Colposcopy, cytology and histology in the diagnosis of squamous intraepithelial lesions of the cervix

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Summary

Objective: to compare colposcopic findings to cytologic and histological diagnoses in women with colposcopic reports of ANTZ and/or HPV infection.

Methods: among 791 hospitalized women referred for colposcopic examination, colposcopy showed ANTZ grade 0-2 and/or HPV infection in 271 patients (34.26%). Only 153 were fully investigated by colposcopy, cytology (under colposcopic observation) and histology (target punch biopsy: 109 patients; surgical specimens of hysterectomy: 42 patients; conization: 2 patients). Cytological and histological diagnoses were reported according to the Bethesda System.

Results: 132/153 Pap smears were estimable for sampling adequacy; 44/63 resulted as normal and were histologically positive for LSIL [1]. Five LSIL-positive Pap tests were negative on histology (false negative and false positive rate of 33.33% and 3.78%). The pap test was diagnostic for intraepithelial neoplasia in 34/65 cases (53.3%) and for invasive cancer in 6/11 cases (54.5%). In 67/132 cases (50.8%) adequate-for-sampling Pap smears could not predict the exact diagnosis. On the other hand, 108/141 patients with colposcopic evidence of ANTZ/cancer showed histological SIL or invasive neoplasm (76.59%): ANTZ 1 was associated to LSIL and HSIL in 74.1% and 2.4%; ANTZ 2 to LSIL, HSIL and invasive cancer in 41%, 30.76% and 10.3%. Colposcopic suspicion of invasive cancer in 8 patients was histologically demonstrated in 7 (87.5%); colposcopic diagnosis of HPV infection was confirmed in 10/12 (83.4%).

Conclusion: a better correspondance was shown between colposcopy and histology than between cytology and histology in the diagnosis of SIL. We suggest a routine colposcopy investigation for all patients admitted to a gynecological clinic and we believe it is very important to take Pap smears under colposcopic observation if colposcopy and cervical smears are performed in the same sitting.

Key words: Cervical intraepithelial neoplasia; Squamous intraepithelial lesions; Cervix neoplasms; Cytology; Histology; Colposcopy; Cytodiagnosis; Vaginal Smears.

Introduction

Preinvasive lesions of the uterine cervix are a variety of histological abnormalities involving the squamous epithelium. These lesions, known initially as cervical intraepithelial neoplasia (CIN) and more recently termed squamous intraepithelial lesions (SIL), differ in degrees of cellular atypia and mitotic activity [1].

According to the Bethesda system, preinvasive lesions may be categorized into two broad cytological groups, specifically, low grade lesions (LSIL), that have a very low risk for progressing to cancer, and high grade lesions (HSIL) that show major atypia and a higher degree of persistence and progression [2]. This classification may also be used for histological findings [3].

In the pathogenesis of CIN a crucial role is played by HPV-infection that has become the most common sexually-transmitted disease in the last ten years [4, 5]. Its manifestations are variable, ranging from occult infection to overt disease in which there is clinical and pathologic evidence of HPV infection.

Although a cause-effect relationship has not yet been demonstrated, there is increasing evidence that HPV infection is the primary risk factor for cervical cancer [6-9].

High grade lesions (CIN II - CIN III) are more often associated with a limited number of HPV types, especially HPV 16, 18, 31, 33 and 35, and a few other types such as 45, 51, 52, 56 and 57 that have been found in invasive lesions too. These HPV are also termed HPV of oncogenic type (HPV-onc) [3, 10].

HPV type 6, 11 and, to a lesser degree, 42, 43 and 44 are detected almost only in low grade lesions and are described as HPV of non-oncogenic type [10].

Therefore, the detection of HPV within genital lesions and the identification of the specific type of HPV may be useful for selecting risk groups and for the management and the follow-up of patients [11].

Recent recombinant DNA techniques allow specific detection of HPV types in genital lesions.

Hybridization techniques identify the nucleic acids directly while polymerase chain reaction (PCR) based techniques amplify nucleic acids first and then detect the amplified product. In general, PCR-based tests yield HPV population prevalence estimates about 2-3 times higher than those of non-amplified tests [12, 13].

Women with high-oncogenic-risk viruses are at substantially greater risk of developing an abnormal Pap smear result compared with women infected with low or intermediate oncogenic-risk viruses [14].

The combination of a Pap smear and HPV DNA screening offers the potential for detecting almost all prevalent

cases of HPV infection but the practical use of this approach is limited because of its expense and complexity [15].

Thus, the diagnosis of HPV infection and CIN is still based mainly on cytology, colposcopy and histology.

Condylomata acuminata have a rather typical colposcopic pattern [16, 17].

Diagnostic difficulties arise in the identification of flat condylomas. Although focal or multiple non-squamocolumnar junctional lesions with surface asperities and an irregular Lugol solution staining are easily related to HPV infection, when acetowhite epithelium is totally flat and contiguous to the squamocolumnar junction (SCJ) a distinction between flat condyloma and CIN is less easy [16, 18].

Colposcopic diagnosis of HPV infection and CIN may be difficult and highly subjective owing to similarities of the flat lesions of early CIN to HPV lesions but, according to Grubb, a skilled colposcopist can almost always differentiate these lesions [19].

It has been reported that colposcopic features do not always show correspondence to the lesional degree of atypia [20].

The aim of this study was to compare colposcopic findings to cytologic testing and histological diagnoses based on target punch biopsy or surgical specimens of hysterectomy or conization.

It includes women with colposcopic evidence of an abnormal transformation zone (ANTZ) and/or HPV infection enrolled with no reference to specific colposcopic characteristics (punctuation, mosaic, atypical vessels, etc.).

Material and Methods

Between October 1995 and January 1998, 791 hospitalized women were referred to the Colposcopic Center of the Department of Obstetrics and Gynecology, University of L'Aquila (Italy) for colposcopic examination. This is performed on a regular basis, whenever possible, on all gynecological patients admitted for the first time to our Department.

The mean age of the patients was 46.4 years (range 20-77); the most common age group was from 41 to 50 years.

In 271 women (34.26%), colposcopy showed one or more areas of ANTZ grade 0,1 or 2 and/or HPV infection, or lesions suggesting invasive cancer.

Only 153 patients were fully investigated by colposcopy, cytology and histology.

Colposcopic examinations were performed following a standard procedure which includes cleansing of the cervix with a 5% acetic acid solution.

The colposcopic lesions were reported according to the Italian colposcopy classification [21] as follows: ANTZ grade 0, ANTZ grade 1; ANTZ grade 2; suspected invasive cancer.

Association with HPV infection was not remarkable, whereas colposcopic findings suggesting only the presence of viral infection, (florid condylomata, keratosing-mosaic- and punctate-like lesions) were classified apart.

Papanicolau smears were taken under direct colposcopic observation with a cytobrush from the endocervix and by cervical scraping: both cytological and histological diagnoses were reported according to the Bethesda System of classification [2].

Selected spot biopsies were performed in the areas showing atypical colposcopic patterns under colposcopic guidance in 109 patients using an Alexander forcep; in the other women histological specimens were obtained by hysterectomy performed for uterus prolapse, myoma or ovarian cancer in 42 patients and by surgical conization of the cervix in 2 cases (nulliparous fertile women with a relapsing lesion not entirely visible at colposcopy).

All cytological smears and histological samples from the study patients were separately examined by the Department of Histopathology, S. Salvatore Hospital, L'Aquila.

Results

The colposcopic findings in the 153 cases were: ANTZ grade 0 in 9 cases; ANTZ grade 1, in 85; ANTZ grade 2 in 39; suspected invasive cancer in 8 patients (squamous carcinoma in 7 cases and adenocarcinoma in one), HPV infection without coexistence of ANTZ in 12 women.

Table 1 shows the results of the comparative analysis between colposcopic patterns and histological findings.

Four of the 9 cases (44.50%) with grade 0 ANTZ were low grade SILs; out of the 85 cases with grade 1 ANTZ, 63 (74.12%) were LISLs and only 2 (2.35%) were HSILs (CIN II).

Among the 39 women with grade 2 ANTZ, 16 (41.02%) and 12 (30.76%) cases were LSILs and HSILs respectively, subdivided as follows: LSIL without HPV infection in 6 patients, LSIL-HPV in 10, HSIL in 9, HSIL-HPV in 3. Invasive cancer was diagnosed in 4 cases comprising one from the cervical canal and one early stromal invasive cancer associated with HSIL foci.

Seven (87.50%) out of 8 cases with colposcopic suspicion of invasive disease were confirmed by histological examination; the other one, that was suspected to be adenocarcinoma due to the presence of an endocervical neoformation with atypical vessels and hypertrophic papillae, was histologically a Müllerian adenofibroma.

Among the 12 women with colposcopic suspicion of HPV infection, without ANTZ, the histological finding was negative only in two cases (16.60%) and positive for HPV in the remaining 10 patients (83.40%).

A comparison of cytological and histological diagnosis is shown in Table 2.

Histology confirmed as negative only 14 (22.22%) of the 63 normal Pap tests; but in 43 cases (68.25%) cervical cytology was unable to detect a low grade SIL and in 1 case (1.58%) a high grade SIL (CIN II).

Among the 41 Pap tests suggesting a LSIL, 30/41 (73.17%) were confirmed by histology, but in 6/41 cases (14.63%) the lesion was underestimated by cytology; in 5 patients (HSIL-HPV) the histological diagnosis was one step worse than the cytological diagnosis; only in 1 case (HSIL) was histological diagnosis two steps worse than cytological diagnosis.

In the 9 women in whom a high grade lesion was found in the cytological smears the biopsy confirmed the Pap test diagnosis, but in 5/9 patients (55.56%) histology suggested that the lesion was of greater severity (invasive cancer).

Table 1. — *Comparative analysis between colposcopy and histology*

COLPOSCOPY			HISTOLOGY		
	Normal	Other*	LSIL	HSIL	Cancer
ANTZ 0 (no. 9)	3 (33.30%)	2 (22.20%)	4 (44.50%) HPV = 2 CIN 1 = 1 CIN 1 + HPV = 1	–	–
ANTZ 1 (no. 85)	12 (14.12%)	8 (9.41%)	63 (74.12%) HPV = 26 CIN 1 = 10 CIN 1 + HPV = 27	2 (2.35%) CIN 2 = 2	
ANTZ 2 (no. 39)	1 (2.56%)	6 (15.38%)	16 (41.02%) HPV = 5 CIN 1 = 6 CIN 1 + HPV = 5	12 (30.76%) CIN 2 = 4 CIN 2 = HPV = 3 CIN 3 = 5	4 (10.25%)
Susp. invasive cancer	–	1# (12.50%)	–	–	7 (87.50%)
HPV (no. 12)	2 (16.60%)	–	10 (83.40%) HPV = 9 CIN 1 = 0 CIN 1 + HPV = 1	–	–

*Chronic cervicitis; mature/immature metaplasia; hyperplasia; #Müllerian andenofibroma

Table 2. — *Comparative analysis between cytology and histology*

PAP-TEST				HISTOLOGY		
		Normal	Other*	LSIL	HSIL	Cancer
Normal (no. 63)		14 (22.22%)	5 (7.93%)	43 (68.25%) HPV = 22 CIN 1 = 5 CIN 1 + HPV = 16	1 (1.58%) CIN 2 = 1	–
ASCUS# (no. 5)		1 (20%)	2 (40%)	2 (40%) HPV = 2	–	–
Metaplasia (no. 7)		1 (14.28%)	2 (28.47%)	4 (57.14%) HPV = 2 CIN 1 = 2	–	–
LSIL (no. 41)	HPV (no. 13)	1	1	11 HPV = 8 CIN 1 = 1 CIN 1 + HPV = 2	–	–
	CIN 1 (no. 22)	–	3	13 HPV = 2 CIN 1 = 5 CIN 1 + HPV = 6	6 (14.63%) CIN 2 = 4 CIN 2 + HPV = 1 CIN 3 = 1	–
	CIN 1 + HPV (no. 6)	–	–	6 HPV = 3 CIN 1 = 1 CIN 1 + HPV = 2 30 (73.17%)	–	–
HSIL (no. 9)	CIN 2 (no. 4)	–	–	–	2	2
	CIN 3 (no. 5)	–	–	–	2	3
Cancer (no. 7)				–	4 (44.44%)	5 (55.56%)
				–	1 (14.28%)	6
		–	–	–	CIN 3 = 1	(85.71%)
Inadequate smear (no. 21)		1 (4.76%)	4 (19.04%)	14 (66.66%) HPV = 3 CIN 1 = 3 CIN 1 + HPV = 8	2 (9.52%) CIN 2 = 1 CIN 3 = 1	–

*Chronic cervicitis; mature/immature metaplasia; hyperplasia; Müllerian andenofibroma
Atypical squamous cells of undetermined significance

Table 3. — *Comparison between colposcopy, cytology and histology*

COLPOSCOPY			CYTOLOGY AND HISTOLOGY				
		Normal	Other*	LSIL	HSIL	Cancer	Correspondence
ANTZ 0 (no. = 9)	Pap-test	7	–	2	–	–	55.55%
	Histology	3	2	4	–	–	
ANTZ 1 (no. = 85)	Pap-test	42	19	24	–	–	51.76%
	Histology	12	8	63	2	–	36.92%
ANTZ 2 (no. = 39)	Pap-test	10	12	8	7	2	58.97%
	Histology	1	6	16	12	4	
Susp. invasive cancer (no. = 8)	Pap-test	–	1	–	2	5	85.71%
	Histology	–	1	–	–	7	
HPV (no. 12)	Pap-test	4	2	6	–	–	66.6%
	Histology	2	–	10	–	–	

*Histology: Chronic cervicitis; mature/immature metaplasia; hyperplasia; Müllerian adenofibroma.
 Pap test: Inadequate smear; squamous metaplasia; ASCUS
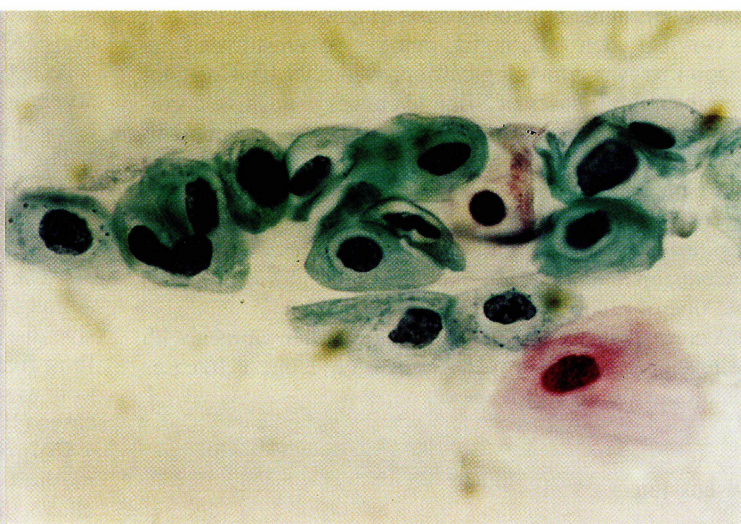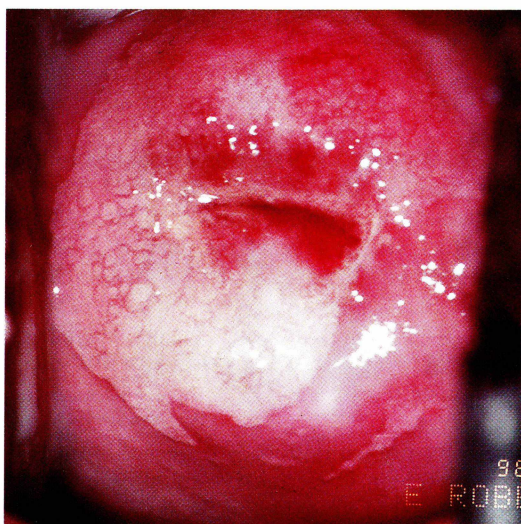§ Correlation between cytology and histology related to LSIL and HSIL.
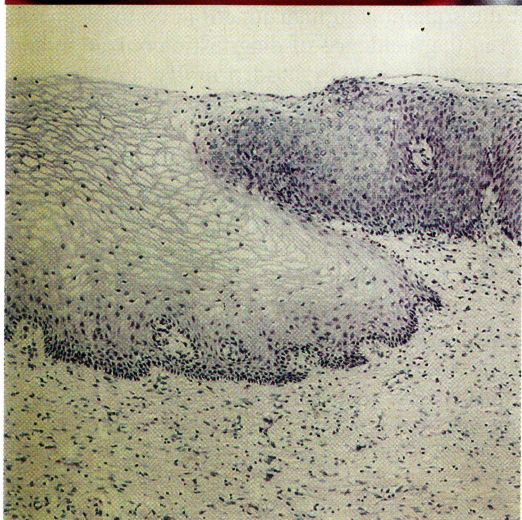
Figure 1. — ANTZ G2 with thick epithelium on the whole cervix. Irregular mosaic with satellite lesion on the posterior lip and regular mosaic on the anterior lip. Lack of thick glandular outlet *(colposcopic appearance, 12x magnification)*.

Figure 2. – High grade SIL (CIN 2 with HPV cellular alterations): smear showing dyskeratosis, nuclear membrane with condensed edge and spiculae, cluster-shaped chromatin, perinuclear halo, increased nucleo/cytoplasm ratio *(cytological appearance; Papanicolau staining, 400x magnification)*.

Figure 3. – Transformation zone between regular squamous epithelium and areas of CIN 2 with HPV cellular alterations *(histological appearance, 40x magnification)*.

Only in one (14.28%) of the 7 cases with cytological diagnosis of carcinoma, did the results of the punch biopsy and the subsequent surgical specimen of hysterectomy (HSIL) not agree with those of cytology.

Among the 21 cases with inadequate smears, 14 (66.66%) were LSILs and 2 (9.52%) histologically diagnosed HSILs; in these last two cases a concomitant flogosis prevented the exact identification of the lesion.

A comparison of colposcopic, cytological and histological results is shown in Table 3 (Figs. 1, 2, 3).

Among the patients with a colposcopic pattern of grade 0 ANTZ, the Pap test did not detect two of the 4 cases of LSIL histologically diagnosed (55.5% of correspondence between cytology and histology); cytology identified properly only 24 of the 63 cases of LSIL and none of the 2 cases of HSIL histologically diagnosed in the group of women with colposcopic characteristics of ANTZ G 1, (36.92% of the exact correlation between cytology and histology).

Among the cases with colposcopic features of grade 2 ANTZ, the Papanicolau test ignored 8 of the 16 cases of LSIL, 5 of the 12 cases of HSIL and 1 of the 4 cases of invasive cancer detected by histology (underestimating the lesion as CIN III in two women and CIN II in the other one); in the remaining case, diagnosed by a Pap test as cervical adenocarcinoma, cytology overestimated the lesion that was a histologically proven CIN III. Considering the overall cases of SIL and cancer, a positive correlation between cytology and histology was found in 58.97%.

A better rate of concordance (85.71%) was observed in the colposcopic suspected invasive disease group: the Pap test correctly identified 5 of the 7 cases of cancer; it underestimated the lesion in one case of grade 1 (CIN III) and one of grade 2 (CIN II).

A correspondence of 66.66% was found in women with colposcopic diagnosis of HPV infection: 6 out of 10 cases histologically detected.

Discussion

Cervicovaginal cytology as a method of screening for cervical neoplasia has limitations resulting from the various methods of sampling and categorization. Furthermore, the reliability of the Pap test may be influenced by the methods and quality of sampling, by the examiner's and the whole laboratory's experience which relies on the overall number of smears handled yearly [22-30].

It has long been recognized that false negative cervical smears are not rare, ranging from 10 to 30% of the cases [29-34]. Yule [32] and Beilby [33] found a false negative rate of about 18% which means that nearly one out of five lesions are missed on Pap tests. A recent review reported that Pap test error rate for cervical invasive cancer may be 50% and data concerning preinvasive neoplasias show that in about 30% of the cases the grade of the lesion is underestimated [29].

In our study (Tab. 2) a false negative rate of 33.33% (calculated on 132 Pap tests estimable for sampling ade-quacy) was found: 43 cases of LSIL and 1 case of HSIL histologically detected in 44 Pap tests reported as normal. The false positive rate of abnormal smears was only 3.78% (five Pap tests positive for LSIL were negative after histological examination of both cervix biopsy and surgical specimen of hysterectomy).

Evaluating only abnormal cervical smears, in 8 cases (15.4%) the histological diagnosis was one-step worse than the cytological one; in 3 cases (5.8%) the histological diagnosis was two-steps worse than the cytological report.

In total, the grade of lesion was underestimated in 21.14% of the cases. Altogether, the Pap test was diagnostic for intraepithelial neoplasia (CIN I, II, III) in 34 out of 65 cases histologically detected (52.3%) and for invasive cancer in 6 out of the 11 cases histologically demonstrated (54.5%).

In 67 out of 132 women with adequate Pap tests (50.8%) the cytology could not predict the exact histological diagnosis.

As shown in table 1, a better correspondence was observed between colposcopy and histology than between cytology and histology. As a matter of fact there was histological evidence of SIL or cancer in 108 out of 141 patients (76.5%) with positive colposcopic examinations (ANTZ or cancer).

As expected, an increase in colposcopic degree of atypia is associated to a greater severity of histological lesion [35-37].

The evidence of grade 1 ANTZ was associated to low grade and high grade SIL, respectively, in 74.1% and 2.4% of the cases. Colposcopic features of grade 2 ANTZ corresponded to LSIL in 41% of patients, to HSIL in 30.76% and to invasive cancer in 10.3% of the cases. Among the 8 women with colposcopic suspicion of invasive disease, 7 (87.5%) were invasive cancers (stage Ia or Ib in five women). Colposcopic diagnosis of HPV infection was demonstrated histologically in 83.40% of the cases (10/12).

Colposcopy is not considered to be a diagnostic method, but rather an investigative technique which allows the evaluation of the extent of the lesion and localization of the squamocolumnar junction, contributing to a reduction in the incidence of diagnostic conization and ruling out invasive cancer; additionally, colposcopy directs diagnostic biopsies for the appropriate management of cervical lesions [38-42]. Nevertheless, we should emphasize that, even without recognizing colposcopy as a method of screening for the early diagnosis of cervical neoplasia, its routine use in patients admitted to our Clinic allowed us to detect 62 cases of cervical lesions missed by Pap tests. Two women with invasive cancer (36 and 48 years old) were admitted to the hospital after an episode of menometrorrhagia; the Pap test, performed at the time of colposcopic examination, revealed only an HSIL. In both cases, such as in the other 9 detected as invasive disease by histology, colposcopy showed an area of grade 2 ANTZ with atypical vessels (4 cases) or direct signs of cancer (7 cases) and allowed, by the subsequent biopsy, a correct diagnosis and therapeutic approach.

Conclusion

On the basis of these data, even if colposcopy is not proposed as a "first level" technique for the screening of cervical pathology, it is suggested that all women admitted to a gynecological clinic should undergo a colposcopic examination as a routine diagnostic investigation, independently from admission diagnosis. If colposcopy and cervicovaginal smears are performed in the same sitting it is very important to always take the Papanicolau smears under colposcopic observation [42-46].

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