Gynecologic Oncology 133 (2014) 480–484

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Characteristics of clear cell ovarian cancer arising from endometriosis: A two center cohort study

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HIGHLIGHTS

- Clinical and histological features of the largest series of clear cell carcinomas arising in endometriosis are analyzed.
- No difference in stage, grade, survival and endometrial cancer incidence was found between tumors arising or not in endometriosis.
- Younger age, unilateral ovarian involvement and absence of ascites were more frequently found in cases arising in endometriosis.

ARTICLE INFO

Article history:
Received 19 January 2014
Accepted 10 March 2014
Available online 15 March 2014

Keywords:
Endometriosis
Clear cell ovarian cancer
Endometriosis associated ovarian cancer

ABSTRACT

Objective. Endometrioid and clear cell ovarian tumors have been referred to as "endometriosis associated ovarian cancers". However, very few studies have compared clinical and prognostic features of endometriosis-associated cancers or cancers not associated with endometriosis according to specific histotypes. We have investigated clinical and histological features of the largest published series of clear cell ovarian cancers arising in endometriosis using a retrospective database.

Methods. Seventy three patients with a primary diagnosis of either pure clear cell ovarian cancer and mixed endometrioid-clear cell ovarian cancer have been divided into two groups according to the detection of cancer strictly arising from ovarian endometriosis or not (n = 27 and n = 46, respectively). Clinical and pathological data have been compared.

Results. Patients with clear cell carcinomas arising from endometriosis tend to be significantly younger (51.4 ± 10.0 and 58.4 ± 11.2 years, $p = 0.02$). FIGO stage, laterality, prevalence of pure versus mixed histology, and presence of synchronous endometrial carcinoma were not significantly different between the two groups. Unilateral ovarian involvement was more frequent in cases arising in endometriosis (85% vs 63%, $p = 0.04$). Ascites was not found in any of the endometriosis-associated cancer cases vs 19.5% in patients without endometriosis. The presence of endometriosis did not affect 5-year overall survival rates.

Conclusions. Endometriosis per se does not appear to be associated with a lower stage tumor or to predict prognosis in ovarian clear cell cancers. Unilateral involvement and reduced presence of ascites may be linked to the cystic nature of endometriosis which frequently presents as monolateral and in which associated tumors are more likely to be longer confined to the ovary before spreading.

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Introduction

Endometriosis is a risk factor for epithelial ovarian cancer [1,2]. Based on the results of a large international collaborative study, self-reported endometriosis was associated with an overall risk increase of nearly 50% [Odds Ratio, 1.46; 95% confidence intervals (CIs), 1.31–1.63] [3]. This issue is of particular clinical relevance given the prevalence of endometriosis, estimated to be around 5%, with a peak between 25 and 35 years of age [4].

It is also well known that tumors associated with endometriosis are confined to specific subcategories of disease, endometrioid and clear cell ovarian cancers, and the risk of detecting these histotypes is estimated to be about 4-fold higher in women with the disease [5].

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http://dx.doi.org/10.1016/j.ygyno.2014.03.017
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Controversy remains regarding the possibility that endometriosis-associated cancers might represent a distinct entity from the correspondent typical histotype. Some studies have indeed suggested that patients with endometriosis tend to be younger, to be diagnosed in earlier stages and with lower grade lesions and to have an overall better survival rate whereas other studies fail to confirm these findings [6–13]. Importantly, very few of these studies have evaluated clinical and prognostic differences between endometriosis-associated cancers or cancers not associated with endometriosis according to the specific histotype [8,9,13,14]. This might have prevented the identification of characteristics potentially linked to a specific subcategory of disease.

In this context, in a recent study [8], we have analyzed a cohort of patients diagnosed with endometrioid ovarian cancer and confirmed that women with endometriosis-associated cancer were significantly younger at the diagnosis, had a lower disease stage and a less prevalent high grade tumor. A difference in survival rate could not be confirmed between patients with and without endometriosis. Importantly, a synchronous endometrial precancerous or cancerous condition has been detected at a significantly higher rate in endometriosis-associated endometrioid cancers, possibly leading to various and novel interpretations for the mechanisms of this cancer development.

Along this line, in this study, we have evaluated the clinical and prognostic features of endometriosis-associated ovarian cancers of clear cell histotype and compared them with those of clear cell tumors without endometriosis.

Results of the present study considering the most numerous series of cancers of clear cell and mixed endometrioid-clear cell histotype arising in endometriosis and of our previous study on ovarian endometrioid tumors [8] tend to support the idea that endometrioid and clear cell cancers associated with endometriosis should be no more considered a single entity with similar risk and prognostic factors and biologic mechanisms of development.

Materials and methods

This is a retrospective study of 73 cases of clear cell ovarian carcinoma consecutively observed at two centers, the Department of Obstetrics and Gynecology of the Fondazione Ospedale Maggiore Policlinico and the Obstetrics and Gynecology Unit of the Scientific Institute San Raffaele in Milan, Italy between 1990 and 2012. Institutional Review Board approval has been obtained for this retrospective study.

All patients with a primary diagnosis of either pure clear cell ovarian cancer or mixed endometrioid-clear cell ovarian cancer have been included in the study. Patients whose diagnosis was made elsewhere were excluded. Patients older than 75 were not included in survival analysis. Some data from 33 patients have been already included in a previous paper [7].

All patients underwent surgery, received chemotherapy and were followed up at our institutions. Surgical staging was performed according to FIGO guidelines for ovarian cancer, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and removal of all macroscopic diseases [15]. Radical upper abdominal techniques were applied in selected cases to achieve optimal cytoreduction. All pathological analyses were performed by the same two gynecologic pathologists, who, in both institutions, are completely dedicated to gynecological cases.

Patients were divided into two groups according to the detection of cancer arising from ovarian endometriosis or not, on the basis of pathological reports. The definition of ovarian cancer arising from endometriosis was given according to Sampson's [16] and Scott's criteria [17], that included: 1) the coexistence of carcinoma and endometriosis in the same ovary; 2) presence of tissue similar to endometrial stroma surrounding characteristic epithelial glands; 3) exclusion of a metastatic tumor to the ovary; and 4) presence of benign endometriosis histologically contiguous to the malignant tissue. Patients with clear cell carcinoma associated with but not arising in endometriosis were excluded.

Data including age at diagnosis, clinical presentation, disease status, last follow-up and all pathological information, such as histology, stage, laterality, and presence of concurrent endometrial carcinoma were collected from surgical and pathology reports. Stages higher than IIA were classified as advanced, while lower stages were considered early.

All the abovementioned variables were described for each of the two groups and statistically compared. The Pearson Chi-square test or Fisher Exact test, as required, was used to assess the significance of differences in clinical and pathological characteristics between the two groups.

Survival comparisons were obtained using the long-rank test in an unadjusted Kaplan Meier model, survival rates being calculated from the date of histological diagnosis. Finally, to account for the effect of potential confounding factors simultaneously, we used the Cox regression model (after checking the proportional hazards assumption) to obtain the hazards ratio (HR) and their corresponding 95% CIs. In all analysis, a p value of <0.05 was considered statistically significant. Follow-up was updated in May 2013, being median follow-up of 68 months (95% CI, 55–103).

Results

Seventy-three patients met the inclusion criteria. Of these, n = 27 (37%) cases have been affected by tumors arising in endometriosis (Fig. 1), while n = 46 patients (67%) had no concomitant endometriosis. Patients and tumor characteristics of the two groups are summarized in Table 1.

In both groups, the most common diagnosis was incidental, followed by the detection of an abdominal mass. Symptoms did not differ statistically between the two groups except for presence of ascites that was only detected in patients without endometriosis (19.5% versus none of the patients in the endometriosis group).

Patients with endometriosis-associated clear cell carcinomas or of mixed histology tend to be significantly younger than cases without endometriosis with mean age ± SD being 51.4 ± 10.0 and 58.4 ± 11.2 for tumors arising in endometriosis and not, respectively ($p = 0.02$).

Among endometriosis-free patients, n = 23 (50%) were diagnosed in early stages while 50% in advanced stages. In the other group, n = 18 (66.7%) were in early stages, and n = 9 (33.3%) were in advanced.

FIGO stages were not significantly different between the two groups ($p = 0.16$).

The prevalence of patients with pure clear cell histology and mixed histology was respectively 76.1% and 23.9% in the endometriosis-free group and 70.4% and 29.6% in the endometriosis group. No statistically significant difference was detected ($p = 0.59$).

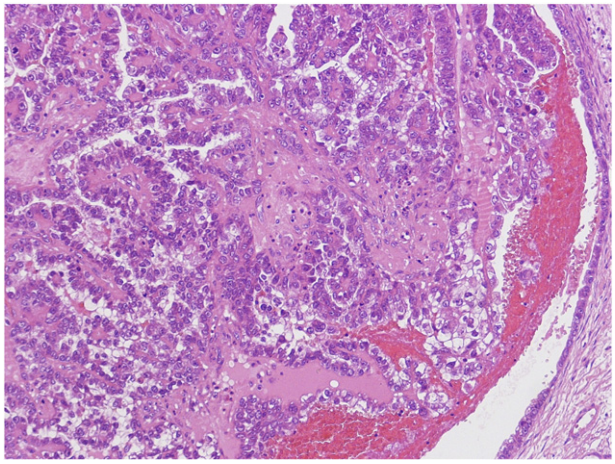

Fig. 1. A typical ovarian clear cell carcinoma of papillary type, grown into the lumen of an endometriotic cyst lined by columnar endometrioid type cells. (Hematoxylin and eosin × 125.)

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