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Endometrial Glandular Dysplasia: A Newly Defined Precursor Lesion of Uterine Papillary Serous Carcinoma. Part I: Morphologic Features[1]

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Dysplastic epithelium frequently bridges the changes between normal epithelium and noninvasive carcinoma. However, such a dysplastic lesion has not been previously described in the development of uterine papillary serous carcinoma (UPSC) or between resting endometrium and serous endometrial intraepithelial carcinoma (EIC), which is composed of indisputably malignant noninvasive cancer cells. In this study, we hypothesize that there is a lesion bridging benign endometrium and serous EIC. Based on current understanding of carcinogenesis in general, the lesion should exhibit dysplastic features that are more atypical than "resting endometrium" but fall short of serous EIC. If the putative dysplastic endometrial lesion exists, it should be highly associated with UPSC rather than uterine endometrioid carcinoma (UEC). We examined the morphologic appearance of the endometrium from 32 uteri with UPSC, 16 with serous EIC, and 60 with UEC. The endometrial dysplastic lesions were identified and their pathologic features were characterized. Immunohistochemical staining with p53 and MIB-1 were performed in all sections containing endometrial dysplastic lesions, serous EICs, and benign areas. In addition, 25 postmenopausal endometrial biopsies including 6 benign resting endometria, 8 dysplastic lesions, and 11 serous EICs were also compared for the level of p53 overexpression and cellular proliferative activity. We found that endometrial dysplastic lesions do exist in the endometrial specimens we speculated and examined. We designate it as endometrial glandular dysplasia (EmGD). EmGD was present in 17 (53%) uteri with UPSC compared with 1 (1.7%) uterus removed for UEC ($p = 0.001$). EmGD was identified in 12 (75%) of 16 serous EIC uteri. Areas of both EmGD and serous EIC were found in 15 (47%) of the 32 UPSC uteri. Transitions from either EmGD to serous EIC or serous EIC to UPSC were present in 8 (25%) of the UPSC cases. No transitions from EmGD to UPSC were identified in any hysterectomy specimen. EmGD was frequently found in endometrial polyps. There was no statistically significant difference between EmGD in a polyp (48%) and EmGD in nonpolypoid endometrium (52%). The majority of EmGDs were multifocal and involved superficial endometrial glands. However, single glandular involvement and endometrial surface epithelial involvement were also seen. Immunohistochemically, EmGD lesions mostly showed intermediate scores/indices of p53 and MIB-1 in comparison with serous EIC and resting endometrium. EmGD is a morphologically distinct entity, which is commonly and specifically associated with uterine tumors with serous differentiation. EmGD may represent the earliest identifiable morphologic change in the development of UPSC. Characteristics of p53 and MIB-1 immunostains of EmGD may be of diagnostic usage in surgical pathology practice. Recognition of EmGD may provide an opportunity to improve the management of UPSC. *Int J Surg Pathol 12(3):207–223, 2004*

Key words: EmGD, endometrial carcinoma, uterine surface carcinoma, serous EIC, UPSC.

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Endometrial carcinoma is the most common gynecologic malignancy occurring in American women [1]. It has 2 major histologic types, uterine endometrioid carcinoma (UEC) and uterine papillary serous carcinoma (UPSC). UPSC comprises approximately 10–15% of all endometrial carcinomas, but it causes a disproportionate number of endometrial cancer deaths [2]. UPSC is a clinically aggressive tumor that can present with bulky primary disease and extrauterine spread, resulting in a poor prognosis despite therapy [2–5]. Fifty percent of apparent stage I UPSC cases are found to have spread beyond the uterus at the time of surgical staging. Therefore, effective early detection methods are needed to improve clinical management of the disease.

The morphologic and clinical features of the typical UPSC have been well delineated, but its precursor lesion is still under debate in terms of morphology as well as terminology. The putative 'precursor lesion' of UPSC, previously designated as endometrial intraepithelial carcinoma (EIC) [6,7] or endometrial adenocarcinoma *in situ* [8] or uterine surface carcinoma [9], is now being referred as serous EIC [10]. Serous EIC is defined morphologically as replacement of endometrial surface epithelium and glands by frankly malignant cells that resemble the cells of the invasive high-grade endometrial carcinoma, UPSC [5,11]. Serous EIC is commonly associated with extrauterine serous carcinoma [5,12–14]. Therefore, serous EIC may be a form of cancer rather than a precursor lesion when one considers its morphology and clinical behavior. From this perspective, the real form of UPSC precursor(s) or a step earlier than serous EIC has not been explored.

It is generally accepted that UPSC arises in atrophic endometrium [2–4,6–8,14]. Morphologically, serous EIC shows typical features of adenocarcinoma *in situ*, which is composed of indisputably malignant glandular cells within the uterus. It seems apparent that something is missing between the completely benign endometrium and obviously malignant endometrial glands. The sequence of benign epithelium, to dysplastic epithelium, to carcinoma *in situ*, and then to invasive carcinoma is commonly seen in the uterine cervix, breast, prostate, and other organs. Dysplastic epithelium frequently bridges the changes between normal epithelium and carcinoma *in situ*. However, a dysplastic lesion has never been described morphologically in the process of UPSC development or between benign endometrium and serous EIC. In this study, we hypothesize that there is a lesion connecting benign endometrium to serous EIC. We attempted to identify this lesion and to characterize its morphologic features. After we identified such a lesion, then we designated it as endometrial glandular dysplasia (EmGD), which exhibits serous-like differentiation and has cytologic features that are more atypical than "resting endometrium" but fall short of serous EIC. Markers of p53 and MIB-1 were used to further distinguish EmGD from either serous EIC and benign resting endometrium.

Materials and Methods

Study Design

Since a transition from benign resting endometrium to serous EIC is missing, we have hypothesized that an endometrial dysplastic lesion bridges the resting endometrium and serous EIC in the line of UPSC development. To identify this putative endometrial dysplastic lesion, definitions of the serous EIC and resting endometrium with benign changes were established since we believe potential EmGD should show nuclear features in between the 2 ends. We used the definition of serous EIC as described previously [6,8,9] from the standpoint of characterizing the maximum degree of cellular atypia as our benchmark so that the lesions with lesser degree of nuclear atypia could be studied. Benign resting endometrium included atrophic endometrium, inactive-looking or weakly proliferative or proliferative endometrium. Resting endometrium with benign cellular changes include squamous, mucinous, ciliary, hobnail, clear cell, eosinophilic, and surface syncytial changes. These changes are different from the single, basal, small, uniform nuclei of normal resting endometrial cells, but the nuclear shape and size and the slightly increased, evenly dispersed hyperchromatin are clearly benign [15]. We used these benign conditions as the minimal degree of atypia as another benchmark for the study. Occasional benign changes showing severe atypical changes were not included in this study. Endometrial hyperplasia with or without atypia or endometrial intraepithelial neoplasia was also excluded because they do not have serous differentiation. To be considered as an endometrial dysplastic lesion, we had to have lesions showing serous-like differentiation and having nuclear features that fall short of serous EIC but are more than benign resting endometrium with or without associated benign changes. Serous-like differentiation is defined by presence of the endometrial glandular epithelial cells that do not look like classic endometrioid, mucinous, or clear cells. In this regard, the lesions are referred as serous EmGD if other type of EmGD may emerge in the future.

Case Selection

All retrospective cases in this study were obtained from the Departments of Pathology of the Yale University School of Medicine and of the Los Angeles County Women's and Children's Hospital of the University of Southern California from 1990 to 2003. We first studied hysterectomy specimens with a diagnosis of endometrial cancer to see if the endometrial dysplastic lesion is present in cancer uteri. One hundred and eight (108) hysterectomy specimens were studied. These included 32 classic UPSC, 16 serous EIC, and 60 UEC uteri. These uteri showed those in which slides of adjacent noncancerous endometrium were available. Cases in which the entire endometrium was replaced by invasive cancers were not included. Cases with mixed histology (2 or more histologic components with each more than 25% of total tumor volume) and other histologic types (endometrial carcinosarcomas, clear cell, mucinous carcinomas, squamous and villoglandular carcinomas) were also excluded. We mainly recruited classic type I (endometrioid or UEC) and type II (UPSC and serous EIC) endometrial cancers for the study in an attempt to examine if the putative dysplastic endometrial lesion is specifically associated with serous EIC or UPSC. Particular attention was paid to identify areas of transitions (from endometrial dysplasia to serous EIC), locations (in endometrial polyp or nonpolyp endometrium), and the number of dysplastic lesions in all hysterectomy specimens. In 14 of 16 serous EIC uteri, the entire endometrium had been examined histologically, while the remaining 2 uteri all had 6 endomyometrial sections. Nine of 32 UPSC uteri contained endometrial polyps. Seventeen UPSC uteri and all the uteri with endometrial polyps had their entire endomyometrium histologically examined. All of the remaining 15 uteri had at least 8 endomyometrial sections. In the 60 UEC uteri, 7 had the entire endomyometrium examined, 12 had 10 sections of endomyometrium each, 33 had 8, and 8 had 6 endomyometrial sections available for histological examination. Sections containing endometrial dysplastic lesion, serous EIC, and benign resting endometrium were subject to p53 and MIB-1 immunostainings.

We also studied 35 endometrial biopsies showing "atypical endometrial glands," which were originally diagnosed as suspicious for serous EIC or UPSC. Among these 35 cases, 25 were suitable for immunohistochemical and comparison studies in subsequent recut levels.

The age of patients and histologic types of the tumors at diagnosis were collected. No patient with a history of prior radiation or chemotherapy was included in this study. All specimens were obtained under the approval of the Human Investigative Committee.

Tissue Handling and Routine Histology

All cases were fixed in 10% buffered formalin and processed routinely for paraffin embedding. Tissue was obtained either from endometrial curettings, hysterectomy specimens, or from both. Five-micron sections for immunohistochemistry were cut and placed on Super Plus slides (Fisher Scientific, Pittsburgh, PA) followed by a section of each specimen that was stained with hematoxylin and eosin and examined microscopically to confirm the diagnosis.

Pathological Analysis

The diagnosis and histologic classification of the endometrial carcinomas was made by using the criteria proposed by The International Federation of Gynecologists and Obstetricians and the World Health Organization [15]. Serous EIC was defined as serous intraepithelial carcinoma without stromal or myometrial invasion [15]. Endometrial carcinomas composed of a mixture of serous and endometrioid components were classified as serous carcinoma if less than 25% of the tumor was endometrioid. Similarly, tumors were classified as endometrioid carcinoma if serous or other components were less than 25% of total tumor volume. Endometrium uninvolved by invasive carcinoma was classified as atrophic, proliferative including weakly proliferative, hyperplastic, dysplastic, and serous EIC. Endometrial hyperplasias were divided into those with and those without atypia categories. No further classification of simple or complex hyperplasia was used. When 2 or more pathology categories presented in a single uterus, such as 1 area showing hyperplasia and the other areas showing proliferative endometrium and dysplastic lesion, all the lesions were counted. Any endometrial glands or surface epithelium with diagnostic features of endometrial dysplastic lesion or serous EIC were recorded as such. The appearance, extent, and the relationship of potential EmGD to serous EIC and/or to invasive carcinomas were recorded. Histologic transitions were defined by the presence of gradual changes from dysplastic epithelium to intraepithelial carcinoma or from noninvasive carcinoma to invasive carcinoma. Abrupt transitions such as carcinoma cells abutting benign resting endometrium were considered as either "pagetoid" spreading or intraepithelial invasion, which was not recorded in this study. Topographically, dysplastic lesions separated by more than 1 mm were considered as mul-

tifocal. Endometrial dysplastic lesions in endometrial polyps or in nonpolyp endometrium was recorded separately.

P53 and MIB-1 Immunohistochemical Analyses

The markers of p53 and MIB-1 were used because they have been reported as useful markers to diagnose serous EIC and/or UPSC [16]. Monoclonal antibody PAB1801 (Ab-2; Oncogene Science, Manhasset, NY) is affinity purified and recognizes a linear epitope in the human p53 protein located between amino acids 32 and 79 [16]. MIB-1 (Ki-67 paraffin), a mouse monoclonal antibody (IgG1) recognizing a nuclear antigen expressed in all phases of the cell cycle except G_0 [17], was obtained from Immunotech, Inc. (Westbrook, ME). Five-micrometer parallel sections of the endometrial lesions were cut and placed on Super Plus slides (Fisher Scientific, Pittsburgh, PA) for IHC. Immunohistochemical (IHC) analysis was performed using the streptavidin-biotin-peroxidase methodology. P53 and MIB-1 antigens were unmasked with the heat-mediated antigen retrieval method described previously [9,18]. Visualization was carried out with diaminobenzidine tetrahydrochloride as the chromogen.

UPSC from 3 patients and carcinoma of the fallopian tube from another 3 patients with known p53 alteration including p53 overexpression and mutation [16,19] served as positive controls for p53 IHC staining. Proliferative endometrial tissue sections served as positive controls for MIB-1 staining. Negative controls were carried out by replacing primary antibodies with class-matched mouse IgG proteins on parallel sections. Immunostaining was repeated at least 2 times for each case.

Assessment of Staining for p53 and MIB-1

Quantitative assessment of IHC results for both p53 [9] and MIB-1 [20] was based on distinct nuclear staining. Overexpression of p53 was scored according to our previous definition using a 0- to 3-point score system for percentage of cells stained, intensity, and heterogeneity in a range of total scores from 0 to 9 [9]. Intensity was judged based on a known positive control case, which was always included in each batch of staining. For the current study, the positive control case came from a serous carcinoma with a known p53 mutation and diffuse strong p53 overexpression [19]. Heterogeneity was defined as nonuniform or sporadic immunostaining patterns in representative areas. Individual IHC scores were assigned by 2 gynecologic pathologists (WZ and SL) to every section without their knowing the histopathologic diagnosis. The final score was calculated by adding the average of 3 parameters [9]. Occasional cytoplasmic p53 staining was ignored. The MIB-1 index (percentage of stained cells) was calculated after our counting a total of 500 glandular cell nuclei from each case. No cytoplasmic staining for MIB-1 was noted.

Statistical Analysis

The patients' age and pathologic features in each of the endometrial carcinoma types was compared by using the Chi-square test. The difference of grouped p53 scores and MIB-1 indices between cases with endometrial dysplastic lesion and those without dysplasia was assessed by Fisher's Exact Test and the p value was two-sided.

Results

We have verified that an endometrial dysplastic lesion does exist in the endometrial samples we studied. Therefore, we have designated it as endometrial glandular dysplasia (EmGD) for communication convenience. Histologic examples of EmGDs in comparison with serous EIC and resting endometrium are illustrated in Figs. 1 and 2.

Selected Clinical and Pathological Features of EmGD

The age of the patients undergoing hysterectomy ranged from 45 to 90 years with a mean of 63 years. The mean age of patients with UPSC including serous EIC was 68 years (range: 59 to 90) compared with 57 years (range: 45 to 77) for women with UEC ($p < 0.001$). The age of patients with lesions designated as EmGD ranged from 57 to 79 years with a mean of 65 years. Five of the 17 cases with EmGDs in UPSC/serous EIC uteri had a history of a mastectomy for an invasive breast cancer; 4 had synchronous papillary serous carcinoma of the ovary, 2 had peritoneal serous carcinoma, and 1 had fallopian tubal carcinoma *in situ*. Among the 5 patients with breast cancer, 3 had been on a tamoxifen treatment regimen for an average of 6 years (range: 4 to 9 years). All but 7 patients presented with postmenopausal bleeding. Among the 7 patients who did not have postmenopausal bleeding, 4 had an abnormal-appearing pap smear, 2 had an increased endometrial stripe thickness on ultrasound, and 1 was found to have an enlarged uterus by routine pelvic examination. A history of hormone replacement was not studied.

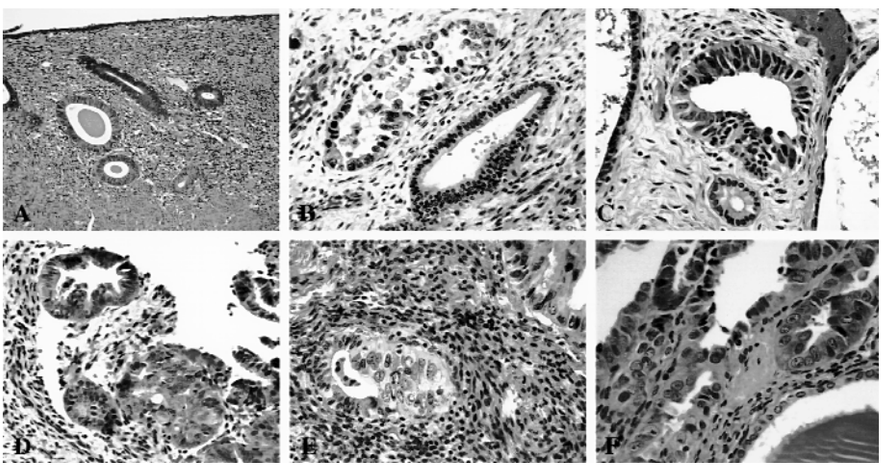

Fig. 1. Histologic examples of EmGD. For comparison, resting endometrium (**A**), with no nuclear atypia, and serous EIC (**F**), with severe anuclear atypia, are illustrated. EmGD lesions from 4 different cases (**B to E**) show less nuclear atypia than serous EIC (**F**). EmGD gland in case B shows loss of cell polarity and nuclear hyperchromasia in upper left in comparison with resting endometrial gland in the lower right. EmGD gland in case C, derived from an endometrial polyp, shows 2-3 fold nuclear enlargement with visible nucleoli (center) compared to the resting atrophic endometrial glands (peripheral and lower center). Case D shows EmGD glands with cribriform (lower right) and minimal luminal papillary formation (upper left). Case E shows an EmGD gland (center) probably arising in a resting endometrial gland (left). A similar dysplastic gland is seen in the upper right corner. Serous EIC cells (**F**) show 4-5 fold nuclear enlargement compared with the adjacent atrophic endometrium (lower right) (original magnifications: 200×).

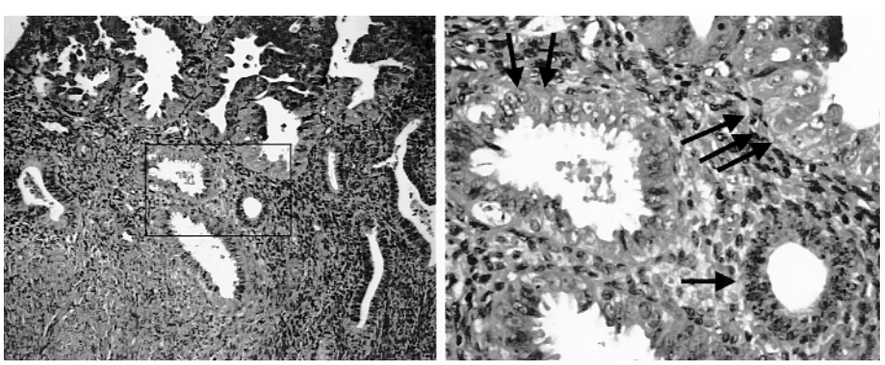

Fig. 2. EmGD glands admixed with serous EIC and resting endometrium. This figure captures EmGD, serous EIC, and resting endometrium in the same field. The left figure (intermediate power,100×) shows serous EIC on the top, 2 EmGD glands in the middle, and resting endometrium in the center and periphery. The squared area is further enlarged (400×) in the right side to show the differences among the 3 types of endometrial glands in detail. EmGD cells (2 arrows) show nuclear features closer to serous EIC (3 arrows) than resting endometrium (1 arrow). Compared to serous EIC, EmGD cells are smaller and nucleoli are less prominent. Both EmGD and serous EIC show more open chromatin pattern than the cells of resting endometrium.

Presence of EmGD is Highly Associated with Uteri with UPSC

The microscopic findings of the noncancerous endometrium for UEC and UPSC hysterectomy specimens are summarized in Table 1. Atrophic endometrium was found in 14 (44%) of 32 UPSC uteri, which was about 4 times more frequent than in the cases of UEC ($p < 0.001$). Among the 32 UPSC uteri, proliferative endometrium was observed in 11 (34%), endometrial hyperplasia without atypia in 1 (3%), and endometrial hyperplasia with atypia in 1 (3%). In contrast, 33 (55%) of 60 UEC uteri were associated with proliferative endometrium, 14 (23%) were associated with nonatypical hyperplasia, and 27 (45%) were associated with atypical hyperplasia. Proliferative-type endometrium was not statistically significant between the 2 groups. These findings are similar to those described in the original serous EIC study described previously [21]. However, EmGD was found to be 17-fold higher in association with UPSC than with UEC ($p < 0.001$).

EmGD Shows Distinctive p53 and MIB-1 Immunohistochemical Staining Patterns

On the basis of the morphologic criteria described above, we recorded the number of potential EmGD lesions. They were present in a total of 29 of the 48 uteri (12 from serous EIC and 17 from UPSC cases). Sixteen of the 29 uteri were suitable for p53 and MIB-1 IHC stainings. We processed the histologic sections containing at least 2 of the 3 areas of EmGD, serous EIC, and benign resting endometrium. Nine of the cases had tissue sections with all 3 targeted areas. The remaining 7 cases had all 3 targeted areas from different blocks. The total p53- and MIB-1-measurable areas from the above-cited 16 uteri included 14 benign resting endometria, 16 potential EmGDs, and 12 serous EICs. Among the 25 endometrial biopsy samples with suitable immunostains for p53 and MIB-1, we (WZ and SL) further separated them into 6 benign, 8 EmGD, and 11 serous EIC based on the nuclear features we defined under microscope. The purpose of this arbitrary separation was to examine if microscopically identified "EmGD" is different from benign or serous EIC with these 2 biomarkers.

With our previously defined p53 IHC score system, we found that the majority of histologically benign areas (93% from hysterectomy specimens and 83% from biopsies) had p53 overexpression scores of 3 or less. Only 2 cases (1 from hysterectomy and 1 from biopsy) showed IHC scores between 4 to 6. None of the benign areas showed p53 scores of equal or more than 7. This was in sharp contrast to serous EIC lesions, none of which had scores 3 or less, all had a score of 7 or more except 1 biopsy sample with a score of 4-6. In terms of EmGDs, 11 (69%) of 16 from hysterectomy uteri and 7 (87%) of 8 from endometrial biopsies showed p53 IHC scores of 4-6. Five (31%) of 16 and 1 (13%) of 8 from hysterectomy and biopsy specimens had a p53 overexpression scores of 7 or more, while none of them had a score of 3 or less. The p53 IHC scores of EmGD were significantly different from benign as well as serous EIC groups ($p < 0.001$). The data are summarized in Tables 2 and 3. All positive control cases showed strong diffuse nuclear staining of p53 in every batch of the IHC, while negative controls were negative.

In addition to p53, the cell proliferative marker MIB-1 (monoclonal Ki-67) has also been shown to be useful in the differential diagnosis of serous EIC from its morphologic mimics [14,22]. In this study, we found that 16 (80%) of 20 benign resting endometrium showed low proliferative indices (< 20), 4 (20%) of them in the middle range of proliferative indices (21 to 50), and none were in a high prolifer-

Table 1. Correlation of EmGD and the Microscopic Appearance of the Endometrium Uninvolved with Invasive Endometrial Cancers

Noncancerous Areas	UPSC (n = 32) Number (%)	UEC (n = 60) Number (%)	UPSC vs UEC p Values
Atrophic	14 (43.8)	7 (11.7)	0.001
Proliferative*	11 (34.4)	33 (55)	0.06
Hyperplasia w/o atypia	1 (3.1)	14 (23.3)	0.012
Hyperplasia with atypia	1 (3.1)	27 (45)	0.001
EmGD	17† (53)	1‡ (1.7)	0.001

*Proliferative endometrium included inactive or weakly proliferative and typical proliferative endometrium seen in follicular phase of menstrual cycle. †Presence of any EmGD in cases of UPSC was classified into this category although many of the cases were also associated with atrophic endometrium. ‡This case of UEC showed a focal area (15%) of serous differentiation. Since a single uterus may have more than 1 pathology category (such as hyperplasia in 1 area and proliferative endometrium in another), the total percentage of all categories exceeds 100%.

Table 2. Comparison of p53 Immunoreactivities Among Areas of Benign Resting Endometrium, EmGD, and Serous EIC from Hysterectomy Specimens

Diagnostic Areas	No. of Cases	Number of Cases with p53 IHC Scores (%) 0–3	4–6	7–9	p Values
Benign	14	13 (93)	1 (7)	0 (0)	
EmGD	16	0 (0)	11 (69)	5 (31)	<0.001
Serous EIC	12	0 (0)	0 (0)	12 (100)	<0.001

Individual p53 IHC score was given based on criteria described previously by Zheng et al [9]. The p53 IHC scores of 3 morphologically different areas were significantly different from each other ($p < 0.001$).

Table 3. Comparison of p53 Immunoreactivities Among Cases of Benign Endometrium, EmGD, and Serous EIC from Endometrial Biopsy Specimens

Diagnosis	No. of Cases	Number of Cases with p53 IHC scores (%) 0–3	4–6	7–9	p Values
Benign	6	5 (83)	1 (17)	0 (0)	
EmGD	8	0 (0)	7 (87)	1 (13)	0.003*
Serous EIC	11	0 (0)	1 (9)	10 (91)	0.001†

Statistically, the 3 groups of the disease entity were significantly different from each other based on their p53 IHC scores ($p = 0.001$). *The p value was 0.003 when EmGD was compared with benign endometrium. †The p value was 0.001 when EmGD was compared with serous EIC.

Table 4. Comparison of MIB-1 Index Among Areas of Benign Resting Endometrium, EmGD, and Serous EIC from Hysterectomy Specimens

Diagnostic Areas	No. of Cases	Number of Cases with MIB-1 Index (%) < 20	21–50	> 50	p Values
Benign	14	12 (86)	2 (14)	0 (0)	
EmGD	16	2 (12.5)	12 (75)	2 (12.5)	<0.001
Serous EIC	2	0 (0)	2 (16.7)	10 (83.3)	<0.001

MIB-1 index is defined by the percentage of positively stained cell nuclei by counting a maximum of 500 cells in interested areas. The p value was < 0.001 when EmGD was compared with benign endometrium and serous EIC groups.

Table 5. Comparison of MIB-1 Index Among Cases of Benign Endometrium, EmGD, and Serous EIC from Endometrial Biopsy Specimens

Diagnosis	No. of Cases	Number of Cases with MIB-1 Index (%) < 20	21–50	> 50	p Values
Benign	6	4 (67)	2 (33)	0 (0)	
EmGD	8	1 (12.5)	6 (75)	1 (12.5)	0.091*
Serous EIC	11	0 (0)	3 (27)	8 (73)	0.030†

*The p value was 0.091 when EmGD was compared with benign endometrium, which did not reach to the statistical significance. †The p value was 0.03 when EmGD was compared with serous EIC.

ative index (> 50). This was in contrast to EmGD and serous EIC lesions, the majority of which showed middle to high proliferative indices. EmGDs mostly showed proliferative indices in the middle range while serous EICs were mostly in the high indices range. In contrast to the p53 IHC scores, the proliferative indices of EmGD were more dispersed. Among the total of 24 EmGD measurable lesions, 3 (12.5%) showed less than 20, 18 (75%) were between 21 to 50, and 3 (12.5%) were more than 50. However, the proliferative index in this study remained statistically different among the 3 groups ($p < 0.05$) except in biopsy samples when EmGD was compared to benign resting endometrium ($p = 0.091$). The data are summarized in Tables 4 and 5. Positive control of proliferative endometrium showed an average labeling index of 30% as expected.

In summary, most EmGD foci showed intermediate immunoscores of p53 and proliferation indices in comparison with areas of serous EIC (high scores and indices) and resting endometrium (low scores and indices). The representative morphologic pictures of EmGD as well as their corresponding p53 and MIB-1 staining results in comparison with benign endometrium and serous EIC are illustrated in Fig. 3.

Pathologic Characteristics of EmGD

Grossly, no visible lesions could be identified in the corresponding areas of EmGD. There was no gross difference between polyps with and without EmGD. We used EmGD with at least intermediate scores of p53 and MIB-1 as targets to characterize microscopic features. The cells of EmGD showed oval or round nuclei with a 2-3 fold nuclei enlargement compared with the benign resting endometrium. This was calculated by using the light arrowhead under the microscope. The nuclei were either hyperchromatic or with open chromatin patterns. When hyperchromatic, the degree of hyperchromasia was less than that of frank malignant cells seen in serous EIC. Nucleoli were usually conspicuous instead of prominent. Partial loss of cell polarity was seen when nuclear stratification was present. Single layer glands or surface endometrial linings with the above-mentioned degree of cellular atypia were typical. A few stratifications may be seen. Mitotic figures and apoptotic bodies were appreciable, but not easily identified. The following microscopic patterns are common: (1) a single or a group of EmGD glands within the endometrium or within an endometrial polyp, (2) a flat single layer of epithelium on the surface of the endometrium or a polyp. Both patterns of EmGD were composed of atypical cells showing a degree of atypia less than that of serous EIC and more than that of benign resting endometrium with or without associated metaplastic changes.

EmGD lesions were closely associated with resting endometrial glands. Among 17 EmGD containing UPSC uteri, 7 were associated with atrophic endometrium, 4 with inactive or weakly proliferative,

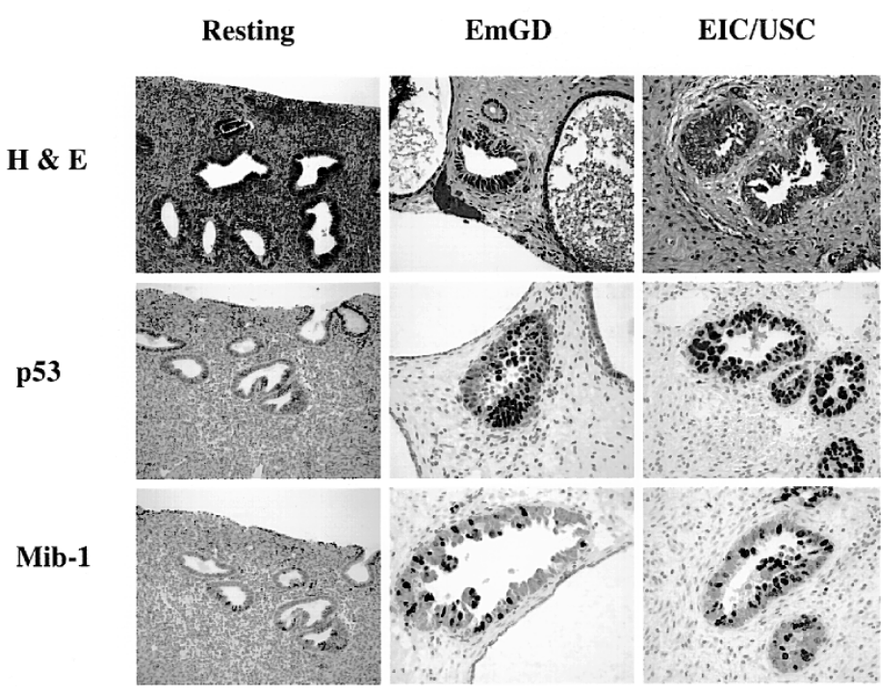

Fig. 3. Morphologic appearance of EmGD and its corresponding p53 and MIB-1 stainings in comparison with benign endometrium and serous EIC. The resting endometrium (left panel) shows negative p53 staining (midleft) and minimal MIB-1 index (lower left). This is in sharp contrast with the serous EIC lesion (right panel), which shows strong diffuse nuclear p53 overexpression with an IHC score of 9 (midright) and high MIB-1 labeling index (40%, lower right). The EmGD lesion (center panel) shows an intermediate p53 staining score of 6 (center) and MIB-1 index of 25% (lower center) (original magnifications: 200×).

and 6 with proliferative endometrium. One EmGD was found in a UEC uterus, which actually showed endometrioid carcinoma with focal serous differentiation (15%). The noncancerous endometrium of this particular case was also proliferative. Fifteen (88%) of 17 EmGDs were 1 or 2 layers thick, but 2 (12%) reached to a stratification of 3-4 layers (Fig 4). Loss of cellular polarity (Fig. 1B) was present in 4 (24%) of the 17 cases. A small papillary structure was identified in 2 EmGD cases. The thin fibrovascular cores of the EmGD papillae were also lined by dysplastic cells instead of malignant cells as in serous EIC or UPSC (Fig 5). One case showed hobnailing features (Fig. 6). EmGD cells were mostly cuboidal or polygonal, but cells that were columnar were also seen (Fig. 1C and lower right corner of Fig. 4). The cells had large nuclei that were up to 3-fold larger than nuclei in adjacent benign resting endometrium but smaller than nuclei of classic serous EIC (Fig. 7). The nuclei of EmGDs were either hyperchromatic with slightly irregular contours or vesicular with clumped chromatin. Nucleoli were appreciable but not prominent as in serous EIC (Figs. 1, 2, and 7). Occasional mitotic figures were present, but no abnormal mitosis was seen in EmGD lesions. Apoptotic bodies ranged from 0 to 5 per gland with an average of 1.5/gland, which can be identified in many of the figures cited above.

EmGD foci were usually smaller than 1 mm in size. This may mainly be related to the fact that they often presented as a single or a group of a few glands. However, occasionally, potential EmGD glands formed clusters (Fig. 4), which reached 1 to 2 mm in size. When in endometrial polyps, the overall size of EmGD lesions may reach several millimeters (Fig. 8). The stroma around the EmGD glands was usually fibrotic, but desmoplastic reactions were not seen.

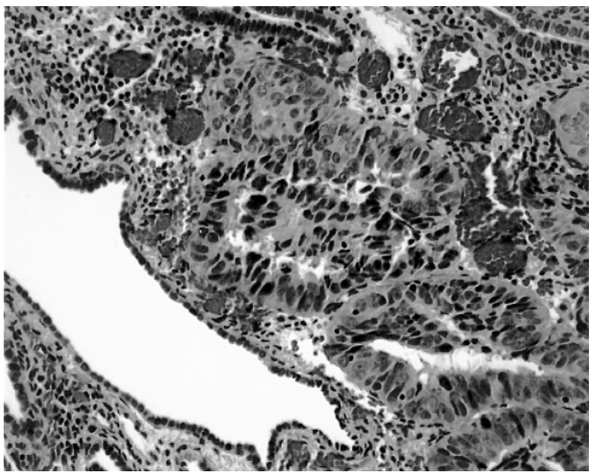

Fig. 4. EmGD clusters. Typically, EmGD lesions are smaller than 1 mm mainly because they are often single or in a group of a few glands. The figure shows a cluster of EmGD glands, which measures 1.5 mm under the microscope. Apoptotic bodies are present. Atrophic glands are seen in an adjacent area (original magnifications: 200×).

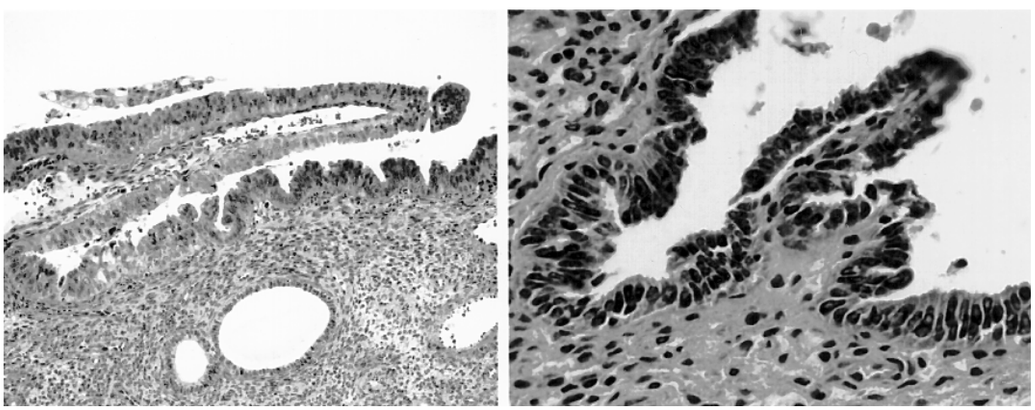

Fig. 5. EmGD lesions have a papillary structure. The papillary structure is evident in these 2 cases. The left one showing papillae lined by atypical cells was on the endometrial surface in a postmenopausal woman. Underlying atrophic endometrial glands are present (lower center) for the comparison. The right side EmGD lesion with papillae formation was derived from an endometrial polyp. The degree of nuclear atypia in these lesions falls short of serous EIC. (original magnifications: left, 100x; right, 200×).

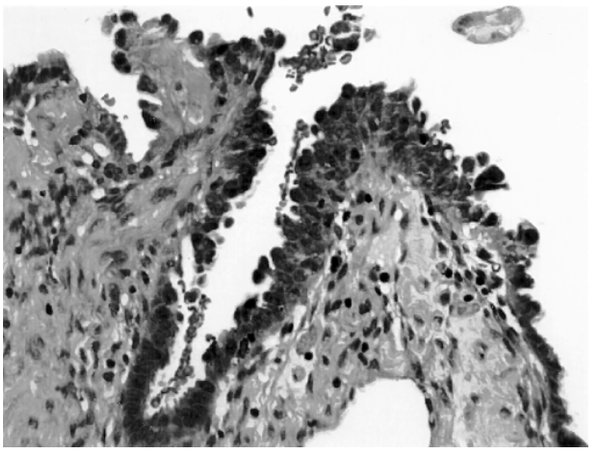

Fig. 6. EmGD cells show hobnailing features. Some of the dysplastic cells in this lesion show atypical nuclei protruding to the apical part of the cytoplasm (hobnailing). This is particularly evident on the right side of the figure. Although the atypia is evident, features of frank malignancy are not seen in this lesion. Therefore, morphologic evidence of serous EIC is not present (original magnifications: 200×).

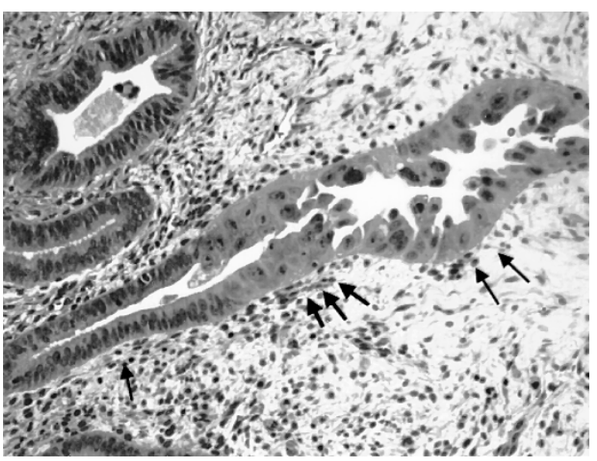

Fig. 7. Morphologic transitions from resting endometrium to EmGD and from EmGD to serous EIC. This picture shows a single endometrial gland with resting endometrium (1 arrow) in the lower left, EmGD in the center (3 arrows), and serous EIC in the upper right (2 arrows). The gradual transition from minimal or no atypia to moderate atypia and to severe atypia is clearly demonstrated in this figure. Nucleoli are appreciable in the EmGD area (3 arrows) but less prominent than in the serous EIC area (2 arrows). Adjacent endometrial glands are proliferative/resting (original magnifications: 200×).

Topographic Distributions of EmGD in Hysterectomy Specimens

EmGD lesions were identified in 29 (60%) of 48 total uteri. Within the 16 serous EIC uteri, areas of potential EmGD were identified in 12 (75%). Among the 12 potential EmGDs, 6 showed the transitional areas from EmGD (dysplastic) to serous EIC (malignant cells). In the 32 UPSC uteri, we found serous EIC and EmGD were present in 20 (62.5%) and 17 (53%) of the uteri, respectively. Areas of both serous EIC and EmGD in the same case were found in 15 (47%) of the 32 UPSC cases. Transitions from either EmGD to serous EIC or serous EIC to UPSC were present in 8 (25%) of 32 UPSC cases. No transitions from EmGD to UPSC were identified in any hysterectomy specimen. The data are summarized in Table 6. Examples of the morphologic transitions from resting endometrium to EmGD are illustrated in Figs. 7 and 9. All serous EIC and 18 (56%) UPSC uteri showed benign (nondysplastic and noncancerous) areas in addition to the stated diseases.

In terms of the number of EmGDs in uteri, the majority were multifocal. A single focus of EmGD was seen only in 4 (14%) of 29 uteri. EmGD with 2-5 foci within a single uterus was seen in 18 (62%), while more than 5 were identified in 7 (24%) of the 29 uteri. Four (24%) of 17 EmGDs concurrently had EmGDs on surface. A representative figure of surface EmGD is illustrated in Fig. 10.

Relationship Between EmGD and Endometrial Polyps

In this study, we also examined the relationship between EmGD and endometrial polyp (EMP). EMP was seen in 7 (44%) of 16 serous EIC and 9 (28%) of 32 UPSC uteri. Among 12 EmGDs from the 16 serous EIC uteri, 6 were found in EMPs and the other 6 were in nonpolypoid endometrium. There were 4 cases showing features of EmGD in both EMP and nonpolypoid areas within the uteri. Foci of EmGD were confined to the tip of an EMP in 3 of the 6 cases. Among 17 EmGDs from the 32 UPSC uteri, 8 (47%) were identified in EMPs, 9 (53%) in nonpolyp endometrium, and 5 (29%) in both. Only 1 EMP had neither EmGD nor serous EIC. A substantial number of EMPs were present in the cancer uteri in this study. However, there was no statistical difference between potential EmGD in EMPs (48%) and in nonpolyp (52%) endometrium. The data are summarized in Table 7.

Discussion

In this study, we have designated a distinctive lesion as EmGD, which is characterized by replacement of endometrial surface epithelium or glands by dysplastic cells in the endometria. EmGD is a histologically identifiable entity in about half of the

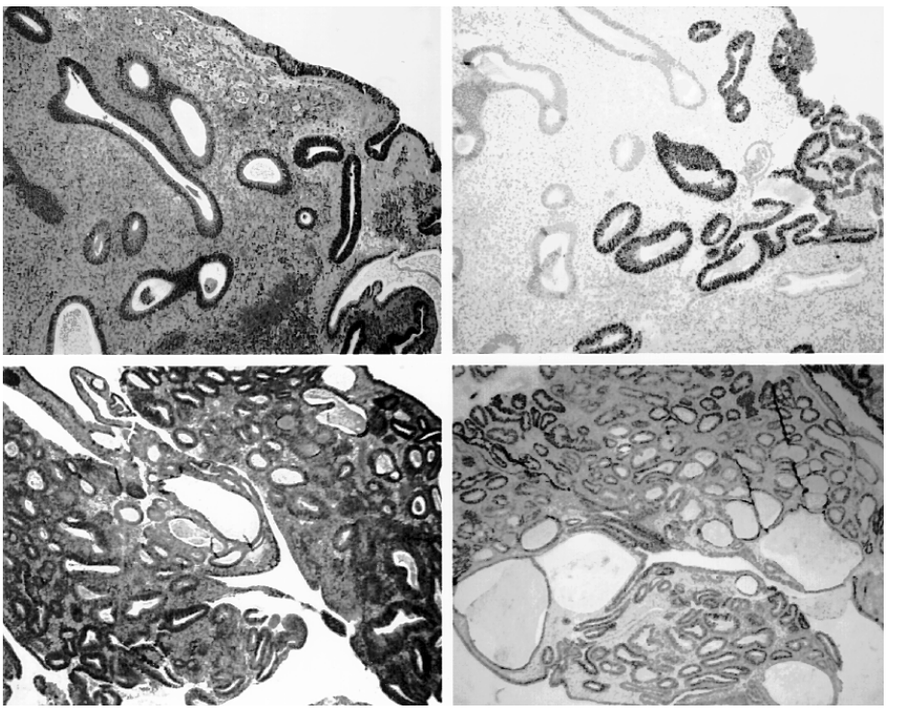

Fig. 8. EmGD involving endometrial polyps, H & E with corresponding p53 immunohistochemical stainings. This endometrial polyp contains several dysplastic endometrial glands (EmGD), which look hyperchromatic on H&E section (upper left). The corresponding p53 immunostaining section shows that the majority of hyperchromatic glands have p53 protein overexpression (upper right). The p53 IHC score for this case is 8. The lower panel shows clusters of dysplastic glands, which measure 3.5 mm in greatest dimension under the microscope, in an endometrial polyp (lower left). The corresponding p53 staining shows overexpression of p53 in the majority of dysplastic glands with an immunostaining score of 6 (lower right). The atrophic and less hyperchromatic glands are either negative or weakly positive for p53 (original magnifications: 200×).

Table 6. Morphologic Identification of EmGD in Association with Serous EIC and UPSC in Hysterectomy Specimens

Diagnosis	No. of Cases	Serous EIC (%)	Areas of EmGD(%)	Transitions (%)	Benign (%)
Serous EIC	16	16 (100)	12 (75)	6 (37)*	16 (100)
UPSC	32	20 (62.5)	17 (53)	8 (25)†	18 (56)
Total	48		29 (60)	14 (29)	

*Only included transitions from EmGD to serous EIC. †The transitional areas included transitions from serous EIC to UPSC and EmGD to serous EIC. Fifteen (47%) of 32 UPSC cases had areas of both serous EIC and EmGD. Morphologically, direct transitional areas from EmGD to invasive UPSC have never been seen in our series.

uteri containing serous EIC or UPSC, but it is rarely found in uteri containing typical UEC. EmGD is mainly found in postmenopausal women in this study. This is in contrast to endometrial hyperplasia and endometrial intraepithelial neoplasia, which are more commonly associated with and preceding the occurrence of UEC. Identification of EmGD, therefore, strongly suggests that the endometrial tumor is likely to be a serous carcinoma. Although the study is not designed to compare the clinicopathologic features of UPSC and UEC, the findings suggest that EmGD is a precursor lesion of UPSC rather than UEC.

Serous EIC has been proposed as the putative noninvasive precursor lesion of UPSC [7,14]. However, the significant number of serous EIC or stage 1A serous carcinoma presenting concurrently with

extrauterine disease and their high recurrence rates argue against EIC being a noninvasive lesion of UPSC. Wheeler and colleagues [14] reported on 21 serous EIC cases without myometrial invasion. Of these 21 patients, 7 were associated with extrauterine disease. Silva and Jenkins [12] reported on 16 cases with early serous carcinoma involving an endometrial polyp. Although all of them had no or minimal myometrial invasion on histologic examination, 10 had clinical stage I disease at presentation. Of these 10 patients, 6 experienced abdominal recurrences and 4 died of their diseases. Carcangiu et al [13] reported that 2 of the 13 patients with stage IA serous carcinoma died of disease with intraabdominal carcinomatosis at 10 and 14 months, respectively, after their initial complete surgical staging. The high incidence of extrauterine disease and recurrence in "noninvasive" serous carcinoma has also been reported in other studies [5,23]. At the molecular level, a few studies on the early forms

Table 7. Frequency of EmGD in Endometrial Polyp or Nonpolypoid Endometrial Serous EIC in Hysterectomy Specimens

Diagnosis	No. of Cases	Number of EmGD	EmGD (%) in Polyps	EmGD (%) in Nonpolyp	EmGD (%) in Both*	Polyp Numbers w/o Lesions†
Serous EIC	16	12	6 (50)	6 (50)	4 (33)	1
UPSC	32	17	8 (47)	9 (53)	5 (29)	1
Total	48	29	14 (48)	15 (52)	9 (31)	2

*EmGD was present in both endometrial polyp and nonpolypoid areas within the uteri. Endometrial polyp(s) was seen in 7 (44%) of 16 serous EIC and 9 (28%) of 32 UPSC uteri. †Only one endometrial polyp in each category contains no EmGD or serous EIC. The number of EmGD in nonpolypoid endometrium (52%), compared to EmGD in polyps (48%), was not significantly different.

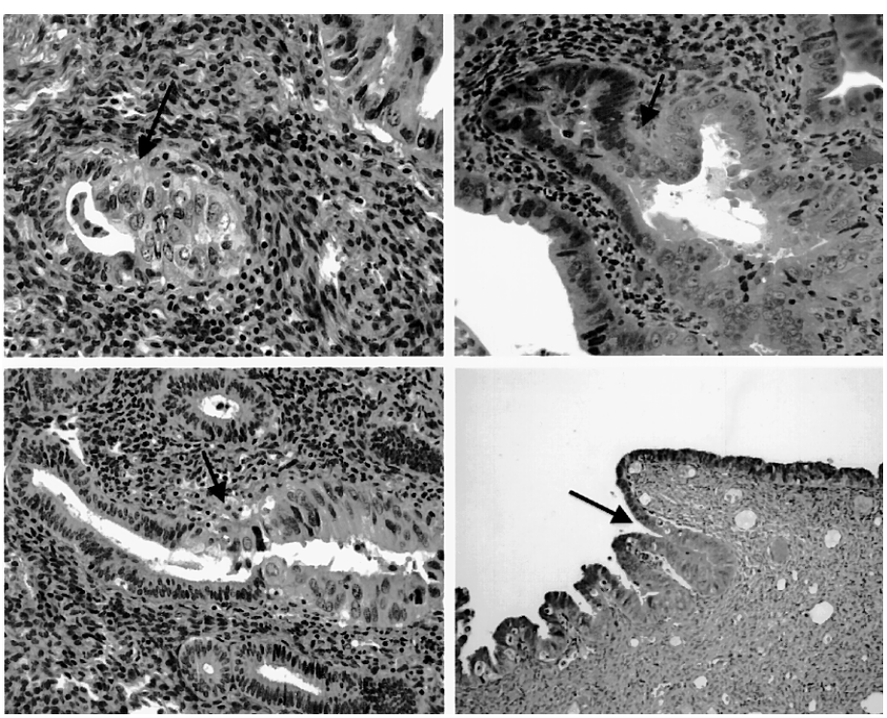

Fig. 9. Examples of morphologic transitions from resting endometrium to EmGD. Cases in the left panel show a single endometrial gland with half being resting endometrium and the other half being EmGD. Cases in the right panel show a dysplastic gland with half hyperchromatic nuclei and the other half with open nuclear chromatin pattern and prominent nucleoli. The transitional areas are indicated with arrows (original magnifications: 200×).

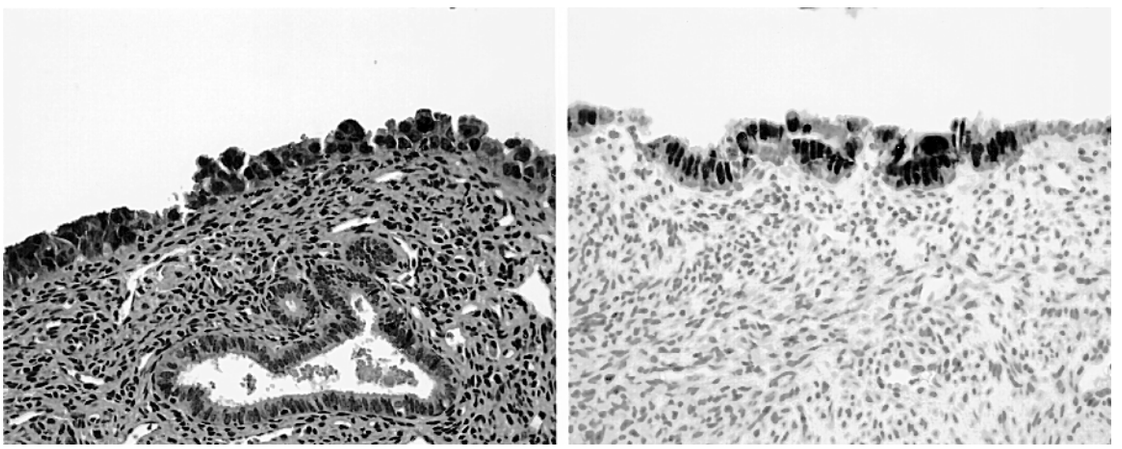

Fig. 10. EmGD on the endometrial surface, H&E and p53 immunostainig (from a hysterectomy specimen with area of UPSC). A focal area of the noncancerous endometrium with stratified atypical cells (left) shows p53 overexpression in cell nuclei (right) with a score of 7. The underlying endometrial stroma and myometrium is negative. The resting endometrial glands on H&E section disappeared on the corresponding IHC staining section (original magnifications: 200×).

of UPSC suggest that extrauterine serous carcinoma represents metastases of serous EIC [22,24]. This is supported by the presence of identical p53 gene mutations in comparing the intrauterine to extrauterine diseases [24,25]. In surgical pathology, serous EIC has been found to have endometrial stromal invasion in the absence of myometrial invasion [9,14]. Clinically, many gynecologic oncologists in the United States treat serous EIC patients with a complete staging surgical procedure (including total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph nodes dissections, omentectomy, peritoneal biopsies, and pelvic washings) in a belief that serous EIC does not behave like a classic intraepithelial carcinoma or *in situ* endometrial cancer. Indeed, there have been numerous reports of widely disseminated UPSC that showed only minimal and focal endometrial stromal or myometrial invasion [3,8,12,13,22,23]. On the basis of the above-stated facts, we propose that serous EIC most likely represents an early form of UPSC instead of a noninvasive precursor lesion.

If we accept serous EIC as an early form of UPSC, we speculate that EmGD may represent the earliest morphologically identifiable intraepithelial precursor lesion in the process of UPSC development. EmGD appears to precede the occurrence of serous EIC. This conclusion is limited by the retrospective nature of this study. However, we believe that EmGD may be a true precursor lesion of serous EIC and, therefore, of UPSC based on the following observations. First, we frequently observed morphologic transitions from EmGD to serous EIC and from serous EIC to UPSC, but no direct transitions were observed between EmGD and UPSC. Second, in the UPSC cases, EmGD is often multifocal and involves sites that are noncontiguous with the main tumor mass. Instead they are intimately associated with serous EIC. Third, in addition to a close association with serous EIC, EmGD is cytologically less atypical than serous EIC, which strongly argues against the notion of pagetoid spreading or intraepithelial invasion from serous EIC or UPSC. Fourth, immunophenotypically, EmGD p53 overexpression scores and MIB-1 cell proliferative indices are mostly less than those of serous EIC but more than those of benign resting endometrium. We are cognizant that unequivocal evidence for EmGD being a precursor lesion of UPSC is lacking. Cases with EmGD alone on biopsy, which precedes and predicts the development of UPSC on follow-up, would provide supporting evidence that EmGD is a true precursor.

It is generally considered that UPSC arises in atrophic endometrium [2,5,11,26]. In our current study we have found that a significant portion (34%) of UPSC cases are associated with proliferative endometrium in addition to 44% in association with atrophic endometrium. The increased number of proliferative endometria in these cases may be related to an increased usage of hormone or estrogen replacement therapy in postmenopausal women. Therefore, UPSC does not always arise in a background of atrophic endometrium. It is more proper to state that UPSC is most commonly associated with resting endometrium, which covers the majority of benign endometria including atrophic, inac-

tive, weakly proliferative, and proliferative endometrium in postmenopausal women. This has a practical value. In other words, nonatrophic endometrium may also be associated with UPSC and UPSC-related lesions such as EmGD and serous EIC.

The diagnosis of EmGD can be difficult because it does not present as a mass. It may be a focal finding in an otherwise unremarkable endometrial polyp. This is particularly true when a biopsy sample is encountered. The recognition of EmGD in an endometrial biopsy or a curettage specimen may aid the pathologist to diagnose serous EIC or to raise concerns for the presence of concurrent UPSC before a hysterectomy. EmGD is usually multifocal when it is found in serous EIC or UPSC uteri. It can be either immediately adjacent to or away from the main lesions of serous EIC or UPSC in those uteri. Presence of serous EIC or UPSC should be considered for any endometrial specimen associated with multifocal EmGD. Attention should be paid in the interpretation of hysterectomy specimens because many benign reactive changes such as papillary syncytial, tubal, and eosinophilic metaplasia are commonly present following an endometrial curetting [27]. It is possible that the lesion we describe may represent a reactive process. In our experience, reparative epithelial glands do not show the architectural patterns of EmGD. They are composed of less atypical cells than those found in EmGD. Caution should be also exercised in the differential diagnosis of serous EIC since they are commonly associated with each other. The most useful characteristic in making this distinction is nuclear atypia. The atypia in serous EIC is marked, identical to those malignant cells in UPSC. The cytologic atypia in the various endometrial metaplasias is almost always minimal and is associated with bleeding or breakdown changes in adjacent endometrium. In contrast, EmGD cellular atypia is in between these 2 ends, which falls short of serous EIC but more than benign endometrium with or without metaplastic changes. In addition, mitotic figures in serous EIC are frequent [6,8,9], mitotic figures are less frequent in EmGD, and are rarely found in endometrial metaplasia. The main morphologic difference is summarized in Table 8. One common mistake for a pathologist is to ignore the presence of EmGD when serous EIC is identified.

Could EmGD be simply a local response to something elaborated by serous EIC and/or UPSC? To answer the question it will be necessary to compare EmGDs to serous EIC, UPSC, and benign resting endometrium in molecular/genetic levels [21]. More importantly, could the lesions of EmGD we identified in the uteri of serous EIC and UPSC just simply represent a mixture of benign endometrium and serous EIC instead of a distinct intermediate lesion? The answer is no. As we stated clearly in the text, the nuclear atypia of EmGD does not reach to the level of malignancy; therefore, they are not qualified as serous EIC. The majority EmGD lesions showed intermediate scores of p53 and MIB-1 immunoreactivities, which are also distinctive from serous EIC. We did observe a few foci of EmGD with

Table 8. Comparisons of Morphologic Features Among RE, EmGD, and Serous EIC

Feature	RE	EmGD	Serous EIC
Cell size	As baseline 1	2-3 fold	4-5 fold
Cell polarity	Maintained	May be lost	Lost
Cytoplasm	Minimum	Less abundant	More abundant
Nuclei			
Enlargement	As baseline 1	1.5-2 fold	2-4 fold
Stratification	Usually not present	May be present	May be present
Hyperchromasia	Mild	Mild to moderate if present	Moderate to severe if present
Chromatin pattern	Dense smooth	Finely to moderately granular	Open with coarse granular
Shape	Oval to low columnar	Oval to elongated	Oval to irregular
Nucleoli	Usually not seen	Identifiable But less prominent	More prominent identical to those in UPSC
Mitosis	Usually not seen	Occasional	Frequent
Apoptosis	Usually not seen	Commonly seen	Obviously present
Glandular pattern			
Surface involve	N/A	Common	Common
Single gland	N/A	Typical	Common
Cluster glands	N/A	May be present	May be present
Cribriform	N/A	Absent	May be present
In polyp	N/A	Common	Common
Background		RE	RE

RE: resting endometrium; N/A: not applicable.

p53 scores of 7 or more, which is similar to serous EIC. But morphologically, these lesions did not have nuclear features of serous EIC. The finding of EmGD with high p53 expression level in some cases may suggest that some EmGD lesions may have similar level of p53 alterations as in serous EIC. Further studies in the molecular level on the alteration of p53 gene will be helpful to clarify this assumption (further discussions, see below). On the other hand, EmGDs do show features of atypia, which exceed the level of the classic form of benign reactive or metaplastic changes. We understand that occasional endometrial metaplasia such as eosinophilic papillary syncytial metaplasia may show a significant degree of nuclear atypia, which may be difficult to be differentiated from EmGD, serous EIC, or even UPSC. We did not include such lesions in this study. We used classic resting endometrium and its associated metaplastic changes as the bottom end of the standard to compare. It is unknown if p53 and MIB-1 staining will distinguish EmGD from resting endometrium with metaplastic changes, particularly those with striking nuclear atypia. Such studies to address these particular questions are needed in future. Furthermore, before we consider EmGD as a potential diagnosis, endometrial hyperplasia or endometrial intraepithelial neoplasia should also be excluded since these lesions are associated with UEC. We did not experience any diagnostic difficulty in this regard, mainly because UEC with its precursors are apparently different from UPSC and its precursor lesions.

In the current study we showed that about half of the EmGD lesions are present in endometrial polyps. The presence of an endometrial polyp in a postmenopausal patient, particularly beyond the sixth decade of life, should prompt a careful search for EmGD and serous EIC. The most important differential diagnosis of concern in this scenario is to exclude metaplastic changes within the polyp. Our study failed to show EmGD preferential involvement of endometrial polyps over nonpolypoid endometrium.

The immunostains of p53 and MIB-1 have previously been reported to be very helpful in distinguishing serous EIC from benign mimicking conditions [6,7,9,22,27]. We have found in this study that p53 and MIB-1 immunostains can also be helpful in the distinction of EmGD from benign resting endometrium and from serous EIC. Serous EICs almost invariably show diffuse strong immunoreactivity of p53 with an overexpression score of 7 or more and are proliferative lesions with high (>50%) MIB-1 indices, which is incompatible with benign resting endometrium. The majority of EmGD display intermediate scores for both p53 (4–6) and MIB-1 (21–50%). Nevertheless, approximately a quarter of EmGD cases showed p53 overexpression scores of 7 or above, which is identical to those of serous EIC lesions. The main difference between EmGD and serous EIC remains in the degree of nuclear atypia. Diffuse strong p53 overexpression in serous EIC or UPSC cases is highly associated with the detection of p53 mutations [28]. The relatively high expression level of p53 in EmGDs may also be suggestive of p53 gene alterations since alteration of p53 is a recognized early event for UPSC development [7,9,16,28,29]. We believe it is feasible to recognize EmGDs correctly when a pathologist uses the above-mentioned morphologic characteristics with the aid of p53 and MIB-1 stainings. However, an entirely negative p53 staining may not completely exclude the possibility of EmGD or serous EIC since occasional endometrial lesions contain p53 mutant proteins that may not be detectable with routine p53 IHC [9,28]. It is currently unknown if a p53 gene mutation is truly present in those EmGD lesions with p53 intermediate scores or more. The molecular analyses including potential p53 gene alterations in EmGD lesions will be presented in the October 2004 issue of this journal [21].

The finding of EmGD may have clinical significance. Serous EIC cases even without apparent myometrial invasion may be associated with extrauterine disease. Although the mechanism of this extrauterine disease association is not clear, it is believed most likely to be metastatic disease [3,8,12,13,22,23]. If this is the case, pathologic identification of EmGD may offer an earlier opportunity to perform a hysterectomy before the development of serous EIC/UPSC. However, before this becomes routine clinical management, prospective studies with a reasonable sample size and pertinent clinical follow-up data are needed to confirm the precursor nature and its malignant potential. These studies will include the proportion of cases of serous EIC/UPSC preceded by EmGD, the proportion of cases of EmGD that progress to serous EIC/UPSC, and the time interval between the appearance of EmGD and serous EIC/UPSC. In etiology perspective, the present study provides the morphologic criteria of EmGD for use in future molecular and clinical follow-up studies, which may help us to understand the pathogenesis of serous EIC/UPSC at the molecular level and ultimately improve the clinical management.

In summary, this study represents the first attempt to establish the entity called EmGD. EmGD morphologically bridges resting endometrium and serous EIC, the latter of which may represent an

early form of UPSC. EmGD is commonly associated with serous EIC and/or UPSC, but not UEC. It occurs mostly in postmenopausal women in this study. Cytologically, the degree of nuclear atypia of EmGD cells fall short of that of serous EIC but more than that of resting endometrium with or without benign reactive changes. Immunophenotypically, EmGD cells mostly show intermediate scores of p53 overexpression and cell proliferation indices (MIB-1). Although the current study provides strong morphologic evidence that EmGD, which may represent an earlier step preceding serous EIC, additional supporting evidence awaits pertinent molecular genetic and clinical correlation studies. Similar morphologic studies by other groups may also be necessary to address the issues of diagnostic reproducibility and sensitivity and specificity of p53 and MIB-1 in the diagnosis of EmGD.

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