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Original Research Article

Histopathological Spectrum of Endometrial Lesions in Patients with Abnormal Uterine Bleeding

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Abstract

Background: Abnormal uterine bleeding is a frequent clinical presentation in gynecology and endometrial sampling is crucial for the diagnosis of functional, benign, pre-cancerous, and cancerous lesions.

Patients and Methods: This is a retrospective observation study to analyze the histopathological spectrum of endometrial lesions in the patients who have presented with AUB. Over three years 420 endometrial biopsy/curettage specimens were reviewed for age, bleeding pattern, menopausal status, endometrial thickness and histopathological diagnosis.

Results: The mean age was 43.6 +/- 9.8 years, and the largest group was 41-50 years (44.0%). The most common presentation was heavy menstrual bleeding (47.6%) followed by intermenstrual bleeding (18.1%) and postmenopausal bleeding (15.2%). A normal functional pattern was observed in 222 cases (52.9%) of which 31.4% showed a proliferative pattern. The organic lesions were endometrial hyperplasia without atypia (14.3%), endometrial polyp (8.8%), chronic endometritis (5.7%), atypical hyperplasia/endometrial intraepithelial neoplasia (3.1%) and endometrial carcinoma (3.8%). Increased incidence of pre-malignant and malignant lesions were seen in women of age >50 years and in women with post-menopausal bleeding ($p<0.001$). Hyperplasia or carcinoma was related to endometrial thickness >=12 mm ($p=0.002$).

Recommendations: This study highlights the importance of histopathological investigation in cases of abnormal uterine bleeding particularly in older women in the perimenopause and post-menopause.

Keywords: Abnormal Uterine Bleeding, Endometrial Biopsy, Endometrial Hyperplasia, Endometrial Carcinoma, Histopathology, PALM-COEIN.

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Introduction

One of the most common causes for patients to seek a gynecologists attention is abnormal uterine bleeding (AUB), which can happen in any stage of a women's reproductive life, perimenopausal and post-menopausal [1]. The FIGO PALM-COEIN system gives a classification system for abnormal uterine bleeding that is based on the structural and non-structural causes [2]. Though, for the confirmation of endometrial pathology and to rule out premalignant and malignant disease, histopathological examination of endometrial tissue is still essential [3].

The endometrium is hormonally responsive and undergoes cyclical changes that can be characterized as physiological, disordered proliferative, hyperplastic, inflammatory or neoplastic in the context of the clinical situation [4]. Anovulatory cycles and endometrial patterns that are functional are seen commonly among younger women, while endometrial patterns of hyperplasia and carcinoma are more important in the perimenopausal and postmenopausal women [5]. Endometrial hyperplasia, especially atypical endometrial hyperplasia or endometrial intraepithelial neoplasia (AEG/AEIN), is of clinical importance because it can occur concurrently with or be an early stage in the development of endometrioid carcinoma [6].

Proper histopathological classification is therefore a direct impactor of medical treatment, surveillance or hysterectomy. The aim of the present study was to assess the histopathological spectrum of the

lesions of endometrium in women with AUB, and to evaluate the correlation between age, menopausal status, bleeding pattern and endometrial thickness.

Materials and Methods

It was a retrospective, observational study, which was conducted in the Department of Pathology of a tertiary care hospital. Patients with abnormal uterine bleeding undergoing endometrial biopsy or fractional curettage and dilatation and curettage (D&C) were included from January 2021 to December 2023. Products of conception, gestational trophoblastic disease, inadequate samples and specimens obtained from patients who had known malignancy and were treated with neoadjuvant therapy were not included.

Information about age, menstrual status, presenting bleeding pattern, parity, endometrial thickness on ultrasound and clinical impression was collected from requisition forms and records.

The specimens were fixed in 10% neutral buffered formalin, processed routinely and stained with hematoxylin and eosin.

Histopathology was classified as functional endometrium, disordered proliferative endometrium, endometrial polyp, chronic endometritis, hyperplasia without atypia, atypical hyperplasia/EIN, carcinoma and other lesions.

SPSS version 26 was used for statistical analysis. Age was grouped into <=30, 31-40, 41-50 and >50 years. Chi-square test or Fisher exact test were used to compare categorical variables. Continuous variables were presented as mean and standard deviation and compared (t test) as appropriate. Statistically significant was considered a p-value less than 0.05.

Results

A total of 420 endometrial specimens were analyzed. The mean age was 43.6 +/- 9.8 years, and most patients were in the perimenopausal age group.

Heavy menstrual bleeding was the most frequent symptom, followed by intermenstrual bleeding and postmenopausal bleeding.

Functional endometrial patterns were the largest diagnostic category. Proliferative endometrium was the commonest individual diagnosis, followed by secretory endometrium and disordered proliferative endometrium. Among organic lesions, hyperplasia without atypia was most frequent. Atypical hyperplasia/EIN and endometrial carcinoma were uncommon but clinically important, together accounting for 6.9% of cases. Premalignant and malignant lesions increased with age and were particularly frequent among women above 50 years and those presenting with postmenopausal bleeding. Endometrial thickness >=12 mm was significantly associated with hyperplasia or carcinoma. Chronic endometritis was more common in reproductive-age women presenting with intermenstrual bleeding.

Table 1: Age distribution and bleeding patterns

Variable	Category	Number (%)
Age group	<=30 years	48 (11.4)
Age group	31-40 years	112 (26.7)
Age group	41-50 years	185 (44.0)
Age group	>50 years	75 (17.9)
Bleeding pattern	Heavy menstrual bleeding	200 (47.6)
Bleeding pattern	Intermenstrual bleeding	76 (18.1)
Bleeding pattern	Irregular/frequent bleeding	80 (19.0)
Bleeding pattern	Postmenopausal bleeding	64 (15.2)

Total specimens = 420.

Table 2: Histopathological spectrum of endometrial lesions

Diagnosis	Number	Percentage
Proliferative endometrium	132	31.4
Secretory endometrium	62	14.8
Disordered proliferative endometrium	28	6.7
Atrophic endometrium	34	8.1
Endometrial hyperplasia without atypia	60	14.3
Atypical hyperplasia/EIN	13	3.1
Endometrial polyp	37	8.8
Chronic endometritis	24	5.7
Endometrial carcinoma	16	3.8
Other/non-specific	14	3.3

EIN = endometrial intraepithelial neoplasia.

Table 3: Association of premalignant/malignant lesions with clinical variables

Variable	Hyperplasia/EIN/carcinoma present	Absent	p-value
Age <=50 years	45	300	<0.001
Age >50 years	44	31	<0.001
Postmenopausal bleeding	31	33	<0.001
Other bleeding patterns	58	298	<0.001
Endometrial thickness <12 mm	36	220	0.002
Endometrial thickness >=12 mm	53	111	0.002

Hyperplasia group includes hyperplasia without atypia, EIN and carcinoma.

Discussion

The present study revealed that the perimenopausal age group was the most commonly presented age group with regard to abnormal uterine bleeding and the largest diagnostic category comprised of the functional endometrial patterns. This is consistent with earlier studies reporting that anovulatory cycles and hormone imbalance are common complaints of women entering menopause [7].

The most common pattern was proliferative endometrium; a secretory pattern was the second most common. In women with abnormal bleeding, these patterns can be a normal cyclical endometrium from the time of bleeding or from a hormonal imbalance based on the clinical timing [8]. Disordered proliferative endometrium was seen in 6.7% and it is a morphological link between persistent estrogenic stimulation and hyperplasia.

The most prevalent organic lesions were endometrial hyperplasia without atypia. Adenomatous hyperplasia/EIN and carcinoma were less common, but were closely associated with age and postmenopausal bleeding. This is a clinically significant finding because there is significant risk of concurrent or subsequent carcinoma in patients with atypical hyperplasia/EIN [9].

Endometrial thickness was significantly related to hyperplasia or carcinoma. While ultrasonography can aid in triaging patients, histopathology is the gold standard for diagnosis, because endometrial polyps, focal carcinoma, and limitations in ultrasound may make the interpretation difficult [10]. Recommendations are for endometrial sampling of selected women in reproductive age who have risk factors and of women who are post-menopausal with bleeding [11].

Retrospective design, absence of long-term follow up and non-uniform hormonal history are limitations. Blind curettage may fail to identify some focal lesions and sampling by hysteroscopy may increase the diagnostic success. However, this study shows that there are age-dependent differences in endometrial abnormalities and encourages broad pathological evaluation in perimenopausal and postmenopausal women with abnormal uterine bleeding [12-15]. This was a predominance of perimenopausal women due to the clinical expectation that as ovarian follicular reserve decreases, so do the chances of ovulatory dysfunction. In this transition, estrogenic stimulation without any rhythm of progesterone counteraction could result in prostatic proliferative effect/disorder and may lead to hyperplasia in susceptible patients [1,2].

Heavy menstrual bleeding was the most frequent presentation, but bleeding pattern was not a good predictor of histology. Normal cyclical endometrium was found in some patients with heavy menstrual period; polyps, hyperplastic, and carcinoma were found in others. This highlights the importance of taking a symptom-led approach along with age, risk factors, imaging and tissue diagnosis [3,4].

Proliferative and secretory endometrium should not be ruled out as irrelevant findings solely based on the fact that a patient is in her reproductive years. They can be abnormal in patients sampled at a time other than the expected cycle phase, they can represent ovulatory dysfunction, luteal phase abnormality, or exogenous hormonal effect. The pathologist's report should therefore correlate with the last mense and history of female hormones if available.

In the current cohort, intermediate findings were disordered proliferative endometrium. It is important because it is the representation of persistent estrogen effect with the irregularity, not reaching hyperplasia. Clear reporting facilitates clinical decision making about the need for hormonal therapy or for repeat sampling or hysteroscopic assessment [6].

Most of the organic lesions were endometrial polyps. If focal, polyps may not be detected by blind sampling and can lead to intermenstrual bleeding. If polyps are detected, it should include a comment on the background endometrium and on any endometrial hyperplasia or atypia found in the polyp; the management will vary depending upon these [7,8].

The strong association with age over 50 years and post-menopausal bleeding was for atypical hyperplasia/EIN and endometrial carcinoma. In keeping with the natural sequence of events from unopposed estrogenic stimulation to endometrial

glandular crowding and a subset of patients progressing to endometrioid carcinoma [9,10]. The use of ultrasonic evaluation of endometrial thickness was valuable but not completely accurate. Having a thickened endometrium also raised the risk of either hyperplasia or carcinoma, while focal lesions can be present even if it is thicker, and atrophic bleeding can be present even if it is thinner. In the right patient, histopathological sampling is still considered to be the confirmatory test [11,12].

When reporting, words must have a uniform meaning. The two-tier WHO method for distinguishing hyperplasia without atypia from atypical hyperplasia/EIN eliminates ambiguity and helps to correlate diagnosis with management. Peculiar words should be avoided if there is no doubt of glandular crowding, cytological atypia or carcinoma [6,13].

The study also suggests that there should be better coordination between the gynecology and pathology departments. Good clinical information, menopausal status, ultrasound data and information about the prior treatment with hormones significantly enhances interpretation. Prospective studies with hysteroscopic correlation and follow up would assist in determining if hyperplastic lesions persist, regress or progress in this population [14,15].

The sampling of the endometrium is individualised in women of reproductive age. Biopsy is valuable even if the age of 40 is not met, because of persistent bleeding, obesity, polycystic ovarian syndrome, failed medical therapy or family history of endometrial carcinoma. Thus, on the one hand, the age and on the other hand, the clinical selection due to risk, influence the pathology workload [1].

Special attention should be given to postmenopausal bleeding. Atrophy is a frequent cause but the event should always be carefully assessed as carcinoma can bleed little or not at all and intermittently. This group showed the highest percentage of hyperplasia, EIN and carcinoma in the present study, in line with the recommendations for early evaluation [11,12].

A small number of patients had chronic endometritis diagnosed. Plasma cells can be difficult to identify on routine sections and when they are present ancillary CD138 staining may be helpful when infertility, recurrent pregnancy loss or persistent intermenstrual bleeding is seen. For the general AUB, however, routine morphology is the initial approach.

The most common findings were atrophic endometrium, primarily in the older women and in postmenopausal bleeding. Bleeding may occur in absence of hyperplasia due to fragility of atrophic glands and vessels. If atrophy is recognised, then it is not an alarm and the specimen needs to be sufficient in size to rule out a focal lesion or carcinoma.

The pre-analytical aspect of sampling adequacy is a critical issue. Limited tissue, broken parts and excessive blood clot can compromise interpretation. It is important to report the absence of tissue for diagnosis, since a benign diagnosis on an inadequate specimen may delay the diagnosis of focal hyperplasia or malignancy.

The results also indicate the critical role of gynecologic-pathology feedback. If the histology reveals a normal cyclical endometrium, structural PALM causes like leiomyoma, adenomyosis or polyp might warrant imaging or hysteroscopy. Histopathology is a component of an integrated approach to diagnosis [2,15].

The incidence of carcinoma in this series was small but significant since abnormal bleeding is one of the earliest symptoms of endometrial cancer. Systematic sampling of high-risk groups, including persistent bleeding from the womb or having risk factors, such as perimenopausal women and women who are postmenopausal, should be performed even if the percentage is low [12,15].

Correlation with BMI, diabetes, hypertension, parity, hormone therapy, and polycystic ovarian syndrome would enhance risk analysis for future audits. These factors were only partially available from the present retrospective records, but are well recognised as factors which modify the risk of endometrial hyperplasia and/or endometrial carcinoma and should be recorded in prospective studies [6,13].

Conclusion

Abnormal uterine bleeding patients most frequently had functional endometrial patterns, whereas patients aged older and postmenopausal tended to have hyperplasia, atypical hyperplasia/EIN and carcinoma. Endometrial biopsy continues to be an invaluable tool for definitive diagnosis and early detection of pre-cancerous and cancerous conditions.

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