Cytology, histology, and colposcopy in the diagnosis of neoplastic non-invasive epithelial lesions of the cervix

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Summary

The purpose of our study was to examine the concordance among colposcopy, cytology, and histology in the diagnoses of intraepithelial lesions of the uterine cervix. We compared the results of Pap tests, biopsies, and colposcopy in 190 patients, who had histologically proven CIN and/or HPV infection, using histology as "the gold standard". The X^2 (chi square) test was used for the statistics analysis. The sensitivity of cytology for the detection of CIN was 70%, and was lower for LGL (low grade lesions) than for HGL (high grade lesions): 61.2% *versus* 88.5%, respectively ($p<0.0001$). We obtained a high rate of false negative smears (30%), with a relatively high rate of inadequate samples (59.6%). The sensitivity of colposcopy was 92%. Our results suggest that the Pap test alone is no longer sufficient for the screening of precancerous lesions of the cervix, and colposcopy is compulsory each time the smear is inadequate or altered.

Key words: HPV; CIN; Colposcopy; Cytology; Histology.

Introduction

The early diagnosis and the timely treatment of cervical intraepithelial neoplasia have contributed to a significant reduction in the rate of invasive cancer of the uterine cervix [1]. The detection tools that have made this decrease possible are the Pap (Papanicolau) test, colposcopy, and colposcopically directed punch biopsy.

It is not always conceeded that patients presenting with abnormal cervical smears should be immediately referred for a colposcopically directed punch biopsy [2].

Each of these detection procedures has its own limits, as pointed out by several authors. There is a false-negative rate for the Pap test as high as 30 to 40% [3, 4]. The adequacy of smears plays a very important role in the high rate of false-negative Pap tests. In fact, according to the Bethesda system, the criteria to classify a Pap test as "adequate" are: the presence of endocervical cells or cells with metaplastic changes (which make one sure that the sampling includes the transformation zone); a conspicuous number of epithelial cells; the absence of a large amount of blood or high number of inflammatory cells or other factors that prevent the interpretation of 75% of the epithelial cells, if not more [5].

In spite of these limitations, the Pap test remains an easily available, well-accepted and cheap screening test, that it is not yet replaceable. Colposcopy with a possible punch biopsy could underestimate a certain amount of pathologies, especially as far as the diagnosis of microinvasion is concerned, should the biopsy not include cervical stroma and should the lesion not be entirely visible on the ectocervix [6].

However, colposcopy is necessary for the identification of the lesion and the evaluation of its extension, to estimate whether a biopsy is indicated, and for a correct therapeutic approach.

In this study we evaluated the diagnostic accuracy of cytology and colposcopy, using histology as the "gold standard".

Materials and Methods

During the period January 1990 - December 1995 we performed 1012 colposcopically directed punch biopsies of the cervix in patients who attended the outpatient clinic of the Department of Obstetrics and Gynaecology of Università Cattolica del Sacro Cuore di Roma, Italy, presenting with abnormal smears or abnormal colposcopies. Among these, we selected 190 cases. The criterion of selection was the existence of condylomatous changes, and/or dysplasia at a histological level, and we correlated them with the respective colposcopy and Pap test. Cases of invasive carcinomas were not included in this study.

Colposcopy was performed by several experienced colposcopists, before and after application of 5% acetic acid.

All the cases we considered had a visible trasformation zone. The smears had been examined by two trained screeners, and only the suspicious ones were reviewed by pathologists.

The biopsies were diagnosed by several experienced pathologists.

Histological and cytological diagnoses resulted to be according to established criteria [7].

For colposcopies, we used the Italian classification of Mossetti [8]. The agreement between cytology and histology was evaluated by dividing the cytological cases into two groups, partly according to the Bethesda system [9]:

– low grade lesions (LGL), including cellular changes associated with human papillomavirus (HPV), that we classified as "coilocytosis", and CIN 1;

– high grade lesions (HGL), including CIN 2 and CIN 3.

For statistical analysis the X^2 (chi square) test was used.

Results

The median age among the 190 women was 32.5 years (range 17-71).

Cytology yielded the following results: 57 out of 190 smears (30%) were negative. Among these, 34 samples (59.6%) were inadequate, while 23 (40.3%) were adequate.

Twenty-one cases out of 190 (11.0%) showed changes associated with the presence of HPV, without dysplasia (coilocytosis), 58 cases out of 190 (30.5%) were CIN 1, with contemporaneous HPV infection in 44 (75.8%), while 27 cases out of 190 (14.2%) were CIN 2, with coexistent HPV infection in 16 (59.2%).

Finally, 27 cases out of 190 (14.2%) were diagnosed as CIN 3, with HPV in 8 cases (29.6%). See tables 1 and 2.

The histological diagnoses were as follows: 32 cases (16.8%) showed signs of HPV infection without dysplasia (coilocytosis), 82 cases (43.1%) were diagnosed as CIN 1, with HPV in 58 (70.7%), and, 38 cases (20.0%) were CIN 2, with coexistent HPV infection in 27 (71.0%). The diagnosis was CIN 3 in 38 cases (20.0%), with contemporaneous HPV in 24 (63.1%). See tables 3 and 4.

Altogether, signs of the presence of HPV were found in 141 out of 190 biopsies (74.2%).

The comparison between histology and cytology and between histology and colposcopy is shown in tables 5 and 6, respectively.

Cytology and histology were in complete agreement in 113 out of 190 cases (59.4%).

The Pap test underestimated the level of CIN in 75 out of 190 cases (39.4%), reporting them as negative or as LGL instead of HGL. In two out of 190 cases (1.0%) the Pap test overestimated the lesions.

There was complete agreement between the cytology and histology results in 61 out of 114 cases (53.5%) for LGL and in 51 out of 76 cases (67.1%) for HGL. Cytology and histology results agreed in 53 out of 114 cases (49.4%) of LGL and 25 out of 76 cases (32.8%) of HGL.

The sensitivity of cytology, calculated as true positives/true positives+false negatives, was 70%.

The sensitivity of cytology for low grade lesions (coilocytosis and CIN 1), calculated considering only cases for coilocytosis and CIN 1 as cytological false negatives, emerged as being noticeably lower (61.2%) than that calculated for high grade lesions (CIN 2 and CIN 3), (88.5%), considering only cases of CIN 2 and CIN 3 as cytological false negatives. This difference between the two groups proved to be statistically significant (X^2=24.445; p<0.0001). Colposcopic examination showed 169 (88.9%) abnormal transformation zones (ANTZ). Among these, 80 (11.8%) were ANTZ 0, 82 (48.5%) ANTZ 1, 67 (9.6%) ANTZ 2.

The diagnosis of CIN was histologically confirmed in 145 out of 169 ANTZ (85.7%).

Fifty-five out of 67 ANTZ 2 (82.0%) were CIN 2 and CIN 3, while only 17 out of 82 ANTZ 1 (21.0%) were CIN 2 and CIN 3; 52 out of 82 ANTZ 1 (63.4%) were CIN 1, versus 7 out of 67 ANTZ 2 (10.4%). The correlation between ANTZ 2 and CIN 2 and 3 was higher than that between ANTZ 1 and CIN 2 and 3, and this proved to be statistically significant (X^2=18.132; p<0.0001). The overall agreement between colposcopy and histology was calculated at 71.0% (135/190), while the non-agreement rate was 28.9% (55/190).

Thus, the sensitivity of colposcopy turned out to be 92.0%, while the sensitivity of colposcopy and cytology combined was 97.8%.

Discussion

From our study it is apparent that colposcopy has a higher diagnostic sensitivity for dysplastic lesions of the uterine cervix than the Pap test: 92% *versus* 70%. These results are similar to those reported by other authors, as far as colposcopy is concerned (89.0%) [10], and also cytology (rates vary from 60% to 70%) [3].

Cytology turns out to be more sensitive in diagnosing high grade lesions than low grade lesions. In fact, diagnostic agreement between cytology and histology rises in proportion to the increase of severity of displastic lesions. As seen in table 5, only seven out of 57 cytological negative cases (12.2%), were histologically HGL, while the majority of negative smears was made up of LGL (50.8%).

The high rate of false negative smears (30%) found in our study, although affected by the presence of a lot of inadequate samples (59.6%), justifies our belief that it is no longer possible to consider the Pap test sufficient for a correct screening of preneoplastic lesions of the uterine cervix.

Table 1. — *Cytology*

Number of cases		
Negative	57	(30.0%)
Coilo	21	(11.0%)
CIN 1	58	(30.5%)
CIN 2	27	(14.2%)
CIN 3	27	(14.2%)
Total	190	

Table 2. — *Cytology*

Total number of cases		Cases with coexistent HPV	
CIN 1	58	44	(75.8%)
CIN 2	27	16	(59.2%)
CIN 3	27	8	(29.6%)

Table 3. — *Histology*

Number of cases		
Coilo	32	(16.8%)
CIN 1	82	(43.2%)
CIN 2	38	(20.0%)
CIN 3	38	(20.0%)
Total	190	

Table 4. — *Histology*

Total number of cases		Cases with coexistent HPV	
CIN 1	82	58	(70.7%)
CIN 2	38	27	(71.0%)
CIN 3	38	24	(63.1%)

Table 5. — *Histology*

Cytology	Coilo	CIN 1	CIN 2	CIN 3	Total
Nega	17	33	6	1	57
Coilo	10	9	0	2	21
CIN 1	4	38	12	4	58
CIN 2	1	2	17	7	27
CIN 3	0	0	3	24	27
Total	32	82	38	38	190

Table 6. — *Histology*

Colposcopy	Coilo	CIN 1	CIN 2	CIN 3	Total
Normal	7	5	1	1	14
HPV	1	6	0	0	7
ANTZ 0	6	12	1	1	20
ANTZ 1	13	52	12	5	82
ANTZ 2	5	7	24	31	67

Table 7. — *Colposcopic diagnoses*

	N°	%
ANTZ 0	20	11.8
ANTZ 1	82	48.5
ANTZ 2	67	9.6
Total	169	85.7

The Pap test must certainly be accompanied by colposcopy each time the smear results are inadequate, considering that "it is misleading to obtain a second smear within a few days or weeks after the first, because, for unknown reasons, it may be completely negative in about 60% of patients with significant neoplastic lesions [1]". Of course this integration is even more important if cellular changes suggesting HPV infection are found in cytological smears. We agree with authors who believe that it is compulsory that all patients showing with abnormal smears, even if they are minimal, should immediately be referred for colposcopy and biopsy [11, 12, 13, 14] also because "many precancerous lesions or cancers can be represented in smears only by a few cells with trivial abnormalities, confined to the presence of a few coilocytes. This is particularly true in smears obtained without the proper care, but also in optimal samples [15]".

We do not agree with authors who suggest a more conservative approach, based exclusively on cytological follow-up, continuing with other procedures only if the cellular alteration persists [16].

Colposcopy is, therefore, an indispensable procedure in the study of cervical lesions, but it requires considerable training and experience.

Colposcopy, however, does not offer a correct assessment of the level of the intraepithelial lesions, although it it may be said that most ANTZ 1 correspond to histological CIN 1 (63.4%), while most CIN 2 and CIN 3 (82%) are associated with ANTZ 2.

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