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GYNAECOLOGICAL PATHOLOGY

Endometriosis-associated ovarian neoplasia

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Summary

This article reviews the most relevant pathological and molecular features of ovarian tumours that are associated with endometriosis. Endometriosis is a common condition, affecting 5–15% of all women, and it has been estimated that 0.5–1% of cases are complicated by neoplasia. The most common malignant tumours in this setting are endometrioid adenocarcinoma and clear cell adenocarcinoma, each accounting for approximately 10% of ovarian carcinomas in Western countries. A minority of cases are associated with Lynch syndrome. These carcinomas are often confined to the ovaries at presentation in which case they have relatively favourable outcomes. However, high-stage tumours, particularly clear cell carcinomas, generally have a poor prognosis and this partly reflects relative resistance to current treatment. Histological diagnosis is straightforward in the majority of cases but some variants, for example endometrioid carcinomas with sex cord-like appearances or oxyphil cells, may create diagnostic difficulty. Similarly, clear cell carcinomas can show a range of architectural and cytological patterns that overlap with other tumours, both primary and metastatic, involving the ovaries. Endometriosis-associated borderline tumours are less common, and they often show mixed patterns of differentiation (seromucinous tumours). Atypical endometriosis may represent an intermediate step in neoplastic progression and some of these lesions demonstrate immunohistological and molecular alterations similar to those observed in endometriosis-related tumours. *ARID1A* mutations are relatively common in all of these tumours, but each has additional characteristic molecular alterations which are likely to be of increasing clinical relevance as targeted therapies are developed. Less is known of the pathogenesis of rarer endometriosis-associated ovarian tumours including endometrioid stromal sarcoma, mesodermal (Müllerian) adenosarcoma, and carcinosarcoma. This article also briefly reviews the issue of synchronous endometrioid carcinomas of the endometrium and the ovary, including the most recent developments on pathogenesis.

Key words: Endometriosis; tumour; endometrioid; clear cell; molecular; immunohistochemistry.

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INTRODUCTION

Neoplasia is a rare but significant complication of endometriosis, occurring in approximately 0.5–1% of cases.[1] Endometriosis-associated neoplasms (EANs) usually occur in the ovaries, often arise in younger patients, and encompass a range of tumours most of which are clinically malignant.[2] However, many of these tumours are confined to the ovaries at the time of diagnosis (stage I) and the overall prognosis is favourable. The most common EANs are endometrioid ovarian carcinoma (EOC) and clear cell carcinoma (CCC), each accounting for approximately 10% of all ovarian adenocarcinomas in Western countries.[3] Borderline endometrioid and clear cell tumours are also associated with endometriosis but occur much less commonly. The third major category of EANs are those epithelial neoplasms which demonstrate Müllerian mucinous (endocervical-like) or mixed differentiation, also known as Müllerian mucinous/mixed epithelial (MM/ME) or seromucinous tumours.[4] EANs demonstrate distinctive and partly overlapping molecular alterations which may lead to the development of specific targeted therapies for high-stage and recurrent tumours. Synchronous endometrioid neoplasms involving the ovary and endometrium as well as extrauterine endometrial (endometrioid) stromal neoplasms, mesodermal (Müllerian) adenosarcomas and carcinosarcomas may also be associated with endometriosis. Although not discussed further here, it should be noted that these tumours also rarely arise in extraovarian sites such as the pelvic peritoneum or bowel wall, often in association with endometriosis.

ENDOMETRIOSIS

Endometriosis affects 5–15% of women in the reproductive age range and is defined by the presence of endometrial-like tissue (epithelial and/or stromal elements) outside the uterine corpus.[5,6] The most commonly affected sites are the peritoneum and the pelvic organs, particularly the ovaries. While the pathogenesis of endometriosis remains disputed, and is probably multifactorial, the likeliest mechanism in most cases is transtubal dissemination of endometrial tissue into the peritoneal cavity with subsequent implantation and growth in susceptible women.[6] In support of this mechanism is the finding that the eutopic endometrium of patients with endometriosis shows functional alterations such as altered cell cycle regulation and an increased capacity to implant and induce angiogenesis.[7–9] It is noteworthy that some endometriotic lesions, particularly those involving the ovary,

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appear to be monoclonal, a feature usually considered a hallmark of neoplasia.[10,11] Moreover, a proportion of endometriotic lesions demonstrate immunophenotypic and/or molecular alterations that also characterise EANs, and these are found more commonly when endometriosis is associated with an ovarian tumour.[2,12] However, it has been shown recently that deep infiltrating endometriosis (typically extra-ovarian), which is rarely associated with the development of EANs, also demonstrates cancer-associated somatic mutations in a significant proportion of cases.[13]

The morphological features of endometriosis are well-documented and most cases present no diagnostic difficulty. However, histological variants such as those in which the epithelial and/or stromal components demonstrate metaplastic or reactive changes may be more challenging, and endometriotic lesions that mainly or entirely comprise stromal elements are probably under-recognised.[14] As with the eutopic endometrium, the appearances of endometriosis can be significantly influenced by treatment including hormonal therapy. One variant, polypoid endometriosis, is worthy of specific comment since this may be misinterpreted clinically and histologically as a true neoplasm.[15] Some such cases reflect microanatomical location of endometriosis close to a mucosal surface or cyst lining since this facilitates a polypoid growth but other cases more closely resemble polyps developing in the endometrium (Fig. 1).[16]

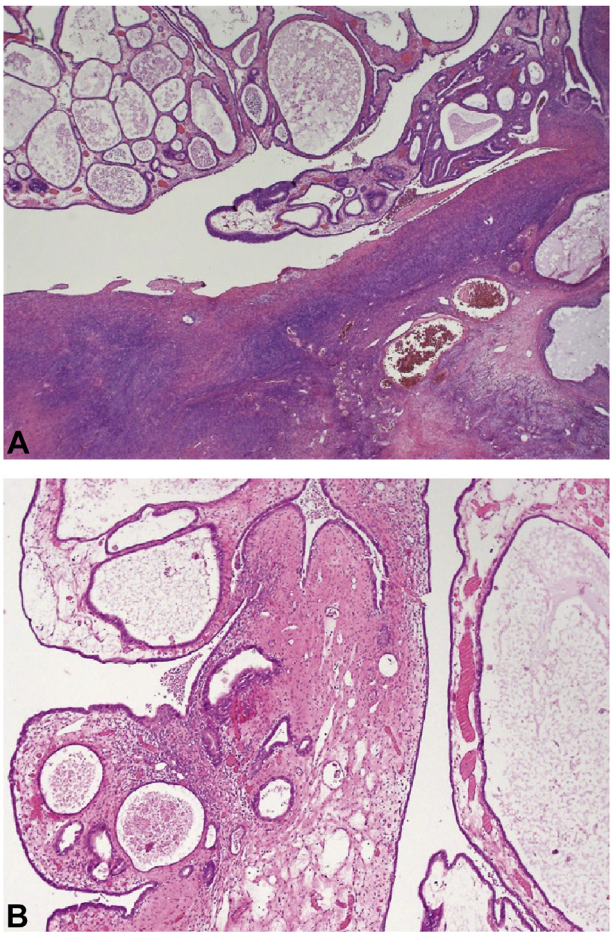

Fig. 1 (A) Polypoid endometriosis (upper) projecting from the ovarian capsular surface. (B) Variably sized and focally cystic glands are separated by oedematous fibrous stroma resembling that of an endometrial polyp.

A further important variant is atypical endometriosis. This term has been applied to two processes, both of which occur most frequently in the ovary.[17–19] The first corresponds to architecturally complex and cytologically atypical proliferative lesions that resemble atypical hyperplasia/intraepithelial neoplasia arising in the endometrium. These lesions sometimes coexist with EOC, further emphasising a neoplastic continuum analogous to that observed in the endometrium. Second, and more common, are alterations in the lining epithelium of endometriotic cysts characterised by varying degrees of cellular stratification and disorganisation, inflammation and cytological atypia, often accompanied by 'metaplastic' alterations (ciliated, eosinophilic, hobnail, squamous and/or clear cell) (Fig. 2).[20] It is often less clear whether such changes are reactive or degenerative in nature, or whether they represent a step in the neoplastic progression of endometriosis towards an EAN. While most lesions are clinically benign, possibly representing analogous changes to those sometimes observed in the endometrium,[21] some demonstrate similar molecular alterations to those seen in EANs,[22] and there may be anatomical continuity between atypical endometriosis and an ovarian neoplasm, usually EOC or CCC (Fig. 3). Some EANs include cystic elements where the lining epithelium is cytologically malignant and in such cases it can be difficult to determine whether this represents cystic change within an overtly malignant tumour or '*in situ*' carcinoma developing within an endometriotic cyst. From a pathogenetic perspective, it has been proposed that the combination of an inflammatory milieu, hyper-oestrogenic state and high iron levels may potentiate carcinogenesis within endometriotic cysts.[1,12]

ENDOMETRIOSIS-ASSOCIATED OVARIAN NEOPLASIA

Endometrioid adenocarcinoma

EOC arises most commonly in the perimenopausal or postmenopausal age group, in the fifth and sixth decades of life, with a mean age of 56 years.[23] It has been suggested that a high proportion of EOCs arise from endometriotic cysts, since ipsilateral ovarian and pelvic endometriosis is seen in up to 42% of these patients.[24] EOC is associated in 15–20% of cases with endometrioid carcinoma of the endometrium.[25] The pathogenesis of this association and the possibility that some ovarian tumours represent metastasis of the uterine neoplasms is discussed below. Patients with tumours associated with endometriosis are 5–10 years younger on average than those not associated with endometriosis. EOC may be asymptomatic, or present as a pelvic mass, with or without pain, but presentation is typically non-specific. Serum CA 125 is elevated in over 75% of patients, and some have endocrine-related symptoms/signs secondary to steroid hormone production by peritumoural or intratumoural luteinised ovarian stroma. Like other EANs, most EOCs are low-stage at the time of diagnosis, being confined to the ovary and adjacent pelvic structures. Approximately 20% of tumours are bilateral.

Grossly, EOC are typically large with mean size of 15–20 cm. The external surface is usually smooth while the cut surface usually shows friable solid soft masses associated with haemorrhage (Fig. 4). Cystic areas may be seen, and may be filled with mucoid material. Remnants of an endometriotic cyst may be identified at the periphery of the mass. Occasionally, the tumour presents as a mural nodule in the

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