A rare case of ovarian carcinosarcoma with neuroendocrine differentiation

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A 60-year-old woman presented with worsening right lower extremity swelling for 2 days. The patient had no history of trauma or prolonged immobilization and denied further symptoms, including lower extremity pain, fever, dyspnea, chest pain, and abdominal pain. The patient's medical history included chronic hepatitis C secondary to intravenous drug use, a history of deep venous thrombosis 25 years prior to her presentation, and a history of right-sided breast cancer 20 years prior to that was treated with lumpectomy, radiation therapy, chemotherapy, and tamoxifen (discontinued by the patient after 3 years). The family history was unknown as the patient was adopted. The review of systems revealed a 2-month history of abdominal bloating, without vaginal bleeding, discharge, or rectal bleeding. The gynecologic history included a normal pelvic exam and Papanicolaou smear 2 years prior to presentation, menopause at age 45 years, and 1 pregnancy that was voluntarily terminated. The physical examination revealed a markedly distended abdomen with a large, palpable mass encompassing a significant portion of the abdomen. The exam of the right lower extremity revealed pitting edema extending to the upper thigh, and tenderness on palpation. The remainder of the exam was negative for significant findings.

Initial laboratory evaluation revealed a normocytic anemia, mildly elevated liver function tests, and normal electrolytes. Further lab work revealed an elevated N-terminal pro-brain natriuretic peptide level (NT-pro BNP; 1,170 ng/L; normal, ≤ 300 ng/L), and a normal troponin I level. Venous duplex imaging of the lower extremity was positive for deep venous thrombosis extending from the right common femoral vein through the popliteal vein. A computerized tomography (CT) scan of the chest, abdomen, and pelvis revealed extensive bilateral pulmonary emboli, including saddle embolism (Figure 1A); 3 small pulmonary nodules in the right lung; a large multilobar, heterogeneously enhancing mass projecting from the pelvis into the midabdomen (20.6 x 14.2 x 21.7 cm; Figure 1B); and peritoneal carcinomatosis. Echocardiographic evaluation showed a normal left ventricular ejection fraction (50%-55%), a mildly dilated right ventricle, and no evidence of pulmonary hypertension.

Enoxaparin was initiated for the treatment of venous thromboembolism in the presence of suspected malignancy. The CT scan finding of a large pelvic mass prompted a tumor marker evaluation. Findings included an elevated CA-125 (237 U/ml; normal, 35 U/ml), and normal values for CA 19-9 (16 U/ml) and carcinoembryonic antigen (0.8 ng/ml). Subsequently, the patient underwent an elective total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy. Pathology evaluation with hematoxylin and eosin staining revealed a high-grade malignant tumor with both epithelial and mesenchymal differentiation (Figure 2A). The epithelial component was focally highlighted by epithelial membrane antigen (EMA) and rare pankeratin. The epithelial component was also strongly reactive with the neuroendocrine markers synaptophysin (Figure 2B) and chromogranin (Figure 2C). The mesenchymal component was remarkable for strap-like malignant cells testing positive for the skeletal muscle markers desmin (Figure 2D) and myogenin. The final pathologic diagnosis was carcinosarcoma consisting of a high-grade neuroendocrine epithelial component and a rhabdomyosarcomatous mesenchymal component. The tumor was most consistent with an ovarian primary. The patient declined further treatment and was discharged to hospice.

Discussion

Ovarian malignancies have the highest mortality,

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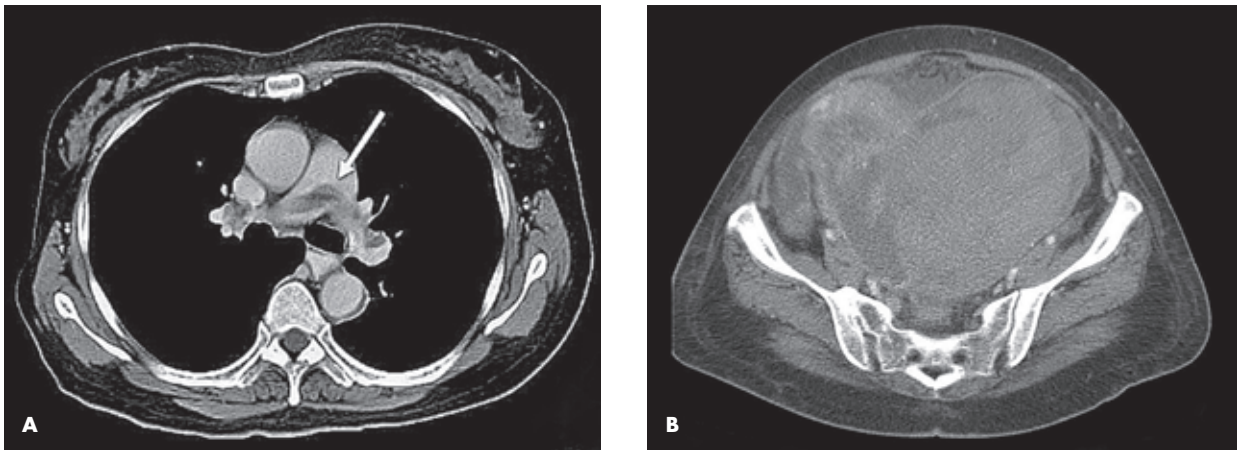

FIGURE 1 A computerized tomography scan of the chest, abdomen, and pelvis shows extensive bilateral pulmonary emboli, including saddle embolism (A, white arrow) and a large multilobar, heterogeneously enhancing mass projecting from the pelvis into the midabdomen (B).

and lowest 5-year survival, of all gynecologic tumors in the United States.[1] The American Cancer Society estimated there would be 22,240 incident cases of ovarian cancer in 2013, and 14,030 deaths from the disease.[2] Relative to other cancers, ovarian is the 10th most common, but the 5th most deadly among American women.

Ovarian tumors can be classified according to the originating cell type: surface epithelial cell, germ cell, sex cord-stromal cell, or metastatic cells to the ovary. Epithelial tumors account for 90% of ovarian malignancies, whereas germ cell tumors and sex cord-stromal tumors account for 3%-5% and 2%-3%, respectively.[3] Carcinosarcomas (ie, malignant mixed mesodermal (Mullerian) tumors, or MMMT) have been categorized inconsistently by different classification systems. The World Health Organization classification of malignant ovarian tumors, categorizes carcinosarcomas as a rare subtype of endometrioid tumors.[4] The Surveillance, Epidemiology, and End Results program of the National Cancer Institute classifies carcinosarcomas under "other specified types."[5] Whichever classification is used, carcinosarcomas are extremely rare tumors, accounting for less than 1%-2% of all ovarian malignancies.[6]

Histopathologically, carcinosarcomas contain both malignant epithelial and sarcomatous elements. The epithelial component is often serous, endometroid, or undifferentiated adenocarcinoma, but may also be clear cell adenocarcinoma or squamous cell carcinoma.[7] The sarcomatous element may be homologous tissue native to the ovary such as endometrial stromal sarcoma, fibrosarcoma, and leiomyosarcoma, or heterologous tissue not native to the ovary such as chondrosarcoma, rhabdomyosarcoma, and osteosarcoma.[8] Ovarian carcinosarcomas with neuroendocrine differentiation in the epithelial component are among the rarest of all tumors. Our literature review found no reported

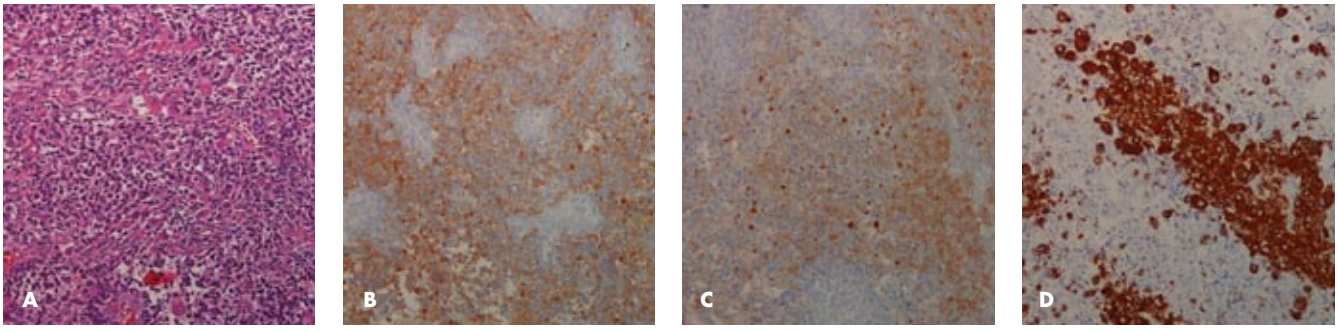

FIGURE 2 Pathology evaluation with hematoxylin and eosin staining revealed a high-grade malignant tumor with both epithelial and mesenchymal differentiation (A). The epithelial component was strongly reactive with the neuroendocrine markers synaptophysin (B) and chromogranin (C), and the mesenchymal component was remarkable for strap-like malignant cells testing positive for the skeletal muscle markers desmin (D) and myogenin.

cases of primary ovarian origin in the United States. Worldwide, one case of adnexal carcinosarcoma with neuroendocrine differentiation has been reported.[9] Carcinosarcoma with neuroendocrine differentiation has been described in case reports at other anatomic sites, including the stomach, esophagus, mesentery, and uterine cervix.[10-13]

Patients present with symptoms similar to women with epithelial ovarian cancer, but have comparatively worse outcomes.[14] The clinical presentation is that of advanced stage disease, including pelvic or abdominal pain, early satiety, and bloating, none of which were described by our patient. The poor prognosis of carcinosarcoma is due to multiple factors, including older age at diagnosis (60-70 years), worse performance status at diagnosis, and a poorer response to platinum-based chemotherapy.[7] As in most malignancies, though, stage of disease remains the most important predictor of survival.[15] The rarity of this malignancy compounds the effect because of the difficulty in finding cases for clinical trials. Patients with advanced stage carcinosarcoma of the ovary have a poor 5-year overall survival of 7%-20%, with a median survival of 4-27 months.[6,16] In a recent case-control study, the median disease-free survival for ovarian carcinosarcoma was 11 months, whereas this measure was 16 months for epithelial ovarian cancer.[14] Overall survival was also decreased for patients with ovarian carcinosarcoma (24 months), compared with epithelial ovarian cancer (41 months). In addition, 75% of women with carcinosarcoma of the ovary will present with stage III or IV disease at initial surgery, and in more than 90% the disease will have spread beyond the ovary at diagnosis.[8] Another prognostic indicator is the CA-125. A pre-operative level >75 U/mL portends a poor outcome.[8] Our patient, as in most patients with ovarian carcinosarcoma, had extensive disease at presentation, consisting of likely pulmonary metastases as well as peritoneal carcinomatosis. The preoperative CA-125 level of 237 U/mL also predicted a poor prognosis for our patient. Inherent tumor heterogeneity poses a therapeutic problem, and is the likely reason for the poor response of carcinosarcomas to platinum-based chemotherapy relative to epithelial ovarian cancer.[14,17] Despite this, the consensus recommendation is to follow the protocol for epithelial ovarian cancer and give platinum-based chemotherapy with a taxane after primary cytoreductive surgery.[18] Studies examining treatment regimens specific for ovarian carcinosarcoma have shown similar results for platinum-based chemotherapy combined with either a taxane or ifosfamide.[15, 19] One study has shown decreased efficacy with combination therapy that included either doxorubicin or cyclophosphamide.[15]

This case is important for 2 reasons. First, we describe a rare tumor that has not yet been documented in the United States. In fact, a recent review of ovarian carcinosarcomas did not mention neuroendocrine differentiation as a possible epithelial component.[7] Our literature review revealed 1 case of adnexal carcinosarcoma with neuroendocrine differentiation that was published in Korea in 1998.[9] That description was important, but may have been overlooked by the medical community in the United States. Furthermore, the authors of that case report describe a chemotherapy regimen that is no longer the standard of care for ovarian carcinosarcomas.[9,18] Second, the clinical implications for this carcinosarcoma subtype are concerning. Carcinosarcoma of the ovary presents a daunting therapeutic problem because of its inherent heterogeneity, but in our patient's case, the problem was further complicated by the tumor's neuroendocrine differentiation. As already described in this report, the standard of care is to treat ovarian carcinosarcomas as epithelial ovarian cancers, but that may not be the correct approach when the epithelial component is primarily neuroendocrine tissue. The only documented case of adnexal carcinosarcoma with neuroendocrine differentiation was treated with cisplatin and doxorubicin, which was likely targeting the epithelial and soft-tissue components, respectively.[9] Perhaps chemotherapy aimed at a neuroendocrine primary tumor would be a more effective approach. Only further recognition of this tumor and subsequent research into novel treatment modalities will assist in improving the dismal prognosis associated with ovarian carcinosarcomas.

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