

بنام خداوند جان و

# Atypical endometriosis

Dr Soheila Sarmadi  
Prof of Pathology  
TUMS

# Definition of endometriosis and Localization:

- ▶ Endometriosis is the presence of endometrial glandular and stromal elements at extrauterine sites, including the cervix.
- ▶ Endometriosis is usually seen in the pelvis, including the peritoneum and adnexae, and less commonly in the bowel (particularly in the rectosigmoid colon), ureter, and caesarean section scar.
- ▶ Endometriosis-related tumours almost always arise in the ovary, with the rectovaginal septum being the most common extraovarian site .

- ▶ Endometriosis is an extremely common condition and, in most cases, establishing a histological diagnosis is straightforward, although a variety of benign alterations may result in problems with interpretation.
- ▶ The propensity of endometriosis to undergo neoplastic transformation is well known, and, although it would be wrong to consider endometriosis as a premalignant lesion, given the relatively low incidence of malignant transformation, endometriosis can be considered to be a disease with the potential to develop malignancy.
- ▶ The various neoplasms that arise in endometriosis have been collectively termed endometriosis-associated neoplasms (EANs).

# Atypical endometriosis

## WHO

- ▶ Has been recorded in 1.7-4.4% of endometriotic lesions, almost always in the ovary, and it has been proposed as a potential precursor in the development of endometriosis-related neoplasia.
- ▶ May be associated with, and can be in anatomical continuity with, an endometriosis-related neoplasm.

## Atypical endometriosis

- ▶ Was first described by Czernobilsky and Morris in 1979.
- ▶ Is considered to have premalignant potential.
- ▶ Is characterized by dysplastic features with cellular atypia, and is different from typical endometriosis .
- ▶ Endometriosis-associated tumorigenesis involves pathophysiological progression of endometriosis to atypical endometriosis, followed by formation of a well-defined borderline tumor and development of ovarian malignancy .
- ▶ However, it is difficult to diagnose accurately the atypical endometriosis.
- ▶ In the real world, there are few cases diagnosed as atypical endometriosis, so clinicians do not fully understand the clinical significance of atypical endometriosis.

# Pathogenesis

- ▶ Atypical endometriosis represents a transition from endometriosis to carcinoma that may occur in the process of endometriotic tissue undergoing chronic inflammation and oxidative stress .
- ▶ Several molecular and genetic mechanisms have been demonstrated to support that endometriosis may lead to epithelial ovarian carcinoma.
- ▶ EAO is associated with overexpression of vascular endothelial growth factor (VEGF), and VEGF expression in atypical endometriosis may be associated with the malignant transformation of endometriosis.
- ▶ Somatic mutations such as ARID1A, PTEN, and PIK3CA have been reported in patients displaying atypical endometriosis and development of endometrioid and clear cell carcinomas.



## REVIEW

# Endometriosis-related pathology: a discussion of selected uncommon benign, premalignant and malignant lesions

W Glenn McCluggage 

*Department of Pathology, Belfast Health and Social Care Trust, Belfast, UK*

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- ▶ The concept of so-called 'atypical endometriosis' is a contentious issue, and various authors have used the term for different lesions.
- ▶ A degree of nuclear atypia is a very common finding, involving the epithelial lining of ovarian endometriotic cysts.
- ▶ Usually, the atypia is mild, but on occasions it is quite striking and may be focal, multifocal, or widespread.

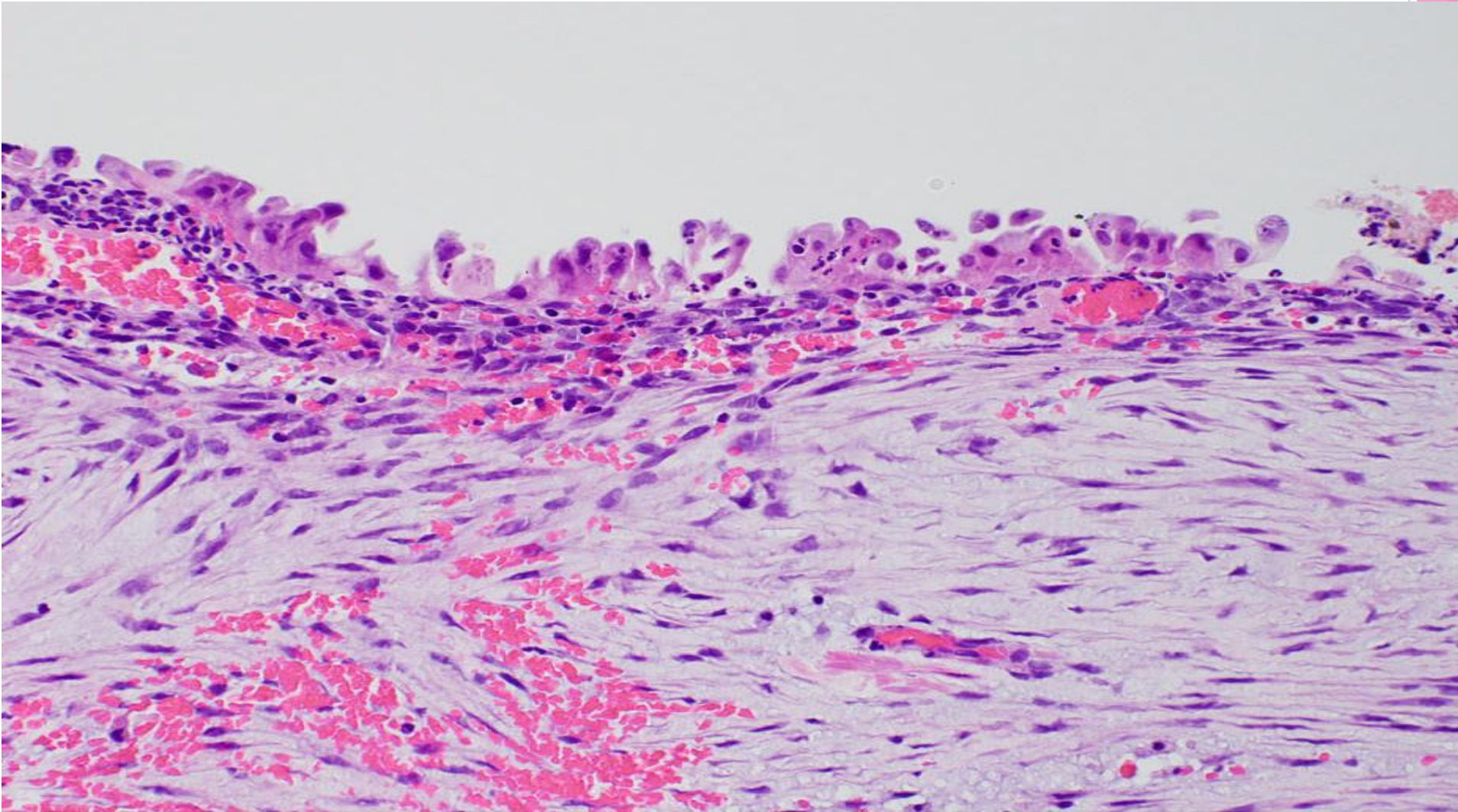
# Histology

- ▶ The atypical cells usually have a hobnail appearance, with enlarged nuclei, prominent nucleoli, smudged chromatin, abundant eosinophilic or clear cytoplasm, and a low nuclear/cytoplasmic ratio, and they are often infiltrated by polymorphs.
- ▶ There is often stratification, with small micropapillary formations.
- ▶ The term 'atypical endometriosis' has been used for such changes in ovarian endometriotic cysts, but I dislike this term, because there is no firm evidence that this is a premalignant change, and the use of this terminology may result in confusion and management problems for clinicians, especially if a cystectomy has been performed.

# Histology

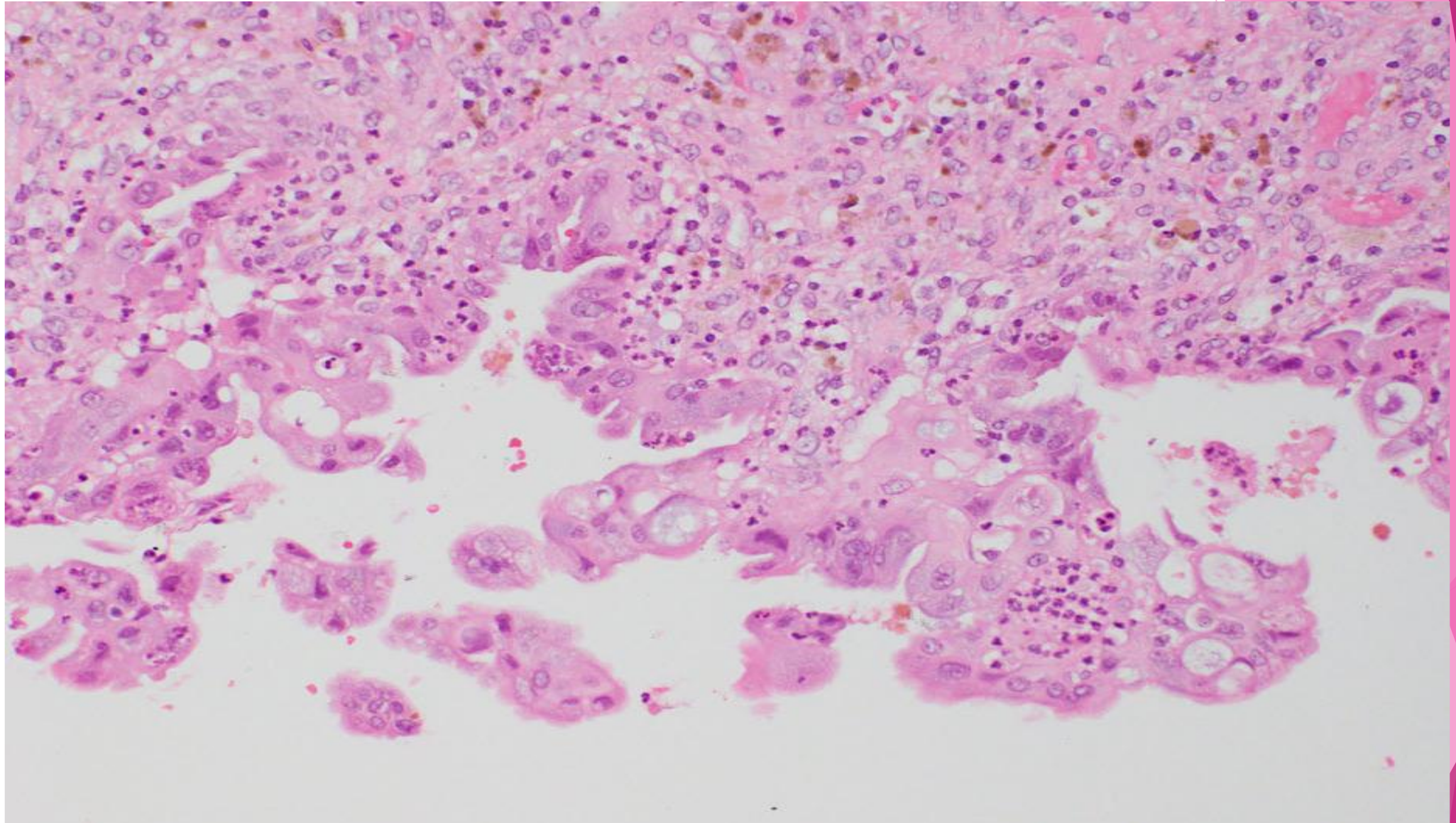
- ▶ This atypia usually occurs in endometriotic cysts, often with abundant fibrosis, inflammation, pigment-laden macrophages, and loss of the endometrioid-type stroma, and it is likely that it is a reactive change secondary to repeated episodes of haemorrhage.
- ▶ When reporting such cases, I describe the nuclear atypia, but do not use the term 'atypical endometriosis' and state that this is a reactive process with no known clinical consequence.
- ▶ Follow-up studies in such cases have, in the main, identified no increased risk of subsequent carcinoma, although it could be argued that surgical removal negates any risk of subsequent development of malignancy.

- ▶ Czernobilsky and Morris describe the term "mild atypism" in endometriosis, which we use synonymously with the term "inflammatory atypia."
- ▶ This is characterized by endometrial-type glands with epithelium that is still one cell layer thick, with minimal nuclear hyperchromatism and pleomorphism and sometimes eosinophilic cytoplasm.
- ▶ All this is in association with marked stromal inflammation.
- ▶ Its reported frequency obviously depends on the diagnostic threshold for this diagnosis. Morris found mild atypia in 22% of their cases of ovarian endometriosis, whereas severe atypia was present in only 3.6% of cases.
- ▶ Morris found that the changes described as moderate atypia are probably reactive to severe local inflammation and/or superficial ulceration with regenerative activity. In most cases, cytologic atypia in endometriotic cysts is likely a reactive or degenerative changes.



The lining epithelium of an endometriotic cyst is composed of cells with significant nuclear atypia and a hobnail appearance. There is a low nuclear/cytoplasmic ratio and there is infiltration by polymorphs





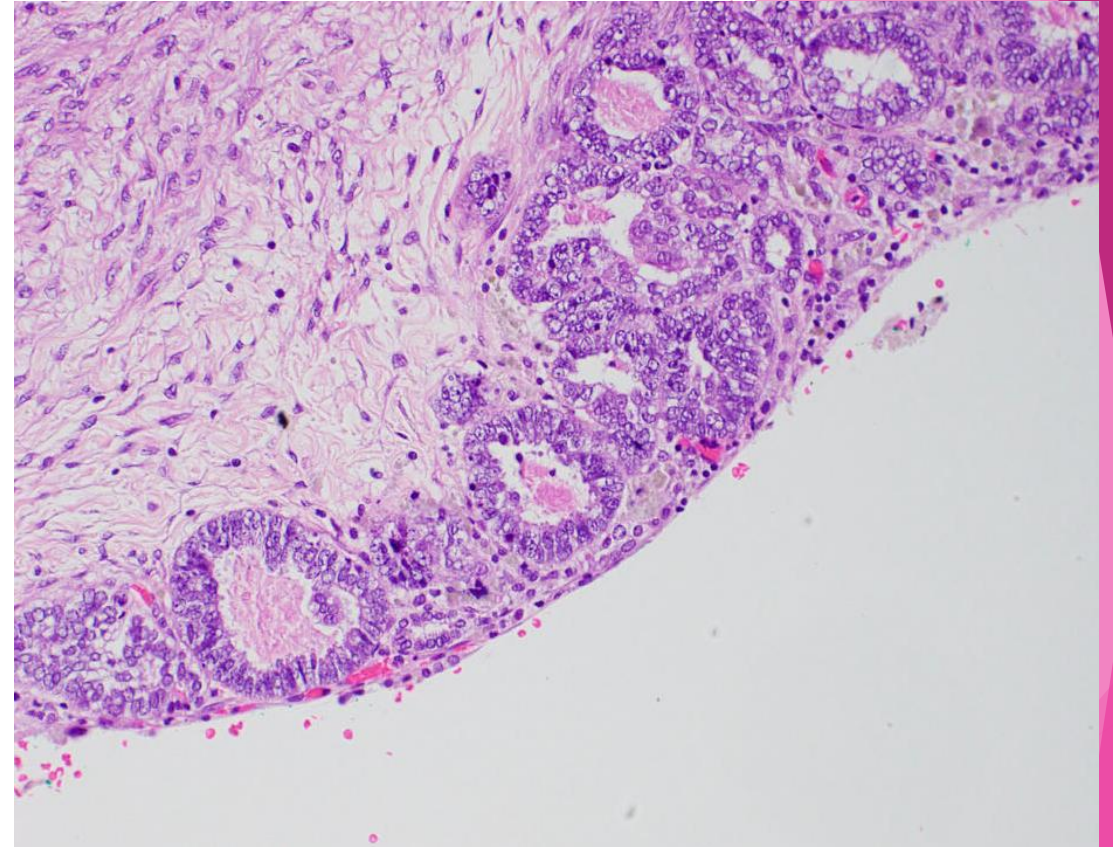
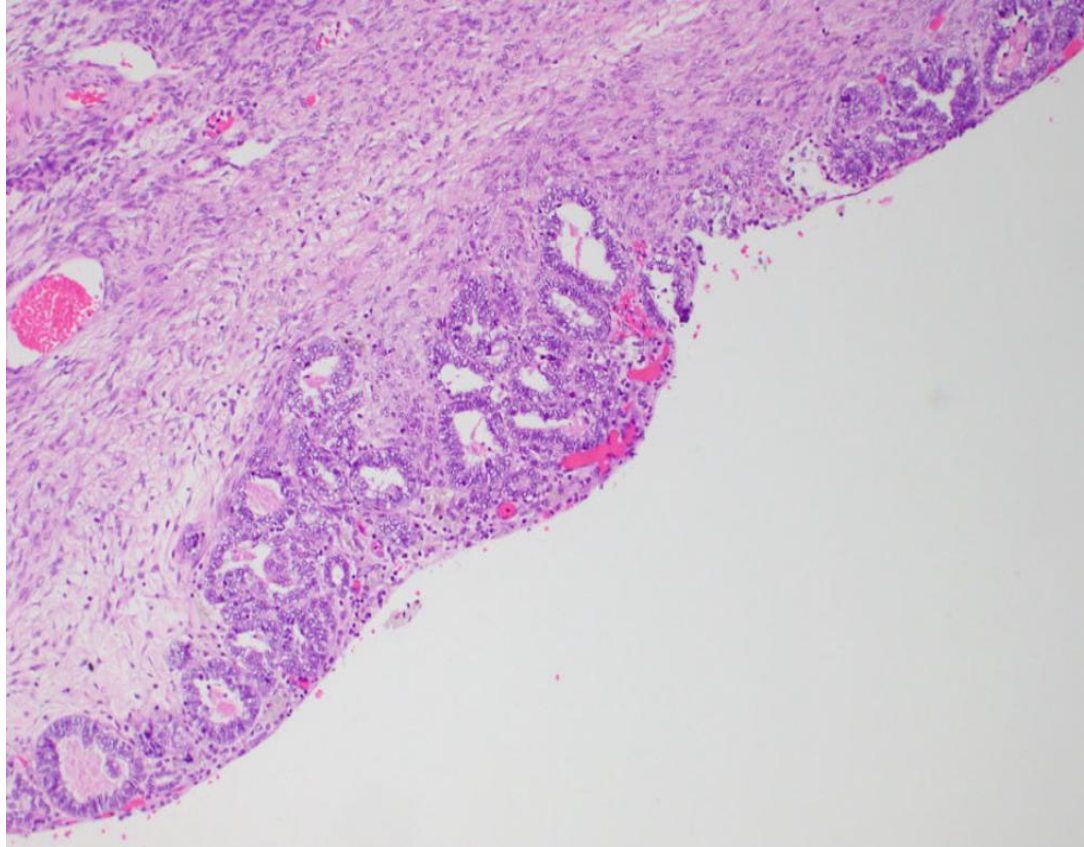
On occasion, the degree of nuclear atypia can be quite striking

# Histology

- ▶ Another much less common but potentially premalignant change in endometriosis is the presence of foci resembling hyperplasia, especially atypical hyperplasia, in the eutopic endometrium. Other authors have used the term 'atypical endometriosis' for such features.
- ▶ When encountering such features, which are uncommon and mostly involve the lining of an endometriotic cyst, I recommend descriptive terminology along the lines 'glandular crowding resembling the features seen in non-atypical (or atypical) endometrial hyperplasia'. When the features resemble atypical hyperplasia, I feel that categorisation as a borderline endometrioid tumour is appropriate.

- ▶ There is limited information in the literature regarding the significance of such lesions, although these features are sometimes seen adjacent to an endometrioid carcinoma; when such features are identified, this should prompt additional sampling to exclude an endometrioid carcinoma.



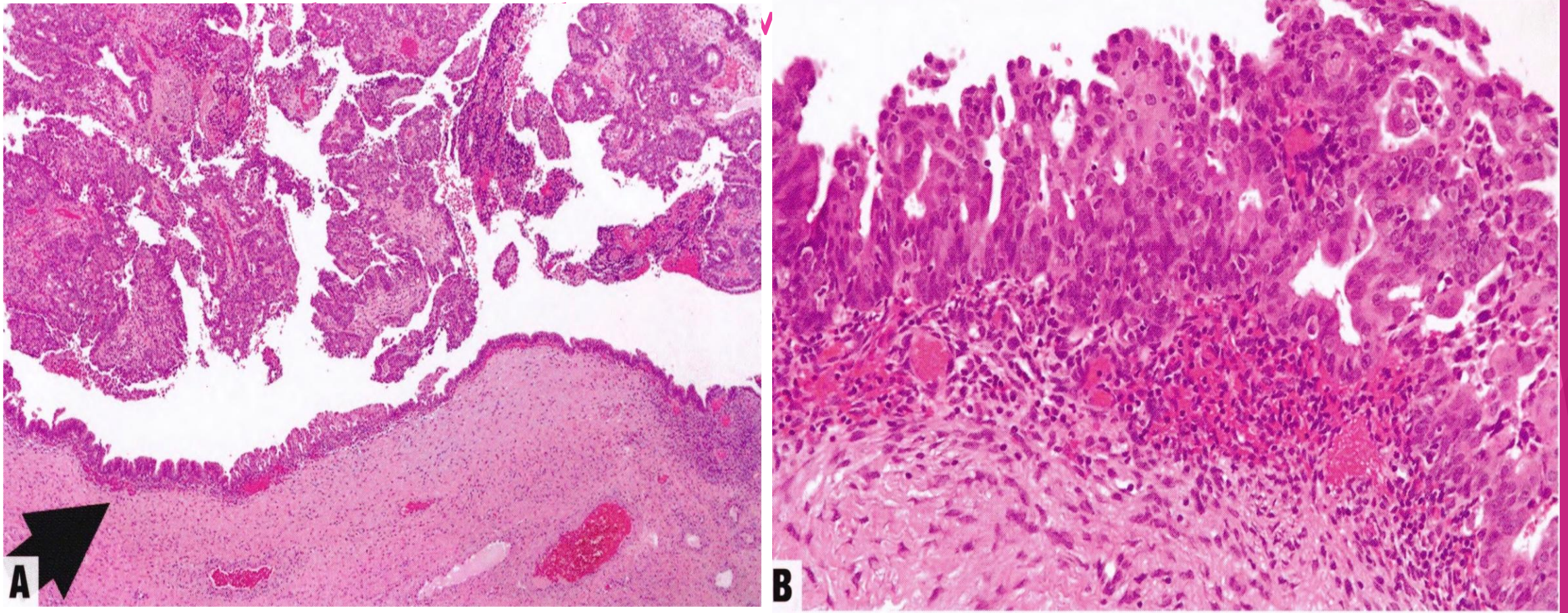


Proliferation involving the lining of an endometriotic cyst, resembling atypical hyperplasia within the endometrium (A).

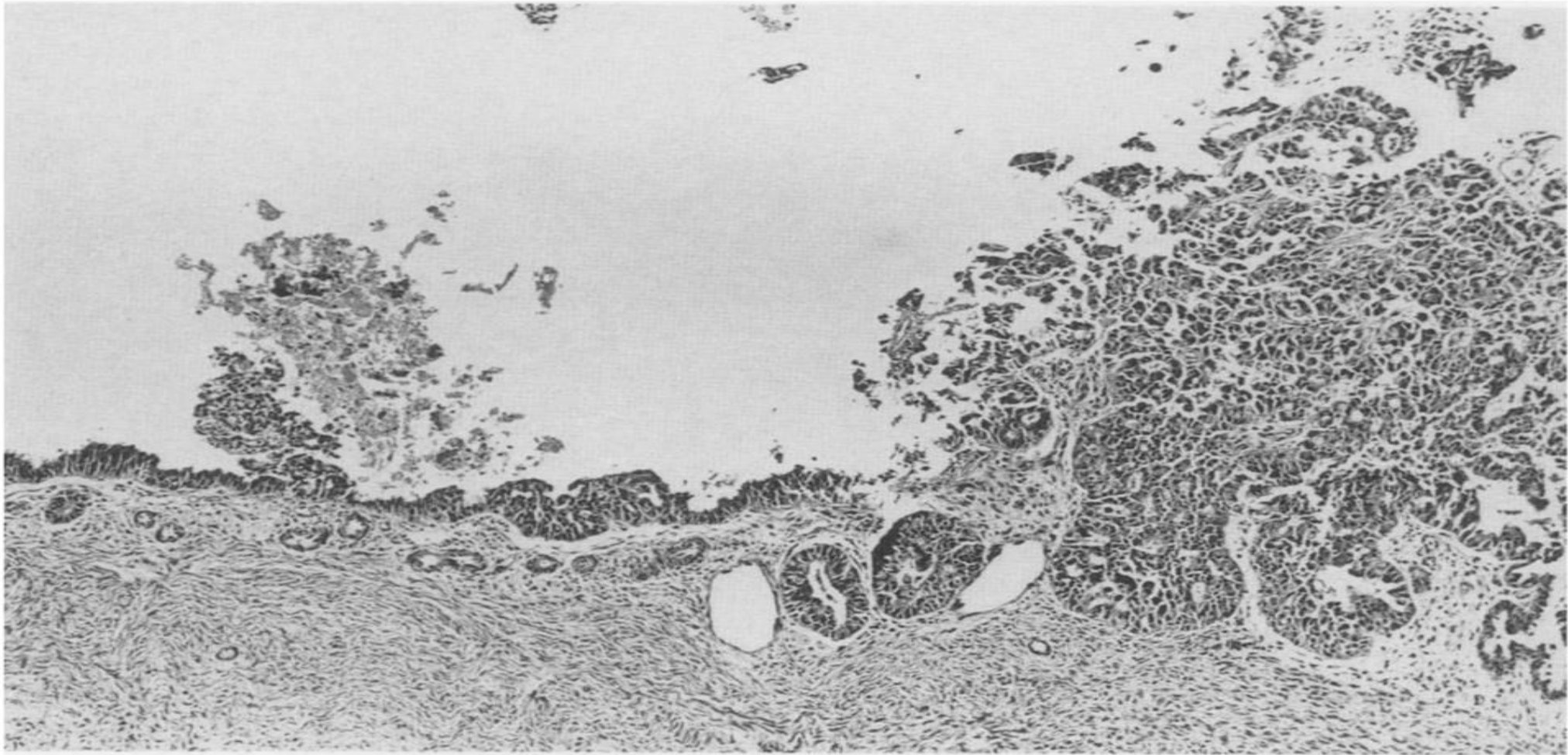
At higher power, there is nuclear rounding and cytological atypia (B).



Ovarian low-grade endometrioid carcinoma within an endometriotic cyst. The cyst lining shows transition from conventional endometriosis (right)







Cyst lining showing atypical endometriosis [left]  
in continuity with endometrioid carcinoma [right].

- ▶ The large size of atypical endometriotic cyst was associated ovarian malignancy.
- ▶ Serum tumor marker levels did not distinguish patients with malignant ovarian tumors associated with atypical endometriosis.
- ▶ The risk of ovarian malignancy in patients with atypical endometriosis was not completely understood because of small sample size.
- ▶ However, atypical endometriosis has been implicated in the development of ovarian malignant tumor—a small number of patients will progress along the continuum from endometriosis to EAOC.