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Spectrum of Histopathological Findings in Postmenopausal Bleeding

Muhammad Usman Tariq, Romana Idrees, Ahmed Raheem and Naila Kayani

ABSTRACT

Objective: To determine the frequencies of histopathological findings in endometrial and endocervical biopsy samples with clinical history of Postmenopausal Bleeding (PMB).

Study Design: Descriptive cross-sectional study.

Place and Duration of Study: Section of Histopathology, Department of Pathology and Laboratory Medicine, The Aga Khan University Hospital, Karachi, from February 2012 to January 2013.

Methodology: A total of 157 consecutive endometrial and endocervical biopsy specimens with history of postmenopausal bleeding were included. After microscopic examination, frequencies of histological findings in different age groups were generated. Chi-square and independent sample t-tests were applied to see whether the difference was significant which was set at $p < 0.05$.

Results: One hundred and twenty-one (77.1%) specimens showed benign pathologies while 36 (22.9%) were malignant. Endometrial polyp was seen in 67 (42.7%) cases followed by endometrial carcinomas in 25 (15.9%), endometrial hyperplasia in 21 (13.4%), cervical carcinoma in 12 (7.6%) and cervical polyps in 9 (5.7%) cases. A highly significant increase in the percentage of malignant and pre-malignant lesions was seen with increasing age group ($p < 0.001$). Mean age of patients with type-2 endometrial carcinoma was higher than type-1 endometrial carcinoma but statistical significance was not observed (70.2 ± 6.5 vs. 61.8 ± 9.1 years respectively, $p=0.069$).

Conclusion: Although benign pathologies were more common in postmenopausal bleeding but the collective proportion of endometrial and cervical malignancies and pre-malignant conditions was quite high. Therefore, PMB should be urgently evaluated for cause and early commencement of treatment.

Key Words: Postmenopausal bleeding. Endometrial polyp. Endometrial hyperplasia. Endometrial carcinoma. Cervical carcinoma.

INTRODUCTION

Postmenopausal Bleeding (PMB) is defined as "bleeding through female genital tract, 12 months after the cessation of menstrual cycles (menopause)".¹ It is a manifestation of diverse diseases, accounting for 5 - 10% of the gynecology clinic visits.² Postmenopausal bleeding occurs over a wide age range and can result from a number of pathologies arising in any of the female genital tract organs, particularly uterus and cervix.³ PMB can result from the normal physiologic atrophic changes, infections, benign lesions such as polyps, hyperplastic (pre-malignant) conditions and aggressive malignant conditions. A number of systemic disorders, especially blood dyscrasias are also associated with this symptom.⁴

The incidence of malignancies in women with postmenopausal bleeding has varied over the period of time and with study setting.⁵⁻¹³ Two of the studies conducted in Pakistani setting by Dawood *et al.* and Jilani *et al.*

have reported a higher incidence of malignancy in comparison with the rest of the world.^{5,8}

PMB is a warning symptom as it has significant association with malignancies and it might be the only and/or initial presenting symptom of these conditions.¹⁴⁻¹⁶ Dilatation and Curettage (D&C) is considered to be a method of choice.¹⁷ Current guidelines mandate immediate clinical evaluation and Trans-vaginal Ultrasound (TVS) assessment followed by D&C or hysteroscopy guided endometrial / endocervical biopsy and subsequent histological evaluation.¹⁸

The incidence of carcinoma cervix has fallen significantly in the developed countries due to regular screening programs and subsequent detection at an early level. Similarly, due to high public awareness about the signs and symptoms of carcinoma endometrium, women with PMB have early visit and detection at initial stage.^{11,12} Because of lack of screening programs, poverty, lack of health facilities and high illiteracy rate in our country, this symptom is usually ignored along with other medical problems and the women present at a very late stage. Moreover, adoption of urban lifestyle has led to an increase in obesity, hypertension and diabetes mellitus in our population which are known risk factors for endometrial cancer.¹⁶ Therefore, this threatening medical situation necessitates the estimation of the recent burden of these diseases.

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The aim of this study was to determine the frequencies of different histopathological findings in specimens received with a history of postmenopausal bleeding, at histopathology section in a major referral centre in Karachi, Pakistan.

METHODOLOGY

It was a prospective cross-sectional study conducted at Section of Histopathology, Department of Pathology and Microbiology, The Aga Khan University Hospital. The study did not directly involve human subjects. Only the results of diagnoses made on the biopsy material submitted for histopathological examination were analyzed and no additional intervention or test was performed. Consecutive endometrial and endocervical biopsy specimens with clinical history of PMB, received over a period of one year, were included with lowest age limit for inclusion being 32 years, being the lowest age of menopause reported in Pakistan.³ Scanty biopsy specimens and poorly fixed specimens were excluded. The gross examination was performed according to the guidelines by Rosai and Ackerman.¹⁹ Formalin-fixed, paraffin embedded tissue sections were stained with Haematoxylin & Eosin (H&E). The microscopic examination was performed by two pathologists. Variables including age and histopathological findings were obtained on a pre-designed proforma.

Data was analyzed by using SPSS Version 19. Mean value and standard deviation for age of women were computed. Frequencies with percentages for outcome variables including atrophic endometrium, endometrial hyperplasia, endometrial carcinoma, carcinoma cervix, polyps and other diagnosis were generated and presented on pie charts. Cases were divided into four age groups (≤ 50 years, 51 - 60 years, 61 - 70 years and ≥ 71 years). Cross tabulation was done with age groups and types of histopathological findings and chi-square test was applied to see the distribution of these findings according to age. With 95% confidence interval and 5% level of significance, p-value of < 0.05 was considered significant. Independent sample t-test was applied to compare the mean age of patient with type-1 and type-2 endometrial carcinoma. With 95% confidence interval, 5% level of significance (p-value < 0.05) was considered significant.

RESULTS

Patients' age ranged from 38 - 80 years with a mean value of 57.6 ± 8.1 years. Most of the patients (45.2%) were in the sixth decade.

Out of 157 samples, 133 (84.7%) were endometrial biopsies and 24 (15.3%) were endocervical biopsies. Overall, endometrial polyp was the most common histopathological finding which was seen in 67 (42.7%) cases. Carcinoma of endometrium was the second most

common finding which was seen in 25 (15.9%) cases, endometrial hyperplasia in 21 (13.4%) cases, carcinoma cervix in 12 (7.6%) cases, cervical polyps in 9 (5.7%) cases and atrophic endometrium in a single (0.6%) case. Other, less common histopathological findings comprised of 22 (14%) cases and included 6 (3.8%) cases of glandular and stromal breakdown, 4 (2.5%) cases of disordered proliferative pattern, 2 (1.3%) cases of progesterone effect, 2 (1.3%) cases of anovulatory cycle change, 2 (1.3%) cases of endometritis and a single case, each of cervical dysplasia, cervical leiomyoma, cervical ulcer, proliferative endometrium, excessive estrogen effect and non-secretory endometrium.

Among the endometrial biopsies, polyps comprised 50.3% (Figure 1). Among cervical biopsies, carcinomas comprised the majority, i.e. 50%, polyps (Figure 2).

In the 21 cases of endometrial hyperplasia, 10 (47.6%) cases were simple hyperplasia without atypia, 9 (42.8%) were complex hyperplasia with atypia and 2 (9.5%) were complex hyperplasia without atypia. Simple hyperplasia with atypia was not seen in any case.

In the 25 endometrial carcinomas, 20 (80%) cases were endometrioid carcinoma (type-1), 2 (8%) cases were serous adenocarcinoma, 2 (8%) cases were clear cell adenocarcinoma (type-2) and a single case was Malignant Mixed Mullerian Tumor (MMMT). Among the 20 cases of endometrioid adenocarcinomas, 4 (20%)

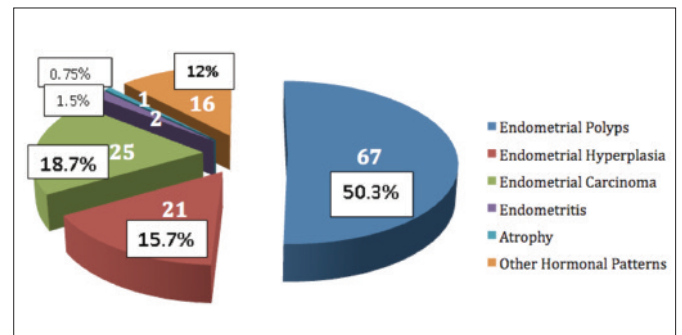


Figure 1: Frequencies of histopathologic findings in endometrial biopsies.

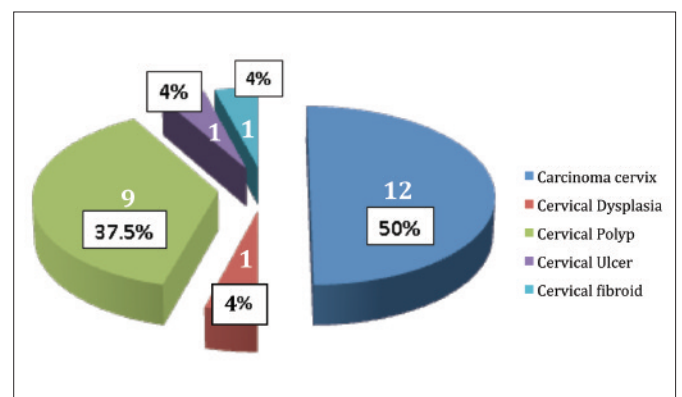


Figure 2: Frequencies of histopathologic findings in endocervical biopsies.

Table I: Comparison of age-wise distribution of benign, pre-malignant and malignant cases.

	Benign	Pre-malignant and malignant	p-value
≤ 50 years	29 (87.9%)	4 (12.1%)	p <0.001
51-60 years	51 (71.8%)	20 (28.2%)	
61-70 years	28 (67.7%)	14 (33.3%)	
≥ 71 years	2 (18.2%)	9 (81.8%)	

Table II: Proportion ages (in years) of type 1 and type 2 endometrial carcinomas patients in different age groups.

	Type-1 endometrial carcinoma (n=20) overall mean (61.8 ± 9.1 years)	Type-2 endometrial carcinoma (n=5) overall mean (70.2 ± 6.5 years)	p-value
≤ 50 years	29 (87.9%)	4 (12.1%)	p = 0.069
51-60 years	51 (71.8%)	20 (28.2%)	
61-70 years	28 (67.7%)	14 (33.3%)	
≥71 years	2 (18.2%)	9 (81.8%)	

were FIGO grade I, 10 (50%) were FIGO grade-II and 6 (30%) were FIGO grade-III.

Among the 12 cases of carcinoma cervix, 6 (50%) were well differentiated, 4 (37.5%) were moderately differentiated and 2 (12.5%) were poorly differentiated.

These histopathologic findings were distributed in all four age groups. Ten cases of pre-malignant lesions (complex hyperplasia with atypia and cervical dysplasia), 25 cases of carcinoma endometrium and 17 cases of carcinoma cervix were combined in a single group of malignant and pre-malignant lesions. The percentage of malignant and pre-malignant cases increased with ascending age group. With 95% confidence interval and 5% level of significance, Chi-square test was applied and a highly significant p-value was observed (p < 0.001, Table I).

Mean ages of type-1 endometrial carcinoma (n=20) and type-2 endometrial carcinoma (n=5) were 61.8 ±9.1 years and 70.2 ±6.5 years, respectively (p=0.069, Table II).

DISCUSSION

Postmenopausal bleeding is one of the common complaints which are encountered in the period secondary to cessation of follicular activity.²⁰ PMB not only causes disturbance of the normal routine itself, but it can also become related to additional morbidity due to underlying gynecologic or systemic pathology. The histologic evaluation of endometrium, after clinical and TVS examinations, is mandatory according to recent guidelines. Endometrial sampling is obtained by safe, quick and an easy procedure performed in clinic setting.¹⁸

Mean age of menopause in Pakistani population has been reported to range from 32 to 62 years.³ The age range of women with history of postmenopausal bleeding in this study ranged from 38 to 80 years with

mean age of 57.1 ±8.1 years, which is comparable to the other studies. Most of the studies conducted internationally with a large dataset have included endometrial as well as endocervical biopsy specimens. However, few of the studies conducted in our country had a small sample size and included endometrial biopsies only and, therefore, ignored readily performed endocervical biopsies which contribute a significant percentage of pathologies responsible for PMB.¹¹ In this study, 24 endocervical biopsy specimens were included which comprised 15.3% of the total specimens and provided a good idea of the PMB causes of cervical origin.

Benign pathology was observed in majority (70%) of the cases. Endometrial Polyp (EP) was the most common finding that was seen in 67 (42.8%) cases and this incidence was much higher than that reported in the literature as the incidence of EP in postmenopausal age group has ranged from 2.03 to 12%.^{1,8} Removal of the polyps and thorough histological examination become important as these lesions have the rare ability to give rise to pre-malignant and malignant conditions.²¹ Those cases of study, which showed such transformation were included in the malignant or pre-malignant category for the sake of simplicity.

Endometrial Hyperplasia (EH) was observed in 21 (13.4%) cases which was in concordance and the incidence reported in various national and international studies (5 - 17%).⁵⁻¹⁰ The risk of malignant transformation increases with increase in complexity and atypia from 1 to 29% and, therefore, sampling of such lesion becomes mandatory in order to rule out malignancy.²² Among different types of hyperplasia in this study, complex hyperplasia with atypia and simple hyperplasia without atypia constituted the major bulk i.e. 47.6% and 42.8% cases respectively.

Endometrial Carcinoma (EC) is the third most common malignancy of females in Pakistan with peak incidence in sixth and seventh decades.²² The incidence of EC has ranged from 4.8 to 22.5% in different studies conducted in the local setting.⁵⁻¹⁰ In a recent international study conducted in postmenopausal women, Burbos *et al.* reported a lower incidence (5%) of endometrial carcinoma.⁷ EC comprised 15.9% of the present reported histological findings. Out of these 25 cases, 20 (80%) were type-1 and 5 (20%) were type-2. Out of these type-2 lesions, two were serous adenocarcinoma, two were clear cell adenocarcinoma and 01 was Malignant Mixed Mullerian Tumor (MMMT). Majority of the endometrioid (type-1) endometrial EC were of FIGO grade-II. The percentage of EC is similar to the incidence reported earlier in the country. However, we think that the failure to reduce the malignancy rate, as achieved in the western countries, can be attributed to high illiteracy rate, lack of health facilities, delay in seeking medical advice and an increase in the risk

factors for EH, such as hypertension and diabetes mellitus.²³ The mean age of type-1 EC (61.8 ± 9.1 years) was lower than the mean age of type-2 EC (70.2 ± 6.5 years) which is in concordance with the reported literature.²⁴ But statistical significance was not observed, probably because of small number of cases in each cohort.

Carcinoma of cervix is the third most common malignant cause of mortality in females. The incidence has decreased over the past few decades in western countries.²⁵ In Pakistan, the incidence of carcinoma cervix ranges from 2.5 to 25.5%.⁵⁻¹¹ Carcinoma of cervix was observed in 7.6% of these cases and apart from these 12 cases, a single case of cervical dysplasia was also observed. All over the world, the peak incidence is seen in 5th decade but the peak incidence in this study was seen in sixth and seventh decades which also points to the late presentation due to poverty and unawareness.

Atrophic endometrium has been the most common cause of PMB worldwide but we surprisingly noted a single case with atrophic endometrium.^{1,2,6,7} In the authors' opinion, the increased use of estrogen to avoid the other estrogen withdrawal symptoms in the postmenopausal period may have prevented the atrophic process.

CONCLUSION

A variety of histopathological findings are seen in PMB. Although benign pathologies were more common but the collective proportion of endometrial and cervical malignancies and pre-malignant conditions is considerably higher in this study. The clinicians should educate the patients about the alarming symptom of PMB and emphasize the need for seeking urgent medical advice and early commencement of treatment.

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