



The Association Between Endometriosis and Surface Epithelial Ovarian Tumors: A Review of Pathological Data

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Abstract

Background: Endometriosis is a prevalent benign condition arising from female reproductive system and affects about 7% to 10% of females. The association of this disorder with epithelial ovarian tumors has been a matter of interest in gynecology.

Objectives: The present study was conducted to assess the association between endometriosis and different types of surface epithelial ovarian tumor.

Methods: Microscopic slides of 182 cases with the diagnosis of surface epithelial ovarian carcinoma and borderline tumor from 2007 to 2014 were reviewed for the presence of endometriosis in a tertiary gynecological center. Additional data included age, tumor size and laterality, site of endometriosis, presence of atypical endometriosis, and concomitant uterine endometrial carcinoma.

Results: Endometriosis was found in 32 out of the 182 (17.58%) of reviewed ovarian epithelial tumor cases. They included endometrioid carcinoma (46.87%), clear cell carcinoma (18.75%), borderline epithelial tumor (31.25%), and low-grade serous papillary carcinoma (3.12%).

Conclusions: Endometrioid and clear cell types of ovarian tumors were most frequently associated with endometriosis.

Keywords: Endometriosis, Atypical Endometriosis, Epithelial Ovarian Tumor

1. Background

Endometriosis is a common gynecological disease, first described by Carl Freiherr Von in 1860 and defined as the presence of endometrial-like glands and stroma outside of uterine cavity and musculature. The estimated prevalence of endometriosis is 2% to 10% in the premenopausal, 2% to 4% in postmenopausal women, and 25% to 80% of infertile ones (1-7). The most common site of occurrence in endometriosis is ovary, but different locations in pelvic area are frequently involved. Although endometriosis is recognized as a benign disease, it has tendency to adhere, invade, and damage the affected organ. Additionally, it has potential to increase the risk of ovarian epithelial tumor in nearby location. The mentioned association has frequently been reported in English-language literature (2, 4, 8, 9). In 1925, Sampson et al. described the first histopathological criteria for identification of ovarian tumors arising from endometriosis, including the proximity of endometriotic site and the tumor, the evidence of origination of tumor from endometriosis, and rule out tumor invasion into the endometriotic foci from other sources as well as the presence of endometrial stromal tissue around

the endometrial glands (8, 10).

Van Gorp et al. classified ovarian tumors associated with endometriosis into 3 categories, according to the relations and proximity of endometriotic foci and tumor site; category A consists of ovarian tumors with transition from endometriotic area. This category fulfills the mentioned Sampson criteria; category B consists of all ovarian tumors with the same laterality of ovarian endometriotic foci but with no obvious transition; category C consists of all ovarian tumors with the associated detection of endometriosis in any location of pelvic cavity (11, 12).

Scott et al. in 1953 added another point to Sampson criteria, which was noticing transitional area between innocent endometriosis and premalignant atypical endometriotic lesion (13). Atypical endometriosis is reported to be the precursor of ovarian endometrioid and clear cell carcinomas, which are the most frequent reported endometriosis-associated ovarian epithelial tumors. The mentioned atypical transitional area has been noted in 15% to 35% of all cases (14). The concomitant presence of endometriosis in ovarian tumors is seen in 3.4% to 52.6% of cases. The standardized incidence ratio of ovarian cancer in patients with

endometriosis is 1.43% to 8.95% (15).

2. Objectives

The current study is designed to assess the prevalence and histomorphological characteristics of endometriosis-associated surface epithelial ovarian tumors, both in and extra-ovarian sites.

3. Methods

3.1. Patients

This cross sectional study was conducted between 2007 and 2014. Prior to data collection, the study was reviewed and approved by the ethical committee of Tehran University of Medical Sciences (code: 43500). In this study, patients with a histologic diagnosis of surface epithelial ovarian carcinoma and borderline tumors were recognized in the files of the department of pathology in YAS hospital, Tehran University of Medical Sciences. All the slides were reviewed and data regarding tumor side, tumor classification, presence or absence of endometriosis, type of endometriosis, and other histological features were collected. The histological classification of ovarian cancer was based on World Health Organization (WHO) classification of surface epithelial ovarian tumors, whose diagnosis were categorized into serous, mucinous, clear cell, and endometrioid, borderline, and carcinoma. The histological review of all tumors was performed. Sampson's criteria along with Scott's modification were used to make a diagnosis of endometriosis-associated ovarian tumors (7).

Endometriosis was defined as the presence of endometrial glandular epithelium accompanied by endometrial stroma in a site other than the uterine corpus. Considering stromal hemosiderin deposition for the diagnosis of endometriosis is only helpful when the foci is located in a separate site from tumor; otherwise, intra-tumoral cyst formation and tumor hemorrhage may result in hemosiderin deposition close to tumor and should not be mistaken as endometriotic foci.

Also, atypical endometriosis was diagnosed according to LaGrenada and Silverberg criteria. Atypical endometriosis may show large nuclei, pale pleomorphic hyperchromasia, nuclear crowding, tufting, stratification, and eosinophilic cytoplasm. At least, the presence of 3 among the mentioned features is necessary for the diagnosis of atypical endometriosis (16).

Metastatic cases were excluded from the present study. We also analyzed the patient's age at the time of ovarian

tumor diagnosis. Additional gathering data included tumor size and laterality, site of endometriosis, differentiation degree of endometrioid carcinoma, and synchronous uterine endometrial carcinoma.

In this study, H&E slides were accessible in entirely all of the cases and the mean number of slides was 9 per case.

3.2. Statistical Analysis

A $P < 0.05$ in a two-sided test considered a significant difference and all results were statistically analyzed, using SPSS-21 software. Student t test was used for comparing study groups. One-sample Kolmogorov-Smirnov Test was used to check normality distribution.

4. Results

A total of 182 cases with diagnosis of epithelial ovarian carcinoma and borderline tumor, in a 7-year period between 2007 and 2014 were recognized in the files of the department of pathology. According to the above-mentioned criteria, endometriosis was found in 32 out of the 182 cases (17.58%). Out of 182 cases, 25 (13.73%) cases with diagnosis of endometrioid carcinoma and 13 (7.14%) with clear cell carcinoma was found. Out of 25 endometrioid carcinoma, 15 (60%) cases associated with endometriosis and 4 (16%) cases have atypical endometriosis. Out of 13 clear cell carcinoma, 6 (46.15%) cases associated with endometriosis and atypical endometriosis were not seen.

Ten (31.25%) cases of borderline tumor and 1 (3.12%) case of low-grade serous papillary carcinoma were associated with endometriosis. None of high grade serous carcinoma and mucinous carcinoma had endometriosis.

The mean age was 41.06 years in endometriosis-associated surface epithelial ovarian tumors and 43.14 years in without endometriosis.

The average size of tumor among patients diagnosed with endometrioid or clear cell carcinoma with endometriosis (8.93 cm) was less than those who have these types of cancer without endometriosis (11.58 cm).

Among 15 cases of endometrioid carcinoma with endometriosis, 13 cases (86.66%) were diagnosed as well differentiated and 2 (13.33%) moderately differentiated, 10 cases (66.66%) had squamous metaplasia and 2 cases (8%) with primary synchronous ovarian and endometrial endometrioid carcinoma.

In this study, we found 10 borderline tumors associated with endometriosis, including 7 cases (70%) of mucinous with 2 different types (4 cases endocervical type and 3 cases seromucinous or mullerian type) and 3 cases (30%) with serous papillary type. No intestinal type of mucinous borderline tumor was found. The categorization of patients

with endometriosis associated surface epithelial tumors is illustrated in [Table 1](#).

In 10 cases of endometrioid carcinoma without endometriosis, 6 cases (60%) were well differentiated and 3 cases (30%) moderately differentiated and 1 case poorly differentiated (10%). Also, 4 cases (40%) had squamous metaplasia.

5. Discussion

The aim of this study was to find the proportions of ovarian epithelial tumors, which are associated or concurred with endometriosis and to evaluate whether these tumors are originated from endometriosis or not. Endometriosis-associated ovarian tumors have been investigated and described in several studies (15). The most common histological subtypes of ovarian epithelial tumors found to be associated with endometriosis are endometrioid and clear cell subtypes (15, 17).

We reviewed all diagnosed surface epithelial ovarian tumors including carcinoma and borderline tumors in a 7-year period. Out of 182 cases, only 32 (17.6%) had concomitant endometriosis, which gave the impression to be similar that reported by other studies. As reported in an Iranian study, the prevalence of endometriosis was 38% in infertile and 11.6% in fertile females.

There are many pitfalls regarding the diagnosis of endometriosis in patients with ovarian tumors, leading to misestimating the prevalence of endometriosis in such patients. Firstly, there are numerous criteria for the diagnosis of endometriosis-associated ovarian tumors and also detection of a small focus of endometriosis demands extensive sampling of the specimen, which is not always possible. Also in cases that the tumor is adjacent to endometriosis, the main problem is the destruction of the endometriotic foci by tumor and the detection of endometriosis is not always possible and, finally, sometimes the endometriotic site is marsupialized or never treated during the surgery causing underestimating endometriosis in such cases (12, 18).

The association between ovarian tumor and endometriosis was reported in the literature by 2 different categories. A transition point from an endometriotic lesion (atypical endometriosis) to a frankly ovarian invasive carcinoma has been demonstrated in 36% to 42% of cases (19-24). In the remaining cases, the tumor simply coexists with endometriosis without a transition point.

Atypical endometriosis has been known to be premalignant lesion of ovarian carcinoma. In 1979, Morris et al. categorized atypical endometriosis according to histomorphological features from mild to severe. Endometriotic foci with mono-layered epithelium consist-

ing of eosinophilic cuboidal cells with pleomorphic enlarged nuclei are considered mild atypical endometriosis and those cases with tufting, crowding, stratification, and intraluminal projections of cells with eosinophilic cytoplasm and large hyperchromatic pleomorphic nuclei are categorized as severe atypical endometriosis. Glandular proliferation with mild atypia can be a reactive condition due to local inflammation and it should not be considered as a premalignant lesion, on the other hand, severe atypia is only expected in potentially premalignant lesions (12).

In a study conducted by Fukunaga et al. the prevalence of endometriosis-associated ovarian cancer was 24%, of which 61% were accompanied with atypical endometriosis and in our study, 12.5% (4 out of 32 cases) of patients with endometriosis-associated surface epithelial tumor had atypical endometriotic changes in the background, all of which were endometrioid carcinoma. In the remaining 28 cases, endometriotic foci could not fulfill the criteria for atypical endometriosis.

As a result, we concluded according to Van Gorp et al. the occurrence of endometriosis-associated ovarian tumors is minimum considering only definite cases with a proven atypical transition (Category A) and it is maximum when other cases with separated foci of endometriosis (Category B and C) are included. However, in either way, the estimated prevalence of endometriosis-associated ovarian epithelial tumors is lower than the actual prevalence. The reason of the mentioned problem is scarcity of the examined specimen and further missing of the transitional area, and destruction of premalignant endometriotic foci in some cases. This observation in a surgical specimen should aware the pathologist to examine the entire lining of the cyst such as surface epithelial ovarian borderline tumors and the patient should be under close follow up.

The histological subtypes of clear-cell and endometrioid ovarian cancer are four-fold higher in patients with endometriosis; therefore, these subtypes are recently regarded as "Endometriosis-associated ovarian tumors" (6). Another study described a two-fold increase of low grade serous carcinomas in patients with endometriosis, but mucinous or high-grade serous carcinomas were not related with endometriosis in other studies (25).

According to the results of this study, only 1 low-grade serous carcinoma (3.12%) associated with endometriosis was not found with high-grade serous carcinoma. If we define ovarian cancer as type I and type II according to Kurman and Shih's classification (26), coexisting endometriosis was more commonly detected in type I cancers. It should be mentioned that endometrioid, clear cell and low-grade serous carcinoma are considered as type I cancer. Consistently, in a study carried out by Wang et al., 18.3%

Table 1. Categorization of 182 Patients with Surface Epithelial Ovarian Tumor

Tumor	Association with endometriosis	Tumor type	Category	Subtype	
Surface Epithelial ovarian tumors (182 patients)	Tumors associated with endometriosis (32 patients)	Endometrioid Carcinoma (15 patients)	Well differentiated (13 patients)		
			Moderately differentiated (2 patients)		
		Clear Cell carcinoma (6 patients)			
		Borderline ovarian Tumor	Mucinous type (7 patients)	Endocervical type (4 patients)	
			Seromucinous type (3 patients)		
			Serous papillary type (3 patients)		
		Serous carcinoma (low grade) (1 patient)			
Tumors not associated with endometriosis (150 patients)					

Table 2. Classifications of Endometriosis

Histological Subtype	Number of Cases	Atypical Endometriosis	Typical Endometriosis	A	B	C
Endometriotic carcinoma	15	2	13	2	11	2
Clear cell carcinoma	6	2	4	2	2	2
Borderline serous carcinoma	3	-	3	-	7 (seven out of ten borderline tumors)	3 (three out of ten borderline tumors)
Borderline mucinous carcinoma	7	-	7	-		
Low grade mucinous carcinoma	1	-	1	-	1	-
Total	32	4	28	3	21	7

of endometriosis-associated ovarian tumors were type I ovarian carcinoma and endometriosis was postulated to be one of precursor lesions for type 1 ovarian carcinoma (27). These studies give some clues for discovering pathogenesis mechanism of type 1 ovarian carcinoma and emphasizing the difference between type 1 (low-grade serous) and type 2 (high-grade serous) ovarian carcinomas.

The mean age of our patients was 41.6 years that was less than patients without endometriosis, (43 years). In a study conducted by Aris et al. the mean age of women was 48.3 years, which is higher than the value in this study (20). In Aris's study, there was a statistically significant difference between the mean age of patients with ovarian cancer, which is not the case for endometriosis (53.9 years) and ovarian cancer with endometriosis (48.3 years) ($P = 0.003$), suggesting an early onset of ovarian cancer in women having endometriosis (17, 18), but we have not found statistically significant differences in the present study ($P = 0.57$).

Also we have not found statistically significant differences between various ages and concomitant endometriosis with endometrioid and clear cell carcinoma, when age was divided into decades, a statistically significant differ-

ence was obtained in age 40 to 50 years ($P = 0.034$).

In the present study, out of 32 endometriosis-associated surface epithelial ovarian tumors, the endometriosis was found: 25 cases were in the same side, 4 cases bilateral, 1 case in opposite ovary, 1 case within fallopian tube, and the last one in abdominal wall. These distributions show that malignancies were more common in ovaries that contained endometriosis (78%) than in the opposite ovary or extra ovarian locations of endometriosis. It seems that some local factors have a significant role in the transformation pathway from endometriosis toward malignancy.

The findings of this study revealed only a single case of extra-ovarian endometriosis-associated clear cell carcinoma (in abdominal wall related to previous cesarean scar). In ovarian endometriosis, endometrioid adenocarcinomas accounted for 69% of tumors, clear cell carcinoma 14%, and sarcomas 12% (4). In contrast, clear cell carcinoma and adenosarcoma were more associated with extraovarian endometriosis (4).

We have found that 2 out of 15 cases of concomitant endometriosis with endometrioid carcinoma of ovary

have shown endometrioid carcinoma in the uterine cavity (13.3%). Concurrent primary neoplasms in female genital tract are a matter of interest for clinicians. Estrogen receptors may play a role in synchronous or multifocal malignancies in this region. Endometriosis has been shown to be associated with such situations. Thus, these findings show that ectopic endometrium as well as normal endometrium can be stimulated by estrogen hormone (10). Data regarding features and classification of endometriosis-associated ovarian epithelial tumors in this study are illustrated in Table 2.

We concluded that the actual prevalence of endometriosis-associated ovarian tumors is underestimated. One reason is the lack of enough confident criteria for the diagnosis of endometriosis-associated ovarian tumors and also extensive sampling of surgical specimen for detecting small or destructed foci of endometriosis is not always possible.

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Footnotes

Authors' Contribution: Soheila Sarmadi was the corresponding author, designed the study, signed H&E, and analyzed the data and writing-up process. Narges Izadi-Mood designed the study, signed H&E, and cooperated in editing process. Parisa Hajeri prepared and analyzed the data. Dorna Motevalli and Mehdi Masoumian revised the article.

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