Case Report

Angiosarcoma originating from an ovarian mature teratoma, a rare disease with complex treatment modalities ☆

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Introduction

Angiosarcomas are rare, accounting for 2% of soft tissue sarcomas, with only a fraction of these cases being located in the ovary (Penel et al., 2008). Exceedingly rare is a malignant transformation of a mature cystic teratoma into an angiosarcoma.

Mature cystic teratomas are the most common type of ovarian neoplasm and are usually benign (Koonings et al., 1989). Rarely (0.8–2%) a mature cystic teratoma undergoes malignant transformation of which squamous cell is the most common histology (Koonings et al., 1989; Contreras and Malpica, 2009). The clinical prognosis, and hence the adjuvant therapy, of a patient with such transformation depends on the histology of the transformed cells rather than the teratoma itself (den Bakker et al., 2006).

There have been only 5 reported cases in English literature to date of a mature cystic teratoma with transformation to angiosarcoma. Angiosarcomas have aggressive clinical behavior with poor patient prognoses. This case is the 6th report of this disease. We also review the current adjuvant treatment strategies.

Case

A 64 year-old female with a history of type 2 diabetes mellitus, hypertension, and vaginal hysterectomy for uterine leiomyomas 30 years ago, presented to the emergency room with acute abdominal pain and fever. She had lower abdominal pain and bloating for the last 2 months with decreased appetite, nausea, and a 22-pound weight loss.

On examination, the patient had a palpable abdominal mass with diffuse rebound tenderness and rigidity. Computed tomography (CT) scan showed a complex pelvic mass measuring $19.8 \times 17.8 \times 14.5$ cm invading and perforating the sigmoid colon (Fig. 1).

Exploratory laparotomy showed infected ascites from a sigmoid colon perforation. This mass also extended to the right ovary and invaded the terminal ileum and the cecum. Optimal debulking to no visible disease was performed with bilateral salpingo-oophorectomy, resection of the terminal ileum and cecum with side-to-side anastomosis, resection of sigmoid and upper rectum, and a formation of a permanent descending end colostomy. The patient was discharged home after four days of inpatient hospitalization.

Pathologic evaluation of the mass showed angiosarcoma involving bilateral ovaries with extensive necrosis associated with the cystic teratoma of the left ovary (Fig. 2). Microscopic examination revealed atypical cells, varying from spindled to an epithelioid character with abundant cytoplasm, and large hyperchromatic, pleomorphic nuclei. The tumor showed solid, sheet-like areas and vascular spaces. Immunohistochemisty of the tumor showed intense staining for CD31 and vimentin, reacted weakly for FLI-1, but had lost expression of CD34 and factor VIII related antigen. Additional staining for CD117, DOG-1, S100, desmin, muscle-specific actin, myogenin, melanoma cocktail, and cytokeratin AE1/AE3 were negative. The tumor additionally involved the left peri-fallopian soft tissue, pelvic soft tissue, and right peri-adnexal tissue. Metastatic foci involved full thickness of the sigmoid colon wall, terminal ileum, and one regional lymph node.

After extensive counseling and given the extent of the disease, the decision was made to start adjuvant chemotherapy to be followed by radiotherapy (RT). Three weeks after recovering from her surgery, the patient received intravenous paclitaxel (175 mg/m^2 = 362 mg) to be scheduled every 3 weeks. More studies have looked in to the use of paclitaxel as a single agent in sarcoma literature rather than combination chemotherapy. Considering this and the patient's medical co-morbidities and performance status, single agent paclitaxel was used as an adjuvant treatment. However, she was readmitted 2 weeks later with a recurrence of her original symptoms and CT scan showing recurrence of her cancer to the pelvis and upper abdomen. With a rapid clinical deterioration, the patient developed multi-organ failure and elected to be at home with hospice care. She passed away 2 weeks later—8 weeks after initial diagnosis and 4 months after her symptoms began.

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Fig. 1. Angiosarcoma CT.

Comment

Mature cystic teratomas are relatively common ovarian neoplasms (Koonings et al., 1989). Rarely, malignant transformation of a mature cystic teratoma can occur (Koonings et al., 1989). These malignancies are typically squamous cell carcinomas, and only a few cases have been reported of transformation of a mature cystic teratoma into an angiosarcoma (Contreras and Malpica, 2009). The overall survival of those patients with mature cystic teratoma transformation to angiosarcoma varies from 2 to 29 months (Contreras and Malpica, 2009; den Bakker et al., 2006; Nielsen et al., 1997; Devouassoux-Shisheboran et al., 2000). It is difficult to study the optimal adjuvant therapy, because of the paucity of cases and their aggressive clinical behavior. No study has focused solely on the treatment of ovarian angiosarcomas.

Adjuvant treatment of angiosarcomas in general varies according to the anatomic location of primary tumor site. Those originating above the clavicle have better prognosis than those originating below it (Penel et al., 2008).

In head and neck (mainly scalp) angiosarcomas, surgical excision should be followed by radiotherapy if the surgical margins are positive. In patients with negat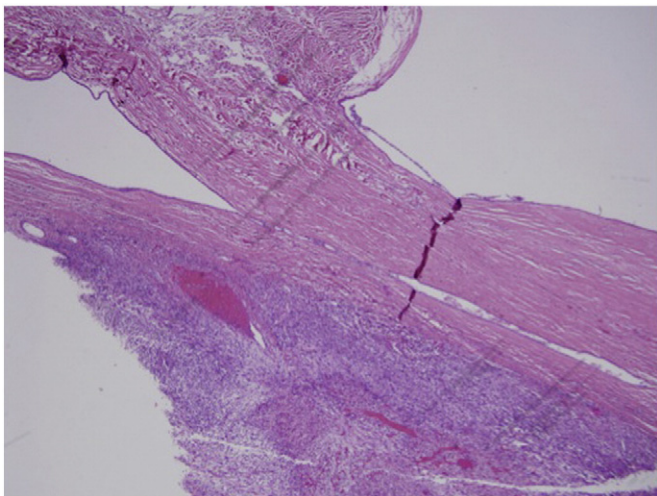ive surgical margins, radiotherapy is optional. Intra-abdominal angiosarcomas are most likely metastatic and hence necessitate surgical excision with adjuvant chemotherapy, which can be in the form of intra-operative radiotherapy (IORT), or post-operative radiotherapy (RT), or chemotherapy.

Post-treatment surveillance with CT can be done every 3–6 months for 2–3 years.

English literature review revealed only five cases of angiosarcoma derived from mature cystic teratoma. Three of these case reports focused on the pathologic diagnosis of angiosarcomas from mature cystic teratomas (Contreras and Malpica, 2009; den Bakker et al., 2006; Nielsen et al., 1997). Another report evaluated the genotypes of the malignant components of mature teratomas in a patient with two separate malignant teratomas that transformed into angiosarcomas with independent genetic origin (Devouassoux-Shisheboran et al., 2000). These cases, in addition to the current case, are summarized in Table 1.

Doxorubicin-based chemotherapy was considered the standard-of-care treatment in metastatic soft tissue sarcomas (Penel et al., 2008). However, recent literature suggests that paclitaxel, docetaxel, vinorelbine, sorafenib, sunitinib, and bevacizumab can be considered for angiosarcomas as a single or multiple agent therapy.

The ANGIOTAX phase II trial suggested the utility of paclitaxel in advanced angiosarcomas (Penel et al., 2008). At low concentrations of continuous infusion, paclitaxel has potent anti-angiogenic effects, but is more active against angiosarcomas above the clavicle (Penel et al., 2008). One retrospective study has suggested that the efficacy of paclitaxel may differ depending on the location of the angiosarcoma in the body (Fury et al., 2005). Paclitaxel was more effective when the angiosarcoma was above the clavicle, with a progression free survival of 6.8 ± 4.3 months. Non-paclitaxel regimens used for treating unresectable angiosarcomas below the clavicle provided a progression free survival of 3.7 ± 0.9 months while paclitaxel provided 2.8 ± 0.2 months progression free survival for these patients (Fury et al., 2005). However, paclitaxel is the most commonly used therapy for angiosarcomas and there is a paucity of randomized trials evaluating the efficacy of paclitaxel below the clavicle (Fury et al., 2005).

As more knowledge is gained about biologic markers that are associated with angiosarcomas, therapies can be developed to target these growth factors and receptors. VEGF and KDR (VEGF-R2) are believed to play a role in angiosarcoma growth and may be potential targets for future therapies (Ray-Coquard et al., 2012). A phase II study assessed sorafenib (inhibitor of several tyrosine protein kinases, including VEGF and Raf kinases) in patients with recurrent or metastatic sarcomas showed a progression free survival rate of 3.8 months (Ray-Coquard et al., 2012). However, this study also showed that standard cytotoxic treatments continue to have better response rates (Ray-Coquard et al., 2012). Another phase II trial by the French Sarcoma Group suggested that sorafenib had very limited anti-tumor activity in patients that had been pre-treated with another chemotherapy and had no utility in patients who had not been pre-treated (Ray-Coquard et al., 2012). Sorafenib may be useful in the therapy in the future, as in vitro studies have shown high sensitivity to angiosarcomas with an activating mutation in the *KDR* protein (Ray-Coquard et al., 2012).

Angiosarcoma of the ovary is a rare but aggressive disease.

Current literature suggests management with chemotherapy, radiation therapy, palliative surgery, or supportive care for recurrent unresectable disease. Paclitaxel may provide some additional survival benefit in addition to standard therapy. The aggressive nature of intra-abdominal angiosarcomas warrants further research on newer anti-angiogenic chemotherapies that may provide longer progression-free survival.

Fig. 2. Cyst wall with adjacent angiosarcoma; H&E.

Table 1
Summary of previous case reports on cystic teratomas with transformation to angiosarcoma.

Case report	Number of cases	Age of patient (years)	Stage of cancer	Surgery	Therapy	Time from diagnosis to death (months)
Neilsen (6)	2	20–32 (average 26)	III	Not available	Not available	2, 15, 30 (average 15.7)
Devouassoux-Shisheboran (3)	1	40	IV	Not available	Not available	Not available
den Bakker (2)	1	30	Probable IIIC	Exploratory laparotomy, left oophorectomy and removal of cystic tumor, staging and subtotal omentectomy. Recurrence at 5 months: debulking, hysterectomy, right oophorectomy and removal of residual omentum.	3 cycles of BEP (bleomycin, etoposide and cisplatin); 1 course of EP	9
Contreras (1)	1	32	Not available	Total hysterectomy, bilateral salpingo-oophorectomy, tumor debulking, omentectomy, and appendectomy.	5 cycles of high-dose ifosfamide + 1 doxorubicin;	29
Albertin (current case)	1	64	IIIC	Exploratory laparotomy, debulking, bilateral salpingo-oophorectomy, resection of the terminal ileum and cecum with side-to-side anastomosis, resection of sigmoid and upper rectum, and formation of a permanent descending end colostomy.	1 cycle of paclitaxel	1.5

beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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