Primary ovarian carcinosarcoma: a case report and review of the literature

M. Varras[1], *M.D., Ph.D.*; **Ch. Akrivis**[2], *M.D., Ph.D.*; **N. Antoniou**[2], *M.D., Ph.D.*; **C. Tolis**[3], *M.D., Ph.D.*; **S. Stefanaki**[4], *M.D., Ph.D.*; **E. Salamalekis**[1], *M.D., Ph.D.*

[1]*3rd Department of Obstetrics and Gynaecology, University General Hospital "ATTIKON", Athens, Third District National Health System, Athens;*
[2]*Department of Obstetrics and Gynaecology, "G. Chatzikosta" General State Hospital, Ioannina, District National Health System, Epirus;*
[3]*Department of Internal Medicine, Medical School, University Hospital, Ioannina, District National Health System, Epirus;*
[4]*Department of Pathology, "G. Chatzikosta" General State Hospital, Ioannina, District National Health System, Epirus (Greece)*

Summary

Primary ovarian carcinosarcoma is characterized by an admixture of malignant epithelial and stromal elements. This neoplasm is extremely rare with fewer than 400 cases reported in the English literature. Its histogenesis, clinical features and optimal treatment remain unclear because of the rarity of primary ovarian carcinosarcoma. This study focuses on the clinical, pathological, immunohistochemical features and survival of a 73-year-old patient with primary ovarian carcinocarcoma. The patient was treated with surgery followed by combined chemotherapy with carboplatin and taxol and assigned to FIGO Stage IIIc. She died from the disease 17 months after surgery. In conclusion, ovarian carcinosarcoma is a very aggressive tumor, especially when it is diagnosed at advanced stage.

Key words: Carcinosarcoma; Ovary; Malignant mixed mesodermal; Mixed Müllerian; Tumor; Pathology; Chemotherapy; Survival.

Introduction

Primary ovarian carcinosarcoma is an extremely rare neoplasm representing less than 1% of all ovarian malignancies [1] with less than 400 cases having been reported in the English language literature since the 1950s [2]. In the current classification, carcinosarcoma is synonymous with the terms: (i) malignant mixed mesodermal tumor; (ii) malignant mixed Müllerian tumor [2, 3]. Primary ovarian carcinosarcomas are combined mesenchymal and epithelial neoplasms [4] and are of two different types: the homologous type and the heterologous type. The homologous type of ovarian carcinosarcoma contains sarcomatous elements originating from tissue normally present in the ovary [5], while the heterologous type contains elements such as bone, cartilage, fat tissue or striated muscle [5].

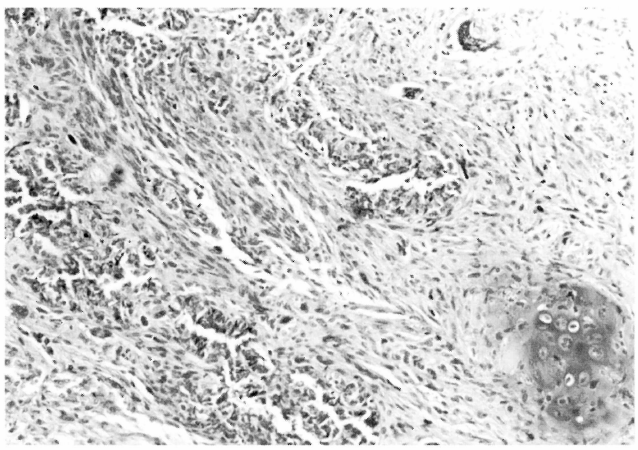
Because of the exceedingly rare occurrence of this tumor, its histogenesis, clinical features and optimal treatment remain unclear [2]. Survival data for carcinosarcomas of the ovary appear comparable to those reported for advanced uterine carcinosarcoma, as the majority of patients with primary ovarian carcinosarcoma present with Stage II to IV disease [6]. A median survival of 12 to 25 months has been reported and only a few long-term survivors are seen [5]. Prognosis depends on stage, residual tumor at surgery and is largely independent of histology, tumor grade and characteristics of the epithelial components [1].

Revised manuscript accepted for publication March 18, 2004

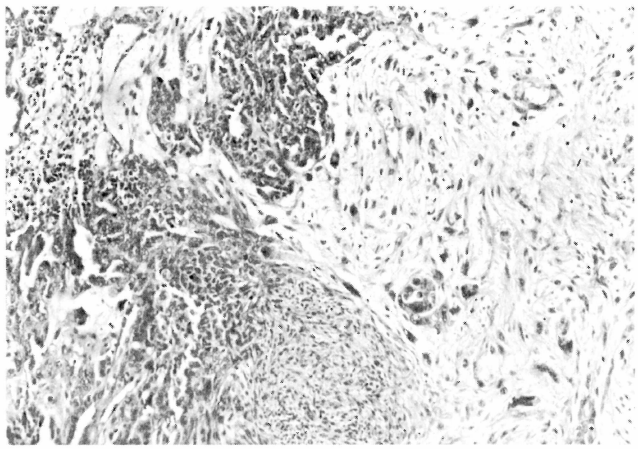
The purpose of this study is to report another case of primary ovarian carcinosarcoma diagnosed in advanced FIGO stage and to discuss the clinical findings, pathological, immunohistochemical features and survival of this rare neoplasm. In addition, the international literature is reviewed.

Case Report

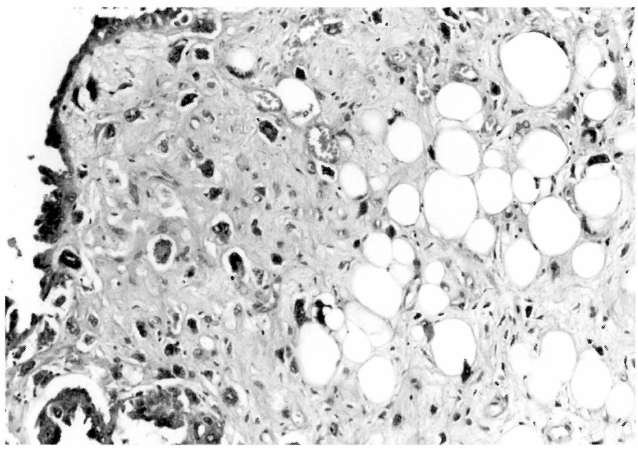
The patient, a 73-year-old woman, para 4, gravida 4, was admitted to the hospital because of abdominal fullness of six months duration. Her last menstrual period was at the age of 51. Past medical history was significant for cardiac insufficiency. She had a history of appendectomy 30 years before. The physical examination revealed a markedly distended abdomen with evidence of free fluid in the peritoneal cavity. Ultrasonographic examination of the abdomen showed the presence of ascites and a pelvic mass measuring 8 x 3 cm. Paracentesis of the abdomen was performed and the cytological examination of the ascitic fluid showed the presence of malignant cells. The endoscopic examination of the peptic system was negative. The preoperative diagnosis was ovarian cancer and the patient was referred to the Obstetrics and Gynaecology Department of the same hospital. On bimanual gynaecological examination a fixed mass was felt occupying the lower abdomen. The uterus could not be defined separately from the mass. CT scan of the upper and lower abdomen showed an adequate amount of ascitic fluid in the subdiaphragmatic and subhepatic spaces, in the colic flexures, between the interstitial helixes and especially in the pelvis; a huge mass occupying the pelvis was also detected. The liver and spleen had a homogeneous texture. There was no abnormal dilation of the bilateral ureters. No definite inguinal, iliac or para-aortic lymphadenopathy was identified. Chest X-ray showed lungs without evidence of malignancy; no pleural fluid was found. Prior surgery, the tumor marker assays included the following: α-fetoprotein (AFP), 4.3 ng/ml (normal < 20 ng/ml);



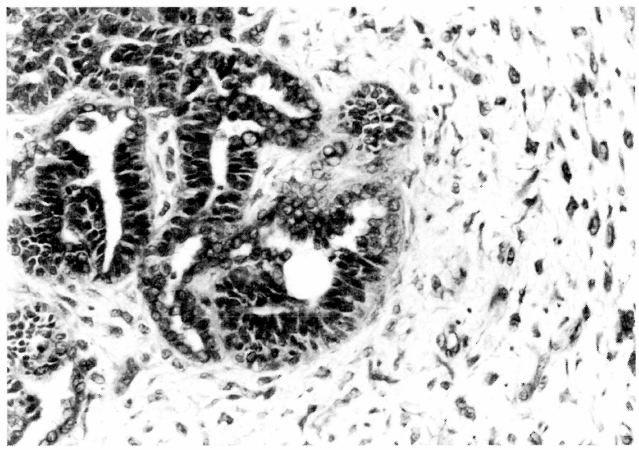
1



2



3



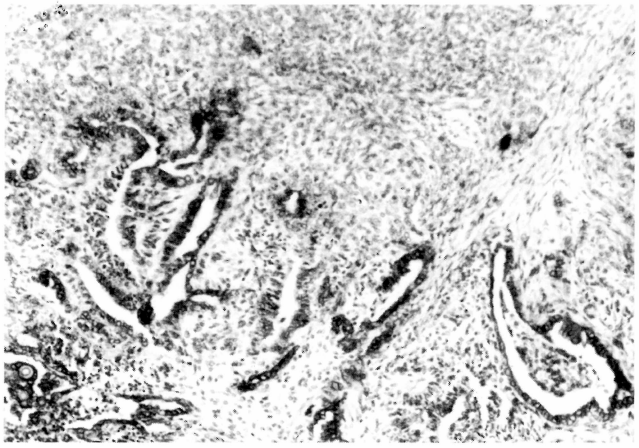
4

Figures 1 and 2. — Malignant epithelial (serous) and stromal (chondrosarcoma) elements (H&E x 40).
Figure 3. — Serous elements - liposarcoma and psammoma bodies (H&E x 40).
Figure 4. — Expression of epithelial antigen (Ber-EP4) in the carcinomatous portion of the tumor.

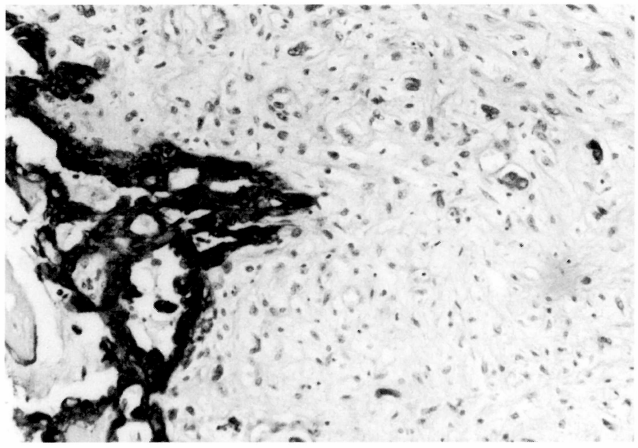
CEA, 0.7 ng/ml (normal < 5 ng/ml); CA 15-3, 10.3 IU/ml (normal < 30 IU/ml); CA-125, 345 IU/ml (normal < 37 U/ml); CA 19-9, 6.7 IU/ml (normal < 37 IU/ml).

Exploratory laparotomy revealed massive hemorrhagic ascites (about 2 liters) and extensive neoplasmatic dissemination of the upper and lower abdomen. The surgical procedure consisted of cytoreduction; hysterectomy was not possible to be performed. Residual neoplastic deposits were more than 2 cm in diameter. Microscopically, the resected tissues from the region of the left ovary and the omentum showed massive invasion from a biphasic malignant ovarian tumor, composed of an intimate admixture of malignant epithelial and stromal components. The epithelial component was adenocarcinomatous with a serous papillary pattern and areas of mucinous differentiation with intracellular and extracellular production of acid mucin. The tumor was mainly solid with a high grade of malignancy, but also some well-differentiated areas were recognized. The stromal-sarcomatous component of the tumor was mainly composed of spindle-shaped cells and bizarre cells with extensive mitotic activity. Also, foci of chondrosarcoma (Figures 1 and 2) and liposarcoma (Figure 3) were recognized. The neoplasm presented very extensive necroses. Neoplasmatic plugs were found within the lymphatic vessels of the intensively sclerotic interstitial substrate, mainly in the omentum. Metastatic implants associated with psammoma bodies were present on the omentum. The final diagnosis was ovarian carcinosarcoma. Immunohistochemically, the epithelial element of the neoplasm exhibited strong positivity for epithelial membrane antigen (EMA), epithelial antigen (Ber-EP4) (Figure 4), pancytokeratin (AE1/AE3) (Figure 5) and cytokeratin 7 (Figure 6). Carcinoembryonic antigen (CEA) was positive in the regions of the mucous differentiation. Vimentin exhibited intense positivity both in carcinomatous and sarcomatous areas (Figure 7). Leu-7 antigen gave limited positivity in both components (Figure 8). The S-100 protein showed intense positivity in the regions of chondrosarcoma and liposarcoma, while it was focally expressed in the regions of the malignant epithelium and the sarcomatous stroma. Also, positive reaction showed the alpha-smooth muscle actin (SMA), while the actin HHF-35 exhibited positivity in the isolated interspersed sarcomatous stromal cells. There was no tumor immunoreactivity in either the epithelial or sarcomatous components for desmin, chromogranin and neurofilament.

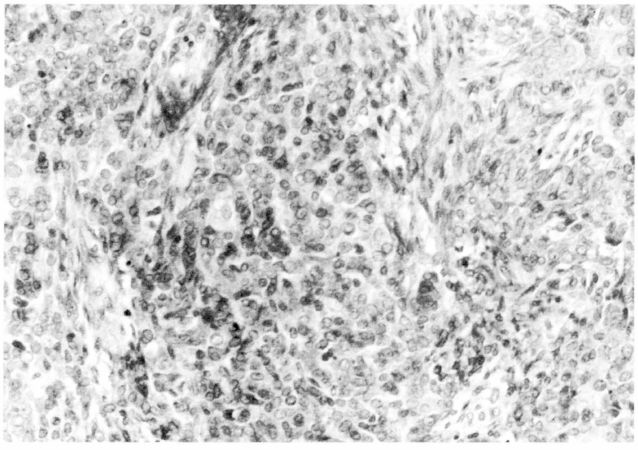
According to FIGO criteria, the patient was Stage IIIc. Six cycles of combined chemotherapy (carboplatin and taxol) were given. The serum levels of CA-125 during the monthly treatment with chemotherapeutics, from the first to the sixth cycle, were 135 IU/ml, 57 IU/ml, 29 IU/ml, 20 IU/ml, 18.6 IU/ml and 12.6 IU/ml, respectively. Eight months after the initial surgery, the CT scan and the ultrasonographic examination of the abdomen demonstrated the presence of liver metastases and adequate quantity of ascitic fluid in the subhepatic and intraperitoneal spaces. Also, neoplasmatic masses were found in the pelvis. The CT scan of the chest was without abdormalities. The patient died from the disease 17 months after surgery.



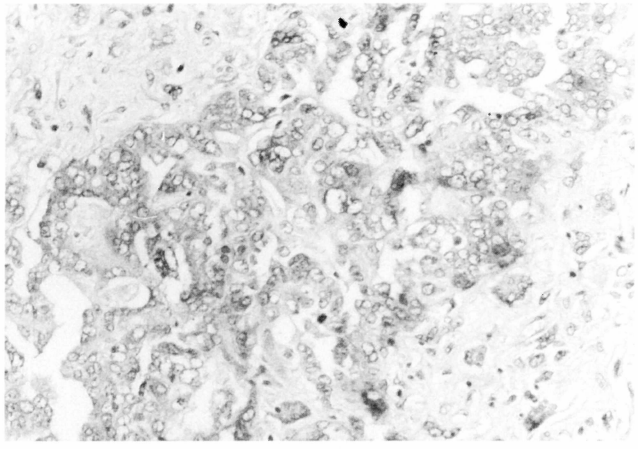
5



6



7



8

Figure 5. — Expression of pancytokeratin (AE1/AE3) in the carcinomatous portion of the tumor.
Figure 6. — Expression of cytokeratin 7 in the carcinomatous portion of the tumor.
Figure 7. — Expression of vimentin in both carcinomatous and sarcomatous portions of the tumor.
Figure 8. — Limited expression of Leu-7 in both carcinomatous and sarcomatous portions of the tumor.

Discussion

Carcinosarcomas are highly virulent and rare neoplasms, which are observed most commonly in endometrium and, in decreasing order of frequency in the endocervix, vagina, ovaries and fallopian tubes [7]. Other extrauterine sites include the parametrium, rectosigmoid colon, pelvic peritoneum and omentum [3]. Regarding the histopathogenesis of primary ovarian carcinosarcomas some authors have expressed the opinion that the epithelial and stromal components of these neoplasms come from Müllerian tissue [1] or at least these neoplasms behave like carcinomas [6]. However, other authors believe that ovarian carcinosarcomas represent a heterogeneous group of tumors, including both carcinomas and sarcomas and behave as true carcinosarcomas [6, 8]. Primary ovarian carcinosarcomas occur most commonly in postmenopausal women with a median age at presentation of 57 to 66 years [7]. The clinical presentation of ovarian carcinosarcomas is similar to that of ovarian carcinomas [2]. The most common physical findings are a large pelvic or lower abdominal mass and ascites [2, 7]. The most common symptoms are abdominal distention (as in our patient) abdominal pain, changes in bowel habits, gastrointestinal complaints, urinary bladder symptoms and vaginal discharge and bleeding [2, 3, 5, 7]. A high incidence of nulliparity has been noted in patients with ovarian carcinosarcomas although our patient was multiparous [3, 7].

Stage I disease is rare because, in general, it is asymptomatic in early stages [1]. The management of ovarian carcinosarcomas presents a difficult problem for two reasons. Firstly, they are highly aggressive neoplasms and secondly, their rarity has made it impossible to determine the optimal treatment [7]. At the present time, the management of patients with ovarian carcinosarcomas consists of aggressive surgical cytoreduction combined with chemotherapy [2, 6]. In the past, it was felt reasonable to treat these patients with adjuvant radiotherapy, either of the pelvis or of the whole abdominal cavity [6]. However, this treatment policy has not improved the outlook for these patients because ovarian carcinosarcomas tend to metastasize outside the abdominal cavity [6]. Although different schedules of chemotherapy drugs have been tried, the prognosis of patients with ovarian carcinosarcoma remains poor. In a review of 201 cases of ovarian

carcinosarcomas by Hanjani *et al.* the authors found that the one-year mortality of the disease was 78% for all tumor stages and 56% for Stages I and II [9]. Therefore, the patients had a poor prognosis irrespective of tumor stage [9]. Morrow *et al.* [10] reported 30 cases of ovarian carcinosarcomas, of which 23 died from one to 16 months following their initial surgery. Andersen *et al.* [11] achieved an impressive initial response rate with platinum-based chemotherapy, but ultimately maintained a poor overall survival. Pfeiffer *et al.* [12] reported 13 cases with a median suvival of 12 months. Six of their patients received platinum-based chemotherapy; two of these patients without measurable disease became long-term survivors (survival times 42+ and 92+ months). Bicher *et al.* [13] reported 36 patients with ovarian carcinosarcoma treated with cisplatin combinations; the five-year survival was 30%. Le *et al.* [14] reported 36 cases of ovarian carcinosarcomas; the five-year survival was 35% with cisplatin and doxorubicin. The follow-up ranged from one to 11 years with a median of two years. Hellström *et al.* [5] reported 36 cases with ovarian carcinosarcoma. The overall prognosis was poor with only 18% five-year actuarial survival (median survival 16.6 months). Fifteen patients treated with melphelan, doxorubicin (andriamycin) and cisplatin (MAP) had a five-year actuarial survival of 33.3% and a median survival of 19.8 months [5]. The authors concluded that the ovary seemed to respond in a fashion similar to ovarian epithelial tumors towards chemotherapy and less as sarcomas. Therefore, the authors suggested that the combinations VAC (vincristine, dactinomycin and cyclophosphamide) and VBC (velbe, cisplatin and bleomycin) might be less successful than combinations with melphalan, doxorubicin and cisplatin (MAP) in the treatment of patients with ovarian carcinosarcomas [5]. In our case the patient was treated with carboplatin and taxol; as the FIGO stage of our patient was IIIc and the residual neoplastic deposits were more than 2 cm in diameter, the patient died 17 months after initial surgery.

In conclusion, we have reported a rare case of ovarian carcinosarcoma with regard to the clinical, pathological and immunohistochemical features. Also, we presented the survival of the patient after postoperative combined chemotherapy with carboplatin and taxol.

References

[1] Melilli G.A., Nappi L., Carriero C., Loizzi V., Caradonna F., Quaranta M., Putignano G.: "Malignant mixed mullerian tumor of the ovary: report of four cases". *Eur. J. Gynaecol. Oncol.,* 2001, *22,* 67.

[2] Wei L.H., Huang C.Y., Cheng S.P., Chen C.A., Hsieh C.Y.: "Carcinosarcoma of ovary associated with previous radiotherapy". *Int. J. Gynecol. Cancer,* 2001, *11,* 81.

[3] Elbers J.R.J., Wagenaar S.S.: "Malignant mixed mesodermal tumor of the ovary". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1980, *10,* 47.

[4] Grover V., Dhall K., Grover R.K., Choudhry T.: "Malignant mixed mesodermal tumor of ovary". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 1985, *20,* 241.

[5] Hellström A.C., Tegerstedt G., Silfverwärd C., Pettersson F.: "Malignant mixed müllerian tumors of the ovary: histopathologic and clinical review of 36 cases". *Int. J. Gynecol. Cancer,* 1999, *9,* 312.

[6] Van Rijswijk R.E.N., Tognon G., Burger C.W., Baak J.P., Kenemas P., Vermorken J.B.: "The effect of chemotherapy on the different components of advanced carcinosarcomas (malignant mixed mesodermal tumors) of the female genital tract". *Int. J. Gynecol. Cancer,* 1994, *4,* 52.

[7] Prendiville J., Murphy D., Renninson J., Buckley H., Crowther D.: "Carcinosarcoma of the ovary treated over a 10-year period at the Chritie Hospital". *Int. J. Gynecol. Cancer*, 1994, *4,* 200.

[8] Meiss J.M., Lawrence W.D. "The immunohistochemical profile of malignant mixed Müllerian tumor". *Am. J. Clin. Pathol.*, 1990, *94,* 1.

[9] Hanjani P., Petensen R.O., Lipton S.E., Nolte S.A.: "Malignant mixed mesodermal tumours and carcinosarcoma of the ovary: report of eight cases and review of the literature". *Obstet. Gynaecol. Sur.,* 1983, *38,* 537.

[10] Morrow C.P., D'Ablaing G., Blady L.W.: "A clinical and pathologic study of 30 cases of malignant mixed mullerian epithelial and mesenchymal ovarian tumors. A Gynecologic Oncology Group Study". *Gynecol. Oncol.,* 1984, *18,* 278.

[11] Andersen WA., Young D.E., Peters W.A. 3rd, Smith E.B., Bagley C.M., Taylor P.T. Jr.: "Platinum-based combination chemotherapy for malignant mixed mesodermal tumors of the ovary". *Gynecol. Oncol.,* 1989, *32,* 319.

[12] Pfeiffer P., Hardt-Madsen M., Rex S., Hoelum B., Bertelsen K.: "Malignant mixed müllerian tumors of the ovary. Report of 13 cases". *Acta Obstet. Gynecol. Scand.*, 1991, *70,* 79.

[13] Bicher A., Levenback C., Silva E.G., Burke T.W., Morris M., Gershenson D.M.: "Ovarian malignant mixed müllerian tumors treated with platinum-based chemotherapy". *Obstet. Gynecol.,* 1995, *85,* 735.

[14] Le T., Krepart G.V., Lotocki R.J., Heywood M.S.: "Malignant mixed mesodermal tumor treatment and prognosis: A 20-year experience". *Gynecol. Oncol.*, 1997, *65,* 237.

Address reprint requests to:
M.N. VARRAS, M.D., Ph.D.
Obstetrician-Gynaecologist
Consultant in Obstetrics and Gynaecology
Platonos 33
Politia (Kifisia) 14563
Athens (Greece)
E-mail: mnvarras@otenet.gr