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Solitary Parenchymal Splenic Recurrence of Ovarian Adenocarcinoma: A Case Report and Review of the Literature

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Abstract. *We report a rare case of solitary parenchymal splenic recurrence of epithelial ovarian cancer which developed 27 months after the initial treatment. The patient, a 53-year-old woman, with a history of breast cancer, underwent total abdominal hysterectomy bilateral salpingo-ophorectomy (TAH & BSO), omentectomy and pelvic lymph node sampling for a serous carcinoma of the ovaries (stage IIIB). She subsequently received 6 cycles of cisplatinum chemotherapy. During follow-up, rising CA 125 serum levels heralded the 6 x 6 cm parenchymal splenic lesion which was documented by CT scan. She underwent splenectomy after pneumococcal vaccination, sandostatin and chemoprophylaxis. Histopathological evaluation revealed metastatic parenchymal disease consistent with recurrent ovarian cancer. She remains alive and disease-free for 20 months since the last operation. Isolated parenchymal splenic lesions are very rare and may occur as a late recurrence in epithelial ovarian cancer. Splenectomy can be performed with acceptable morbidity and confers a substantial survival benefit to patients.*

Ovarian cancer is the most common cause of death from gynecological malignacies in Europe and in the United States (1).

The intraperitoneal route of dissemination is considered the most common in epithelial tumors. However, malignant cells may also metastasize through the lymphatic channels and hematogenous route (2). Capsular splenic invasion itself is not rare and typically has been associated with extensive disseminated peritoneal carcinomatosis. Autopsy studies suggest that the spleen is involved in 19-52% of epithelial ovarian cancer cases (2, 3). Parenchymal splenic involvement is infrequent, confers unknown prognostic significance and, according to the FIGO classification, does not constitute stage IV disease. Several authors have reported over 100 cases of parenchymal and capsular splenic metastases that were identified during primary or secondary cytoreduction for extensive abdominal carcinomatosis (4-16). However, solitary parenchymal splenic recurrence is considered a rare event and only 16, clearly designated cases have been reported in the literature to date (17-24). Breast, lung cancer and melanoma are the most common primary sites of solitary intrasplenic metastases (25).

The current treatment of advanced ovarian cancer relies on a combination of aggressive surgical cytoreduction and platinum/taxane-based chemotherapy. The role of secondary cytoreduction is still a matter of controversy. However, patients with solitary recurrences, presented after a long interval from primary treatment, especially with platinum-sensitive tumors, seem to derive a survival benefit from optimal secondary debulking (26, 27).

We present a case of epithelial ovarian carcinoma which recurred in the splenic parenchyma 27 months after the primary treatment.

Case Report

A 53-year-old woman was admitted to the author's department in July 2000, due to an asymptomatic, rapidly growing adnexal mass. The cystic and solid ovarian tumor was initially identified during routine follow-up for breast cancer, which she had suffered 8 years previously. Preoperative clinical and laboratory tests suggested this was a second primary tumor. Serum CA 125 was elevated (CA 125=2621 IU/ml). The patient underwent exploratory laparotomy which revealed a 15 x 15 x 10 cm multilobular hemorragic, solid and cystic mass in the left ovary filling the pelvis. Hemorragic malignant ascites were also present and multiple tumor nodules (max diameter <2 cm) were identified in the parietal peritoneum, small and large bowel mesentery, pouch of Douglas, paracolic gutters and

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hemidiaphragms (IIIb). Total abdominal hysterectomy and bilateral salpingo-ophorectomy, omentectomy, pelvic and para aortic lymph node sampling were performed. Optimal cytoreduction (max. diameter of the largest residual tumor was <0.5 cm) was achieved and the postoperative course was uneventful.

Histopathological examination revealed a poorly-differentiated serous cystadenocarcinoma with metastatic foci in the resected abdominal tissues. There were no retroperitoneal lymph node metastases. She was classified as Figo stage IIIB and received systemic cisplatinum 100mg/m^2 chemotherapy for 6 cycles. She refused taxol because of fear of alopecia, which she had suffered before during breast cancer chemotherapy. Her postoperative serum CA 125 decreased from 2621 U/ml to normal levels (19.11 U/ml) after the first course of chemotherapy.

A review of the patient's past history revealed she had suffered from histologically verified breast me dullary adenocarcinoma Gr III, 8 years previously and had undergone lumpectomy and axilla lymph node resection followed by 6 cycles of CMF chemotherapy. According to her family history, her twin sister had suffered from breast and "gynecological cancer". She also had 15 other third degree relatives with breast cancer and other malignant tumors. After primary treatment for her ovarian cancer, the patient remained free of clinical and radiological evidence of disease for 27 months, then she relapsed. During the routine follow-up examination in October 2002, the CA 125 serum level was elevated (597 IU/ml). The patient was asymptomatic but a CT scan of the abdomen and pelvis demonstrated an enlarged spleen with cystic parenchymal lesion of 6 x 6 cm. In November 2002, she underwent a second exploratory laparotomy, after pneumococcal vaccination, sandostatin and chemoprophylaxis. The abdomen and pelvis were negative for macroscopic and palpable disease nodules, except for an enlarged spleen with a smooth capsule. She underwent splenectomy, *via* the anterior route, cytology and multiple biopsies of the peritoneum and adhesions were also taken. Her postoperative course was uneventful. Histopathological evaluation revealed metastatic parenchymal disease consistent with recurrent ovarian adenocarcinoma. Multiple biopsies and cytology revealed no other evidence of microscopic disease. The patient received 6 cycles of carboplatin chemotherapy 400-600 mg. She has remained alive and disease-free for 20 months since the last operation.

Discussion

Data from the literature concerning distant metastases in ovarian carcinoma are scarce. In a retrospective chart review of 162 patients with epithelial ovarian carcinoma, distant metastases were present in 8% of the patients at the time of diagnosis and in 22% during the course of the disease (28).

Autopsy studies demonstrated that about 50% of the sites of distant metastases were asymptomatic, silent clinically and unknown during life (2, 3). Also unidentified microscopic splenic metastases were found in 4 out of 6 cases where splenectomies were performed for iatrogenic complications (6). Therefore, the true incidence of distant dissemination seems to be even higher than that reported in clinical studies (29). The most frequent sites of metastases are: liver (30), pleura (29, 30), lung (31), central nervous system (32), skin (30), bone (33), breast (34) and spleen (18).

Ovarian cancer usually grows around the spleen and not into it. Parenchymal metastases probably represent hematogenous spread of disease, whereas capsular lesions represent peritoneal seeding (29). Several theories have been proposed, but none satisfactorily explains why epithelial ovarian cancer usually spares the splenic tissue. Some authors advocate that a humoral substance in the spleen destroys all tumor cells reaching the organ (11, 22, 28). Others believe that contractions force the blood from the sinusoids to the splenic veins and keep tumor cells in constant motion, preventing them from settlement (35, 36). Metastatic tumor cells are thought to reach the parenchyma of the organ *via* hematogeneous channels. A paucity of afferent lymphatics to the splenic parenchyma and the rarity of simultaneous regional lymph node involvement corroborate this notion (17, 18, 37).

We present a case of solitary parenchymal splenic recurrence in the absence of other metastatic lesions. The identification of truly isolated parenchymal splenic recurrences in the reported data is not easy. Many authors have reported splenectomy series, that were performed either at primary or repeat laparotomy, but do not clarify whether splenic involvement was solitary or capsular as part of disseminated abdominal disease spread. To our best evaluation, only 16 cases in the literature fulfill the criteria of "recurrence", "solitary" and "parenchymal" splenic disease (17-24). We believe ours to be the seventeeth such case reported. All reported cases in the literature presented a splenic lesion at 2 to 15 years after initial treatment (17-24). This late recurrence may indicate the slow growth of a single clone of an otherwise polyclonal and heterogeneous cell population, which had escaped from extensive and combined treatment (17-24). It is noteworthy that other genital and non genital tumors also present with an intrasplenic recurrence after a long disease-free interval (38).

A number of common disease characteristics seem to emerge from the review of the compiled data of case studies reporting parenchymal splenic recurrences, which are illustrated in Table I. All patients had initially stage III disease and were aggressively treated with extensive surgery and primary combination, platinum-based chemotherapy. Solitary, parenchymal organ recurrence was mostly

Table I. *Solitary parenchymal splenic recurrence as reported in the literature.*

Author/year	No cases	Interval years	Stage	1st treatment	Symptoms	CA 125	2nd treatment	FU
Minagawa 1991	1	5 yrs	IIIb	Optimal	No	+	5-FU (p.o)	12 m NED
Eisner 1993	4	1.5-10 yrs	IIIc IIIc IV IIIc	Optimal	No	2+/2-	2-/2WART NED,AD	6-36 m
Max 1996	1	2.5 yrs	Ic	Optimal	No	+	6#CDDP+Taxol	12 m NED
Kobayashi 1997	1	24 m	III	Optimal	No	+	CDDP+Taxol	
Klinger 1998	1	2 yrs	III	Optimal	No	+	Not Stated	6 m NED
Gemignani 1999	6	~57 m	IIIc,	Optimal	No	+4/6	5#CDDP+Taxol	~25 m NED
Balat 1996	1	5.5 yrs	IIIc	Optimal	Pain	-	6#Carbo	6 m AD
Lauro 2002	1	15 yrs	Ic	Optimal	No	-	6#Carbo+cyclophosphamide	8 yrs NED
Present	1	27 m	IIIb	Optimal	No	+	6#Carbo	20 m NED

D: Dead
DD: Dead from disease
FFD: Free from disease
AD: Alive with disease
NED: No evidence of disease

asymptomatic, suspected possibly by tumor marker elevation and pictured by CT imaging after an unusually long disease-free interval of 2-15 years. In cases where the diagnosis was in question and surgery not possible, CT-guided fine-needle aspiration was successfully utilized for diagnosis (39) (in another study not included in Table I).

Ascites were rarely present in these 16 unusual confirmed solitary recurrences that are presented in the literature (17-24). Splenectomy was applied in every case and was practically uneventful, especially if prior vaccination had been applied. A long disease-free survival after secondary cytoreduction was another optimistic, unusual disease characteristic shared by all patients (17-24).

The open surgical approach was used in 14 out of the 16 cases reported. However, 2 patients were successfully operated upon using a laparascopic approach (18, 21).

As shown in Table I, the first report of an isolated parenchymal splenic recurrence of epithelial ovarian cancer was reported by Minagawa *et al.* in 1991 (17), five years after primary treatment. The patient was submitted to splenectomy which was successful and prolonged survival by at least one year. Eisner *et al.* published a paper on this topic in 1993 (19). In that report, 4 patients with solitary splenic metastasis of ovarian cancer were treated by splenectomy. Two of these had an abnormal CT scan before CA 125 elevation (3). One patient was subsequently treated with intraperitoneal cisplatin, 2 with intravenous carboplatin and one declined further treatment. Three out of 4 patients in this report remained free of disease for 6 to 36 months. The time from primary therapy to recurrence in the spleen was, on average, 5 years (19).

The largest series on isolated parenchymal splenic recurrences was reported from the Memorial Hospital, USA, by Gemignani *et al.* (18). Thirteen patients underwent splenectomy for relapse and in 6 of them solitary parenchymal lesions were found. Their mean age was 50 years (58-60) and all had initially stage III disease. In 5 out of 6, optimal cytoreduction was achieved at initial treatment. After 6-8 cycles of CDDP and endoxan, 5 underwent second-look laparotomy and 4 were found with residual disease and underwent salvage chemotherapy. A subsequent rise in CA 125, in otherwise asymptomatic patients, was the first sign of relapse, which occurred in a median time of 57 months after the first operation (28-88 months). Splenectomy was carried out successfully and all patients were alive at 25.5 months (18).

In our case, a rise in serum CA 125 was identified before the CT showed evidence of disease.

Table II. *Parenchymal splenic involvement in widespread disease (in primary or secondary cytoreduction) as reported in the literature.*

Author/Year	Parenchymal metastases/ splenectomies (N0)	Primary or secondary cytoreduction	Follow-up
Deppe 1983	1/1	secondary	12 m D
Glezerman 1986	1/1	primary	26 m NED
Sonnedecker 1989	1/6	primary	14 m NED
Morris 1991	7/24	Primary, secondary	Not Stated
Niclin 1994	3/18	secondary	21 m DD 9 m DD 9 m DD
Darai 1995	1/1	Primary	12 m FFD
Scarabelli 1998	9/40	2 pt primary 7 pt secondary	17 m D (median survival)
Ushijima 1999	1/1	secondary	17 m FFD
Lee 2000	17/23	Primary,secondary	21m – 3.9 yrs D (median survival)
Mastroianni 2000	3/2	Primary,secondary	10-16 m (median) 1 pt NED 2 pt NED 3 pt AD
Chen 2000	16/35	3 primary, 13 secondary	57 m D (median survival)
Yano 2002	1/1	secondary	Not stated
Cormio 2003	5/5	Not stated	18 m (median) 4 pt DD 1 pt NED
Ayhan 2004	14/34	primary	28.9 m D (median survival)

D: Dead
DD: Dead from disease
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As previously mentioned, only 2 patients were treated by laparoscopy (Table I). Since 1991, when the first laparoscopic splenectomy was reported, a number of authors have advocated that this is a safe procedure, convenient to the patients. However, oncological surgery at times warrants palpation of suspicious areas. Hand-assisted laparoscopic surgery was developed in order to improve the direct handling of tissues and provide assistance to hemostases (10, 21).

Yano *et al.* and Klinger *et al.* each reported a case of solitary splenic metastasis from ovarian cancer successfully treated by hand-assisted laparoscopic splenectomy (10, 21). The advantages of the laparoscopic approach over open splenectomy are a shorter hospital stay and less time to complete recovery. Moreover, these patients can be given chemotherapy soon after surgery, which could achieve a better prognosis (10, 21). Several other laparoscopic modifications have also been tried including: "hanging spleen" position, prior embolization of the splenic artery or CUSA aspiration of capsular involvement (10, 21, 40, 41).

Apart from solitary splenic recurrences, over a hundred cases with parenchymal and capsular disease in the context of disseminated abdominal disease have been published and are illustrated in Table II (5-16). Deppe *et al.* reported, in 1983, the first such case in a patient with recurrent multiple metastases of ovarian cancer. In that report, splenectomy was performed as part of a secondary debulking surgery, after which the patient received 9 courses of adjuvant platinum-based chemotherapy (5). The performance of splenectomy at the time of primary cytoreductive surgery was initially reported by Glezerman *et al.* in 1986 (13). In this series, splenic metastases from carcinoma of the ovary were demonstrated by CT scan and ultrasound. One patient also had parenchymal metastasis in the spleen associated with widespread ovarian cancer. Sonnedecker *et al.* reported on 6 patients with ovarian cancer who had splenectomy performed as part of their primary cytoreductive surgery, mostly for splenic capsular involvement (15).

Splenectomy as part of cytoreductive surgery was reviewed by Niclin *et al.*, in 18 patients from the Ohio State University, USA, in 1994 (12). Three patients were found to have splenic parenchymal metastases, but these were not solitary and the patients died at a median time of 12 months. The largest series on splenectomies for gynecologic malignancies was reported from the MD Anderson Cancer Center, USA, in 1991 (7). Morris *et al.* described 45 splenectomies of which 24 were performed for ovarian cancer. Parenchymal involvement was present in 7 patients, but it was not clear in how many patients this was an isolated disease manifestation. Tumor cytoreduction to less than 2 cm was achieved in 62.5% of patients.

The next largest series of splenectomies for splenic metastases was reported by Chen *et al.*, in 2000 (9). The majority (22 out of 35) of the splenic metastases were due to ovarian cancer. More than half (13/22) of the cases had a parenchymal component but, again, it was not clear in how many the spleen was the only site of metastatic disease. The median survival after secondary cytoreduction was 41 months. The aim of the study was to evaluate the role of

splenectomy as a surrogate marker for aggressive tumor cytoreduction in ovarian cancer and its morbidity and survival. The authors concluded that splenectomy at the time of primary and secondary cytoreduction for ovarian cancer can be performed with acceptable morbidity.

Another large series of 31 splenectomies for isolated splenic metastases was reported by Lee *et al.* in 2000 (8). Of the 31 splenectomies for metastases, 23 were performed for ovarian neoplasms, 5 during primary operative procedures, and 18 during secondary cytoreductive procedures or exploration for late recurrences at an average of 3.9 years after the original operation. The mean survival was 22.9 months. The majority of these patients had parenchymal splenic involvement (12 patients parenchymal and 5 parenchymal and capsular) (8).

Scarabelli *et al.*, in 1998, (6) presented data from Italy reviewing the outcome of 40 patients undergoing splenectomy as a part of primary or secondary cytoreduction for ovarian carcinoma. The spleen was removed because of parenchymal splenic metastasis in 9 patients (22.5%). All patients were left with less than 2 cm disease. Left-sided pleural effusions were noted in 10 (25%) patients. In 4 out of 6 cases where splenectomy was performed for iatrogenic complications, microscopic metastatic foci were identified. Morbidity was acceptable and 2-year survival was 78% for patients that were debulked to microscopic disease compared to 24% when debulked to macroscopic residual disease. However, no patient remained alive at 3 years (6).

In general, the patient characteristics in the studies illustrated in Table II are not so well designated, since these cases were scattered in larger series on splenectomies performed during primary or secondary cytoreduction. Therefore, identification of cases with solitary parenchymal disease is difficult and, at times, impossible. However, some conclusions regarding capsular and or parenchymal splenic disease, as part of disseminated abdominal spread of ovarian cancer, can be drawn. A short disease interval between primary therapy and capsular splenic recurrence is common among these cases. Secondary cytoreduction was often non optimal. Treatment complications in relation to splenectomy were more frequent and, at times, fatal. Morbidity included pulmonary emboli, infections, sepsis, hemorrhage, thrombocytosis, thromboembolic phenomena, pancreatitis, injury to the pancreatic tail or to the stomach, pneumonia, respiratory failure, myocardial infarctions (4-7, 9, 12, 15) *etc.* It is well known that splenectomy might result in decreased bacterial clearance from the blood, decreased IgM levels and decreased opsonic activity. Therefore, patients are more susceptible to infections with encapsulated bacteria, particularly *S.pneumoniae*, *H. influenzae* and *N. meningitidis*. Vaccinations with polyvalent pneumococcal vaccine is recommeded prior to splenectomy and reduces infections (7, 9, 12, 18, 42-45). A small percentage of this group of patients had received preoperatively pneumococcal vaccination, since splenic metastases were not apparent prior to laparotomy (4, 7, 9, 12, 18).

A comparative review of the literature regarding parenchymal splenic recurrences, either solitary or in the context of extensive abdominal disseminated disease, favors secondary cytoreductive surgery for localized, isolated splenic disease. Solitary parenchymal splenic recurrence might develop after a long disease-free interval and can be identified by CT scan. Splenectomy in this setting is feasible with minor morbidity and patients present a prolonged disease-free survival thereafter.

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