International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

Endometrial Intraepithelial Neoplasia and Its Correlation with WHO Classified Endometrial Hyperplasia

Supriya Sandeepa, Jayaprakash H T, Ashwini M C

Department of Pathology, Dr B R Ambedkar Medical College, Bangalore, Karnataka, India.

Corresponding Author: Supriya Sandeepa

Received: 14/09//2014 *Revised: 15/10/2014* *Accepted: 24/10/2014*

ABSTRACT

Introduction: Endometrial hyperplasias are precursors of endometrial carcinoma. WHO hyperplasia classification system has confusing and overlapping criteria which prompted the development of a system based on Endometrial Intraepithelial Neoplasia (EIN).

Objectives

1. To review Endometrial Intraepithelial Neoplasia.
2. To reclassify WHO classification of endometrial hyperplasia into EIN and non-EIN category.

Materials And Methods: In 102 patients diagnosed as WHO hyperplasia reclassification was done using EIN criteria 1) Glandular crowding.2) Cytologic demarcation. 3) Size of the lesion should exceed 1mm. 4) exclude benign processes 5) exclude carcinoma.

Results: Out of 102 cases, 53(51.96%) cases were diagnosed as simple typical hyperplasia, 12(11.76%) cases as complex typical hyperplasia, 21(20.58%) cases as simple atypical hyperplasia and 16(15.68%) cases as complex atypical hyperplasia. 26% were re-classified as EIN and 64% as non-EIN lesions. 23(62.16%) out of 37 cases of atypical hyperplasia were reclassified as EIN. None of the simple hyperplasias turned out to be EIN and 4(33.33%) of 12 cases of complex hyperplasia were reclassified as EIN.

Conclusion: EIN criteria can be easily applied to routine haematoxylin and eosin sections and has good reproducibility. EIN diagnosis prevents the progression to endometrial adenocarcinoma and helps in clinical management which is less intensive than for adenocarcinoma.

Keywords: Abnormal uterine bleeding, hyperplasia, endometrial intraepithelial neoplasia.

INTRODUCTION

Abnormal uterine bleeding is a common problem having a long list of causes in different age groups which interferes significantly with the quality of life. [1,2] AUB can present in many patterns and can be assessed by light microscopy which remains the diagnostic standard for the clinical diagnosis of endometrial pathology. Out of the list of organic lesions the most common is endometrial hyperplasia accounting for 30% cases. AUB may be the symptom of endometrial carcinoma in 8 – 50% of cases. [1,3,4]

The criteria for diagnosis of precancerous lesions of the endometrium are not standardized because of many shortcomings in the WHO endometrial

hyperplasia classification system. [5-7] The Endometrial Collaborative Group classified the endometrial lesions into endometrial hyperplasia and endometrial neoplasia. Endometrial neoplasia was divided into intra-epithelial and invasive neoplasia. Endometrial hyperplasia without atypia rarely progresses to neoplasia but atypical hyperplasias which are presently reclassified as Endometrial Intraepithelial Neoplasia (EIN) is a monoclonal endometrial prEINvasive glandular proliferation and carries a significant risk of progression into invasive carcinoma. [8-10]

According to Endometrial Collaborative Group, the advantages to diagnose premalignant endometrial disease as EIN are 1) Pre-cancers should be placed in a single diagnostic category 2) Pre-cancers are monoclonal and thus neoplastic and parallelism with other pre-cancerous nomenclature systems elsewhere in the female genital tract is required 3) Endometria which do not meet diagnostic criteria for EIN can be diagnosed as "Endometrial Hyperplasia" to distinguish them from EIN lesions. The prognostic superiority of EIN system than other commonly used systems is proved by long term prospective multicenter studies. [11] Based on these considerations, the present study was designed to review Endometrial Intraepithelial Neoplasia (EIN) and to correlate it with WHO classification of endometrial hyperplasia.

MATERIALS AND METHODS

The hematoxylin and eosin stained slides of one hundred and two patients between 2006 to 2012 were studied. The patients who presented with abnormal vaginal bleeding and were diagnosed as endometrial hyperplasia under the WHO system of reporting hyperplasia were included in this study. The patients were not on hormonal therapy. The formalin fixed samples were routinely processed and 4-5µ thick sections were cut from paraffin blocks. The sections were stained by routine haematoxylin and eosin stains and additional special stains if required. Reclassification was done using EIN criteria [12] such as 1) Glandular crowding (volume percentage stroma< 55%): EIN lesions have a stromal volume less than that of the glands 2) Cytologic demarcation: EIN lesions have an abnormal cytology within the crowded glands comprising an EIN focus. 3) Size of the lesion should exceed 1mm. 4) exclude confounding benign processes like secretory endometrium, polyps, repair etc. 5) exclude carcinoma. The percentages of each WHO hyperplasia category that was re-classified as EIN were then determined and classified as EIN lesion or Non-EIN lesion.

RESULTS

In the present study, one hundred and two cases of endometrial hyperplastic lesions were examined. The age of the patient ranged from 18-83 years. Majority of patients with WHO classified endometrial hyperplasias were from 4^{th} and 5^{th} decade of life whereas Endometrial Intraepithelial Neoplasia lesions were more prevalent in $5^{th}$and 6^{th}decade of life. Out of one hundred and two cases, 53(51.96%) cases were diagnosed as simple typical hyperplasia, 12(11.76%) cases as complex typical hyperplasia, 21(20.58%) cases as simple atypical hyperplasia and 16(15.68%) cases as complex atypical hyperplasia.(Table 1)

Table 1.Showing distribution of cases in WHO hyperplasia classification.

WHO hyperplasia	no of cases
Simple hyperplasia	53(51.96%)
Simple hyperplasia with atypia	21(20.58%)
Complex hyperplasia	12(11.76%)
Complex hyperplasia with atypia	16(15.68%)

Reclassification of WHO classified hyperplastic lesions using EIN criteria led to the diagnosis of EIN cases out of which

most of them were classified earlier as simple and complex atypical hyperplasia. 23(62.16%) out of 37 cases of atypical hyperplasia were reclassified as EIN. None of the simple hyperplasias turned out to be EIN and 4(33.33%) of 12 cases of complex hyperplasia were reclassified as EIN. (Table 2)

Table 2. WHO Endometrial hyperplasia re-classification using EIN criteria

WHO hyperplasia	EIN criteria	Total
Simple hyperplasia	0 (0%)	53(51.96%)
Simple hyperplasia with atypia	11(52.38%)	21(20.58%)
Complex hyperplasia	4(33.33%)	12(11.76%)
Complex hyperplasia with atypia	12(75%)	16(15.68%)
TOTAL	27(26.47)	102(100%)

Table 3. Various studies comparing WHO classified hyperplasia with EIN

Authors	Simple hyperplasia	EIN	Complex hyperplasia	EIN	atypical hyperplasia	EIN
Khanna R et al	83	3(3.5%)	38	18(47%)	79	57(72%)
Baak et al	65	9(13%)	6	2(34%)	61	35(58%)
Hech et al	56	2(3.5%)	18	8(45%)	23	18(78%)
Baak et al	289	37(12.8%)	67	29(43%)	123	58(47%)
Present study	53	0(0%)	12	4(33.33%)	37	23(62.16%)

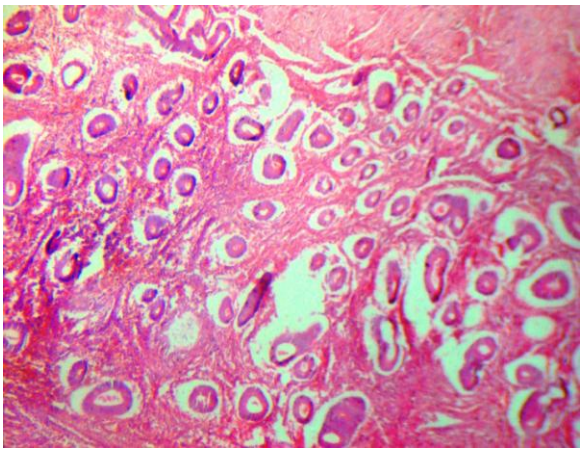

Figure 1. Microphotograph showing simple hyperplasia (Hand E X10)

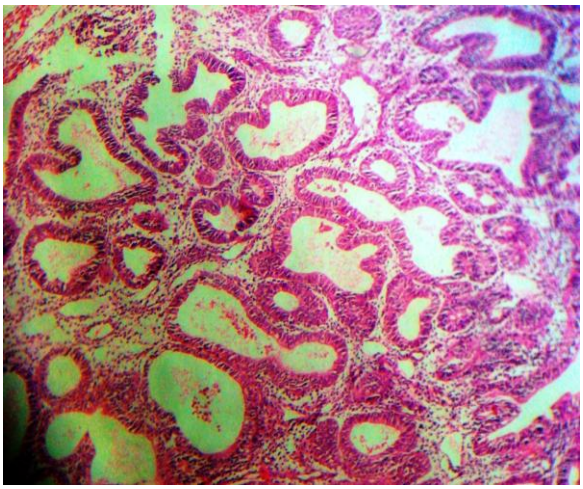

Figure 2. Microphotograph showing complex hyperplasia (Hand E X10)

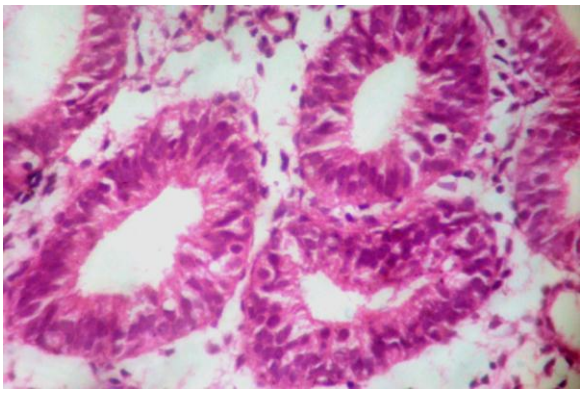

Figure 3. Microphotograph showing simple hyperplasia with atypia (Hand E X40)

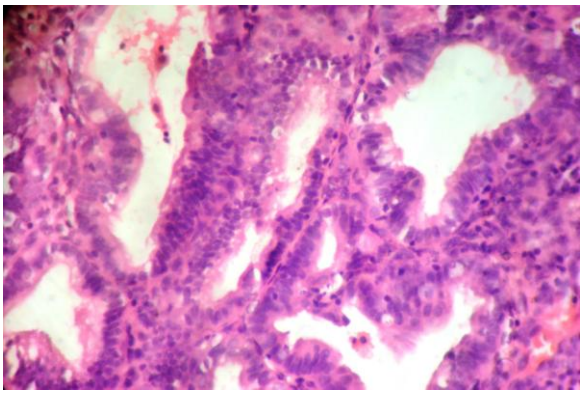

Figure 4. Microphotograph showing complex hyperplasia with atypia (Hand E X40)

DISCUSSION

EIN usually presents with postmenopausal bleeding or vaginal bleeding or irregular menses in perimenopausal women. Gross specimen

hardlyshow any pathological findings in EIN unless there is thin atropic background in postmenopausal patients where it can be visible as local thickenings. EIN is focal in origin hence low power screening to identify the focus and then high power observation of that focus for cytologic features is pre-requisite in diagnosis of EIN. Apart from fulfilling the diagnostic criteria EIN must be differentiated from benign mimics and carcinoma.

Normal tissues with extrinsic compression may show artifactually crowded glands but will not show cytologic features of EIN. Fibrous stromal content and quiescent epithelium will be seen in irregularly placed glands of lower uterine segment. Menstrual endometrium shows irregular glands but crumbled stroma will be present. Thus for the diagnosis of EIN intact stroma must be present.

There are few benign processes which mimic EIN. Endometrial polyps exhibit altered stroma, thick vessels apart from random irregular glands. Benign endometrial hyperplasia shows generalized endometrial involvement unlike EIN which is localized. Collections of bland endometrial cysts on atropic endometrium or senile polyps also can be confused with EIN. Certain features are helpful in excluding adenocarcinoma. Specific patterns like solid, cribriform, mozaic and maze like growth will be seen in adenocarcinoma and absent in EIN. Myometrial invasion with stromal desmoplastic response is also indicator of adenocarcinoma. [13]

To estimate the risk of progression to carcinoma and guide clinical management the histopathologic diagnosis of endometrial biopsies is very important. [14] The overall reproducibility of WHO atypical hyperplasia diagnosis is poor, because of nonspecific reporting patterns and intra/inter-observer variation. Uncertainty in predicting the natural history of individual lesions, inconsistency of diagnosis, and unclear therapeutic implications for each diagnostic group complicates standardized clinical management of women with premalignant endometrial disease. Furthermore, the four classes of WHO hyperplasia do not define biologically distinctive subgroups. [6,15] Endometrial intraepithelial neoplasia (EIN) is a localized lesion with objective histologic criteria and is a monoclonal premalignant endometrial glandular lesion. It has 45-fold elevated risk of the development of endometrioid-type endometrial adenocarcinoma. EIN arises through complex interactions involving the sequential accumulation of genetic damage in endometrial glands and the positive selective pressure of unopposed estrogen. To preserve the high predictability of EIN for concurrent/subsequent adenocarcinoma, strict adherence to defined diagnostic criteria is essential. [16,17]

In this study, majority of cases of endometrial hyperplasias and EIN lesions were seen in 5th decade of life. Similar results were obtained in study done by Khanna R et al [18] Mutter et al [19] and Kurman et al. [20] The number of cases of simple typical hyperplasias in the present study was found to be similar with the study done by Khanna R et al [18] Kurman et al, [20] Baak et al, [11] Baak et al [21] and Hecht et al. [22] Twenty seven cases (26.47%) of EIN lesions were re-diagnosed from one hundred and two cases of WHO classified endometrial hyperplasia which was relatively similar to study done by Khanna et al [17] and Hecht et al. [22] Lacey JV et al concluded that EIN and AH were both found to have similarly increased risks of progression to carcinoma among women observed for at least 1 year after receiving a biopsy-based EH diagnosis. [14] In a study done by Yang YF et al the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for

atypical EH vs. non-atypical EH in biopsy specimen was 95.2%, 45.4%, 43.0% and 95.7%, respectively. For EIN vs. benign, the sensitivity was 100% and the specificity was 37.1%. [23] Table 3 shows comparison of WHO classified simple typical hyperplasia, complex typical hyperplasia and atypical hyperplasias with EIN as studied by different authors.

CONCLUSION

Endometrial Intraepithelial Neoplasia (EIN) lesions which are premalignant are commonly seen in 5th and 6th decade of life. EIN criteria can be easily applied to routine haematoxylin and eosin stained histopathological sections. EIN criteria have good reproducibility. EIN diagnosis if made at an earlier date will prevent the progression to endometrial adenocarcinoma. Diagnosis of EIN is essential as clinical management of EIN is less intensive and totally different from endometrial adenocarcinoma.

REFERENCES

1. Mirza T, Akram S, Mirza A, Aziz S,Mirza T, Mustansa T. 2012. Histopathological Pattern of Abnormal Uterine Bleeding in Endometrial Biopsies. Journal of Basic & Applied Sciences.8:114-117.
2. Edward RG.2007.Endometrial bleeding. Hum Reprod Update. 13(5): 421-31.
3. Baral R, Pudasaini S.2011. Histopathological pattern of endometrial samples in abnormal uterine bleeding. Journal of Pathology of Nepal.1: 13-16.
4. Dangal G. 2003.A study of endometrium of patients with abnormal uterine bleeding at Chitwan valley. KUMJ .1:110-2.
5. Kurman R, Norris H: Endometrial hyperplasia and metaplasia in Blaust EIN's Pathology of the Female Genital Tract. Springer-Verlag; 322-337,1987.
6. Mutter GL. 2000. Endometrial intra-epithelial neoplasia (EIN). Will it bring order to chaos? The Endometrial Collaborative Group.GynecolOncol.76 (3):287-90
7. Scully RE, Bonfiglio TA, Kurman RJ, Silverberg SG, Wilkinson EJ: Uterine corpus Histological typing of Female Genital Tract Tumors.New York,Springer-Verlag;13-31,1994
8. Kenneth M, Feeley Michael Wells: Advances in Endometrial Pathology. Recent advances in Histopathology – No.19; P 20-21.
9. Mutter GL: EIN Central [On Line]; http:/www.endometrium.org, 2001.
10. Usubutun A, Mutter GL, Saglam A, Dolgun A, Ozkan EA, Ince T.2012. Reproducibility of endometrial intraepithelial neoplasia diagnosis is good, but influenced by the diagnostic style of pathologists.Mod Pathol. 25 (6): 877-84
11. Baak JP, Orbo A, van Diest PJ, Jiwa M, de Bruin P, Broeckaert M, Snijders W, Boodt PJ, Fons G, Burger C, Verheijen RH, Houben PW, The HS, Kenemans P.2001.Prospective multicenter evaluation of the morphometric D-score for prediction of the outcome of endometrial hyperplasias. Am J Surg Pathol. 25(7):930-5.
12. Mutter GL.2002. Diagnosis of premalignant endometrial disease. J Clin Pathol. 55(5):326-31.
13. Quade BJ, Robboy SJ. Uterine smooth muscle tumours. In : Robboy SJ, Mutter GL, Prat J, Bentley RC, Russell P, Anderson MC, editors. Robboy's pathology of female reproductive tract.(2nd edition). China: Churchill Livingstone Elsevier, 2011: 457- 484.
14. Lacey JV Jr, Mutter GL, Nucci MR, Ronnett BM, Ioffe OB, Rush BB.2008. Risk of subsequent endometrial carcinoma associated with endometrial intraepithelial neoplasia classification of endometrial biopsies. Cancer. 113(8): 2073-81.
15. Sobczuk A, Wrona M, Pertyński T.2007. [New views on hyperplastic endometrial lesions classification—

endometrial intraepithelial neoplasia (EIN)].Ginekol Pol.78(12):986-9.
16. Elke A. Jarboe, George L. Mutter.2010.Endometrial intraepithelial neoplasia.Seminars in Diagnostic pathology.27(4):215–25.
17. Kane SE, Hecht JL.2012. Endometrial intraepithelial neoplasia terminology in practice: 4-year experience at a single institution.Int J GynecolPathol. 31(2): 160-65.
18. R. Khanna, G. Rupala, V. Khanna: Endometrial Intraepithelial Neoplasia And Its Correlation With WHO Classified Endometrial Hyperplasia. The Internet Journal of Pathology. 2011 Volume 12 Number 1
19. Mutter GL, Ince TA, Baak JP, Kust GA, Zhou XP, Eng C.2001 Molecular identification of latent precancers in histologically normal endometrium. Cancer Res .61(11):4311-4.
20. Kurman RJ, Kaminski PF, Norris HJ.1985.The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. Cancer. 56(2):403-12.
21. Baak JP, Mutter GL, Robboy S, van Diest PJ, Uyterlinde AM, Orbo A, Palazzo J, Fiane B, Løvslett K, Burger C, Voorhorst F, Verheijen RH.2005. The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. Cancer. 103(11):2304-12.
22. Hecht JL, Ince TA, Baak JP, Baker HE, Ogden MW, Mutter GL.2005. Prediction of endometrial carcinoma by subjective endometrial intraepithelial neoplasia diagnosis. Mod Pathol. 18(3):324-3
23. Yang YF, Liao YY, Peng NF, Li LQ, Xie SR, Wang RB.2012.Prediction of coexistent carcinomas risks by subjective EIN diagnosis and comparison with WHO classification in endometrial hyperplasias. Pathol Res Pract.208(12):708-12.

How to cite this article: Sandeepa S, Jayaprakash HT, Ashwini MC. Endometrial intraepithelial neoplasia and its correlation with WHO classified endometrial hyperplasia. Int J Health Sci Res. 2014;4(11):55-60.

****