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Retrospective study of 112 patients who had colposcopy-guided biopsy: Comparison of the cytology results with histology

Kolposkopik biyopsi yapılan 112 hastanın retrospektif incelemesi: Sitolojik bulguların histoloji ile karşılaştırılması

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ABSTRACT

We aimed to examine Papanicolaou smear results with histology for determining the false-negative/positive rate and also discussing reasons of discrepancies. The medical records of 112 patients with cervical intraepithelial neoplasia (I, II and III), atypical squamous cells on Papanicolaou smears and benign cellular changes, who underwent colposcopy-guided biopsy, over a 36 months period were reviewed. All Papanicolaou smears and histology slides showing any discordance were retrieved and reviewed to determine reasons of any discrepancies. Based on the results of our study, we determined a 5.3% of false-negative rate and a 3.5% of false-positive rate for the Papanicolaou smear examination. The efficiency of the Papanicolaou smear was 90.7%. Our study results are quite similar to those of previous reports. Despite the relative small number of cases, our false-negative and positive rates are acceptable. We recommend comparing the histology with cytology results regularly for determining causes of any discrepancies and also for obtaining an optimal internal quality assurance mechanism.

Key words: Pap smear, cervical biopsy, CIN, colposcopy

ÖZET

Servikal sitolojide yalancı negatiflik ve pozitiflik oranlarını belirlemek ve yine uyumsuzluk nedenlerini tartışmak amacıyla Papanicolaou smearlerin sonuçları histoloji ile kıyaslanmak istendi. Otuz altı aylık süre içinde, Papanicolaou smearlerinde atipik skuamöz hücreler, benign hücresel değişiklikler ve servikal intraepitelyal neoplazi (I, II ve III) olan, ve kolposkopik biyopsileri olan 112 hastanın tıbbi kayıtları gözden geçirildi. Uyumsuzluk gösteren tüm smear ve histoloji preparatları, uyumsuzluğu belirlemek amacıyla ayrıldı ve gözden geçirildi. Çalışma sonuçlarımıza göre, Papanicolaou smear incelemesinde yalancı negatiflik oranı %5.3 ve yalancı pozitiflik oranı %3.5 olarak saptandı. Bulgularımız daha önceki yayınlara kısmen benzerdir. Vaka sayısının göreceli olarak azlığına rağmen, yalancı negatiflik ve pozitiflik oranlarımız kabul edilebilir düzeydedir. Bölüm içi optimal kalite kontrolü mekanizmasının sağlanması ve uyumsuzlukların nedenlerini saptamak için, histoloji ve sitoloji bulgularının düzenli olarak kıyaslanmasını önermekteyiz.

Anahtar sözcükler: Pap smear, servikal biyopsi, CIN, kolposkopi

INTRODUCTION

Reducing morbidity and mortality is the main aim of the health system in the world. The incidence of cervical cancer has been declining in the last decades due to the Papanicolaou (Pap) smear which is the preferred screening test for cervical squamous cell carcinoma and its precursors. Cervical cytology is not a diagnostic test, and while its specificity is as high as 97%, its sensitivity has been reported as low as 51%

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(1). A zero error standard does not exist in cytopathology. The false-negative or positive rates were determined by many factors (2,3).

We aimed to examine the final histological findings, and to determine the false-negative and positive rate in 106 patients who had a cervical intraepithelial lesion (CIN/dysplasia) and atypical squamous cells (ASC) on Pap smears and underwent colposcopy-guided biopsy. We also added to our study 6 benign (negative) Pap smears whom colposcopic examination revealed dysplasia.

MATERIALS and METHODS

This retrospective study is a review of 112 conventional cervical smears obtained from patients who had colposcopy-guided biopsy between 2002 to 2004 in a single centre (Istanbul University, Istanbul Faculty of Medicine) where 10.000 Pap smears have been screening annually. Pap smears were generally sampled by residents, while colposcopic examinations were usually performed by expert gynaecologists. All cervical smears and biopsies were examined by expert gynaecopathologists. None of them were pre-screened by cytotechnologists. All Pap smears and histology slides showing any discordance were retrieved and reviewed to determine reasons (if any) for discrepancies. In our department, CIN classification system is preferred for reporting Pap smears when dysplasia is present. For any case showing atypical squamous cells, the term ASC (similar to Bethesda system) was used. Since we had been using CIN terminology, the category of ASC had always been used with a commentary note. Pap smears findings are categorised as benign, ASC, CIN I, CIN II and CIN III. Similarly, biopsy materials are also categorised as benign, CIN I, CIN II and CIN III. The false-negative rate is defined as cases diagnosed cytologically as negative (benign) and histologically as positive (CIN/dysplasia), and while the false-positive rate is defined as cases diagnosed cytologically as positive (CIN/dysplasia) and histologically as negative (benign). The efficiency or accuracy is defined as the chance, which is expressed as a percentage, that Pap smear result is correct.

RESULTS

A total of 112 patients between the ages of 18 and 60 years were studied. Mean age at presentation was 36.8 years. Inter-menstrual bleeding, post-coitus bleeding, unhealthy cervix, cervical erosion, lesion bleeding on touch were present in the minority of patients. Cytologically, we detected 6 benign cellular changes, 23 ASC, 37 CIN I, 15 CIN II and 31 CIN III. The comparison of the cytological and histological findings are summarised in the Table 1.

Of 37 patients who had CIN I on the Pap smear, 34 had CIN I or higher lesion and 3 had benign changes (inflammation, reparation, etc.) on the final histology (Table 1). All of 15 patients who had CIN II on the Pap smear, had at least CIN I on the biopsy (Table 1). Only in one of the 31 patients diagnosed as CIN III on the Pap smear, dysplasia can not be found on the final histology. We later found out that this patient has recently received chemotherapy for leukaemia and the patient was on the remission phase. After the first cytologic examination, a colposcopy-guided biopsy was performed and its result was free of dysplasia and leukaemia. History of radiotherapy was also absent. Six months later, Pap smear revealed again bizarre squamous cells mimicking CIN III and reported as ASC. Following this, a colposcopy-guided biopsy was undertaken and only signs of minimal atrophy was found. Then total abdominal hysterectomy revealed only focal reparative changes restricted to previous colposcopy-guided biopsies areas.

Of 23 patients diagnosed as ASC on the Pap smear, 9 had CIN I, 4 had CIN II, 5 had CIN III and 5 had benign changes such as reparation and inflammation (Table 1). Of 23 patients 18 who had CIN I, CIN II and CIN III on the histo-

logy, diagnosed as ASC favour dysplasia on the Pap smear. Six patients who had benign cytologic changes, had undergone colposcopic examination, which revealed CIN I in four and CIN II in two patients (Table 1).

After the reassessment of six patients having benign cytological features (false-negative group), we found that sampling errors in five of six (83%) (Table 2). Laboratory and detection errors were found in only one of six (17%), whom cervical smear had a few cells compatible with CIN I (Table 2).

Based on the results of our study, we determined a 5.3% of false-negative rate and a 3.5% of false-positive rate for the Pap smear examination (Table 2). The efficiency of the Pap smear was 90.7%.

Table 1. Comparison of the cytological and histological findings

	Histological findings in colposcopy-guided biopsies				
Pap Smear	**Benign (n, %)**	**CIN I (n, %)**	**CIN II (n, %)**	**CIN III (n, %)**	**Total**
Benign	0 (0)	4 (67)	2 (33)	0 (0)	6
ASC	5 (22)	9 (39)	4 (17)	5 (22)	23
CIN I	3 (8)	30 (81)	3 (8)	1 (3)	37
CIN II	0 (0)	6 (40)	6 (40)	3 (20)	15
CIN III	1 (3)	1 (3)	2 (7)	27 (87)	31
Total	9	50	17	36	112

Table 2. The false-negative and positive groups, rates and causes

	Histological findings in colposcopy-guided biopsies	
Parameters	**False-negative group**	**False-positive group**
Number of cases	6	4
Rates	5.3%	3.5%
Causes	5/6: Sampling errors	1/4: No adequate clinical history
	1/6: Detection errors	3/4: Disinterpretation

DISCUSSION

Although considerable variation has been reported in the sensitivity and specificity of cervical cytology, Pap smear is still one of the most cost-effective and preventive procedure for screening cervical cancer (1,2). At present, the detection of abnormal cervical tissue and diagnosis of a disease must be followed by histological examination of colposcopy-guided biopsy. Even with optimal conditions, about 5-10% of false-negative rate exists in cervical cytology (3,4). According to recent data from a review of cervical cytological abnormalities, approximately two thirds of false-negative results are caused by sampling errors, and the rest are caused by detection errors (2). Sampling errors may reflect a situation when abnormal cells are not transferred on the Pap smear or when abnormal cells are misinterpreted or missed. The latter can explain the importance to have optimal sampling, smearing, fixation and staining for reducing sampling errors. Use of a cytobrush or the Ayre spatula can be selected instead of a cotton swab (5). Poor fixation, presence of foreign material, or excess blood can easily obscure abnormal cells, which can lead to a misinterpretation or missing cells.

Recently, Allard et al. have reported that CIN lesions are not randomly distributed across cervix and there is a predilection for the locations anterior and posterior to the cervical os (6). This can also explain why some cases cytologically are false-negative, whereas biopsy materials contain abnormal cells.

In our institute, cervical smears are more performed by residents, whereas it is usually expert gynaecologist who perform colposcopic examination and biopsies. Furthermore, representative cells of a pre-cancerous lesion may be present in the specimen, but may not be identified as pathological cells on the Pap smear. This situation may be explained by sampling errors of the cytology.

It is well-known that, in the United States, at least 10% of cervical smears diagnosed as negative from cytotechnologist are needed to be re-screened by a pathologist or a qualified cytotechnologist (3,4,7). Detection errors, which are responsible for false-negative cytological diagnosis, can be reduced by re-screening of slides

initially reported to be normal or re-screening by using computerised technologies (AutoPap, PAPNET etc.) (2,3). Even with new automated devices, the lowest false negative fraction is around 5% (3). As we do not have cytotechnologists to have Pap smears pre-screened or an automated system, a 5.3% of false negative rate can be interpreted as being acceptable.

After the reassessment of six patients having benign cytological features (false-negative group), similarly to what it is expected, we found that sampling errors in five of six (83%), which were possibly related to small lesions or those exfoliating few cells, were practically the main reason of the false-negative rate in our study (Table 2). Laboratory or detection errors were found in only one of six (17%), whom cervical smear had a few cells compatible with CIN I (Table 2).

ASC is a relatively recent phenomena which was firstly described in 1988 and finally subdivided into ASC-US and ASC-H subcategories (8). Although we had been using CIN terminology during the study period, in order to establish a similar way to ASC-US & ASC-H subdivisions, we had also used a constant commentary note when an ASC diagnosis had been made. It is accepted that about 15% women with ASC on smear will have at least CIN II (CIN II, CIN III, carcinoma) at follow-up, and one third of them are reported to have high grade lesions (9). In spite of small-sized groups, we determined that 78% of ASC was diagnosed as CIN I-III on histology. Other studies stressed that 40-66% of ASC cases were diagnosed as CIN I-III on histology (10,11). According to Yarandi et al, ASC could be considered as a good marker for detecting underlying CIN and condyloma (12).

Another problematic area is the interpretation of postmenopausal smears with marked atrophic changes. It has been recently shown that cyto-morphological features favoring CIN III in postmenopausal smears include increased number of abnormal single cells with high nuclear/cytoplasmic ratio accompanied by an irregular nuclear membrane (13,14). Furthermore, nuclear enlargement, abnormal chromatin pattern with a granular background can also be seen in reactive changes and may lead to an interpretation error (13,14). However, other benign hormone induced cellular changes may be diagnosed as ASC. Similarly, cases of atypical reparative changes and atypical parakeratosis may be interpreted as ASC favour dysplasia depending on cell size, nuclear/cytoplasmic ratio and the number of abnormal cells (13). Those criteria should be remembered when examining a Pap smear.

Cellular morphology may be altered by a variety of iatrogenic factors such as radiotherapy, ablative procedures and instrumentation (15-17). These changes may increase both false-positive and negative interpretations. In our study, one of the false-positive case had a chemotherapy history for leukemia. During the cytologic analysis of this case, in addition to signs of atrophy, numerous bizarre squamous cells had been observed. But the histological examination was free of dysplasia and leukemia. History of radiotherapy was also absent. The rapid rate of mucosal and epidermal turnover results in a high degree of susceptibility to the effects of chemotherapeutic agents. It is well-known that, in addition to impaired maturation, epithelial surface (mucosa, oral) may be disorganised by the individual presence of enlarged and pleomorphic nuclei (15). The possibility of intermittent cytological atypia due to chemotherapy is postulated in the presented false-positive case based on histological and cytological findings. However, radiation is also a well-known cause of reactive atypia, we suggest that chemotherapy might induce epithelial cells to degenerate in a various forms of atypia (16,17). In the vagina and, or cervix the epithelium becomes atrophic due to chemotherapy and changes may mimic those of dysplasia or carcinoma (16,17). Furthermore, it is well-known that megaloblastic anemia also induces cellular atypia

mimicking those of dysplasia or carcinoma. Necessary clinical data is tremendously important for an optimal cellular interpretation. For this reason, medical history of patients is important for interpreting cellular distribution.

The pathology laboratories play a major role in the prevention of cervical cancer. The constant exchange of information between the pathologist and clinician are extremely important for improving the quality, sensitivity and specificity of Pap smears. Our study results are quite similar to those of previous reports. Despite the relative small number of cases, our false-negative and positive rates are acceptable. We recommend comparing the histology with cytology regularly for determining causes of any discrepancies and also for obtaining an optimal internal quality assurance mechanism.

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