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Endometrial Intraepithelial Neoplasia Is Associated With Polyps And Frequently Has Metaplastic Change

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Abstract

Aims—Endometrial Intraepithelial Neoplasia (EIN) is a monoclonal precursor to endometrioid endometrial adenocarcinoma characterized by a geographic cluster of crowded glands with epithelial cytology altered relative to the background. They may demonstrate epithelial metaplastic changes, or arise within polyps, but the frequencies of these features as encountered in practice is unknown.

Methods and Results—We here report the epithelial differentiation state and polyp context of 83 sequential EIN lesions diagnosed over a 2-year period. EIN is a rare lesion, seen in only 1.4% of endometrial biopsies in a busy hospital based practice. 39 of 83 EIN cases contained metaplastic changes (18% squamous morular, 14% tubal secretory, and 5% each of secretory, mucinous or ciliated change). Endometrial polyps were more likely (OR 5.2, $p < 0.001$) to occur in the endometrial biopsies of women with EIN lesions (43.3%), compared to the background polyp rate (12.9%) of comparable specimens from the same patient population.

Conclusions—Non-endometrioid differentiation and occurrence within polyps are frequent presentations of EIN lesions. Possible mechanisms of polyp association with EIN include: non-shedding of polyp tissue creating a shelter for persistence of pre-existing neoplastic glands, or promotion of expansion of premalignant glandular clones by unique polyp stroma.

Keywords

Endometrial Intraepithelial Neoplasia; metaplasia; histopathology; precancer; polyp

INTRODUCTION

The sequence of hormonal alterations, Endometrial Intraepithelial Neoplasia (EIN), and adenocarcinoma correspond to clinicopathologic stages of multistep epithelial carcinogenesis in the endometrium. EIN was originally defined by its combined molecular, histological, and clinical outcome features¹. It emerges from a polyclonal background as a benign neoplasm with a high propensity to undergo malignant transformation to carcinoma. Its monoclonal nature is evident through conservation of shared mutations amongst cells that comprise the EIN lesion², a continuous lineage to subsequent carcinoma³, localized origin, and centripetal pattern of spread. Glandular epithelium of EIN lesions occasionally demonstrate metaplastic changes to mucinous, squamous, tubal, or other differentiation states⁴, and they may arise completely or partially within endometrial polyps⁵. Although these are documented features of subsets of EIN lesions, their frequency and diagnostic implications are poorly understood.

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A 2004 National Institutes of Health consensus conference⁶ defined five robust and generalizable lines of evidence that must be achieved to define a premalignant lesion of clinical relevance. They are: 1) increased risk of cancer; 2) lineage continuity between cells of the premalignant and malignant phases of tumorigenesis; 3) precancers differ from their normal source tissues; 4) precancers differ from the cancer into which they develop; and 5) the precancer can be diagnosed. EIN has met all of these criteria⁷. In addition to the molecular and biologic foundation mentioned above, specific histologic criteria have been developed for routine EIN diagnosis^{1, 5, 8}, and the presence of an EIN lesion has been shown to increase long term cancer risk 45-fold⁹.

With a few exceptions^{10, 11}, the bulk of the published EIN literature has focused upon elucidation of mechanisms of origin, discovery of useful diagnostic features, and validation of clinical outcome prediction. This falls short of describing the typical experience that a pathologist is likely to encounter upon implementation of EIN diagnostic strategies to a series of sequentially encountered endometrial biopsies in practice. What fraction of endometrial biopsies contain EIN, and what is the rate of coexistent cancer at diagnosis? Furthermore, many longstanding questions of the relationships between premalignant endometrial disease and common lesions such as endometrial polyps, or endometrial “metaplasias” are worth revisiting in light of improved precancer diagnosis. This last issue is of some diagnostic relevance, as altered cellular differentiation with an EIN lesion, and presentation of an EIN lesion within an endometrial polyp, present novel diagnostic challenges.

A crucial element of EIN diagnosis is identification of a cytologic difference between architecturally crowded clonal glands and the patient’s background endometrium, and in some cases this is manifest as an altered differentiation state⁴. We prefer the term “altered differentiation” to “metaplasia” because of the common misconception that metaplasias and neoplasias are mutually exclusive. We here present a description of non-endometrioid differentiation in EIN lesions. Our goal was not to derive new criteria for metaplasia diagnosis, but rather to simply identify those instances of altered differentiation that a second pathologist is likely to confirm, and describe their frequency in the context of EIN.

We here relate the experience of a busy group practice in diagnosis of EIN lesions over a two year period. The seven subspecialty gynecologic pathologists in our institution (Brigham and Women’s Hospital) have now applied the EIN schema as a diagnostic standard for 6 years. The practice includes large numbers of endometrial biopsies and curettings received as wet tissue from individual and group gynecology practices. This body of this material, representing patients of diverse demographics with a wide variety of sampling indications, encompasses most instances of newly diagnosed EIN and endometrial adenocarcinoma arising in the gynecology practices that we serve directly.

MATERIALS AND METHODS

Case Selection

Diagnostic pathology reports of endometrial biopsy and curettage specimens received as wet specimens (excluding consultation material and hysterectomy specimens) in the Department of Pathology, Brigham and Women’s Hospital during a two year period beginning August, 2004 were screened for a diagnosis of “Endometrial Intraepithelial Neoplasia.” A total of 105 specimens representing the first EIN diagnosis in 105 different patients were identified after excluding repeat biopsies (n=9) in the same patients. We were able to retrieve the original diagnostic H&E stained sections in 99 of 105 specimens. Of these, 2 were excluded as technically inadequate (fragmented, cautery artifact), 2 due to superimposed active progestational therapy, and 8 because EIN was not represented in the slides available. This left a total of 83 sequential cases of a first diagnosis of confirmed EIN for more detailed review.

This work was performed following approval by the BWH Human Research Committee.

Case Review

Hematoxylin and eosin stained histologic sections from 83 EIN cases underwent independent review by two gynecologic pathologists (GLM and JWC) for determination of presence or absence of coexisting adenocarcinoma, endometrial polyps, and when polyps were present, involvement of the polyp by EIN. Each pathologist independently reviewed all slides, and discordant cases were resolved by adjudication at a multiheaded microscope (adjudicated consensus).

EIN diagnostic criteria were as previously published: a 1 mm or larger focus of cytologically altered architecturally crowded glands (gland area exceeds that of stroma), exclusive of carcinoma or benign mimics^{1, 8}. Well differentiated carcinoma is diagnosed if lesion epithelium architecture is cribriform, solid, or mazelike. Endometrial polyp diagnosis required at least two of three features to be present (altered stroma, irregular glands, thick walled vessels) in a surface endometrial fragment¹².

Non-endometrioid differentiation was next scored within the EIN lesional glands. Tubal ciliated, tubal secretory (round) cell, squamous morular, squamous luminal surface, mucinous, secretory vacuolar, micropapillary, and eosinophilic differentiation were all scored as present or absent for each lesion. Multiple metaplasias were scored when present. These interpretations were made independently by each of two pathologists, and considered as confirmed only when their mutually blinded interpretations agreed (independent consensus).

Case Comparison Groups

Additional diagnostic and demographic characteristics of patients from which the study EIN cases were selected was determined by pathology report review of all diagnostic endometrial biopsies and curettings processed by our laboratory during the study period. Referral cases (consultations received as glass slides) and hysterectomy specimens were excluded. The background frequency and age profile of women newly diagnosed with endometrial adenocarcinoma, endometrioid type, in the same specimen pool was estimated by pathology report diagnostic retrieval and collection of demographic information. The background frequency of endometrial polyps in the source population was estimated by pathology report review of endometrial biopsies and curettings from a one year sample (calendar year 2005, n=3351) in the middle of the EIN study interval.

Clinical Outcome

Medical records were reviewed for all 83 patients with EIN, and pathology report results of followup tissue sampling was scored for presence or absence of adenocarcinoma from the pathology reports.

RESULTS

Demographics of Confirmed EIN Cases

83 cases of confirmed EIN were entered into the study. Median patient age was 52.4 years, ranging from 23.6 to 93.1. Sampling format was endometrial biopsy (n=31, 37%) or curettage (n=52, 63%).

During the interval of receipt of the 83 confirmed sequential EIN specimens, 6,535 endometrial biopsies or curettings were accessioned in the same institution. The proportion of all endometrial samplings with a first diagnosis of EIN by report (n=91) or central pathologist review (n=83) is thus 1.4% and 1.3%, respectively.

Well differentiated endometrial adenocarcinoma, endometrioid type, was confirmed in 11% (9/83) of biopsies with EIN.

In the same interval as EIN case accrual, 51 new cases of endometrioid endometrial adenocarcinoma (35 well differentiated, 13 moderately differentiated, 3 poorly differentiated) were diagnosed in biopsies or curettings. Patients with endometrioid adenocarcinoma had a median age of 60.2, ranging from 40.7 to 90.4 years. The ratio of EIN to endometrioid carcinoma diagnosed in biopsies/curettings was 1.6 (83/51).

Endometrial Polyps and EIN (Table I)

Concordance of polyp diagnosis between original pathology reports and central consensus review was very high, with agreement in 31/36 polyps. Inter-observer concordance during re-review was excellent as well, with a kappa value of 0.755 (95% CI: 0.612-0.897).

Endometrial polyps were diagnosed by report in 43.3% (36/83) of EIN cases, and an identical number (36/83) were diagnosed upon consensus review (by GLM and JC). In those EIN cases that contained an endometrial polyp somewhere in the specimen, the polyp was usually (91.7%, 33/36) involved by the EIN lesion itself.

Background polyp frequency in patients presenting for endometrial biopsy or curettage at our institution was estimated by endometrial pathology report review of a one year sample that included 3351 accessioned biopsies or curettings. Four hundred and thirty one endometrial polyps were identified, for a background endometrial polyp frequency of 12.9% (431/3351).

Endometrial polyps were more likely (OR 5.19, 95% CI 3.3 - 8.1) to occur in the endometrial biopsies of women with EIN lesions (43.3%), compared to the background polyp rate (12.9%) of comparable specimens from the same patient population (Fishers Exact $p < 0.001$).

The age of women with EIN and a co-existing endometrial polyp (mean 59.5) was significantly greater (t-test $p < 0.001$) than those who presented with EIN alone (mean 49 years).

Non-Endometrioid Differentiation in EIN

The ability of reviewers to achieve an independent concordant diagnosis of metaplasia within an EIN focus is reflected in kappa scores for each differentiation state, ranging from a low of 0.26 for papillary differentiation to a high of 0.89 for squamous morules and 1.0 for squamous surface differentiation (Table II). For purposes of this study, only those metaplasias diagnosed independently by both pathologists were considered confirmed. Of 83 EIN cases, 39 (47%) contained confirmed metaplastic features, including 32 cases with one type of metaplasia, and 7 cases with 2 types of metaplasia (Table III). Mucinous and secretory tubal differentiation states were most commonly encountered in those EIN lesions with multiple metaplasia types. Figure 1 illustrates metaplasia types identified by consensus within EIN lesions.

For most metaplastic subtypes of EIN there were inadequate numbers of occurrences to determine whether the age of affected women differed by presence or absence of metaplasia. Even the two most common metaplastic subtypes, squamous morular, and secretory tubal (round cell type) showed no significant differences (t-test $p = 0.12$ and 0.87 , respectively), although the median age of women with and without morules in their EIN lesions was noted to be 47.4 and 52.9 years, respectively.

Clinical Outcomes

Clinical outcome information was limited by the relatively short interval of just under one year between capture of the last case and writing this report. 15 patients had no available followup

specimens, and of those that did, median followup interval was 68 days (range 8-811 days). This is probably too short a period for biologic progression from EIN to adenocarcinoma, so observed cancer occurrences might be construed as concurrent. Of the 83 EIN cases, 9 had carcinoma in the same specimen as the initial EIN diagnosis, and another 9 had cancer diagnosed during followup. This makes for an overall “concurrent” cancer rate of 22% (18/83). Amongst women with EIN, presence or absence of an endometrial polyp does not correlate with concurrent carcinoma (Fishers Exact $p=0.41$).

Mucinous differentiation within an EIN lesion showed a significant association with concurrent carcinoma (Fisher exact test $p=0.048$), although the total number of cases was very small ($n=4$). Concurrent cancers were not otherwise specifically associated with particular metaplastic EIN subgroups.

The average interval between EIN and adenocarcinoma could not be estimated directly in our individual cases, because an insufficient followup period was available. We thus compared the average age of EIN diagnosis with that for well differentiated endometrial carcinomas in the same patient population. Patients with EIN had a median age of 52.4 years, compared to 60.2 years for endometrioid endometrial adenocarcinoma. Peak incidence of EIN and well differentiated adenocarcinoma was thus separated by an interval of 7.8 years, providing an estimate of progression interval from EIN to adenocarcinoma.

DISCUSSION

Our observations within a single specimen pool, encompassing a common patient population, provides a measure of relative frequency of premalignant to malignant lesions. EIN is an uncommon finding amongst outpatient endometrial biopsies, occurring in only 1.3-1.4% of the 6,535 endometrial samples accessioned during the two year study interval. Its derivative malignancy, endometrioid endometrial carcinoma, comprised only 0.8% of all specimens, providing a ratio of 1.6 EIN lesions to every endometrioid cancer.

Comparison of the average age of presentation with EIN (52.4 years) with that for endometrioid endometrial adenocarcinoma (60.2 years) permits an interval estimate for EIN progression to carcinoma as 7.8 years. This is somewhat longer than the average progression interval of 4 years previously described for individual patients with EIN who develop cancer during clinical followup⁹. Unfortunately, in current practice by the time EIN is first diagnosed much or all of this grace period has elapsed, and many patients already have a concurrent carcinoma. In a retrospective study, 39% of women with EIN were diagnosed with carcinoma within 1 year⁹. Similar results were obtained in a prospective clinical trial of 153 women with EIN of which 37% had endometrial carcinoma at immediate hysterectomy¹³. The high rate of concurrent premalignant and malignant disease is due to a combination of inefficiency of current screening methods to capture premalignant lesions early in their course, and indolent tumor growth that preserves adjacent precursors. 22% of EINs in this series were associated with concurrent carcinoma, one third as EIN and adenocarcinoma lesions coexisting within a single specimen, and two thirds in independent specimens separated by a short interval.

EIN diagnosis can be difficult within a polyp⁵. By their nature, endometrial polyps have an irregular gland density and the cytology varies somewhat, both within the polyp and by comparison with native functionalis. Nonetheless, guidelines for diagnosis of EIN lesions within polyps are the same as elsewhere, with the specific requirement to use the benign components of the polyp as the background reference point. When EIN lesions occur within polyps, they usually have the appearance of a localized lesion with altered cytology (Figure 2).

Endometrial polyps were significantly (Odds Ratio 5.2, $p < 0.001$) more common in women with, compared to those without, EIN. Polyps arise as monoclonal overgrowths of genetically altered endometrial stromal cells with secondary induction of polyclonal benign glands through as yet undefined stromal-epithelial interactive mechanisms^{14, 15}. If such interactions act as positive selection factors for pre-existing mutant cells they may promote clonal expansion and development of a histologic lesion. Additionally, resistance of endometrial polyps to hormone induced shedding might create a sheltered site for persistence of pre-existing neoplastic glands, compared to the cycling areas of normal endometrium. The fact that EIN was commingled with the substance of the polyp in 92% of cases having polyps is consistent with preferential induction or persistence of EIN within the polyp environment itself. Ascertainment bias is likely contributor for discovery of otherwise occult EIN lesions in women with polyps, as women with polyps are more likely to be symptomatic, and thus biopsied. In our data, and that of others¹⁶, the positive association between endometrial polyps and premalignant glandular lesions becomes stronger with increasing age. This suggests that conditions favorable for EIN development within a polyp increase in the postmenopausal period (average age 59) compared to polyp-unassociated EIN lesions which tend to occur perimenopausally (average age 49).

Other studies¹⁷ have reported a high rate of endometrial polyps in women with adenocarcinoma, but these are non-definitive, either because they lack unbiased polyp background rates for comparison, or employ antiquated diagnostic criteria for recognition of polyps¹⁸. The current study employs standardized diagnostic criteria applied by a cohesive group of pathologists practicing in a dedicated subspecialty practice. EIN and endometrial polyps, as retrieved by routine diagnostic report review, were reconfirmed by study pathologists in the majority of cases (84% and 86%, respectively). This concordance rate provides a high level of confidence that incidence estimates as calculated by simple report review are comparable to those obtained by centralized re-review performed as part of this study.

A general association¹⁹ between altered endometrial glandular differentiation and endometrioid endometrial carcinoma is well documented, including squamous morular²⁰, mucinous²¹, tubal²², and eosinophilic²³ subtypes. All of these patterns have also been seen in various categories of hyperplastic endometrium²⁴, but at varying rates in different patient populations²⁵. Some are associated with peculiar genetic abnormalities, such as beta-catenin mutations in morule bearing glandular lesions^{26, 27}, whereas others appear to be hormonally induced²⁸. Endometrial metaplasias are also seen in completely benign endometrium, common examples of which include tubal differentiation in response to unopposed estrogens, and “papillary syncytial metaplasia” seen in areas of repair or breakdown. Because metaplastic processes in the endometrium can occur in a benign, premalignant, or malignant context, it is always preferable to clearly specify the underlying context of altered differentiation. Thus “anovulatory endometrium with tubal metaplasia” or “endometrial adenocarcinoma, endometrioid type, with tubal differentiation” both encompass the entity of tubal metaplasia. One of the more commonly encountered metaplastic contexts is that of premalignant glandular lesions.

EINs with altered glandular differentiation vary widely in their ease of recognition and frequency. Squamous and mucinous differentiation are sufficiently distinctive that they are independently identified by pathologists with high reproducibility ($\kappa > 0.64$). Fair to poor reproducibility ($\kappa < 0.4$) is the rule for all other differentiation states examined, including ciliated and secretory tubal, eosinophilic, micropapillary, and secretory endometrial types. Verified altered differentiation with EIN lesions, those concordantly recognized upon independent review of two pathologists, varied in frequency. The most common altered differentiation states were squamous morular (18% of all EIN cases) and tubal secretory (14% of all EIN cases).

EIN carries a high risk of concurrent (approximately 39%), or future (approximately 45-fold increased) carcinoma⁹, so management is driven by the EIN diagnosis. This study does not provide any rationale for modifying EIN treatment based upon a polyp context or presence of altered differentiation within the EIN. Furthermore, isolated polyps and endometrial metaplasia outside of the context of EIN cannot be assigned the high cancer risks of EIN itself. Pathologists must be aware, however, that many EIN lesions do demonstrate altered differentiation or arise within endometrial polyps. Therapy of the patient with EIN is directed towards ruling out concurrent carcinoma and controlling long term risk through surgical or hormonal ablation of the premalignant lesion.

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Figure 1. Types of endometrial metaplasia in EIN glands

These panels show metaplastic patterns of epithelial differentiation within the EIN focus that were lacking in the normal background endometrium. Squamous Morular (Panel A), Squamous Surface (Panel B), Tubal Ciliated (Panel C), Tubal Secretory (round cell, Panel D), Mucinous (Panel E), Secretory (Panel F), Eosinophilic (Panel G), and Papillary differentiation (Panel H). Hematoxylin and eosin stain.

Figure 2. EIN within an endometrial polyp

Two different endometrial polyps with localized EIN. Low magnification views show discrete clusters (arrows Panels A, C) of cytologically altered glands (arrowheads, Panels B,D) contrasting with the irregular polyp glands (asterisk, Panels B,D) in a fibrous background. These can be recognized as an EIN by comparison with other areas of the polyp. Hematoxylin and eosin stain.

Table I

Background endometrial polyp rate compared to women with EIN

Polyp Status	Biopsies with EIN	All Biopsies (Background)
Present	36 (43.3%)	431 (12.0%)
Absent	47 (56.7%)	3153 (78.0%)
Total	83 (100%)	3584 (100%)

Fishers Exact p<0.001, OR 5.2 (95% CI: 3.3-8.1)

Table II
Inter-Observer Consensus Diagnosis of Metaplasia in 83 EIN Cases

Metaplasia Type	Agree Present, %	Agree Present, n	Agree Absent, n	Disagree, n	Cohen's kappa
Squamous Morular	18.1	15	65	3	0.887
Tubal Secretory	14.5	12	46	25	0.297
Mucinous	4.8	4	75	4	0.641
Tubal Ciliated	4.8	4	69	10	0.381
Secretory	4.8	4	67	12	0.319
Eosinophilic	3.6	3	69	11	0.312
Papillary	3.6	3	67	13	0.259
Squamous Surface	1.2	1	82	0	1.000

Table III

Multiple metaplasia types in 7 of 39 individual EIN cases with metaplasia

First Metaplasia	Second Metaplasia	EIN Cases, n
Mucinous	Secretory	1
Mucinous	Squamous Surface	1
Mucinous	Tubal Secretory	1
Tubal Secretory	Squamous Morular	1
Tubal Secretory	Tubal Ciliated	3
	Total	7