

“Endometrial Cells in Pap smears- Role in prediction of Endometrial Pathology- A three year study”

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Abstract- Introduction: Endometrial Carcinoma is one of the most common malignancy of female genital tract and third most common worldwide. No widely accepted screening test for endometrial carcinoma exists. However, cervical cytology has been found to be useful in detecting endometrial disease. The 2001 Bethesda system recommends the reporting of endometrial cells in women of 40 years and more, regardless of menstrual status or clinical history. **Aims & objectives:** The purpose of the current study is to identify the endometrial cells in Pap smears and correlate with the presence or absence of significant endometrial pathology. **Materials & methods:** A total of 29,736 conventional Pap smears, during a three year study period (July 2010 to June 2013) were studied and evaluated for presence of any significant endometrial pathology on histopathology. In all these patients, clinical information including age, menopausal status, use of hormonal replacement therapy, presence of abnormal bleeding were noted. **Results:** In the current study, 49 of 189 women had histopathological correlation. 85.7% cases of endometrial carcinoma on biopsy had abnormal cells in Pap smears except 1 case which showed benign EMCs. 1 of the 5 cases of endometrial hyperplasia had atypical endometrial cells. Other benign conditions had benign EMCs in Pap smears. Most of the women with significant endometrial pathology on biopsy had benign EMCs (13/20 cases) in Pap smears. However, abnormal EMCs were noted in 6 of 7 cases of endometrial carcinoma. Only 1 case with benign EMCs in Pap had endometrial carcinoma on follow up. No malignancy was noted in women aged <40 years of age. **Conclusion:** Underlying significant endometrial pathology is likely to be present in symptomatic women aged >40 years with benign EMCs on cytology, post-menopausal women with or without symptoms and in women with abnormal EMCs in Pap smears regardless of their age and necessitates further evaluation.

Index Terms- Endometrial cells, Endometrial carcinoma, Hyperplasia, Polyp, Pap smears.

I. INTRODUCTION

Endometrial Carcinoma is one of the most common malignancy of female genital tract and third most common worldwide. It accounts for 97% of all uterine carcinoma and arise from glands in the endometrium¹. Endometrial hyperplasia is a precursor lesion. It is most often diagnosed in post-menopausal age. No widely accepted screening test for endometrial carcinoma exists. The goal of cervical cytology is to detect cervical pre-cancer/ cancer; it is not a screening method for endometrial abnormalities. Over 60% of cervical smears obtained from women in the first few days of menstrual cycle may have endometrial cells (EMCs). Clusters of stromal, glandular or mixed origin can be observed². However, if normal EMCs are observed in smears when physiological exfoliation is not expected; i.e. second half of menstrual cycle, pathological significance may be greater, although cell shedding at times can be associated with oral contraceptive pills (OCPs), Intrauterine devices (IUDs) and use of hormone replacement therapy (HRT)³.

The presence of benign appearing EMCs in Pap smears must be noted. Several studies have suggested that spontaneously exfoliated benign EMCs on Pap smears might indicate endometrial pathology in post-menopausal women, necessitating further investigations^{4, 5}. The 1991 Bethesda system (TBS) recommended that the presence of benign EMCs in post-menopausal women, which may be harbinger of endometrial carcinoma or its precursors, should be reported in Pap smear report⁶. However, menopausal status often is not documented in test requisition forms. If clinical information is provided, it may be incorrect. A cut-off age of 40 years rather than the menopausal status was included in the TBS 2001 based on studies of the clinical significance of benign EMCs in Pap smears⁶.

Reporting a cytological diagnosis of benign EMCs in all women aged 40 years and older may create the potential for unnecessary clinical intervention because there is no recommended approach for managing women with benign EMCs. Setting an appropriate cut-off age of 40 years is an example of the question of sensitivity versus specificity of reporting benign EMCs in Pap smears. Presence of abnormal EMCs in Pap smear has been reported to be associated with higher rate of significant endometrial pathology⁷.

In the present study attempts have been made to identify EMCs in Pap smears and assess their role in prediction of endometrial pathology.

II. AIMS & OBJECTIVES

AIM:

To ascertain the relevance of endometrial cells detected in routine cervical Pap smears in predicting endometrial pathology.

OBJECTIVES OF THE CURRENT STUDY:

- 1) To identify endometrial cells in conventional Pap smears.
- 2) To categorize endometrial cells into benign and abnormal (atypical/malignant) subtypes.
- 3) To correlate their presence with clinical, radiologic and histopathological findings whenever available.
- 4) Evaluate whether significant endometrial pathology exists in postmenopausal women with EMCs in their Pap smears
- 5) Correlate cases of abnormal EMCs in Pap smears with histopathological findings.

III. MATERIALS & METHODS

A retrospective & prospective review was done of the archives of the Department of Pathology, Kasturba Medical College & Hospital, Manipal, from July 2010 to June 2013. Twenty-nine thousand seven hundred and thirty-six Pap smears were performed during this 3-year period. All of these smears were conventional Pap smears.

Inclusion Criteria:

All cervical Pap smears performed on women attending Kasturba Hospital, Manipal from July 2010 to June 2013 that contained endometrial cells were included in the study.

Exclusion Criteria:

All cervical Pap smears lacking endometrial cells and inadequate smears, performed on women attending Kasturba Hospital, Manipal from July 2010 to June 2013 were not part of the study.

One-hundred and eighty-nine of 29,736 Pap smears were identified to have endometrial cells. The patients were divided into two groups:

- 1) With presence of benign-appearing endometrial cells with or without stromal cells, necrotic debris, histiocytes, inflammatory cells in the smears.
- 2) Abnormal (atypical/malignant) endometrial cells.

Clinical information like age, menopausal status and use of hormone replacement therapy, use of tamoxifen and history of abnormal bleeding, ultrasound findings including endometrial thickness as assessed on transvaginal ultrasound was obtained from medical records department. These patients were subdivided into pre- and postmenopausal group, 44 of 189 being postmenopausal women. Endometrial biopsy/ curettage was performed in 49 of 189 cases and correlated with the cytological findings. Pathological findings from endometrial biopsy were documented for correlation.

IV. RESULTS

In a three year study period (July 2010 to June 2013); 29,736 conventional cervical Pap smears received in Kasturba Hospital were analyzed.

- 1) One-hundred and eighty-nine (0.64%) smears showed presence of endometrial cells. Most of the women in the study were in the age group of 41-50 years.
- 2) Different patterns and cytological features of EMCs were observed and classified as benign appearing and abnormal EMCs. Presence of top-hat appearance (Fig 1) was noted in benign EMC clusters whereas stromal cells, histiocytes and debris were noted in both the groups i.e., benign appearing EMCs & abnormal EMCs (Fig 2).
- 3) One-hundred and sixty-nine women had benign EMCs in Pap smear; menorrhagia was common presenting symptom. Fifty-two women were asymptomatic. Significant endometrial pathology was noted in 13 of 41 biopsied cases in this group including one case of endometrial adenocarcinoma (Fig 3).
- 4) The mean age of 20 women with abnormal EMCs in Pap smear was 53.65 years; most common presenting symptom being post-menopausal bleeding. One of these 20 women was asymptomatic. Eight of these 20 cases had biopsy correlation; six

showed endometrial adenocarcinoma. The other two biopsied cases showed one case each of endometrial hyperplasia and secretory endometrium.

- 5) Forty-seven women in the age group of <40 years with a mean age of 32.3 years showed endometrial cells on Pap smears. Dysfunctional uterine bleeding (23.3%) was the most common presenting symptom among symptomatic women (63.8%). Forty-six of these 47 smears showed benign EMCs. One case with abnormal EMCs had no follow up data. None of the cases with histopathological correlation had underlying malignancy.
- 6) One-hundred and forty-two women were identified in the age group of ≥ 40 years with EMCs on Pap with a mean age of 49.2 years. Sixty-seven percent women were symptomatic; postmenopausal bleeding the common presenting symptom (Fig 4).
- 7) Thirty-eight of 123 women aged ≥ 40 years with benign EMCs on Pap underwent histopathological examination. Significant pathology was observed in eleven cases ($\approx 29\%$) including endometrial polyp (18.4%), endometrial hyperplasia (7.9%) and endometrial adenocarcinoma (2.6%) (Fig 5).
- 8) Among 123 women aged ≥ 40 years, 20 women showed benign EMCs along with debris on Pap smears. Though 65% of these women underwent endometrial biopsy, significant pathology i.e., endometrial hyperplasia was identified in one of them.
- 9) Nineteen women aged ≥ 40 years had abnormal EMCs on Pap smears; 42% of them had histopathological correlation (8 of the nineteen cases). Six of these 8 women i.e., 75% had underlying endometrial malignancy (Fig6,9-10).
- 10) Forty-four women were postmenopausal. Six of 30 women with benign EMCs among postmenopausal women underwent endometrial biopsy; significant pathology being observed in 4 cases. However, no endometrial malignancy was noted. The positive and negative predictive value of benign EMCs in postmenopausal women in predicting significant endometrial pathology was 54.6% and 72.7% respectively.
- 11) Fourteen postmenopausal women showed abnormal EMCs on Pap smears. Five of these 14 women who were biopsied showed endometrial adenocarcinoma (Fig7,8,11).
- 12) Post-menopausal bleeding was the most common presenting symptom noted in the postmenopausal women (65.1%). Nine of 11 cases biopsied showed significant endometrial pathology; five being endometrial carcinoma. Further, 7 of the 9 cases with significant endometrial pathology were symptomatic.
- 13) Seven of 30 postmenopausal women with benign EMCs had history of HRT. Two of them had endometrial biopsy that showed endometrial polyp and endometrial hyperplasia, one case each. Rest of the women in this group had no history of HRT. Four of these 23 underwent follow up histopathological examination; 2 showed significant endometrial pathology, i.e., one case each of endometrial polyp and hyperplasia.
- 14) Eight of 14 postmenopausal women with abnormal EMCs on Pap had history of HRT use. Three of these 8 cases showed endometrial malignancy on biopsy. Six of 14 postmenopausal women had no history of HRT; 2 of them showed endometrial malignancy.
- 15) History of intrauterine contraceptive device use was available in 6 of 189 cases. Two cases had biopsy for correlation with one case each of endometrial polyp and leiomyoma.

V. DISCUSSION

The Pap test which was introduced nearly 80 years ago is now proven to be one of the best procedures for cervical cancer screening and prevention. In contrast, endometrial carcinoma, currently emerging as common malignancy of the female genital tract, has no cost-effective universal screening test.

It has been observed that the Pap test has low sensitivity & low positive predictive value in detection of endometrial cancer. Though there is discrepancy regarding the clinical significance of finding benign exfoliated endometrial cells in Pap test, it has been seen that significant endometrial pathology is present whenever abnormal endometrial cells are observed in Pap smear.

In the present study, an attempt was made to analyze the frequency of different types of endometrial cells in Pap smear and their role in predicting endometrial pathology in relation to age group (<40 years & ≥ 40 years), menopausal status, hormonal therapy and history of use of intrauterine contraceptive devices.

One-hundred and eighty nine Pap smears with endometrial cells were identified in the three year study period. These findings were correlated with clinical, radiological and histopathological findings whenever available.

Incidence of endometrial cells on Pap smears in the present study was 0.64%. Similar findings were observed by Karim et al¹ (1.71%). However, Voojjs & coworker² noted a much higher rate of EMCs in Pap smears in their study (12%).

In the current study, the presence of benign appearing EMCs accounted for 0.56% of all the conventional Pap smears studied. These findings are similar to the observations of Lai et al³ (0.24%). However, Cherkis & coworker⁴ noted a lower rate of benign EMCs (0.06%).

In the present study, 13 of 41 cases biopsied with benign EMCs on Pap showed significant endometrial pathology with endometrial polyp (19.51%), endometrial hyperplasia (9.76%) and one case (2.44%) of endometrioid adenocarcinoma. However, Cherkis et al⁴

noted higher rate of endometrial adenocarcinoma (11.2%) in their study. Rest of the cases observed by them was endometrial polyp (11.7%) and endometrial hyperplasia (12.84%). In contrast, Yancey et al⁵ noted a lower rate of endometrial carcinoma (0.8%).

In the present study, twenty of the 189 women had abnormal EMCs on Pap smears of which atypical EMCs were noted in 14 (i.e. 7.4%) cases. The mean age of women with atypical EMCs was 53.3 years. Thrall et al⁶ noted fewer cases of atypical EMCs [1.24% (48/3863)] and in younger women as compared to our study i.e., mean age was 44 years.

Six of 14 (43%) women with atypical EMCs had histopathological follow up. Significant pathology was noted in 5 cases (83.3%). Cherkis et al⁷ and Yancey & coworkers⁵ noted significant endometrial pathology in 41.8% and 29.2% respectively in women with atypical EMCs in their studies. In the present study, 66.7% cases with biopsy in this group of women showed endometrial carcinoma. However, lower rate of endometrial carcinoma was observed by Cherkis et al⁷(20%) and Yancey et al⁵ (21%).

In the present study, the frequency of malignant endometrial cells was 3.2% [6 of 189 cases]; the mean age of women in this group was 54 years. However, Thrall et al⁶ noted a lower prevalence rate (0.13%) and a higher mean age (62 years). In the study by Li & coworkers⁸, the incidence was 1.01% with a mean age of 64.3 years. In the present study, 2 of 6 cases with biopsy available for correlation showed endometrial adenocarcinoma. Li et al⁸ had similar findings with endometrial adenocarcinoma on biopsy in all 21 cases with malignant EMCs on Pap smears in their study. However, Yancey et al⁵, noted malignancy in 75.8% of cases with suspicious/malignant EMCs in Pap.

In the present study, 142 women aged ≥ 40 years showed EMCs on Pap smears, with a mean age of 49.2 years. These findings are in concordance with those observed by Thrall et al⁶ who noted a mean age of 46 years in their study.

In the current study, the prevalence rate of benign EMCs in women aged ≥ 40 years was 0.4%, a finding similar to the results of Beal et al⁹ (0.9%) and Browne et al¹⁰ (1.1%).

Presence of atypical EMCs was noted in 6.9% of our cases with a follow up biopsy in 46.2% of these cases. Li et al⁸ however noted a higher frequency of atypical EMCs (21.9%) and biopsy rate of 81.7%. The mean age of women with atypical EMCs was 53.3 years in our study group. These findings are similar to those of Li et al⁸.

It was noted that 66.7% of our cases with atypical EMCs in Pap smears in women aged ≥ 40 years showed malignancy on follow up biopsy. Shin et al¹¹ noted abnormal endometrial cells in 38% of patients with endometrial carcinoma in their study. In contrast, a much lower rate was observed in study by Eddy & coworkers¹² (15%).

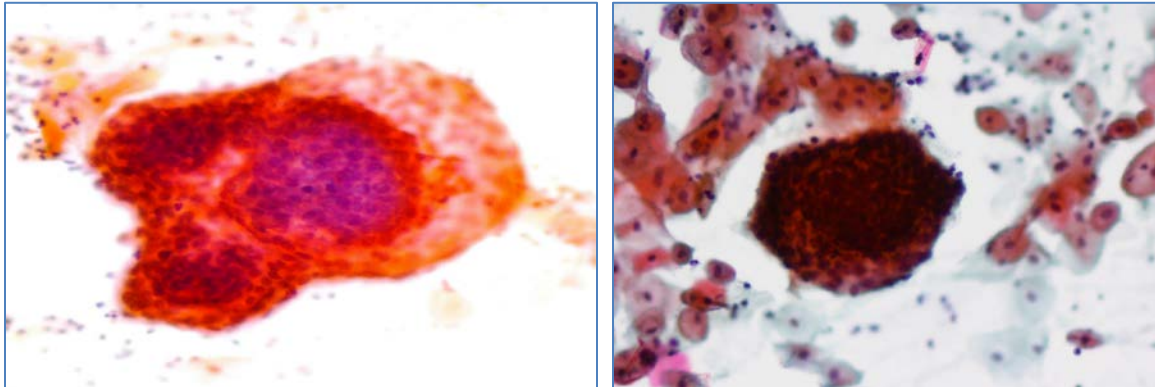
In the current study, it was observed that 6 (85.7%) of the 7 cases of endometrial carcinoma had abnormal EMCs in their Pap smears. DuBeshter et al¹³ noted 77% cases of endometrial carcinoma with abnormal EMCs in their Pap smears.

It can be concluded from the present study that symptomatic women aged ≥ 40 years with benign EMCs in Pap smears and postmenopausal women irrespective of symptoms and history of HRT with normal or atypical EMCs on cervical cytology screening should be evaluated for any underlying endometrial pathology. All women with abnormal EMCs in their Pap smears should be subjected to further clinicoradiologic examination and close follow up irrespective of age, symptoms or history of HRT or IUD use.

VI. CONCLUSION

It can be concluded from the current study that normal exfoliated endometrial cells in both the first half and second half of menstrual cycle in asymptomatic menstruating women are unlikely to be associated with significant endometrial pathology and need not be evaluated unless otherwise clinically indicated. Underlying significant endometrial pathology is likely to be present in symptomatic women aged ≥ 40 years with benign EMCs on cytology, postmenopausal women with or without symptoms and in women with abnormal endometrial cells in Pap smears regardless of their age and necessitates further evaluation. In the absence of demographic and clinical information including history of symptoms and menstrual status, age might be used to stratify the risk of underlying endometrial pathology.

IMAGES AND TABLES:



Fig/Table 1: Clusters of Benign EMCs with “top-hat” appearance (A.Pap X200;B.Pap X100)

Fig/Table2: EMCs in PAP smears: Cytomorphological features [n=189]

Features	Benign EMCs (n=169)	Abnormal EMCs (n=20)
1) Top-hat appearance of EMCs	21	0
2) Stromal cells	35	6
3) Histiocytes & necrotic debris	20	8
4) EMCs only	93	6
Total	169	20

Fig/Table3 : Comparison of patient groups with benign and abnormal endometrial cell clusters [n=189]:

Features	Benign EMCs (n=169)	Abnormal EMCs (n=20)
1) Age range	22-85 years	35-67 years
2) common age group (in years)	41-50	51-60
3) Number of cases symptomatic	111 (65.7%)	19 (95%)
4) Number of postmenopausal women	30 (17.8%)	14 (70%)
5) Number of cases with biopsy correlation	41	08
6) Significant endometrial pathology*	13	07
7) Number of cases of endometrial carcinoma on biopsy	01	06

*[“Significant endometrial pathology” includes: endometrial polyp, endometrial hyperplasia & endometrial carcinoma]

Fig/Table no. 4: Comparison of patient groups with respect to age category [n=189]:

Features	<40 years (n=47)	≥40 years (n=142)
1) Mean age (in years)	32.3	49.2
2) Common presenting symptom	DUB (23.3%)	Postmenopausal bleeding (29.5%)
3) Benign EMCs only	35	67
4) Benign EMCs + stromal cells	9	36
5) Benign EMCs + debris	2	20
6) Abnormal EMCs	1	19

Fig/Table No. 5: Biopsy correlation with types of EMCs in their Pap smears & age group. [n=49]

		Type of EMCs in Pap smears			Age group	
					<40 years	≥ 40 years
Histopathological diagnosis	Number of cases	Benign EMCs	Atypical EMCs	Malignant EMCs		
Leiomyoma	12	12	-	-	1	11
Proliferative endometrium	06	6	-	-	-	6
Secretory endometrium	10	9	1	-	-	10
Adenomyosis	1	1	-	-	-	1
Endometrial polyp	8	8	-	-	1	7
Endometrial Hyperplasia	5	4	1	-	1	4
Endometrial carcinoma	7	1	4	2	-	7

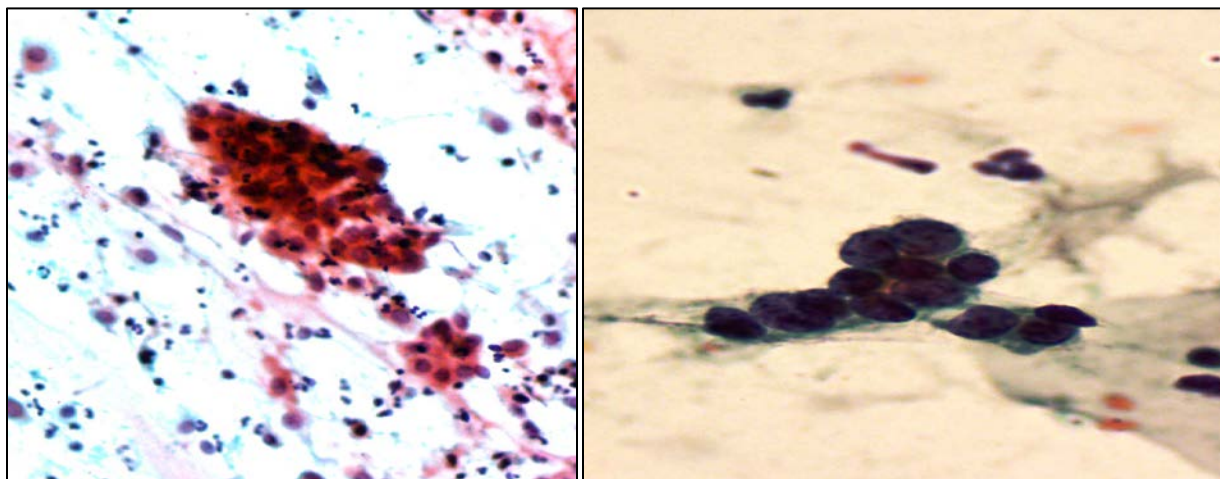


Fig 6 :Clusters of atypical EMCs with neutrophils & debris (A: Pap X100; B: Pap X200)

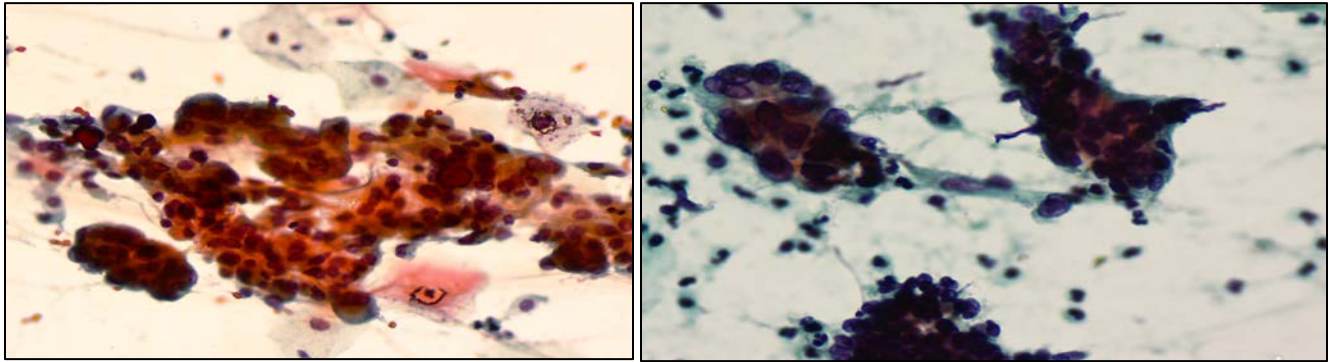


Fig 7: cluster of malignant EMCs with neutrophils (A:Pap X100; B:Pap X200)

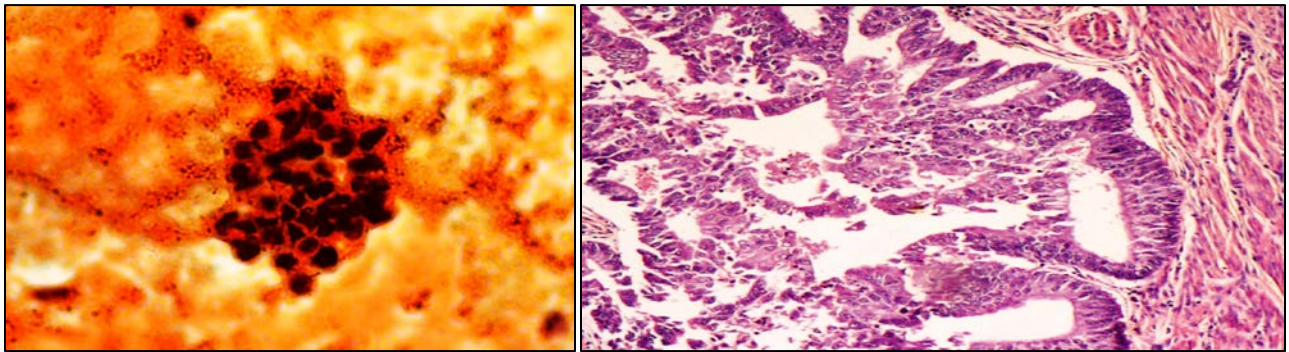


Fig 8(A): Cluster of benign EMCs (Pap X200)

Fig 8(B): Corresponding histopathological image showing poorly differentiated endometrial carcinoma, grade III. (H&E X200)

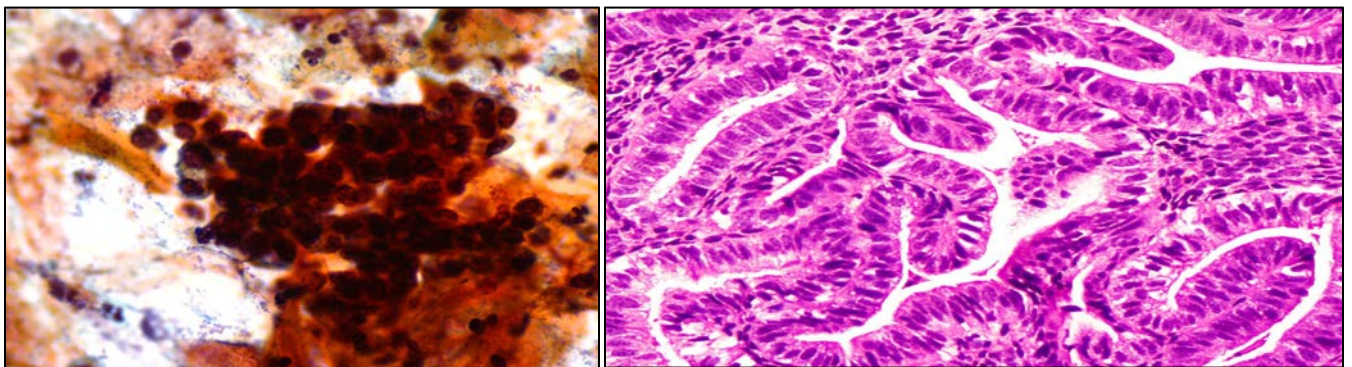


Fig 9(A): Cluster of atypical EMCs with neutrophils & debris (Pap X200)

Fig 9(B): Corresponding histopathological image showing endometrial hyperplasia. (H&E X200)

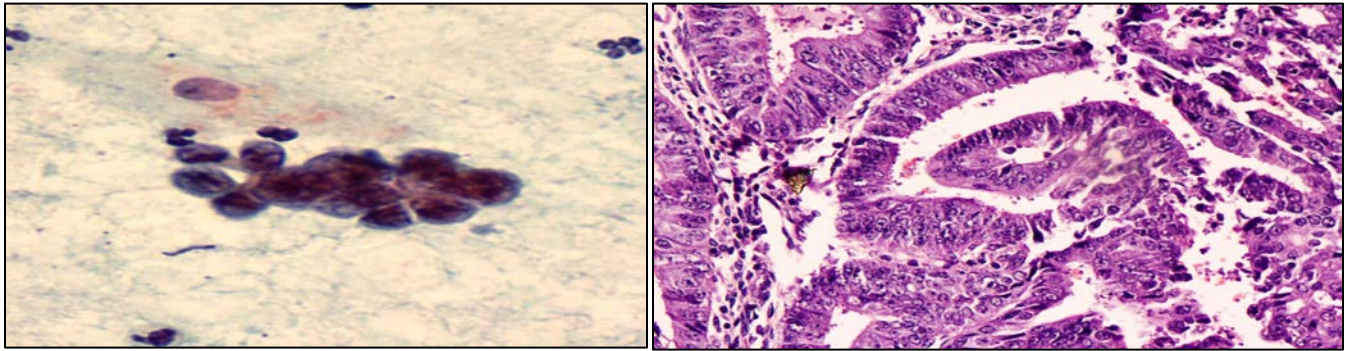


Fig 10(A): Cluster of atypical EMCs with few neutrophils (Pap X200)

Fig 10(B): Corresponding histopathological image showing grade 1, villoglandular endometrial carcinoma. (H&E X200)

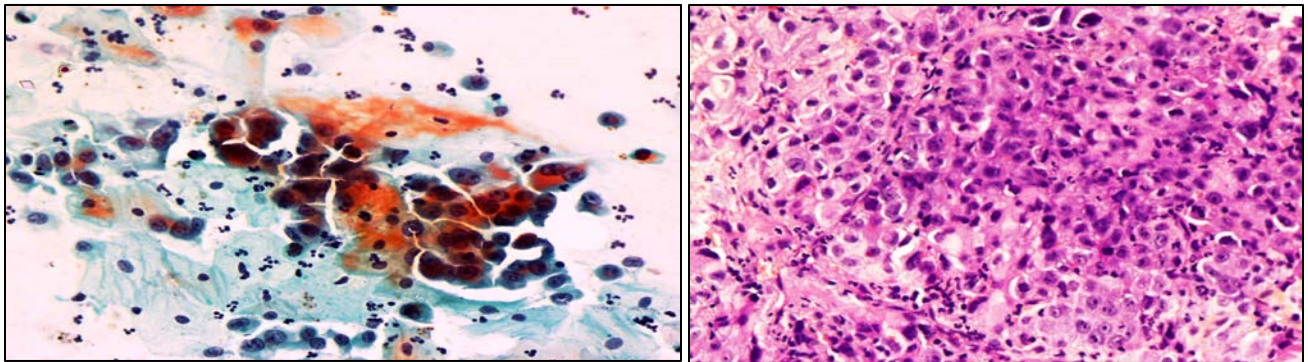


Fig 11(A): Cluster of malignant EMCs with neutrophils & debris (Pap X100)

Fig 11(B): Corresponding histopathological image showing poorly differentiated endometrial carcinoma, grade III. (H&E X200)

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