (12.9%) had a history of previous abdominal operation. Twenty-one patients (6.2%) had an underlying history of infertility. All operations were non emergency procedures. The most common presenting complaint was low abdominal pain, present in 45 (34.62%), the other presenting symptom was menstrual disorders in 15 (11.53%) cases while the remaining 70 cases had no clinical symptoms. In the latter 70 cases the ovarian masses were detected through physical examination and US. On physical examination all patients had a palpable mass or increased abdominal girth. Preoperatively all women had normal serum tumor markers.

Laparoscopy was performed in 130 cases, while laparoscopy in 12 (9.2%) was then converted to laparotomy. From the laparotomy group in one case the bag could not be removed laparoscopically and minilaparotomy was performed.

In the laparoscopy group the mean operative time was 101.2 ± 17.6 min while in the laparotomy group the overall time plus the diagnostic time of the preceding laparoscopy was 123.6 ± 23. Min. In 12 cases (9.2%) we needed to proceed to laparotomy due to suspicious macroscopic findings or size larger than 8 cm of the mass, or difficulties in the operative approach and removal. The diameters of the masses laparoscopically removed ranged between 5 and 8 cm, while in the laparotomy group they ranged between 8 and 10 cm.

According to US findings the cases were divided into the following categories: i. ovarian cyst (110 cases, 84.6%), ii. paraovarian cyst (10 cases, 7.7%), iii. hydrosalpinx (5 cases, 3.8%), iv. endometriosis (5 cases, 3.8%) (Figure 1).

In the laparoscopy group the findings were: 57 (43.8%) cases with ovarian cysts, 18 (13.8%) with endometriosis, 17 (13.1%) with paraovarian cysts, 12 (9.2%) with dermoid cysts, six (4.6%) with hydrosalpinges, six (4.6%) with cystadenomas, six (4.6%) with inflammation, four (3.1%) fibromas and four (3.1%) Morgagni cysts (Figure 2). In the laparotomy group the findings were: four (33.3%) suspicious cystadenomas, three (25%) dermoid cysts, three (25%) endometriosis, one (8.3%) suspicious fibroma and one (8.3%) suspicious inflammation (Figure 3).

Histological findings were divided into 11 diagnoses: ovarian cysts (57 cases, 43.8%), endometriosis (18 cases, 13.8%), paraovarian cysts (17 cases, 13.1%), dermoid cysts (12 cases, 9.2%), hydrosalpinx (6 cases, 4.6%), inflammation (5 cases, 3.8%), Morgagni cysts (4 cases, 3.1%), BOT (4 cases, 3.1%), fibroma (3 cases, 2.3%), cystadenoma (2 cases, 1.5%), and cancer (2 cases, 1.5%) (Figure 4).
Descriptive statistical analysis of laparoscopic and histological findings

In a more detailed analysis we found:

**Ovarian cysts:** Of the 57 total cases of laparoscopic findings of an ovarian cyst, 57 cases (100%) were confirmed from histology reports as ovarian cysts.

**Paraovarian cysts:** Of the 17 total cases of laparoscopic findings of paraovarian cysts, 17 cases (100%) were confirmed from histology reports as simple cysts.

**Endometriosis:** Of the 18 total cases of laparoscopic findings of endometriosis, 18 cases (100%) were confirmed from histology reports as endometriosis.

**Dermoid cysts:** Of the 12 total cases of laparoscopic findings of a dermoid cyst, 12 cases (100%) were confirmed from histology reports as dermoid cysts.

**Hydrosalpinx:** Out of the six total cases of laparoscopic findings of hydrosalpinx, six cases (100%) were confirmed from histology reports as hydrosalpinx.

**Cystadenoma:** Out of the six total cases of laparoscopic finding of cystadenoma, two cases (33.3%) were confirmed from histology reports as cystadenomas. The remaining four cases (66.6%) had a histological diagnosis of BOT.

**Inflammation:** Out of the six total cases of laparoscopic finding of inflammation, five cases (83.3%) were confirmed from histology reports as inflammation. The remaining case (16.7%) had a histological diagnosis of cancer.

**Morgagni cysts:** Out of the four total cases of laparoscopic findings of a Morgagni cyst, four cases (100%) were confirmed from histology reports as Morgagni cysts.

**Fibroma:** Out of the four total cases of laparoscopic finding of fibromas, three cases (75%) were confirmed from histology reports as fibromas. The remaining case (25%) had a histological diagnosis of cancer.

We found a statistically significant association between laparoscopic and histological findings ($\chi^2 = 1.013E3$, $p < 0.01$) (Table 1).

In 12 cases out of the total 130 we proceeded with a laparotomy procedure.

### Table 1. — Correlations between ultrasound, laparoscopy, laparotomy with histological findings.

<table>
<thead>
<tr>
<th>Correlation</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
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<td>$2.108E2$</td>
<td>30</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Laparoscopy-histology findings</td>
<td>$1.013E3$</td>
<td>80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laparotomy-histology findings</td>
<td>$36$</td>
<td>12</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

$df$ = degrees of freedom.

Descriptive statistical analysis of laparotomy and histological findings.

**Cystadenoma**

There were four cases of laparotomy findings of cystadenoma. (4 out of a total of 12 cases, 33%) which were confirmed as BOT by the histology report (100% association between laparotomy and histological findings).

**Dermoid cysts**

There were three cases of laparotomy finding of dermoid cysts (3 out of a total of 12 cases, 25%) which were confirmed as dermoid cysts by the histology report (100% association between laparotomy and histological findings).

**Endometriosis**

There were three cases of laparotomy findings of endometriosis (3 out of a total of 12 cases, 25%) which were confirmed as endometriosis by the histology report (100% association between laparotomy and histological findings).

**Inflammation**

There was one case of a laparotomy finding of inflammation (1 out of a total of 12 cases, 8.3%) which was confirmed as cancer by the histology report.
Fibroma

There was one case of a laparotomy finding of fibroma (1 out of a total of 12 cases, 8.3%) which was confirmed by the histology report as cancer.

There was a 100% association between laparotomy and histological findings in the cases of endometriosis, cystadenoma and dermoid cysts.

There was a statistically significant association between the findings of the laparoscopic surgeries that proceeded into laparotomies and the histological findings ($\chi^2 = 36, p < 0.01$) (Table 1).

We found a statistically significant association between US and histological findings ($\chi^2 = 2.108E2, p < 0.05$) (Table 1).

In the majority of cases either laparoscopic or laparotomy treated cyst enucleation was the most commonly applied procedure, while in 20 cases unilateral ovariectomy and in two cases complementary salpingooophorectomy. The reasons for ovariectomy or salpingooophorectomy were: patient’s age, size of ovarian mass (> 9 cm), suspicion of malignancy and effort for complete removal without spillage.

Intraoperative complications occurred in two patients with bleeding from the trocar entry site for the “lap sac” and were successfully managed during the operation. There were no postoperative complications. The mean hospitalization time was 3 + 0.8 days in the laparoscopy group and 4.7 + 1.1 days in the laparotomy group.

Two years postoperatively, the study patients had no clinical symptoms. Over a follow-up period of up to 24 months, ovarian folliculogenesis was confirmed by US. During this period, we did not find any recurrence of adnexal mass cysts in the treated or the contralateral site.

Discussion

In adults, epithelial neoplasms, or tumors that originate from the epithelium which cover the ovarian surface, are the most common, accounting for almost 85% of all neoplasms after the age of 50 years [11]. The peak incidence of benign epithelial tumors occurs between the ages of 20 and 40 years [11]. A suspected ovarian neoplasm is a common clinical problem affecting women of all ages [12]. Malignant adnexal neoplasms are uncommon in premenopausal and younger women but become more frequent with increasing age. The risk that an ovarian neoplasm could be malignant increases 12-fold from the ages of 20-29 to 60-69 [13]. The overall risk that an ovarian neoplasm was malignant has been reported as 13% in premenopausal women and 45% in postmenopausal women [13-15]. Bimanual examination appears to be a limited screening test for the female upper genital tract even under the best possible circumstances [16]. US is now frequently used for evaluation of pathological findings discovered on gynecological examination [17]. Based on the recognition of characteristic US patterns alone, the positive predictive value of transvaginal US for the diagnosis of these common benign cysts in premenopausal women is very high and can be used reliably to select women for appropriate surgery [18]. US imaging is a useful investigative tool for the clinician, and its use as a diagnostic tool is quite sensitive, as in our study there was a statistically significant association between the US and histological findings, but nevertheless not as strong as the association between laparoscopy and histological findings.

Parovarian and paratubal cysts, which constitute about 10% of adnexal masses are difficult to diagnose before surgery with the use of transvaginal US [19].

It was not possible to differentiate by transvaginal US between benign, borderline, and malignant cysts when solid parts or papillary formations were visualized [20]. The risk for malignancy in cysts containing papillary formations or solid parts (group 2) was three to six times higher than that in unilocular echo-free cysts [20]. The US appearance of the cyst, the woman’s family history as well as her own feelings must be considered if a persisting cyst is to be surgically removed or followed by repeated transvaginal US [21].

The management of adnexal masses involves several steps: establishing the diagnosis of an organic ovarian cyst, avoiding a useless and iatrogenic surgery of a functional cyst, and recognizing that functional cysts may persist more than three months and may occur even on low-dose oral contraceptives [22]. The laparoscopic approach is effective and safe for managing patients with adnexal masses of unknown pathology [23].

A great deal of gynecologic laparoscopic surgery involves adnexal mass evaluation and removal Laparoscopic management of preselected benign masses has been a common practice and standard criteria for patient selection and has been reported extensively. Such criteria include clinical examination, transvaginal US, Doppler US and serum CA-125 levels [24, 25]. As for CA-125 levels, a discrepancy between pre- and postmenopausal women has been revealed as an elevated value detected in only 15% of premenopausal women with malignancy, while an 80% sensitivity was demonstrated in women older than 50 years [26]. Both sensitivity and specificity of CA-125 were better in postmenopausal than in premenopausal women. In modeled outcomes, combinations of imaging and CA-125 were both more sensitive and more specific than either alone [26]. Finkler et al. demonstrated that the addition of the CA-125 level measurement did not improve the negative predictive value of US in premenopausal women, but raised to 100% its value in the postmenopausal group. The high rate of false positivity of CA-125 due to common premenopausal conditions like pregnancy, endometriosis, leiomyoma, adenomyosis, dermoid cysts and pelvic inflammatory disease decrease its value in detecting malignancy in this age group [27].

As far as the clinical examination is concerned the fixed irregular and solid masses, especially in the presence of ascites, are suspicious for malignancy and such features exclude these patients from the laparoscopic approach [28]. Furthermore, the lack of sonographic findings like irregular borders, excrescences, solid areas,
thick septa and ascites could accurately predict benign masses in 90% of patients [28]. Especially the number of excrescences were highly sensitive in predicting malignancy [29]. On the other hand, a low resistance index measured by transvaginal Doppler US was highly correlated with malignancy [30]. However, it has been reported that with advanced technology and advanced operative skills early-stage ovarian cancer may be removed laparoscopically according to the general principles of gynecologic cancer surgery [31]. Laparoscopy is the gold standard for the surgical diagnosis of adnexal masses, but puncture should be avoided whenever possible [32]. Furthermore, studies have shown that tumor spillage during operative laparoscopy does not adversely affect survival [33]. The surgical treatment of invasive ovarian cancer should be by laparotomy, whatever the stage [34]. In contrast, restaging of early ovarian cancer initially managed as a benign mass is a good indication for the laparoscopic approach. The laparoscopic management of low malignant potential tumors should include a complete staging of the peritoneum [35]. In our study laparoscopy was converted to laparotomy in five patients in whom malignancy was suspected during observation of the macroscopic features of the ovarian masses. In the five histological suspicious cases the final histological examination confirmed three borderline epithelial ovarian tumors, one Brenner tumor in Stage IA and only one carcinoma metastasis to the ovary in Stage IVb.

The ovarian carcinoma was a mixed tumor. During the surgery the patient was found to have extensive intraabdominal metastases from an occult primary extra ovarian tumor with histological characteristics of primary ovarian cancer. This lesion was composed of epithelioid cells containing clear or focally granular pale cytoplasm with slightly enlarged hyperchromatic nuclei. The presentation of a Stage IA Brenner ovarian tumor was associated with lack of extensive infiltrative invasion. No additional treatment was recommended in the first patient because she had generalized metastases and in the second one because of non aggressive behavior. One of the six cystadenoma cases was the borderline mucinous cystadenoma, which diagnosis was not confirmed at frozen section. It seems that a laparoscopic diagnosis is highly accurate, but not recommended as a sole diagnostic tool without the simultaneous and immediate availability of frozen section. It is also important to stress that in our series we had only the above-mentioned difference between frozen section and histological diagnostic results, and a discrepancy of 7.3% between them is reported in the international literature [36-38]. The incidence of complications in our series does not differ from that reported in the international literature [39, 40]. On the other hand laparoscopic findings were strongly associated with the histology reports. In our study there was a statistically significant association between the laparoscopic and histological findings of those surgeries that proceeded into laparotomies ($\chi^2 = 1.013E3$, $p < 0.001$). In the cases of ovarian, paraovarian, Morgagni, and dermoid cysts, endometriosis and hydrosalpinx, there was a 100% association between laparoscopic and final histological findings. In the cases of inflammation, cystadenoma, BOT, and fibroma the proportion of association was adequate.

In conclusion, operative laparoscopy is directly correlated with the available technology and surgical skills, seems to be a safe and efficient therapeutic management of adnexal masses in selected premenopausal women, providing many advantages compared to the open approach and without compromising the optimal outcome.

The advantages of laparoscopic surgery are today well established and include shorter hospitalization time, decreased postoperative pain and recovery time, less adhesion formation, diminished cost for society, and additionally in the cases of women in reproductive age their fertility is affected in a lesser degree compared to the open approach.

References

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Accuracy of intraoperative frozen section during laparoscopic management of early endometrial cancer

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1Institute for the Care of Mother and Child, 23rd Faculty of Medicine, Charles University, Prague (Czech Republic)

Summary
Objective: The aim of our retrospective study was to correlate the intraoperative frozen section (FS) and permanent section (PS) diagnosis among patients with early-stage endometrial cancer (FIGO Stage I). Methods: Retrospective analysis of clinical data. A set of 63 women were operated by the technique of laparoscopic assisted vaginal hysterectomy with bilateral salpingo-oophorectomy (LAVH with BSO). All probands had intraoperative FS biopsy performed with grading and myometrial invasion assessment. These data were then compared with PS diagnosis. Statistical evaluation was used to detect diagnostic accuracy of FS (sensitivity, specificity and positive vs negative predictive value, and accuracy rate). Results: The average age was 61 years, BMI 32.4 kg/m2 and operation time including lymphadenectomy (LAE) was 108.7 minutes. Sensitivity of FS was 77.8%, specificity 98.1%, positive predictive value (PPV) 87.5%, negative predictive value (NPV) 96.4% and accuracy rate 95.2%. Suboptimal surgical management due to underevaluation of FS biopsy compared to PS diagnosis occurred in 2 patients (3.2%). Conclusion: Combination of LAVH with BSO and use of intraoperative FS enables the surgeon to individualize surgical treatment for every patient to the extent of either performing complete operation together with LAE or not.

Key words: Endometrial cancer; Frozen section; Laparoscopy; Surgical staging; LAVH.

Introduction
Endometrial cancer is a malignant disease with increasing incidence not only in the Czech Republic but also worldwide [1-3]. At the present time there are 1,500 newly diagnosed patients in the Czech Republic every year which is an incidence of 32/100,000 women. Treatment and prognosis for patients with endometrial cancer depends on the staging of the disease. Since the clinical staging was not very accurate in 1988, it was replaced with so-called surgical-pathological staging. When deciding about the treatment options we need to take into consideration the fact of low and high risks for spreading endometrial cancer into the lymphatic system [4]. Patients with a high risk of lymphatic spreading need adequate operative treatment that includes not only peritoneal lavage and hysterectomy with bilateral salpingo-oophorectomy (BSO), but also lymphadenectomy (LAE) [5].

Intraoperative frozen section (FS) biopsy has quite a high accuracy (80-96.5%) [6, 7] when dividing the patients with endometrial cancer into groups of low and high risk for lymphatic spread. Many recent studies have evaluated the significance of intraoperative FS for endometrial cancer when operating using the standard abdominal technique [8-10]. Endometrial cancer is the first oncological diagnosis in which laparoscopic staging becomes the standard at early stages of the disease [1, 4]. The combination of intraoperative FS and laparoscopically assisted vaginal hysterectomy (LAVH) with BSO enables a surgeon to decide in a very short time about the extent of surgical treatment [11, 12].

The aim of our study was to evaluate the significance of intraoperative FS, including the stage of tumor differentiation and its myometrial invasion among our patients with Stage I endometrial adenocarcinoma. The extent of operative treatment was always decided according to the result from intraoperative FS. The results from FS biopsies were later on compared with permanent section (PS) diagnosis. We mostly concentrated on the cases in which intraoperative FS differed from PS diagnosis. These cases represent a group of patients who are at the highest risk of getting suboptimal surgical treatment.

Materials and Methods
Our group of patients consisted of 63 Caucasian women with endometrial adenocarcinoma in Stage I who were operated on in our department between the years of 2003 and 2008. All patients had their disease confirmed by preoperative biopsy which was obtained from curettage (D&C) or hysteroscopy. Those patients whose results showed > 50% of myometrial invasion, those with low-differentiated tumor, and also those with clear-cell and serous-papillary tumors were excluded from our study because all had been enrolled in complete surgical staging from the beginning. The standard choice of operative method was LAVH with BSO. At the beginning of every surgical treatment peritoneal lavage was carried out. The uterus and both adnexa were sent for FS analysis right after removal. FS was immediately analyzed in the same department by the consultant in gynecological pathology. The depth of tumor infiltration into the myometrium and tumor grade according to given criteria were analyzed in all cases. Each FS biopsy was cut into 1-4 sections according to distribution and macroscopic appearance of the tumor. The result of FS was always announced to the surgeon before finishing the final laparoscopic part of the operation.

The aim of our study was to compare the accuracy of FS (myometrial invasion and tumor grade) to PS diagnosis, i.e.,...
Results

Our group of patients consisted of 63 women with Stage I endometrial adenocarcinoma. Forty women (63.5%) were diagnosed after hysterectomy and endometrial biopsy, and 23 women (36.5%) were diagnosed from D&C only. Four women (6.3%) had no cancer found in FS nor in PS diagnosis; this could have resulted from the total removal of cancer during the intrauterine diagnostic procedure. The average age of our patients was 61 years (40-86) and the average BMI was 32.4 kg/m² (17.6-57). The average duration of the surgery with LAVH and BSO and peritoneal lavage only was 92.4 minutes (55-190). Eight patients (12.7%) out of the 63 women were indicating to undergo complete laparoscopic staging due to the FS result. The time duration of the operation was statistically longer (p < 0.05), on average 225.5 minutes (90-325) when laparoscopic assisted endoscopy (LAE) was included. Perioperative complications were not high, and occurred only in one case (1.6%). Bleeding occurred from a tributary vein from the inferior cava vein (ICV) while performing LAE, and conversion to laparotomy was indicated.

The concordance rate between intraoperative FS and PS diagnosis when comparing myometrial invasion was found in 55 (87.3%) cases (Table 1). When evaluating myometrial invasion there were six cases in which PS diagnosis showed deeper myometrial invasion than FS did. We found out by detailed study that three of our patients had no tumors found in FS but were later on discovered in PS diagnosis. One patient had Stage IA localized only in the endometrium, and the two other patients had Stage IB (myometrial invasion 1 mm and 3 mm with the thickness of myometrium 25 mm, respectively of 20 mm). Two cases of complex atypical hyperplasia (CAH) showed tumor limited to the endometrium with myometrial infiltration < 50% in PS diagnosis. Only one woman had myometrial invasion > 50% even though FS revealed myometrial invasion < 50%.

Only two patients had smaller myometrial invasion from PS diagnosis than the one revealed from FS. In one case in which invasion was estimated to be from FS localized only in the endometrium the PS diagnosis showed CAH. In the second case where FS revealed myometrial invasion > 50%, reclassification was made according to the PS diagnosis since myometrial invasion was only < 50%.

We also compared the tumor grading obtained from FS and PS diagnosis (Table 2). Correlation of tumor grading between FS and PS diagnosis was proven in 54 cases (85.7%). There were eight patients (12.7%) who had higher tumor differentiation in PS diagnosis than in FS. In three cases there was no tumor found in FS but later there was well differentiated adenocarcinoma discovered in PS diagnosis. This finding correlates with three above-mentioned cases when tumor was not discovered while evaluating myometrial invasion (Table 1). Diagnosis of CAH during FS was finally reclassified to well differentiated tumor G1 in two cases, and two cases in which the grading was estimated to reveal well differentiated tumor had to be reclassified according to the PS diagnosis, in which medium differentiated tumor G2 was found. In one case the PS diagnosis found medium differentiated tumor instead of dedifferentiated tumor which was obtained from FS.

In this study we have also summed up sensitivity, specificity, PPV, NPV and accuracy rate of FS (Tables 3 and 4).

Table 1. — Correlation of myometrial invasion between intraoperative FS and PS diagnosis.

<table>
<thead>
<tr>
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<th>CAH</th>
<th>IA</th>
<th>IB</th>
<th>IC</th>
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<td>Not found</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
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<td>0</td>
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<td>0</td>
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<td>6</td>
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<td>IB (invasion &lt; 50%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>IC (invasion &gt; 50%)</td>
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<td>7</td>
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</table>

Table 2. — Correlation of tumor grading between FS and PS diagnosis.

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<tr>
<td></td>
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<tr>
<td>G1</td>
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<td>G2</td>
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</tr>
<tr>
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</table>

Table 3. — Accuracy rate of FS compared to PS diagnosis at different stages and at different degrees of tumor differentiation.

<table>
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<th>Accuracy rate %</th>
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<td>20</td>
</tr>
<tr>
<td>G3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4. — Significance of FS in patient differentiation into low and high risk groups.

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<table>
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<tr>
<td>Sensitivity</td>
<td>77.8%; 95% CI 40.0-97.2%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.1%; 95% CI 90.1-99.9%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>90%; 95% CI 47.4-99.7%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>96.2%; 95% CI 87.5-99.6%</td>
</tr>
<tr>
<td>Accuracy rate</td>
<td>95.2%; 95% CI 86.7-99.0%</td>
</tr>
</tbody>
</table>
Discussion

Treatment and prognosis of patients with endometrial cancer depends greatly on the complete staging of this disease [14]. Grade 1-2 and invasion into a maximum of 50% myometrial thickness are so-called prognostic factors of low-risk disease. On the other hand grade 3, invasion deeper than 50% of myometrial thickness, lymph node invasion, positive peritoneal lavage, spread in the cervix and unfavorable histological types (clear cell cancer, serous-papillary cancer and carcinosarcoma) are high-risk prognostic factors.

Complete surgical staging including pelvic and paraaortic LAE is always indicated in patients with a high risk of lymphatic spreading. The biggest problem is still an exact assessment of radical surgical extent depending on tumor invasion into the myometrium and tumor grade [15, 16]. FS is one of the possibilities to determine the extent of surgical treatment needed [17, 18]. We have used the combination of LAVH with BSO and FS as the standard management method for patients with early-stage endometrial cancer since 2003.

The challenge of FS biopsy is the risk of having tumors under-evaluated [19-21]. In the past there were some studies published that retrospectively but also prospectively evaluated the accuracy rate of FS compared to PS diagnosis [7, 9, 16-18]. The difference in results depends on the evaluation accuracy of myometrial invasion and tumor differentiation [8, 10, 12]. Accuracy can be also increased by the number of sections through the myometrium during FS [9, 10]. In 2000 Kucera et al. published an analysis of 624 patients with Stage I adenocarcinoma in which correlations were made between FS and PS diagnoses [7]. The average accuracy rate of FS biopsies in this study when evaluating myometrial invasion was around 88% with tumor grade 84%. Quinlivan et al. analyzed the accuracy rate of FS biopsies when evaluating myometrial invasion and tumor grade among 260 cases [18]. The accuracy rate of FS in this retrospective study was 94.7% and 88.9%, respectively. The accuracy rate of FS in our study when evaluating myometrial invasion was 87.3% and tumor grade was 85.7%.

The concordance rate between intraoperative FS and PS diagnosis in our group when comparing myometrial invasion was found in 55 (87.3%) cases and in 54 cases (85.7%) when comparing tumor grade. The most significant problem is under-evaluation of FS, which leads to understaging of disease, and therefore the patient does not get appropriate surgical treatment. In our study this had happened to two patients (3.2%). In one case the PS showed myometrial invasion > 50% and in the second case the grading showed nondifferentiated tumor. In these two cases the extent of surgery was suboptimal, limited to LAVH with BSO only.

Our data also suggest, in agreement with the Indermaur study, that intraoperative FS is not a reliable indicator of final pathology in patients with a diagnosis of congenital adnexal hyperplasia [19]. However this discrepancy does not affect the extent of surgical treatment. We also need to realize that during the D&C a surgeon can take away not only tumor limited to the endometrium but also from places where less differentiated tumor is located. We always take into account higher grading in cases when the worse grading is obtained from hysteroscopy or D&C, which is then in discrepancy with the FS result. The highest accuracy of FS was achieved in the evaluation of medium differentiated tumors (97.5%) with myometrial invasion < 50% (95.2%).

In this study we have summed up sensitivity, specificity, PPV, NPV and accuracy rate of FS while trying to identify patients with a high risk of disease spread and thus giving them sufficient surgical treatment (Table 4). The sensitivity in our study was 77.8% (95% CI; 40.0-97.2%). This result is connected with the low number of true-positive patients in this study (n = 7). These patients received appropriate treatment. The specificity reached 98.1% (95% CI; 90.1-99.9%) and thus can give us high reliability in predicting patients who will not require complete surgical staging. Only in one case (1.6%) did the upstaging of FS result in surgical overtreatment. The total accuracy rate of FS in this study was 95.2% (95% CI; 86.7-99.0%). Although we are aware of the limited potential of FS, our results do not support some critical studies published by Frumovitz et al. and Case et al. recently [20, 21].

Conclusion

Intraoperative FS biopsy evaluates tumor differentiation and myometrial invasion, and thus gives us on one hand highly accurate information if LAE is needed, and on the other hand helps prevent surgical overtreatment when it is not necessary. In our opinion the biggest profit of not providing all-inclusive treatment (LAE) and individualized treatment strategy for every patient is for obese and polymorbidity patients. The condition which plays a very important role in the evaluation of FS is the experience and erudition of the histopathological department with this method. The question is, can we expect increasing rates of achievement from FS, especially when evaluating specificity and sensitivity, if we are aware of FS limits (e.g., formation of artifacts, number of sections, time for evaluation). Novel histochemical methods that are under development in experimental pathology (rapid enzymatic tracing of cell types in FS, detection of epithelial-to-mesenchymal transdifferentiation in pathological lesions and developmental anomalies) may further increase the accuracy of diagnosis based on FS in the future [22, 23]. However, there are some studies that show a quite low predictive value of FS when evaluating myometrial invasion, tumor differentiation and clinical stage of the disease [20, 21]. Therefore, the role of FS biopsy is still controversial when considering all results from the retrospective and prospective studies mentioned above.
Accuracy of intraoperative frozen section during laparoscopic management of early endometrial cancer

References


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Assessment of the predictivity of preoperative serum CA 125 in the differential diagnosis of uterine leiomyoma and uterine sarcoma in the Turkish female population

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Introduction

Uterine leiomyomas are the most common benign tumors of the uterus. Unfortunately, the diagnostic imaging criteria for distinguishing leiomyosarcomas from leiomyomas remain vague. Our aim was to study the preoperative diagnostic value of CA 125 in the differential diagnosis of leiomyoma and uterine sarcoma. Methods: The subjects of the study included a total of 2,382 patients aged between 20-71 years operated for uterine myoma between the years 2005 and 2008 at our hospital, and in the same period 26 patients diagnosed with uterine sarcoma who were assessed retrospectively. Results: Assessment of the predictivity of CA 125 values in the preoperative diagnosis of uterine sarcoma showed it was not significant according to the 95% CI related to the area below the curve. The assessment of CA 125 values in the uterine sarcoma group showed that those with carcinosarcoma had higher CA 125 mean values than other sarcoma groups. The relation between staging and CA 125 in all sarcomas could not be statistically assessed. Conclusion: We concluded that in the differential diagnosis of myoma and uterine sarcoma, the preoperative serum CA 125 level did not have any predictivity. Additionally, there was no association between staging and CA 125 in uterine sarcomas.

Key words: Uterine leiomyoma; Uterine sarcoma; CA125.

Summary

Aims: Uterine leiomyomas are the most common benign tumors of the uterus. Unfortunately, the diagnostic imaging criteria for distinguishing leiomyosarcomas from leiomyomas remain vague. Our aim was to study the preoperative diagnostic value of CA 125 in the differential diagnosis of leiomyoma and uterine sarcoma.

Methods: The subjects of the study included a total of 2,382 patients aged between 20-71 years operated for uterine myoma between the years 2005 and 2008 at our hospital, and in the same period 26 patients diagnosed with uterine sarcoma who were assessed retrospectively.

Results: Assessment of the predictivity of CA 125 values in the preoperative diagnosis of uterine sarcoma showed it was not significant according to the 95% CI related to the area below the curve. The assessment of CA 125 values in the uterine sarcoma group showed that those with carcinosarcoma had higher CA 125 mean values than other sarcoma groups. The relation between staging and CA 125 in all sarcomas could not be statistically assessed.

Conclusion: We concluded that in the differential diagnosis of myoma and uterine sarcoma, the preoperative serum CA 125 level did not have any predictivity. Additionally, there was no association between staging and CA 125 in uterine sarcomas.

Key words: Uterine leiomyoma; Uterine sarcoma; CA125.

Leiomyosarcoma symptoms often include vaginal bleeding, abdominopelvic pain, and pelvic or abdominal tumors. The possibility of uterine sarcoma should be considered in uterine tumors that reach a 6-week pregnancy size in a one-year period, necessitating preoperative assessment [9].

Unfortunately, the diagnostic imaging criteria for distinguishing leiomyosarcoma from benign leiomyomas remain vague and ill-defined. It is unlikely that diagnostic imaging techniques can distinguish leiomyosarcoma from benign leiomyomas. It is routine to find necrosis in leiomyomas greater than 10 cm in diameter and this criteria alone is not diagnostic of leiomyomas. When compared to other imaging methods, magnetic resonance imaging (MRI) is better at identifying the localization, size and degenerative changes in tumors. It is not cost-effective to perform MRI on patients diagnosed with leiomyoma and referred for surgery; however, a preoperative predictive test may be useful in selecting patients for MRI. Therefore it may be important from a clinical perspective to determine the predictivity of CA 125, a high molecular mass glycoprotein, in the preoperative differential diagnosis of uterine tumors. CA 125 is a differentiation antigen associated with coelomic epithelium and its normal and neoplastic derivatives. Although it was shown to be a marker for epithelial ovarian cancer by radioimmunoassay methods [10], there are very few reports linking its expression with musculoskeletal tumors [11-13].

Our aim in this study was to investigate the preoperative diagnosis value of CA 125 in the differential diagnosis of leiomyoma and uterine sarcoma.
Material and Methods

The subjects of the study included a total of 2,382 patients aged between 20-71 years, operated for uterine myoma between the years 2005 and 2008 at our hospital, and in the same period 26 patients diagnosed with uterine sarcoma who were assessed retrospectively. Of the 2,382 patients, those with a preoperative serum CA 125 value were admitted to the study. Those with systemic and endocrine pathology, additional pelvic pathology other than uterine myoma, endometrial or ovarian malignancy prediagnosis, and peritoneal acid were excluded from the study. A total of 815 patients who were admitted to the study were diagnosed clinically and sonographically with uterine myoma. The pathological assessment of the patients was conducted by senior pathologists working at the pathology laboratory in our hospital. The age, tumor size, CA 125 values and pathological diagnosis of patients were recorded. The CA 125 assay was performed by an electrochemiluminescence immunoassay (ECLIA) according to manufacturer’s instructions. CA 125 range 0.600-5000 IU/ml, sensitivity 0.60 IU/ml (Roche Diagnostics).

Statistical analysis

The data were analyzed with the SPSS 11.5 package program. The Shapiro-Wilk’s test was used to test the normality of distribution for CA 125. Data were expressed as mean ± standard deviation. Comparisons of CA 125 between independent groups were performed by Mann-Whitney U and Kruskal Wallis tests. Receiver operating characteristic (ROC) curves were employed to describe the performance of CA 125 regarding predictivity of sarcoma. The area under the curve and 95% confidence interval (CI) were calculated. A p value of < 0.05 was considered statistically significant.

Results

The mean age of women diagnosed with uterine myoma was 45.74 ± 7.07, and that of those diagnosed with uterine sarcoma was 53.73 ± 12.54. A statistically significant difference was observed between these mean ages (p < 0.001). The mean pelvic tumor size of patients diagnosed with pathological myoma was 5.71 ± 1.73 cm, while that of patients diagnosed with uterine sarcoma was 8.57 ± 2.50 cm. The difference was statistically meaningful (p < 0.001). The distribution of patients with respect to pathological diagnosis and CA 125 values is presented in Table 1. A statistically significant difference was observed between the preoperative mean CA 125 values of patients diagnosed with uterine myoma and uterine sarcoma (p < 0.005). When the groups were assessed within themselves with respect to CA 125 values, the group diagnosed with sarcoma was observed to have a statistically meaningful difference within itself (p < 0.005). When the uterine myoma group was assessed within itself according to the pathological diagnosis, no statistically meaningful difference was observed with respect to CA 125 values. To assess the predictivity of CA 125 values in the preoperative diagnosis, a ROC curve was made and the area below the curve was identified as 0.620 (p < 0.05) (Figure 1). Though the area below the curve was shown to be significant by the p value, this was not so according to the 95% CI related to the area below the curve.

The assessment of CA 125 values in the uterine sarcoma group showed that women with carcinosarcoma had higher CA 125 mean values than the other sarcoma groups. A meaningful difference was observed between the carcinosarcoma, leiomyosarcoma and endometrial stromal sarcoma groups (p < 0.001 to p < 0.01). Two patients pathologically diagnosed with carcinosarcoma were Stage I-II whereas another four patients were Stage III-IV. Despite this difference between stages, all patients displayed high CA 125 values. The distribution of patients according to surgical stage and their CA 125 values is presented in Table 2. Due to the limited number of cases, the relationship between staging and CA 125 in all sarcomas could not be statistically assessed.

Table 1. — Distribution of patients according to pathological diagnosis and CA 125 levels.

<table>
<thead>
<tr>
<th>Pathological diagnosis</th>
<th>CA 125 (IU/ml)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine sarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>21.50 ± 6.24</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Stromal sarcoma</td>
<td>19.50 ± 0.70</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>28.21 ± 18.87</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>166.92 ± 121.11</td>
<td></td>
</tr>
<tr>
<td>Uterine myoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipoleiomyoma</td>
<td>18.75 ± 2.87</td>
<td></td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>800 ± 21.03</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cellular myoma</td>
<td>19.91 ± 5.99</td>
<td></td>
</tr>
</tbody>
</table>

p < 0.005 is significant; n.s. = not significant.

Figure 1. — CA 125 predictivity in uterine pelvic masses.
Discussion

Uterine sarcomas are malignancies not easily diagnosed preoperatively as they cannot be detected in early stages through ultrasound or laboratory methods. The preoperative distinction of uterine sarcomas from uterine myomas is still difficult. The existence of conservative treatment options for uterine myoma leads to the postponement of surgical treatment in patients in the reproductive stage, therefore delaying the diagnosis of uterine sarcoma despite the endometrial sampling and imaging techniques. There are a limited number of studies focusing on a cost-effective biochemical test which allows early preoperative diagnosis in the differential diagnosis of myoma and sarcoma, and no test has yet been identified with preoperative diagnosis predictivity.

Although serum CA 125 is used commonly for diagnosis as well as efficiency of treatment, particularly in epithelial origin ovarian and endometrial tumors, the literature does not contain enough data about its use in uterine sarcomas except case reports. While CA 125 immune reactivity was not observed in epithelial and ovarian origin tumors in tissue preparations examined by using immunohistochemical methods, in certain sarcomas CA 125 antico may give immune reactivity at differing levels [14, 15].

Despite the existence of tissue studies, however, very few studies have been conducted on serum CA 125 levels in nonepithelial malign tumors and in mesenchymal sarcomas. CA 125 anticore may give immune reactivity in certain sarcomas CA 125 anticore may give immune reactivity at differing levels [14, 15].

In a study comparing 42 leiomyosarcoma and 84 leiomyoma patients, Juang et al. [13] reported a meaningfully higher level of preoperative serum CA 125 level in the leiomyosarcoma group when compared to the leiomyoma group. They also reported a difference between the distributions of CA 125 values between early- and late-stage leiomyosarcomas in a premenopausal and postmenopausal patient group. Hoskins and Le also reported a positive correlation between preoperative serum CA 125 levels and uterine sarcoma stage [17].

Parallel to the literature, our study found a higher mean age in the sarcoma group than in the myoma group [1]. Also in line with the literature, we found that the group diagnosed with uterine sarcoma had a meaningfully larger tumor size than the group diagnosed with uterine myoma [1]. Different from the results of Juang et al. and Hoskins and Le, we observed that although the preoperative serum CA 125 level may be statistically meaningful in the differential diagnosis of uterine myoma and uterine sarcoma in a larger case series, it did not have predictivity in the 95% CI.

However, when the group causing the difference was identified, it was seen that within the sarcoma group, the preoperative serum CA 125 values of carcinosarcoma patients were higher than other malign and benign pathologies. The assessment of serum CA 125 levels and surgical staging of all sarcoma cases did not lead to a statistically meaningful finding due to the limited number of cases in the subgroups. The failure to identify a relationship with staging despite the high level of serum CA 125 points to a need for future case series.

In sum, we concluded that in the differential diagnosis of myoma and uterine sarcoma, the preoperative serum CA 125 level did not have any predictivity. Additionally, we did not associate staging and CA 125 in uterine sarcomas. However, future case series with a larger scale will help clarify this.

References

Uterine cervical neoplasia prevention in Parque Indigena do Xingu


Department of Gynecology, Nucleo de Prevencao de Doencas Ginecologicas (NUPREV), Department of Preventive Medicine, Universidade Federal de São Paulo (UNIFESP) S.P. (Brazil)

Introduction

Low social-economic status and screening failure make uterine cervical neoplasia one of the most frequent neoplasias in developing countries [1]. Mortality ranged from 4.6 to 4.8 per 100,000 women between 1995 and 2005 [2].

The principal etiologic agent of preneoplastic lesions and cervical neoplasias is human papillomavirus (HPV). It is possible to diagnose a preneoplastic lesion early, therefore it is necessary to have well organized screening programs. The Pap test reveals cytological changes, then patients are sent for a colposcopy test and directed biopsy. To resolve the problem well established guidelines are necessary. Reduction in the incidence of uterine cervical cancer has reached 50-80% of cases in developed countries with organized screening. One cervical oncological cytology at 35 years of age is enough to reduce the risk the neoplasia by 50% [3].

Hybrid capture (CH2-Digene) detects ongogenic HPV without established disease. In 2003 the FDA approved the DNA-HPV test associated with cytology in women over 30 years old to establish the real risk of developing a uterine cervical lesion. This program includes screening for a three- to five-year interval if it is negative. One cervical oncological cytology at 35 years of age is enough to reduce the risk the neoplasia by 50% [3].

There are few epidemiologic data about Brazilian aboriginal women. There are basic precarious conditions before birth, uterine cancer, and sexually transmitted disease (STD) prevention. One of the few trials has made evident the multiplicity of problems such as high parity, numerous STD and gynecologic diseases, abdominal pain and genital discharge [6]. Moreover, few trials have shown the real frequency of uterine cervical cancer inside aboriginal populations. O’Brien et al. evaluated Australian aboriginal women and showed that death risk by such neoplasia is related to prevention failure and late diagnosis [7].

In Brazil, native women are much more exposed to STD as a consequence of not only a great racial mix with caucasian men, but also due to their increased presence in urban centers, the presence of non native people in native areas, and difficult access to prevention information [8].

Brito studied the Parakanã tribe in Brazilian Amazonia and revealed HPV frequency in 42% of women [9].

In Parque Indígena do Xingu, preventive screening was infrequent before 1991 according to the history of the Xingu Project. Many deaths due to uterine cervical cancer were recorded as a consequence. Delay in the return of cytological results and difficulty in sending native women to referral therapeutic centers have also contributed.
Since 2005, the Xingu Project, a result of an agreement established among Fundação Nacional de Saúde (FUNASA) and Universidade Federal de São Paulo (UNIFESP), allowed significant changes in preventive screening and treatment for the natives of Parque Indígena do Xingu. In 2005 and 2007 the covered index was 97.6 and 92.6%, respectively. In a cohort of 511 native women cytological changes of some gravity were detected in 4.6% of cases in 2005 and 0.88% of cases in 2007 (personal research report).

All women with atypical cytology were subjected to colposcopy, directed biopsy and treatment according to the guidelines of NUPREV/UNIFESP. The health staff, doctors, and nurses together with medical equipment were sent to Parque Indígena making it possible to give assistance to most of the native women without sending them to large urban centers.

The aim of the study was to show the clinical evolution of 37 aboriginal women who were diagnosed and treated for low- or high-grade cervical squamous lesions and invasive cancer from 2005 to 2007.

Methods

From 2005 the Xingu Project sent gynecologists of NUPREV to check the cervical cytological results of selected atypical cases for referral of native women to colposcopy and treatment if necessary. Thirty-seven native women were treated. From those, ten women were sent to São Paulo for treatment in NUPREV. The other 27 were submitted to therapeutic procedures inside their area by gynecologists who moved to Canarana and Sinop villages, near Parque Indígena do Xingu.

Cytopathological presurgical results were: seven low-grade squamous lesions (19.1%), 28 high-grade lesions (75.6%), and two suspected invasive carcinomas (5.4%). Surgical treatment included 32 large electrical excision procedures (LEEPs), three cold knife conizations, one vaginal hysterectomy and one Werthein-Meigs procedure.

Results

Two of 32 LEEPs were complemented by abdominal hysterectomy because they had cervical involvement with high-grade squamous intraepithelial lesions (HSIL). Seventeen cases (53.1%) showed free surgical borders, nine (28.1%) had compromised endocervical edges, five sections (15.6%) had positive ectocervical borders, and one case (3.1%) had both borders compromised.

Intrasurgical complications occurred in five cases (15.6%): copious bleeding needing cervical sutures in two cases and electocoagulation in another two. Those procedures were done 24 hours after the first treatment and another one after one week.

Colposcopic evaluations of all patients were carried out after six months. At that time four cases had unsatisfactory colposcopy due to no visible squamocolumnar junction (SCJ), but only one had endocervical stenosis. The cytological endocervical slides were satisfactory in three of those cases.

Two out of three patients submitted to cold-knife conization had clinical Stage Ia1 microinvasive carcinoma and total hysterectomy was performed. The only case of frankly invasive neoplasia, clinical Stage Ib1, was treated with a Werthein-Meigs’s procedure.

Thirty-two patients were followed-up with negative cytological and colposcopic controls after two or three evaluations. Three patients were not followed-up because those women were residents of a far away village, Alto Xingu, outside of the area of the Xingu Project. Another two women recently underwent LEEP but have not yet had post-treatment follow-up.

Discussion

Preventive screening for uterine cervical cancer in Parque Indígena do Xingu is performed by a specialized nurse who collects cytopathological materials inside native villages where she goes periodically by land, water or via air. After pathologic results are obtained doctors carry out colposcopy and therapeutic procedures in selected cases with portable equipment inside the native village. Native women have many children to care for and tasks to perform. Thus it is difficult to send those patients to a large urban center especially because of the cultural impact.

The therapeutic action adopted was that suggested in the guidelines of the American Society of Cervical Pathology and Colposcopy using LEEP for HSIL, cytohistological discordance and endocervical lesions [12]. Cold-knife conization and Werthein-Meigs procedure, were performed when invasion was suspected.

Post-treatment follow-up was high. Three out of 37 women treated have had no follow-up. Thus, 86% of women had two or three controls with quarterly intervals, and all examinations were negative for squamous intraepithelial lesions, corresponding to a 100% cure.

Large cervical lesions were observed in hypertrophic cervices, probably due to multiparity and frequent infections, which is why intra- and post-surgical procedure for bleeding occurred in 15.6% and 3.1% of cases. The literature index for bleeding is 1-3%; coagulation tests such as coagulation and bleeding time have been performed in most women without changes [13].

All patients underwent serological testing for HIV, hepatitis B and C and syphilis, with negative results. All women had immunoreaction to hepatitis B (anti-HBc positive) as a consequence of mass immunization.

Cervical stenosis and no visible SCJ occurred in four cases post-LEEP. One case of stenosis was a consequence of bleeding needing electrocoagulation. Three cases (9.4%) showed SCJ inversion with unsatisfactory colposcopy. Two of those women were in menopause. Mathew et al. showed 19% of unsatisfactory colposcopy in their cases [14].

Involvement of surgical borders did not change the procedure, except in two cases that showed lesion persistence inside the cervical canal. Those patients were submitted to hysterectomy because they had completed their families and would be safer to follow-up. There was
residual neoplasia in both cases. According to Dores [15], positive borders with negative controls did not mean residual disease. Murdoch et al. showed 95% therapeutic success, although they had compromised borders in 56% of cases.

Within two years of implementing the Xingu project it was possible to detect that regular preventive screening associated with treatment can promote a decreased incidence of high-grade cervical lesions and invasive cancer. Statistical data showed nine deaths due to uterine cervical neoplasias between 1985 and 2006. Five new cases were recorded and treated in the period of 2000-2005. Those data have not been repeated since 2005 due to the effective action of the health staff of NUPREV and UNIFESP.

Conclusion

Health staff actions have been effective in the prevention, diagnosis and treatment of precursor and invasive lesions of the uterine cervix of aboriginal people. The movement of specialized health professionals and medical equipment to native villages have made the treatment of these women easier and more precocious. A frank reduction of advanced cases and decreased mortality due to uterine cervical cancer in native people have been shown.

References


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The role of immunonutrition in gynecologic oncologic surgery

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Summary

Background: This study assesses the effect of immunonutrition on biochemical and hematological parameters, incidence of infection, postoperative complications, mortality rate and length of hospital stay. Material and Methods: A total of 50 patients operated on for gynecological malignancies were randomly assigned to two groups, each receiving two days preoperative and seven days postoperative enteral nutrition after intestinal movements started. The patients in group 1 were given 1000 kcal/d immun-enhancing enteral nutrition (IEN). The patients in group 2 received 1000 kcal/d standard enteral nutrition. The nutritional (albumin, prealbumin), immunologic (CRP, white blood cell (WBC) count, lymphocyte population) parameters, length of hospital stay (LOS) and clinical outcomes were examined. Results: The two groups did not differ in terms of demographic data, nutritional status, surgical status, mortality rate (p > 0.05), WBC count, lymphocyte population, CRP levels were significantly higher in group 1 compared with group 2 in the postoperative period (p < 0.05). Pulmonary and urinary tract infection rates were similar in both groups (p > 0.05) but wound infection, and LOS rate were significantly lower in group 1 than group 2 (p < 0.05). Conclusion: Perioperative immunonutrition proved to be safe and useful in increasing the immunologic response. It may decrease postoperative complications and LOS in patients undergoing surgery for gynecological malignancy.

Key words: Gynecological malignancy; Immunonutrition; Complications.

Introduction

Poor nutritional status in patients undergoing surgery is well known to increase postoperative morbidity and mortality by deteriorating various organ functions and the immune system of the host [1]. Soon after surgery – which entails invading the body – rapid changes in metabolism may occur, and the risk of complications such as infection; therefore multifaced management including nutritional and immunological control appears to be necessary [2].

Malnutrition has been known to be an important risk factor of postoperative mortality and morbidity [3]. Gynecologic oncologic patients are most effectively treated by radical surgery. Radical surgeries carry a high risk of postoperative complications. These surgeries are followed by a catabolic state characterized by proteolysis, the consumption of ramified amino acids, weight loss, and immunosuppression of a multifactorial origin [3, 4]. Amino acid loss and immunosuppression can provoke organ dysfunction [5] and per-operative nutrition has an important role because of its positive effect on metabolic status, nutritional status, and physiological status of the patients. A primary goal of nutritional intervention is to provide necessary calories and substrates. Another goal of nutritional intervention is to restore optimal metabolic and immune response. This goal is based on the evidence that some specific nutrients, when supplied in the enteral or parenteral diet, produce some effects beyond their basic nutritional value [6]. These nutrients include glutamine, arginine, omega-3 fatty acids, nucleotides, and trace elements [7]. Glutamine influences nitrogen transport between organs and reduces protein catabolism [8]. In addition, glutamine attenuates proinflammatory cytokine responses as well as improves mucosal barrier function and cellular defense. Arginine produces metabolic, immunological and hemodynamic effects via nitric oxide dependent and independent pathways. Trace elements can improve the antioxidant defenses [5].

The aim of this study was evaluate the effects of perioperative immunonutrition for patients undergoing gynecologic oncologic surgery.

Materials and Methods

This study was conducted on patients who had a diagnosis of gynecological malignancy and were admitted to the Department of Gynecologic Oncology, Selçuk University.

This prospective, randomized study was conducted according to the international ethical recommendation on clinical research established by the Helsinki Declaration. All the patients included in the study gave their informed consent. This study includes 50 patients submitted to elective gynecologic oncologic surgery with the standard anesthetic regimen.

The exclusion criteria specified neoplasms treated with radio or chemotherapy, chronic inflammatory bowel diseases, renal insufficiency ( creatinine > 3 mg/dl; hemodialysis), cardiac insufficiency (NYHA > 3), hepatic insufficiency, severe respiratory insufficiency (partial pressure of arterial oxygen PaO₂ < 70 mmHg), current infection, diabetes mellitus receiving medical and dietary treatment, and congenital or acquired immunodeficiency.
**Study protocol**

The patients were randomly assigned to two groups. The randomization was performed using blinded envelopes. Equal numbers of envelopes with protocols for either group 1 or group 2 were prepared in a blinded fashion. The first group received immune-enhancing enteral nutrition (IEN) (Impact, Novartis, Switzerland) for two days before surgery. The amount of non-protein calories was 30 kcal/day. After the intestinal peristalsis started during the postoperative period, the patients received IEN for seven days on postoperative period.

The second group received standard enteral nutrition formula orally (Ensure standard, Abbott, Holland). The nutritional status of the patients was evaluated according to the subjective global assessment (SGA) system [9]. In this system, the patients with normal nutritional status were considered as SGA-A, moderate malnutrition as SGA-B and severe malnutrition as SGA-C.

Daily energy and total protein requirement were calculated as 30 kcal/kg/d and 1 g/kg/d, respectively.

The patients in both groups received 1000 kcal/d enteral nutrition for two days before surgery. After intestinal peristalsis started, 500 kcal/d for the first day and 1000 kcal/d after the second day enteral nutrition were applied in the postoperative period (totally seven days in the postoperative period). Enteral nutrition was received (1000 kcal/d) and total calories were completed by normal hospital food in the two groups.

**Biochemical hematological parameters**

Biochemical and hematological parameters (red blood cell (RBC), white blood cell (WBC), platelet count, hemoglobin (Hgb), hematocrit, PPT, PTT, aPTT) were examined before surgery and 1, 3, 5 and 7 days after surgery.

**Postoperative period**

The groups were compared in terms of length of hospital stay (LOS), postoperative complications, and mortality. The primary end-point were infections which included intraabdominal (abscess, wound infection) and extra-abdominal (pneumonia, endocarditis) sites.

Abnormal chest X-ray with fever (≥ 38°C), and white blood cell count > 15000 cell/mm³ were diagnosed as pulmonary infection. On the other hand, more than 10⁷ microorganisms per ml of urine as a urinary infection and two consecutive positive blood cultures without shock were evaluated as bacteremia. Early disruption of the fascia was defined as wound dehiscence.

**Statistical analysis**

The unpaired t-test was used for comparison between groups. The chi-square test was used for comparison of incidences of postoperative complications; p < 0.05 was considered statistically significant.

Table 1. — Clinical background and other factors of patients in groups.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 25)</th>
<th>Group 2 (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.5 ± 8.6</td>
<td>62.6 ± 5.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.2 ± 12.7</td>
<td>90.9 ± 9.8</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>166.4 ± 21.2</td>
<td>142.6 ± 18.7</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>680.4 ± 56.8</td>
<td>724.8 ± 46.5</td>
</tr>
<tr>
<td>Blood transfusion (n)</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>SGA-A (n)</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>SGA-B (n)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>SGA-C (n)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Endometrial cancer (n)</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Ovarian cancer (n)</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

**Results**

Demographic data, nutritional status, duration of TPN, operation time, anesthesia time, blood loss and blood transfusion were similar between the two groups (p > 0.05) (Table 1).

There were no significant differences in duration of nutritional support between the groups (p > 0.05). The number of patients in SGA-A, SGA-B and SGA-C were 18, five, and two in group 1 and 17, five, and three in group 2, respectively (p > 0.05) (Table 1).

Total lymphocyte count, WBC count, and CRP were significantly higher in group 1 than group 2 in the postoperative period (p < 0.05 for all comparisons, Table 2). Interestingly, we found that albumin and prealbumin were higher in the immunonutrition group than the control group but these results were not statistically significant between groups (p > 0.05) (Table 2). RBC, PTT, PT, aPTT and platelet count, and serum electrolyte levels were similar in both groups (p > 0.05).

Nausea, vomiting, urinary and pulmonary tract infections were similar in both groups, the rate of wound infection (1 patient in group 1, 7 patients in group 2), and wound dehiscence (no patient in group 1, 2 patients in group 2) were significantly lower in group 1 than the control group (p < 0.05 for all comparisons, Table 3).

First defecation occurred on postoperative day 1.5 ± 0.8 in group 1 and 1.9 ± 1.1 in group 2 (p > 0.05). First intestinal peristalsis occurred on postoperative hour 20.6 ± 4.8 in group 1 and on hour 22.4 ± 5.2 in group 2 (p > 0.05) (Table 3).

Table 2. — Changes in immunological markers, prealbumin, albumin and total protein.

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>POD1</th>
<th>POD3</th>
<th>POD5</th>
<th>POD7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg dl⁻¹)</td>
<td>0.6 ± 0.02</td>
<td>0.5 ± 0.03</td>
<td>12.8 ± 3.4</td>
<td>10.8 ± 2.7</td>
<td>22.6 ± 6.1*</td>
</tr>
<tr>
<td>PreAlb (mg dl⁻¹)</td>
<td>21.2 ± 3.4</td>
<td>20.6 ± 4.8</td>
<td>24.6 ± 4.3</td>
<td>21.6 ± 5.1</td>
<td>26.8 ± 3.9</td>
</tr>
<tr>
<td>Albumin (g dl⁻¹)</td>
<td>3.1 ± 1.0</td>
<td>3.3 ± 1.1</td>
<td>3.2 ± 0.3</td>
<td>3.1 ± 0.1</td>
<td>3.5 ± 0.1</td>
</tr>
<tr>
<td>WBC count (×10⁹)</td>
<td>10.8 ± 1.8</td>
<td>9.4 ± 1.2</td>
<td>12.8 ± 1.1</td>
<td>11.4 ± 1.1</td>
<td>11.9 ± 1.0*</td>
</tr>
<tr>
<td>Lym fr (%)</td>
<td>10.2 ± 2.6</td>
<td>9.6 ± 3.1</td>
<td>13.2 ± 4.0*</td>
<td>8.8 ± 3.6</td>
<td>16.4 ± 3.2*</td>
</tr>
</tbody>
</table>

p < 0.05 group 1 (immunonutrition) vs group 2 (control); PreAlb: prealbumin; Value × 1000 in WBC; WBC: white blood cell; Lym fr: lymphocyte fraction.
decreasing intestinal motility with surgical manipulation, gynecologic cancer patients because of intraabdominal and an increase in permeability which may lead to subsequent changes in intestinal morphology and function, intestinal luminal starvation, which in turn in humans leads to changes in metabolic rate and increased protein loss. Gynecologic oncologic surgery is a major surgical procedure and nutrition is an important part of the management of surgical patients [10].

In this study, we used enteral and parenteral nutrition. Intestinal permeability changes have been noted in patients undergoing major surgery for cancer, following multiple traumas, in severe burns and major vascular procedures [11]. Preoperative and early postoperative enteral nutrition help to preserve intestinal motility and permeability, and decrease the incidence of infectious complications [12]. These beneficial effects are supported by a review of randomized clinical trials comparing early with delayed enteral nutrition, indicating that the rate of infectious complications in patients receiving early enteral nutrition after abdominal surgery was significantly lower than that in patients receiving delayed enteral nutrition [13].

A consensus of opinion is emerging that parenteral nutrition per se predisposes patients to an increased incidence of systemic, non-catheter-related infection [11]. This is thought to be related, at least in part, to the fact that this form of nutritional support is synonymous with intestinal luminal starvation, which in turn in humans leads to changes in intestinal morphology and function, and an increase in permeability which may lead to subsequent translocation of endotoxin and bacteria [14].

However, enteral nutrition was not tolerated by many gynecologic cancer patients because of intraabdominal ascites and mass compression of the gastrointestinal tract, decreasing intestinal motility with surgical manipulation, and high incidence of postoperative emesis [15]. We used enteral nutrition in this study and two patients in group 1 and three patients in group 2 did not tolerate enteral nutrition, thus these patients were excluded.

This study demonstrated effects of peroperative immunonutrition on nutritional biomarkers, hematological values, and postoperative complications in gynecologic oncologic patients.

Many studies have demonstrated the effectiveness of immunonutrition in reinforcing immune response, controlling inflammatory response and improving intestinal microperfusion, reducing septic complications and postoperative mortality rates [8, 16-18].

In this study, we used immune-enhancing enteral nutrition and patients continuously received peroperative nutrition with the enteral and parenteral route.

Surgical trauma induces an altered protein metabolism that is characterized by a negative nitrogen balance and changes in the pattern of plasma-free amino acids [19]. Depletion of plasma free amino acids, especially glutamine stores, might lead to severe complications, such as infection, impaired immunity, and poor wound healing [20]. Previous reports have shown that immunonutrition increases T-lymphocyte and B-lymphocyte proliferation and IgG, IgM synthesis [12, 21, 22]. We found that WBC count, total lymphocyte population, and CRP were more increased in group 1 than group 2.

Immunonutrition may have some benefit in preventing postoperative infectious complications because of immunonutrients which may be beneficial for regulating production of inflammatory mediators and B-, T-lymphocyte proliferation [12]. Our study demonstrated that wound infection and wound dehiscence were significantly higher in group 2 than group 1.

Glutamine is an immunonutrient and most abundant free amino acid in plasma and the tissue pool. Glutamine, under normal situations, is readily synthesized and this classifies it as a dietary non-essential amino acid. However, during situations of extreme stress such as surgery, the endogenous supply cannot match increased demand and conditional deficiency develops. Depletion of plasma-free amino acids, especially glutamine stores, might lead to severe complications, such as infection, poor wound healing, impaired immunity and multiple organ failure [20]. The improvement of clinical outcome could be explained by the influence of glutamine on intestinal and immune function. Glutamine modulated inflammatory cytokine production by gut mucosa, decreasing proinflammatory cytokines or increasing anti-inflammatory cytokines and it restores immune defense [5, 18]. In addition, it is metabolized to citrulline and converted to arginine. Arginine is a key substrate for the synthesis of nitric oxide. Arginine has also been shown to improve protein metabolism [21, 23]. Previous studies demonstrated that arginine and glycine had a positive effect on wound healing [22, 24-26]. As for the nutritional parameters, there was only a slight, but not statistically significant, drop in protein, albumin and prealbumin levels in the group given immunonutrition compared

Table 3. — Postoperative complications, LOS, first intestinal peristaltism time and first defecation time.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 25)</th>
<th>Group 2 (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (n)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting (n)</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>First intestinal peristaltism time (hours)</td>
<td>20.6 ± 4.8</td>
<td>22.4 ± 5.2</td>
</tr>
<tr>
<td>First defecation time (days)</td>
<td>1.5 ± 0.8</td>
<td>1.9 ± 1.1</td>
</tr>
<tr>
<td>Urinary infection (n)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Pulmonary infection (n)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Wound infection (n)</td>
<td>1*</td>
<td>5</td>
</tr>
<tr>
<td>Wound dehiscence (n)</td>
<td>0*</td>
<td>2</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>4.1 ± 1.3*</td>
<td>7.8 ± 1.2</td>
</tr>
<tr>
<td>Mortality (n)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*p < 0.05; LOS: Length of stay.

No postoperative mortality occurred. The length of hospital stay was significantly shorter in group 1 (4.1 ± 1.3 days) than group 2 (7.8 ± 1.2 days) (p < 0.05) (Table 3).

Discussion

We evaluated the effects of immunonutrition supplementation on the serum CRP, total protein, albumin, prealbumin, WBC count, lymphocyte count and postoperative complications.

Gynecologic oncologic patients are at risk of nutritional depletion, like other oncologic patients because of inadequate nutritional intake, surgical stress, increased metabolic rate and increased protein loss. Gynecologic oncologic surgery is a major surgical procedure and nutrition is an important part of the management of surgical patients [10].

In this study, we used enteral and parenteral nutrition. Intestinal permeability changes have been noted in patients undergoing major surgery for cancer, following multiple traumas, in severe burns and major vascular procedures [11]. Preoperative and early postoperative enteral nutrition help to preserve intestinal motility and permeability, and decrease the incidence of infectious complications [12]. These beneficial effects are supported by a review of randomized clinical trials comparing early with delayed enteral nutrition, indicating that the rate of infectious complications in patients receiving early enteral nutrition after abdominal surgery was significantly lower than that in patients receiving delayed enteral nutrition [13].

A consensus of opinion is emerging that parenteral nutrition per se predisposes patients to an increased incidence of systemic, non-catheter-related infection [11]. This is thought to be related, at least in part, to the fact that this form of nutritional support is synonymous with intestinal luminal starvation, which in turn in humans leads to changes in intestinal morphology and function, and an increase in permeability which may lead to subsequent translocation of endotoxin and bacteria [14].

However, enteral nutrition was not tolerated by many gynecologic cancer patients because of intraabdominal ascites and mass compression of the gastrointestinal tract, decreasing intestinal motility with surgical manipulation,
References


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Analysis of the results and long-term follow-up of second-look laparotomy in advanced ovarian cancer

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Department of Gynecology and Gynecologic Oncology, Medical University of Gdansk (Poland)

Summary

Objective: The goal of the study was to analyze results of 171 second-look laparotomy and compare survival of patients with advanced ovarian cancer depending on SLL results. Results: We obtained the following results: complete pathologic response (CPR) – 56.2% (96 patients), microscopic disease (Rmicro) – 12.8% (22 patients), macroscopic disease (Rmacro) – 31% (53 patients). In patients with negative SLL results disease recurrence was diagnosed in 38.5%. We compared survival in separate groups of patients depending on SLL results: no difference between the CPR group and Rmicro group. Significantly longer survival of patients in the Rmicro group was found compared to patients with recurrence after negative SLL. There were no differences between the group with recurrence after negative SLL and the Rmacro group. Conclusions: An important observation is that the survival rate in patients with recurrence after negative SLL was significantly lower compared to patients with microscopic disease. The probable explanation for favorable prognosis in the group with microscopic disease was early administration of chemotherapy after SLL.

Key words: Ovarian cancer; Second-look laparotomy; Complete clinical remission.

Introduction

One of the most problematic issues in ovarian cancer treatment is the lack of reliable methods to evaluate response to first-line chemotherapy. Despite diagnosis of complete clinical response a large percentage of patients in reality have residual disease, usually in the form of small volume disease. Second-look laparotomy (SLL) is the only procedure which enables us to precisely identify this group of patients. The biggest concern regarding second-look laparotomy is the lack of confirmed advantage in survival of patients undergoing SLL compared to the group with clinical follow-up after achieving clinical remission. Available data is insufficient to unequivocally conclude what the impact of second-look laparotomy in ovarian cancer patients is [1-6]. In the recent most reliable reports from Greer et al. and Rahaman et al. conclusions regarding the role of the SLL are partially inconsistent. In the non-randomized comparison of optimally debulked patients from Greer et al. there was no impact of SLL on patient survival [5]. In the study of Rahaman et al. in a subgroup of patients with suboptimal debulking at primary surgery who had a SLL procedure had significantly longer survival compared to patients refusing SLL [6].

Nevertheless SLL does enable early treatment of persistent disease, which is one of the essential principles in oncology. Lack of the confirmed efficacy of SLL is caused by ineffective second-line chemotherapeutics - it is probable that if new drugs are developed the use of SLL will be discussed once again.

In this study we have analyzed the results of second-look laparotomy and compared the survival of particular groups of patients depending on SLL results.

Patients and Methods

From January 1990 to December 2002 at the Department of Gynecology, Medical University of Gdansk, 793 patients with an initial diagnosis of ovarian cancer were operated on. During this period a group of 171 patients, FIGO Stage II-IV, with complete clinical remission underwent SLL. Complete clinical remission after accomplishing first-line chemotherapy was assessed using the following criteria: no abnormalities in the physical and gynecologic examination, CA125 serum concentration up to 35 IU/ml and no changes in available imaging procedures. This group of patients was included in the analysis. Patients with other malignancies were excluded. Data regarding the analyzed population are summarized in Table 1.

Overall perioperative morbidity was 14.1% - intraoperative complication rate was 3.2% and postoperative complication rate was 10.9%. There was no death due to perioperative complications in the analyzed population.

Complete data regarding survival was obtained in all 171 patients. The mean observation time was 2006.5 days (range 184-6130 days). Survival times were calculated from the time of diagnosis until the date of death or last contact. Actuarial survival curves were obtained using the Kaplan Meier method and comparisons of survival were performed with the log-rank and chi-square tests. In this study, a p value of 0.05 or less was considered significant.

Results

In the group of the 171 patients undergoing SLL we obtained the following results:

- Complete pathologic response (CPR) – 56.2% (96 patients).
Analysis of the results and long-term follow-up of second-look laparotomy in advanced ovarian cancer

- Microscopic neoplastic disease (R\textsubscript{micro}) - 12.8% (22 patients).
- Macroscopic neoplastic disease (R\textsubscript{makro}) - 31.0% (53 patients).

The 5-year survival rate for the entire population was 50.8%; the 5-year survival for the group with complete pathologic response was 66.6% and for persistent neoplastic disease it was 30.5% (microscopic disease – 49.6%, macroscopic disease – 22.6%). Additionally a subgroup with recurrence after complete pathologic remission was isolated – 5-year survival in this group was 24.3%. The recurrence diagnosis was based on the gynecologic examination, CA125 level and imaging procedures. In the group of patients with negative SLL result (n = 96) in 38.5% of these cases (37 women) disease recurrence was diagnosed. The mean disease-free survival in this group was 1465.2 days (range 412-4684 days).

We compared survival curves in separate groups of patients depending on the SLL result. The following results were obtained:

1) Statistically significant longer survival of patients with complete pathologic response (n = 96) compared to patients with macroscopic disease (n = 53), CPR > R\textsubscript{makro}, p < 0.001.

2) Statistically significant longer survival of patients with microscopic disease (n = 22) compared to patients with macroscopic disease (n = 53), R\textsubscript{micro} > R\textsubscript{makro}, p = 0.002.

3) No difference was found in survival between patients with complete pathologic response (n=96) and patients with microscopic disease (n = 22), CPR vs R\textsubscript{makro}, p = 0.382.

From the group of patients with negative SLL results we isolated women with disease recurrence. The outcomes in this group (Recurrence) were compared with the survival of patients with persistent disease (R\textsubscript{micro} and R\textsubscript{makro}):

4) Statistically significant longer survival of patients with microscopic disease (n = 22) compared to patients with recurrence (n = 37), R\textsubscript{micro} > Recurrence, p = 0.024.

5) No difference was found in survival between patients with recurrence (n = 37) and patients with macroscopic disease (n = 53), Recurrence vs R\textsubscript{makro}, p = 0.024.

Discussion

The results of SLL in the literature have remained consistent through the past years.

A comparison between the published series of SLL procedures is difficult because of the different distribution of prognostic factors. Usually during SLL persistent disease is found in 23-70% of cases – in our series this rate was 43.8% [5-22]. These results show that SLL is so far the most accurate method of evaluating response for first-line therapy in the group of patients with complete clinical remission.

In our study the outcome in separate groups of patients after SLL could indirectly confirm the potential benefits of early treatment of patients with persistent disease. The relationship between survival rates in patients depending on SLL results observed in our study are comparable to data in the literature [21, 23, 24]. The only unexpected relation was no difference in survival rates between patients with pathologic remission and patients with microscopic disease (R\textsubscript{micro}). A probable explanation is that the survival rate in the group with pathologic remission was influenced by the subgroup of patients who developed recurrence. A very interesting and important observation from our study is that the survival rate in patients with recurrence was significantly lower compared to patients with microscopic disease (Figure 1). Certainly poor prognosis in the recurrence group was expected but at the time of the second-look laparotomy (Recurrence and R\textsubscript{micro}) the extent of disease was comparable in both groups. In the recurrence group the result of the SLL could have been false-negative or the SLL pro-
cEDURE was not sensitive enough at that time to detect per-
sistent disease. The main difference between these two
groups was the time of introducing second-line therapy.
The probable explanation for favorable prognosis in the
group with microscopic disease was the early administra-
tion of chemotherapy after SLL as opposed to the recur-
rence group where treatment was delayed until clinical
evidence of disease.

These data suggest that early administration of therapy,
based on the results of SLL, can result in improved out-
come. This issue will probably remain unresolved as it is
not possible to verify these findings using a random-
ized study due to ethical concerns – one group of patients
after SLL with persistent disease did not receive
chemotherapy until the presence of clinical manifestation
of disease. It is important to note that the only group that
benefited from second-look laparotomy were the patients
with persistent disease. The early administration of
chemotherapy after SLL can improve survival rate in this
group and despite lack of proven efficacy such treat-
ment is reasonable and generally acceptable. Second-look
laparotomy gives the opportunity of beginning therapy
before there are any clinical signs of disease and allows
potential tumor growth to be avoided.

Another limitation of the SLL is the fact that a large
number of patients will develop recurrence after a nega-
tive result of SLL. In our study recurrence rate was
38.5%. In other studies analyzing second-look proce-
dures the recurrence rate ranged from 19.5-56.8% [7-18,
25, 26] – such variance is due to the different distribution
of prognostic factors. A high recurrence rate reflects the
very aggressive biology of ovarian cancer rather than a
possibility of a high-false negative rate in the group with
pathologic remission.

Because of the high recurrence rate the negative result
of SLL has low prognostic significance and all these
patients need to undergo adequate follow-up. So far
studies analyzing consolidation therapy have not con-
irmed its beneficial effect [27] but in the future after the
implementation of new therapies such treatment should
be reconsidered.

In conclusion, the most important advantage of SLL is
the possibility of an early administration of therapy in
cases with persistent disease which could potentially
influence the outcome in this subgroup of patients. An
important and unresolved issue is the high rate of recur-
rence after pathologic remission. Because of unconfirmed
efficacy of the consolidation therapy the only strategy for
these patients is careful follow-up. At this moment
second-look laparotomy, although not recommended as
the standard of care, can be proposed, especially for
patients with a high risk of persistent disease [25]. More-
over SLL, as the most sensitive method to assess
response after first-line treatment, should be considered
in clinical trials. It needs to be remarked that the uncon-
firmed impact of SLL on survival is not a result of SLL
in itself, which is mainly a diagnostic procedure, but the
lack of effective second-line chemotherapy.

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Peritoneal tuberculosis mimicking peritoneal carcinomatosis

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Department of Obstetrics and Gynecology, Uludag University Medical Faculty, Bursa (Turkey)

Summary

Purpose: The data of 11 peritoneal tuberculosis (TB) patients is discussed in an attempt to better understand this disease. Methods: Nine patients with clinical features mimicking ovarian cancer and two with infertility were evaluated retrospectively. Results: The mean age was 40.8 ± 18.3 years. None had any past/family history of TB. Abdominal swelling and pain, appetite loss, nausea/vomiting, and primary infertility were the most common complaints. Chest X-ray suggested TB in one cachexic patient. Six patients had ovarian/primary peritoneal cancer on laparotomy. Laparoscopy was performed to determine therapeutic modality in one patient and for primary infertility in one patient. Three patients were not operated because of suspected TB in one and neoadjuvant chemotherapy in two with poor performance scores. They underwent peritoneal or omental biopsies; histopathology revealed caseous granulomatous TB lesions. Mycobacterium tuberculosis was identified in only two ascitic fluid cultures. Conclusion: Peritoneal TB should be suspected in endemic areas, especially in young patients considered to have peritoneal carcinomatosis.

Key words: Peritoneal tuberculosis; Peritoneal carcinoma; Ovarian carcinoma.

Introduction

Almost one-third of the world population harbors Mycobacterium (M.) tuberculosis infection, and 10% of these people will become symptomatic during their lifetime. Nearly 8-10 million new tuberculosis (TB) cases are diagnosed each year, and 2-2.5 million TB patients succumb to the disease [1]. In 1993, the WHO declared for the first time that TB was a global health emergency [2]. Almost 10-20 million Turkish people are estimated to have been infected with M. tuberculosis. The incidence rate of TB is < 20/100,000 and 100-300/100,000 in the developed and developing countries, respectively, and 30-40/100,000 in Turkey [3, 4].

M. tuberculosis mostly affects the lungs, but in 30% of cases it may spread to other organs [5]. Peritoneal TB is especially important because it has the same clinical picture as ovarian or primary peritoneal carcinoma, and misdiagnosis leading to delay in initiating appropriate treatment can be harmful to the patients [6]. Peritoneal TB presents with nonspecific signs and symptoms such as abdominal distention and pain, and ascites or as a nodular pelvic mass at gynecological examination. Anemia, leukocytosis, and increased erythrocyte sedimentation rate are nonspecific markers of infection and are not useful in detecting the disease. Furthermore, imaging modalities have remained unsatisfactory in discriminating peritoneal TB thus far. Therefore, suspicion of TB is considered a milestone in a patient’s disease progression.

Here, we present and discuss the data of 11 peritoneal TB patients from the viewpoint of increasing the awareness and understanding of the disease.

Materials and Methods

We retrospectively evaluated nine patients admitted to the Department of Obstetrics and Gynecology, Uludag University Medical Faculty, between 2003 and 2007 with symptoms and signs suggestive of ovarian cancer and two others with complaints of infertility. Pelvic examination, ultrasonography (US), computerized tomography (CT), and serum tumor markers also suggested ovarian neoplasia in all patients, except in one with incidental perioperative findings. Primary surgery was performed in eight patients, and neoadjuvant chemotherapy was planned for two patients who underwent biopsies. All patients were administered anti-TB treatment upon histopathological diagnosis.

Results

Abdominal swelling and pain, loss of appetite, nausea and vomiting were the most common complaints at admission (Table 1). The mean age of the patients was 40.8 ± 18.3 years (mean ± S.D.). After excluding the two patients with primary infertility, the gravida, parity, and abortion values were 2.3 ± 1.4, 1.9 ± 1.3, and 0.4 ± 0.7, respectively. Menstrual cycles were regular in all patients except in two menopausal patients and in one patient with regular cycles but heavy bleeding. The mean duration of complaints was 4.67 ± 1.87 months (Table 1). Past history included left nephrectomy and migraine in one patient each; family history included diabetes mellitus (2 patients) as well as gastric and colon cancer (1 patient each). None of the patients had a past or family history of TB. At admission, the mean hemoglobin level was 11.8 ± 1.5 g/dl, leukocyte count was 7019.1 ± 1907.4 /μl, and platelet count was 294.9 ± 55.8 × 10^9/μl. One of the patients was thought to have hepatic TB because of the following serum levels: fasting glucose, 120 mg/dl; AST, 222 U/l; and ALT, 273 U/l. She responded to anti-TB treatment. After excluding this case, the mean serum levels were as follows: fasting glucose, 87.30 ± 6.80 mg/dl; urea, 27.6 ± 9.1 mg/dl; creatinine, 0.7 ± 0.2 mg/dl; AST, 32.40 ± 17.37 U/l; and ALT, 23.00 ± 7.89 U/l.
On physical examination, abdominal distention was observed in seven patients, and cachexia was present in one patient. Lower genital tract examination revealed no abnormalities, except atrophy in two patients. The uterus was not palpable in four patients due to abdominal distention, but was normal in the remaining seven patients. A solid mass with an irregular surface occupied the pelvis in one patient, and multiple implantations could be palpated on the pelvic peritoneum in two patients. In the remaining patients, no structure was palpable on adnexal examination due to abdominal distention. Chest X-ray findings were suggestive of TB in only one cachexic patient but were normal in the remaining patients. All cervical smears were negative for neoplasia. The other clinical characteristics of the patients at admission are shown in Table 1.

Colonoscopic examination of four patients revealed diminutive polyps, one in the cecum and the other in the rectum in two patients; an ulcer in the proximal ascending colon, which was found to be benign on biopsy, in one patient; and external rectal compression in one patient. The findings were normal in the remaining four colonoscopies and in eight esophagogastroduodenoscopies. Gastrointestinal endoscopy was not performed in three patients.

The tuberculin skin test was negative in five patients and was not performed in six patients. Laparotomy was performed with a preoperative diagnosis of ovarian or primary peritoneal cancer in six patients. Laparoscopy was performed to determine between neoadjuvant chemotherapy or cytoreductive surgery and for primary infertility in one patient each. Three patients did not undergo surgery because chest X-ray findings raised the suspicion of TB in one patient and neoadjuvant chemotherapy was planned for two patients because of their poor performance scores. Of these three patients, two underwent peritoneal biopsies and one underwent omental biopsy; the histopathology examination found caseous granulomatous lesions of TB in the samples from all three patients. In all patients, the ascitic fluid was exudative and had lymphocyte predominance. Acid-fast staining of the ascitic fluid was negative in six patients and was not performed in five patients. Ascitic fluid cultures for *M. tuberculosis* were positive only in two patients. The surgical procedures and pathological results of the patients are shown in Table 2.

All patients were referred to the Department of Chest Disease and combination therapy comprising isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin was given. The patient with microinvasive serous carcinoma additionally received three courses of chemotherapy including 75 mg/m² cisplatin and 135 mg/m² paclitaxel.

Discussion

*M. tuberculosis* mostly involves the lungs, but in 30% of cases it may spread to the other organs [5]. Genitourinary organs, mainly the fallopian tubes, are the most common sites of spread. Peritoneal TB is of considerable importance since it accounts for 4% of all extrapulmonary disease [7]. Infertility is known to be a common consequence of TB; two of the 11 patients discussed herein had complaints of primary infertility at admission to our department. One had undergone laparoscopy, while the other had undergone laparotomy because solid-
Table 2. — Surgical procedures and pathological results of the patients.

<table>
<thead>
<tr>
<th>Name</th>
<th>Operation</th>
<th>Perioperative findings</th>
<th>Frozen section</th>
<th>Permanent section</th>
<th>Peritoneal cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>SK</td>
<td>n.o.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>benign</td>
</tr>
<tr>
<td>MA</td>
<td>n.o.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>benign</td>
</tr>
<tr>
<td>NO</td>
<td>L/T: multiple biopsies</td>
<td>t.p., &lt; 1 cm m.w.g.n. on uterine and tubal serosa</td>
<td>c.g.l.</td>
<td>c.g.l., TB</td>
<td>benign</td>
</tr>
<tr>
<td>KS</td>
<td>L/T: omental biopsy</td>
<td>ascites, t.p., omental cake, &lt; 1 cm m.w.g.n. on intestinal serosa</td>
<td>benign</td>
<td>c.g.l., TB</td>
<td>benign</td>
</tr>
<tr>
<td>BK</td>
<td>L/S: bilateral salpingectomy &amp; adhesiolysis</td>
<td>ascites, t.p., d.a., bilateral hydropic fallopian tubes</td>
<td>N.A.</td>
<td>c.g.l., TB</td>
<td>benign</td>
</tr>
<tr>
<td>HO</td>
<td>L/T: left USO</td>
<td>d.a., 1-2 cm m.w.g.n. on peritoneum &amp; left ovary</td>
<td>c.g.l.</td>
<td>c.g.l., TB</td>
<td>benign</td>
</tr>
<tr>
<td>SU</td>
<td>L/T: myomectomy &amp; adhesiolysis</td>
<td>ascites, t.p., d.a., leiomyomas (6 × 4 cm and 5 × 4 cm), smooth masses in the right (10 × 10 cm) and left (4 × 4 cm) adnexal regions, &lt; 1 cm m.w.g.n. on uterine serosa</td>
<td>benign</td>
<td>leiomyoma/c.g.l., TB</td>
<td>benign</td>
</tr>
<tr>
<td>OA</td>
<td>n.o.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>benign</td>
</tr>
<tr>
<td>AV</td>
<td>L/S: multiple biopsies</td>
<td>ascites, t.p., &lt; 1 cm m.w.g.n. on peritoneum</td>
<td>c.g.l.</td>
<td>c.g.l., TB</td>
<td>benign</td>
</tr>
<tr>
<td>RS</td>
<td>L/T: multiple biopsies</td>
<td>ascites, t.p., d.a., solid-cystic masses in the right (4 × 4 cm) and left (2 × 2 cm) adnexal regions, t.p., &lt; 1 cm m.w.g.n. on peritoneum</td>
<td>c.g.l.</td>
<td>c.g.l., TB</td>
<td>benign</td>
</tr>
<tr>
<td>NU</td>
<td>L/T: BSO + BPPLND + Omen + Appen</td>
<td>cystic-solid masses in the left (15 × 13 cm) and right (8 × 7 cm) adnexal regions, bilateral hydropic fallopian tubes</td>
<td>borderline tumor, right ovary</td>
<td>s.b.t. and focal m.s.c.</td>
<td>benign</td>
</tr>
</tbody>
</table>

n.o.: not operated, N.A.: not available, L/T: laparotomy, L/S: laparoscopy, USO: unilateral salpingo-oophorectomy, BSO: bilateral salpingo-oophorectomy, BPPLND: bilateral pelvic and paraaortic lymphadenectomy, Omen: omentectomy, Appen: appendectomy, m.w.g.n.: multiple white granulomatous nodules, t.p.: thickened peritoneum, d.a.: dense adhesions, c.g.l.: caseous granulomatous lesions, TB: tuberculosis, s.b.t.: serous borderline tumor, m.s.c.: microinvasive serous carcinoma.

cystic masses (measuring 8.0 × 6.0 cm², 3.5 × 1.5 cm², and 1.0 × 6.0 cm²) were detected in the pelvis preoperatively. The histopathological diagnosis from permanent sections was peritoneal TB.

The microorganism may stay dormant for a long time and can easily invade the abdominal viscera upon activation. The microorganism may originate from its primary focus in the lungs and may spread hematogenously or may primarily infect the intestines and rarely the liver via ingestion of contaminated food [8, 9]. *M. tuberculosis* colonizing the colon may invade mesenteric lymph nodes resulting in their ulceration or rupture and the subsequent release of the organism into the peritoneal cavity. In the present study, none of the endoscopy findings were reminiscent of gastrointestinal colonization. The primary lesion of *M. tuberculosis* may disappear during the latent period, and the disease may escape diagnosis until the patient develops symptoms and signs of intraabdominal carcinoma [9]. Among the 11 patients, only one patient showed chest X-ray changes compatible with TB.

On physical examination, the most evident sign of peritoneal TB is ascites and abdominal distention [9, 10]. Pelvic examination frequently reveals adnexal masses or implantations on the pelvic peritoneum [11-14]. However, peritoneal TB may present in either the wet or dry form. While the wet form is most common and presents with ascites and inflammation of the serosal surfaces, the dry form is devoid of ascites and is less common. We observed ascites and abdominal distention in eight patients; in these patients, the peritoneum was inflamed with thickening of the mesentery and omentum and formation of septa between the viscera. The two patients with primary infertility and another with an adnexal cyst and serosal nodularities were free of ascites.

A tuberculin skin test can be used for the diagnosis of TB, and a strongly positive test indicates the presence of *M. tuberculosis* in the active form. Discriminating the weakly positive test, which is observed in vaccinated individuals, is especially important because vaccination against TB in infancy and thereafter is mandatory in Turkey. However, the tuberculin skin test has been reported to have only 55% sensitivity and 80% specificity [15]. Because we thought that the great majority of the patients would have been vaccinated, we performed the test in only five patients; surprisingly, all tested negative.

Because surgery is not indicated in most cases, paracentesis for bacterial culture, acid-fast staining and polymerase chain reaction (PCR) analysis, and image-guided percutaneous biopsy for histopathological examination are recommended in suspicious cases [16]. However, only one patient was suspected of having TB based on chest X-ray findings, and the remaining nine patients were diagnosed with ovarian or primary peritoneal carcinoma.

In the present study, ascitic fluid cultures were positive in only two of eight patients. *M. tuberculosis* was reported to be cultured in 20%-83% of cases in the literature [1, 6, 7]. PCR analysis of ascitic fluid can be performed rapidly and has 93% sensitivity and 84% specificity; however, it is expensive and is not commonly used [17, 18]. Ascitic fluid may also be examined for the presence of *M. tuberculosis* by Ziehl-Neelsen staining for acid-fast bacilli, but the sensitivity of the test is just 3.2% [19]. Bacteriological evaluation of the ascitic fluid and peritoneum and histopathological evaluation of biopsy specimens are necessary for a definitive diagnosis [20-23].

Measurement of ascitic fluid adenosine deaminase (ADA) has been recommended as a noninvasive method to rule out malignancy [24, 25]. ADA is a marker of T-
lymphocyte and macrophage activity and has 100% sensitivity and 96% specificity.

In many studies, the serum CA125 level was reported to increase in such patients, but it is a rather nonspecific marker. Serum CA125 levels may increase not only in peritoneal TB but also in ovarian, primary peritoneal, and many other malignancies [13, 22, 24, 26, 27]. High serum levels may accompany all conditions associated with peritoneal or serosal surface inflammation, such as endometriosis, pelvic inflammatory disease, and pancreatitis [20, 28-30]. However, when high serum CA125 levels are accompanied by ascites and a pelvic mass, ovarian carcinoma should be suspected, unless proven otherwise [31]. Preoperative gastrointestinal endoscopy and CT of the whole abdomen can exclude gastrointestinal carcinoma, as in our case. High levels of serum tumor markers have value in follow-up examinations rather than in the diagnosis of peritoneal carcinomatosis or TB. In the present study, serum CA125 levels were high in all patients, CA15.3 was high in seven, and CA19.9 was high in one; these levels normalized after anti-TB treatment. Some authors have proposed that a serum CA125 level < 500 U/ml indicates peritoneal TB, but our observations as well as those of others do not support this view [20, 30]. We found a high serum AFP level in a patient with elevated serum levels of AST, ALT, and fasting glucose. She responded to anti-TB treatment, and the serum levels normalized after two months; hence, she was thought to have hepatic TB.

Although endometrial biopsy was reported to reveal genital TB, its sensitivity is at best 50% (32). We detected endometrial fluid at US in three patients. Of these, one had suspicious chest X-ray findings and was diagnosed with peritoneal TB following US-guided peritoneal biopsy. The other two patients were thought to have ovarian or primary peritoneal carcinoma and underwent laparotomy. Left salpingo-oophorectomy with multiple peritoneal biopsies was performed in one patient, and peritoneal TB was diagnosed from frozen sections. The other patient underwent bilateral salpingo-oophorectomy, bilateral pelvic and paraaortic lymphadenectomy, omentectomy, and appendectomy because bilateral microinvasive ovarian serous carcinoma was diagnosed from the frozen sections, while peritoneal TB was diagnosed from the permanent sections. The uterus was retained in all three patients, and the endometrial fluid disappeared after the institution of anti-TB treatment.

In peritoneal TB, US and CT show particulate or septated ascites, thickening of the peritoneum, omentum, and intestinal serosa, peritoneal implantations, lymphadenomegaly, and sometimes adnexal solid-cystic masses [33]. ([18F]-Fluorodeoxyglucose positron emission tomography has been reported to be useful in the diagnosis of peritoneal TB, but some authors have reported opposite findings [34]. The high cost of this imaging technique should also be considered.

Peritoneal TB peaks at the age of 20-40 years, which is earlier than that in ovarian or primary peritoneal carcinoma [20]. The mean age of the current patients was 40.8 ± 18.3 years and is compatible with that reported in the literature. Laparoscopy may be the diagnostic modality of choice in young patients with suspicious clinical features of ascites, high serum CA125 levels, and multiple peritoneal implantations. Perioperative inspection may reveal ascites, septa formation, and miliary implantations on the peritoneum and viscera, which are not definitive findings, but multiple biopsies can be taken for frozen section examination. When the diagnosis of cancer is confirmed through frozen section, the patient can undergo appropriate surgery either by laparoscopy or laparotomy, based on the perioperative findings. However, when the frozen section reveals TB, laparoscopy should be terminated in most cases to prevent postoperative complications. Such an approach may prevent unnecessary extensive surgery and the associated morbidity in patients with peritoneal TB. Among the present patients, six had undergone laparotomy and only two had undergone laparoscopy.

The relatively large number of articles on peritoneal TB originating from Turkey may indicate the high incidence rate of the disease. In Turkey, law dictates that TB patients be reported to the Ministry of Health, and treatment is free of charge and mandatory as well as the vaccination. Although TB has been traditionally accepted as a disease associated with poverty, it is surprising that patients are reported from the biggest and most industrialized cities of Turkey. This could be due to the increased rate of immigration from the endemic parts to the industrialized parts of the country due to economic reasons. Local authorities are facing problems in implementing public health and sanitation programs due to budgetary constraints compounded by unbridled urbanization.

Conclusion

Peritoneal TB should be suspected in endemic areas, especially in young patients suspected of having peritoneal carcinomatosis. Imaging techniques are not adequately accurate in discriminating peritoneal TB. Although bacteriological diagnosis may be helpful, it has its limitations and is not diagnostic in most cases. Serum CA125 and CA15.3 levels are of no value in the diagnosis but may be relevant in the follow-up examination of TB patients. When paracentesis is not diagnostic, laparoscopy may be performed to obtain biopsy specimens for frozen section examination, thereby avoiding extensive surgery.

References


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Estrogen receptor α (ER-α) gene polymorphism in patients from the Lodz region of Poland with sporadic endometrial cancer

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Summary

Objective: Estrogens play a crucial role in the pathogenesis and progression of endometrial cancer. The gene ER-α is polymorphic and gene variability could contribute to the level of protein biosynthesis. Methods: The aim of this study was to evaluate PvuII and XbaI polymorphism of the ER-α gene in 120 postmenopausal women with endometrial cancer in DNA samples obtained from cancer tissue. The polymorphisms were determined by PCR-RFLP methods. Results: The distribution of the genotypes of PvuII and XbaI polymorphism of ER-α in both controls and patients did not differ significantly from those predicted by the Hardy-Weinberg distribution. There were no significant differences in genotype distributions and allele frequencies between subgroups assigned to histological stage. Conclusions: The results suggest that the PvuII polymorphism of ER-α gene as well as XbaI polymorphism may not be linked with appearance and development of endometrial cancer.

Key words: Estrogen receptor α; Gene polymorphism; Endometrial cancer; PCR-RFLP.

Introduction

Endometrial cancer is one of the most common malignant neoplasms that appear in the uterine corpus [1]. About 80% of cases are diagnosed after menopause. The highest incidence estimated at 57-58 years is moving to the 6th and 7th decade of life at present [2]. Endometrial cancer is the fourth most common female carcinoma [3]. Annually 150,000 new cases of this cancer are noted worldwide. Every year in the age group 65-75 years, 65 new cases of endometrial cancer are diagnosed among every 100,000 women.

Some risk factors have been identified, related to reproduction (such as early age at menarche, late age at menopause and nulliparity) or more directly estrogen-related (i.e., conditions such as polycystic ovarian syndrome) [2, 4].

The estrogen receptor (ER) is an important mediator of hormonal response in estrogen-sensitive tissues such as the endometrium, breast, and bone. Since ER functioning is reflected in the proliferation of these tissues, it is plausible that variation in the function of the receptor could have clinically significant effects.

Polymorphisms in the ER gene, hypothetically related to biological function, have inconsistently been associated with bone density [5-11] but seem not to be related to breast cancer risk [10-17]. There are two known ERs, ER-α and ER-β.

ER-α expression has been used in clinical practice as an indicator for selecting hormone therapy and loss of ER expression is often associated with poor survival.

Changes in ER-α biosynthesis are usually proceeded by changes in its gene transcription and mRNA level. Gene variability could contribute to the level of estrogen receptor biosynthesis [18]. Of the known polymorphisms of the ER-α gene, PvuII, XbaI, and the recently identified (GT)n polymorphism have been reported to be associated with breast cancer risk [19, 20]. The three polymorphisms are located in different areas of the ER-α gene. The GT repeat polymorphism is located at 2.8 kb to exon 1D, and PvuII and XbaI are located on intron 1. These polymorphisms are not in close linkage disequilibrium in the Chinese population [20]. Cai et al. suggest the presence of the (GT)n or (GT)2 allele of GT polymorphism, or PP allele of PvuII polymorphism to an reduced risk of breast cancer in the Chinese population [20]. Moreover, variants of the ER gene may be associated with an altered risk of endometrial cancer [21]. Since ER-α is an important mediator of hormonal responses such as proliferation in estrogen-sensitive tissues, we hypothesized that polymorphisms in the ERα gene could be functional and associated with endometrial cancer risk.

In the present work the distribution of genotypes and frequency of alleles of the ER polymorphism in subjects with endometrial cancer were investigated.

Materials and Methods

Endometrial cancer samples

One hundred and twenty patients with a histologically proven diagnosis of endometrial cancer were included in the study (mean age ± SD 63.75 ± 4.72 years). Tumor tissues were obtained from postmenopausal women with endometrial carcinoma treated at the Department of Obstetrics and Gynecology at the Medical University in Lodz between 2006 and 2007.

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Tissues were frozen immediately and stored at −70°C. All tumors were staged according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO). There were 21 Stage I tumors, 62 Stage II and 37 Stage III in total. DNA from normal endometrial tissue (n = 120) served as a control.

DNA was extracted using the commercially available QIAamp Kit (Qiagen GmbH, Hilden, Germany) DNA purification kit according to the manufacturer’s instructions.

Determination of ER-α genotype. PvuII and XbaI genotypes were established for each subject by the PCR-RFLP method. Primer sequences were as follows: forward, 5'-CTG CCA CCC TAT CTG TAT CTT TTC CTA TTC TCC-3' and reverse, 5'-TCT TCT TCT GCC ACC CTG GCG TCG ATT ATC TGA-3'. After amplification, all samples were digested overnight with PvuII and XbaI restriction endonuclease. PP and XX, signifying the absence of restriction sites, gave one 1.3-kb fragment; pp, signifying the presence of PvuII restriction sites on both alleles, was digested into two fragments (0.85 and 0.45 kb). The xx genotype was revealed by XbaI digestion into two fragments (0.9 and 0.4 kb).

The PCR was carried out in a 25 μl reaction mixture containing 200 ng genomic DNA, 2.0 mM magnesium chloride, 250 μM dNTPs, 0.5 μM of each primer, and 0.5 U Tag DNA polymerase. All PCR was carried out in a DNA Thermal Cycler (GeneAmp PCR System 2400; Perkin-Elmer, Norwalk, CT). Statistical analysis. The allelic frequencies were estimated by gene counting and genotypes were scored. The observed numbers of each PvuII and XbaI genotype were compared with that expected for a population in Hardy-Weinberg equilibrium by using a chi-square test. The significance of the differences of observed alleles and genotypes between groups was tested using chi-square analysis; p values < 0.05 were considered significant.

Results

From the PCR analysis, all the patients and controls were divided into three genotypes of the ER-α gene: pp, Pp and PP. Table 1 shows genotype distribution between endometrial cancer patients and controls. Neither distribution differed significantly (p > 0.05) from those predicted by the Hardy-Weinberg equilibrium. Additionally, there were no differences in the frequencies of the P and p alleles between patients and controls.

Distributions of the xx, xX and XX genotypes of the ER-α gene as well as the frequencies of the x and X alleles for endometrial cancer subjects and controls are displayed in Table 2. It can be seen from the table that there were no significant differences between these two groups in both genotype distribution and allele frequencies (p > 0.05).

Table 2. — Distribution of xx, xX and XX genotypes and frequencies of the x and X alleles of ER-α in patients with endometrial cancer (n = 120) and controls (n = 120).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Endometrial cancer patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Frequency</td>
</tr>
<tr>
<td>xx</td>
<td>22</td>
<td>0.18</td>
</tr>
<tr>
<td>xX</td>
<td>70</td>
<td>0.58</td>
</tr>
<tr>
<td>XX</td>
<td>28</td>
<td>0.23</td>
</tr>
</tbody>
</table>

p < 0.05 as compared with Hardy-Weinberg distribution; *p > 0.05 as compared with the controls.

Table 3. — Dependency of genotypes and frequencies of the alleles of PvuII and XbaI gene polymorphism on the tumor stage in patients with endometrial carcinoma.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Genotype</th>
<th>I (n = 21)</th>
<th>II (n = 62)</th>
<th>III (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>Frequency</td>
<td>Number</td>
</tr>
<tr>
<td>pp</td>
<td>6</td>
<td>0.29</td>
<td>14</td>
<td>0.23</td>
</tr>
<tr>
<td>Pp</td>
<td>14</td>
<td>0.67</td>
<td>29</td>
<td>0.47</td>
</tr>
<tr>
<td>PP</td>
<td>1</td>
<td>0.04</td>
<td>19</td>
<td>0.31</td>
</tr>
</tbody>
</table>

p < 0.05 as compared with Hardy-Weinberg distribution; *p > 0.05 as compared with the controls.

Discussion

Estrogen mediates cellular growth and differentiation in tissues such as the endometrium, mammary gland, bone, cardiovascular system, brain and urogenital tract in men and women [22-24], with intracellular ER functioning as a hormone-dependent transcriptional regulator [25]. Polymorphisms in the ER have been studied mostly in relation to bone mass and mammary cancer. Postmenopausal breast cancer patients with positive ER tumor status have higher bone-mineral density. Positive ER tumor status may be associated with higher cumulative exposure to estrogen [26].
PvuII and XbaI polymorphism of the ER-α gene are associated with cardiovascular disease risk [27], and possibly modify the effects of estrogens on HDL cholesterol level and changes in bone mineral density [28] and vertebral fractures [29]. Women with Pp genotype who received hormone replacement therapy had a significantly more pronounced response in outcome than women with other genotypes (i.e., a greater increase in HDL cholesterol levels and bone mineral density). These studies suggest that this polymorphism may have an interactive effect with hormones.

Reports on associations between PvuII and XbaI polymorphisms and bone mineral density are inconsistent. While in some studies no association between PvuII or XbaI ER genotypes and bone mineral density were reported [30, 31] other studies suggest an association between the xx [9] and PP genotypes [11] and low bone mineral density. Estrogen levels and bone mineral density are related and a high bone mineral density is associated with an increased risk of breast cancer [32, 33]. Although polymorphisms in the ER gene have been linked to altered tissue responsiveness to estrogens, the functional impact of these ER-α polymorphisms is not well understood [34].

The XbaI X allele has been associated with an increased risk of breast cancer in a study from Norway [17].

However, the PvuII restriction site polymorphism is apparently not associated with expression of ER in breast cancer [35-37] and was not related to breast cancer risk in two analyses that did not consider covariates such as hormone replacement therapy and reproductive history [17]. The study by Parl et al. found the pp genotype to be related to a younger age at breast cancer diagnosis [35]. Boyapati et al. did not find that the associations between ER-α genotypes and breast cancer risk vary according to ER/PR status [18].

Since the ER-α is an important mediator of hormonal responses such as proliferation in estrogen-sensitive tissues, Weiderpass et al. hypothesized that polymorphisms in the ER gene could be functional and associated with endometrial cancer risk [38]. The variants of the ER gene may be associated with an altered risk of endometrial cancer.

In light of substantial evidence that polymorphisms in the ER gene have been associated with increased hormone-dependent cancer risk in some populations, it seems reasonable to check a possible correlation between the polymorphism and clinical status of endometrial cancer patients. In this work conducted on 120 endometrial cancer patients we did not find any correlation between PvuII and XbaI genotypes and occurrence of cancer. Moreover, we did not detect any significant difference between genotypes in subgroups assigned to histological stages, which suggests a lack of association between polymorphism and cancer invasiveness.

Our study implies that it is possible that the polymorphism of the ER-α gene may not be directly associated with appearance and development of endometrial cancer but further research, conducted on larger populations, are needed to clarify this point.

References


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Paclitaxel and carboplatin are frequently used in advanced gynecological cancer following cytoreductive surgery. Generic drugs are typically less expensive than brand-name drugs, and prices for generics have historically increased less than those for brand-name drugs. The U.S. Food and Drug Administration (FDA) examines generic formulations and approves as its bioequivalent to brand-name drugs in activity and absorption [1, 2]. The FDA does not require bioequivalence testing for the drug products for intravenous infusion. Therefore, the bioequivalence and its toxicity between generic and brand-name anticancer products remain unresolved. Our objective was to examine the toxicity of a generic substitution of carboplatin in combination chemotherapy with paclitaxel for patients with primary advanced gynecologic cancer. This may be a first prospective study examining the clinical or laboratory assessment produced by generic substitution of anticancer products.

Patients (total 44 cases; 23 with ovarian cancer, 17 endometrial cancer and 4 cervical cancer, mean age; 59 ± 12 years) had undergone primary surgery with the aim of maximal tumor reduction and received 237 cycles of chemotherapy. The treatment protocol included paclitaxel (175 mg/m²) i.v. over three hours immediately followed by a 30 min infusion of generic carboplatin i.v. [SANDOZ] AUC 5 mg/ml/min. This dose remained fixed for all cycles, unless toxicity necessitated any dose reduction. Standard premedication was administered, including 20 mg dexamethasone orally at 12 and six hours before paclitaxel. Cycles repeated at three-weekly intervals, and routine weekly hematologic assessments were done. Toxicity was graded according to the National Cancer Common Toxicity Criteria [3, 4]. Patients did not receive primary supportive granulocyte-colony-stimulating factor (G-CSF).

Hematological toxicity data are summarized in Table 1. A high incidence of grade 2-4 leukopenia was noted, but no patient developed neutropenic fever. There were no unexpected adverse drug effects. No severe non-hematological toxicity was detected. Of note, 21 patients (8.8%) encountered neurotoxicity, and peripheral sensory neuropathy. This may be a rather paclitaxel-associated toxicity profile; the incidence of neuropathy in patients treated with paclitaxel and brand-name carboplatin was estimated at 13% [5].

In this reasonable cohort of patients, paclitaxel and generic carboplatin was associated with a high incidence (25.7%) of grade 2-4 hematological toxicity. The incidence of grade 2-4 leukopenia in patients treated with paclitaxel-brand-name carboplatin was estimated at 25-30% [3, 4]. All other detected toxicities did not exceed those reported for the brand-name product regimen. The bioequivalence of some drugs is controversial; generic drugs are widely believed to provide the same therapeutic effects as their brand-name alternatives [1, 6]. In Japan, there are market concerns with regard to switch-

Table 1. — Hematological toxicity.

<table>
<thead>
<tr>
<th></th>
<th>White blood cells (x 10³/ml)</th>
<th>Grade II/III/IV leukopenia</th>
<th>Hemoglobin (g/dl)</th>
<th>Platelets (x 10⁴/ml)</th>
<th>AST (IU/l)</th>
<th>BUN (mg/dl)</th>
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<tr>
<td>Ovarian cancer</td>
<td>4.6 ± 1.2</td>
<td>2.4 ± 0.8*</td>
<td>33 cycles</td>
<td>11.7 ± 1.0</td>
<td>13.3 ± 1.1</td>
<td>22.1 ± 5.8</td>
</tr>
<tr>
<td>(23 patients, 111 cycles)</td>
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<tr>
<td>Endometrial cancer</td>
<td>4.4 ± 1.8</td>
<td>2.2 ± 1.0*</td>
<td>25 cycles</td>
<td>11.6 ± 1.5</td>
<td>11.1 ± 1.6</td>
<td>20.8 ± 4.9</td>
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<tr>
<td>(17 patients, 101 cycles)</td>
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<tr>
<td>Cervical cancer</td>
<td>4.8 ± 1.1</td>
<td>2.4 ± 1.1*</td>
<td>3 cycles</td>
<td>11.0 ± 0.9</td>
<td>10.8 ± 1.2</td>
<td>27.9 ± 6.0</td>
</tr>
<tr>
<td>(4 patients, 15 cycles)</td>
<td></td>
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<tr>
<td>Overall</td>
<td>4.5 ± 1.5</td>
<td>2.3 ± 0.9*</td>
<td>61 cycles</td>
<td>11.63 ± 1.2</td>
<td>11.2 ± 1.3</td>
<td>22.9 ± 18.7</td>
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<tr>
<td>(44 patients, 237 cycles)</td>
<td></td>
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</table>

*p < 0.01 versus vor value; vor = generic; nadir = brand name.

Valid generic substitution of carboplatin for patients with gynecological cancer

A. Imai, N. Ito

Department of Obstetrics and Gynecology, Gifu University School of Medicine, Yanagido (Japan)
ing from brands to generics as one possible mechanism for limiting drug expenditures. Our prospective study comparing the generic substitution with brand-name carboplatin in combination chemotherapy with paclitaxel was able to identify the best regimen with the best therapeutic index.

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Synchronous endometrioid carcinoma of the uterine corpus and ovary. A case report and review of the literature

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Introduction

Synchronous endometrioid carcinoma of the uterine corpus and ovary is an uncommon but well recognized event. Diagnosis as either a separate independent primary or as a metastatic tumor requires careful consideration of a number of gross and histological features. These features illustrate the criteria helpful in distinguishing independent primaries from metastatic carcinomas which have a different therapeutic implication. The possible link between fertility drugs and carcinogenesis still remains controversial. We report a case of a 52-year-old woman who came to our hospital with a cystic left ovarian mass (8 cm). Hysterectomy and bilateral salpingo-oophorectomy were carried out. Histological examinations showed well differentiated endometrioid ovarian cancer and well differentiated endometrioid endometrial cancer. The endometrial tumor was intramucosal without myometrial or vascular invasion and was associated with atypical complex hyperplasia. The woman had not been previously treated with ovulation induction drugs. She was free of recurrence two years after surgery. Patients with synchronous endometrioid tumors of the endometrium and ovary are generally younger than reported for either endometrial adenocarcinomas or ovarian adenocarcinomas. They tend to be low grade and early stage and are frequently associated with endometriosis. The prognosis of endometrioid type carcinomas is better than other histological types of carcinoma.

Case Report

A 52-year-old woman presented to our hospital with abdominal pain, persisting for about two months. There was no family history or gynecological disease. Physical examination and CT-scan revealed a cystic left ovarian mass (8 cm). Hysterectomy and bilateral salpingo-oophorectomy with omentectomy were carried out. The histology of the surgical specimen showed well differentiated endometrioid ovarian cancer and well differentiated endometrioid endometrial cancer. The endometrial tumor was intramucosal without myometrial or vascular invasion and was associated with atypical complex hyperplasia (Figures 1-3). The fallopian tubes were normal and the right ovary was 3.5 x 2.5 x 1 cm. After additional clinical and laboratory screening there was no other evidence of disease at other sites. The woman has not been previously treated with ovulation induction drugs. She was alive and well with no evidence of recurrence two years after surgery.

Discussion

Synchronous primary cancer of the endometrium and ovary are found in 10% of women with ovarian cancer and 5% with endometrial cancer. It is often unclear whether this represents a synchronous primary tumor or metastasis from the endometrium to the ovary or from the ovary to the endometrium. Consequently, staging, therapy and expected outcome are uncertain. When the tumor histology is completely different, it is easy to diagnose double primary cancers. No definitive diagnostic marker exists that allows discrimination between synchronous tumors and metastatic disease. Several studies have identified genetic alterations in ovarian cancer, particularly loss of heterozygosity on chromosome 17. Further studies will be necessary to determine the possible involvement of tumor suppressor genes on chromosome 22 in endometrioid ovarian tumor development. Conversely, different genetic alterations in the ovarian and endometrial tumor would suggest that the two tumors developed independently. Patients with synchronous endometrioid tumors of the endometrium and ovary are generally younger than reported for either endometrial adenocarcinomas or ovarian adenocarcinomas. The most common presenting symptom is abnormal vaginal bleeding (70%) and most of the women are obese, premenopausal and nulliparous. The possible link between fertility drugs and car-
cinogenesis still remains controversial because some cases of ovarian carcinomas have been reported to occur in women previously treated with ovulation induction drugs [1-8]. The tumors tend to be low grade and early stage and are frequently associated with endometriosis. Endometriosis is found in the ovary in 31% of the patients [3, 4]. Endometrial tumors that are intramucosal without myometrial invasion are often associated with atypical complex hyperplasia [4]. The ovarian tumors are uninnodal and unilateral without hilar invasion. The prognosis of endometrioid type carcinomas is better than other histological types of carcinoma with median survival approaching ten years. Moreover the prognosis in synchronously detected carcinomas of the uterus and ovary with gross disease confined to the pelvis is surprisingly good [10-14].

References


Synchronous endometrioid carcinoma of the uterine corpus and ovary. A case report and review of the literature


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Primary ovarian leiomyosarcoma associated with Brenner tumor

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¹Department of Pathology, ²Department of Gynecology, Shanghai First Maternity and Infant Health Hospital, Tongji University, Shanghai (China)

Summary

Background: Primary ovarian leiomyosarcoma (POL) is rare. To the best of our knowledge, POL associated with a Brenner tumor has not been previously documented. Case: A case of POL associated with a Brenner tumor is reported. Although the poorly differentiated component of the tumor was negative for SMA, the presence of spindle cells in the higher differentiated component with fascicle arrangement and immunoreactivity for SMA and strong staining of a poorly differentiated component for desmin and vimentin established the diagnosis. Conclusion: This case indicates that since malignant tumor cells may lose some antigen markers, thorough sampling and immunohistochemistry are necessary. EMA-immunopositivity only could not preclude the diagnosis of leiomyosarcoma.

Key words: Primary ovarian leiomyosarcoma; Brenner tumor; SMA; EMA.

Introduction

Primary leiomyosarcoma of the ovary is extremely rare, accounting for 0.1% of ovarian malignancies, with less than 50 cases documented in the literature [1, 2]. We report a unique case of leiomyosarcoma with associated Brenner tumor which has not been reported before.

Case Report

A 71-year-old postmenopausal woman presented with a painless abdominal mass and weight loss. The palpable mass was noticed five months before and was rapidly growing. Physical examination revealed a large mass with its upper pole near the inferior aspect of the umbilicus. Color Doppler sonography showed solid masses in the bilateral adnexal areas and cul-de-sac. CA125 was 120.2 U/ml (3 U/ml is within normal values), and other serum tumor markers including CEA, AFP, CA199 were normal. The patient underwent an ovarian mass biopsy and the frozen section was diagnosed as malignant tumor. Total abdominal hysterectomy and bilateral salpingo-oophorectomy, and the frozen section was diagnosed as malignant tumor. Total abdominal hysterectomy and bilateral salpingo-oophorectomy, bilateral pelvic lymph nodes sampling, peritoneal sampling and immunohistochemistry are necessary. EMA-immunopositivity only could not preclude the diagnosis of leiomyosarcoma.

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Primary ovarian leiomyosarcoma associated with Brenner tumor

patients with surgery and chemotherapy died, while 40% died with surgery only. The majority of living patients had no residual disease after the initial surgery [1-5].

The origin of smooth muscle cells in POL is similar to that of ovarian leiomyoma: 1) Smooth muscle wall of blood vessels in the cortical stroma [6]. In our case, there was no evidence to prove this theory because the neoplastic cells were not arranged around the blood vessels. 2) Smooth muscle cells in the ligaments close to the ovary. Our case did not show the leiomyosarcoma in this region. 3) The smooth muscle component of the associated teratoma. Our case was not associated with teratoma. 4) Ovarian mesenchyme. It is widely accepted that the cells in the mesenchyme retain the capability of developmental potency [7]. The smooth muscle cells in our case may have originated from the mesenchyme.

Brenner tumors are relatively rare neoplasms accounting for 1-2% of all ovarian neoplasms. Most patients are between 30 and 60 years old. The relationship between Brenner tumor and POL remains to be elucidated.

Interestingly, the poorly differentiated component of POL was weakly EMA-positive and SMA/caldesmon-negative. A study by Iwata and Fletcher [8] demonstrated 44/100 cases of EMA-positive leiomyosarcomas (focal or diffuse). They regarded it as random and disorganized events happened in the leiomyosarcoma. The negativity for SMA and caldesmon might suggest that the poorly differentiated component occasionally lost some antigen marker that is classical of a highly differentiated component. The reactivity of these tumor cells to desmin, vimentin and the expression of SMA and caldesmon in the higher differentiated component may help in facilitating the diagnosis. Moreover, it should be emphasized that depending on the results of immunoreactivity for one single antibody may not be trustworthy. A panel of antibodies, careful morphological examination and thorough histologic sampling will offer a more confident diagnosis. This immunohistochemical phenomenon has not been described in other ovarian leiomyosarcomas.

In conclusion, to our knowledge we have reported the first case of POL associated with a Brenner tumor. It indicates that a thorough immunohistochemical and morphological examination is necessary to establish the diagnosis because parts of the tumor may lose some markers and EMA positivity can not preclude the diagnosis of leiomyosarcoma.
References


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Paratubal endometrioid cystadenocarcinoma: case report and review

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¹Department of Surgery, ²Department of Pathology, Claudius Regaud Institute, Toulouse Cedex (France)

Summary

Background: Paratubal masses are common, but paratubal carcinoma is an extremely rare entity. Case: We report a case of a 44-year-old nulliparous female who suffered from abdominal pain for three months. Abdominal and pelvic ultrasound revealed a 30 cm left adnexal mass originally. Laparotomy with bilateral salpingo-oophorectomy was performed. Final pathology indicated a heterogeneous tumor with benign, borderline, and endometrioid carcinoma areas. A repeat surgery was decided in order to complete hysterectomy, omentectomy, pelvic and paraaortic lymphadenectomy. Surgical staging did not reveal residual disease at pathological examination. After 36 months of follow-up, no recurrence has occurred. Conclusion: To our knowledge, no case of paratubal invasive endometrioid adenocarcinoma has previously been described. This case has been managed according to the recommendations of ovarian cancer, which seems to be an acceptable option.

Key words: Endometrioid adenocarcinoma; Paratubal carcinoma; Ovarian carcinoma.

Introduction

Paratubal masses are common. They usually arise from the mesothelium covering the peritoneum or from paramesonephric and mesonephric remnants [1].

Paratubal cysts, generally known as Morgagni's hydatid cysts, are small, round cysts attached by a pedicle to the fimbriated end of the tube [2]. Primary carcinomas of the fallopian tube account for about 0.3% to 1.8% of all gynecologic cancers. The incidence of paratubal malignancies is not known [3]. We report here the first case of paratubal endometrioid adenocarcinoma.

Case Report

A 44-year-old nulliparous female was referred with a 3-month history of abdominal swelling, abdominal pain, and nausea. No other medical condition than a history of right breast comedocarcinoma 16 years earlier was noticed. Her abdomen was diffusely tender on palpation, with no ascites. A palpable mass was detected in the left pelvis. Abdominal and pelvic ultrasound (US) revealed a 30 cm left adnexal mass featuring endocystic vegetations. There was no peritoneal carcinomatosis on computed tomography (CT) scan. Laboratory tests showed a slightly elevated CA-125 level (32 UI/ml). A borderline or malignant ovarian mass was suspected.

Midline laparotomy was performed because of tumor size. A left paraovarian mass without extracapsular growth was found (Figure 1). No peritoneal disease or enlarged node was found. A frozen-section was performed and diagnosed a benign paraovarian cyst. Bilateral salpingo-oophorectomy was performed. Final pathology examination revealed at macroscopy a cystic tumor independent from the ovary and paratubal tube, measuring 16 x 14 x 5 cm with a soft surface. It contained a fungated surface mass of 5 cm in diameter. Microscopic examination revealed a mixed tumor (Figure 2). It showed features of a well differentiated endometrioid carcinoma mixed with borderline and benign areas. The stroma was fibroblastic and of variable amount. The tumor also displayed foci of squamous metaplasia. No endometriosis was observed. Immunohistochemistry showed that the proliferation was positive for cytokeratin 7 (CK7+) and for estrogen and progesterone receptors, but negative for cytokeratin 20 (CK20-) and vimentin. The ipsilateral ovary and paratubal, and contralateral adnexa were normal. Final diagnosis was left paratubal intracystic endometrioid cystadenocarcinofibroma grade 1 (WHO classification). Peritoneal cytology was clear of malignant cells. Repeat laparotomy was performed in order to complete surgery. Hysterectomy, omentectomy, pelvic and paraaortic lymphadenectomy and multiple peritoneal biopsies were performed. Definitive pathologic examination did not reveal any residual tumor. No complementary treatment was proposed by the multidisciplinary staff. After 36 months of follow-up, no recurrence has occurred.

Figure 1. — Macroscopic features during laparotomy: paraadnexal mass apparently independent from the ovary (double arrows) and the fallopian tube (single arrow).
Discussion

Paratubal carcinoma is a rare entity. Approximately 10% of all adnexal masses are represented by paratubal or paraovarian cysts [4, 5], most are left undiagnosed at the time of pelvic ultrasonography. Barloon et al. [5] reported on the accuracy of US imaging in diagnosing paraovarian and paratubal cysts. Preoperative transvaginal US correctly identified paratubal or paraovarian cysts in 44% of adnexal masses [6]. The management of paraovarian masses is thus similar to any other adnexal mass [5].

Most reported cases of paratubal masses concern benign masses [5]. Nine cases of malignant paratubal cysts have been reported in the literature (Table 1). Five of them were transitional cell carcinomas (TCCs) of urothelial tract origin [7-9], in which management is different because of urothelial tract appearance. In medical oncology, treatments are directed according to specific histologic types instead of site of tumor origin. TCC of the urothelial tract is a chemosensitive tumor. There is no consensus. Maluf et al. suggest after radical primary surgery, that triple-drug chemotherapy containing cisplatin, paclitaxel, and gemcitabine followed by intraperitoneal (IP) triple-drug chemotherapy is a feasible and effective treatment against TCC of the paratubal tube [9]. Only three cases of cystadenocarcinoma have been described in the literature: two cases of primary paraovarian serous tumors in postmenopausal women [10] and one case of an invasive paratubal papillary tumor [11].

Our case of an endometrioid cystadenocarcinoma is rare. To our knowledge, the only paratubal endometrioid carcinoma documented so far is a borderline endometrioid tumor which was treated by laparoscopic salpingo-oophorectomy [2]. In the literature, no case of paratubal adenocarcinoma with extra fallopian extension has been described. This case has been managed according to the recommendation of ovarian cancer, which seems to be an acceptable option (www.sor-cancer.fr).

Table 1. — Clinicopathologic characteristics of patients with small cell carcinoma of the uterine cervix.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases</th>
<th>Histology examination</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salamon et al. [2]</td>
<td>1</td>
<td>Borderline endometrioid</td>
<td>USO; (l_{case}: \text{TAH/BSO, omentectomy, node dissection (pelvic/paraortic) + chemo + 2 and 3 look-surgery} )</td>
<td>NOD, 12</td>
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<tr>
<td>Maluf et al. [9]</td>
<td>2</td>
<td>TCC</td>
<td>(l_{case}: \text{TAH/BSO, omentectomy, node dissection (pelvic) + resection para-rectal + chemo + 2^{nd}-look surgery} )</td>
<td>NOD, 26</td>
</tr>
<tr>
<td>Narurkar et al. [11]</td>
<td>1</td>
<td>Papillary cystadenocarcinoma</td>
<td>not available</td>
<td>NOD, 14</td>
</tr>
<tr>
<td>Federman et al. [7]</td>
<td>1</td>
<td>TCC</td>
<td>USO; (l_{case}: \text{TAH/BSO} )</td>
<td>NOD, 64</td>
</tr>
<tr>
<td>Thomason et al. [8]</td>
<td>1</td>
<td>TCC</td>
<td>not available</td>
<td>NOD, 20</td>
</tr>
<tr>
<td>Paner et al. [7]</td>
<td>1</td>
<td>TCC</td>
<td>TAH/BSO</td>
<td>NOD, 6</td>
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<tr>
<td>Altaras et al. [10]</td>
<td>2</td>
<td>Serous cystadenocarcinoma</td>
<td>(l_{case}: \text{TAH/BSO} )</td>
<td>NOD, 53</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(l_{case}: \text{TAH/BSO + omentectomy + infracolic resection} )</td>
<td>NOD, 51</td>
</tr>
</tbody>
</table>

USO: unilateral salpingo-oophorectomy; TCC: Transitional cell carcinoma; TAH/BSO: total abdominal hysterectomy/bilateral salpingo-oophorectomy; chemo: chemotherapy (cisplatin/paclitaxel/gemcitabine); NOD: no evidence of disease (months).

References
Paratubal endometrioid cystadenocarcinoma: case report and review


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Large retroperitoneal schwannoma mimicking ovarian carcinoma: case report and literature review

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Summary

In this article we present a case of retroperitoneal schwannoma localized in the pelvic cavity with complete cystic degeneration, mimicking ovarian carcinoma. Case: A 25-year-old nulligravid woman was admitted to our gynecology out-patient clinic with the complaint of abdominal distension, right flank pain and pollakiuria. Sonographic study showed a cystic mass containing necrotic areas and filling the whole pelvic cavity. Computed tomography and colonography suggested the possible diagnosis of a right ovarian malign tumor. Laparotomy revealed a retroperitoneal cystic lesion. Microscopic examination of the pelvic mass confirmed the diagnosis of cystic degenerative schwannoma. After six months of initial surgery she is still alive without any evidence of disease. Conclusion: In the present case, it is emphasized that it is easy to make an error and misdiagnose a pelvic mass as an ovarian tumor when it is in fact a tumor from another origin. Additionally, clinicians should keep in mind that retroperitoneal schwannoma may mimic cystic ovarian carcinoma even in young women.

Key words: Pelvic mass; Ovarian carcinoma; Retroperitoneal schwannoma.

Introduction

Schwannoma (neurilemmoma) is a peripheral nerve sheath tumor and commonly occurs singularly on the head, neck, and trunk. Giant schwannoma is rarely located in the retroperitoneum and pelvic cavity [1]. Retroperitoneal schwannomas are very rare except in patients with Von Recklinghausen’s disease. In fact, only a few such cases have been reported in the literature [2]. Schwannomas are solid tumors with a markedly hypoechoic appearance on sonography. Very rarely, a schwannoma can present as a completely cystic lesion and may mimic ovarian carcinoma [3].

In this report the patient was diagnosed with a pelvic tumor with possible malignant potential. Surgical diagnosis using histologic results led to a change of diagnosis to Schwannoma of retroperitoneal origin. Hence, we report this case with a review of the current literature.

Case Report

A 25-year-old nulligravid woman was admitted to our gynecology out-patient clinic with the complaint of abdominal distension, right flank pain and pollakiuria. She had regular menses. Her medical history was unremarkable. On physical examination, a palpable abdominal mass extending from the pelvis to the umbilicus was revealed. The mass was firm, smooth surfaced and semi-mobile.

On admission complete blood count was unremarkable for a hemoglobin level of 11.1 g/dl (12-16), a hematocrit value of 36%, platelet count of 359.000/µl (140.000-440.000) and 111600/µl (4200-10000) white blood cells. Biochemical levels including liver, renal and thyroid functions tests and tumor markers (including CA 125, CA 19-9, CEA) were all within normal limits. All other coagulation parameters were also in normal limits.

Sonographic study showed a cystic mass containing necrotic areas and filling the whole pelvic cavity. Computed tomography scan confirmed a cystic mass of 13 x 12 x 11 cm in size displacing the uterus left anterolaterally. Colonography revealed a segmental narrowing in length of 6 cm involving the sigmoid colon (Figure 1). At first the patient was diagnosed as having a right ovarian tumor.

Considering the diagnosis of a right ovarian malign tumor, laparotomy was performed. The uterus, fallopian tubes and ovaries had a grossly normal appearance. A capsulated and bright gray mass arising from the retroperitoneal region obliterating the rectouterine pouch was observed. It was smooth surfaced and purely cystic. Grossly, it had no septation. It was excised through a lower midline incision. There was no sign of surrounding tissue invasion. Microscopic examination revealed a Verocay body with Antoni type A and type B tissue (Figure 2). The cells were immunoreactive for S100 protein. The tumor was diagnosed as a cystic degenerative schwannoma. The postoperative period was uneventful. Six months after initial surgery the patient is still alive without any evidence of disease.

Discussion

Schwannomas are generally benign tumors arising from Schwann cells which are found in peripheral nerve sheaths. The retroperitoneal form of schwannomas is commonly located in the paravertebral space or presacral region [4]. They occur most commonly between 40 and 60 years of age and affect women twice as often as men [4, 5]. The reported incidence is only 0.7-2.7%. On gross appearance, schwannomas are solitary, well circumscribed, firm and smooth-surfaced tumors. Extracranial and large sized tumors may manifest degenerative

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changes. Cystic degeneration can occur in the lesion resulting from secondary degenerative changes caused by inadequate blood supply to the center of the tumor and completely cystic schwannomas can be seen. Other degenerative changes of the tumor are calcification, hemorrhage, and hyalinization [1].

Histologically, schwannomas may consist of compact cellular (Antoni type A) and loose hypocellular myxoid lesions with microcystic spaces (Antoni type B) [5, 6]. They are usually benign and slow growing tumors. Malignant change is extremely rare. Malignancy is usually suggested histologically by mitosis, pleomorphism and blood vessel infiltration [7]. The presence of mitotic figures is the most reliable feature correlating with malignancy. Benign schwannoma has a low rate of recurrence and very good prognosis, whereas malignant schwannoma has a high rate of recurrence and very poor prognosis [8]. Malignant schwannomas are generally insensitive to chemotherapy and radiotherapy and are associated with von Recklinghausen’s disease. They act as high-grade sarcomas with distant metastasis [1].

Retroperitoneal schwannomas are mainly located in the pelvis. They are usually solid and fixed in the retroperitoneum. On physical examination they have a smooth surface and intraabdominal organs are freely movable over the mass. The size of tumor is usually more than 8 cm when diagnosed. Diagnosis is difficult and usually made by chance when a patient undergoes routine physical examination because the symptoms are vague and nonspecific [9, 10]. The most frequent presenting symptom is abdominal distension. Dull abdominal pain with or without any other associated symptom may be present [8].

Radiologic studies are fundamental in the diagnostic evaluation. Schwannomas are solid tumors with a markedly hypoechoic appearance on sonography [11]. The differential diagnosis should be made with psoas abscess. Complete cystic schwannomas can mimic other entities such as a cystic benign/malign ovarian mass, retroperitoneal pseudocyst, hydrosalpinx, loculated collection urinoma and bladder diverticulum. A variety of ovarian lesions can show cystic changes ranging from a simple functional cyst to cystadenoma and carcinoma. It is hard to differentiate retroperitoneal schwannoma from other retroperitoneal tumors. The presence of calcified foci and cystic changes in ultrasound study is sensitive. Larger lesions typically appear to be heterogeneous, hyperechoic and containing prominent cystic components which are nonspecific [12]. CT and MRI may be more helpful than sonography in the preoperative diagnosis. CT scans typically show well defined low or mixed attenuation with cystic necrotic central areas. Cystic changes...
occur more commonly in retroperitoneal schwannomas than other retroperitoneal tumors [13]. Sonography or CT-guided fine-needle aspiration is also helpful in the preoperative diagnosis only if the sample contains enough schwann cells to visualize microscopically. Many authors do not recommend CT-guided biopsy because of tumor seeding and risk of infection. Therefore surgical resection is the only accurate approach for pathologic evaluation to enable diagnosis of retroperitoneal schwannoma [9, 13].

Surgical resection without injuring the nerve is recommended for the therapy of retroperitoneal schwannoma. Before starting the resection sending a biopsy for frozen section is highly recommended to identify whether the tumor is malignant or benign. Surgical excision has severe hemorrhage risk because the tumor may adhere to the presacral venous plexus and major nerve roots. Some authors believe that since schwannoma is a benign mass, partial excision is sufficient. Morbidity associated with resection of adjacent tissue would not be justified in the treatment of benign lesions [14]. Laparoscopic excision can be considered as an alternative treatment because hemostasis is a major complication due to limited access [5].

Since malignancy can not be excluded accurately preoperatively or even intraoperatively with frozen section analysis, some authors recommend aggressive resection for schwannoma to attain negative margins and reduce the recurrence rate [9, 15]. Local recurrence rate ranges from 16% to 54% after conservative intraliesional enucleation [16].

The prognosis of retroperitoneal benign schwannoma is extremely good. As malignant transformation and metastasis after resection of histologically benign schwannoma have been reported, careful monitoring is necessary after removal of benign retroperitoneal schwannoma [1].

In the present case it has been emphasized that it is easy to make an error and misdiagnose a pelvic mass as an ovarian tumor when it is in fact a tumor from another origin. It is important to try to make a clear preoperative diagnosis so that proper management can be prepared. Additionally, clinicians should keep in mind that retroperitoneal schwannoma may mimic cystic ovarian carcinoma even in young women.

References


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Prolonged clinical benefit from platinum-based chemotherapy in a patient with metastatic triple negative breast cancer

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Summary

Triple negative breast cancer is a recently defined subgroup of tumors which do not express receptors for estrogen or progesterone and which do not show any overexpression of HER2 receptors. Tumors with these histopathologic features have an unfavorable prognosis and at present there is no standard chemotherapy regimen available. However, experimental studies and very recently some clinical data showed a benefit from platinum-based chemotherapy. We treated a 52-year-old caucasian female with metastatic triple negative breast cancer. She suffered from extensive liver disease resistant to taxane treatment and yttrium radiotherapy. Cisplatin/ifosfamide (12 cycles) induced regression of the liver metastasis from over 30 cm to 6 cm as revealed by CT scan. Dose-limiting toxicity was impairment of renal function and pancytopenia. The patient has now been stable for over ten months on a metronomic regimen of oral cyclophosphamide. This case report adds to recent evidence suggesting good clinical benefits of platinum-based regimens in early and advanced triple negative breast cancers.

Key words: Triple negative breast cancer; Metastatic; Platin compounds; Liver metastases.

Introduction

Breast cancer is the most common malignancy and ranks second as a cause of cancer-related deaths among women. In 2005 it was estimated that about 40,000 women in the United States would die from breast cancer [1]. The great majority of patients succumb to this disease not because of their primary cancer, but because of metastases.

This definition of triple negative breast cancer refers to a group of tumors which do not express receptors for estrogen or progesterone and which do not express HER2. This subgroup shows distinctive clinical features and accounts for 17-21% of all breast carcinomas [2, 3]. Triple negative breast cancers tend to more frequently affect younger patients [4], are more prevalent in African Americans [5, 6] and clinically more aggressive than tumors belonging to the other known molecular subgroups [6-9]. These clinical findings underline the importance of establishing effective treatment strategies for this disease as so far no standard therapy for early or late stage triple negative breast cancer has been established.

Some recent experimental and clinical data suggest that platinum-based therapy is efficient in triple negative breast cancer patients [10].

We present the case of a female patient with extensive liver metastases from this type of breast cancer that was successfully treated with platinum-based chemotherapy.
apy due to increasing renal toxicity and myelotoxicity leading to pancytopenia, a treatment holiday was recommended to the patient. Other side effects were cisplatin-induced impairment of her hearing capacity and ifosfamide-induced encephalopathy. At the end of platinum-based therapy the reference metastasis had regressed to a size of 6 cm (Figure 2).

As the patient desired further therapy, metronomic chemotherapy with daily oral cyclophosphamide (50 mg qd) was initiated. The liver metastases have been stable for ten months under the current treatment as revealed by US every six weeks.

Discussion

Currently there is no established treatment regimen for the therapy of advanced triple negative breast cancers. We therefore administered platinum-based chemotherapy in a patient with metastatic breast cancer, who previously had failed to respond to taxanes. Therapy with 12 cycles of cisplatin/ifosfamide induced partial regression of the disease. Subsequent metronomic therapy with oral cyclophosphamide did not lead to disease progression. Disease stabilization in our patient has been ongoing for ten months. Our therapeutic decision to incorporate a platin compound was triggered by experimental data available at that time, which suggested that triple negative breast cancer may have increased sensitivity to platinum-based chemotherapy [11-13].

Interestingly, our therapeutic strategy was confirmed very recently by a retrospective clinical study, which reported that neo-adjuvant complete response rates of platinum-based treatment were significantly higher in triple negative tumors than in other breast cancer subtypes. This finding was reflected by an increased 5-year overall survival for triple negative tumors following platin containing neo-adjuvant chemotherapy. For patients with advanced breast cancer, overall response rate was 41% for triple negative tumors and 31% for other subtypes of breast cancer (p = 0.3). Patients with triple negative tumors had a significantly prolonged progression-free survival of six months compared with four months (p = 0.05), although the overall survival was not statistically significantly different between the two groups (11 vs 7 months) [14]. In a second recent trial, Torrisi and co-workers also found remarkable response rates of neoadjuvant platinum-based chemotherapy in triple negative breast cancer patients with an objective response rate of 86% and pathological complete remission in 40% [15].

Thus, this case report adds further evidence to a rationale for platinum-based chemotherapy for triple negative breast cancers. However, prospective randomized trials are required to confirm these preliminary results and to establish a treatment regimen for breast cancers of this subtype.

References

Prolonged clinical benefit from platinum-based chemotherapy in a patient with metastatic triple negative breast cancer


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Broad ligament leiomyosarcoma in a premenopausal nulliparous woman: case report and review of the literature

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Summary

Leiomyosarcomas of the broad ligament of the uterus are extremely rare tumors. Most of the time they are diagnosed in older women and despite radical surgical treatment prognosis is dismal. We present a rare case of a 38-year-old nulligravida presenting with a large, firm mass, fixed in the pelvis. After enucleation of the tumor, histological examination revealed the presence of a broad ligament leiomyosarcoma, leading to total abdominal hysterectomy and bilateral salpingo-ophorectomy three weeks later. Management options and cases reported in the literature are reviewed.

Key words: Leiomyosarcoma; Broad ligament; Radical surgery.

Introduction

Localization of tumors in the broad ligament of the uterus is rare. Most of the time such tumors are benign fibroids originating from the uterus [1], while malignant tumors are very rare. Several types of malignant tumors have been reported to be located or extend to the broad ligament, including leiomyosarcoma [2], myxoid leiomyosarcoma [3], liposarcoma [4], extraskeletal Ewing’s sarcoma [5, 6], mixed mesenchymal sarcoma [7], endometrial stromal sarcoma [8] and hyalinizing spindle cell tumors [9]. Histologically malignant-appearing, but biologically benign tumors have been also reported [10, 11]. We report herein a rare case of a leiomyosarcoma of the broad ligament, with no vascular connections to the uterus or the adnexa, in a premenopausal nulliparous woman.

Case Report

A 38-year-old nulliparous woman presented complaining of frequency of micturition and mild constipation during the previous year, and a recently discovered solid mass in the left side of the lower abdomen. There were no complaints of menstrual irregularities. The last gynecological examination had taken place seven years earlier, and the cervical smear was negative. Besides heavy smoking (40 cigarettes daily) the patient’s medical and family history were unremarkable. On clinical examination, a large, firm mass filling the left iliac fossa, fixed to surrounding anatomical structures was noted. Inspection of the cervix was not possible due to excessive dislocation. Abdominal ultrasound (US) examination revealed a large, solid mass measuring 20 x 15 x 8 cm. The uterus was dislocated, lying superior to the mass. No other abnormal imaging findings were noted on abdominal US, abdominal CT, and chest X-ray. A large uterine fibroid appeared to be the most likely diagnosis, and surgical removal was offered to the patient.

Midline laparotomy was performed and a large solid tumor of the broad ligament was found, fixed in the pouch of Douglas. The uterus and both adnexa had normal appearance, and there were no signs of other fibroids, nodules or masses in the entire peritoneal cavity, including the omentum and the liver surface. After adhesiolysis and opening of the broad ligament, enucleation of the tumor was performed with blunt dissection. The tumor appeared not to be connected to the uterine vasculature at all. The patient was discharged three days later after an uneventful postoperative course. Histological examination however, revealed that the tumor was an aggressive leiomyosarcoma, with nuclear atypia and more than ten mitotic figures per ten high-power fields (HPF), suggestive of malignant behavior, according to the Zaloudek and Norris criteria [12]. After detailed patient counseling, total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) were recommended. The options of postoperative radiotherapy and/or systemic cytotoxic chemotherapy were also thoroughly discussed with the patient. TAH-BSO and histological examination of the internal genitalia did not show any signs of disease dissemination. The patient again had an uneventful postoperative course and she was discharged four days after the operation, declining however any further treatment.

Six months after the second operation, the patient presented with abdominal pain. Bimanual examination revealed a mass over the vaginal vault, suggesting local disease recurrence, necessitating repeat laparotomy. However, the patient refused further surgical treatment, declined the options of radiotherapy and/or chemotherapy, and succumbed eight months after initial diagnosis.

Discussion

Primary leiomyosarcomas of the broad ligament are extremely rare. To the best of our knowledge only 17 cases have been previously reported in the literature (Table 1) [2, 13-27]. Clinically, signs and symptoms are non-specific, including abdominal pain, abdominal distention, constipation, frequency of micturition, urine retention, anorexia and malaise. Interestingly, none of the
reported cases could be accurately diagnosed before primary surgical treatment, and definitive diagnosis was possible only after histological examination of the surgical specimens. In the present case, the patient presented with non-specific signs and symptoms, and the definitive diagnosis was made postoperatively. The patient presented herein was 38 years old and premenopausal, while patients in the majority of reported cases were postmenopausal, and only four patients were younger than 40 years of age.

Due to the limited number of cases, the optimal management of leiomyosarcomas of the broad ligament is not well established. In most cases, the same management as in leiomyosarcomas of the uterus is followed [28]. Leiomyosarcomas of the uterus are large, solid masses with soft, fleshy cut surfaces, exhibiting hemorrhage and necrosis, and they usually coexist with uterine fibroids; TAH/BSO is the optimal treatment. High-grade uterine leiomyosarcomas relapse by distant spread in 30% of cases. A multivariate analysis of prognostic factors in patients with uterine leiomyosarcomas showed that leiomyosarcomas surrounded by hyalinization with few mitotic figures limited to the central part of a leiomyoma have a better prognosis, while the presence of coagulative tumor cell necrosis is a negative predictive factor [29]. Radiotherapy can be helpful against local recurrence, but its impact on overall survival has not been established [30]. Systemic cytotoxic chemotherapy with agents such as doxorubicin and ifosfamide is usually followed by clinical response, and may improve recurrence-free survival in patients with leiomyosarcomas [30]. Preservation of the ovaries is an option for premenopausal women in early disease stage [29].

In summary, a rare case of leiomyosarcoma of the broad ligament in a relatively young premenopausal woman has been presented. Only four such cases have been reported in the past. Signs and symptoms are non-specific and definitive diagnosis is usually established postoperatively. Due to the rarity of this clinical entity, no standard treatment exists. Multimodality treatment with radical surgery followed by systemic cytotoxic chemotherapy and/or radiotherapy appears to be the most appropriate option, given the poor prognosis of these tumors.

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Umbilical metastasis of serous component as a first sign of mixed type epithelial ovarian cancer

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Summary

Umbilical metastasis (Sister Mary Joseph’s nodule) of malignant neoplasms is a rare condition. These nodules usually arise from the gastrointestinal or genitourinary tract and may present the first sign of a previously unknown primary tumor. We describe a 49-year-old woman presenting with Sister Mary Joseph’s nodule as the first sign of an extremely aggressive Stage IV mixed type epithelial ovarian carcinoma, who died 15 months after the initial diagnosis. This is the first case of a Sister Mary Joseph’s nodule from the gastrointestinal or genitourinary tract and may present the first sign of a previously unknown primary tumor. We describe a 49-year-old woman presenting with Sister Mary Joseph’s nodule as the first sign of an extremely aggressive Stage IV mixed type epithelial ovarian carcinoma.

Key words: Sister Mary Joseph’s nodule; Ovarian carcinoma; Metastasis.

Introduction

Ovarian cancer is the most common cause of death from gynecologic malignancy in Europe and United States [1]. Most cases of epithelial ovarian carcinoma are diagnosed at advanced stages associated with widespread disseminated disease. Although the intraperitoneal route of dissemination is considered the most common, ovarian cancer may also metastasize through the lymphatic channels and the hematogenous route [2]. Sister Mary Joseph’s nodule is a rare condition that is determined in patients with intraabdominal and/or pelvic malignancy [3] and survival is usually poor [4]. We describe a patient with Sister Mary Joseph’s nodule originating from a serous component of mixed type epithelial ovarian carcinoma, which is the first presenting sign of an underlying malignancy.

Case Report

A 49-year-old woman, gravida 4, para 4, presented with a one-month history of an umbilical mass, constipation and extremely tense abdominal pain but denied having melena, or rectal bleeding. She had no history of smoking or alcohol use and no family history of cancer. Physical examination revealed a 2 cm, tender, erythematous nodule of the umbilicus. With the suspicion of a Sister Mary Joseph’s nodule associated with an underlying malignancy, we evaluated the patient with chest X-ray, abdominal and transvaginal ultrasonography, tumor markers, gastroscopy, colonoscopy, mammography and abdominopelvic computed tomography (CT). Carbohydrate antigen (CA) 125 was > 500 U/ml (normal range below 35 U/ml) but serum CA 15-3 and CA 19-9 were normal. Abdominopelvic CT showed omental caking, ascites, and a lobulated, heterogeneous, pelvic mass of 140 x 108 mm in diameter which was inseparable from the subcutaneous tissue and umbilicus. Gastroscopy, colonoscopy, mammography and chest X-ray did not reveal any tumor in January 2006. Three cycles of neoadjuvant combination carboplatin at the target dose (AUC 6) and paclitaxel (175 mg/m²) were given every three weeks because of widespread dissemination. After the combination chemotherapy, she underwent exploratory laparotomy. At laparotomy, the peritoneal cavity contained a great amount of ascites fluid. Extensive peritoneal disease was found consisting of nodules with a diameter of 2-4 cm, including lesions in the omentum, spleen and bowel, with massive adhesions on the anterior abdominal wall. Macroscopically, both ovaries were enlarged with abnormal fallopian tubes. The liver grossly appeared normal. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, splenectomy, and resection of the subcutaneous tissue and skin of the umbilical region were performed. The defect in the fascia of the anterior abdominal wall was carefully repaired. Microscopic examination demonstrated the following:

1. Ovarian epithelial carcinoma, mixed type, composed of endometrioid (FIGO grade 3) and serous cystadenocarcinoma.
2. Capsular invasion in the bilateral ovaries.
3. Metastatic serous cystadenocarcinoma was identified within the subcutaneous tissue (Figure 1) and umbilicus (Figure 2).
4. Tumor was found in the omentum, hilus of the spleen, and in seven resected pelvic lymph nodes.
5. Metastatic carcinoma was seen on the peritoneal surface of the rectum.
6. No tumor was found in the ascites fluid, uterus, appendix, and paraaortic lymph nodes.

Because of widespread dissemination, the tumor was considered FIGO surgical Stage IV. After the patient had postoperative recovery, she was treated with six cycles of carboplatin (AUC 6) and paclitaxel (175 mg/m²) every three weeks. Over the following months, the patient’s condition was relatively stable but after six cycles of adjuvant chemotherapy, there was a significant rise in serum CA-125 and progression of metastasis. Considering the continual tumor progression, chemotherapy was advised. The patient did not consent and was only given palliation. She died of widespread metastatic disease 15 months after the time of diagnosis.

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Discussion

Sister Mary Joseph (1856-1939), superintending nurse at Saint Mary’s Hospital in Rochester (at present Mayo Clinic, Minnesota), was the first person to draw the attention of Dr. William Mayo to the presence of a periumbilical nodule as a sign of an intraabdominal malignancy. In 1949, the English surgeon Hamilton Bailey in his textbook “Demonstrations of physical signs in clinical surgery” first used the term “Sister Mary Joseph’s nodule” to describe umbilical metastases [5]. Sister Mary Joseph’s nodule may be painful and ulcerated, sometimes with purulence, blood, or serous discharge. The size is usually between 0.5-2 cm, although lesions up to 10 cm have been reported [6].

There are many theories that try to explain the pathogenesis of umbilical metastases in intraabdominal or pelvic malignancy: direct extension through the peritoneum, retrograde suberosal lymphatic spread from the axillary, inguinal, and paraaortic lymph nodes, vascular spread through the anastomoses between the epigastric, thoracic lateral, internal mammary vein. Furthermore, spreading may occur through the urachus, remains of the omphalomesenteric duct, and falciform ligament [6-8]. Therefore, theoretically, any type of cancer may metastasize to the umbilical region. However, the most common primary tumor sites are intraabdominal and pelvic. The most common sites of distant metastasis from ovarian carcinoma are the pleura, liver, lung, and lymph nodes [4]. In our patient, umbilical, omental, spleen, and pelvic lymph node metastases were confirmed by histopathological examination. The presence of cutaneous metastases from a primary ovarian carcinoma as detected in our patient is a rare condition, occurring in about 3.5% of the patients, and only a few cases are reported in literature [9]. To the best of our knowledge, this is the first case of a Sister Mary Joseph’s nodule from a serous component of Stage IV mixed type epithelial ovarian cancer. Moreover, a Sister Mary Joseph’s nodule is an important sign of widespread intraabdominal neoplasia and patients usually die from their malignancy within a year [9].

Some authors approve an aggressive approach including surgery and adjuvant therapy [8, 10, 11], while others suggest palliation [12, 13]. However, recent studies show better survivals (17.6 months) for patients receiving surgery and adjuvant treatment compared with patients receiving surgery (7.4 months) or chemotherapy alone (10.3 months) [12]. Since our patient was considered unresectable at the initial staging procedure, we started “neoadjuvant chemotherapy” to achieve overall tumor reduction. After neoadjuvant chemotherapy, at explorative laparotomy optimal cytoreductive surgery was achieved. Subsequently we started “adjuvant chemotherapy” followed by surgery but she survived for only 15 months.

In conclusion, we have described a 49-year-old woman who presented with umbilical metastasis as a first sign of an extremely aggressive Stage IV mixed type epithelial ovarian cancer. This is the first case of umbilical metastasis from a serous component of Stage IV mixed type epithelial ovarian cancer. Furthermore, umbilical metastasis is usually a reflection of an underlying widespread malignancy and patients with umbilical metastases have a poor prognosis.

References


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Paget’s disease of the vulva in a patient with scleroderma and underlying adenocarcinoma: case report

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Summary

Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by fibrosis of the skin and internal organs. Several studies have demonstrated an increased frequency of cancer in patients with SSc. We report a case of a 71-year-old woman with SSc, who presented with an eczematous lesion of the vulva. The diagnosis of Paget’s disease of the vulva (PVD) was established. The patient underwent radical vulvectomy, but 18 months later died due to adenocarcinoma of unknown primary origin. SSc and PVD are associated with various types of malignancies and patients suffering from these diseases should be under surveillance in order for any suspicious symptoms of malignancy to be early detected and investigated.

Key words: Paget’s disease of the vulva; Scleroderma; Malignancy.

Introduction

Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by fibrosis of the skin and internal organs. Several studies have demonstrated an increased frequency of cancer in patients with SSc [1, 2]. We report a case of a 71-year-old woman with SSc, who presented with an eczematous lesion of the vulva. The diagnosis of Paget’s disease of the vulva (PVD) was established. The patient underwent radical vulvectomy, but 18 months later died due to adenocarcinoma of unknown primary origin.

Case Report

A 71-year-old woman was referred to the Gynecological Department with an eczematous and reddish lesion of the vulva. She had a 25-year history of limited scleroderma, with Raynaud phenomenon, interstitial pulmonary fibrosis, digital ulcers and mild pulmonary hypertension. She also had severe osteoporosis under treatment with biphosphonates.

The patient underwent radical vulvectomy with groin and femoral node dissection. The biopsy of the tissue showed Paget’s disease of the vulva without extension beyond the base membrane. The nodes and the margins were clear.

Three months after surgery the patient experienced sudden dyspnea and was admitted to the hospital. The diagnosis was right pleural effusion. A Bulleau tube was placed and chest fluid was removed. Many malignant cells of unknown origin were detected in the fluid analysis. Computed tomography (CT) of the lungs showed pleural effusion with atelectasia of the right lung with no lymph node involvement and no neoplastic lesions. CTs of the abdomen and the brain were normal.

The pleural effusion reappeared two weeks later and the patient was referred to the Department of Cardiosurgery, where she underwent pleurectomy of the right thorax, decortication of the pleura and aspiration of the pleural fluid. The biopsy of the pleura showed adenocarcinoma of unknown primary origin. The patient was referred to us in order to investigate the origin of the adenocarcinoma. All blood tests, including tumor markers, were normal. The patient underwent a new CT of the brain, lungs and abdomen, mammography, gastroscopy, colonoscopy, bone scan, magnetic resonance imaging, of the abdomen and ECHO exam of the lower abdomen. No primary origin was found. She refused chemotherapy. As a result she was discharged and she was in very good clinical condition, without symptoms of any malignancy or local recurrence of the disease for about one year.

One year later the patient was referred to us with severe low back pain and dyspnea. The X-ray exams showed fracture of Th10 and large pleural effusion of the right thorax. The bone scan showed osteolytic lesions of the spine and the CT of the lungs showed pleural effusion with a metastatic lesion in the liver. The patient and her relatives refused any further diagnostic or therapeutic evaluation. A few days later the patient died and the diagnosis was adenocarcinoma of unknown primary origin.

Discussion

PDV is a rare condition that accounts for < 1% of vulvar neoplasms [3], and affects mainly postmenopausal white women with a mean age of diagnosis at 64 years [4]. After treatment about one-third of women experience local recurrences over many years [5, 6]. Underlying adenocarcinoma is found in 10% to 20% of the cases [7]. Commonly associated malignancies are breast, basal cell, rectal, genitourinary and cervical carcinoma [5].

In our case a 71-year-old woman with a history of scleroderma experienced itching and burning of the vulva with a reddish lesion which proved to be PDV. Population-based surveys reveal a higher incidence of malignancy in scleroderma patients [1, 2]. The types of cancer reported include lung cancer, non-melanoma skin cancer and liver cancer [1]. Possible reasons for this includes fundamental aspects of scleroderma biology – a number of cellular oncogenes are overexpressed, and there are reports of a reduction in the level of tumor suppressor genes [8]. Other relevant factors may be the use of potentially carcinogenic chemotherapies like cyclophosphamide and the possible effects of long-term immunomodulation treatment [9].
At the time of diagnosis, the patient was under therapy with low-dose prednizolone (10 mg/day) and nifedipine (30 mg/day). She also had received azathioprine (100 mg/day) for pulmonary fibrosis, bosentan (125 mg/day) for pulmonary hypertension and intravenous pulses with iloprost for digital ulcers and the Raynaud’s phenomenon. She had never received cyclophosphamide.

Despite the detailed investigation and search, no origin of the malignancy was found. To the best of our knowledge this is the first report of PDV co-existing with scleroderma in the same patient. PDV may be a longstanding problem but few patients die of this condition. On the other hand systemic sclerosis is a multisystem disease that is often fatal due to respiratory involvement (pulmonary fibrosis and pulmonary arterial hypertension) [10] and other complications. In our case the cause of death was adenocarcinoma, which may be related to both diseases.

In conclusion, PDV and scleroderma are two rare conditions associated with various types of malignancies. Patients suffering from these diseases should be under diligent surveillance and any suspicious symptoms of malignancy should make this more intensive.

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Vulvar neoplasm and reconstruction of a lesion with a vertical rectus abdominis myocutaneous flap: case report

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Summary

A 41-year-old nulliparous woman was admitted to the Institute of Gynecology and Obstetrics in 2007 with a painless tumor mass invading the whole vulvoperineal and gluteal region. Pathohistological biopsy revealed FIGO Stage II squamocellular invasive carcinoma, but clinically it was Stage IVa verrucal vulvar carcinoma because of malignant infiltration to the distal part of the vagina and bilateral gluteal region. The patient underwent radical vulvectomy with bilateral inguineofemoral lymphadenectomy and partial vaginectomy. Reconstruction was performed after three weeks using a distally based vertical rectus abdominis myocutaneous flap (VRAM). A new entrance of the vagina was created. The patient was further treated with radiation therapy.

Key words: Carcinoma; Vulva; Reconstruction.

Introduction

Vulvar carcinoma is a rare malignant disease with an incidence of 5% of gynecological malignacies according to FIGO, 1994 [1, 2]. Squamous carcinoma is the most frequent type and appears in 90% of vulvar cancers. Verrucous carcinoma is a specific type of squamous carcinoma that clinically appears as a vegetative mass [1]. Statistical examinations show that in 39% of cases, vulvar carcinoma is diagnosed in Stage III and IV [3, 4].

Treatment of vulvar neoplasms often necessitate resection of perineal structures. With Stage III and IV vulvar lesions, there is often tumor extension to the vagina and anus as a result of the common lymphatic drainage of these structures. However, because distant metastases are uncommon, radical excision can still produce adequate tumor control in most cases [3, 5]. Radical vulvectomy consists of wide excision of the vulvar region with an absolutely clean resectional edge, removing the skin, subcutaneous lipid tissue and the muscles till the fascia [3].

Plastic surgery enlarges the spectrum of available operative therapy for vulvar cancer, especially in large tumors, and its application leads to a favorable oncological outcome as well as excellent cosmetic results [6]. Extensive defects of soft tissues after radical vulvectomy ablations present a challenge for the reconstructive surgeon. The rectus and gracilis myocutaneous flaps have been the traditional flaps of choice for reconstruction of massive vulvoperineal defects [5]. In the case of the smaller defects, the use of flaps allows free-tension closure, thus avoiding wound diastase and delayed healing [7].

Case Report

A 41-year-old nulliparous woman was admitted to the Institute of Gynecology and Obstetrics in 2007 with a painless tumor mass invading the whole vulvoperineal and gluteal region. Vulval and perineal changes were vegetant and necrotic; there was differentiation and bleeding with a necrotic smell (Figure 1). Her clinical condition was poor, as well as the blood analyses - anemia gravis (Hgb 25, MCV 61.4), leukocytes 25.9 and platelets 505. According to her anamnesis the mass had increased rapidly during the last six months. The pathohistological biopsy revealed a squamocellular invasive carcinoma FIGO Stage II, but clinically it was a verrucous vulvar carcinoma Stage IVa, because of malignant infiltration to the distal part of the vagina and bilateral gluteal region.

The patient underwent radical vulvectomy with bilateral inguineofemoral lymphadenectomy and partial vaginectomy (Figure 2). Reconstruction was performed using a distally based vertical rectus abdominis myocutaneous flap (VRAM). The size of the defect was 25 x 12 cm. The postoperative period was uneventful. After three weeks, the second stage was performed with restoration of the rectoanal junction. A new entrance to the vagina was created, taking care not to disturb the vascular pedicle of the flap (inferior epigastric vein and venae comitantes) (Figure 3). The urethra and anal sphincter were spared during the first operation. The patient was further treated with radiation therapy.

Discussion and Conclusion

Unfortunately many patients are initially diagnosed with advanced disease in Stage III and IVa, and thus need radical to extensive vulvectomy [3, 6]. Radical vulvectomy with bilateral inguineofemoral lymphadenectomy and partial vaginectomy (Figure 2). Reconstruction was performed using a distally based vertical rectus abdominis myocutaneous flap (VRAM). The size of the defect was 25 x 12 cm. The postoperative period was uneventful. After three weeks, the second stage was performed with restoration of the rectoanal junction. A new entrance to the vagina was created, taking care not to disturb the vascular pedicle of the flap (inferior epigastric vein and venae comitantes) (Figure 3). The urethra and anal sphincter were spared during the first operation. The patient was further treated with radiation therapy.

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Summary

A 41-year-old nulliparous woman was admitted to the Institute of Gynecology and Obstetrics in 2007 with a painless tumor mass invading the whole vulvoperineal and gluteal region. Pathohistological biopsy revealed FIGO Stage II squamocellular invasive carcinoma, but clinically it was Stage IVa verrucal vulvar carcinoma because of malignant infiltration to the distal part of the vagina and bilateral gluteal region. The patient underwent radical vulvectomy with bilateral inguineofemoral lymphadenectomy and partial vaginectomy. Reconstruction was performed after three weeks using a distally based vertical rectus abdominis myocutaneous flap (VRAM). A new entrance of the vagina was created. The patient was further treated with radiation therapy.

Key words: Carcinoma; Vulva; Reconstruction.
extension to the vagina, urethra and anus as a result of the common lymphatic drainage of these structures [5]. Distant metastases are uncommon as was the case in our patient so radical excision can still produce appropriate local tumor control in most cases [3, 5].

Reconstruction of the vulva and perineum following radical vulvoperineal resection is a challenging task for every surgeon. Traditional reconstructive approaches for extensive defects of the vulvoperineal region have included the pedicled gracilis and the rectus abdominis musculocutaneous flaps [5]. The use of a highly vascularized flap provides a major benefit to healing by bringing a generous bulk of healthy non irradiated tissue and a new blood supply to the vulvoperineal region [5, 7]. In our case the regional pedicle rectus abdominis flap was found to be highly reliable for reconstruction of the extensive vulvoperineal defects after an advanced neglected case of vulvar malignancies.

The pedicled VRAM flap is a reliable and versatile flap for extensive perineal resurfacing [5, 8]. It has also been used as a tubed flap for vagina reconstruction [8, 9]. Harvesting of the flap preserving its vascular pedicle of the inferior epigastric vein and venae comitantes is technically simple and allows a wide arc of rotation of the flap in order to cover the upper and lower perineal areas. Rectus flaps have a low failure rate, and the advantage is that the donor region can be closed primarily [5].

In our case the major part of the defect was reconstructed with a VRAM flap with maximum dimensions to facilitate direct closure of the donor region. The closure of the donor region had to be without any tension to avoid complication of hernias. In cases of larger defects, some authors also suggest combining two local fasciocutaneous flaps and a rectus myocutaneous flap facilitating covering of an extensive vulvoperineal defect without any tension and preserving a more natural appearance and function of the region as well [5, 8].

In cases of neglected disease, after radical excision of the tumor a larger flap for reconstruction is needed. The VRAM flap enables closure of every kind of defect, even deep ones and those extending to the surrounding tissue.

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