Original Article

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The Diagnostic Value of Endometrial Biopsy in Postmenopausal Uterine Bleeding

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Abstract

Post-menopausal uterine bleeding is the cause of discomfort and inconvenience, affecting millions of women. Endometrial sampling is the effective means of evaluating the women with post- menopausal uterine bleeding. *Objectives:* To study the histopathological pattern of the endometrial biopsies of patients with post-menopausal uterine bleeding and to correlate the abnormal endometrial pattern with different clinical presentations and age groups. *Methods:* The present study included evaluation of 60 cases of post-menopausal uterine bleeding diagnosed in the Department of Pathology, Vijayanagar Institute of Medical Sciences, Ballary, over a period of 1 year, from June 2015 to June 2016. The specimens were processed, embedded and cut into sections of 3-5 microns. The histopathological patterns of the endometrial biopsies were studied. *Results:* Atrophic endometrium formed the bulk of post-menopausal bleeding (50.0%). Non-neoplastic and benign neoplastic lesions including endometritis, polyp and hormone induced lesions formed 25.0%. 11 cases of endometrial hyperplasias (18.3%) and 4 cases of adenocarcinoma (6.7%) were encountered. The incidence of postmenopausal bleeding decreased with increasing age while the probability of cancer as the underlying cause increased. The peak incidence of endometrial carcinoma was found in women between 65 and 69 years of age. *Conclusion:* Endometrial biopsy is a valuable means for differentiating various benign lesions of uterine cavity, including atrophic endometrium, endometritis, endometrial polyp, and hormone-induced changes. Microscopic assessment of postmenopausal bleeding has great value in the identification of endometrial hyperplasia and carcinomas. Endometrial biopsy should be a part of diagnostic work up of the patients with postmenopausal bleeding to ensure accurate diagnosis and correct management.

Keywords: Post-Menopausal Bleeding; Endometrial Biopsy; Histopathology; Patterns**.**

Introduction

Abnormal uterine bleeding is one of the most common presenting complaints encountered in gynaecological clinic. Amongst them postmenopausal bleeding ranks as the most sinister as it is often associated with malignancy [1]. Definition of Postmenopausal bleeding (PMB) is self-explanatory, as any bleeding from the genital tract occurring in the postmenopausal period, arising after 12 months of amenorrhoea in a women of menopausal age [2].

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The list of differential diagnostic considerations in abnormal uterine bleeding in postmenopausal patients is extensive and includes, non-organic causes, benign anatomic lesions, inflammatory processes and pelvic malignancies. Endometrial biopsy is the most commonly used diagnostic test for abnormal uterine bleeding and provides an adequate sample for diagnosis of endometrial problems in most of the cases [3].

The significant frequency with which malignancy occurs in patients with postmenopausal bleeding mandates careful diagnostic evaluation. Unlike other malignancies, endometrial cancer often presents at an early stage when there is a possibility of curative treatment by hysterectomy. Survival decreases with increased staging and lower histological

differentiation, thus accurate and timely diagnosis is important. Endometrial biopsy is the most widely used method of excluding endometrial hyperplasia and carcinoma, in postmenopausal women with abnormal uterine bleeding [2].

The present study has been undertaken to review the myriad causes of abnormal uterine bleeding in post-menopausal women.

Material and Methods

The present study was conducted in the Department of Pathology, Vijayanagar Institute of Medical Sciences, Ballary from June 2015 to June 2016. Post-menopausal women of abnormal uterine bleeding attending outpatient department, admitted in OBG Department of VIMS, Ballary and other peripheral hospitals formed the source of data. Relevant clinical details like age, parity, age at menopause, interval between last menstrual period and onset of PMB and duration of bleeding were collected.

Inclusion Criteria

Post-menopausal women presenting with abnormal uterine bleeding.

Exclusion Criteria

1. Abnormal bleeding secondary to systemic diseases like coagulation disorders, hypothyroidism and cirrhosis.
2. Abnormal bleeding secondary to cervical and vaginal lesions.

The material consisted of endometrial biopsy and dilatation and curettage of patients with post-menopausal bleeding.

The specimens were fixed in 10% formalin and examined grossly for amount, colour and consistency. They were processed using automatic tissue processor and embedded in paraffin, according to the procedures given in the handbook of histopathology and histochemical technique by Culling[4]. Sections of 3-5 μ were cut using rotary microtome and stained with Hematoxylin & Eosin. Appropriate special stains like per-iodic acid Schiff was done as and when required.

Results

A total number of 65 samples of post-menopausal bleeding were received in the Department of Pathology, Vijayanagar Institute of Medical Sciences, Ballary during the study period, from June 2015 to June 2016. Out of 65 cases, 5 biopsies were inadequate, showing only the fragments of blood clots without any glands. So, a total of 60 cases were taken for histopathological study.

The Following Data were Recorded and Analyzed

In the present study, age distribution varied from 45 years to 70 years. Mean age of attaining menopause was 51.4 years. The interval between menopause and first episode of PMB varied from 13 months to 21years and the mean was 5.6 years. Most patients presented with PMB 2-4 years after attaining menopause. Hyperplasia was commonly observed in the age group of 50-60 years. Endometrial carcinoma was observed in the age group of more than 61 years.

Duration and severity of bleeding are documented. 23% of the patients had spotting, 55% had moderate flow and 22% had heavy flow. 35% presented after one weak of onset of bleeding, 50% within one month and 15% after a month of onset of bleeding.

The average parity of the patients was 3 and it ranged from nullipara to para 6.

Revive of benign causes of PMB indicates that endometrial atrophy is the commonest cause.

Atrophic Endometrium

Atrophic Endometrium accounted for 50.0% of cases in the present study. Microscopy showed sparse small glands lined by cuboidal epithelium. Stroma contained small spindle cells.

Table 1: Distribution of lesions of postmenopausal bleeding

Lesion	Number	Percentage
Atrophic Endometrium	30	50.0
Proliferative phase	5	8.3
Hormone replacement therapy	2	3.4
Endometritis	5	8.3
Polyp	3	5
Hyperplasia	11	18.3
Carcinoma	4	6.7
Total	60	100

Endometritis

Out of 5 pateints of endometritis, four patients were of chronic nonspecific endometritis. Histopathologically the nonspecific endometritis showed infiltration by chronic inflammatory cells consisting of plasma cells, lymphocytes and macrophages.

The patient of tubercular endometritis presented with spotting. Microscopy showed granulomas composed of epithelioid cells, lymphocytes and Langhans giant cells (Figure 1).

Endometrial Polyp

All the three cases of endometrial polyps were small (less than 3 cm), sessile masses. Two polyps showed early proliferative phase. Third polyp was a case of hyperplastic polyp and it showed simple hyperplasia.

Hormone Replacement Therapy

Three patients presented with irregular bleeding due to hormone replacement therapy. They were younger than 55years and had proliferative endometrium on histology.

Out of 15 cases, hyperplasia amounted for 11 cases and neoplasia amounted for 4 cases.

Hyperplastic Lesions

11 cases of hyperplastic lesions were encountered, out of which simple hyperplasia was the commonest pathology detected, amounting to 46.7%. It was followed by complex hyperplasia 20% and atypical hyperplasia 6.7%.

Table 2: Distribution of hyperplastic and neoplastic lesions

Lesion	Number	Percentage
Simple hyperplasia	7	46.7
Complex hyperplasia	3	20
Atypical hyperplasia	1	6.7
Endometrial carcinoma	4	26.6
Total	15	100

Simple Hyperplasia

Histologically showed both small tubular glands and cystically dilated glands lined by columnar cells with oval nuclei. Minimal budding and papillary infoldings against a compact stroma were seen

Complex Hyperplasia

On microscopy, showed marked crowding with back-to-back arrangement of glands. Frequent intraluminal epithelial projections and intraglandular bridging were noticed. Nuclear stratification without atypia was also noted (Figure 2).

Atypical Hyperplasia

The patient of atypical hyperplasia was aged 40 years, para 3 and presented with moderate flow of 2 months duration.Microscopic examination showed crowded glands with intraluminal epithelial projections and intraglandular bridging. The stromal invasion was absent. The cells were hyperchromatic with increased nucleo-cytoplasmic ratio (Figure 3)

Endometrial Carcinoma

4 cases of endometrial carcinoma were encountered, accounting to 26.6% of hyperplastic and neoplastic lesions. Microscopy showed well-differentiated adenocarcinoma with irregular glands showing back to-back arrangement.

Small amount of stroma was seen between the glands. The glands showed acinar and villoglandular pattern. Glands were lined by 2-3 layers of pleomorphic columnar cells with hyperchromatic nuclei. Many glands showed vesicular nuclei with prominent nucleoli. Mitotic figures were seen (Figure 4). Areas of squamous metaplasia were noticed in two cases (Figure 5).

The ratio of neoplastic lesions (hyperplasia and carcinoma) to all other histologic types in postmenopausal women was 1:3. Endometrial carcinoma constituted 6.7% of postmenopausal bleeding.

Discussion

AUB can arise from a bewildering number of sources. It may represent a normal physiological state and observation alone may be warranted. Alternatively, the bleeding can be a sign of a serious underlying condition, necessitating aggressive treatment, especially in postmenopausal patients [5]. An endometrial biopsy is considered the gold standard for evaluation of PMB [2,6]. Endometrial sampling

Table 3: Distribution of neoplastic and non-neoplastic lesions

Type	Number	Percentage
Non-neoplastic & benign neoplastic lesions	45	75
Hyperplasia and carcinoma	15	25
Total	60	100

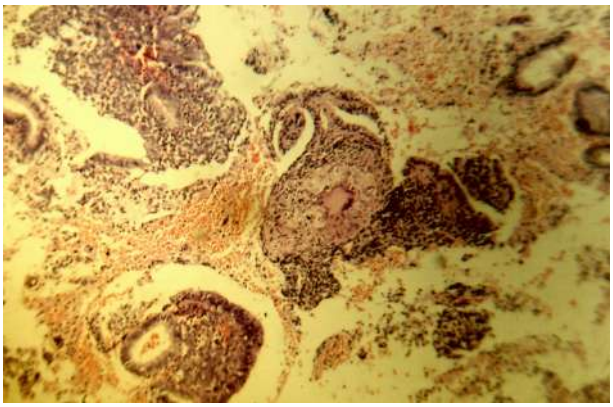

Fig. 1: Tubercular Endometritis – Granuloma with Langhans giant cells (H & E) x 10 (S 534/06)

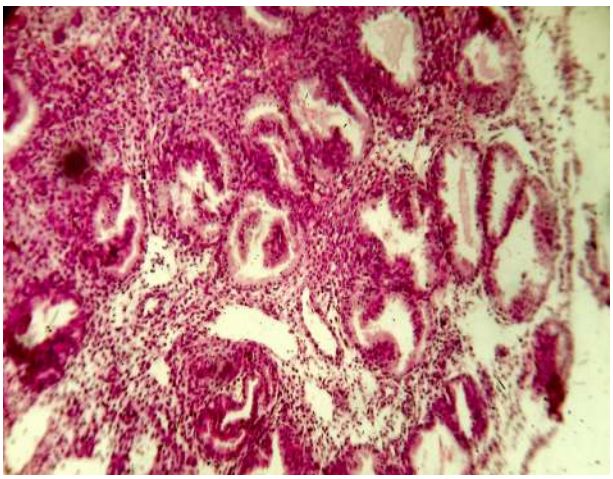

Fig. 2: Complex hyperplasia – Back to back arrangement of glands with scant stroma (H&E) X40 (S 462/05)

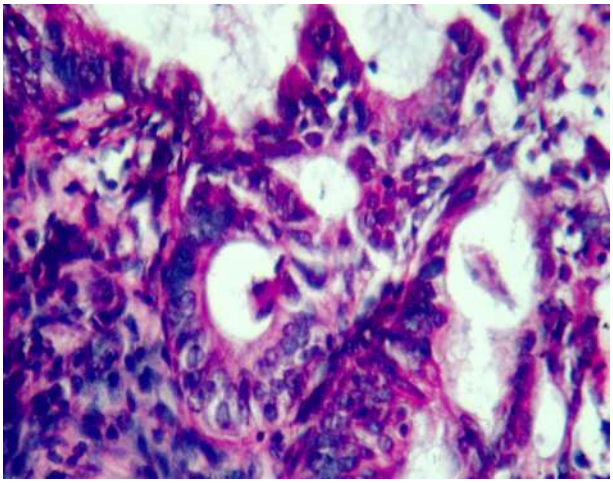

Fig. 3: Atypical Hyperplasia - intraglandular bridging with nuclear atypia (H & E) x 40 (S 2031/05)

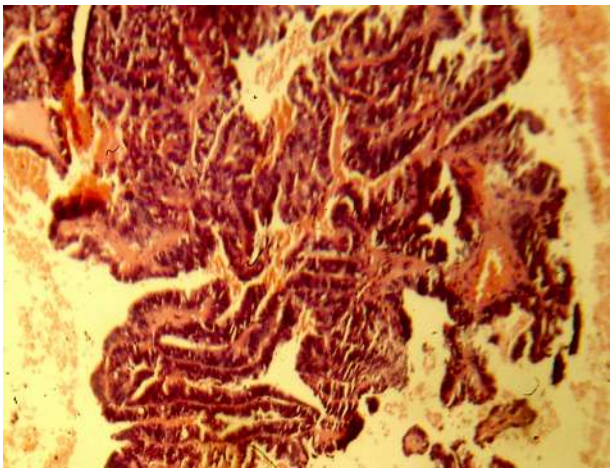

Fig. 4: Endometrial adenocarcinoma-complex glands with papillary projections (H & E) x 10 (S 186/06)

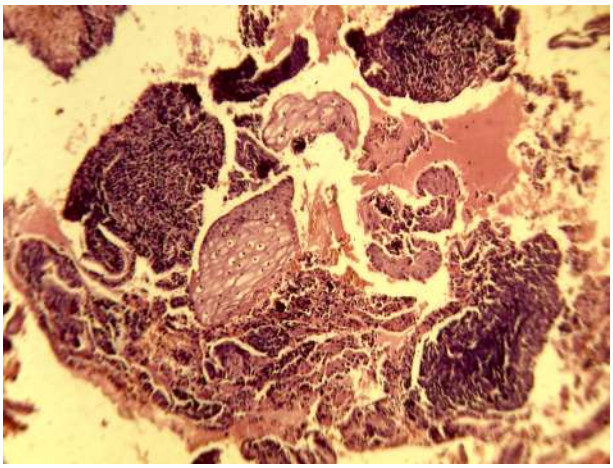

Fig. 5: Endometrial adenocarcinoma – Focus of squamous metaplasia. (H&E) X10 (S 186/06)

could be effectively used as the first diagnostic step in AUB, although at times, its interpretation could be quite challenging to the practicing pathologists.[7] This study was done to evaluate histopathology of endometrium for identifying the endometrial causes of AUB in postmenopausal bleeding.

In the present study 60 patients with PUB were studied and data were compared with standard studies.

Most of the patients presented before the age of 60 years in the present study. This is comparable to observation by Kok Hain Tan [1]. Most patients presented after 2-4 years of attaining menopause. The incidence of postmenopausal bleeding decreased with

increasing age while the probability of cancer as the underlying cause increased. The peak incidence of endometrial carcinoma was found in women between 65 and 69 years of age. 23% of patients presented with spotting, indicating the necessity of full and complete evaluation of any PMB, regardless of the amount of bleeding. 15% of patients presented after one month of onset of bleeding. This observation indicates the lack of awareness of the importance of PMB in general public, warranting the need of education in this regard.

In the post-menopausal period uterus is lined only by basalis and there is no functionalis. Stroma is cellular and the glands are small, narrow and tubular. Glands are lined by cuboidal epithelium. Some years after menopause, some women develop cystically dilated glands, lined by single layer of cuboidal epithelium. This is called senile cystic atrophy [8].

Atrophic endometrium formed the bulk of cases of PMB in all the reported series. In the present study atrophy formed 50% of cases. This is comparable to Kok Hain Tan study (52%) and Thomas Gred Mark study (50%) [1,9]. Escoffery et al reported lesser incidence (21.3%) [10].

The diagnosis of endometritis depends entirely on histopathological examination because clinical features are variable. Many features are normally present in endometrium, which would indicate an inflammatory process in other tissues. Thus, occasional lymphocytes are seen in the normal endometrium. The interstitial hemorrhage, necrosis and polymorphonuclear infiltrate are seen during menstruation. So, for the diagnosis of endometritis, findings of plasma cells and eosinophils are needed [11].

Tuberculous granulomas are localized commonly to mucosa during reproductive period. The biopsy shows small ill-defined granulomas composed of epithelioid cells and lymphocytes. Caseation and giant cells are rare. Tuberculous endometritis is rare after menopause and when present, shows well-formed caseating granulomas [12].

Endometritis formed 2.8% of cases of AUB in the present study. This is similar to Moghal N [13], who reported 3.3% of endometritis. Domingo [14] reported 7.2% of cases of endometritis. McElin TW [15] did not report endometritis in his study.

Majority of the endometrial polyps are not true neoplasms, but represent circumscribed foci of hyperplasia. Grossly, they are pedunculated lesions, bulk of which is composed predominantly of collagenated fibrous stroma populated by cystically dilated and occasionally crowded glands lined by inactive, atrophic to weakly proliferative endometrium. All types of endometria including those showing signs of hyperplasia can be found in polyps. Occasionally adenocarcinoma or carcinosarcoma can be found in polyps. In this study 3 cases (11%) of polyps were studied, Thomas Gredmark reported 11.2% [9].

Endometrial hyperplasia is a condition of prolonged hyperestrogenism, displaying a variety of cytological and architectural variations [16]. A distinction between a case of atypical hyerplasia and well-differentiated adenocarcinoma can be difficult. Microscopic features favoring carcinoma include:true intraglandular epithelial bridges devoid of stromal support, sheets and masses of pleomorphic cells, abnormal mitotic figures, presence of polymorphs and nuclear debris within glandular lumen and evidence of stromal invasion [17-19].

In the present study, 11 cases of hyperplasia are encountered, out of which 7(11.6%) were of simple hyperplasia. This is comparable to study by Thomas Gredmark, who reported 10%[9].

Endometrial adenocarcinoma is the most common gynecological malignancy in developed countries. In India carcinoma and other malignancies of the body of the uterus are not as frequently encountered as other gynecologic malignancies like cervical and ovarian malignancies [20]. It occurs in elderly individuals, 80% of the patients being postmenopausal at the time of diagnosis [21]. Multiple factors increase the risk of developing endometrial carcinoma, including obesity, nulliparity, unopposed estrogen, and late menopause [22].

Endometrial Carcinoma is Divided into two Distinct Types on the Basis of Their Pathogenesis

1. Occurring as a result of excess estrogenic stimulation and developing against a background of endometrial hyperplasia.
2. Developing de novo [23].

It is stated that endometrial adenocarcinomas form 97% of all the carcinomas of uterus. Well-defined glands lined by cytologically malignant stratified columnar epithelial cells characterize them histologically. Three types of architectural patterns are identified:

1. Large back-to-back, architecturally complex, compressive macroglands.
2. Extensively budding and branching glands with little stroma.
3. Branching exophytic papillary pattern [24].

Variants of endometrioid carcinoma include secretory and ciliated cell carcinoma [25].

In this study 4 (6.7%) of endometrial carcinoma were encountered, which is comparable to Thomas Greg (10%) [9] and Kok Hain Tan (11%) [1].

Conclusion

The microscopic examination of endometrium bears the pivotal role in diagnosing the various etiopathological factors in the cases of abnormal uterine bleeding in postmenopausal women. Histopathological examination of endometrium is a valuable means for differentiating various benign lesions of uterine cavity, which include endometritis, endometrial polyp, and hormone induced changes.The rate of endometrial hyperplasia in the present study is 12%, sufficient to warrant endometrial sampling. Endometrial hyperplasia can be accurately graded, which helps to predict the likelihood of progression to carcinoma. About 1/15th of the patients with post-menopausal bleeding presented with endometrial carcinoma. So, diagnostic endometrial sampling is mandatory in all cases of post-menopausal bleeding to rule out malignancy.

Key Messages

Assessment of endometrial biopsy of women with postmenopausal bleeding has great value in the identification of etiopathological factors including endometrial cancer. Endometrial biopsy should be a part of diagnostic work up of the patients with postmenopausal bleeding to ensure accurate diagnosis and correct management.

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