

## CLINICAL STUDY

# Detection of large histiocytes in Pap smears: Role in the prediction of endometrial pathology?

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**Abstract:** *Objective:* The objective of this study was to clarify the prognostic significance of large histiocytes in Papanicolaou smears.

*Method:* During a 2-year period, 893 smears were assessed by the Cytology Laboratory of our Hospital. Twenty-one smears were reported including large histiocytes (2.4 %). Colposcopy was also performed in all of these women.

*Results:* 9/21 of the women (43 %) presented vaginocervicitis, whereas 3/21, 1/21, 1/21, 1/21 and 1/21 revealed endometrial polyps, complex hyperplasia with atypia, simple hyperplasia after tamoxifene use, submucosal myoma and endometrial carcinoma respectively. On the other hand, colposcopy revealed suspicious cervical areas in none of the patients. Therefore, the positive prognostic value for endometrial pathology was 7/21 (33.3 %).

*Discussion:* Various forms of histiocytes are found in inflammatory processes in vaginal and cervical smears. According to our results, large histiocytes could be considered as an indicator for endometrial pathology but not for endometrial cancer. However, when histiocytes are found, further clinical evaluation and work up should be done. Finally, in the present study, the detection of large histiocytes seems to be a good prognostic factor for cervical pathology (Ref. 10). Full Text (Free, PDF) [www.bmj.sk](http://www.bmj.sk).

Key words: histiocyte, Pap smears, colposcopy, endometrial pathology, endometrial cancer.

Endometrial carcinoma is the most common gynecological malignancy. The role of histiocytes in predicting endometrial pathology is investigated by many clinicians.

Histiocyte is a cell that is part of the human immune system. All categories of histiocytes are derived from the bone marrow by multiplication from stem cells. The derived cells migrate from the bone marrow to the blood as monocytes. They circulate through the body and stop in various organs where they undergo differentiation into histiocytes which are part of the mononuclear phagocytic system. Many hypothesized that the combined histiocytes-inflammatory cell reaction could be a prediction of pre-existing endometrial pathology (1). Various forms of histiocytes are found in inflammatory processes in vaginal and cervical smears.

We conducted the present retrospective study in order to evaluate our hospital's data and add our findings to the limited data available in the literature.

## Patients and methods

Between January 2004 and December 2005, 893 Pap smears were assessed by the Cytology Laboratory of our Hospital.

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Twenty-one smears showed large histiocytes and these women were referred to our Colposcopy Unit for further colposcopic inspection. It should be mentioned that only symptomatic women underwent endometrial biopsies. All these women formed the studied population. The medical records of each patient were reviewed. Our data were analyzed by using MS Access and Excel 2000.

## Results

Twenty-one out of 893 cervical smears showed the presence of large histiocytes giving an incidence of 2.4 %. We performed a retrospective study focusing on Papanicolaou smears with a diagnosis of large histiocytes in perimenopausal or postmenopausal women. Our women were aged between 44–62 years with mean age of 48 years. The majority of women that took part in the study had their first sexual intercourse at a mean age of 17 years. 40 % of them had multiple sexual partners (more than 4), most of them (66.6 %) were smokers and most of them (76.2 %) did not use any barrier methods of contraception.

After the completion of their work-up mentioned above, vaginocervicitis was detected in 9/21 patients (43 %). In 4, 3, and 2 of these 9 women *Gardnerella vaginalis*, *Candida albicans* and *Trichomonas vaginalis* were revealed respectively. In 6 out of the twenty-one women benign pathology was revealed, such as polyps (3/21), hyperplasia (2/21), complex hyperplasia with atypia (1/21), simple hyperplasia after use of tamoxifene (1/21) and submucosal myoma (1/21). On the other hand, 1/21 showed endometrial carci-

noma. No cervical pathology was revealed. It should be mentioned that our study included ten perimenopausal and eleven postmenopausal women. In the majority of the former group (9/10) vaginitis was revealed, whereas most serious endometrial pathology was detected in the postmenopausal group. The above data showed a relationship between the histiocyte detection in Pap smears and the diagnosis of endometrial pathology. However, owing to the small sample size, this finding needs further investigation.

## Discussion

Although Pap-smear identifies cervical carcinoma, its main contribution remains in the early detection of women with pre-invasive cervical lesions (dyskaryosis-intraepithelial neoplasias) and of course their follow-up. Still, Pap smear is not a sensitive screening test for the identification of endometrial pathology.

The current criteria for further colposcopic, endocervical and endometrial evaluation due to high probability of cervical malignancy are post-menopausal bleeding, post-coital bleeding, inter-menstrual bleeding, palpable pelvic mass, suspicious cervical or vulvar lesion, Pap smear suggestive of frank invasive cancer, and Pap smear showing glandular dyskaryosis (2, 3).

It is known that histiocytes as a single result of pap smears may indicate pathology, although many studies disagree with this opinion. The 2001 Bethesda System for Reporting Cervical Cytology does not recommend reporting histiocytes in women aged 40 or older.

In their retrospective studies focused on postmenopausal women, Hall et al and later Nassar et al concluded that the isolated finding of increased histiocytes in the absence of postmenopausal bleeding or endometrial cells or atypical glandular cells in a Pap smear was a poor indicator of uterine disease (4, 5). Nassar et al showed that the positive predictive value for cancer was 1.3 % in women with histiocytes as an isolated finding compared with 20 % for women with histiocytes and additional clinical or Pap smear findings (5). A similar opinion was also expressed by Tambouret et al (6) and Wen et al (7). It should be noticed that Wen et al tried to evaluate the significance of histiocytes by classifying them into three types as follows: type 1: large foamy, type 2: resembling superficial endometrial stromal cells and type 3: variably sized in association with inflammation or multinucleated cells (7). Small correlation was found in any of these types with endometrial pathology (7). Nguyen et al found that histiocytes alone could not be used as predictive factors of carcinoma or hyperplasia (1). On the other hand, Zarcone et al qualified histiocytes as minimal (<5 hpf), moderate (5–10 hpf) or heavy (>10 hpf) (8). They indicated that especially in women with moderate or heavy histiocytes and absence of other endometrial cells, the presence of histiocytes on cervicovaginal smears was associated with more elevated relative risk for endometrial carcinoma (8). Similar results were also detected previously by Blumenfeld et al (9). Furthermore, Gupta et al showed that the histiocyte count appeared to have no relationship with immediate or remote prognosis in patients with carcinoma of cervix uteri (10).

Our findings support the conclusion that when other clinical or cytologic findings are absent the presence of histiocytes alone in cervicovaginal smears from peri- or post- menopausal women

is non-specific and of no major clinical significance in the prediction of endometrial pathology. Of course, it should be mentioned that the period of follow-up in our study is short (two years at maximum).

It is known that large histiocytes (15–25  $\mu$ ) could be seen in the presence of cervical erosion or ulceration. We tried to correlate these cytologic findings with cervical pathology by doing colposcopy. No cervical pathology was detected.

According to our results, large histiocytes could be considered as an indicator of endometrial pathology but not of endometrial cancer. However, when histiocytes are found, further clinical evaluation and work-up should be done.

Some reservations may be expressed such as the fact that 893 smears is a small volume of samples. Although the sample is very small, the observation that 7 out of 21 patients with large histiocytes on Papanicolaou smear were found to have some sort of endometrial pathology is an interesting finding. We conducted the present study in order to evaluate our hospital's data and add our findings to the available literature. However, due to our small sample size we believe that further studies should be done in this specific field of interest.

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