Case Report

Beyond the Background: Diagnostic Significance of Prominent Histiocytes in Cervicovaginal Smears of a Reproductive-Age Woman

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Abstract

Histiocytes are frequently encountered in cervicovaginal cytology and are usually considered to be benign background cells. However, the prominence of these cells in Pap smear findings has been linked to underlying endometrial pathology to varying degrees, especially in perimenopausal and postmenopausal women. The clinical implication of isolated histiocytes in the context of reproductive-age women is less clear. Herein, we present the case of a 36-year-old woman presenting with symptoms of vaginal discharge and Pap smear findings showing the prominence of histiocytes in the absence of epithelial cell atypia. This case brings to mind the cytomorphology of these cells, their mimickers, and the predictive value for underlying endometrial pathology.

Key words

Histiocytes, Pap smear, Cervicovaginal cytology, Endometrial pathology, Foamy histiocytes, Reactive changes.

Introduction

"Cervicovaginal cytology is still considered one of the cornerstones in the screening of cervical neoplasia and in the detection of various gynecologic pathologies." Though the abnormalities in the squamous and columnar cell types are the major focus of attention, the background cellular elements such as inflammatory cells, histiocytes, and cell debris may offer significant clues in the diagnosis of cervical pathology [1]. Histiocytes are tissue macrophages that are normally present in the cervical stroma and endometrium and may appear in the vaginal smears in various physiological and pathological conditions. Histiocytes have the characteristic cytologic features of having round to oval or bean-shaped nuclei with fine chromatin and inconspicuous nucleoli. The cytoplasm is usually moderate to abundant and may have vacuolation and/or phagocytic inclusions. These may occur as single cells or in clusters. Small-sized histiocytes, which have been referred to as “sticky histiocytes,” may occur in cohesive clusters and may mimic the superficial endometrial stromal cell group, which is problematic in the interpretation of the cell types [2]. Histiocytes have also been classified based on morphology into three types. Type A histiocytes are large, foamy cells with many small cytoplasmic vacuoles, resembling the appearance of lipophages or xanthomatous cells. Type B histiocytes are relatively uniform, small to medium-sized cells that resemble endometrial stromal cells [3]. Type C histiocytes vary in size, may contain inflammatory debris, hemosiderin, or may be multinucleated. The clinical importance of histiocytes found in Pap smear preparations has long been an issue for debate. Several studies investigated the possibility that an increased number of histiocytes, especially foamy types, may be indicative of underlying hyperplasia or carcinoma of the endometrium. Although some authors believe that histiocytes should be thoroughly investigated when they are numerous, especially in postmenopausal women, others found that histiocytes, when present alone, had limited predictive value [4].

This report describes a histiocyte-rich Pap smear in a reproductive-age woman and discusses the diagnostic implications in light of existing literature.

Case report

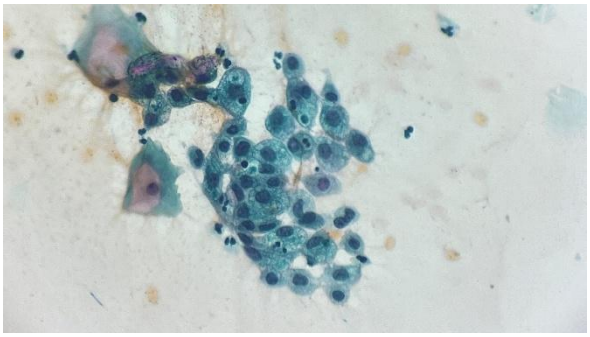
A 36-year-old multiparous female patient complains of white discharge per vaginum. The discharge has been present for the past three months. The discharge has not been foul-smelling and has not been accompanied by itching, burning micturition, dyspareunia, postcoital bleeding, lower abdominal pain, intermenstrual bleeding, or postmenopausal bleeding. She has not had any fever, loss of weight, or any systemic complaints. Her menstrual cycles have been regular, occurring at an interval of 28 to 30 days, with a moderate amount of blood discharge lasting 4 to 5 days. She has no history of any recent pregnancy, abortion, insertion of an intrauterine contraceptive device, or any hormone therapy. Her past medical history has been unremarkable, without any history of diabetes mellitus, hypertension, tuberculosis, or any gynecologic malignancies.

On general physical examination, the patient was found to be afebrile with stable vital signs. On examination of the abdomen, the patient was found to have a soft, non-tender abdomen without any palpable mass or organomegaly. On examination by the per speculum method, the cervix was found to be hypertrophied with circumoral erosion. There was no mass, ulcer, or any lesions seen on the cervix, while whitish vaginal discharge was seen in the vaginal canal. On examination by the per vaginum method, the uterus was found to be 8 weeks in size, anteverted, firm, and mobile, while the bilateral fornices were free and non-tender, without any adnexal mass being palpable. Considering the presence of vaginal discharge, a Pap smear was taken for evaluation.

Cytological Findings

Pap smear was satisfactory for the evaluation. Inflammatory cells were present in abundance, mostly neutrophils and lymphocytes. Abundant histiocytes were seen, either singly or in a loose group in the smear. The histiocytes were seen to have a round to oval nucleus with a finely granular chromatin pattern. The nuclei were not indented. Nucleoli were not prominent. The amount of cytoplasm was moderate to abundant, and there were areas of vacuolation in the cells. Some cells were seen to have a foamy appearance with several small-sized vacuoles in the cytoplasm. However, there were no abnormal cells. There were no atypical squamous cells, atypical glandular cells, or malignant cells in the smear. Benign endocervical cells and squamous cells were present in the smear. However, endometrial cells were not seen in the smear. The smear was given a report as follows: Negative for Intraepithelial Lesion or Malignancy (NILM) with prominent reactive histiocytes and inflammatory cells, consistent with chronic cervicitis (**Figure - 1, 2**). Since there were no abnormal uterine bleeding symptoms, no endometrial sampling was advised. The patient was given symptomatic relief for cervicitis.

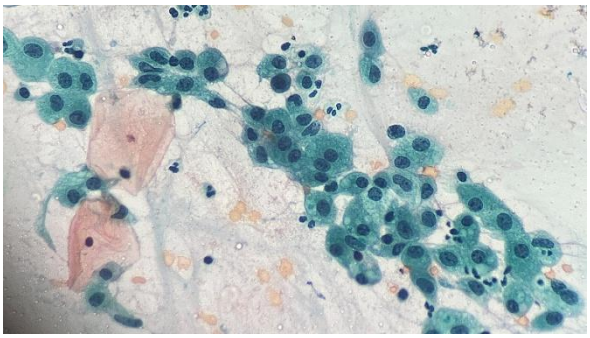
Figure – 1: Conventional Papanicolaou-stained smear showing numerous histiocytes in loose aggregates in an inflammatory background. The histiocytes exhibit round to oval nuclei with fine chromatin and moderate cytoplasm (Pap stain, 400X).



Discussion

Histiocytes are commonly encountered in cervicovaginal smears and consist of exfoliated tissue macrophages from the cervical stroma or endometrial tissue. Though they are regarded as background cells, the occurrence of increased numbers of histiocytes has long been of interest due to the possible association with endometrial pathology [3]. The clinical relevance of the presence of histiocytes is related to the clinical situation, the age of the patient, menopausal status, and the associated cytologic findings. The present case highlights the importance of the clinical context of the presence of histiocytes in the smear of a premenopausal woman without abnormal uterine bleeding. Physiologically, the presence of histiocytes is seen during the early proliferative phase of the menstrual cycle, particularly during the exodus phase from day 5 to day 11 of the menstrual cycle. During this time, there is endometrial shedding and regeneration, leading to the presence of macrophages that are involved in the phagocytic activity of cellular debris [4, 5]. Similarly, the presence of histiocytes is also seen in postpartum smears, following abortion, following instrumentation of the uterus, and during pregnancy. In these circumstances, their presence reflects normal reparative or inflammatory processes rather than underlying pathology. Therefore, correlation with menstrual history and recent obstetric or surgical events is essential in interpretation.

Figure – 2: High-power view demonstrating histiocytes with indented (bean-shaped) nuclei and finely granular chromatin. The cytoplasm is moderate and focally vacuolated. No nuclear atypia is identified (Pap stain, 400X).



Cytomorphologically, the cells show a variety of patterns. Generally, the cells have a round to oval or indented nucleus with finely granular

chromatin and inconspicuous nucleoli. The amount of cytoplasm is moderate to ample and may show the presence of vacuoles, phagocytosed inflammatory cells, hemosiderin, and lipid. The presence of foamy histiocytes, in which the cells show several vacuoles in the cytoplasm, can be prominent. These cells have led to the morphologic subclassification into large foamy cells resembling lipophages, smaller homogeneous cells resembling superficial cells of the endometrial stromal cells, and varied cells showing the presence of debris and multinucleation. It is important to recognize the presence of such variations to avoid the misinterpretation of the cells as atypical glandular cells or malignant processes [6].

The possible association of histiocytes and endometrial disease has been investigated in several studies. Nassar et al., in their study on the value of the detection of histiocytes in Pap smear, observed that though the presence of histiocytes has been noted in the context of endometrial pathology, the isolated presence of these cells was not sufficiently specific to be used as a predictor of malignancy. They emphasized the need to consider the presence of histiocytes as a criterion for further investigation only if accompanied by other abnormal findings such as the presence of atypical glandular cells, benign endometrial cells in women aged over 40, or abnormal bleeding symptoms [1]. Another such study by Tambouret, carried out on peri- and postmenopausal women, observed that the isolated presence of histiocytes was a poor predictor of significant endometrial pathology, particularly in asymptomatic women [5]. Another study by Wen et al., which observed the presence of histiocytes in the normal cervical smear of postmenopausal women, did not observe a strong correlation of the presence of these cells with carcinoma, thus reiterating the need to consider the presence of these cells in the context of the overall clinical picture [2].

On the other hand, it has also been proposed that moderate to abundant histiocytes may heighten the suspicion for endometrial hyperplasia or carcinoma when they are accompanied by necrotic debris or an inflammatory background [7]. This emphasizes the potential role of histiocytes as an indirect clue for intrauterine pathology. These conflicting results may be explained by differences in patient demographics, such as the proportion of postmenopausal women and women presenting with abnormal bleeding symptoms. The role of foamy histiocytes has also been separately assessed for their potential association with lipid deposits and degenerative changes in the endometrium. Kır et al. investigated foamy histiocytes in cervical smears of postmenopausal women. Although they did show a positive association with endometrial pathology, their predictive value was limited in the absence of symptoms. These studies suggest that although cytoplasmic vacuolation is a reflection of active phagocytic activity or degenerative changes, it does not independently confirm the presence of malignancy [6].

Differential diagnosis of the histiocytes in cervicovaginal smears should always be given due consideration. Endometrial stromal cells in the superficial layer can sometimes resemble small histiocytes, especially during the early proliferative phase. Endometrial stromal cells usually occur in loose groups with minimal cytoplasm and can also lack the cytoplasmic vacuolation seen in the case of histiocytes. However, the distinction can sometimes be very narrow. At times, basal cell squamous cells can also resemble the histiocytes due to the small size and minimal cytoplasm [8]. However, the basal cell squamous cells usually tend to form cohesive groups and do not possess any phagocytic activity. Inflammatory and infective changes can sometimes pose difficulties in the diagnosis. For example, in the case of granuloma inguinale, the presence of Donovan bodies can sometimes be seen within the cytoplasmic vacuoles of the histiocytes. However, the classical forms may not always be evident in alcohol-fixed material. Degenerative necrotic endometrial debris with the presence of macrophages can also sometimes be seen in the

case of endometrial carcinoma and can resemble the tumor diathesis-like background [9, 10].

In the current case, the patient is a 36-year-old woman with regular menstrual cycles and no history of abnormal uterine bleeding. The smears contained many histiocytes in an inflammatory background but no benign endometrial cells, atypical glandular cells, or necrotic tumor diathesis. The patient's symptoms of persistent white discharge and cervical erosion strongly pointed towards a diagnosis of chronic cervicitis as a potential cause for the histiocytic cells. In the absence of any risk factors for endometrial cancer in a young woman, histiocytes in the background of a Papanicolaou smear are usually reactive.

This case reiterates the importance of not making a cytologic diagnosis in isolation without correlation with clinical details. Overinterpretation of the presence of histiocytes can result in unwarranted anxiety, unnecessary investigations, and increased health expenditure. Conversely, the lack of awareness of the potential significance of the presence of these cells in a high-risk setting can result in a delay in the diagnosis of endometrial pathology. A balanced approach, therefore, is the need of the hour, as evidenced by the literature. Thus, the presence of a large number of histiocytes must be carefully evaluated for glandular atypia on the smear, as well as the presence of symptoms, especially in the setting of peri- or postmenopausal bleeding in the patient, whereas in young asymptomatic women, these cells are likely to be associated with benign inflammatory or physiological conditions.

Overall, the literature suggests that histiocytes play a role as a contextual cytologic feature rather than a diagnostic feature per se. Their importance is related to the patient demographics and associated cytologic abnormalities. This current case illustrates the importance of recognizing the broad cytomorphologic spectrum of histiocytes and the integration of this knowledge to arrive at an accurate and judicious diagnosis.

Conclusion

Histiocytes are frequently encountered cells in cervicovaginal smears, and their spectrum of morphology is diverse. Abundant or foamy histiocytes may be associated with endometrial pathology on occasion; however, their presence alone, particularly in the reproductive-age group of women without clinical risk factors, is consistent with benign reactive changes.

Accurate diagnosis requires careful cytomorphologic evaluation and clinicopathologic correlation. Knowledge of the morphology of histiocytes and their mimics is crucial to avoid misinterpretation of this cellular component of the sample. The importance of the presence of histiocytes cannot be overstated; however, their interpretation must be placed into context.

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