Chapter

Endometriosis and Cancer

Sushil Kumar Giri and Bhagyalaxmi Nayak

Abstract

Endometriosis is a chronic debilitating inflammatory disease of women, with the growth of ectopic endometrium in extrauterine sites like rectovaginal septum, peritoneal surfaces, or ovaries, etc. Though endometriosis is not regarded as a malignant disorder, it does have some features common to malignant disease. They are; local and distant metastasis, invasion and destruction to adjacent structures, unrestricted growth, development of new blood vessels. The association between endometriosis and ovarian, endometrial, and cervical cancers and between endometriosis and extra-ovarian malignancies has been reported in different kinds of literature. Clear cell and endometrioid ovarian carcinomas are presumed to have developed from endometriosis. Ovarian seromucinous borderline tumors, low-grade serous ovarian carcinomas, adenosarcoma, and endometrial stromal sarcomas may also arise from endometriosis. However, it is not very clear whether endometriosis has undergone malignant transformation or simply is found co-existent with cancer. Endometriosis itself may increase a woman's risk of developing non-Hodgkin's lymphoma, malignant melanoma, and breast cancer.

Keywords: endometriosis, common genetic instability, cancer

1. Introduction

Endometriosis is a chronic debilitating inflammatory disease of women, with the growth of ectopic endometrium in extrauterine sites like uterosacral ligaments, pelvic peritoneum, rectovaginal septum, other peritoneal surfaces, ovaries, etc. It is an extremely heterogeneous clinical entity as regards etiopathogenesis, clinical features, and treatment. The genetic basis of this disease has been quite clear and endometriosis running in families has been quite established. The exact etiopathogenesis and treatment option of the disease is still evolving. Though endometriosis is not regarded as a malignant disorder, it does have some features akin to malignant disease. They are local and distant metastasis, invasion and destruction of adjacent structures, unrestricted growth, resistance to apoptosis, development of new blood vessels etc [1]. With the increasing availability of new gene sequencing methods, the genetic profiling of endometriosis has given way to new findings that endometriosis and certain cancers share the same aberrant genetic sequences.

Sampson et al. in 1925 postulated a histological link between endometriosis and cancer and proposed the three criteria for the diagnosis of endometriosis-associated ovarian cancer (EAOC). They were (1) evidence of endometriosis close to the tumor, (2) exclusion of invasion from other sources, (3) presence of tissue resembling endometrial stroma surrounding characteristic epithelial glands [2]. Scott et al. in 1953 revised the criteria and added the fourth criterion, i.e., histological proof of transition from benign changes in endometriosis to malignant changes

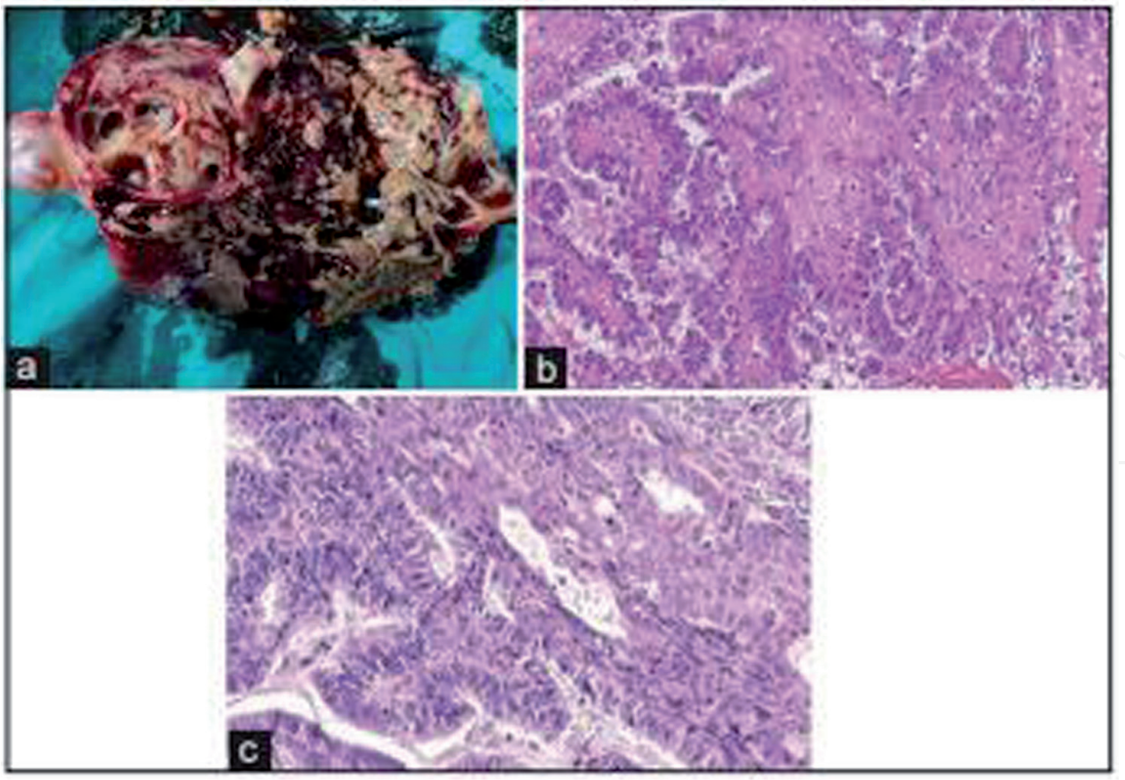

Figure 1.
(a) Cut section of an ovarian mass showing chocolate material with solid components, (b) clear cell carcinoma ovary associated with endometriosis, (c) endometrioid adenocarcinoma in the vicinity of endometriosis.

[3]. All four criteria are continued in practice to diagnose endometriosis-associated malignancy (EAM) (**Figure 1**).

Endometriosis is associated with genetic instability and several genetic alterations. Loss of heterozygosity (LOH) at 10q23, PTEN, ARID1A, and p53 mutations have been found in both endometriosis and EAM [4]. It is presumed that EAM arises from atypical endometriosis, which is an intermediate lesion between endometriosis and cancer. About 80% of EAM is found in the ovary and the rest are localized in the abdominal wall, pleura, intestine, rectovaginal septum etc [5].

Considering the above facts, obvious controversies ensue as to the role of endometriosis as the cause of malignant transformation or a mere association with cancers.

2. The mechanism for malignant transformation of endometriosis

The exact mechanisms of malignant transformation of endometriosis are not fully established. It is proposed that chronic inflammation and immune dysregulation are the main factors related to the malignant transformation of endometriosis due to most probably iron-triggered oxidative stress leading to genetic alteration [6]. It is reported that endometriotic cysts have more concentration of iron than non-endometrioid counterparts, because of periodic hemorrhage into the cyst with the accumulation of free iron. Moreover, genomic alteration also is a resultant of hyperoestrogenic state associated with endometriosis, leading to inactivation of tumor suppressor genes like p53, PTEN, ARID 1A, and activation of KRAS and p13 oncogenic pathways, thus favoring the development of hormone-dependent malignant diseases like Type-I epithelial ovarian cancer and breast cancers [7]. Some authors have also established an association of endometriosis with ovarian cancer,

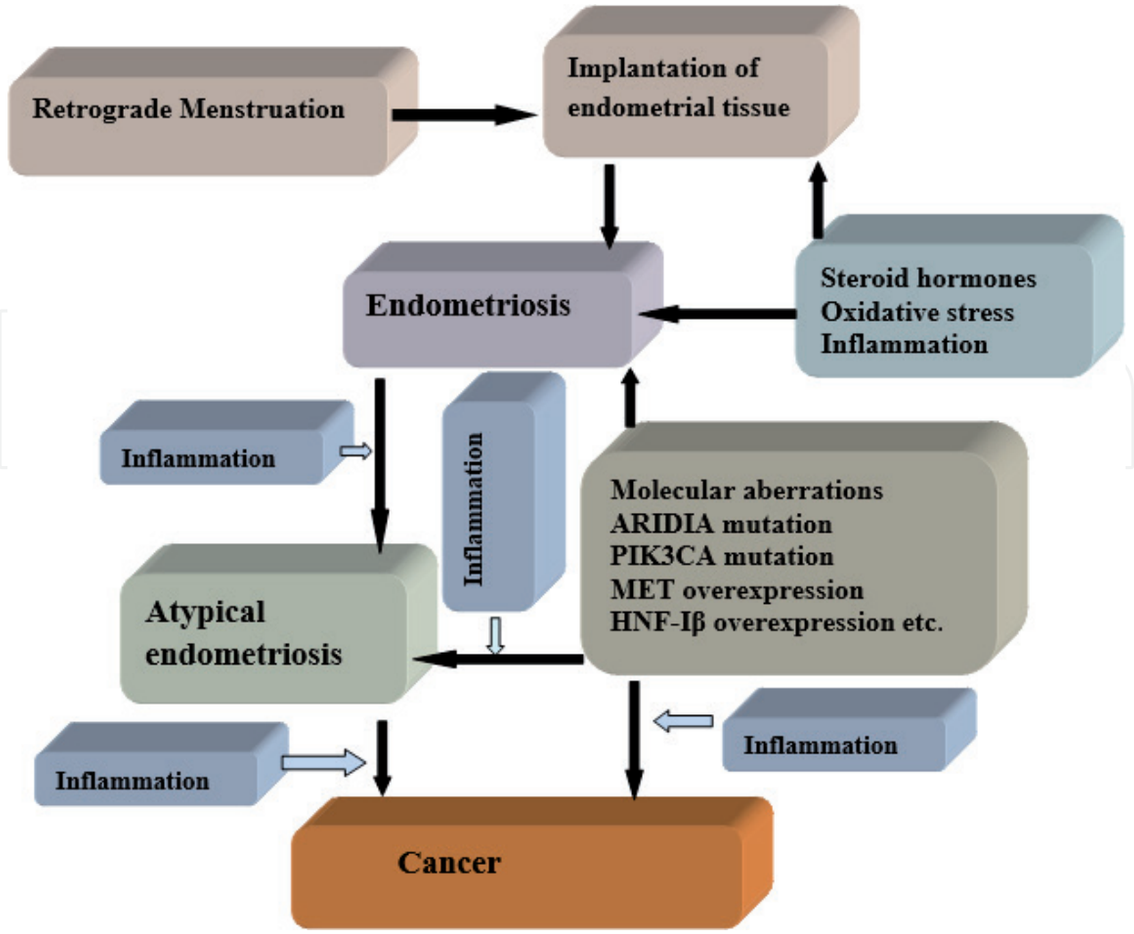

Figure 2.
Probable pathway for transformation of endometriosis to cancer.

breast cancer (BC), cutaneous melanoma, and non-Hodgkin's lymphoma [1, 8]. It is presumed that endometriosis-associated, and endometriosis independent neoplasms may develop from different molecular pathways with distinct genetic alteration with significant clinical and prognostic implications. The estrogen-dependent pathogenesis of ovarian endometrioid carcinomas associated with endometriosis is corroborated also by the increased incidence of synchronous primary endometrial (Type I, estrogen-dependent) and ovarian, endometriosis-associated, endometrioid adenocarcinomas (**Figure 2**).

3. Endometriosis and specific cancers

3.1 Endometriosis and ovarian cancer

In a recently completed large cohort study "The ENOCA population-based cohort study" analyzing 2043 women of ovarian cancer in the endometriosis cohort and 471 women with ovarian cancer in the nevus cohort, the authors observed an increased incidence of endometrioid and clear-cell ovarian cancer in women with histologically proven endometriosis and the median age of ovarian cancer diagnosis was 56 years and 60 years in endometriosis and nevus cohort respectively [9]. The exact mechanism of development of EAOC is yet to be understood. However, the presence of some factors is implicated in a higher risk of the development of EAOC. In a recent study, it was observed that increasing age, postmenopausal status, high level of CA-125, ovarian endometrioma >8 cm size, long-standing endometriosis of >5 years

duration was found to have a higher risk of coexistent malignancy in both univariate and multivariate analysis. Longer use of oral contraceptive pills does have a protective effect. A significantly increased risk of development of ovarian cancer was observed after 1–4 years of diagnosis of endometriosis and 5–9 years of follow-up, but not ≥10 years after initial diagnosis. The highest risk was observed when diagnosed at the age of 50 years [10]. The relative risk of developing ovarian cancer is about 4.2 times higher than the general population in women with long-standing endometriosis and such women are 10–20 years younger [11]. To establish the EAOC, it is proposed that, in addition to the presence of ovarian cancer, there should have at least one of the following criteria: (1) coexistence of carcinoma and endometriosis within the same ovary; (2) endometriosis of the contralateral ovary, (3) pelvic endometriosis, or (4) histology-proven transition from benign endometriosis to cancer [12].

Endometrioid and clear cell carcinoma are the most common types of ovarian carcinoma of EAOC, whereas the endocervical type of mucinous borderline tumor, endometrial stromal sarcoma, and Mullerian adenosarcoma are less frequently encountered [5]. It was described that women with endometriosis have a 2–3 times higher risk of developing endometrioid and clear cell ovarian tumors [13]. It was observed in a recent study that out of EAOC, 32% and 28% constituted clear cell ovarian carcinoma (CCOC) and endometrioid ovarian carcinoma (EnOC) respectively. About 62% of ovarian malignancy cases were diagnosed in early-stage and overall optimal surgery could be achieved in 88% [11]. As CA-125 is raised both in endometriosis and carcinoma ovary, estimation of serum HE4 can differentiate between the two as its higher level is detected mostly in ovarian carcinoma.

The molecular genomic alteration, inflammation, hyperestrogenism, and oxidative stress, etc. in combination are thought to be involved in the transformation of endometriosis from benign to atypical (borderline) and then to EAOC [11]. Other risk factors involved are obesity and the use of unopposed estrogen. EAOC develops from atypical endometriosis with common molecular alteration such as mutations of ARID1A, PI3KCA, and loss of heterozygosity of PTEN, hepatocyte nuclear factor-1b (HNF-1b) upregulation, and mutation of CTNNB1 (catenin beta 1) [14]. However, a higher frequency of ARID1A mutations of 46–57% has been observed in CCOC in comparison to 30% in EnOC [15]. In both situations, atypical endometriosis has been identified as a direct precursor [16].

Diagnosis of malignant transformation in endometriosis or endometrioma is very challenging. Some degree of caution should be exercised in women at high risk of malignant transformation, like women with a long-standing history, endometriosis diagnosed at an early age, large endometrioma, endometriosis-associated infertility, and/or history of infertility treatment. Early detection is of paramount importance to improve the prognosis. As the EAOC presents at an early stage, optimal cytoreduction is feasible, and fertility promoting surgery is possible as the case may demand. Features of malignant transformation can be picked up by high-resolution ultrasound and by expert ultrasonologist. In a retrospective multicenter study involving 239 women of endometrioid carcinoma, the authors observed unilocular cyst with papillary projection without ascites in most instances of EAOC, whereas endometrioid carcinoma without evidence of endometriosis had a large central solid component entrapped within locules, giving the tumor a cockade-like appearance [17]. Unilateral cystic mass containing hemorrhagic fluid and mural nodule is the characteristic feature of T1 weighted images of contrast-enhanced MRI in the diagnosis of malignant transformation of endometrioma. The disappearance of shading on T2-weighted images with enlargement of endometrioma is suggestive of malignant transformation [18].

The long-standing persistence of endometriosis plays an important role in the development of EAOC. It was observed that there is an increased risk of

development of both EnOC and CCOC after 10 years of diagnosis of endometriosis. Moreover, when the first diagnosis of endometriosis is at 50 years or more, there is an increased risk of serous ovarian cancer, though the increased risk of CCOC was observed in all age groups at first diagnosis of endometriosis [8].

Some authors observed that EAOCs present in the low stage and low-grade disease status with a significantly better prognosis compared with non-EAOC counterparts [19]. However, other experts had contradictory views and opined that the better outcome was due to early-stage and grade of the disease and not because of associated endometriosis [20]. Surgery followed by standard chemotherapy is the treatment of choice when deemed necessary, though the response to chemotherapy is not so encouraging. However, in a large population-based cohort study, longer survival was observed in ovarian cancer patients with histologically proven endometriosis than those without endometriosis even after adjusting stage, grade, type, age at diagnosis, treatment protocol, and residual tumor after surgery [9]. Given the poor response to standard chemotherapy and as mutation of ARID1A, PI3K/AKT/mTOR, MET, and HNF-1β pathways are frequently activated, targeted inhibitors for these pathways can be considered as a future in the treatment strategy for EAOC, especially OCCC [21].

It will not be out of the place to mention that most women with endometriosis will not develop carcinoma of the ovary. Though evidence from several studies demonstrates increased risk, the lifetime risk of developing ovarian cancer is still low in women with endometriosis and is not different from women without endometriosis. The clinician and the woman need to be aware of the risk, but need not be worried about the cancer risk [22].

3.1.1 Prevention strategies for EAOC

As of now, there is no availability of any specific biological markers to stratify which endometriosis case will develop into a malignant one. A recently published report suggests that ovarian endometriosis is prone to develop into ovarian cancer, while there is no association between peritoneal or deep endometriosis and ovarian cancer [23]. As mutations in ARID1A, PTEN, PIK3CA, and KRAS are associated both in endometriosis and ovarian cancer of the same patient, detection of these and other mutations may predict future development of EAOC.

The application of sensitive and specific molecular biomarkers needs to be explored to identify endometriosis with oncogenic potential. Employing the study of circulating tumor DNA (ctDNA) can play a major role in detecting cancer precursor lesions present in some endometriosis [24]. Few interventions can reduce the risk of ovarian cancer in general and EAOC in particular. It is evident that 5 years of use of oral contraceptive pills results in a 20–30% reduction of EnOC and CCC [25]. Tubal ligation shows almost 50% risk reduction of EnOC and CCC [26]. Risk-reducing salpingo-oophorectomy may be considered in endometriosis to prevent EAOC as well as symptom relief. Unilateral oophorectomy with complete resection of all visible endometriotic lesions has been observed to have a protective effect in the development of ovarian cancer [27]. As the risk of development of ovarian cancer is more when endometriosis is detected in women aged ≥50 years, complete surgical resection is of paramount importance in older women diagnosed with endometriosis [28].

3.2 Endometriosis and endometrial carcinoma

Pathogenesis of both endometriosis and endometrial carcinoma is not well defined and thought to be multifactorial with an uncertain underlying molecular

mechanism. However, mutation of the gene as observed in EAOC has been identified to be associated with endometrioid endometrial carcinoma [29]. Both estrogen stimulation and chronic inflammation have been attributed as causative factors of the two disorders. The endometrioid histopathology of co-existent ovarian and endometrial carcinoma (synchronous) with evidence of ovarian endometriosis in 30% of cases points towards the association of endometriosis and endometrial cancer [30]. J.B. Mogensen, et al. [7] observed a statistically significant increased risk of development of mostly Type-I endometrial carcinoma after 10 years of initial diagnosis of endometriosis [7]. They detected a 40% increased risk of endometrial carcinoma as opposed to other studies showing no association [31]. H.C. Yu HC.et al. had the same observation of the increased association of endometriosis and endometrial cancer [32]. A. Dahiya et al. detected 104 (13%) cases of different malignancies from 800 patients of histologically proven endometriosis. Out of which 33 cases had endometrial carcinoma with endometrioid histology in 87.8% of cases and 81.8% were in stage I [10]. In a population-based retrospective cohort study of 129,862 women with histologically proven endometriosis/adenomyosis, M. Hermens et al. observed an increased incidence of endometrial cancer. They suggested evaluating endometrium before hysterectomy for endometriosis to exclude endometrial carcinoma so that inappropriate surgery can be avoided [33].

3.3 Endometriosis and breast cancer

Data are inconsistent to establish a relationship between endometriosis and breast cancer [34]. Both are associated with a high oestrogenic environment. Farland et al. in their prospective cohort study did not find an increased risk of ER & PR+ve, or ER & PR−ve breast cancer in women with laparoscopically proved endometriosis in a follow-up period of 24 years. Rather they observed an increased risk of ER+ve and PR−ve breast cancers in women with endometriosis [35].

3.4 Endometriosis and cervical cancer

Saavalainen et al. found a strongly decreased risk of squamous cell carcinoma of the cervix in women diagnosed with peritoneal endometriosis. This can be explained that screening for cervical cancer as such can have an impact on such reduction and reduced sexual activity, because of dyspareunia, thereby reducing exposure to HPV infection [23].

3.5 Endometriosis and non-gynecological cancers

The association of endometriosis and non-gynecological cancers is not well established nor well studied. However, some association has been attributed in some studies as described below.

3.5.1 Endometriosis and colorectal cancer (CRC)

In a prospective study of 2266 women with endometriosis, with 9842 patient-years of follow-up, a marked (13-fold) increase in the incidence of CRC was observed in women with adenomyosis and extragonadal endometriosis. This is attributed to the malignant transformation of endometriotic implants over colorectal tissue, partly due to the hyperoestrogenic environment [36].

3.5.2 Non-Hodgkin's lymphoma

A study by J.E. Olson et al. reported 3.2 times increased risk of development of diffuse non-Hodgkin's lymphoma and extranodal disease in women with endometriosis as compared to those without it [37]. A similar observation was described by A. Melin et al. in their study using National Swedish Inpatient Register [38]. They linked this association to abnormal cellular and humoral immune function. As polyclonal B-cell autoimmune activation is observed in endometriosis, it is postulated to associate B cell lymphoma to B cell activation of endometriosis.

3.5.3 Endometriosis and Thyroid Cancer

In a large cohort study from the Finish Cancer registry, L. Saavalainen et al. observed an increased risk of thyroid cancer especially of papillary type in women with diagnosed endometriosis [39]. Women do have three times more risk of development of thyroid cancer than men and attribute it to female sex hormones. So hormonal abnormality, mostly estrogen disorder may be a risk factor for thyroid cancer, which is also a factor for endometriosis [40].

3.5.4 Endometriosis and brain tumor

Melin et al. in a large study demonstrated the association of endometriosis to brain tumour [41]. E.B. Claus et al. in a large study observed endometriosis as a risk factor for meningioma and attributed hormonal factors for such incidence [42].

3.5.5 Endometriosis and skin cancer

L.V. Farland et al. observed that women with endometriosis do have an increased risk of skin cancers, mostly associated with melanoma. They also found no association of endometriosis with basal cell carcinoma and squamous cell carcinoma [43]. A similar association was also observed by M. Kvaskoff et al. They attributed hormonal hypothesis and some molecular genetic alteration in both the conditions [44].

3.5.6 Endometriosis and other cancers

Saavalainen et al. observed a 40% decreased risk of oral and pharynx carcinoma. This decrease might be due to less exposure to HPV infection and complex alteration of immune response associated with HPV and endometriosis. Though not HPV-related, about $\frac{1}{5}^{th}$ decrease in the incidence of pancreatic carcinoma was observed in women with endometriosis. The cause of this lower risk might be attributed to lifestyle modification and hormonal treatment for endometriosis [23].

4. Conclusion

The link between endometriosis and different cancers is yet to be well understood. Though evidence dates back to the early 1990s, we still need robust data to back the hypothesis. Genetic alteration and hormonal role are postulated to be factors in the development of different cancers in women with endometriosis. The exact mechanism of this complex process is yet to be established. First, we need to understand the basics of endometriosis, the physiological changes, genetic

aberration associated with the disease, and morbidity issues. All women with endometriosis should be evaluated clinically and with appropriate imaging studies and be managed appropriately by specific drugs, fertility-enhancing surgery, or surgical removal of all visible lesions which may necessitate hysterectomy and bilateral oophorectomy. These women need strict follow-up even years after menopause. This will reduce the risk of future development of EAOC. More methodically robust prospective research with a large population is the need of the day to attribute the relationship of endometriosis and cancers as a cause or association. Our knowledge is growing and our understanding is evolving.

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