

Evaluation of Pap Smears of Cases with Significant Endometrial Histopathology for the Presence and Morphology of Endometrial Cells

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Abstract

Background: Endometrial cells are rarely seen in pap smears. Their presence in postmenopausal women > 45 years may suggest endometrial pathology. **Aims:** To evaluate the pap smears of cases with significant endometrial histopathology for the presence of endometrial cells; its association with age and menopausal status and its sensitivity in detection of endometrial pathology. **Settings & Design:** Cross sectional retrospective case control study. **Materials and Methods:** Endometrial biopsies grouped as cases (significant endometrial pathology-hyperplasia, carcinoma, polyps, carcinoma) and control (basal, proliferative, secretory) were collected for a period of two years. Their pap smears were evaluated for the presence of endometrial cells. **Statistical Analysis:** Descriptive statistics was used. **Results:** Among the 58 cases and 58 controls, endometrial cells were present in 31% (18/58) of cases and 17% (10/58) of controls. Age >45 years, menopausal status and postmenopausal bleeding had no association. 25% of simple hyperplasia, 50% of complex hyperplasia, 37.5% of endometrial polyp and 50% of endometrial carcinoma cases had endometrial cells. The sensitivity of detection of significant endometrial pathology by endometrial cells was 31%; specificity 82%; positive predictive value 64% and negative predictive value 54%. The average number of clusters were >2 in the cases and <2 in the control. The clusters had papillae/club like/swirl morphology or atypical in cases. **Conclusion:** We conclude from our study that we should document the presence of endometrial cells in patients with any symptom of irregular bleeding irrespective of age and menopausal status especially when there are more than two clusters with distinct morphologies like papillae/ club/swirls.

Keywords: Endometrial Cells; Pap Smears; Significant Endometrial Pathology.

Introduction

Papanicolaou (pap) smear is a simple screening tool for the detection of uterine cervical cancer and early intraepithelial lesions [1]. It has played a significant role in prevention of invasive cervical cancer by early detection [2] and reduced the mortality rate [3]. Routine cervical pap smears shows four types of squamous cells namely basal cells, parabasal cells, intermediate cells, superficial cells and few endocervical glandular cells [4]. Infrequently endometrial cells can be seen in the Pap smears.

Endometrial cells have a three dimensional architecture, tight cohesive clusters, small

inconspicuous nucleoli and scanty cytoplasm. [4] Exfoliated endometrial cells are normally seen in the first week of menstruation, however in post menopausal women > 45 years their presence is considered abnormal and requires further evaluation to rule out endometrial pathology [4]. The most recent update of the Bethesda system which is the standard reporting format of pap smears has recommended reporting benign endometrial cells in women > 45 years, Atypical Endometrial cells-Not otherwise specified, Atypical glandular cells favours neoplastic and endometrial carcinoma [5].

Previous studies on the significance of endometrial cells on pap smears were prospective analyzing the outcome of pap smears with endometrial cells. Cherkis et al found 11.2% of cases with benign appearing endometrial cells to have endometrial carcinoma on follow up [6]. Gomez-Fernandez et al found no significant endometrial pathology in cases with endometrial cells on Pap smears [7]. Jueng et al had

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reported 41% of women with benign endometrial cells on Pap smears to have significant pathology [8]. We propose to retrospectively study how many of the cases with significant endometrial pathology had endometrial cells in their Pap smears. We also analyzed the association with age > 45 years as recommended and menopausal status.

Materials and Methods

All the histopathology cases of endometrial biopsies were collected for a period of two years (2014, 2015) from the archives of the department of Pathology of our Institute. They were grouped as cases (significant endometrial histopathology -hyperplasia, polyp, carcinoma) and control (basal, proliferative or secretory endometrium). Their corresponding pap smears and clinical details were collected from the archives of the department. The cases where pap smears were not available or inadequate / under stained were excluded from the study. Equal number of pap smears of cases and control were evaluated for the presence of endometrial cells, whether benign appearing, atypical -NOS, atypical- favors neoplastic or adenocarcinoma by two independent observers blinded of the histopathology diagnosis. Descriptive analyses, sensitivity, specificity, positive and negative predictive value was used for statistical analysis. The Institute Research and Ethics committees' approval was obtained.

Result

We collected 380 cases of histopathology biopsies of endometrium of which 170 were grouped as cases (simple & complex hyperplasia, polyps, endometrial carcinoma) and 210 controls of normal endometrial histopathology (basal, proliferative, secretory) from the department of pathology of our Institute for a period of two years (2014-15). Of the 170 cases of significant endometrial pathology, Pap smears were available for 58 cases. An equal number of pap smears of the control group were collected. The clinical details and pap smears of the 58 cases and 58 controls which comprise our study population were analyzed.

Cases-Demographic Features

The mean age of the cases was 44 years. (Range-28-60). The presenting symptoms were dysfunctional uterine bleeding in 16 cases (27%), menorrhagia in 13 cases (22%), postmenopausal bleeding in eight cases

(13%) and pelvic inflammatory disease in two cases (3%). Complaints of 19 cases were not documented. The histopathology of the endometrium was simple hyperplasia in 36 cases (62%) (33 cases without atypia and three cases with atypia); complex hyperplasia in four cases (6%) (two cases with atypia and two without atypia), endometrial benign adenomatous polyp in 16 cases (27%) and two cases (3%) of endometrial carcinoma.

Pap smear reports of 58 cases were inflammatory in 38 cases (65%), six cases (10%) of squamous intraepithelial lesions, ten cases (17%) of atrophy and metaplasia, one case of squamous cell carcinoma (0.01%) and three normal pap smears (0.05%).

Endometrial Cells in Cases

On review of the pap smears; endometrial cells were present in 18 cases (31%). The endometrial cells had benign appearance in 14 cases (77%) and atypical in four cases (22%). Mean age of women showing endometrial cells in pap smear was 45. (Range-32-64). Eight cases were of age > 45 years (44%) and ten cases were less than 45 years (55%). The association of age >45 years with the presence of endometrial cells was not statistically significant. (Chi square test $p > 0.05$).

Among the positive cases 15 cases (83%) had dysfunctional uterine bleeding, two cases (11%) had postmenopausal bleeding and one case (5%) of pelvic inflammatory disease. Two of the seven cases (28%) with clinical history of postmenopausal bleeding had endometrial cells on pap smear. This association was not statistically significant.

Endometrial cells were present in the pap smears of nine out of 36 cases of simple hyperplasia (25%); two out of four cases (50%) of complex hyperplasia; six out of 16 endometrial polyp cases (37.5%); and one out of the two cases of endometrial carcinoma (50%). (Summarized in table 1). However the association of endometrial cells with significant endometrial pathology categories was not statistically significant. (Chi square test- $p > 0.05$)

Atypical endometrial cells were found in four cases. (22%) Their mean age was 49 years. Their corresponding endometrial pathologies were simple hyperplasia, complex hyperplasia, endometrial polyp and endometrial carcinoma. Two of the cases of atypical endometrial cells were misdiagnosed as squamous intraepithelial lesions on pap smears.

Control Group

The average age of the control group was 45 years. (Range 32-60). They comprised of eight cases of

ovarian cyst (13%), ten cases of adenomyosis (17%) and 40 cases (68%) of leiomyoma. The histopathology of the endometrium was basal in 12 cases (20%), proliferative in 15 (25%) and secretory in 31 (53%) cases. Their corresponding Pap smears were normal in five cases (8%) and inflammatory in the rest (91%). Ten of the cases had endometrial cells on pap smears (17%). Among these positive cases six had basal (10%), two proliferative (3%) and two secretory (3%) endometrium on histopathology. Table 2 summarizes the characteristics of cases and control samples with endometrial cells on pap smears.

endometrial pathology by the presence of endometrial cells on pap smears was 31%; specificity 82%; positive predictive value 64% and negative predictive value 54%.

The endometrial cells clusters (Figure 1) were more in number with average of five clusters and papillae or club like (Figure 2) in the positive cases group especially the complex hyperplasia cases compared to the other categories.

Occasional swirls (Figure 2) were also seen. Whereas the number of endometrial cell clusters in the control group was single (Range-1-2) with no specific or distinct morphology. Table 2 summarizes the characteristics of the cases and controls with endometrial cells.

Comparing the Cases and Control Groups

The sensitivity of detection of significant

Table 1: Endometrial cells in pap smears of cases of significant endometrial pathology

Endometrial pathology (58 cases)	No of cases with endometrial cells on Pap smears(18)	Percentage (31%)
Simple hyperplasia without /with atypia (36)	9	25%
Complex hyperplasia without/ with atypia (4)	2	50%
Endometrial polyp (16)	6	37.5%
Endometrial carcinoma (2)	1	50%

Table 2: Characteristics of cases and control samples with endometrial cells in Pap smears

Characteristics	Positive Cases (18/58)	Positive controls (10/ 58)
Age > 45	8 (44%)	4 (40%)
Age < 45	10 (55%)	6 (60%)
Complaints		
Dysfunctional uterine bleeding	15 (83%)	1 (10%)
Postmenopausal bleeding	2 (11%)	-
Pelvic inflammatory disease	1 (5%)	-
Fibroid/adenomyosis	-	8 (80%)
Ovarian cyst	-	1 (10%)
Histopathology		
Basal	-	6 (60%)
Proliferative	-	2 (20%)
Secretory	-	2 (20%)
Simple hyperplasia	9 (50%)	-
Complex hyperplasia	1 (5%)	-
Endometrial polyp	6 (33%)	-
Endometrial carcinoma	1 (5%)	-
No. of clusters	2-5	1-2
Morphology	Club/papillae like, swirls	Normal

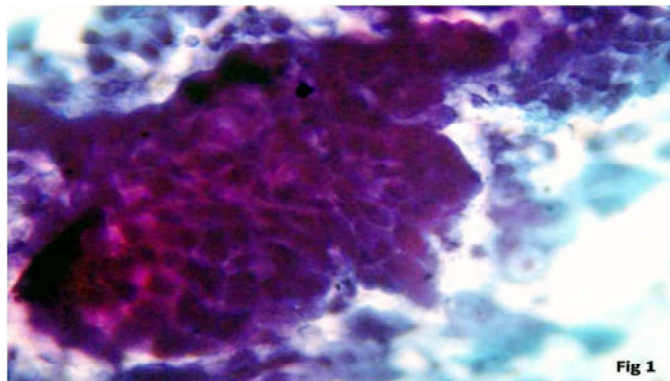


Fig. 1: Shows 3 dimensional cluster of endometrial cells. (PAP 400X)

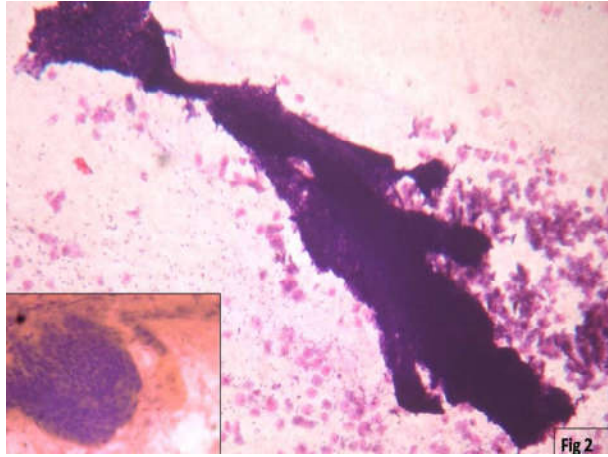


Fig. 2: Shows the papillae/club like morphology of endometrial cells. (PAP 100 X). Inset shows swirl like morphology. (PAP 400 X)

Discussion

The average age of the Pap smears with endometrial cells was 45 years. The presence of endometrial cells in the pap smears of cases with endometrial pathology had no statistical association with age less than or more than 45 years. Previous studies had documented a higher mean age of 49.2 years and recommend reporting the presence of endometrial cells in women > 45 years [5].

The Bethesda system of reporting also recommends reporting of benign endometrial cells in women >45 years [5]. But in our study we found a higher number of women < 45 years (55%) with endometrial cells in pap smear had significant endometrial histopathology.

Menopausal status had no statistical association with the presence of endometrial cells in our study. Previous studies have documented a higher association in postmenopausal women [7,8].

In our study more number of premenopausal women (89%) had endometrial cells in pap smears.

Regarding the association of symptoms postmenopausal bleeding was seen in two cases; higher number of cases (83%) had dysfunctional uterine bleeding (DUB). Kishore et al also documented DUB as the most common symptom in 23.3 % cases with endometrial cells on pap smears [9].

All the pap smears with endometrial cells in the cases group had more than one cluster with some of them having papillae like and club like morphology. Occasional swirls were also seen. Kishore et al had described a top hat appearance and stromal histiocytes of endometrial cells but swirls were not reported [9].

Therefore the presence of more than one endometrial cluster justifies to be documented regardless of age and menopausal status.

In this study the sensitivity of endometrial cells in pap smears in detecting significant endometrial pathology cases was 31%. Juing et al had shown a higher sensitivity of 41% on histologic follow up [8]. Gomez Fernandez et al had found no significant endometrial pathology in cases with endometrial cells in pap smears [7].

In the present study sensitivity of endometrial cells in pap smears in detecting complex hyperplasia and endometrial carcinoma was higher (50%) followed by endometrial polyp (37.5%) and simple hyperplasia (25%). However the numbers of cases are few to draw conclusions.

Seven cases with endometrial cells on Pap smears was misinterpreted as squamous intraepithelial lesion and squamous cell carcinoma on Pap smears. On review of the slides the cases diagnosed as carcinoma had 5 clusters of endometrial cells with exodus pattern and inflammatory background. The other cases had smaller fragments of endometrial cell clusters. Knowledge of the various patterns of endometrial cells helps to avoid misdiagnosis.

Conclusion

The sensitivity of detection of significant endometrial pathology by the presence of endometrial cells in pap smears was low. But the positive group had symptomatic bleeding, irrespective of age and menopausal status. The number of clusters of endometrial cells in the significant cases was more, papillae/club like and occasional swirls.

Summary

We conclude from our study that we should document the presence of endometrial cells in patients with any symptom of irregular bleeding irrespective of age and menopausal status especially when there are more than two clusters with distinct morphologies like papillae/club/swirls. Yet we need to study more number of cases to validate our findings.

Key Message

Presence of >2 clusters of endometrial cells with distinct morphology is associated with significant endometrial pathology.

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