Endometriosis-associated Malignancy

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Abstract

Endometriosis is a common condition in women of reproductive age. According to several epidemiological studies endometriosis may be associated with increased risk of various malignancies. However, endometriosis-associated malignancy (EAM) is defined by certain histological criteria. About 80% of EAM have been found in the ovary, whereas 20% are localized in extragonadal sites like intestine, rectovaginal septum, abdominal wall, pleura and others. Some authors suggest that EAM arise from atypical endometriosis as an intermediate lesion between endometriosis and cancer. Moreover, a number of genetic alterations, like loss of heterozygosity (LOH), PTEN, ARID1A and p53 mutations have been found in both endometriosis and EAM. Endometriosis-associated ovarian cancer (EAOC) mostly a well or moderately differentiated tumor of endometrioid or clear cell histological sub-type. Women affected by EAOC are on average five to ten years younger than non-EAOC patients; in most of the cases EAOC is a low stage disease with favorable clinical outcome. Since EAM is a rare condition systematic data on EAM are still missing. A systematic retrospective study on endometriosis-associated malignancies (EAM study) is currently being conducted by the Endometriosis Research Foundation together with the study groups on ovarian and uterine tumors of the working group for gynecological oncology (AGO) (gyn@mlk-berlin.de).

Zusammenfassung

Introduction

Endometriosis is a common condition in women in which endometrium-like tissue is detected outside the uterine cavity [1]. The incidence of the disease in females of reproductive age is estimated at 5 to 15% [2]; the main symptoms are dysmenorrhea, pelvic pain and infertility [3]. Despite extensive research in this field, the exact pathogenesis of endometriosis remains not fully understood but one widely accepted hypothesis is the implantation of endometrial tissue in the peritoneal cavity due to retrograde menstruation [4]. Although endometriosis is considered a benign condition, it has been demonstrated to share some characteristics with malignant tumors such as tissue invasion and damage, neoangiogenesis or spread to distant organs [5]. Current knowledge about endometriosis-associated malignancies will be presented in this review.

Endometriosis and Cancer Risk – Epidemiological Data

According to several epidemiological studies endometriosis is associated with increased risk of various malignancies with the best evidence for ovarian cancer [6–18]. Furthermore, a number of cohort and case control studies demonstrated an epidemiological association of endometriosis with endometrial cancer, breast cancer, colorectal cancer, non-Hodgkin lymphoma and others [8, 19, 20]. The clinical significance of the association between endometriosis and non-gynecologic malignancies is poorly understood [21]. The majority of the published studies on endometriosis-associated ovarian cancer have reported that ovarian cancer (OC) risk among endometriosis patients is moderately increased (RR, SIR or OR 1.32–1.92) (Table 1). The strongest association between OC and endometriosis was reported by Brinton et al. (SIR = 2.48) [8], Stewart et al. [22] (HR = 2.33) and Buis et al. [23] (HR = 12.4); interestingly, these three studies included only women suffering from infertility, which may be a potential confounding factor for their results. Moreover, a remarkably high increase of ovarian cancer risk (SIR = 8.95) has been demonstrated by Kobayashi et al. [24]. In their retrospective cohort study ovarian cancer risk was analysed in women with sonographically diagnosed endometriomas based on time periods from first diagnosis of endometrioma to first diagnosis of ovarian cancer. Since endometriomas were histologically confirmed in only one-third of the cases, whereas the majority of diagnoses was made based on ultrasound image, the ovarian cancer risk has been possibly overestimated in this analysis: some of ovarian cysts identified as endometriomas might have been in fact ovarian cancers. In summary, there are a number of epidemiological studies, in which at least a modest association between endometriosis and ovarian cancer has been consistently demonstrated. Despite epidemiological evidence, a direct causal association between endometriosis and ovarian cancer has not been elucidated so far [25].

Histological Findings

The histological link between endometriosis and cancer has first been postulated as early as 1925 [26]. Sampson et al., based on microscopic observations, speculated that endometrial ovarian cancer may develop from endometriotic tissue and described the criteria for diagnosis of endometriosis-associated OC: (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 [26]. Scott et al., in their analysis from 1953, added a fourth criterion:

Theories of Pathogenesis

There are two main theories which attempt to explain the origin of endometriosis-associated malignancies. According to a number of histopathological studies endometriosis-associated ovarian cancer (EOC) may arise from atypical endometriosis of the ovary [34,35]. This heterogeneous condition is histologically characterized by hyperplasia of endometrial glands with cytological atypia or presence of atypical hobnail cells within ovarian endometriosis [25,36,37]. A direct association between atypical endometriosis and ovarian cancer was first demonstrated by La Grenade and Silverberg in 1988 [34]; in five cases of ovarian cancer (three clear cell carcinomas and two endometrioid carcinomas) accompanying atypical endometriosis was found in the ovary and in four out of five cases atypical changes were in contiguity with ovarian neoplasm [34]. Furthermore, a significantly higher rate of cytological atypia within endometriotic lesion was demonstrated in cases of EOC compared with endometriosis alone [38]. Although the hypothesis that atypical endometriosis may be a premalignant condition is supported by the fact that it can be detected in up to 80% of EOC, there are still not enough data proving this model [35,39,40]. According to the other theory endometriosis is not a real premalignant lesion, but there is an indirect link involving common environmental, histological, immunological and genetic factors. Several studies have demonstrated that microenvironment of endometriosis and EOC share similar mediators and cytokines [40,41]. Whether EAM arise by malignant transformation of endometriotic cells through intermediary lesions (atypical endometriosis) or similarity of microenvironment represents a link between these both entities has not been definitely understood [40,42].

Genetic Alterations

In the last two decades, evidence has been accumulated that endometriosis-associated malignancies may arise within ovarian endometriomas. Possibly, periodic hemorrhage in ovarian endometriomas may lead to iron-triggered oxidative stress and thus induce genetic alterations. Yamaguchi et al. reported that the concentration of free iron in endometriotic cysts was over one hundred times higher than that in nonendometriotic cysts; the level of oxidative stress related markers, such as lactose dehydrogenase, and antioxidants was higher as well [43]. Accumulation of mutations in tumor suppressor genes and oncogenes is a crucial step during tumor development. Interestingly, numerous mutations in genes linked to carcinogenesis have been identified in endometriotic lesions [44–52]. Several studies have reported genetic aberrations in tumor suppression genes, such as p53 and PTEN, in endometriosis specimens [53–55]. Inactivation of DNA mismatch repair genes through hypermethylation has been observed in endometriotic tissue as well [53]. Furthermore, genetic alterations associated with tumorigenesis are encountered more frequently in benign endometriosis samples from patients with synchronous ovarian cancer than in tumor-free patients who were diagnosed with endometriosis alone. Prowse et al. performed microsatellite analysis in ten patients with ovarian cancer and coexisting endometriosis; the tumor and endometriosis samples were analysed for common molecular genetic alterations [56]. 63 events of loss of heterozygosity (LOH) were detected in cancer specimens; one-third of these was also identified in the corresponding endometriosis samples, suggesting that endometriosis might be a clonal precursor to a subtype of ovarian cancer. Hypothetically, endometriosis-associated and endometriosis-independent ovarian cancer may develop through different molecular pathways with distinct genetic alterations (Table 2).

Risk Factors

Several risk factors for EAM in patients with endometriosis have been reported to date. The size of endometrioma as well as post-menopausal status were demonstrated to be independent predictive factors for the development of ovarian cancer among endometriosis patients in the study by Kobayashi et al. [57]. In this prospective cohort trial which assessed the risk of ovarian cancer in 6398 women with ovarian endometriomas, tumor size ≥ 9 cm in diameter was shown to be associated with increased OC risk. However, as mentioned before, one of the limitations of this study is that endometriomas were diagnosed mostly by sonography, and therefore some of the larger tumors might in fact have been ovarian cancers [57]. Another risk factor for EAM is hyperestrogenism, both endo- and exogenous: in the study by Zanetta et al. obesity as well as therapy with unopposed estrogens after hysterectomy were shown to be a significant risk factor for the development of EAM [58]. Similar effects of estrogen were demonstrated by others [40]. On the other hand, hormonal contraception, childhood, tubal ligation or hysterectomy were found
to reduce the ovarian cancer risk among patients with endometriosis [15,59].

**Clinical Implications**

EAOCC is characterized by an early onset of the disease: Aris et al. reported in their retrospective cohort trial that the mean age of women with EAOCC was 48.3 ± 10.8, on average 5.5 years lower than in non EAOCC patients (p = 0.003) [60]. In a retrospective study by Orezzoli et al. patients with endometriosis-associated clear cell cancer (CCC) of the ovary were even 10 years younger compared with those with non-endometriosis-associated CCC (95% CI 0.6–18 years; p < 0.05) [61]. Interestingly, EAOCC is commonly a low-stage and low-grade disease usually without ascites at initial presentation [62,63]. Furthermore, several authors reported that EAOCC is associated with significantly better prognosis (DFS and OS) compared with non-EAOCC, suggesting that EAOCC represents a biologically distinct entity [28,61,64,65]. However, these findings have not been confirmed by others: after controlling for stage, age, grade and treatment no difference in overall survival between these two patient groups could be demonstrated [62,66,67]; thus, better clinical outcome of EAOCC might be explained by a high rate of well-differentiated early-stage tumors rather than by an association with endometriosis per se [62,63,67].

Table 2  Genetic alterations associated with endometriosis and endometriosis-related malignancies.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Genetic alteration</th>
<th>Current data</th>
</tr>
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<tbody>
<tr>
<td>Oxidative stress</td>
<td>8-OHdG</td>
<td>8-Oxo-2′-deoxyguanosine is a marker of oxidative DNA damage. Endometriosis-related ovarian cancer show significantly stronger staining of 8-OHdG than ovarian cancers not accompanied by endometriosis [43]. Endometriotic cysts and atypical endometriosis also stain positive for this marker. 8-OHdG seems to play a role in pathogenesis of ovarian cancer and was linked to poor prognosis [44].</td>
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<tr>
<td>Tumor suppressor genes</td>
<td>PTEN</td>
<td>Phosphatase and tensin homolog is mutated in many cancer entities, particularly in endometrial and endometrioid ovarian cancer; its inactivation occurs early during tumorigenesis [53]. PTEN somatic mutations are frequently found in endometriotic cysts [45].</td>
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<tr>
<td></td>
<td>p53</td>
<td>As a negative cell-cycle regulator, p53 is involved in tumorigenesis of different malignancies. Several studies showed no expression in benign endometriosis but high expression in benign endometrioid lesions next to the endometrioid or clear cell carcinoma [54].</td>
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<td></td>
<td>ARID1A</td>
<td>ARID1A mutations are significantly more common in two ovarian cancer subtypes associated with endometriosis (clear-cell and endometrioid). In case of endometriosis synchronous with ovarian cancer, mutation was more frequent in clones derived from endometriosis samples directly adjacent of the tumor than in those from distant endometriotic lesions [46].</td>
</tr>
<tr>
<td></td>
<td>DNA repair</td>
<td>hMLH1 corrects errors in DNA replication; hypermethylation of its promoter occurs early in endometrial malignant transformation and can be identified in 10% of typical and in 33% of atypical endometrial hyperplasias [47]. Abnormal methylation can be observed in endometriosis as well [53].</td>
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<td></td>
<td>Oncogene</td>
<td>Bcl-2 Expression of this anti-apoptotic protein is significantly higher in endometriosis accompanying cancer (42–73%) than in benign endometriosis [23%] [54], suggesting its role in the early steps of tumorigenesis.</td>
</tr>
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<td></td>
<td>KRAS</td>
<td>KRAS mutations are significantly more common in endometriosis-associated endometrioid adenocarcinomas (29%) than in tumors not associated with endometriosis (3%) [48].</td>
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<td></td>
<td>Chromosomal aberrations</td>
<td>Aneuploidy Aneuploid frequency seems higher in endometriosis specimen from patients with advanced endometriosis when compared to the background frequency observed in normal specimens, particularly with regard to chromosome 17, on which tumor suppressor gene p53 is located [49,50].</td>
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<tr>
<td></td>
<td>Loss of heterozygosity (LOH)</td>
<td>A trend of increasing LOH frequencies has been described between solitary endometriosis lesions, endometriosis-associated carcinoma and endometrioid ovarian cancer, respectively [51,52]. Common LOH events can be identified in endometriosis synchronous with ovarian cancer [45,56].</td>
</tr>
</tbody>
</table>

Since EAM are mostly low-grade tumors, there is the question of the efficacy of chemotherapy in EAOCC patients [29]. However, in the study by Davis et al., no difference in response to chemotherapy in EAOCC patients compared with controls with papillary serious ovarian cancer has been found [62]. Due to the lack of appropriate data postoperative treatment of EAOCC follows the standard chemotherapy guidelines for ovarian cancer [71]. In case of extra-gonal EAM, especially of rectum or rectovaginal septum, however, surgical resection followed by radiotherapy may be the treatment of choice [29,31,65].

Several epidemiological studies, case reports and case series on EAM have been published in the literature to date. However, a systematic analysis of a large population of patients with EAM is still missing. Thus, a systematic retrospective study on endometriosis-associated malignancies (EAM study) is currently being conducted by the Endometriosis Research Foundation together with the study groups on ovarian and uterine tumors of the working group for gynecological oncology (AGO). Histopathological second opinion by pathology reference laboratory is the core


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