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Bilateral ovarian angiosarcoma arising from the mature cystic teratomas – A case report and review of the literature

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ABSTRACT

INTRODUCTION: Ovarian teratomas undergo the malignant transformation in 0.2–2% of cases. The behavior of malignancies in mature cystic teratomas (MCT) is determined by their phenotype and not their derivation from germ cells. We can recognize pure angiosarcomas or as a part of other tumors like malignant mixed Mullerian tumors and adenosarcomas.

PRESENTATION OF CASE: We present the first case of bilateral ovarian angiosarcoma arising from the mature teratomas. Due to widespread disease, we performed limited surgical procedure consisting of bilateral adnexectomy and omentectomy. Exploratory laparotomy in 44-year old patient showed massive ascites, necrotic tissue of omentum and bilateral tumors originating from both ovaries measuring 8 and 6 cm with necrotic surface. Immunohistochemistry of the tumors showed positive staining for CD31, vimentin, desmin and focal positivity for CD34.

DISCUSSION: Sarcomas of gynecologic origin are extremely rare tumors. They present with unspecified symptoms and are diagnosed in late stages of the disease. The appropriate management of angiosarcomas is difficult due to the rarity of disease and late stage of the diseases. Surgical therapy should contain the hysterectomy with bilateral salpingo-oophorectomy and omentectomy. Pelvic lymphadenectomy was not performed in published cases with no effect on patient survival.

CONCLUSION: This work summarizes the current knowledge in the diagnosis and treatment of angiosarcomas arising in the mature teratomas. Promising results are expected from the trials devoted to antiangiogenic strategies in treatment of aggressive sarcomas.

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1. Introduction

Teratomas are the most common germ cell tumors accounting for 27% of ovarian neoplasms. Their components derive from ectoderm, endoderm and mesoderm that undergo the malignant transformation in 0.2–2% of cases [1,2]. Age over 45 years, postmenopausal status, elevated CA 125 and tumor size greater than 10 cm represent the risk factors for malignancy [3]. The most common neoplasm is squamous carcinoma [2]. Other tumors are very rare e.g. basal cell carcinoma, melanoma, adenocarcinoma, sarcoma, thyroid carcinoma and angiosarcoma [2]. The behavior of malignancies in mature cystic teratomas (MCT) is determined by their phenotype and not their derivation from germ cells.

Ovarian angiosarcoma was first described in 1931 and only about 35 cases have been published in the literature [4]. Angiosarcomas are aggressive tumors with median survival 15–30 months

[5]. The cells represent multiple genetic mutations including TP53 point mutation, trisomy of 5th chromosome and loss of Y chromosome, KDR (knockdown resistance) mutations, PTPRB (gene encoding protein tyrosine phosphatase, receptor type B) and PLCG1 (gene encoding phospholipase C gamma 1) and a novel fusion gene NUP160-SLC43A3 [6].

The review article of Kruse et al. identified and reviewed 51 angiosarcomas of female genital tract: 2 cases of vulvar angiosarcoma, 2 vaginal angiosarcomas, 18 uterine angiosarcomas and 29 ovarian angiosarcomas. Five-year disease free survival was 27% [7].

The most common clinical manifestations of ovarian angiosarcoma are nonspecific gastrointestinal symptoms, abdominal pain and distension with the mean age 37 years at the time of the diagnosis [7]. Macroscopically angiosarcomas represent a fragile hemorrhagic mass 2–29 cm in diameter. They are often unilateral and some of them arise in the wall of mature cystic teratoma [2,7,8]. We present the first case of bilateral ovarian angiosarcoma arising from mature teratomas. The work has been reported in line with the SCARE criteria [9].

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2. Case report

A 44-year old female was admitted to our department in December 2009 complaining of abdominal pain, meteorism and weight loss of 6 kg that she first noticed 2 months ago. Her personal medical history was unremarkable with no drug using. Her family and psychosocial history was uneventful and negative for cancer. She was a non-smoker. Upon arrival there was a severe ascites causing tense abdomen with pale skin and enlarged subcutaneous veins. Her BMI was 23.1 kg/m², she had a temperature of 36.9 °C, blood pressure 112/68 and her pulse rate was 85 beats/min. All laboratory parameters were within normal limits except light hyponatremia 125 mmol/l and hypoproteinemia 46 g/l. The ovarian tumor markers were increased: CA 125 (108,8 U/ml) and CA 19-9 (236 U/ml)

The patient was further evaluated with MRI examination of the abdominal cavity and small pelvis. The examination confirmed bilateral ovarian tumors of mixed composition: 100 × 90 mm on the right side and 63 × 75 mm on the left side. The urinary bladder, uterus and rectosigmoid were without pathologic findings. The chest X-ray also showed the presence of bilateral fluidothorax.

After treating the mineral imbalance and hypoproteinemia we performed exploratory laparotomy. The procedure was performed by a gynecologist specialized in ovarian cancer surgery with 30 years of experience in gynecologic oncology. The laparotomy showed massive ascites, necrotic tissue of omentum and fixed bilateral tumors with necrotic surface originating from both ovaries 60 and 80 mm in diameter. The Douglas pouch, urinary bladder surface, small bowels and parietal peritoneum were covered by reddish necrotic and fragile tissue. Due to the widespread disease and anesthesiological complications we performed only limited surgical procedure including bilateral adnexectomy and omentectomy. The initial postoperative care was smooth. However a paralytic ileus occurred accompanied by severe metabolic imbalance. Despite intensive treatment sudden onset of cardiac arrest occurred three weeks after surgical procedure. No adjuvant therapy was performed right after the laparotomy.

2.1. Histopathological evaluation

Macroscopically the tumors consisted of reddish masses with necrotic surface and multiple atypical varicose vessels. Pathological evaluation showed bilateral teratomas with malignant transformation to angiosarcoma. Teratomatous component was formed by ectoderm (brain tissue, epidermis, hair follicles), endoderm (respiratory and intestinal epithelium) and mesoderm (adipose tissue). The malignant part was composed of pleomorphic and highly mitotic active tumor cells that formed solid lesions and irregular vascular structures with intravascular papillary formations of high grade angiosarcoma. There were vast necrotic parts and new hemorrhages with areas of cholesterol crystals. The tumor infiltrated the paraovarian tissue and fallopian tubes bilaterally and spread to serous surface.

Immunohistochemistry (IHC) of the tumor showed positive staining for CD31, vimentin and focal positivity for CD34 and CK HMW. The staining for Glypican 3 and Sall4 was negative. Images of CD34 and CD31 immunohistochemical staining and hematoxylin-eosin (HE) staining are represented by Figs. 1–5.

The cytological evaluation of the fluidothorax content showed polymorphic population of histiocytes, abnormal, mesotel-like cells in morula-like structures. IHC analysis showed positive vimentin staining and negativity for KL-1, CK7, CK20, TTF-1, HMW CK, KiM1P.

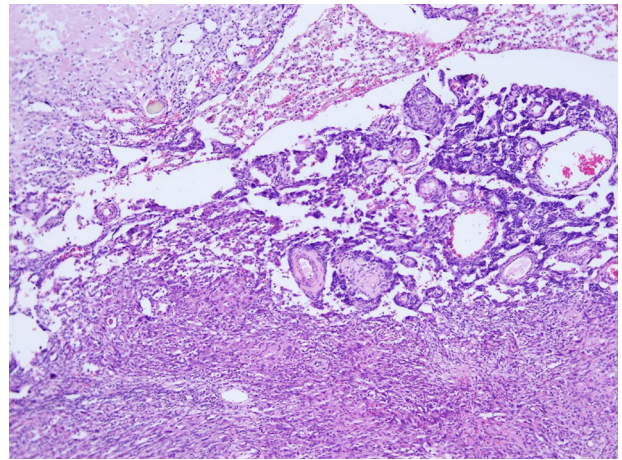


Fig. 1. Hematoxylin-eosin staining of ovarian angiosarcoma components in the ovarian teratoma.

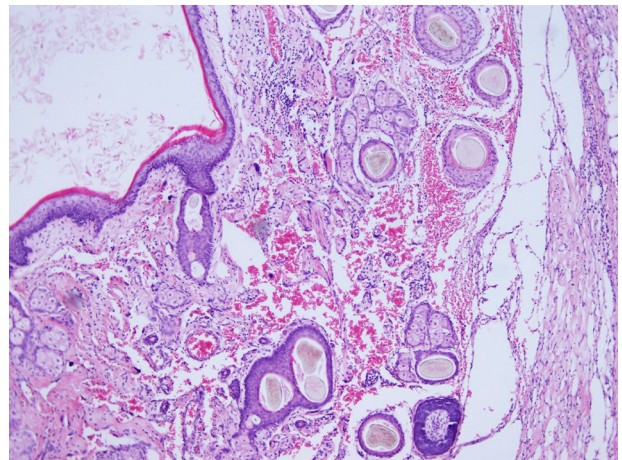


Fig. 2. Hematoxylin-eosin staining of ovarian angiosarcoma components in the ovarian teratoma.

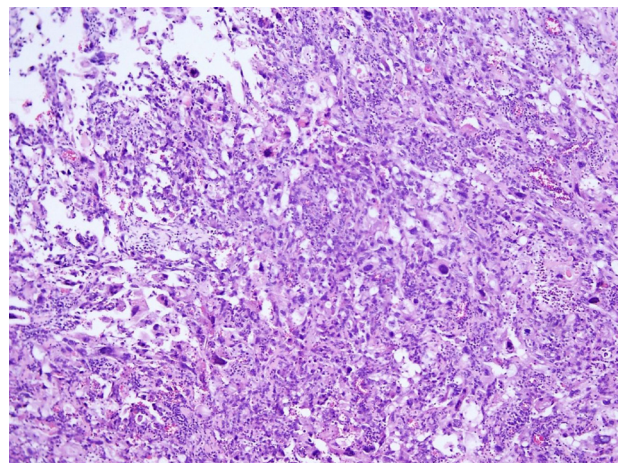


Fig. 3. High power field image showing the HE staining of ovarian angiosarcoma.

3. Discussion

Sarcomas of gynecologic origin are extremely rare tumors. They present with unspecified symptoms and are diagnosed in late stages of the disease. We can recognize pure angiosarcomas or as a part of other tumors like mixed Mullerian malignant tumors,

Table 1
Angiosarcomas originating in mature cystic teratomas – articles published in the English literature (OS – overall survival).

Case reports	Age	Size of the tumor (cm)	Stage	Additional findings on the ovary	Adjuvant therapy	OS (months)
Nielsen et al. (2 cases) [13]	20 32	6 13	III	n.a	n.a.	15 and
Devouassoux-Shisheboran et al. [14]	40	n.a.	IV	n.a.	n.a.	n.a.
den Bakker et al. [8]	30	n.a.	IIIC	cutaneous type angiosarcoma	bleomycin, etoposid, cisplatin	9
Contreras et al. [2]	32	n.a.	n.a.	–	ifosfamid, doxorubicin	29
Takahashi et al. [15]	59	16 × 12 × 4.5	n.a.	clear cell adenocarcinoma	paclitaxel	n.a.
Albertin et al. [12]	64	19.8 × 17.8 × 14	IIIC	–	paclitaxel	1,5
Current case	44	8 and 6	IV	–	no treatment	2

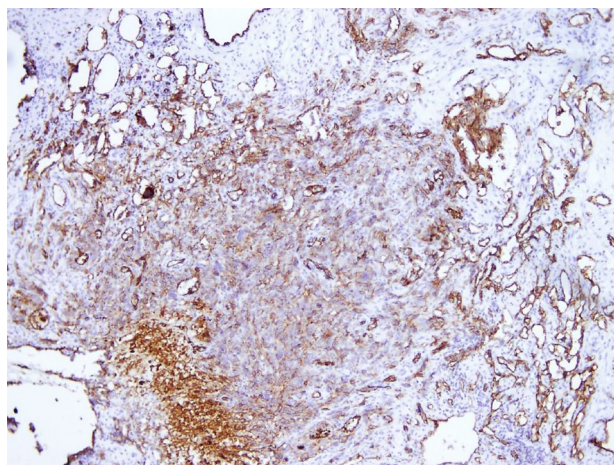


Fig. 4. CD31 immunohistochemical staining of ovarian angiosarcoma.

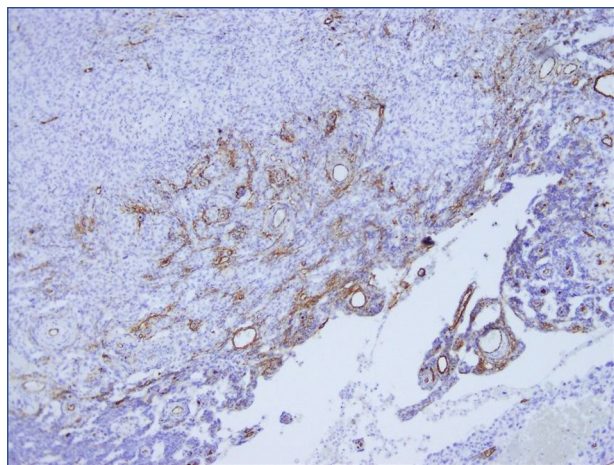


Fig. 5. CD34 immunohistochemical staining of ovarian angiosarcoma.

adenosarcomas and epithelial tumors. The differential diagnosis includes undifferentiated adenocarcinoma, leiomyosarcoma and even malignant melanoma, yolk sack tumor and choriocarcinoma [10]. Immunohistochemical staining helps in diagnosis, especially the vascular markers CD34 and CD31 [11]. For the differential diagnosis, we used wide spectrum of markers not only for vascular tumors, but also for epithelial tumors and germ cell tumors. Similar wide spectrum of immunohistochemical markers was used in the study of Albertini et al. The tumor showed intense staining for CD31 and vimentin, weak staining for FLI-1 and had lost expression of CD34 and factor VIII related antigen. Staining for CD117, DOG-1, S100, desmin, muscle-specific actin, myogenin, melanoma cocktail, and cytokeratin AE1/AE3 were negative [12] All cases of similar, but unilateral angiosarcomas originating in mature cystic teratomas are reviewed in Table 1.

The appropriate management of angiosarcomas is difficult due to the rarity of disease and late stage of the diseases. The average age of women diagnosed with angiosarcoma arising from mature cystic teratoma is 40.1 years and the average overall survival only 11.4 months even with the use of adjuvant chemo and radiotherapy.

Surgical therapy should contain the hysterectomy with bilateral salpingo-oophorectomy and omentectomy. Pelvic lymphadenectomy was not performed in published cases with no effect on patient survival. Albertin et al. presented a wide spread disease with resection of terminal ileum, caecum, sigmoid and upper rectum [12]. Conteras et al. added appendectomy to surgical treatment [2]. In case report published by Den Bakker et al. the patient was diagnosed with liver metastases and enlargement of retroperitoneal and mediastinal lymph nodes, multiple peritoneal tumor nodules and a large pelvic mass with bowels one month after debulking surgery. Curative treatment was not possible and optimal palliative care was provided [8].

The adjuvant therapy is mainly represented by chemotherapy. Albertini et al. used intravenous paclitaxel (175 mg/m² = 362 mg) every 3 weeks. [12]. In cases of pure angiosarcomas doxorubicin (25 mg/m²) and ifosfamide (2.5 g/m²) could be administered on days 1–3 of a three-week treatment cycle. Due to the risk of myelosuppression, pegfilgrastim (6 mg) is routinely given on day 4 [9].

Radiotherapy continues to evolve and can achieve 80% of local control [16], but 50% of angiosarcomas are in late stage, so the radiotherapy does not improve survival.

The NCCN lists several agents with activity against sarcomas: paclitaxel, docataxel, vinorelbine, sorafenib, sunitinib and bevacizumab [17]. Response to preoperative chemotherapy is only 40–50% and the regimen is continued in those patients who respond with tumor shrinkage after two to three courses of multiagent chemotherapy after tumor resection. The standard chemotherapy relates to the use of doxorubicin in all metastatic soft tissue sarcomas [5]. A meta-analysis suggests improved local control and disease-free survival with chemotherapy, but no survival advantage [18]. The ANGIOTAX phase II trial suggested the utility of paclitaxel in advanced angiosarcomas [5]. Ravi et al. report good response to treatment with pazopanib in a patient with angiosarcoma with amplification of vascular endothelial growth factor receptor (VEGFR) and that had not responded to sorafenib [19].

4. Conclusion

We present a unique case of bilateral angiosarcoma arising from mature cystic teratomas that has not been published in the English literature. Palliative surgical treatment and adjuvant chemotherapy could extend the disease-free survival in patients with late stage sarcomas, Promising results are expected from the trials devoted to antiangiogenic strategies in treatment of aggressive sarcomas.

In conclusion we would like to clearly stress the following points to learn from this case report.

1. The extreme rarity of the bilateral ovarian angiosarcoma arising from mature teratomas
2. The differential diagnosis of ovarian angiosarcoma
3. The literature review of current knowledge of diagnostic and treatment modalities of ovarian angiosarcoma.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

None.

Ethical approval

The ethical approval has been exempted by our institution. The patient involved in our study died of her primary diagnosis. All attempts have been made to contact the family for informed consent, but we were not able to obtain it. The paper has been sufficiently anonymised not to cause harm to the patient and the family.

Consent

The patient involved in our study died of her primary diagnosis. All attempts have been made to contact the family for informed consent, but we were not able to obtain it. The paper has been sufficiently anonymised not to cause harm to the patient or their family.

The head of the medical team/hospital or legal team has taken responsibility that exhaustive attempts have been made to contact the family and that the paper has been sufficiently anonymised not to cause harm to the patient or their family.

Author contribution

Kudela E – paper design and composition.
 Nachajova M – paper design and composition.
 Biringir K – therapy and discussion.
 Slavik P – histopathological evaluation.
 Plank L – histopathological evaluation.
 Danko J – study design.

Guarantor

The first author is the guarantor of this study.

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