A study of histopathological spectrum of endometrial lesions in abnormal uterine bleeding with analysis of expression of KI-67 in endometrial hyperplasias and carcinomas

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Abstract---Histopathological evaluation of endometrial samples is an important diagnostic tool in AUB. Our study revealed that proliferative endometrium was the most common pattern for AUB. Incorporation of Ki-67 immunostain in histopathological examination of endometrium in patient’s with AUB will help in understanding its biological behaviour which can help in early diagnosis, targeted treatment strategies and prognostication.

Keywords---endometrium, immunohistochemistry, hyperplasia, carcinoma.
**Introduction**

Abnormal uterine bleeding (AUB) is defined as any bleeding outside of normal menstrual pattern with excessive duration, frequency and amount of loss [1]. It is estimated that 9-30% of women of reproductive age suffer from abnormal uterine bleeding. The prevalence increases with age, peaking just prior to menopause. Excessive menstrual bleeding has several adverse effects, including anaemia and iron deficiency, reduced quality of life and increased healthcare costs because it is a major indication for referral to gynaecological outpatient clinics. About 25.30% of abdominal hysterectomies are done for abnormal uterine bleeding [3]. Endometrial carcinoma is the second most common gynecologic malignancy with an incidence of 5.9 per 100,000 women in the developing countries. In India, the incidence is 4.3 per 100,000 women [4]. It has been recognized that thyroid dysfunction may have significant effects on the female reproductive system. Both hypothyroidism and hyperthyroidism are associated with a variety of changes. The incidence of endometrial hyperplasia and atypical endometrial hyperplasia is estimated to be 355/100,000 woman-years and 56/100,000 woman-years. As hyperplasia precedes all cases of atypical hyperplasia and endometrial carcinoma, it highlights the potential advantages of identifying women at risk of developing endometrial carcinoma by possible analysis of histopathological features supplemented by a pattern of expression by molecular markers involved in the carcinogenesis [5]. Ki-67 is a proliferation marker which is an independent prognostic marker in endometrial carcinomas and its positivity is shown to increase as the severity of endometrial lesion progresses from endometrial hyperplasia to endometrial carcinoma [6].

**Aim of the study**

1. To study the histopathological spectrum of endometrial lesions in abnormal uterine bleeding.
2. To study expression pattern Ki-67 in endometrial hyperplasias and carcinomas.

**Material and Methods**

This study is a prospective study of 100 cases where all patients diagnosed clinically as having abnormal uterine bleeding and who underwent dilatation and curettage, endometrial biopsy and hysterectomy were studied. The study was done in Dr.B.R.Ambedkar medical college and hospital, Bangalore for a period of 4 months from March 2022 to June 2022. The samples underwent routine processing and were stained with Hematoxylin and eosin. Immunohistochemistry for Ki-67 were done on cases diagnosed as endometrial adenocarcinoma and endometrial hyperplasia.

**Results**

Out of the 100 cases studied, maximum number of cases were seen in the age group of 41-50 years. Age of the patients ranged from 29 to 67 years. In premenopausal women the most common histopathologic pattern was proliferative endometrium (43%). Endometrial hyperplasia was noted in 10 cases
(10%) and there were 4 cases (4%) of endometrial carcinoma. Ki-67 done on all endometrial carcinoma showed High Ki-67 expression (>20%), moderate (10-20%) Ki-67 expression in atypical hyperplasia and weak to nil Ki-67 expression (<10%) in simple hyperplasia without atypia.

Table showing different endometrial lesions (n = 100)

<table>
<thead>
<tr>
<th>PATTERN</th>
<th>NUMBER OF CASES</th>
<th>PERCENTAGE(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative phase</td>
<td>43</td>
<td>43%</td>
</tr>
<tr>
<td>Secretory phase</td>
<td>22</td>
<td>23%</td>
</tr>
<tr>
<td>Simple hyperplasia without atypia</td>
<td>10</td>
<td>10%</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Lytic endometrium</td>
<td>4</td>
<td>4%</td>
</tr>
<tr>
<td>Endometrial polyp</td>
<td>5</td>
<td>5%</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>4</td>
<td>4%</td>
</tr>
<tr>
<td>Disordered proliferative phase</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Simple cystic atrophy</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Atrophic endometrium</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Mixed proliferative and secretory</td>
<td>2</td>
<td>2%</td>
</tr>
</tbody>
</table>

![AGE DISTRIBUTION OF AUB](image1)

![Distribution of Endometrial pattern on histopathological examination](image2)
<table>
<thead>
<tr>
<th>LESION TYPE</th>
<th>NO OF CASES</th>
<th>KI-67 +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple hyperplasia without atypia</td>
<td>10</td>
<td>Low (&lt;15%)</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>2</td>
<td>Intermediate(16-30%)</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>4</td>
<td>High (&gt;30%)</td>
</tr>
</tbody>
</table>

Fig 1: Simple hyperplasia without atypia showed weak to nil (<15%) Ki-67 expression.

Fig 2: Atypical hyperplasia showing moderate Ki-67 expression (16-30%).

Fig 3: Endometrial carcinoma showing high Ki-67 expression (>30%).

Fig 4: High magnification of endometrial carcinoma showing high Ki-67 expression.
Discussion

AUB is a general term and cause bleeding patterns like menorrhagia, menometrorrhagia, oligomenorrhea, metrorrhagia, polymenorrhea, mid cycle spotting[1]. The term dysfunctional uterine bleeding is used to describe abnormal uterine bleeding for which no specific organic cause has been found [2] Ki-67, also called pKi-67, is a nuclear protein that is encoded by the MKI67 gene[7]. Ki-67 protein expression is believed to be a valuable marker for cell growth and proliferation. Since the growth of tumor tissue depends on its proliferative activity, the expression of the Ki-67 proliferative marker was assessed in our study to investigate the potential diagnostic and prognostic roles. The over-expression of the Ki-67 protein is accompanying the proliferative activity of the malignant cells, allowing it to be used as a marker and as a good indicator for tumor aggressiveness [7].

A study conducted by Themthingla Zimik et al observed in their study that maximum number of cases of AUB were seen in the age group of 41-50 years. In premenopausal women the most common histopathologic pattern was proliferative endometrium and all the 3 cases of endometrial carcinoma in the study showed high Ki67 index which correlated with our study [6]. A study conducted by Nayar M. et al in 2017 showed that Ki67 index increased as the severity of lesion increased from EH to endometrial carcinoma which was similar to our study. They concluded that the Ki67 IHC markers may be included in every case of endometrial carcinoma to understand the tumour biological behaviour which in turn could help individual treatment strategies.[4] Study by Farhood GR et al noted that with endometrial carcinoma, there was an increased expression of Ki67, compared to proliferative endometrium and simple hyperplasia which correlated with our study[9].

Conclusion

Histopathological evaluation of endometrial samples is an important diagnostic tool in AUB. Our study revealed that proliferative endometrium was the most common pattern for AUB. Incorporation of Ki-67 immunostain in histopathological examination of endometrium in patient’s with AUB will help in understanding its biological behaviour which can help in early diagnosis, targeted treatment strategies and prognostication.

References


