

Cytopathology and More | Endometrial cells in Pap tests—when are they significant?

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January 2013—Use of the Papanicolaou test has significantly decreased the incidence of cervical carcinoma, especially cervical squamous cell carcinoma.¹ For endometrial adenocarcinoma, which is the most common malignancy of the gynecologic tract,^{2,3} there is no cost-effective screening test. The Bethesda system 2001 recommends reporting normal endometrial cells in women 40 years or older and any atypical endometrial cells under the atypical glandular cells category.⁴

Three types of endometrial cells are usually reported on Pap cytology: normal endometrial cells (NEMCs), atypical endometrial cells (AEMCs), and endometrial carcinoma cells (EMCCs). Unlike AEMCs and EMCCs, NEMCs are reported only in women 40 years and older based on the Bethesda system 2001, because age is more consistently available than menopausal status or clinical symptoms and the incidence of significant endometrial pathology in women under 40 years is extremely low.⁴ Although multiple studies have shown that the Pap test has low sensitivity and a low positive predictive value in detecting endometrial cancer,⁶⁻⁹ several other studies have shown that the reporting of NEMCs and follow-up endometrial sampling increased after the Bethesda system was implemented in 2001,^{10,11} but the detection of significant endometrial lesions remains unchanged.¹²

Here, we review the available literature related to endometrial cells on Pap tests and their morphology, differential diagnosis, and clinical significance. We try to address some of the questions in this field: 1) morphological differential interpretations of normal and atypical endometrial cells, and endometrial carcinoma cells on Pap test; 2) significant pathology in women with normal endometrial cells on Pap tests based on menstrual period, symptoms, and age; 3) significant pathology in women with atypical endometrial cells on Pap tests; and 4) management options for women with normal/atypical endometrial cells on Pap tests.

Normal endometrial cells

The Bethesda system 2001 suggests reporting the presence of normal exfoliated endometrial glandular cells only in women 40 years of age and older regardless of the date of the last menstrual period, for the reasons stated previously.⁴ The presence of normal endometrial cells may reflect physiologic shedding or pathologic shedding owing to a pathological process.

Prevalence. NEMCs are noted in a wide range of Pap tests depending on a patient's age and menstrual status. NEMCs are more likely to be identified in the first half of the menstrual cycle (21 to 24 percent) than in the second half of the cycle (two percent)^{13,14}, and more commonly in premenopausal than in postmenopausal women.¹⁵ In women who are older than 40 years or postmenopausal, the frequency of normal endometrial cells is from 0.4 percent to three percent of Pap tests.^{12,16} Liquid-based cytology detects more normal endometrial cells than conventional cytology. This finding might be explained by more consistent use of sampling instruments for liquid-based cytology with better access to the endocervical canal.¹⁶ However, after Bethesda system 2001, the reporting rate of NEMCs increased to 0.49 percent from 0.17 percent due to reporting in women with premenopausal status.¹⁷

Morphology and differential diagnosis. For women of childbearing age, the presence of endometrial cells on a Pap test is closely related to menstrual cycle phase. The endometrial cells are expelled from the endometrial cavity during menstrual bleeding and a few additional days up to the 12th day of the cycle. The presence of endometrial cells on a Pap test after the 12th day of the cycle is considered abnormal. During the first half of the menstrual

period, especially at the onset of the menstrual bleeding, sheets of small endometrial cells are surrounded by blood and cell debris or spherical/oval cell clusters of variable sizes with a central core made up of small, elongated, tightly packed stromal cells and the surrounding periphery made up of larger, vacuolated glandular cells (exodus) (Figs. 1A and 1B). NEMCs are usually packed together like a ball or three-dimensional clusters with no well-defined cell borders. The nuclei of NEMCs are usually round or bean-shaped and small, similar to the nuclei of intermediate cells. The nucleoli are inconspicuous and the chromatin pattern is difficult to discern owing to cell clustering and darkness. The cytoplasm is scant, basophilic, and occasionally vacuolated. The background is often bloody in conventional Pap tests, and it is usually cleaner with less blood and more single cells in liquid-based preparations. Histiocytes and endometrial stromal cells are occasionally present as well.

During the mid-cycle of the menstrual period, NEMCs appear as less compacted clusters of loosely attached endometrial glandular cells without stromal cells, even with detached single endometrial cells. Such individual glandular endometrial cells are round or elongated with a size from 10 to 20 μm . They have a basophilic cytoplasm with occasional vacuoles, spherical nuclei with inconspicuous nucleoli, and a size no larger than the size of the nuclei of intermediate or parabasal squamous cells.

The differential diagnosis of NEMCs from Pap tests includes endocervical cells, inflammatory cells such as macrophages and lymphocytes, and histiocytes and parabasal cells. Endocervical cells (ECCs) are usually arranged in flat sheets or strips of parallel cells, not in three-dimensional clusters. Endocervical cells are larger than NEMCs (approximately 20 μm in length and 8 to 12 μm in width) and columnar in shape with apical nuclei (Figs. 2A and 2B). More cuboidal configuration may also occur. The nuclei of ECCs are spherical/oval, vesicular in configuration, with delicate chromatin and occasional small nucleoli. The cytoplasm of ECC is homogeneous or finely vacuolated, and faintly basophilic with intra-cytoplasmic mucin. Lymphocytes have a distinct coarse chromatin pattern unlike endometrial cells. Macrophages rarely form clusters. Histiocytes vary in size and number of nuclei and occur as individual cells or loose clusters, and have bean-shaped nuclei. Parabasal cells have nuclei resembling other squamous nuclei and more distinct and dense cytoplasm. Parabasal cells are usually present in sheets or small clusters instead of balls.^{18,19}

Significant pathology and management. NEMCs on Pap tests are mostly associated with normal endometrium, such as proliferating endometrium and atrophic endometrium. However, it has been shown that they are also associated with pathologic conditions, including polyps, hyperplasia with and without atypia, low- and high-grade adenocarcinomas, leiomyoma, immediate postpartum state, abortion, acute endometritis, and cervical and vaginal endometriosis.^{7,20} Large reviews demonstrate seven to 16 percent of Pap tests with normal endometrial cells in women age 40 and older were associated with endometrial hyperplasia or carcinoma.^{15,16}

◆*In premenopausal asymptomatic women.* Normal endometrial cells on Pap tests are rarely associated with significant pathology in premenopausal women without abnormal bleeding.^{11,12,21-25} The study done at our institution revealed a similar result, showing that no asymptomatic premenopausal patients shedding NEMCs, no matter before or after day 12 of their menstrual cycle, were found to have significant endometrial pathology, and the total cost for endometrial sampling in asymptomatic premenopausal women was highly significant.²⁶ However, one report, from M.D. Anderson Cancer Center, found that about 2.1 percent of asymptomatic premenopausal patients with NEMCs on Pap tests were identified with significant endometrial pathology, compared with 2.6 percent of symptomatic premenopausal women, and concluded that endometrial cells on liquid-based cytology preparations, even in the absence of symptoms in premenopausal women age 40 years or older, are associated with significant uterine pathology.²⁷ Most endometrial pathology is accompanied by symptoms, and a relatively smaller number of additional cases are identified through follow-up of asymptomatic women.¹⁶

Most experts suggest that no further diagnostic procedures need be performed in premenopausal and asymptomatic women with NEMCs on their Pap tests if there are no clinical indications. However, it is controversial whether endometrial sampling or diagnostic ultrasound should be provided to premenopausal asymptomatic women with NEMCs who are at increased risk for endometrial cancer (anovulation/polycystic ovary syndrome; type 2 diabetes; obesity; hypertension; hormone replacement therapy; tamoxifen use; prior endometrial hyperplasia; family or personal history of ovarian, breast, colon, or endometrial cancer).

◆ *In premenopausal symptomatic women.* Symptoms such as abnormal uterine bleeding are significant indicators for endometrial carcinoma. In followed-up women with NEMCs, most endometrial pathology has been found to be accompanied by symptoms.¹⁶ One study revealed that 162 out of 206 women with abnormal bleeding and NEMCs on Pap tests had undergone endometrial sampling, with 10 hyperplasias and seven carcinomas found. In contrast, of the asymptomatic women who were followed for at least three years, none were found to have significant disease.²⁹ In premenopausal symptomatic women with NEMCs on Pap test, the incidence of significant endometrial pathology is significantly higher than in women without symptoms. Therefore, symptomatic women with NEMCs on Pap test should undergo endometrial sampling regardless of menopausal status.

◆ *In postmenopausal women.* Postmenopausal women with NEMCs may be at higher risk of endometrial lesions, too. One report showed that only those menopausal women with symptoms (mainly bleeding) had significant pathology, but none of the asymptomatic menopausal women were found to have hyperplasia or carcinoma.²⁷ However, one report showed that asymptomatic postmenopausal women with NEMCs in their smear are also at significantly higher risk for (pre)cancerous endometrial lesion than women without NEMCs.²⁸ Similarly, another report also showed significant endometrial pathology was detected in 11.6 percent of postmenopausal patients compared with 2.3 percent in the control group, and in none of the premenopausal patients. Therefore, endometrial assessment is recommended for all postmenopausal women with NEMCs regardless of symptoms.¹⁷

◆ *In women with unknown history.* Although menstrual and symptomatic statuses are very important in evaluating the significance of normal endometrial cells on Pap test, the information is not always available to the pathologist and clinician. This is the reason why the Bethesda system 2001 suggested NEMCs be reported only in women 40 years and older, because age is more consistently available than menopausal status or clinical symptoms. Our recent study demonstrated that significant lesions were present in women 50 years and older with NEMCs found after day 12 of the menstrual cycle or who are postmenopausal (5.19 percent), but not in women with NEMCs before day 12 (0.51 percent) or women under 50 years with NEMCs after day 12 (1.58 percent).³⁰ Similar results also suggest follow-up endometrial sampling may not be indicated in asymptomatic patients age 50 years and younger.²⁵

Atypical endometrial cells

The Bethesda system 2001 suggests reporting the presence of any atypical endometrial glandular cells regardless of age and menstrual status under the category of atypical glandular cells.⁴

Prevalence. A prevalence rate of AEMCs has been reported to be about 1/1,700 from a pool of 300,000 Pap tests.³¹

Morphology and differential diagnosis. AEMCs commonly appear as small three-dimensional clusters of five to 20 cells. The cells are small to moderate in size with scant to moderate cytoplasm. The nuclei are mildly to moderately enlarged and slightly hyperchromatic with or without small nucleoli. But the nuclei are smaller than atypical endocervical cells and adenocarcinoma cells. Cell borders are usually poorly defined, and cytoplasm may be vacuolated^{18,19} (Figs. 3A and 3B). One report examined morphologic features of endometrial cancer in ThinPrep tests and suggested that enlarged nuclei and the presence of nucleoli in endometrial cells were the most reliable indicators of atypical endometrial cells or endometrial cancer.³²

The differential diagnosis of AEMCs includes benign exfoliated endometrial cells, other types of atypical glandular and squamous processes, and adenocarcinoma. Sometimes it is difficult to differentiate benign and atypical endometrial processes, especially when cells show degenerative changes. However, AEMCs should show atypical features, either architectural (crowding, overlapping, or loss of polarity) or cytological (high N/C ratio, nuclear irregularity, hyperchromasia). Atypical endocervical cells are also in the differential diagnosis of atypical endometrial cells, although atypical endocervical cells usually are larger, have abundant cytoplasm, and are flat sheet in arrangement. It is sometimes impossible to tell these two entities apart. Under this circumstance, atypical glandular cells (NOS) would be appropriate. Adenocarcinoma cells (either endometrial or endocervical) usually show prominent pleomorphism with enlarged nuclei, irregular nuclear membrane, and prominent nucleoli.

Background of necrotic debris might be present. High-grade squamous cervical lesions or squamous carcinomas in women may in rare instances be difficult to differentiate from atypical endometrial cells.

Significant pathology and management. The presence of atypia significantly increases the risk of an underlying endometrial pathology (hyperplasia or carcinoma). Postmenopausal women with AEMCs on Pap test have a risk for endometrial carcinoma of nine to 50 percent.^{32,33} Women who are older than 59 years had an even greater frequency of carcinoma.³¹ Our recent study showed that a significant number of precancerous/malignant lesions (18.5 percent) were identified in patients (423 cases) with AEMCs in contrast to only 2.7 percent in women with NEMCs.³⁰ Therefore, all women with AEMCs on Pap tests need endometrial sampling or diagnostic ultrasound regardless of age or menstrual status.

Endometrial carcinoma cells

Compared with AEMCs and NEMCs, endometrial carcinoma cells are more likely to have large and hyperchromatic nuclei with chromatin clearing, prominent nucleoli, and tumor diathesis. Cytoplasm is usually cyanophilic and vacuolation may be present. Neutrophils are usually present^{18,19} (Figs. 4A and 4B). Endometrial carcinoma has a spectrum of morphology depending on grade and subtype. Well-differentiated endometrioid adenocarcinoma generally shows slight nuclear enlargement and atypia, which are difficult to differentiate from benign endometrial cells. Higher grade and serous carcinoma show significantly pleomorphic nuclear features, which are easily differentiated from benign-appearing endometrial cells.

Endometrial carcinoma cells on Pap tests have a significant pathologic meaningfulness, and patients with EMCCs need to be evaluated immediately. Our recent study shows that all patients with EMCCs on Pap tests (21 cases) had malignant lesions upon histological followup.

Summary

Normal exfoliated endometrial cells in both the first half and second half of the menstrual cycle in asymptomatic menstruating women are unlikely to be associated with significant endometrial pathology and need not be evaluated unless otherwise clinically indicated.

Significant endometrial pathology occurs in symptomatic women with normal endometrial cells on cytology, in postmenopausal women, or in any age group of women with atypical endometrial cells on Pap tests and needs to be evaluated.

Clinicians should provide the best demographic and clinical information to the pathologist, so that more specific recommendations can be rendered. If clinical information, such as symptoms and menstrual status, is not available, age might be used to stratify the risk of endometrial pathology.

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