Endometriosis-related ovarian neoplasms: pathogenesis and histopathologic features

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Abstract

A variety of neoplasms have been described to arise in association with ovarian endometriosis, characterized by younger age, earlier detection at lower stages, and better survival. The molecular pathogenesis of these tumours has become a focus of recent studies. Representative endometriosis-associated neoplasms include endometrioid carcinoma, clear cell carcinoma, seromucinous borderline tumour (endocervical-like mucinous borderline tumour; Müllerian mucinous borderline tumour), squamous cell carcinoma, Müllerian adenosarcoma, and endometrioid stromal sarcoma. Inflammation, oxidative stress by reactive oxygen species, and hyperestronism are implicated in the carcinogenesis of these tumours. A subset of endometriosis are monoclonal in nature and atypical endometriosis is considered to be a source of clear cell and endometrioid carcinomas through a variety of genetic alterations, including somatic mutations of *PTEN*, *PIK3CA*, or *ARID1A*. It is crucial to understand the clinicopathologic features and genetic background of endometriosis-related neoplasms in order to establish strategies for early detection and molecular-targeted therapy.

Keywords endometriosis; histopathology; neoplasm; ovary

Introduction

A variety of neoplastic conditions associated with ovarian endometriosis have been the focus of investigation, and their molecular pathogenesis, as well as their histopathologic diversity and clinicopathologic characteristics, have been recently revealed. It is critical to understand endometriosis-associated neoplasms to establish a strategy for early detection, precise diagnosis, and, more importantly, molecular-targeted therapy. In this review article, recent information on this particular condition is reviewed and summarized.

Terminology and definition

In 1925, Sampson first described the malignant transformation of ovarian endometriosis.[1] Judging from the microphotographs in the original paper, the tumour appears to be an endometrioid carcinoma. Thereafter, this phenomenon has been widely recognized and the occurrence of clear cell carcinoma was added as endometriosis-associated malignancy. The terms endometriosis-associated ovarian cancer (EAOC) and endometriosis-associated adenocarcinoma (EAC) have both been used to describe this particular condition. We now know that seromucinous borderline tumour, squamous cell carcinoma, carcinosarcoma, adenosarcoma, and endometrioid stromal sarcoma are also related to ovarian endometriosis, and thus the term endometriosis-related neoplasm (ERON), proposed by Shih et al., appears to be a more appropriate term.[2]

ERON is defined as a neoplastic condition arising from endometriosis through clonal expansion of its constituents, including epithelial or stromal components. Therefore, strictly by definition, it should be continuous with pre-existing endometriosis. However, in reality, it is not uncommon to fail to demonstrate a relationship either because of the replacement of endometriotic tissue by progressing neoplastic processes, or by the vagaries of sampling. Endometriosis is relatively common and it can be incidentally found to co-exist with ovarian neoplasms. Therefore, each case should be carefully evaluated by combining gross and microscopic findings, clinical features, and relationships with endometriosis to make a diagnosis of ERON. Based on the criteria by Sampson[1] and Scott,[3] neoplastic transformation of endometriosis is defined as follows: 1) adjacent to unequivocal foci of endometriosis; 2) absence of any other primary tumour; 3) microscopic features are within a spectrum of well-recognized neoplasms originating from endometriosis; and 4) a transition from neoplastic epithelium (or stromal component) to endometriosis. Based on this definition, for example, high-grade serous carcinoma of the ovary harbouring foci of endometriosis is regarded to be independent of endometriosis since this particular tumour is now well known to arise de novo from surface epithelium or tubal epithelium. Conversely, seromucinous borderline tumour is considered to represent ERON even though there may be no direct transition to endometriosis in a case with endometriotic cysts in the ipsilateral or contralateral ovary.

Clinicopathologic features of ERON

From a clinical point of view, ERON is characterized by: 1) occurrence at a younger age; 2) diagnosis established at an earlier stage; 3) low-grade; and 4) better overall survival. Recently malignant epithelial tumours of the ovary have been divided into two categories: type I and type II tumours.[4] Type II tumours are considered to arise de novo through malignant transformation of pre-existing benign epithelium, and include high-grade serous carcinoma, high-grade endometrioid carcinoma, undifferentiated carcinoma, and carcinosarcoma. In contrast, type I tumours arise through multistep carcinogenesis, as represented by low-grade serous carcinoma, mucinous carcinoma, low-grade endometrioid carcinoma, and clear cell carcinoma. The former two types are commonly associated with serous borderline tumours (SBT) and mucinous borderline tumours (MBT), respectively, and the latter two are considered to be derived from atypical endometriosis. The malignant form of ERON are all type I, and therefore early detection is feasible by following-up of patients with endometriotic cysts of the ovary. The risk of neoplastic transformation of endometriosis has been estimated to range from 0.5% to 1.0%. For instance, a cohort study of 6398 women with clinically defined ovarian endometriosis demonstrated that 0.72% of patients developed ovarian cancers.[5] In this study, patient age exceeding 50 was a risk factors of coexisting cancer and endometriosis.[5]

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Endometriosis as a source of tumourigenesis

Atypical endometriosis has been described as a source of neoplastic transformation of endometriosis, but the definition varies, particularly among earlier studies. The term is typically used in two different settings: 1) endometriosis with surface epithelium showing a degree of cytologic atypia (type-A; Figure 1); 2) glandular proliferation showing closely packed atypical glands similar to endometrial hyperplasia of the uterine corpus (type-B; Figure 2). At least a subset of the former might represent reparative change associated with inflammation, and thus might have been over-estimated. Fukunaga et al., reported that type-A atypical endometriosis was identified in 1.7% and 61% of 255 cases of ovarian endometriosis and 54 endometriosis-associated ovarian cancers, respectively.[6] Prefumo et al., investigated the incidence of atypical endometriosis based on the two above mentioned criteria in 14 cases of endometriosis-associated adenocarcinoma, and showed that type-A and type-B lesions were identified in 100% and 50% of cases, respectively, whereas these lesions were only found in 2% (7/325) and 1% (3/325) among usual endometriotic cysts without any atypia.[7] This result indicates that atypical endometriosis recognized by both definitions indicates a risk for developing malignant transformation.

Aetiology and pathogenesis of ERON

The combined implications of inflammation, oxidative stress caused by haem and free iron, and hyperestronism have been identified in the tumourigenesis of ERON.[8]

Within endometriotic cysts, inflammation provoked by recurrent haemorrhage induces angiogenesis, cell proliferation through a cytokine cascade and production of reactive oxygen species. Additionally, apoptosis is inhibited, and therefore the microenvironment potentiates tumour invasion and metastasis, contributing to both the occurrence and progression of neoplastic processes. Accumulated data indicate that free iron content and stress-related factors, including lactose dehydrogenase, lipid peroxidase, and 8-hydoroxy-2-deoxyguanosine, are increased in endometriotic cysts. In fact, the content of endometriotic cysts induces reactive oxygen species and damages DNA, resulting in carcinogenesis. There is some evidence that hyperestronism also contributes to the progression and tumourigenesis of endometriosis. For instance, increased aromatase activity and inhibited inactivation of oestradiol result in increased oestradiol levels inside endometriosis, which induces production of cyclo-oxygenase (COX)-2 and prostaglandin E2, and thus contribute to tumour progression. Recent studies suggest that G-protein-coupled estrogen receptor (GPER), a transmembrane oestrogen receptor expressed on epithelial and stromal cells, is overexpressed in endometrioid carcinoma, and correlate with matrix metalloproteinase (MMP) 9 expression, and tumour diameter, stage, and node status.[9]

A subset of endometriosis shows neoplastic characteristics. In 1995, Nilbert et al., demonstrated, by X-chromosome inactivation, monoclonality in three of five cases of endometriosis. This result was confirmed by subsequent studies.[10] Approximately 60%−100% of endometriosis display monoclonality, and they also show genetic instability and alterations in tumour suppressor genes, including *PTEN*, TP53, and *ARID1A*.[8] One study demonstrated that ovarian cancer and neighbouring endometriosis share common genetic alterations, including *PTEN* mutations. Two mouse models were established to implicate oncogenes in tumourigenesis associated with endometriosis. In 2005, Dinulescu et al., employed Cre-*loxP* site-specific recombination techniques to induce pelvic endometriosis by activating *KRAS* of ovarian surface epithelium, and demonstrated that inactivation of *PTEN* induced endometrioid carcinoma.[11] On the other hand, Wu et al., using similar techniques, reported that inactivation of *APC* induces endometrioid carcinoma.[12] These results indicate that PI3K/PTEN and WNT/β-catenin pathways are implicated in the carcinogenesis of endometriosis-associated endometrioid carcinoma.

Pathologic features of ERON

A variety of neoplasms arise in association with endometriotic cysts. Heaps et al., reported that endometrioid carcinoma, clear cell carcinoma, and sarcoma represent 69%, 13%, and 12% of ERON, respectively.[13] Notably, in Japan, clear cell carcinoma, which accounts for only approximately 6% of all malignant epithelial-stromal ovarian tumours, is more common, accounting for 20% to 25 % of malignancies arising in endometriotic cysts. Kobayashi et al., reported a high-incidence of clear cell carcinoma in cases of ERON; up to 39%. It should be noted that the incidence of seromucinous borderline tumours has been underestimated, since it can be misdiagnosed as serous borderline tumour or clear cell carcinoma.

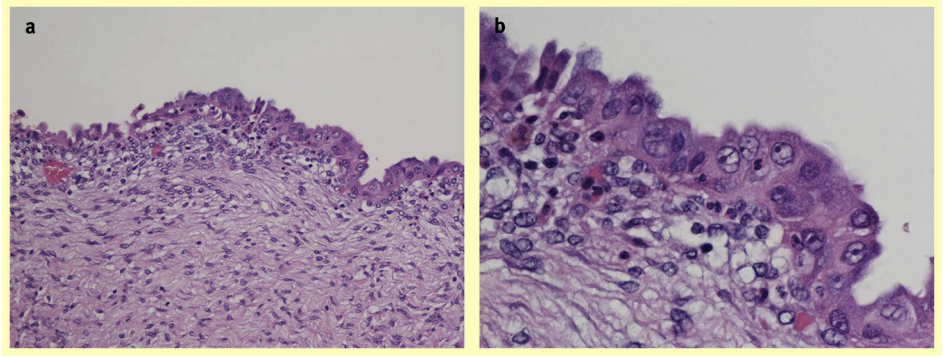

Figure 1 Atypical endometriosis (type-A). The surface epithelium lining endometrial tissue shows nuclear enlargement, heterogeneity in nuclear size and shape, and overlapping.