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Prevalence of endometriosis in malignant epithelial ovary tumours

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Abstract

Objective: To determine the prevalence of ovarian endometriosis in malignant epithelial ovarian tumours. *Study Design*: A retrospective analysis of 160 malignant and 23 borderline ovarian tumours during the period 1995–2001. *Results*: Fourteen (7.7%) of the tumours contained endometriosis. This affected 22% of the endometrioid and 10.8% of the mixed adenocarcinomas. The mean age of the ovarian endometriosis patients was 43 ± 13 range 26–70 years. The incidence in borderline tumours 13% (3/23) was higher than that in ovarian cancer 6.9% (11/160) ($P > 0.05$). Eight (57%) of cases were classified as atypical and six (43%) as typical endometriosis. Nine cases were FIGO (International Federation of Gynaecology and Obstetrics) stage I and 5 stage III. *Conclusions*: Both malignant and borderline ovarian tumours are associated with ovarian endometriosis. In addition, atypical endometriosis was found associated with endometrioid and mixed epithelial ovarian tumours.

Keywords: Atypical endometriosis; Ovarian carcinoma; Endometrioid adenocarcinoma; Borderline epithelial ovarian tumours

1. Introduction

Endometriosis is a benign, but often progressive, disease that has an estimated 10% prevalence in the premenopausal population and only 2–4% of women in the postmenopausal period have endometriosis [1,2]. Since Sampson first described the term endometriosis in the early 1920s, there have been a lot of controversies regarding possible association between endometriosis and carcinoma of the ovary [3]. To date, a considerable number of studies have described an association of ovarian cancer with endometriosis [4–7]. In addition, endometrioid and clear cell carcinoma are the malignancies most commonly reported in women with endometriosis [8,9]. The largest of these was a review paper published by Mostoufizadeh and Scully in 1980 [10]. They quote 31 case reports or series that cite an association between endometriosis and endometrioid carcinoma. In another large study, Vercellini and associates looked at the incidence of endometriosis in 556 patients undergoing surgery for ovarian cancer [11]. In this study, the frequency of endometriosis ranged from 22 to 26 in endometrioid, clear cell, and mixed subtypes. A large, cohort study demonstrated an almost four-fold increase in the risk of ovarian cancer among women with a long history of ovarian endometriosis [12].

Atypical endometriosis first used in 1988 by LaGrenade and Silverberg and it is characterized histologically by endometrial glands with cytological or/architectural atypia [13]. The researchers described atypical ovarian endometriosis as cells that showed epithelial stratification, tufting, crowding of glands, and nuclear enlargement and they highlighted atypical endometriosis as a transitional state from endometriosis into carcinoma.

In this study, we focused on the prevalence of endometriosis and the atypical endometriosis in each histologic type of ovarian malignant epithelial tumours in our patients.

2. Materials and method

The material for this study consisted of all of the (*n*: 183) malignant epithelial tumours of ovary patients who underwent surgery between the years 1995–2001 at the Department of Obstetrics and Gynecology Cerrahpasa Medical Faculty, University of Istanbul. Patients with epithelial tumor of low malignant potential (*n*: 23) were also included

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to this study. Each case was staged according to the current International Federation of Gynecology and Obstetrics (FIGO) staging system. Histologic classification of ovarian cancer was based on the World Health Organization classification of ovarian tumours [14]. Tumours were assigned to the mixed epithelial category only when a second component represented 25% or greater of the sampled tumor tissue. All the slides of 183 cases were reviewed by one of the authors (SI). The presence of ovarian endometriosis (endometrioma or peritoneal endometrioisis) was determined by reviewing the hematoxylin and eosin stained sections of resected specimens. Coexistence of ovarian endometriosis was identified by confirming the presence of glandular epithelium accompained by endometrioid stroma in the ovaries. In the present study, ''malignant epithelial ovarian tumours associated with endometriosis'' was defined as follows: (1) presence of malignant epithelial ovarian tumours and endometriosis identified histopathologically in the same ovary; (2) presence of endometriosis in one ovary and that of malignant epithelial ovarian tumours in the contralateral ovary.

The diagnosis of atypical endometriosis was based on the histopathological criteria designated by LeGrenade and Silverberg, and Czernobilsky and Morris, [13,15]. These features included eosinophilic cytoplasm; large hyperchromatic or pale nuclei with moderate to marked pleomorphism; increased nuclear to cytoplasmic ratio; cellular crowding and stratification or tufting. The cases that contain three or more of these criteria were classified as atypical endometriosis (Fig. 1)

Hendrickson and Kempson's criteria were used to diagnose the various types of endometrial metaplasia [16]. According to this classification, ciliated, eosinophilic, mucinous, papillary, squamous, hobnail, and clear cell metaplasia were identified.

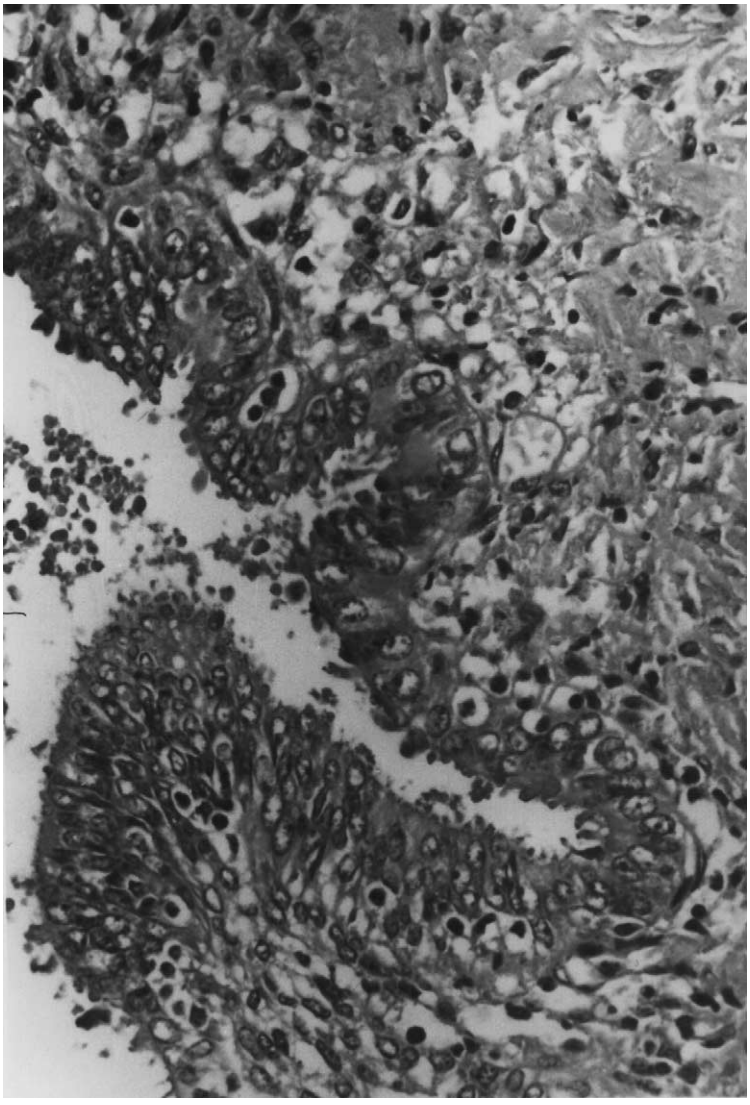

Fig. 1. Atypical endometriosis characterized by striking epithelial tufting, stratification, and nuclear atypia. Hematoxylin and eosin stain, original magnification 400×.

Differences between groups were analyzed by the χ^2-test and level of P-value <0.05 was regarded as statistically significant.

3. Results

During the 6-year time period, there were 183 patients with malignant epithelial tumours of ovary (160 malignant and 23 borderline). Serous adenocarcinoma was the most frequently encountered histological subtype, accounting for the 59 of the 183 tumours (32.2%), followed by mixed 37 (20.2%), mucinous 23 (12.6%), endometrioid 18 (9.8%), clear cell 11 (6%), mucinous borderline tumours 12 (6.6%), serous borderline tumours 11 (6%) and others 12 (6.6%). Endometriosis was found in 14 of the 183 cases (7.65%). Eight cases were stage I–II and six cases were stage III. The mean age of the patients with ovarian endometriosis was 43.4 ± 12.7 (range 26–70) years and four (28.6%) were nulliparous. Four (28.6%) of the women with ovarian cancer and endometriosis were postmenopausal. Table 1 shows the incidence of endometriosis in each histologic type of ovarian cancer and endometriosis being more frequently associated with endometriod (22.2%) and mixed (10.8%) adenocarcinomas than with other histological subtypes. The incidence in endometrioid type was significantly higher compared with that in serous type ($P < 0.05$). The incidence of ovarian endometriosis in borderline tumours 13% (3/23) was higher than that in ovarian cancer 6.9% (11/160) ($P > 0.05$). On the histological review, 8 (57.1%) cases were classified as atypical endometriosis and 6 (42.9%) cases were typical endometriosis. Atypical endometriosis was found in three endometrioid, in three mixed adenocarcinomas, in one mucinous carcinoma, and in one borderline tumour. Metaplasias (Ciliated and hobnail cell) were observed in 9 of 14 (64.3%) cases and were observed in both typical and atypical endometriosis. These 14 cases with endometriosis were classified as International Federation of Gynecology and Obstetrics (FIGO) stage I (n: 9, 64.3%), and stage III (n: 5, 35.7%). Tumours with endometriosis were nine (64.3%) on the left-hand side, 2 (14.2%) on the right-hand side, and three (21.4%) were bilateral.

Table 1
The incidence of ovarian endometriosis in each histologic type of ovarian cancer

Histological type (n)	Number of patients with endometriosis		
	Atypical	Typical	Total (%)
Serous[a] (70)	1	2	3 (4.3)
Mucinous[a] (35)	1	1	2 (5.7)
Endometrioid (18)	3	1	4 (22.2)
Clear cell (11)	0	1	1 (9.1)
Mixed (37)	3	1	4[b] (10.8)
Others (12)	0	0	0
Total (183)	8	6	14 (7.65)

[a] Malignant and borderline tumours.
[b] One case clear cell + serous; one case clear cell + endometrioid; two cases serous + mucinous + endometrioid.

4. Comment

A number of studies have found an association of ovarian cancer and endometriosis [4–8]. Traditionally, it has been considered that only a subset of cases with these ovarian cancer were associated with endometriosis. But one recent study demonstrated that 70% of clear cell carcinomas and 43% of endometrioid carcinomas were associated endometriosis [8]. The incidence of endometriosis in ovarian cancer reported in the literature ranges from 4.2 to 29.1% [7,8,11,17–19] (Table 2). The incidence in the present study (7.65%) seems to be comparable to that reported from the other studies. The incidence of endometriosis in general population is thought to be 2–10% in the premenopausal women and 2–4% in the postmenopausal women [1,2]. Based on our institution surgery data the incidence of ovarian endometriosis was 8% in age under 50 years and 3% in age 50 years older. In our ovarian cancer patients (n: 410) 176 (42%) cases were premenopausal and FIGO stage I and II cases (n: 128) 88 of them (68.8%) were premenopausal period.

The prevalence of endometriosis seems to be slightly higher in ovarian cancer patients that in the general population. One reason for frequent coexistence of endometriosis with ovarian cancer may be that both diseases share the same risk factors, such as infertility and nulliparity.Many reports have suggested that cases of ovarian cancer, especially with clear cell type and endometrioid type, which arose in preexisting endometriosis [4–6]. In some of these cases, a direct transition of the cancer from the lining epithelium of endometriosis was strongly suggested. Other evidence supporting the theory that endometriosis can undergo malignant transformation is the coexistence of carcinoma and endometriosis in a significant number of patients. The incidence of ovarian endometriosis in each histologic type of ovarian cancer in different studies was as follows: 0–13 in serous type; 0–6 in mucinous type; 8–70 in clear cell type; and 943 in endometrioid type [8,20]. These data indicate that clear cell and

Table 2
Summary of the reports on the incidence of ovarian endometriosis in ovarian cancer patients

Reference	Incidence of ovarian endometriosis (%)
Aure et al. [17]	35/831 (4.2)
Russel [18]	46/407 (11.3)
Vercellini et al. [11]	60/504 (11.9)
Jimbo et al. [19]	25/172 (14.5)
Fukunaga and Ushigome [7]	48/179 (26.8)
Ogawa et al. [8]	37/127 (29.1)
Oral et al. (2003)	14/183 (7.6)

endometrioid types are frequently associated with endometriosis. However, it is to be noted that endometriosis in clear cell type in our group was less then the other studies (9.1%). The pathogenesis of ovarian endometrioid and clear cell carcinomas may be different from that of serous tumours. It would seem that ovarian endometrioid and clear cell carcinomas have a unique pathogenesis involving endometriosis, but the mechanisms of that pathway have not yet been determined.

In one study, authors concluded that ovarian endometriosis increases the risk of ovarian cancer, especially in postmenopausal women. Eleven (26%) of the women that study with endometrioid ovarian cancer had evidence of endometriosis next to the cancer and eight of the women (73%) were postmenopausal. [21].The authors did not indicate whether the postmenopausal patients were taking hormone replacement therapy. In our patients, only four (28.6%) of them were postmenopausal and none of the were on hormone replacement therapy.

It has also been recognized that the endometriosis associated with ovarian carcinomas may contain foci of atypia that have been suggested as representing a premalignant phase within the endometriosis [3,13,22]. Fukunaga's group investigated the incidence of ovarian atypical endometriosis and its association with malignant epithelial tumours and found that 54 of 224 ovarian cancers were associated with ovarian endometriosis, of those 21 were typical and 33 were atypical [7]. They concluded that atypical endometriosis possesses a precancerous potential for the clear cell and endometrioid carcinomas. The incidence of atypical endometriosis was found to be 3.6% by Czernobilsky and Morris, 1.7% Fukunaga et al., 5.8% Bayramoglu and Duzcan, and 32.3% by Seidmann [15,7,23,24]. Recently, Ogawa et al. reported that of the 127 ovarian cancer patients, 29 (22.8%) had atypical endometriosis and most of them (86.2%) were associated with clear cell type carcinoma [8]. In our study, incidence of atypical endometriosis was 4.4% (8/183) and most of them were associated with endometrioid and mixed type carcinoma (Table 1). It is noted that so-called 'atypical endometriosis' may represent a step in that pathway, but the factors leading to this atypia are not understood.

Fukunaga and Ushigome in their series, they observed ciliated and eosinophilic metaplasias associated with malignant ovarian epithelial tumor [25]. But, there was no correlation between types of carcinoma and types of metaplasia in endometriosis.

Fukunaga et al. reported 4 in 42 (9.5%) borderline epithelial ovarian tumours were associated with endometriosis and three were mucinous mullerian type [7]. In our group, however it was not the statistically significant, we found that 13% borderline tumours were associated with endometriosis. Rutgers and Scully mentioned that müllerian mucinous borderline tumours were associated with 30% frequency of endometriosis [26]. Among our mucinous borderline tumours (12 cases) one of them was associated mucinous müllerian type with atypical endometriosis.

Vercellini et al. investigated the distribution of early stage epithelial ovarian tumours and they found that proportion of left-sided lesions was higher (65%) in the endometrioid type than the other types [27]. In our series, tumours with endometriosis were 64.3% on the left-hand side but the proportion of left-sided ovarian tumours with endometriosis is very similar in each histologic type.

In this study, we found that atypical endometriosis was frequently to be associated with ovarian carcinoma, especially with endometrioid and mixed type carcinoma.

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