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Original Research Article

Pitfalls in Diagnosis of Endometrial Adenocarcinoma in Biopsy Specimens

Dr. Anil Mohan Rao, S[1*]

[1]Assistant Professor of Pathology Faculty of Medicine, Northern Border University, 9280, Arar 73213, Saudi Arabia

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***Corresponding author:** Dr. Anil Mohan Rao, S
Assistant Professor of Pathology Faculty of Medicine, Northern Border University, 9280, Arar 73213, Saudi Arabia

Abstract

Endometrial Adenocarcinoma is one of the common malignancies of the female genital tract. It is associated with specific risk factors, which can be acquired and genetic. There are various precursor lesions of this condition, which warrants detection by proper screening methods to aid in earlier diagnosis and thereby treat these conditions to prevent their progression to well established adenocarcinoma. There are Several Histo-pathological mimickers which simulate Adenocarcinoma, that need to be differentiated by proper clinicopathological evaluation, so the correct diagnosis is made, which helps in overall management of patient. This study is an attempt to describe various precursor lesions of Endometrial Adenocarcinoma and also the differentiation of Pathological conditions that are the look alike of Endometrial Adenocarcinoma. In addition various clinicopathological methods will be described which help to arrive at proper diagnosis. Risk categories for Endometrial carcinoma will be identified which helps in early diagnosis of Disease.

Keywords: Endometrial Precursors, Diagnosis, Endometrial Biopsy, Differentiate, Dilation and Curettage.

INTRODUCTION

Endometrial Adenocarcinoma is classified into two types, type 1 and type 2, which differ in their causes, mechanisms, morphology and prognosis [1]. Type 1 is commonly seen in peri menopausal women and associated with specific risk factors which include genetic causes such as Mutations in PTEN gene and Lynch Sydrome, whereas acquired factors are Hypertension, Diabetes Mellitus, Obesity, treatment with Anti estrogen drugs like Tamoxifen, progressive Estrogen stimulation [2]. Type 2 is seen in older people with atrophic endometrium and with serous morphology along with relatively poorer prognosis [3]. The Mechanisms in Type 1 Cancer, are Estrogen induced unopposed Endometrial proliferation, leading to mutations in cancer associated suppressor genes and proto-oncogenes [4]. In addition Hyperinsulinemia in Type 1 Endometrial Cancer can lead to increased Endometrial proliferation, decrease Apoptosis, stimulation of factors of Angiogenesis, which can contribute to Endometrial Cancer over the years [5]. Role of parity is emphasized by the fact that pregnant women had decreased incidence of endometrial cancer, due to protective effect of progesterone [6]. With regards to Type 2 cancer it develops in background of Endometrial Atrophy, with possible role of Tamoxifen, which has proliferative effect on Endometrium, leading to Endometrial Cancer, in addition to role of mutations in P53, ErbB2 and p16 proteins [7]. The Precursor lesions of Endometrial cancer, are Various types of Hyperplasia [simple/Complex with or without Atypia] and Endometrial Intraepithelial Neoplasia [EIN] Schema [8]. Studies have proved the value of EIN, with regards to treatment decisions and prognosis as evidenced by prevalence [46%] of Adenocarcinoma diagnosis in Hysterectomy Specimens with preoperative diagnosis of Atypical Hyperplasia on Endometrial biopsies/curettages [9]. Conditions that simulate Endometrial Carcinoma can be varied such as Adenomyosis, Secretory phase, Polyps, Repair and Glands of Basalis layer [10]. Other benign Pathological changes which can be mistaken for Malignancy are Mucinous Metaplasia, Complex Papillary Hyperplasia with Atypia due to use of Hormonal drugs and Polyps and, lastly Aria Stella Reaction [11]. TCGA System [tumor genome atlas] incorporates molecular profiling of involved genes in Endometrial Cancer, and has proven value in terms of prognosis and patient outcome, compared to routine histological grading [12]. Staging by FIGO/TNM methods using imaging by MRI has superior prognostic value, along with assessment of recurrence. The significance of Hysteroscopy guided endometrial biopsy has been established in selection of pathologic areas for biopsy in patients with Atypical

Endometrial Hyperplasia, to predict its transformation to Endometrial Carcinoma [13]. The initial diagnostic tool employed in suspected cases is Sonography by Transvaginal method [14]. The information about endometrial thickness is obtained and biopsy is performed if its thickness is more than 4mm [15].

MATERIALS AND METHODS

This is A Cross Sectional Histopathology Study where in 50 Histopathology Slides of Endometrial biopsy are collected. These slides are analysed and diagnosed Microscopically, there by categorizing them into various Precursor and other lesions which can simulate Endometrial Carcinoma. These Endometrial lesions are differentiated from Endometrial Carcinoma by various described Clinico-Pathological Methods.

Inclusion Criteria

1. Endometrial Lesions which are Precursors of Endometrial Carcinoma are included in the study
2. Endometrial Lesions which simulate Endometrial Carcinoma on Histopathology examination are included in the study

Exclusion Criteria

- Endometrial Lesions which are not Precursors of Endometrial Carcinoma are excluded from study
- Endometrial Lesions which don't simulate Endometrial Carcinoma on Histopathology examination are excluded from the study

RESULTS

In the present study Endometrial Lesions that are diagnosed are Simple Hyperplasia, Papillary Atypical Hyperplasia, Adenomyosis, Endometrial Polyp, Aria Stella Reaction, Secretory Endometrium, Mucinous Metaplasia and Glands of Basalis of Endometrium, Endometrial Adenocarcinoma

Results are included separately in Table and Figures.

Table 1

A. Precursor Lesions
1. Simple Endometrial Hyperplasia
2. Papillary Atypical Endometrial Hyperplasia
B. Endometrial Lesions which simulated Endometrial Carcinoma
1. Endometrial Polyp
2. Secretory Endometrium
3. Basalis Glands of Endometrium
4. Aria Stella Reaction
5. Adenomyosis
6. Mucinous Metaplasia of Endometrium

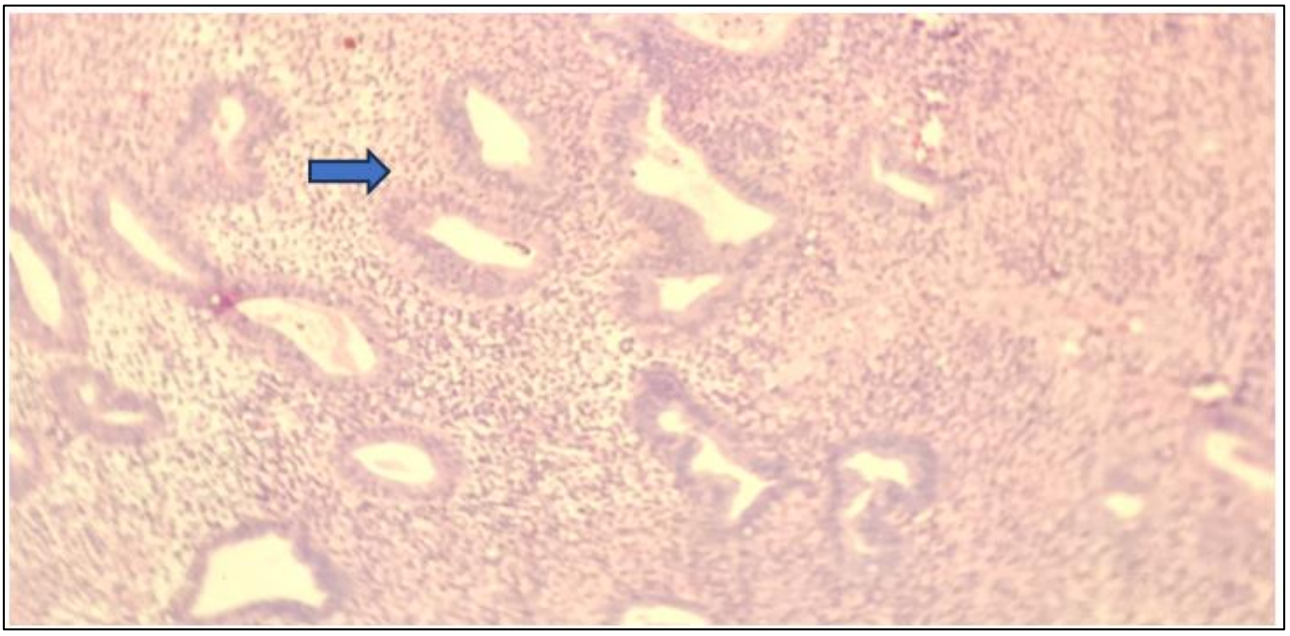

Figure 1: Simple Endometrial Hyperplasia, arrow shows Proliferating irregular Glands with normal stromal density and without atypia

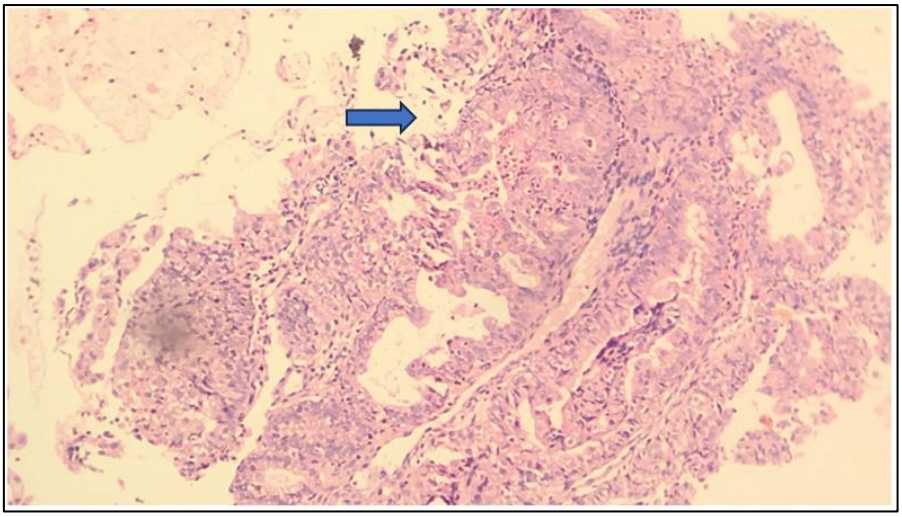

Figure 2: Papillary Atypical Endometrial Hyperplasia arrow shows Endometrial Glands with Papillary Projections, back to back pattern with Atypia and decreased stromal density

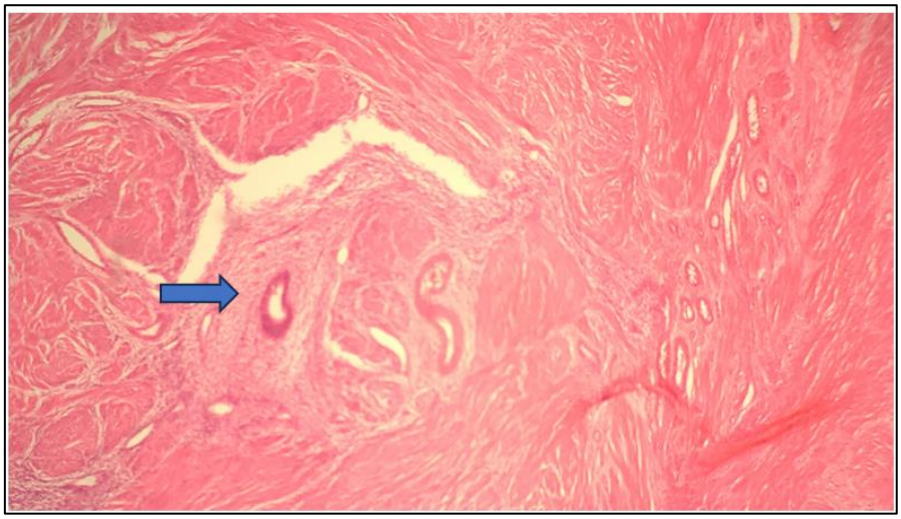

Figure 3: Adenomyosis, arrow shows Endometrial Glands and stroma deep inside myometrial layer

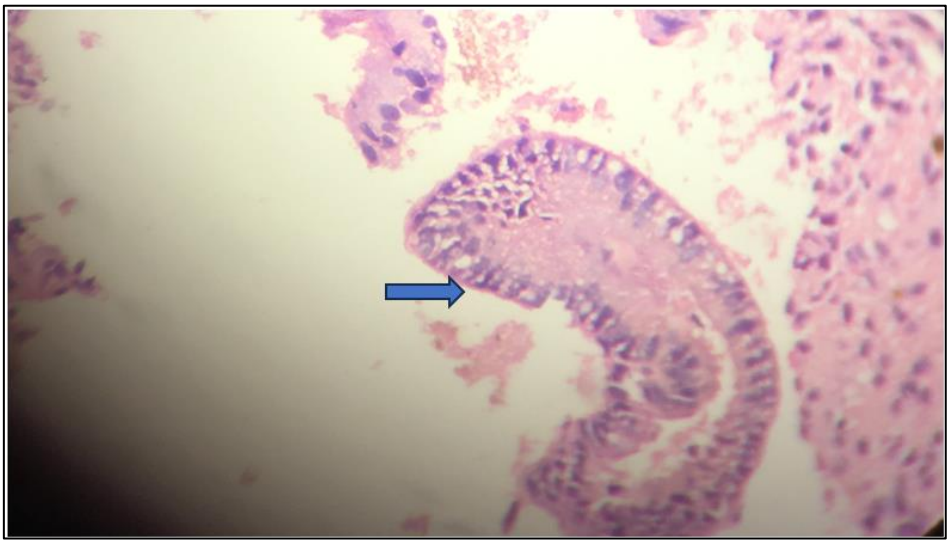

Figure 4: Secretory Endometrium shows Irregular Tortuos Glands with Clear Vacuoles in Lining Epithelium, Stromal edema

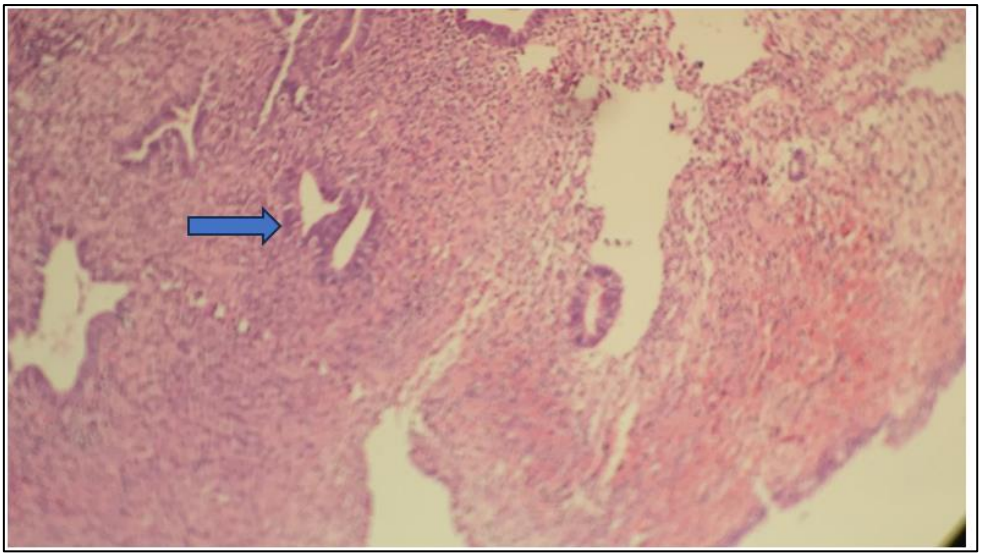

Figure 5: Endometrial Polyp with Polypoidal configuration, arrow shows dilated glands with focal crowding stratification and thick vessels in stroma

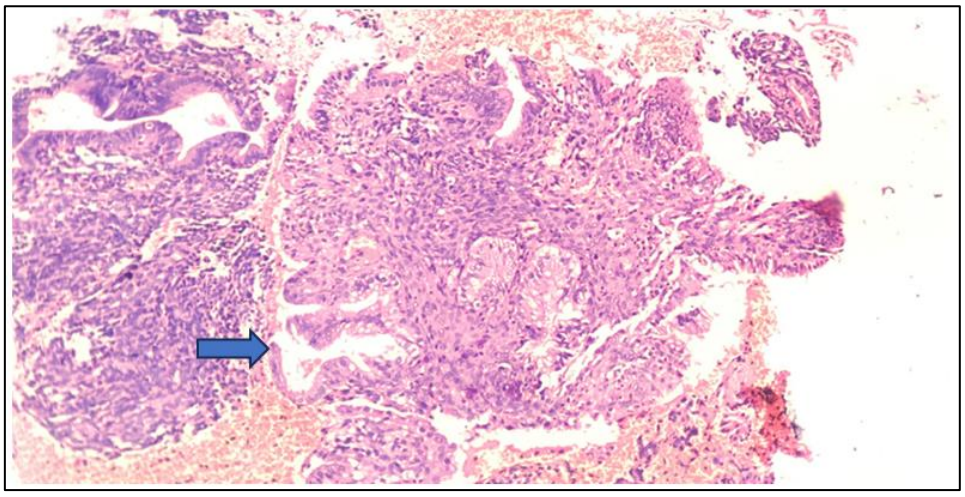

Figure 6: Aria Stella Reaction arrow shows Papillary architecture and lining epithelium shows vacuolated clear cytoplasm along with nuclear enlargement

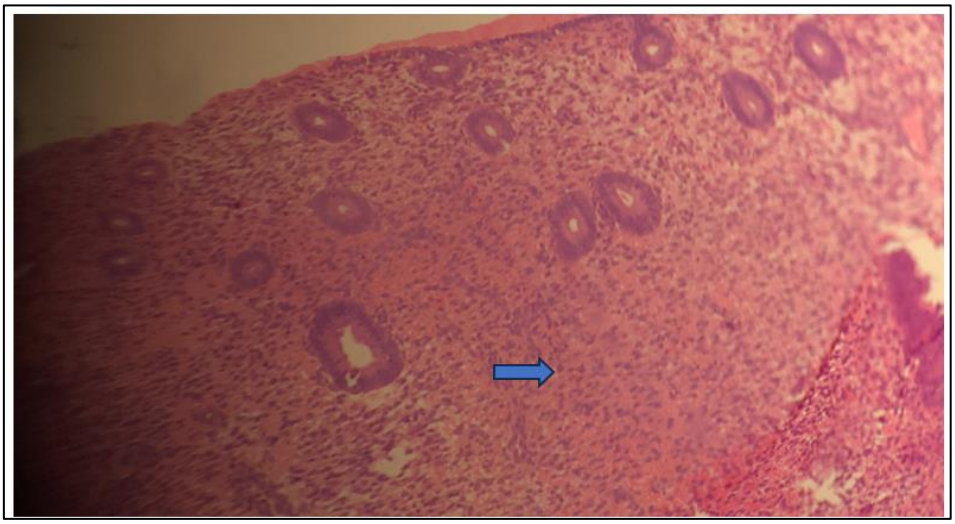

Figure 7: Basalis of Endometrium arrow shows near Myometrium with benign epithelium and fibrous stroma

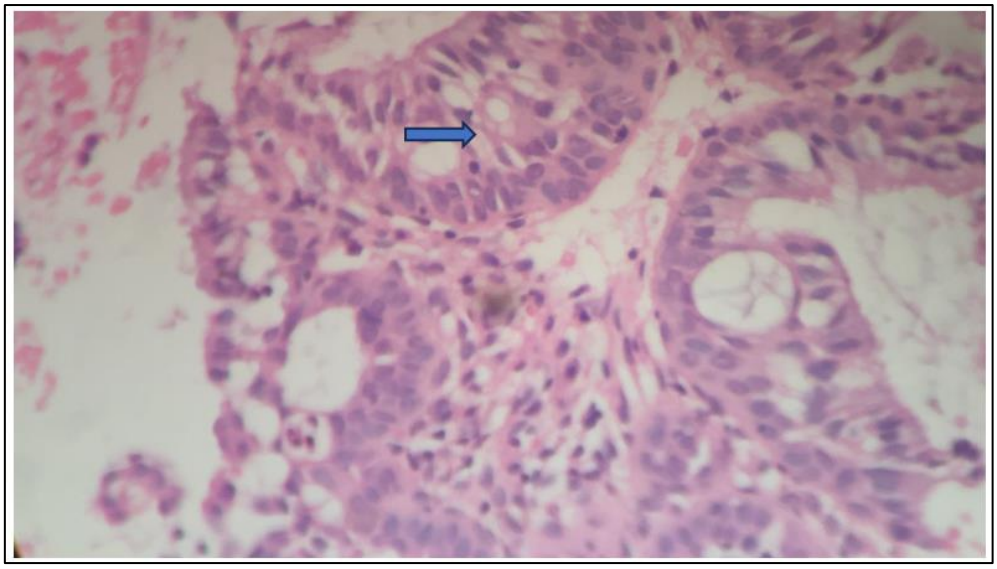

Figure 8: Mucinous Metaplasia of Endometrium arrow shows glands with supra nuclear vacuoles in tall Columnar Epithelium

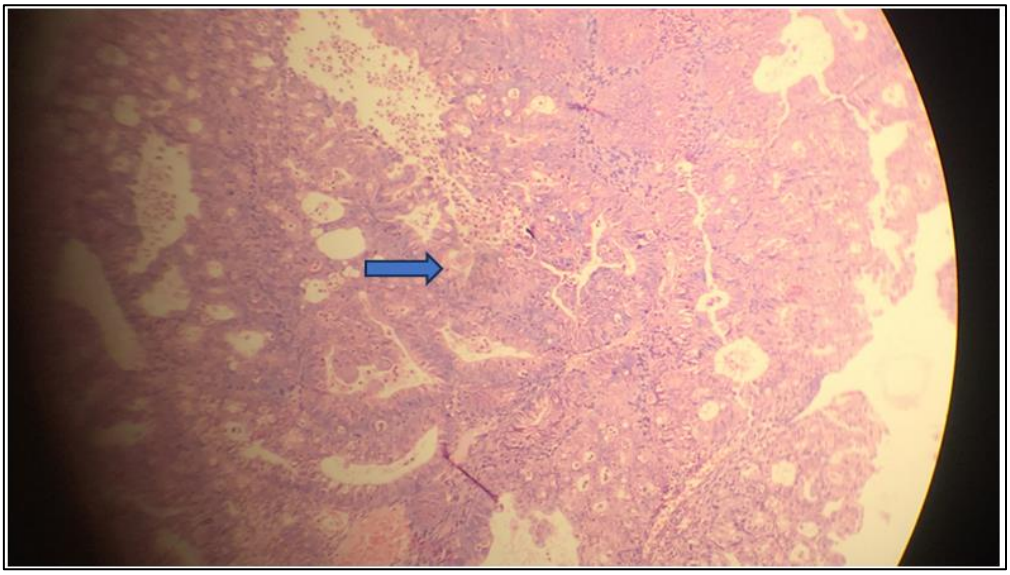

Figure 9: Endometrial Adenocarcinoma arrow shows back-to-back glands lined by atypical epithelium

DISCUSSION

Proper background Clinical history coupled with the technique of Endometrial Sampling, together with meticulous histopathological examination helps in diagnosis of various precursor lesions of Endometrial Carcinoma along with differentiation of Endometrial Carcinoma from mimickers of Endometrial Carcinoma. Costas *et al*., has suggested the identification of women who are using Tamoxifen, have high BMI, Post Menopausal Bleeding, and Lynch Syndrome and subject them for Endometrial Sampling to detect earlier precursor stages of Endometrial Carcinoma [16]. Recently Gynecologists preferred to use curette, suction, and brush over conventional Dilation and Curettage, which has an accuracy of 85-98%. Hysteroscopic Guided Biopsy or Dilation and Curettage is done if sample is scanty, indecisive histopathology report or show hyperplastic changes [17]. Simple Hyperplasia can exhibit areas of epithelial stratification, mitoses which may be mistaken for malignancy in low power, however high-power examination does not show Nuclear Atypia typical of Malignancy [18]. Regards to differentiation of Atypical Hyperplasia from Adenocarcinoma, the former shows little stroma in between the confluent glands and these atypical glands doesn't show evidence of stromal invasion, whereas Adenocarcinoma lacks stroma in between the back-to-back glands and show evidence of stromal invasion, desmoplasia [19]. Adenomyosis shows round glands in myometrium and lack atypia, whereas invading focus of adenocarcinoma shows angular outlines of atypical glands in the myometrium [20]. The unusual variant of Secretory adenocarcinoma should be differentiated from secretory endometrium, Mucinous Metaplasia and Aria Stella reaction, by the presence of

2-3 mitoses/hpf along with PAS positive vacuoles and Atypia in the former, while the latter lack these features [21]. Endometrial Polyp can be sometimes mistaken for EIN [Endometrial intra epithelial neoplasia], but features such as altered stroma and thick blood vessels with focal crowding, Epithelial stratification of former and absence of these in latter helps to overcome the diagnostic difficulty and arrive at proper diagnosis [22]. Basalis layer of Endometrium can lead to suspicion of Edometrial carcinoma due to the fact that these glands are in close proximity to myometrium, creating pseudoinvasion pattern, but these glands has fibrous stroma and benign epithelium which will differentiate from Endometrial carcinoma [22]. Atypical Endometrial Hyperplasia is now termed as EIN [Endometrial Intraepithelial Neoplasia] and studies has shown that preoperative diagnosis of Atypical Endometrial Hyperplasia has proved to be Endometrial Adenocarcinoma in 11% of cases post operatively [23]. The risk of Endometrial Adenocarcinoma after a diagnosis of EIN/Atypical Endometrial Hyperplasia is 45% after more than one year and yearly follow up with Hysteroscopy and Ultrasound is recommended to screen for Endometrial Adenocarcinoma [24]. A batch consisting of only Pax2, Pten, and β-catenin recognized 92.8% of cases of EIN/Endometrial Hyperplasia, suggesting them to be used as Screening biomarkers [25].

CONCLUSION

Proper clinical and pathological correlation along with identification of the risk groups is significant in the diagnosis of Precursor Endometrial Lesions. Careful Pathological examination with clinical correlation is needed to identify conditions which simulate Endometrial Adenocarcinoma and differentiate them .Biomarkers are suggested for screening in those who are at high risk.

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