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Research Article

Histologic Follow-Up of Endometrial Gland Crowding Shows Progression to Hyperplasia

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Abstract

In order to assess the risk of pre-malignant or malignant lesions in women with gland crowding on endometrial samples when full histologic criteria for endometrial hyperplasia are not met, we evaluated gland crowding incidence and follow-up samples in ambulatory gynecology clinics at Sligo University Hospital. Our results show that up to 20% of women with gland crowding may have a more sinister pre-malignant lesion on 6–12-month follow-up sampling. Identification of gland crowding on pipelle and curettage endometrial samples may help prevent endometrial cancer in these patients.

Keywords: Endometrial Gland Crowding; Benign Endometrial Hyperplasia; Atypical Endometrial Hyperplasia; Endometrial Intraepithelial Neoplasia; Endometrial Carcinoma

Introduction

Premalignant endometrial lesions, such as atypical endometrial hyperplasia or endometrial intraepithelial neoplasia, can be diagnosed using specific criteria to include glands/stroma ratio >1 and nuclear and/or cytoplasmic features that differ between architecturally abnormal glands and normal background glands [1]. However, localized groups of crowded endometrial glands may not fulfill all of the criteria and are interpreted as ambiguous, and may be reported as gland crowding. In order to assess any progression to more sinister lesions, we evaluated the incidence of gland crowding and results of follow-up sampling from ambulatory gynaecology clinic endometrial samples submitted to pathology from the first two quarters of 2024 at Sligo University Hospital.

Endometrial samples submitted to Sligo University Hospital histopathology laboratory in the first two quarters of 2024 were identified by CoPath search. Those with gland crowding or focal gland crowding in the report were flagged for audit. Age, symptoms, hysteroscopy and transvaginal sonography findings, medical record review, histology and follow-up were anonymously tabulated. Patients (n = 310) ranged in age from 29 to 73 years (m = 51) and had symptoms including post-menopausal bleeding, menorrhagia, and metrorrhagia. Twenty-three (7.4%) had glandular crowding. Of 15 cases with follow-up sampling to date (at 6-12 months), one had atypical hyperplasia, two cases had hyperplasia without atypia, one had persistent focal glandular crowding, 10 had no further gland crowding or other lesion and one sample was non-diagnostic with insufficient material.

Methods

Endometrial samples, including pipelles and currettings, submitted to Sligo University Hospital histopathology laboratory in the first two quarters of 2024 were identified by CoPath search. Those with gland crowding or focal gland crowding in the report were flagged for audit. Age, symptoms, hysteroscopy and transvaginal sonography findings, medical record review, histology and follow-up were anonymously tabulated. Hematoxylin and eosin slides were available in each case and reviewed by three consultant histopathologists in each case with 100% consensus agreement.

Results and Discussion

Patients (n = 310) ranged in age from 29 to 73 years (m=51) and had symptoms of post-menopausal bleeding (129), menorrhagia (98), and metrorrhagia (61) with the remaining having no symptoms documented on histology requisition. Twenty-three (7.4%) had focal glandular crowding (Figure 1). Of 15 cases with follow-up sampling to date (at 6-12 months), one had atypical hyperplasia (Figure 2 and 3), two cases had hyperplasia without atypia, one had persistent focal glandular crowding, 10 had no further gland crowding or other lesion and one sample was non-diagnostic with insufficient material.

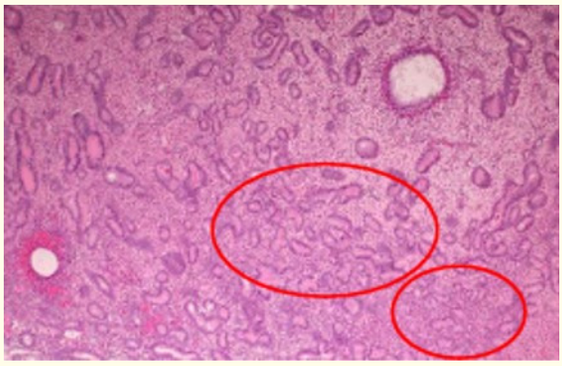

Figure 1: Focal gland crowding, medium power, H & E stain.

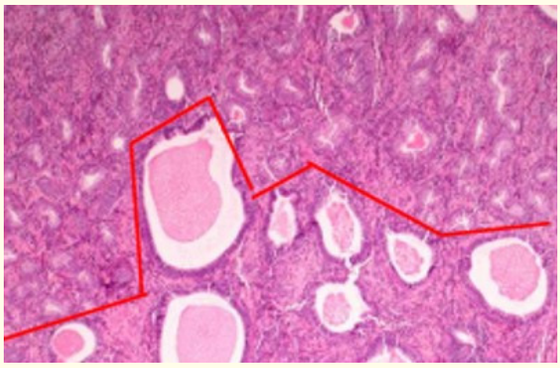

Figure 2: Atypical hyperplasia (above red line, demarcated in appearance from dilated normal glands below red line) medium power, H & E stain.

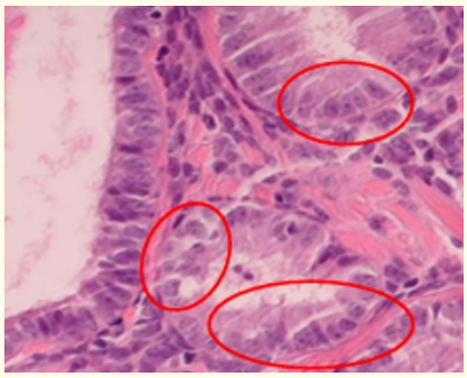

Figure 3: Cytologic atypia, high power, H & E stain.

In order to assess any progression to more sinister lesions, we evaluated the incidence of gland crowding and results of follow-up sampling from the first two quarters of 2024 ambulatory gynaecology clinic endometrial samples at Sligo University Hospital. Repeat follow-up sampling of women with gland crowding on initial endometrial pipelle or curettage may show progression to more definitive premalignant endometrial lesions. Endometrial hyperplasia is the abnormal proliferation of endometrial glands and is a precursor lesion for adenocarcinoma. The largest risk for endometrial hyperplasia is overproduction of oestrogen without the mitigating effects of progesterone [2]. Therapies for treatment of endometrial hyperplasia include introducing artificial progestins through hormone therapy and removing excess oestrogen. This is often done with hysterectomy, but can be achieved in other ways, such as intrauterine devices (IUDs) [3]. There are generally considered to be two types of endometrial hyperplasia: benign and atypical, the latter also known as endometrial intraepithelial neoplasia. Atypia is defined as nuclear and/or cytoplasmic features that differ between architecturally abnormal glands and normal background glands. Endometrial hyperplasia and endometrial intraepithelial neoplasia have a 20-year progression risk of 28% with atypia and 5% without. Although with usual endometrial hyperplasia, the complexity of its glandular architecture can increase the risk of developing endometrial cancer by almost five times [4]. When diagnosing endometrial hyperplasia and endometrial intraepithelial neoplasia, there are criteria that must be met: the area of the glands exceeds that of the stroma, there are atypical nuclear features in the epithelial cells, and the maximum linear dimension is greater than 1 mm [1,5]. However, there are many times when a group of cells meet some but not all of these criteria, which is then referred to as glandular crowding [6].

Previous literature from over 70,000 cases has found an incidence of 0.3% of gland crowding. Of these, follow-up sampling at 6-12 months showed 77% with benign endometrium, 19% with pre-malignant lesions and 4% with carcinoma [6]. It was concluded that even though gland crowding does not effectively classify as endometrial intraepithelial neoplasia or hyperplasia, it represents a significantly increased risk of progression to more sinister lesions. The authors emphasize the need for more frequent/detailed follow-up protocols for ambiguous endometrial lesions [6]. In a similar study including epithelial density (analogous to gland crowding), biopsies or curetting of women enrolled in a gynecologic oncology group clinical trial were analyzed retrospectively [7]. Focusing on histomorphometric parameters of volume percentage epithelium and density, glandular thickness, and nuclear variations (4C rule) to assess high- and low-risk groups, results were compared to hysterectomy samples. The 4C rule showed a sensitivity of 71% for the high-risk group in predicting myo-invasive adenocarcinoma with a specificity of 90% in the low-risk group. Epithelium volume percentage >50% as well as increased nuclear pleomorphism were associated with myometrial invasion.

Koç and Ertürk-Coşkun [8] examined whether features in initial biopsy specimens could predict endometrial intraepithelial neoplasia progression among endometrial polyps with focal gland crowding. Their cohort included 115 polyp cases exhibiting focal gland crowding; 38 underwent follow-up biopsy within one year. Patients divided into two groups: Group 1, 8/38 (21%) progressed to endometrial intraepithelial neoplasia and Group 2, 30/38 (79%) remained benign. Morphology and PAX2 expression were assessed alongside cytologic features, gland size, and secretions. PAX2 loss was significantly more frequent in Group 1 (6/8, 75%) than Group 2 (7/30, 23%); $p = 0.020$. Cytologic atypia was present in 5/8 (62%) vs 4/30 (13%); $p = 0.015$. Focal gland crowding in polyps carries ~21% risk, similar to non-polypoid focal gland crowding. PAX2 immunohistochemistry and cytologic assessment enhance risk stratification.

Although there is no defined standard for endometrial screening, the American College of Obstetricians and Gynaecologists believe that endometrial biopsies should be performed in woman over 45 or woman under 45 who suffer from risk factors like obesity, polycystic ovarian syndrome and persistent abnormal bleeding. On the other hand, the Society of Obstetricians and Gynaecologists of Canada recommend that endometrial biopsies should be considered for women aged 40 or over and those under 40 who have risk factors for endometrial cancer, such as a high body mass index, nulliparity, diabetes, polycystic ovarian syndrome, history of hereditary nonpolyposis colorectal cancer and substantial intermenstrual bleeding. Sabyeying., *et al*. [9] reported that endometrial biopsies specifically for endometrial intraepithelial neoplasia and endometrial carcinoma are sufficient from age 45 and over, or in patients under 45 who suffer from risk factors of diabetes, polycystic ovarian syndrome, nulliparity or an endometrium which is 4mm or thicker. This is due to high sensitivity (94.17%) and specificity

(41.06%) of endometrial biopsies in this age group. Identification and follow-up of gland crowding may improve this sensitivity.

Thongsang., *et al*. [10], in their exploration of the prevalence of occult endometrial carcinoma in patients with endometrial intraepithelial neoplasia who underwent hysterectomy, established pre-hysterectomy risk factors to predict occult endometrial carcinoma. The frequency of patients who develop occult carcinoma after undergoing hysterectomy to treat endometrial intraepithelial neoplasia is 27-53%. Variables associated with occult endometrial carcinoma included endometrial aspiration, body mass greater the 30 kg/m^2 and intraoperative tumour size. Identification and follow-up of gland crowding in patients with these risk factors may improve detection of early pre-malignant lesions before carcinoma develops.

Conclusion

Our results show that up to 20% of women with gland crowding may have a more sinister pre-malignant lesion on 6–12-month follow-up sampling. Identification of gland crowding on pipelle and curettage endometrial samples may further help prevent endometrial cancer in some of these patients. Future work should include larger patient samples and evaluation and follow-up of gland crowding in endometrial polyps.

Bibliography

1. Tavassoli F., *et al.* "Tumours of Breast and Female Genital Organs". WHO Classification of Tumours (2003).

2. Nees L.K., *et al. "*Endometrial hyperplasia as a risk factor of endometrial cancer". *Archives of Gynecology and Obstetrics* 306.2 (2022): 407-421.

3. Mills AM., *et al.* "Endometrial hyperplasia". *Seminars in Diagnostic Pathology* 27.4 (2010): 199-214.

4. Travaglino A., *et al.* "Complexity of glandular architecture should be reconsidered in the classification and management of endometrial hyperplasia". *Apmis* 127.6 (2019):427-434.

5. Allison KH., *et al. "*Diagnosing Endometrial Hyperplasia". *The American Journal of Surgical Pathology* 32.5 (2008): 691-698.

6. Huang EC., *et al.* "Clinical outcome in diagnostically ambiguous foci of 'gland crowding' in the endometrium". *Modern Pathology* 23.11 (2010): 1486-1491.

7. Mutter GL., *et al.* "Biopsy histomorphometry predicts uterine myoinvasion by endometrial carcinoma: a Gynecologic Oncology Group study". *Human Pathology* 39.6 (2008): 866-874.

8. Koç N., *et al.* "Glandular Crowdings in Endometrial Polyps: Clinical Follow-Up and Possible Worrisome Features". *International Journal of Surgical Pathology* 32.6 (2024):1074-1081.

9. Sabyeying P., *et al. "*Age-associated Endometrial Intraepithelial Neoplasia and Endometrial Carcinoma in Patients with Abnormal Uterine Bleeding". *Thai Journal of Obstetrics and Gynaecology* 33.2 (2025): 95-103.

10. Thongsang W., *et al*. "Prevalence of occult endometrial carcinoma in patients with endometrial intraepithelial neoplasia who underwent hysterectomy". *World Journal of Surgical Oncology* 23.1 (2025): 24.