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REVIEW ARTICLE

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Ovarian cancer in endometriosis: molecular biology, pathology, and clinical management

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Abstract Recent molecular and pathological evidence suggests that endometriosis is a monoclonal, neoplastic disease. Moreover, endometriosis serves as a precursor of ovarian cancer (endometriosis-associated ovarian cancer; EAOC), especially of the endometrioid and clear cell subtypes. Although a variety of molecular events, such as *p53* alteration, *PTEN* silencing, K-*ras* mutations, and HNF-1 activation, have been identified in EAOC, its precise carcinogenic mechanism remains poorly understood. Our recent data indicate that microenvironmental factors, including oxidative stress and inflammation, play an important role in the carcinogenesis and phenotype of EAOC. The management of endometriosis from the standpoint of EAOC is not standardized yet. To this end, clarification of the precise natural course and the risk factors that contribute to malignant transformation remain important goals. Among the phenotypes of EAOC, clear cell carcinoma, seems to require a specific treatment strategy, including molecular targeting.

Key words Ovarian cancer · Endometriosis · Pathogenesis · Oxidative stress · Microarray

Introduction

One of the mysterious aspects of ovarian cancer biology is its primary site of origin, because the ovary lacks the glandular epithelia that serve as a direct precursor of the cancer. The most widely accepted candidate for the origin of ovarian cancer is the so-called ovarian surface epithelium (OSE), a single layer of flattened cells covering the ovarian surface. Pathological findings have shown that OSE can be endowed with epithelial characteristics.[1,2] Moreover, we and others have demonstrated that cultured primary OSE can be transformed into carcinoma by transduction with several oncogenes, such as *SV40LT*, activated *Ras*, or *HER2*, indicating that OSE is a potential origin of ovarian cancer.[3,4] Nevertheless, OSE is not the only origin of ovarian cancer. Recent clinical and pathological evidence suggests that endometriosis represents an important site of origin of ovarian cancer (Fig. 1). Unlike typical ovarian cancers, those that arise from endometriosis have discrete features: they are more commonly constituted by clear cell and endometrioid subtypes, they tend to be found in earlier stages, and they have a favorable prognosis.[5,6] Due to these unique characteristics, ovarian cancers derived from the malignant transformation of endometriosis have been specifically referred to as endometriosis-associated ovarian cancer (EAOC).[7,8]

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Endometriosis as a neoplasm

Endometriosis is currently classified as a tumor-like lesion under both the WHO and Japanese ovarian tumor classification schemes.[9,10] However, a number of recent studies suggest that endometriosis is actually a clonal lesion. Clonality analysis using X chromosome-linked polymorphism has revealed that most of the epithelial cells in endometriotic cysts are monoclonal.[11–13] Later, more precise analyses using laser microdissected tissue were performed by two independent groups, one of which again confirmed monoclonality.[14] The other group, using extraovarian endometriotic lesions, showed that only a minority of the foci were monoclonal.[15] These findings suggest that at least the epithelial cells in the endometrial cyst appear to be monoclonal, while the small endometriotic foci might depend on polyclonal growth. In addition to these clonal analyses, many studies have demonstrated that there are various genetic abnormalities in endometriotic cells that also account for the neoplastic nature of this disease. Studies of endometriosis or endometriosis-derived cells using fluorescence in-situ hybridization, comparative genomic hybridiza-

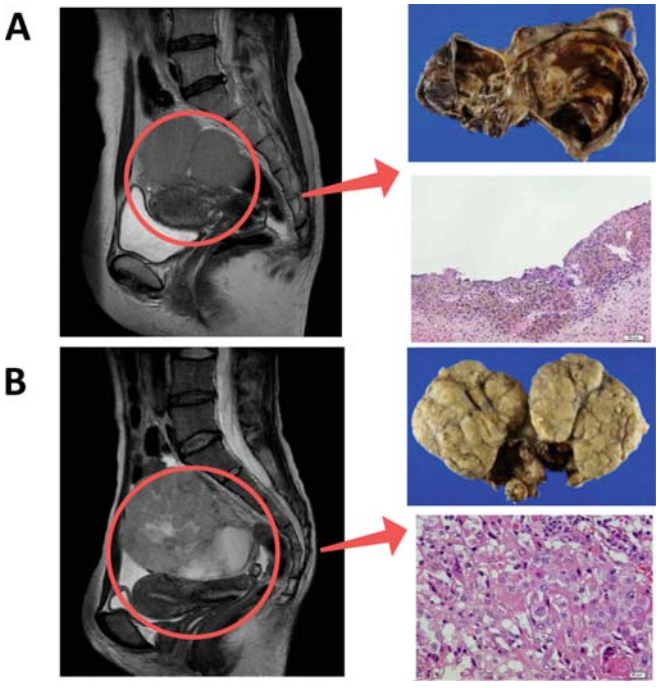

Fig. 1A,B. Typical cases of **A** endometriosis and **B** endometriosis-associated ovarian cancer (EAOC; clear cell carcinoma) (H&E)

tion, or microsatellite analysis have revealed genomic abnormalities, such as loss of heterozygosity (LOH) of chromosomes 1p, 9p, 11q, 17p, and 22q, and amplification of 17q,[16–19] again indicating the clonal evolution of this disease. Sato et al.[20] reported somatic mutation of *PTEN* in solitary endometriosis. Thus, it is becoming widely accepted that endometriosis, especially ovarian endometriotic cyst, is a neoplastic disease and, consequently, may have premalignant potential.

Pathological and molecular evidence that ovarian cancer arises from endometriosis

In 1925, Sampson[21] first suggested the relationship between endometriosis and ovarian cancer and proposed criteria for cancer arising from endometriosis. Later, Scott[22] refined the criteria to more stringent ones, which require the morphological demonstration of benign endometriosis contiguous with the malignant tissue. A small subset of ovarian cancers fulfill these more stringent criteria, providing pathological evidence that ovarian cancer may occur as a result of malignant transformation of endometriosis. Atypical endometriosis, which is a putative precursor of ovarian cancer, is occasionally observed in these transitional areas[23] (refer to the next section).

Several groups have performed allelotyping of endometriosis along with adjacent ovarian carcinoma and found common genetic alterations in most of the cases.[20,24,25] This provides molecular evidence that endometriosis that appears benign already harbors genetic defects and that ovarian cancer may arise from this lesion. In these studies, genetic alterations were detected only in carcinoma, and not in benign epithelium, suggesting a stepwise accumulation of genetic events in the carcinogenic process.

Atypical endometriosis in malignant transformation of endometriosis

Epithelium in endometriosis occasionally shows metaplastic changes, such as ciliated, eosinophilic, hobnail, squamous, and mucinous metaplasia.[26] Though the frequency of these changes differs according to the observer,[27,28] they seem to be commonly encountered under careful observation. Although metaplastic epithelia sometimes share morphological features with specific carcinoma, the biological significance of this metaplasia in tumor development is unclear.

However, once the altered epithelium shows "atypia", it could be implicated in the malignant transformation of endometriosis. It should be noted that the term "atypical" has been used with different meanings among pathologists. Generally, this term refers to two pathological features; namely, cytological atypia and hyperplasia (without atypia).[26] Czernobilsky and Morris[29] reviewed 194 cases of ovarian endometriosis and found severe cytological atypia in only 3.6%, while mild atypia was found in 22% of the cases. On the other hand, in their series, 2.0% showed adenomatous hyperplasia.[29] LaGrenade and Silverberg[30] first described a pathological continuation of atypical endometriosis to carcinoma lesion in 7 cases of EAOC.

Cytological atypia is almost always found in the epithelial lining of endometriotic cysts as a focal or multifocal lesion.[26] In some cases, one can observe hobnail-type cells.[29] Cytological atypia in endometriotic cysts may be a reactive or degenerative change in most cases, and there is no realistic risk in clinical management.[31] Nevertheless, there is evidence that atypical epithelia in endometriosis may be a precursor of malignancy. First, atypical endometriosis is far more frequently found in endometriosis accompanied by malignant tumors than in benign endometriotic cysts.[32,33] Fukunaga et al.[33] reported that atypical endometriotic foci were observed in 61% of endometriosis associated with ovarian malignant tumors, while such foci were seen in only 1.7% of endometriosis cases without cancers. Secondly, pathological reports have demonstrated a continuous transition from benign endometriosis to carcinoma, and in these areas, atypical endometriosis is frequently observed (Fig. 2). Molecular analyses have also revealed that atypical endometriosis harbors various genetic events suggestive of the intermediate nature of this lesion between benign endometriosis and ovarian cancer (cited in the section "Molecular events involved in the malignant transformation of endometriosis" below). Given this evidence, atypical endometriosis is likely a lesion that represents a transition from benign endometriosis to carcinoma. However, this lesion is encountered only in occasional cases and its biological role in the malignant transformation of endometriosis remains unclear.

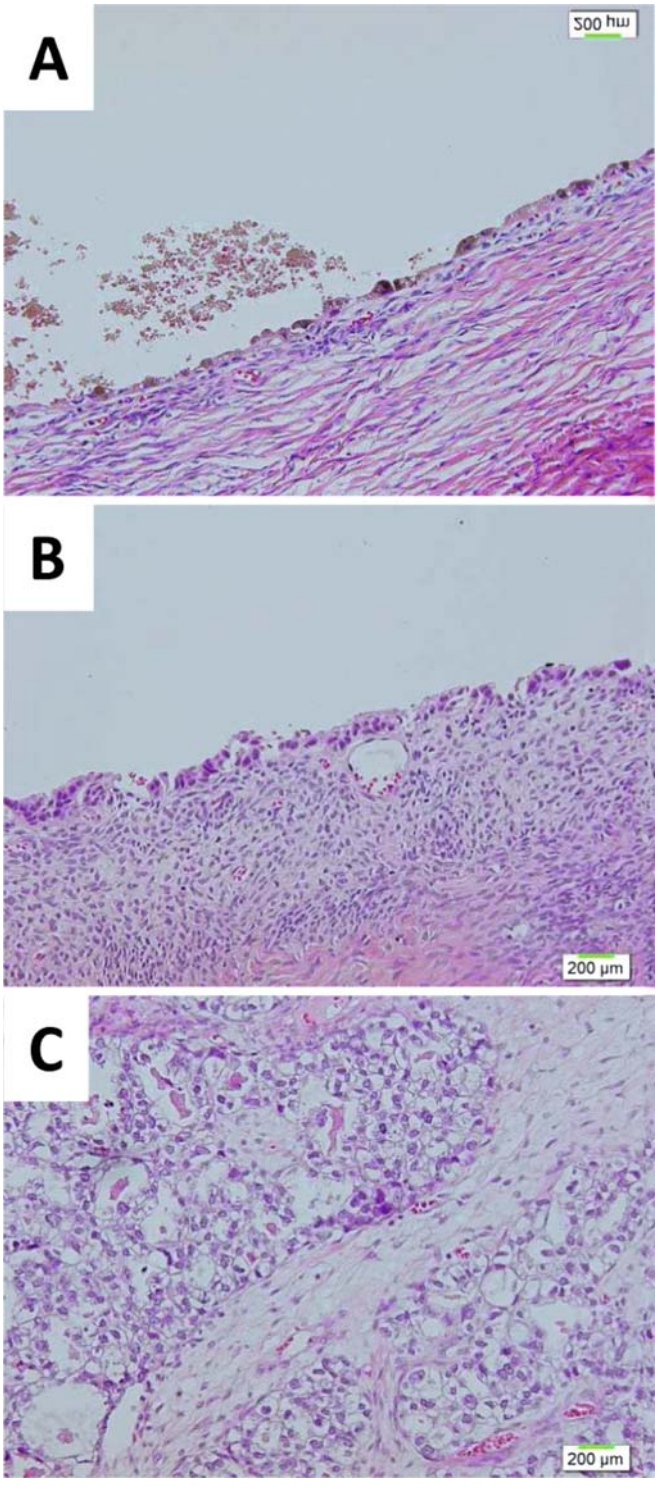

Fig. 2A–C. Atypical hyperplasia coexistent with clear cell carcinoma. **A** Atrophic endometriotic epithelia with hemosiderin condensation; **B** mild-moderately atypical endometriosis; **C** clear cell carcinoma within the same specimen (H&E)

Another type of "atypical endometriosis" is more correctly referred to as "hyperplasia". A variety of hyperplastic changes, with or without cytological atypia, similar to the findings in the endometrium have been described in endometriosis.[26] Hyperplasia is less frequently observed than cytological atypia in endometriosis and is sometimes related to estrogenic stimuli or tamoxifen treatment.[26] The precise relationship between hyperplasia and cancer development in endometriosis is not clear, but it may reflect precancerous growth, because the synchronous presence of hyperplasia and carcinoma has been reported.[28] Prefumo et al.[28] reported that the severity of the epithelial lesion was positively correlated with the age of the patient, which suggests that these lesions are intermediate steps toward carcinoma.

Histological features of carcinoma arising in endometriosis

It is well known that carcinomas derived from the malignant transformation of endometriotic cysts are predominantly of clear cell and endometrioid subtypes. However, it should be noted that other types of malignant tumors also arise in association with endometriosis. Stern et al.[34] collected cases of malignancy in ovarian and extraovarian endometriosis, and 63% of those in ovarian endometriosis were clear cell or endometrioid carcinoma, whereas 30% were serous/serous borderline. Similarly, Modesitt et al.[35] reported that 52% of cancers arising in endometriotic cysts were of endometrioid/clear cell subtype, while 20% were serous carcinoma. In their series, malignant tumors occurring in extraovarian endometriosis were mostly of endometrioid subtype, and clear cell carcinoma was rare. Borderline tumors of Müllerian type also accompany endometriosis at a high frequency.[36–38] More infrequently, other tumors of rare histology also arise in endometriosis.[39,40] Taken together, these findings suggest that: (1) endometriosis, with its neoplastic nature, essentially exhibits the potential to give rise to malignant tumors of various phenotypes, (2) among the malignancies, for unknown reasons, clear cell and endometrioid adenocarcinomas are predominant, and (3) histological and carcinogenic processes differ between ovarian and extraovarian endometriosis.

Molecular events involved in the malignant transformation of endometriosis

A variety of molecular alterations have been reported to be involved in the malignant transformation of endometriosis. These molecular events can be classified into three groups according to their nature and relevant stage of carcinogenesis. First, some events are common in endometriosis and cancers, suggesting they are primarily linked to the development of endometriosis or a very early stage of carcinogenesis. Second, some events are common and universal among various malignancies and are not specific to EAOC. These appear to be late events and include the activation of oncogenes and suppression of tumor-suppressor genes. Third, some events appear to be confined specifically to the malignant transformation of endometriosis, leading to the development of clear cell or endometrioid cancer phenotype.

However, in many cases, it is difficult to clearly define the role of each molecular event.

LOH and genetic instability

As mentioned above, benign endometriotic epithelia frequently have genetic aberrations, such as LOH, which may contribute to the development of endometriosis itself. However, some genetic events that are shared in endometriosis and cancer are thought to be associated with malignant transformation, due to their higher prevalence in the latter.[41]

p53

Mutation or loss of function of the tumor suppressor gene *p53* is the most frequent and important genetic event in the development of ovarian cancer. Although mutation or abnormal accumulation of *p53* is rarely found in benign solitary endometriosis, it is sometimes detected in benign-looking or atypical endometriosis adjacent to ovarian cancer. Bischoff et al.[19] showed that chromosomal loss of the *p53* locus frequently occurred in late-stage endometriosis. Sainz de la Cuesta et al.[42] demonstrated an increased prevalence of *p53* accumulation in the transition from typical to atypical endometriosis and to ovarian cancer. Nezhat et al.[43] reported that *p53* accumulation was found in 17% of benign endometriotic lesions adjacent to carcinoma, while no abnormal staining was found in endometriosis without carcinoma. Undoubtedly, *p53* plays an important role in the malignant transformation of endometriosis, at least in some cases. The frequency of *p53* mutation/accumulation in EAOC in these reports was around 40%-50%, similar to, or somewhat less than, that in serous carcinoma of the ovary.

PTEN and K-*ras*

In 2005, Dinulescu et al.[44] generated an elegant mouse model of endometriosis and endometrioid ovarian carcinoma. Forced expression of oncogenic K-*ras* or conditional *PTEN* deletion in ovarian surface epithelium results in endometrial morphology, while the combination of both gives rise to carcinoma, indicating the potential relevance of these genetic alterations to the malignant transformation of endometriosis.

In human studies, Sato et al.[20] reported *PTEN* mutation in 20% of endometrioid and 8% of clear cell ovarian carcinomas. Martini et al.[45] reported reduced expression of *PTEN* in 15% of cases of malignant transformation of endometriosis, especially in advanced cases. Obata and Hoshiai[46] reported LOH in 10q in 40% of atypical endometriosis, but no *PTEN* mutation was found. Yagyu et al.[47] reported that mammalian target of rapamycin (mTOR), a downstream target of PI3K, was activated in postmenopausal endometriosis and clear cell carcinoma in comparison to premenopausal endometriosis.

K-*ras* mutation was found in 1/12 (8.3%) of endometrioid[48] and 3/24 (12.5%) of clear cell carcinomas[49] accompanied by endometriosis. In contrast, it was not found in benign endometriosis adjacent to carcinoma.[50]

HNF-1β

Using microarray analysis, Tsuchiya et al.[51] found that hepatic nuclear factor (HNF)-1β, a transcription factor, was upregulated in most clear cell carcinomas, but not in non-clear cell carcinoma. Moreover, reduction of HNF-1β mRNA induced apoptotic cell death in ovarian clear cell carcinoma cells.[51] Kato et al.[52] also reported the immunohistochemical expression of HNF-1β only in clear cell carcinomas. Interestingly, they showed that in 9 out of 12 clear cell carcinomas with endometriosis, endometriotic epithelium was also stained for HNF-1β. HNF-1β, a transcription factor involved in pancreatic function and kidney development, may also be a molecular marker of clear cell carcinoma and could be used as a therapeutic target.

Estrogen effect

Unopposed estrogen is associated with an increased risk of endometrial cancer. Several studies have suggested that unopposed estrogen, including internal production in obese women, is also associated with the malignant transformation of endometriotic cysts.[53] Case reports have suggested that malignant transformation of endometriosis occurs under the influence of endogenous estrogen from ovarian tumors[54] or exogenous tamoxifen use.[55,56] In a study of 31 cases of EAOC, Zanetta et al.[57] reported that either endogenous or exogenous hyperestrogenism was a significant risk factor. Several reports have suggested that estrogen stimulation may be related to the malignant transformation of residual endometriosis even after total abdominal hysterectomy and bilateral oophorectomy.[58,59]

Other factors

Previously, del Carmen et al.[60] reported the overexpression of vascular endothelial growth factor (VEGF) in most cases of EAOC but rarely in atypical endometriosis. Yamamoto et al.[61] showed that activation of the platelet-derived growth factor pathway occurred in the transition from non-atypical endometriosis to clear cell carcinoma. Taniguchi et al.[62] reported the expression of keratinocyte growth factor receptor in the epithelium of endometriosis as well as in ovarian cancer cells, but not in normal ovarian surface epithelium. Furuya et al.[63] studied the expression patterns of CXC chemokines, interleukin (IL)-8, ENA-78, GRO-alfa, I-TAC, Mig, and SDF-1, and their receptor, CXCR2–4, by quantitative RT-PCR and immunohistochemistry. Interferon-gamma (IFN-γ)-inducible chemokines and CXCR3 were upregulated in both endometriosis and EAOCs.[63] Martini et al.[45] found abnormal methylation of hMLH in some EAOCs. In contrast, Uzan et al.[64]

reported that *HER1* and *HER2*, genes frequently overexpressed in ovarian cancers, may not play a role in EAOC.

Role of the microenvironment of endometriotic cysts in malignant transformation

Carcinogenesis is significantly influenced by the microenvironment where specific malignancy occurs. We have hypothesized that the characteristic contents of endometriotic (chocolate) cysts, which contain highly concentrated old blood elements, may influence the carcinogenesis of endometriosis. We analyzed the elements in the cystic fluid and found that, as expected, the free iron concentration was markedly high in endometriotic cysts.[65] Free iron has been implicated in cancer development in various organs, such as kidney and liver, through the induction of persistent oxidative stress.[66] We also measured stress-related factors in chocolate cysts. Lactose dehydrogenase (LDH), a marker of tissue damage; potential antioxidant (PAI), a marker of antioxidant; lipid peroxidase (LPO), a marker of oxidative stress; and 8-hydroxy-2-deoxyguanosine, a marker of DNA damage; were all elevated in endometriotic cysts in comparison to nonendometriotic ovarian cysts. Some of these findings were confirmed by immunohistochemical analysis (Fig. 3). Moreover, in vitro experiments revealed that the fluid in chocolate cysts was more mutagenic compared with that of other cysts.[65] These results suggest that epithelial cells in endometriotic cysts are exposed to a stressful microenvironment and that this persistent oxidative stress may lead to carcinogenesis, as is the case in renal cell cancer or hepatic cancer. Our hypothesis is partly supported by the observation that chromosomal aberrations are present at a higher frequency in ovarian endometriosis (chocolate cysts) in comparison to extragonadal endometriosis where epithelium is less exposed to old blood elements.[67] Melin et al.[68] have provided epidemiological evidence that the occurrence of ovarian cancer increases with a longstanding history of endometriosis. Ness and Modugno[69] have proposed that endometriosis is a model for inflammation-hormone interactions in the context of ovarian cancer development. Though the precise mechanisms are still to be clarified, it seems reasonable to consider the possibility that the microenvironment of endometriotic cysts plays a major role in the malignant transformation of endometriosis.

Clear cell carcinoma as a stress-resistant phenotype

Thus far, no clear explanation has been provided to answer the question of why two specific subtypes of ovarian cancer, clear cell and endometrioid, which are rather minor constituents in ovarian cancers, predominantly arise in endometriosis. As stated above, endometriotic epithelium itself appears to have the potential to give rise to ovarian neoplasms. In view of endometriosis as an ectopic counterpart to uterine endometrium, the occurrence of endometrioid carcinoma is plausible, but the frequent occurrence of clear cell carcinoma and its underlying mechanism remain unclear. One possible explanation is that a unique environment in the endometriotic cyst, as discussed previously, may influence the development of the clear cell phenotype. In an attempt to clarify the characteristics of clear cell carcinoma using microarray data, we extracted 437 genes differentially expressed in clear cell carcinoma among ovarian carcinomas, and designated their data as a "clear cell signature". The classification of the genes included in the "clear cell signature" represents those involved in oxidative stress and inflammation, indicating that this cancer specifically expresses stress-responsive genes (article in submission). Accordingly, we speculate that clear cell carcinoma acquires a stress-resistant capacity in the process of carcinogenesis within an environment of high oxidative stress. This phenotype might also account for the observed resistance to chemotherapy of clear cell carcinoma, though our hypothesis should be further tested by additional studies.

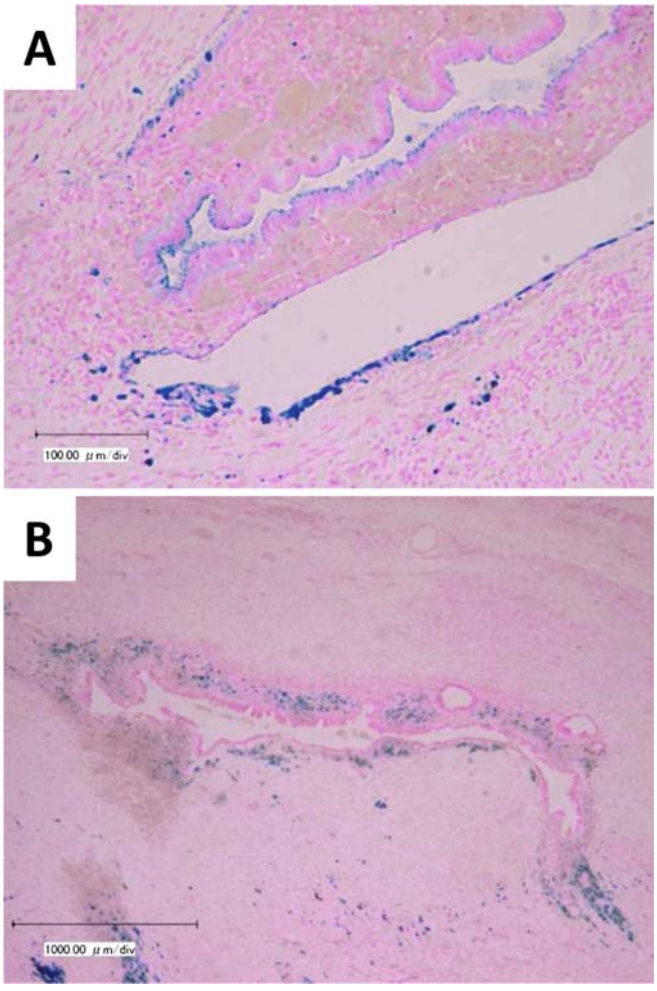

Fig. 3A,B. Iron deposits in **A** epithelial cells and **B** stroma of endometriotic cyst (Prussian blue staining)

Management of endometriosis in view of malignant transformation

There is no definite guideline for the management of endometriosis with special attention to malignant transformation. According to a Japanese cohort study, approximately 0.7% of patients with endometriosis subsequently developed ovarian cancer (standardized incidence ratio [SIR], 8.95; 95% confidence interval [CI], 4.12–15.3).[70] The authors further analyzed risk factors of malignant transformation and found that older age, postmenopausal status, and larger tumor diameter were associated with a higher prevalence of cancer development. They defined postmenopausal women with ovarian endometriosis of 9 cm or larger in diameter as a high risk group and recommended extensive therapy, including surgery.[71]

As mentioned above, estrogen, especially unopposed estrogen stimulation, may facilitate the malignant transformation of endometriotic cysts, though sufficient evidence has not been shown yet.[53,59] In this regard, clinicians should carefully continue to follow up on cases of endometriosis, even after menopause, despite gynecologists as well as patients tending to think that endometriosis remits after menopause. Likewise, we should be careful in conducting hormone replacement therapy (HRT) in women with endometriosis. Although there is no evidence from clinical trials that progestin reduces the risk of EAOC,[59] many authors recommend adding a progestin if HRT is desired after hysterectomy/bilateral salpingoopherectomy (BSO) has been performed.[8,72,73] Debus and Schuhmacher[74] reported a case of endometrial carcinoma that arose during estrogenic treatment 17 years after total abdominal hysterectomy and BSO. Oral contraceptives may reduce the risk of EAOC.[75] There are several reports on the successful treatment of postmenopausal endometriosis with aromatase inhibitors.[76,77]

Treatment is often more difficult in the cases of younger women where preservation of fertility is a desirable goal. A literature review found no reports on whether fertility-sparing surgical interventions decreased the risk of ovarian cancer development in patients with endometriosis. Melin et al.[68] reported that women discharged from a hospital with a diagnosis of endometriosis, the majority of whom had undergone some kind of surgical procedure, exhibited an elevated risk of ovarian cancer, while those women who had undergone hysterectomy at that time had no increased risk. On the other hand, Modesitt et al.[35] reported that 86% of patients with cancer from extraovarian endometriosis had undergone a hysterectomy. In theory, the removal or reduction of endometriotic epithelia along with controlling pelvic inflammation may reduce the risk of ovarian cancer. However, it should be noted that even after a surgical procedure, patients with endometriosis may have an elevated risk of ovarian cancer compared with women without a history of endometriosis. Van Gorp et al.[8] recommend that, if endometriosis is not excised completely and/or atypical change is found, 6-monthly follow up with determination of CA-125 levels and transvaginal sonography should be considered.

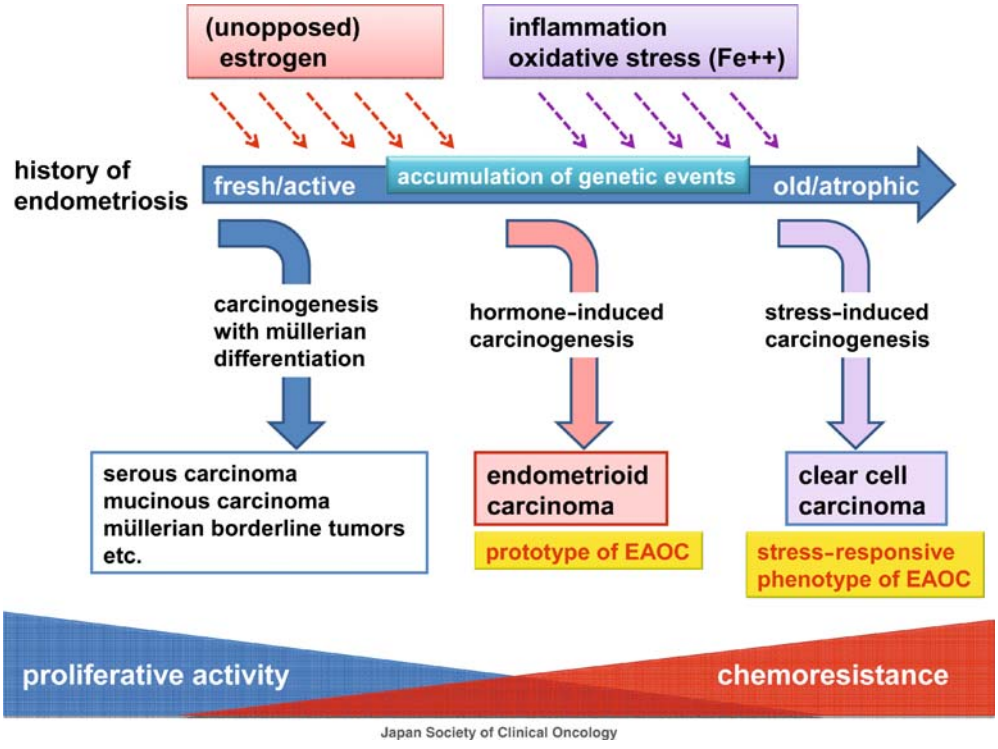

Fig. 4. Hypothetical pathogenesis of malignant transformation of endometriosis

Conclusion: pathogenesis of malignant transformation of endometriosis – current consensus and future directions

The accumulated data suggest that endometriosis is a monoclonal; that is, neoplastic disease, and should be managed as such. Endometriosis is a risk factor for ovarian cancer even after menopause. A variety of molecular events found in EAOC, such as *p53* alteration, *PTEN* silencing, and K-*ras* mutations, are common events in all types of ovarian cancers, while some events, including HNF-1 activation, seem to be unique to clear cell carcinoma arising in endometriosis. Though the precise molecular mechanisms are still to be elucidated, our recent data suggest that microenvironmental factors such as oxidative stress and inflammation play an important role in the carcinogenesis and phenotype of carcinoma occurring from endometriosis.

Figure 4 depicts a hypothetical model of the pathogenesis of malignant transformation of endometriosis, in which three typical and simplified carcinogenic mechanisms are speculated. In the first mechanism, endometriotic epithelium serves as a precursor of tumors in the same manner as normal OSE gives rise to ovarian tumors, and it contributes to the occurrence of various histological epithelial/epithelial-stromal tumors of both malignant and borderline natures. The second mechanism, which resembles the carcinogenic process in the endometrium under the influence of (unopposed) estrogen, primarily gives rise to endometrioid carcinoma via endometrial hyperplasia. The third mechanism is strongly influenced by the unique microenvironment within the chocolate cysts. Persistent exposure to oxidative stress and inflammation results in a stress-resistant and slow-growing phenotype of malignancy, that is, clear cell carcinoma. Though this hypothesis may be simplistic and require further validation, it remains a useful preliminary model of the carcinogenic mechanisms in endometriosis.

With regard to the prevention of EAOC, effective management of endometriosis remains a desirable goal. To this end, clarification of the precise natural course of the disease and identification of the risk factors of malignant transformation of endometriosis are urgently needed.

Management of clear cell carcinoma remains an important challenge in the treatment of EAOC. Using microarray pathway analyses, we recently found that sorafenib, a multikinase inhibitor, had a marked antitumor effect in a clear cell carcinoma cell line/mouse xenograft model. Preparations are now under way to validate these results with a clinical trial at our facility.

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