Synchronous ovarian and endometrial carcinoma: a strong link to endometriosis?

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Summary

Purpose: To further study the clinicopathological features of synchronous ovarian and endometrial carcinomas. *Methods:* We retrospectively studied all cases of synchronous ovarian and endometrial carcinomas diagnosed in our laboratory over the last 15-year period. The pathological findings were correlated with the clinical records of the patients. *Results:* Seven cases of synchronous primary ovarian and endometrial carcinomas were retrieved. The most common presenting symptom was abnormal vaginal bleeding (5 cases, 71.4%). Five patients (71.4%) were postmenopausal and two (28.6%) were nulliparous. All seven patients had Stage I ovarian and endometrial carcinomas of endometrioid histology. Moreover, in all seven ovarian carcinomas endometriosis foci were observed, while atypical endometriosis was found in four of them. With the exception of one patient, who received adjuvant postoperative radiation, all remaining patients were treated with surgery alone. All patients were alive and free of disease at completion of the study. *Conclusion:* The correct classification of synchronous primary ovarian and endometrial carcinomas is often problematic because of the frequent confusion with their metastatic counterparts. Although the exact etiology remains unclear, endometriosis seems to be a major risk factor for their development.

Key words: Ovarian; Endometrial; Synchronous carcinomas; Endometriosis.

Introduction

Multifocal presentation of primary carcinomas in various sites of the female genital tract is a relatively rare but well recognized entity of unknown etiology. Most of these neoplasms seem to involve the ovary and the endometrium, with most reported incidences approximating 10% of all women with ovarian cancer and 5% of those with endometrial cancer [1]. However, many authors believe that these percentages are overestimated, including metastatic rather than true primary neoplasms [1, 2]. On the other hand, the pathological diagnostic criteria of synchronous ovarian and endometrial tumors, as originally described by Ulbright and Roth in 1985 and completed by Scully *et al*. 13 years later, although extremely useful in resolving these diagnostically challenging cases, seem mostly empirical and remain to be validated [1, 3, 4]. As a result of all this controversy, the staging and therapeutic strategies employed in these cases varies significantly among different authors and institutions, and the optimal management of – at least – some of these patients is likely to be compromised.

Endometriosis is an enigmatic disease of unclear pathogenesis, which is defined as the implantation of endometrium-like glandular and stromal cells outside their normal location in the uterus [5]. Although benign in nature and clinical behavior, endometriosis shares many of the features of neoplasia, while it is associated with an increased risk of malignant transformation [5]. Thus, it is estimated that the risk of ovarian cancer is considerably higher (about 4-fold) in the presence of endometriosis, as compared to that in the general population [5, 6]. Furthermore, ovarian endometriosis is identified in about 30% of synchronous endometrial and ovarian cancers, especially of endometrioid type [5, 7, 8].

The aim of the present study was to review the clinicopathological features of all synchronous ovarian and endometrial carcinomas diagnosed in our laboratory over the last 15-year period and shed more light in the pathogenesis of this puzzling clinical entity.

Materials and Methods

After reviewing the archival files of our laboratory over the last 15-year period (years from 1991 to 2005), we retrieved seven cases of synchronous ovarian and endometrial carcinomas, among 1,680 cases of ovarian carcinomas and 300 cases of endometrial carcinomas. Only those cases that fulfilled the criteria proposed by Scully *et al*. were included [4]. For the exclusion of cases of endometrial carcinoma metastatic to the ovaries, similar criteria proposed by Ulbright and Roth were also followed (Table 1) [3]. The relative clinical and pathology reports as well as representative slides for each case were also retrieved.

The clinical data, including patient age, presenting symptoms, parity, menopausal status and outcome were correlated with the pathologic data (both gross and histological). The latter comprised the following features: histological type and grade of tumor, presence and type of endometrial hyperplasia, presence and extent of myometrial, lymphatic and blood vessel invasion, fallopian tube involvement, coexistence of endometriosis, ovarian size and pattern of ovarian involvement (unilateral or bilateral and multinodular or solitary development) and pelvic extension of disease. Staging was also reviewed and updated in order to conform to the current criteria put forth by the International Federation of Gynecology and Obstetrics (FIGO).

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Table 1. — *Pathological criteria for the diagnosis of endometrial primary carcinomas with ovarian metastasis (as described by Ulbright and Roth)* [3].

Pathologic features	Endometrial primary with ovarian metastases
Major	Multinodular ovarian pattern
Minor	Small ovaries (< 5 cm)
	Bilateral ovarian involvement
	Deep myometrial invasion
	Vascular invasion
	Tubal lumen involvement

Tumors were histologically classified according to the World Health Organization (WHO) guidelines. Follow-up data were available for all patients, for a period ranging from six years to 84 months (mean 35 months).

Results

Clinical data

A summary of the clinical findings of all cases included in our study is provided in Table 2.

The patients' age at diagnosis ranged from 48 to 62 years (mean 55.3 years). The most common presenting symptom was abnormal vaginal bleeding (5 cases, 71.4%), followed by lower abdominal pain (2 cases, 28.6%). Five patients (71.4%) were postmenopausal, and two (28.6%) were nulliparous. All patients were submitted to total abdominal hysterectomy and bilateral salpingo-oophorectomy. For the purpose of staging, peritoneal washings, omentectomy and pelvic lymphadenectomy had also been performed, with negative results. With the exception of one patient, who received post-operative radiation, all remaining patients were treated with surgery alone, without any adjuvant therapy. No disease recurrence or death of a patient was noted during the time of the follow-up.

Pathological data

Table 3 shows the clinicopathological features of all cases included in our study.

All seven patients had Stage IA ovarian carcinomas of endometrioid histology four ovarian carcinomas (57.1%) were grade 1 and three (42.9%) were grade 2. Similar results were found with regard to endometrial carcinomas: all cases were of endometrioid histology, stage – tumors: five (71.4%) were Stage IA and two (28.6%) Stage IB. There were three cases (42.9%) with grade 1 tumor, three (42.9%) with grade 2 and one case (14.3%) with grade 3. In all patients, lymphatic and blood vessel invasion were absent and the invasion of the uterine myometrium was either absent (2 cases, 28.6%) or in the upper third (5 cases, 71.4%). The size of the involved ovary ranged from 7 to 25 cm (mean 12.3 cm) and the tumor was solitary in all cases. Moreover, in all seven ovarian carcinomas endometriosis foci were observed (Figure 1). In four of them (57.1%), atypical endometriosis was also found.

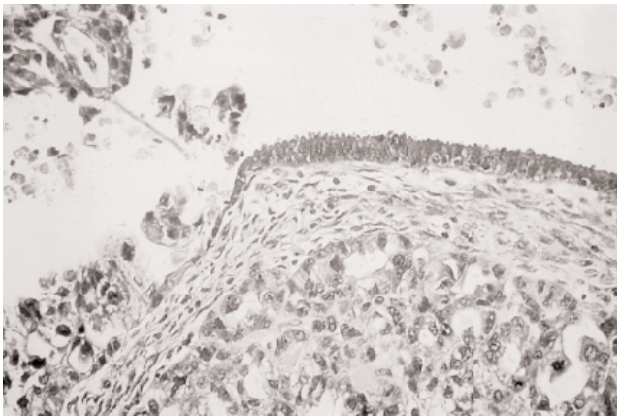

Figure 1. — Ovarian endometrioid adenocarcinoma in the wall of an endometrioid cyst (H&E x 25).

Discussion

To the best of our knowledge, the two largest series of patients with synchronous primary cancers of the ovary and the endometrium are those reported by Zaino *et al*. in 2001 and Soliman *et al*. three years later, comprising 84 and 74 cases, respectively [1, 9]. On the basis of their results, it seems that in the majority of cases these dual primary tumors are of endometrioid histological type, of low stage and grade, present in younger age (about 50 years) than the median age of onset of either ovarian or endometrial carcinomas (63 and 60 years, respectively) and are associated with a surprisingly favorable prognosis. What is also of interest is that most of the remaining smaller series, including our own, present similar results, thus consistently reaffirming the same findings [2, 3, 10-15].

Therefore, there is uniform agreement that synchronous primary ovarian and endometrial carcinomas represent a distinct clinicopathologic entity, whose most prominent feature is their significantly improved overall prognosis in comparison to their metastatic counterparts (Stage II ovarian carcinoma and Stage III endometrial carcinoma) or even to their single primary counterparts (early-stage, low-grade ovarian and endometrial carcinomas) [12, 13]. Most previous studies of synchronous ovarian and endometrial primaries report high 5-year survival rates ranging from 73.3 to 100%, while the corresponding rates for Stage II ovarian carcinoma and Stage III endometrial carcinoma are as low as 60 and 43-58%, respectively [10, 13-17]. In accordance with these data, the overall survival in our series was 100%, with a median follow-up of 35 months. The mean age of our patients at presentation was 53.3 years, which is close to the reported range, and the commonest presenting symptom was abnormal uterine bleeding. Given the insidious nature of ovarian cancer, it is conceivable that its early diagnosis and the subsequent improved survival of patients could at least be partly attributed to the coexistence of a symptomatic endometrial tumor.

Table 2. — *Clinical data, therapy and outcome of seven patients with synchronous ovarian and endometrial carcinomas.*

Cases	Age* (years)	Presenting symptoms	Nulliparous	Menopause	Therapy	Recurrence	Disease-free survival (months)**
1	48	Vaginal bleeding	Yes	No	Surgery	No	6
2	53	Lower abdominal pain	No	Yes	Surgery	No	84
3	60	Lower abdominal pain	No	Yes	Surgery	No	30
4	62	Vaginal bleeding	Yes	Yes	Surgery/Radiation	No	34
5	50	Vaginal bleeding	No	No	Surgery	No	36
6	58	Vaginal bleeding	No	Yes	Surgery	No	28
7	56	Vaginal bleeding	No	Yes	Surgery	No	27

*Mean: 55.3 years. **Mean: 35 months.

Table 3. — *Pathological features of seven cases of synchronous ovarian and endometrial carcinomas.*

Pathological features	Ovarian carcinoma No. of cases (%)	Uterine carcinoma No. of cases (%)
Histology		
– Endometrioid	7 (100%)	7 (100%)
– Other	0 (0%)	0 (0%)
Stage		
– IA	7 (100%)	5 (100%)
– IB	0 (0%)	2 (28.6%)
– IC	0 (0%)	0 (0%)
Grade		
1	4 (57.1%)	3 (42.9%)
2	3 (42.9%)	2 (28.6%)
3	0 (0%)	1 (14.3%)
Endometriosis		
– Yes	7 (100%)	
– No	0 (0%)	
Atypical endometrial hyperplasia		
– Yes	4 (57.1%)*	
– No	3 (42.9%)	

*In endometriosis foci.

Discriminating between two independent primaries and metastatic disease is therefore of crucial importance with regard to the clinical implications in each case. Nevertheless, many of the cases included in some previous reports do not meet all the existing pathological criteria. Furthermore, several researchers support the view that a definite distinction of patients with multiple primary tumors from those with metastatic disease requires the evaluation of molecular data in addition to the standard clinicopathological parameters [1, 2, 18-20]. Molecular profiling of these cases might ideally lead to an improved stratification of patients, and the administration of individualized modes of treatment, thus further improving their outcome [20]. Although most recent molecular studies of synchronous tumors of the ovary and endometrium have thus far failed to prove the diagnostic efficacy of molecular pathology techniques in this field, some of them succeeded in providing significant information regarding the pathogenesis of these cancers [18-22]. However, the differential diagnosis still relies on the evaluation of conventional clinicopathologic findings, while the importance of a careful and extensive clinicopathologic evaluation as a prerequisite for accurate classification is undisputable [2, 3, 13, 18]. In our study only those cases that strictly fulfilled the criteria described by Ulbright and Roth [3] and Scully *et al*. [4] were included for analysis, thus producing a group of patients with the highest possibility of representing true independent primaries. Previously reported incidences of synchronous ovarian and endometrial primaries range from 2-8.5% of endometrial carcinomas and 4.5-30% of ovarian carcinoma cases [10, 11, 23, 24]. The incidence reported in our series is relatively low (2.33% of endometrial carcinoma and 0.42% of ovarian carcinoma patients) in comparison to the aforementioned percentages, especially with regard to ovarian carcinoma. This could be attributed to the limited number of patients included in our study and/or the strict application of the proposed diagnostic criteria.

Despite the fact that the etiology of the synchronous development of carcinoma in the ovary and the endometrium remains unclear, several theories have been proposed for the explanation of this enigmatic entity. The theory of an extended or secondary Mullerian system, comprising the ovarian epithelium, fallopian tube, uterine corpus and cervix and behaving as a single morphologic unit, explains this phenomenon as a response of this entire system towards the development of primary carcinomas in multiple sites [25, 26]. From a molecular point of view, as recently described by Furlan *et al*., this "field effect" in the upper genital tract and the ovaries *"could be the result of either independent molecular events affecting multiple cells separately under the action of a common carcinogenic agent, or one molecular event in a single clonal progenitor that gives rise to multiple foci of tumorigenesis via mechanisms of widespread clonal expansion"* [20]. Pathologically, this multifocal oncogenic transformation is reflected in the synchronous detection of early-stage and low-grade primary cancers both in the ovary and the endometrium [2, 14]. In our study all of the patients had both ovarian and endometrial Stage I tumors, mostly low grade, a fact further supporting the separate and independent rather than metastatic nature of these cases.

Despite an abundance of epidemiologic, histopathologic and molecular data, linking endometriosis to ovarian cancer, it is still unclear whether these two diseases are directly or indirectly associated [27]. Two current theories support a) that endometriotic implants may undergo direct malignant transformation, often through an atypical endometriosis transition phase, and b) that cancer and endometriosis have in common many environmental, immunological, hormonal or genetic pre-

disposing factors [5]. Ovarian endometriosis is a common finding in many cases of synchronous primary ovarian and endometrial carcinomas of endometrioid type, providing an explanation for the synchronous pathogenesis of the dual tumors. Around 60-80% of cases of endometriosis-associated ovarian cancer occur in the presence of atypical ovarian endometriosis [5, 28, 29]. Atypical endometriosis is characterized histologically by endometrial glands with cytological or architectural atypia and has been observed in 12-35% of ovarian endometriosis [5, 30]. In our study, atypical endometriosis was found in the majority of cases, thus further supporting the hypothesis of a potential transition phase of non-atypical to atypical endometriosis and malignancy [5]. As already suggested by other investigators, the association of an endometrioid ovarian tumor with endometriosis represents reasonable evidence of its independent development [3, 31, 32]. Thus, the coexistence of ovarian endometriosis in all of our cases further supports the independent development of ovarian and endometrial carcinomas in our studied material.

In conclusion, the results of our study provide further evidence in support of the involvement of endometriosis in the pathogenesis of synchronous primary ovarian and endometrial carcinoma. To safely discriminate these independent primaries from their metastatic counterparts we should refine our currently applied diagnostic criteria. For this purpose, additional data, both pathological and molecular, are needed which should be derived from large, prospective series including carefully selected and eligible patients.

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