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Cyto-histological correlation of 219 patients submitted to surgical treatment due to diagnosis of cervical intraepithelial neoplasia

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ABSTRACT

INTRODUCTION

Context: Cervical cytology continues to be the most appropriate method for investigating cervical neoplasia and its precursors. Greater diagnostic acuity is obtained by combining cytology, colposcopy and guided biopsy methods.

Objective: To analyze the diagnostic acuity of cyto- and histopathological exams and causes of diagnostic error.

Design: Retrospective study.

Setting: A public tertiary referral center.

Sample: Reports on 219 patients submitted to cone biopsy and/or hysterectomy due to diagnosis of cervical intraepithelial neoplasia (CIN) in the period between January 1982 and March 1997 were reviewed, comparing.

Main Measurements: cytological and histological exams (guided biopsy and surgically-removed tissue). In cases of discordance, the cyto- and histological preparations were reviewed to try to evaluate the causes of errors.

Results: In 193 cases (88.1%) there was cyto-histological agreement but none in 26 (11.9%). Review of the discordant cases showed that in 2 (0.9%) there was invasion of the stromata to a depth greater than 3mm, and in 7 (3.2%) microinvasion, unsuspected via cytology; in 2 (0.9%) microinvasion was suspected via cytology but not confirmed by the final histological exam; and in 15 (6.8%) there was disagreement about the degree of CIN.

Conclusion: The principal causes of error in the cytological exam were the lack of reliable morphological criteria for microinvasion, absence of sampling of the squamocolumnar junction, and scarcity of neoplastic cells in the sample. As for the histological exam, the errors were related to inadequate technical processing and underestimation of focal lesions.

Key words: Cervix. Colpocytology. Cyto-histological correlation. CIN. Microinvasive carcinoma.

Brazil leads the world in the rates of incidence and mortality from cervical cancer, which kills approximately 3500 women per year, many of fertile age. The greatest number of cases occurs in the northern and northeastern regions, and according to the latest surveys, the prevention programs only cover a small portion of Brazil's female population.¹ Cervical cytology continues to be the most appropriate method for investigating cervical neoplasia and its precursors. Greater diagnostic acuity is obtained by combining cytology, colposcopy and guided biopsy methods. The ideal would be to have diagnostic agreement between these methods, although the literature shows that cyto-histological disagreement varies from 11% to 47%.^{2,8} Various factors have a bearing on this discord: collection, processing, reading and interpretation of morphological alterations from the cytological exam; location and extent of the lesions, processing, number of cuts and the interpretation of the histological sample. Studies have indicated that the greatest causes of errors in cyto-histological correlation come from sampling or interpretation problems, or from both.^{7,8} The resulting decisions have implications

for surgical procedures, which are not risk-free and may alter the woman's reproductive and sex life. This places a responsibility on the cytopathology laboratory to require its professionals to have profound competence and periodic retraining, as well as requiring the implementation of a quality control system. The present study was performed with the objective of evaluating the diagnostic acuity of cyto- and histopathological exams, analyzing the cyto-histological correlation of samples obtained from patients submitted to surgical treatment for cervical intraepithelial neoplasia (CIN) and, in cases of diagnostic cone biopsy, investigating possible microinvasion.

METHODS

All patients seen by the Gynecology and Obstetrics outpatient service of our Institution are submitted to triple collection of material for cytological examination. The material is processed according to Papanicolaou's technique and reading is performed by doctors trained as cytologists. Patients presenting macroscopic alterations upon specular or cytological examination are sent to the colposcopy service. The biopsy is guided by colposcopic exam carried out by residents under teaching supervision, and the material is fixed in 4% formaldehyde. There is no standard number of histological cuts for each biopsy fragment, varying from 1 to 10 successive cuts as judged necessary by the

pathologist for each case. The cone biopsy and/or hysterectomy specimens with CIN are marked with sewing thread at the 12 o'clock position and fixed in 4% formaldehyde; the cone biopsy or cervix material is cut into pieces of about 1mm in thickness, perpendicular to the surface of the endocervical mucosa and all the material is processed for inclusion in paraffin. One histological cut of each block is stained with hematoxylin-eosin. Additional cuts are made when necessary.

Reports from 219 patients submitted to cone biopsy and/or hysterectomy for diagnosis of CIN in the period between January 1982 and March 1997 were reviewed, from which six patients presented suspected microinvasion via cytology. The results of the cytological and histopathological exams (guided biopsy and surgically-removed tissue) were compared. In cases with discordance, the cytological and histological preparations were reviewed by 3 cytologists and 2 pathologists, to try to evaluate the causes of errors.

RESULTS

Table 1 shows the cyto-histological correlation of the 219 cases submitted to cone biopsy and/or hysterectomy. There was cyto-histological agreement in 193 (88.1%): 189 cases were CIN III and in 4 cases the suspicion of microinvasion via cytology was confirmed in surgically-removed tissue. In 26 cases (11.9%)

Table 1 - Cyto-histological correlation of 219 patients submitted to surgical treatment for cervical intraepithelial neoplasia

Histology	CIN of indeterminate grade	CIN I	CIN II	CIN III	Microinvasive carcinoma	Invasive carcinoma	Total
Cytology							
CIN of indeterminate grade	0	0	0	1	0	0	1
CIN I	0	0	0	1	0	0	1
CIN II	0	0	0	4	0	1	5
CIN III	2	0	7	189	7	1	206
Suspicion of microinvasion	0	0	0	2	4	0	6
Invasive carcinoma	0	0	0	0	0	0	0
Total	2	0	7	197	11	2	219

there was disagreement about the presence of invasion or the degree of CIN: in 2 (0.9%) there was invasion of the stromata to a depth greater than 3mm and in 7 (3.2%) microinvasion, unsuspected via cytology; in 2 (0.9%) there was the suspicion of microinvasion via cytology, not confirmed by the histological exam; and in 15 (6.8%) there was disagreement about the degree of CIN, which in 11 of these was only a difference of one grade (CIN II/III).

DISCUSSION

The review of the cytological material in the 2 cases of clear invasion of the stromata showed that in one of them the diagnosis was prejudiced by the scarcity of atypical cells and the absence of tumoral diathesis, making the error attributable to the sampling. In the other case, the smear was atrophic and did not contain sampling from the squamocolumnar junction (SCJ). However, there was cellular differentiation and appreciable pleomorphism, which should have led to the suspicion of invasion. We believe that atrophy causes a predisposition to this error of interpretation. This reinforces the idea that in smears of this type, estrogen therapy must be performed before definitive diagnosis.^{9,10}

Concerning the 7 cases of microinvasion diagnosed via the histopathological exam, in which the cytology underestimated the diagnosis, the review showed that in 4 the problem was the sampling and in 3 the interpretation. In these last 3 cases there was significant pleomorphism and cellular differentiation, with "fiber cells", data which could have given rise to suspicions of microinvasion in the initial cytological examination. In the 4 cases where there was a failure of sampling, no morphological alterations were observed which could suggest microinvasion; in only 3 of these was the SCJ represented in the sampling.

In the 2 cases where microinvasion was suspected via cytology but not confirmed by the histopathological exam, the review showed alterations which did not differ significantly from

the 4 cases with the suspicion of microinvasion confirmed by histopathological examination of the surgically-removed tissue. These findings corroborate the data in the literature, indicating that there are no reliable morphological criteria for cytological diagnosis of microinvasion;^{9,11} for this reason, when diagnosing CIN III it may at most be possible to add an observation questioning microinvasion, a procedure adopted in our service.

In the 15 cases where there was disagreement regarding the degree of CIN, the review of the preparations showed that in 6 of them there was a failure in the cytological exam, mainly coming from the predominance of alterations in intermediate cells and scarcity of atypical deep cells and, less frequently, due to the inflammatory process and the absence of SCJ sampling. In the remaining 9 cases the failure came from errors in interpretation of the histopathological preparations, due to their being focal lesions or from technical problems, creating uncertainty regarding the degree of CIN. Nevertheless, we must emphasize that in 11 of these 15 cases of CIN the disagreement was only by one grade, which becomes irrelevant if CIN II and CIN III are grouped as high grade intra-epithelial lesions, as proposed in Bethesda's classification.¹²

The index of cyto-histological disagreement in our material (11.9%)⁸ was similar to that of Jones et al,¹³ Joste et al⁸ and Tritz et al⁶ and much less than that of Cavalcanti et al² and Di Loreto et al.³ It is possible that one of the factors which contributed to the low disagreement in our material was the selection of cases submitted to surgical treatment following diagnosis of CIN (in the vast majority grade III) or due to suspicion of microinvasion, instead of using all the routine cytological preparations.

We conclude that the main discordance was related to microinvasion, confirming the non-existence of reliable cytological criteria for this diagnosis. We further emphasize the importance of cyto-histological review in discordant cases as a method of quality control for the service, as well as for its significant contribution to our

learning, as already mentioned by other authors.^{3,7,13} In our opinion, this review should be done before instituting therapy so as to avoid unnecessary procedures.

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RESUMO

Contexto: A citologia cervical continua sendo o método mais adequado para o rastreamento da neoplasia cervical e seus precursores. Melhor acuidade diagnóstica é obtida através da associação dos métodos citológico, colposcópico e biópsia orientada. **Objetivo:** Analisar a acuidade diagnóstica dos exames cito e histopatológico e causas de erro diagnóstico. **Tipo de estudo:** Estudo retrospectivo. **Local:** Centro de referência terciário, público. **Amostra:** Foram revistos laudos de 219 pacientes submetidas à conização e/ou histerectomia por diagnóstico de neoplasia intra-epitelial cervical (NIC), no período de janeiro de 1982 a março de 1997. **Variáveis Estudadas:** Exame citológico e histológico (biópsia orientada e peça cirúrgica). Nos casos discordantes revisaram-se os preparados cito e histológicos na tentativa de avaliar as causas de erro. **Resultados:** Em 193 (88,1%) casos houve concordância cito-histológica e em 26 (11,9%) não. A revisão dos casos discordantes mostrou que em 2 (0,9%) havia invasão do estroma em profundidade maior que 3mm e em 7 (3,2%) microinvasão, não suspeitadas à citologia; em 2 (0,9%) houve suspeita de microinvasão à citologia, não confirmada pelo exame histológico final e, em 15 (6,8%), discordância quanto ao grau de NIC. **Conclusão:** As principais causas de erro no exame citológico foram falta de critérios morfológicos seguros para microinvasão, ausência de amostragem da junção escamo-colunar e escassez de células neoplásicas na amostra. Quanto ao exame histológico, os erros foram relacionados ao processamento técnico inadequado e subavaliação em lesões focais.