Original Research Article

Interobserver variability in endometrial intraepithelial neoplasia

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Abstract

Introduction: Endometrial hyperplasia is a common disease and precursor of endometrial carcinoma. WHO hyperplasia classification system which is unreliable 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 and to study the interobserver variability. **Materials and Methods:** In 102 patients diagnosed as WHO hyperplasia reclassification was done by 2 separate pathologists using EIN criteria 1) Glandular crowding. 2) Cytologic demarcation. 3) Size of the lesion should exceed 1mm. 4) Exclude benign processes 5) Exclude carcinoma. Inter observer variability was studied. **Results:** Out of 102 cases, 53 (51.96%) cases were earlier 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 by first pathologist. Second pathologist reclassified 28% as EIN and 62% as non-EIN lesions. Interobserver variability existed in only 2 cases of complex hyperplasia with atypia reclassified by second pathologist. **Conclusion:** EIN criteria has less interobserver variability than WHO classified hyperplasia system and can be easily applied to routine haematoxylin and eosin sections. EIN diagnosis prevents the progression to endometrial adenocarcinoma and helps in clinical management which is less intensive than for adenocarcinoma.

Keywords: Endometrial intraepithelial neoplasia, Hyperplasia, Interobserver variability.

Introduction

The most common malignancy of female genital tract is endometrial carcinoma. This cancer is preceded by histologically evident lesion [1]. Abnormal Uterine bleeding may be the symptom of endometrial carcinoma in 8-50% of cases [2, 3, 4]. WHO classified hyperplasia when wrongly diagnosed leads to inappropriate treatment. Hyperplasia progress to cancer with overall risk of 5-10% [5]. Histopathological plasticity of normal and pathological endometrial tissues alike presents formidable barriers for classification of biologically homogenous groups into reproducible morphological diagnostic categories. Different strategies were applied by pathologist to arrive at a workable diagnostic system resulting in many classification systems. There are many shortcomings of each system and are confused by overlapping terminology [1].

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There are many shortcomings in the WHO endometrial hyperplasia classification system [6, 7, 8]. In WHO classification most of the EIN are classified as atypical endometrial hyperplasia [1]. The Endometrial Collaborative Group classified the endometrial lesions into endometrial hyperplasia and endometrial neoplasia which was further divided into intra-epithelial and invasive neoplasia [9, 10, 11].

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 term EIN has been documented to increase the risk of cancer [1, 5, 12]. The knowledge about the features of the EIN system is important for understanding

the features of various physiologic versus neoplastic processes of the endometrium, and it is a powerful method for classifying endometrial lesions. The EIN classification system is gaining widespread acceptance in diagnostic surgical pathology, clinical gynecology, and basic science fields. The key to its success lies in the integration of histologic findings to the underlying genetic changes in a manner that is useful for clinical management. Simply put, EIN is the histologic manifestation of an underlying molecular progression in endometrial carcinogenesis and is a lesion that can be diagnosed for purposes of therapeutic decisions [13].

Pathologist can diagnose EIN haematoxyl in and eosin stained slides of representative endometrial sample. Studies on clinical outcome of women with EIN have proven the increased cancer risk [1]. The EIN system enables pathologists to recognize and separate truly neoplastic lesions with a high rate of progression from those that are due to hormonal imbalances [13]. EIN system is proved prognostically superior by long term prospective multicenter studies with less interobserver variability [1, 5, 12]. The interobserver variability of Endometrial Intraepithelial Neoplasia (EIN) system and its correlation with WHO classification of endometrial hyperplasia is studied here.

Materials and Methods

Type of study: The study is a retrospective study done at department of pathology, Dr. B. R. Ambedkar medical college, Bangalore after the ethical clearance. The hematoxylin and eosin stained slides of 102 patients diagnosed by WHO classified hyperplasia system between 2006 to 2012 were studied. The formalin fixed samples were routinely processed. The paraffin block sections were cut at 4-5µ. Then, the sections were stained by routine haematoxylin and eosin (H&E) stains. The patients were not on hormonal therapy.

Inclusion criteria: H & E slides of women >18 years diagnosed as endometrial hyperplasia WHO classification system.

Exclusion criteria: Women who were on hormonal therapy.

Objectives

1. To review Endometrial Intraepithelial Neoplasia.

2. To reclassify WHO classification of endometrial hyperplasia into EIN and non-EIN category and to study the interobserver variability.

Reclassification was done by two pathologists separately using EIN criteria [12] which includes 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. Inter observer variability of EIN system was studied by comparing the reclassified diagnosis.

Results

In the present study, 102 cases of endometrial hyperplasia were included. The patient age ranged from 18-83 years with Majority of patients with WHO classified endometrial hyperplasia from 4th and 5th decade of life. Endometrial Intraepithelial Neoplasia lesions were more prevalent in 5th and 6th decade of life. Out of one hundred and two cases, 53(51.96%) cases were earlier 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 (Figure 1) and 64% as non-EIN lesions by first pathologist. Second pathologist reclassified 28% as EIN and 62% as non-EIN lesions. Interobserver variability existed in only 2 cases of complex hyperplasia with atypia reclassified by second pathologist. None of the simple hyperplasia turned out to be EIN and 4(33.33%) (Table 1).

Table-1: Interobserver variability using EIN criteria.

WHO hyperplasia	First pathologist EIN	Second pathologist EIN	Total
Simple hyperplasia	0 (0%)	0 (0%)	53 (51.96%)
Simple hyperplasia with atypia	11 (52.38%)	11 (52.38%)	21 (20.58%)
Complex hyperplasia	4 (33.33%)	4 (33.33%)	12 (11.76%)
Complex hyperplasia with atypia	12 (75%)	14 (87%)	16 (15.68%)
TOTAL	27 (26.47%)	29 (28.43%)	102 (100%)

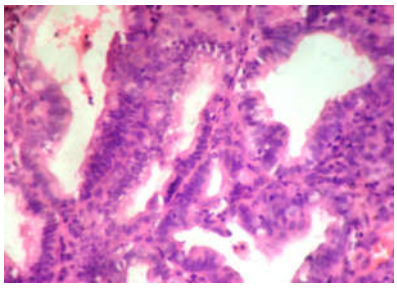

Figure-1: Microphotograph showing Endometrial Intraepithelial Neoplasia (H and E X40)

Discussion

The histopathologic diagnosis of endometrial biopsies is crucial to estimate the risk of progression to carcinoma [14]. The high rate of nonspecific reporting patterns and intra/inter-observer variation makes the overall reproducibility of WHO atypical hyperplasia diagnosis is poor. Furthermore, the four classes of WHO hyperplasia do not define biologically distinctive subgroups [7, 15]. EIN has 45-fold elevated risk of the development of endometrioid-type endometrial adenocarcinoma. It is a localized lesion with objective histologic criteria and is a monoclonal growth of mutated cells [12, 16, 17].

In this study, majority of cases of endometrial hyperplasia 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 hyperplasia 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 [5], Baak et al [21] and Hecht et al [12]. 26% were re-classified as EIN and 64% as non-EIN lesions by first pathologist. Second pathologist reclassified 28% as EIN and 62% as non-EIN lesions. Interobserver variability existed in only 2 cases of complex hyperplasia with atypia reclassified by second pathologist. None of the simple hyperplasia turned out to be EIN and 4(33.33%).

The interobserver variability results were relatively similar to study done by Khanna et al and Hecht et al. [12, 18]. The inter observer variability was better the study done by Zaino et al [22] and Kendall et al [23]. In comparison to the four categories (simple hyperplasia, complex hyperplasia, simple hyperplasia with atypia, and complex hyperplasia with atypia) that comprise the World Health Organization (WHO) 1994 classification system, proponents of the BH/EIN classification system have shown improved reproducibility in the diagnostic setting. In addition, the EIN system accurately stratifies patients who have a high risk of developing endometrioid (type I) endometrial carcinoma. Issues related to intraobserver variability with the WHO classification have been widely published, with j values for all endometrial diagnosis being 0.2 to 0.71 and 0.31 when comparing hyperplasia with, and without, atypia, respectively, which is considered a major therapeutic breakpoint. In comparison, the j value for subjective EIN diagnosis is between 0.73 and 0.90 at the point at which patients receive treatment. 1-2 In addition, the EIN classification system accurately segregates neoplastic lesions with oncogenic mutations, namely PTEN and PAX2, from those without such potential.

The EIN scheme is the result of our evolving understanding of endometrial carcinogenesis. It reflects the synthesis of molecular data with histologic changes that pathologists can readily and reproducibly identify on routine hematoxylin eosin staining. In addition to improved reproducibility, EIN classification enables a more rigorous assessment of the features of neoplasia, which takes into account architectural changes, changes in cytology, and a size cutoff set to achieve appropriate specificity and sensitivity [13].

Kane and Hecht describe the adoption of EIN by a general academic surgical pathology practice. Adoption occurred in 4 phases: (1) general education of both pathologists and clinicians by gynecologic pathologist; (2) creation of sets of pathologist training slides containing EIN that had and had not been previously classified as congenital adrenal hyperplasia, endometrial polyps, and anovulation; (3) pathologist review of the training slides and a teaching seminar; and (4) implementation into clinical practice [13].

The limitations of study are - Premalignant lesions of the endometrium can demonstrate non-endometrioid differentiation (squamous, mucinous, and tubal changes are common) and, similar to normal tissues, may transiently change their architecture and cytology in response to fluctuating oestrogens and progestins. The effects of progestins on endometrial glandular cytology are a particular diagnostic problem. In a progestin rich environment, nuclei of premalignant glands tend to

diminish in size and acquire a rather bland chromatin pattern, which makes them appear less "atypical". Paradoxically, the nuclei of normal glands become enlarged and rounded— features associated with atypia. Carefully the mimics of EIN should be excluded [1].

There are few benign processes which mimic EIN and exclusion of these is the most difficult part of EIN diagnosis [12]. The mimics of EIN are 1. Endometrial polyps with altered stroma, thick vessels apart from random irregular glands 2. Benign endometrial hyperplasia shows generalized endometrial involvement unlike EIN which is localized. 3. Collections of bland endometrial cysts on atropic endometrium 4. senile polyps also can be confused with EIN. Certain features are helpful in excluding adenocarcinoma. Specific patterns like solid, cribriform, mosaic and maze-like growth will be seen in adenocarcinoma and absent in EIN. Myometrial invasion with stromal desmoplastic response is also indicator of adenocarcinoma [24].

The pathologist must be familiar with the overall physiology and varying histologic appearance of the endometrium due to prolonged estrogen exposure, in addition to knowing the EIN diagnostic criteria. Another essential component of adoption is communication with the managing clinician regarding the new terminology and how it translates to suggested treatment. Like any classification system, widespread adoption will reveal new difficulties that will have to be resolved.

Biopsies with significant metaplasia, polyps, or progesterone-treated biopsies are areas of known diagnostic difficulty. In such cases, consultation with colleagues with significant gynecologic pathology experience or expert review would be prudent [13].

Conclusion

Endometrial Intraepithelial Neoplasia (EIN) lesions are premalignant which occurs predominantly in 5th and 6th decade of life. WHO endometrial hyperplasia cytology and architecture are separately graded on a three part scale, yielding nine permutations of endometrial hyperplasia.

An unfortunate side effect is the degradation of reproducibility proportionate to the number of categories used. Furthermore, there is diminishing clinical benefit in having more diagnostic categories than therapeutic responses.

What the study adds to the existing knowledge?

From the standpoint of diagnostic sign-out, the migration to EIN criteria should be relatively easy. EIN criteria can be easily diagnosed to routine haematoxylin and eosin stained histopathological sections. EIN has low interobserver variability and good reproducibility. Prompt diagnosis of EIN in endometrial biopsies will orchestra the appropriate treatment and hence preventing the progression to endometrial carcinoma. One of the major strengths of the EIN system is its correlation to outcome data.

Hysterectomy following the diagnosis of EIN is appropriate because there is a high rate of concurrent, as well as future, endometrioid endometrial carcinoma in women with EIN.

Author's contributions

Dr. Supriya Sandeepa: Data Collection, Analysis and preparation of Manuscript,

Dr. Shwetha Ramu: Analysis and Preparation of the Manuscript.

Dr. Jayaprakash H T: Data Collection, Analysis and preparation of Manuscript.

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References

1. Mutter GL Diagnosis of premalignant endometrial disease. J Clin Pathol. 2002;55(5):326-331.

2. Mirza T, Akram S, Mirza A, Aziz S, Mirza T, Mustansa T. Histopathological Pattern of Abnormal Uterine Bleeding in Endometrial Biopsies. J Basic App Sci. 2012;8(1):114-117.

3. Baral R, Pudasaini S. Histopathological pattern of endometrial samples in abnormal uterine bleeding. J Pathol Nepal. 2011;1(1):13-16. doi: https://doi.org/ 10. 3126 /jpn. v1i1.4443.

4. Dangal G. A study of endometrium of patients with abnormal uterine bleeding at Chitwan valley. Kathmandu Univ Med J. 2003;1(2):110-112.

5. Baak JP, Orbo A, van Diest PJ, Jiwa M, de Bruin P, Broeckaert M, et al. Prospective multicenter evaluation of the morphometric D-score for prediction of the outcome of endometrial hyperplasias. Am J Surg Pathol 2001;25(7):930-935.

6. Kurman R, Norris H: Endometrial hyperplasia and metaplasia in Blaustein's Pathology of the Female Genital Tract. Springer-Verlag. 1987;322-337.

7. Mutter GL Endometrial intraepithelial neoplasia (EIN). Will it bring order to chaos? The Endometrial Collaborative Group. Gynecol Oncol 2000;76(3):287-290. doi: https://doi.org/10.1006/gyno.1999.5580.

8 Scully RE, Bonfiglio TA, Kurman RJ, Silverberg SG, Wilkinson EJ: Uterine corpus Histological typing of Female Genital Tract Tumors. New York, Springer-Verlag; 1994; 13-31.

9. Kenneth M, Feeley Michael Wells: Advances in Endometrial Pathology. Recent advances in Histopathology- 19;20-21.

10. Mutter GL: EIN Central [On Line]; http:/www. endometrium.org, 2001.

11 Usubutun A, Mutter GL, Saglam A, Dolgun A, Ozkan EA, Ince T et al. Reproducibility of endometrial intraepithelial neoplasia diagnosis is good, but influenced by the diagnostic style of pathologists. Mod Pathol. 2012;25(6):877-884. doi: 10.1038/modpathol. 2011.220.

12. Hecht JL, Ince TA, Baak JP, Baker HE, Ogden MW, Mutter GL. Prediction of endometrial carcinoma by subjective endometrial intraepithelial neoplasia diagnosis. Mod Pathol 2005;18(3):324-333.

14. Lacey JV Jr, Mutter GL, Nucci MR, Ronnett BM, Ioffe OB, Rush BB et al. Risk of subsequent endometrial carcinoma associated with endometrial intraepithelial neoplasia classification of endometrial biopsies. Cancer. 2008;113(8):2073-2081. doi: 10.1002/ cncr. 23808.

15. Sobczuk A, Wrona M, Pertyński T. [New views on hyperplastic endometrial lesions classification—endometrial intraepithelial neoplasia (EIN)].Ginekol Pol 2007; 78(12):986-989.

16. Elke A. Jarboe, George L. Mutter.2010. Endometrial intraepithelial neoplasia. Seminars in Diagnostic Pathol. 2010;27(4):215-225.

17. Kane SE, Hecht JL. Endometrial intraepithelial neoplasia terminology in practice: 4-year experience at a single institution. Int J Gynecol Pathol. 2012;31 (2): 160-165. doi: 10.1097/PGP.0b013e318227505a.

18. Khanna R, Rupala G, Khanna V. Endometrial Intraepithelial Neoplasia and Its Correlation with WHO Classified Endometrial Hyperplasia. Int J Pathol. 2011; 12 (1).

19. Mutter GL, Ince TA, Baak JP, Kust GA, Zhou XP, Eng C. Molecular identification of latent precancers in histologically normal endometrium. Cancer Res. 2001; 61(11):4311-4314.

20. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. Cancer. 1985; 56(2):403-412.

21. Baak JP, Mutter GL, Robboy S, van Diest PJ, Uyterlinde AM, Orbo A, et al. 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. 2005;103(11):2304-2312. doi: https:// doi. org/10.1002/cncr.21058.

22. Zaino R, Trimble C, Silverberg S, et al. Reproducibility of the diagnosis of atypical endometrial hyperplasia (AEH); a gynecologic oncology group (GOG) study. Lab invest 2004;84(1):218A.

23. Kendall BS, Ronnett BM, Isacson C, et al. Reproducibility of diagnosis of endometrial hyperplasia, atypical hyperplasia, and well-differentiated carcinoma. Am J Surg Pathol 1998;22(8): 1012-1019.

24. 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.

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