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CASE REPORT

# Pelvic Angiosarcoma Occurring in a Postmenopausal Female: Case Report and Review of the Literature

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## Introduction

Sarcomas of the soft tissue are uncommon tumors which are difficult to diagnose due to their frequency and subtle presentation [1]. Angiosarcomas only count for less than 2 % from all soft tissue sarcomas, which makes the diagnosis even harder [2, 3]. Literature about them is scarce and obtained from small series and case reports. We present a clinic-pathologic reported case of a biphasic pelvic angiosarcoma in a 55-year old female with abdominal pain and ascites.

## Case Report

A previously healthy, non-obese, 55-year old caucasian female sought for medical attention multiple times complaining of sudden, progressive, persistent, dull, diffuse lower abdominal pain, bloating and malaise. She was gravida 3 para 3, with menopause at 54 years old, menarche at 14 years old and history of combined hormonal replace therapy for 3 months. She never used hormonal contraception. Her oldest son had pylocitic astrocytoma at 9 years old but there was no history of ovarian or breast cancer in the family. She did not smoke cigarettes but reported marijuana use on a regular basis. There was no exposure to gases or radiation. Previous screening with Ca-125 in serum was negative.

The patient underwent imaging studies. Of note, previous Magnetic Resonance Imaging (MRI) studies performed 8 and 3 years before showed small cystic lesions in left ovary. Pelvic ultrasound showed a uterine fibroid, partially calcified, and a cyst in the left ovary measuring approximately 2.0 cm. Computerized tomography revealed free fluid in the pelvis and surrounding the liver and mesenteric nodularities in the left abdomen and pelvis with no drainable fluid collection. A new MRI of the pelvis showed a 1.7 cm cyst in the left ovary and several well-defined cystic structures in the posterior and lateral aspect of the left pelvis, some of which had tubular configurations.

With a preoperative diagnosis of ovarian cancer, abdominal hysterectomy and bilateral salpingoophorectomy were performed. Surgery showed a pelvis with retroperitoneal fibrosis and great involvement of the pelvic floor by malignancy which made complete resection technically impossible. A normal uterus with a left ovarian complex mass measuring 10×10 cm was identified, firmly attached to the omentum, bowel, bladder, colon and ureter. It was associated with approximately 1 l of hemoperitoneum. No significant pelvic or aortic lymphadenopathies were identified. With these findings, the case was surgically diagnosed as ovarian cancer and classified as a Stage IIIC (FIGO classification). Extensive enterolysis and ureterolysis were done.

Five days after the surgery the patient suffered from pulmonary embolism and had an increased level of ascites and pain, requiring three therapeutic paracentesis. Later CT scans showed questionable hypoenhancing lesions in the liver and one in the lung. Cytological analysis of the ascitic fluid ruled out malignancy and showed cellular evidence of acute inflammation.

The patient started with palliative chemotherapy with Docetaxel 66.8 mg/m2 and Gemcitabine 1780 mg/m2. A following intent with Gemcitabine 1780 mg/m2 was done on day 8. The chemosensitivity is yet to be determined following 2 or 3 cycles of this regimen. Other possible agents that will be considered are Adriamycin or Sorafenib.

Grossly, the left ovary was 3.5×1.7×1.5 cm and had a 2 cm hemorrhagic, thin-walled cyst bearing a smooth inner

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lining. The external surface had thick fibrous adhesions, suggestive of a tumoral process. Neoplastic involvement was also evident in the bladder, left pelvic sidewall, sigmoid, small bowel and mesentery and omentum. The right ovary and right fallopian tube were within normal limits.

Microscopically, the lesion was highly cellular and composed by very pleomorphic cells arranged in a biphasic pattern (Fig. 1). Extensive areas of the tumor showed a fascicular spindle cell appearance with hyperchromatic tapering nuclei and indistinct pale cytoplasm, associated with foci of stromal hemorrhage (Fig. 2). These areas closely resembled a smooth muscle neoplasm. In other sections, a more strikingly epithelioid cytomorphology and well-developed vasoformative architecture was present (Fig. 3). There were areas where these two patterns merged imperceptibly.

Immunohistochemistry results were consistent with a neoplasm of vascular origin (see Table 1 and Figs. 4, 5 and 6). Vascular markers (CD31, CD34, D2-40 and ERG) were positive in both epithelioid and spindle cell components.

Sections demonstrated a high grade malignant neoplasm with intermixed solid aspect and areas forming vascular spaces, predominantly layering the serosal surface of the leiomyoma and infiltrating into the smooth muscle bundles.

The pelvic tumor was conclusively diagnosed as angiosarcoma, morphologically high grade, with mixed epithelioid and spindle cell features invading into uterine leiomyoma. Pelvic washings, cell block and cytospins did not show evidence of malignancy.

## Discussion

Angiosarcomas are neoplasms with a very aggressive behavior and poor prognosis. They derive from blood and/or lymphatic vessels and extend rapidly lining spaces filled with blood [4]. Angiosarcomas can be very well differentiated with variable endothelial atypia to high-grade spindle cell histology [4]. Around 2 % of soft tissue sarcomas and 5.4 % of cutaneous sarcomas are angiosarcomas [3].

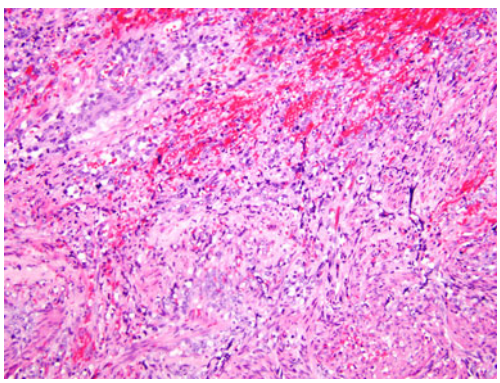

**Fig. 1** (H&E, 200 x): the biphasic histologic nature of this angiosarcoma

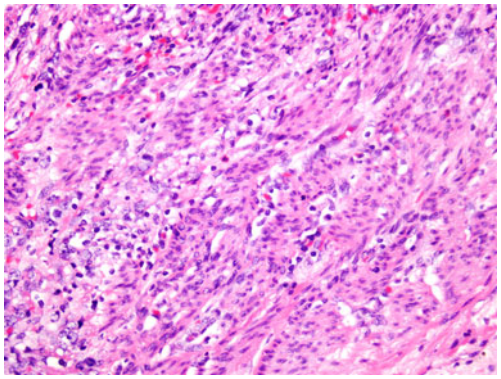

**Fig. 2** (H&E, 200 x): many foci of the tumor were composed by spindle cells in a fascicular arrangement

These malignant tumors usually affects premenopausal women, and, to our knowledge, only three cases have been reported in postmenopausal individuals [5–7]. These neoplasms predominantly emerge in non-genital regions [8]. From 27 % to 50 % of the cases occur in the head and neck [1, 9] and less than 25 % present in deep soft tissue, liver and spleen [10]. The rest mainly derives from breast and cutaneous tissues [6]. Based on imaging studies, surgery and pathological examination, we concluded that the primary site in the present case was the ovary. Angiosarcomas of the ovary are very rare, representing less than 1 % from all ovarian malignancies [8], and are usually seen as a part of mixed müllerian tumors (MMT) [1, 8] or associated with other neoplasms in 25 % of the cases [2, 4, 12, 32].

Primary ovarian sarcomas can present as pure sarcomas or MMTs. Pure sarcomas have a single malignant mesenchymal element while MMTs have both sarcomatous and carcinomatous elements. Pure sarcomas can be classified in stromal cell sarcomas, fibrosarcomas, leiomyosarcomas, neurofibrosarcomas, rhabdomyosarcomas, chondrosarcomas, liposarcomas and angiosarcomas [13]. MMTs are more common than pure sarcomas, and have a sarcomatous component that can be classified in homologous, with tissue from the ovary, and heterologous, when without ovarian tissue [10, 14].

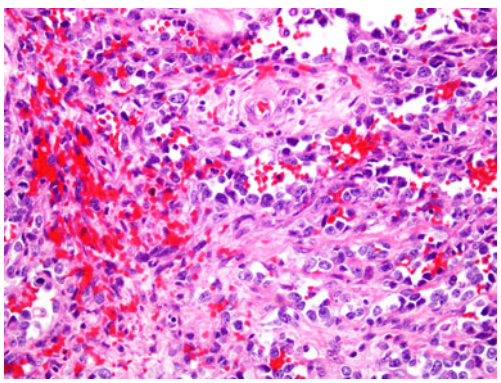

**Fig. 3** (H&E, 200 x): some areas demonstrated a more epithelioid appearance, with polyhedral cells and a more abundant cytoplasm

**Table 1** Immunohistochemistry analysis

| Antibody | Result |
|---|---|
| Pan-keratin (AE1/AE3/PCK26) | Negative |
| Cytokeratin 8/18 | Negative |
| CD31 | Positive, diffuse, strong |
| CD34 | Positive, diffuse, strong. |
| D2-40 | Positive (multifocal, strong) |
| Factor VIII | Negative |
| ERG | Positive (multifocal, strong) |
| Smooth muscle actin (SMA) | Positive in spindle cell areas |
| Desmin | Positive in spindle cell areas |
| Myosin | Negative |
| Myogenin | Negative |
| WT1 | Negative |
| MDM2 | Negative |
| CDK4 | Negative |

The neoplastic cells were positive for vascular/endothelial markers like CD31, CD34, D2-40, ERG. Muscle markers (SMA and desmin) were immunoreactive in the spindle cell component. Epithelial stains (pan-keratin and CK8/18) were negative

From the cases found in the literature, most ovarian angiosarcomas were coexistent with borderline or invasive epithelial carcinoma [8, 15]. Rarely this tumors derive from other benign tumors [10, 16, 17]. Macroscopically, ovarian angiosarcomas commonly are blue-brown, hemorrhagic, soft, and friable. They are usually unilateral but bilateral, presentations have been documented [10].

These malignancies can arise de novo or in association with a combination of radiation and chemotherapy. In the latter instance, those therapies confer a 5-fold risk for developing angiosarcoma in the treated region [18]. Chronic lymphedema has also been described as an associated cause, as also have been vinyl chloride and thorium dioxide for hepatic angiosarcoma [3].

Most common symptoms described in ovarian angiosarcomas are abdominal distension and pain [3, 19, 20], also

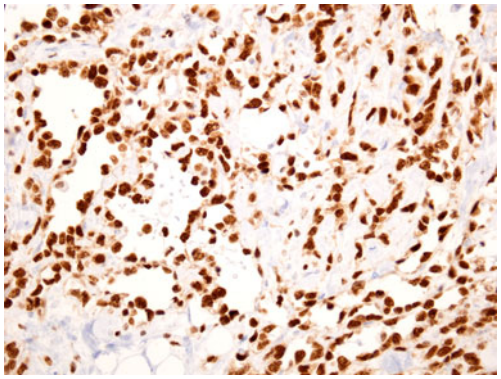

**Fig. 5** (IHC, 400 x): ERG was positive in the neoplastic cells

present in our patient. They affect a comprehensive spectrum of ages, from children to elders [5, 11, 16]. When this tumor arises in other organs from the pelvic area, similar symptoms usually occur, as well as bleeding in those where the gastrointestinal tract is involved [21]. The presence of symptoms may be associated to torsion of the tumor and hemorrhage, but the size of the tumor and the organ involved accompanied by its resultant dysfunction are the main factors for the initial clinical scenario [4, 10].

The differential diagnosis of angiosarcomas from the ovary includes lymphangiosarcoma, epithelial neoplasms, sex-cord stromal and germ cell tumors and malignant melanoma, among others. The possibility of angiosarcoma arising in a teratoma should also be considered. Metastatic angiosarcoma from other anatomic sites to the ovary has also been reported and should be part of the differential [8, 10, 20]. They can also be confused with vascular tumors of intermediate malignancy as well (e.g. hemangioendotheliomas) [8].

Typical areas of anastomosing vessels lined by highly atypical cells support the pathologic diagnosis. Immunohistochemistry is confirmatory in most cases; markers of endothelial differentiation such as CD31, CD34, Factor VIII and D2-40 are usually positive, whereas epithelial markers such as keratin and EMA are in general negative. Of note, Factor VIII has been reported to be negative in up to 25 % of

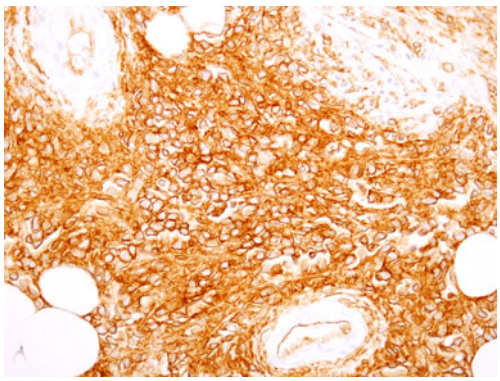

**Fig. 4** (IHC, 200 x): both components showed strong immunoreactivity for endothelial markers like CD34

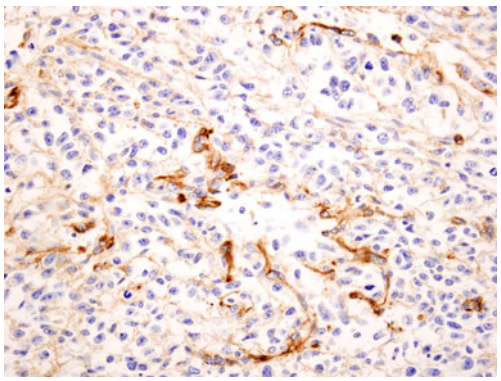

**Fig. 6** (IHC, 400 x): CD31, another endothelial marker, was also immunoreactive in the tumoral cells

the angiosarcomas as seen in this case, but consistent positivity has been described in those that have epithelioid components [4, 17, 22]. As angiosarcomas become less differentiated, sensitivity of the immunohistochemistry drops [12]. Focal myofibroblastic differentiation can occur. Our case had a biphasic pattern with spindle cell areas resembling smooth muscle morphologically and immunophenotypically (positivity for SMA and desmin).

Molecular studies were not performed on this case since more definitive evidences are lacking in regards to specific cytogenetic markers. The genetic alterations seen in angiosarcomas are complex and unbalanced [23], and no comprehensive studies of molecular changes in have been published. Reports typically explore the expression of one or two markers in a small series of tumors, and are insufficient to compare the different subgroups of this malignancy [3].

These neoplasms are highly malignant, multicentric and have a high recurrence rate [5]. Most ovarian angiosarcomas are diagnosed at an advance stage with poor survival, reaching 10 to 38% in 5 years [13, 15, 18, 22, 24]. The mean survival in an advanced-stage disease is around 6 to 10 months and no more than 30 months [10, 15, 18]. From cases reported, around 26 % had distant metastasis to the lungs and die from complications of hemorrhage [11, 12, 17, 24, 25] or had systemic symptoms [11]. Liver, heart, and splenic angiosarcomas have the worst survival rates [26].

Due to the poor prognosis and clinical outcome, an optimal therapy is still needed. Finding epithelioid components increase the risk of local recurrence. Tumors with >5 cm have higher risk of metastasis [9]. Good screening tools are still not available. Ca-125 is not useful for screening, but can be a good parameter of response and predictor of recurrence on treated patients. A Ca-125 cut-off value of <75 U/ml is associated with better survival rate [13, 22, 27].

Extensive surgical cytoreduction, platinum based chemotherapy, doxorubicin, ifosfamide, dacarbazine, vincristine, actinomycin [8, 28–31] have been used as treatment, some with modest results. Several tyrosine kinase receptors involved in angiogenesis, including VEGFR1, VEGFR2, tyrosine kinase with immunoglobulin-like and EGF-like domains (TIE1 and TIE2), are highly expressed in angiosarcoma. Treatment with tyrosine kinase inhibitors such as Bevacizumab, Sorafenib, Pazopanib, and Imatinib [8, 25, 31] alone or in combination with chemotherapy, may be beneficial and are currently being investigated. These biologic agents might have an important role in the near future [8]. Unfortunately, to date there is no standardized effective treatment, being anthracycline-base scheme with ifosfamide the first choice for many, in combination with debulking surgery [2, 10, 17–19, 30, 33]. Myelotoxicity is the main dose-limiting factor with this therapy [19, 24]. Many prefer the use of more than a single therapeutic agent since it has shown a better response rate but this have not improved overall survival [2, 8, 10].

By the time of this report, the patient is on her first cycle chemotherapy and presenting with recurrent ascites.

## Conclusion

In summary, angiosarcomas are very uncommon malignant tumors with a particular clinical presentation and histologic appearance and difficult to diagnose. They should be included in the differential diagnosis of any poorly differentiated neoplasm with epithelioid and/or spindle cell components. Screening tools and novel treatment modalities are in development, aiming to reduce mortality and improve the poor prognosis of this neoplasm.

## References


1. Mankin H, Hornicek F (2005) Diagnosis, classification, and management of soft tissue sarcomas. Cancer Control 12(1):5–21
2. Park M, Ravi V, Araujo D (2010) Inhibiting the VEGF-VEGFR pathway in angiosarcoma, epithelioid hemangioendothelioma, and hemangiopericytoma/solitary fibrous tumor. Curr Opin Oncol 22 (4):351–5
3. Young R, Brown N, Reed M et al (2010) Angiosarcoma. Lancet Oncol 11:983–91
4. Hart J, Mandavilli S (2011) Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis. Arch Pathol Lab Med 135(2):268–72
5. Cambruzzi E, Pegas KL, Milani DM, Cruz RP, Guerra EH, Ferrari MB (2010) Angiosarcoma arising in an ovarian fibroma: a case report. Pathol Res Int 842592
6. Bradford L, Swartz K, Rose S (2010) Primary angiosarcoma of the ovary complicated by hemoperitoneum: a case report and review of the literature. Arch Gynecol Obstet 281:145–150
7. Bösmüller H, Gruber C, Haitchi-Petnehazy S, Dietmar Wagner D, Webersinke G, Hauptmann S (2011) Primary angiosarcoma of the ovary with prominent fibrosis of the ovarian stroma. Case report of an 81-year old patient. Diagn Pathol 6:65–71
8. Ali J, Ko H, Owen D et al (2006) Epithelioid angiosarcoma of the small bowel. Gastrointest Endosc 64(6):1018–21
9. Fayette J, Martin E, Piperno-Neumann S et al (2007) Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann Oncol 18:2030–2036
10. Aragon L, Terreros D, Ho H et al (2011) Angiosarcoma of the ovary arising in a mucinous cystadenoma. J Clin Ultrasound 39:351–355
11. Davidson B, Abeler VM (2005) Primary ovarian angiosarcoma presenting as malignant cells in ascites: case report and review of the literature. Diagn Cytopathol 32(5):307–9
12. Jhaa S, Chan K, Poole C et al (2005) Pregnancy following recurrent angiosarcoma of the ovary- A case report and review of literature. Gynecol Oncol 97:935–937
13. Platt JS, Rogers SJ, Flynn EA (1999) Primary angiosarcoma of the ovary: a case report and review of the literature. Gynecol Oncol 73:443–446
14. Ariyoshi K, Kawauchi S, Kaku T et al (2000) Prognostic factors in ovarian carcinosarcoma: a clinicopathological and immunohistochemical analysis of 23 Cases. Histopathology 37:427–436

15. Treuner J, Koscielniak E, et al (2003) Cooperative Weichteilsarkom Study CWS-2002p, Der Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH); Fassung
16. Contreras A, Malpica A, et al (2009) Angiosarcoma arising in mature cystic teratoma of the ovary: a case report and review of the literature. International Journal of Gynecological Pathology 28(5)
17. Cunningham M, Brooks J, Noumoff J (1994) Treatment of primary ovarian angiosarcoma with ifosfamide and doxorubicin. Gynecol Oncol 53(2):265–8
18. Lahat G, Dhuka A, Hallev Hi et al (2010) Angiosarcoma: clinical and molecular insights. Ann Surg 251:1098–1106
19. Furihata M, Takeuchi T, Iwata J et al (1998) Primary ovarian angiosarcoma: a case report and literature review. Pathol Int 48:967–973
20. Nara M, Sasaki T, Shimura S et al (1996) Diffuse alveolar hemorrhage caused by lung metastasis of ovarian angiosarcoma. Intern Med 35 (8):653–6
21. Virtanen A, Pukkala E, Auvinen A (2007) Angiosarcoma after radiotherapy: a cohort study of 332 163 Finnish cancer patients. Br J Cancer 97:115–117
22. Iljazović E, Tomić S, Mustedanagić-Mujanović J et al (2011) Angiosarcoma of the ovary in an 11 year old girl: case report and review of the literature. Bosn J Basic Med Sci 11(2):132–136
23. Penel N, Marréaud S, Robin YM et al (2011) Angiosarcoma: state of the art and perspectives. Crit Rev Oncol Hematol 80(2):257–63
24. Bösmüller et al (2011) Primary angiosarcoma of the ovary with prominent fibrosis of the ovarian stroma. Case report of an 81-year old patient. Diagnostic Pathology 6:65
25. Sood A, Sorosky J, Gelder M et al (1998) Primary ovarian sarcoma: analysis of prognostic variables and the role of surgical cytoreduction. Cancer 82(9):1731–7
26. Yi D, Keng S, Jing-he L et al (2011) Primary sarcoma of the ovary: clinicopathological characteristics, prognostic factors and evaluation of therapy. Chin Med J 124(9):1316–1321
27. Potter ME, Moradi M, Alexander CW et al (1989) Value of serum 125Ca levels: does the result preclude second look? Gynecolog Oncology 33:201–3
28. Cherie D, Quesenberrya C, Chen A (2005) Primary angiosarcoma of the ovary: a case report of stage I disease. Gynecol Oncol 99:218–221
29. Nielsen GP, Young RH, Prat J et al (1997) Primary angiosarcoma of the ovary: a report of seven cases and review of the literature. Int J Gynecol Pathol 16(4):378–82
30. Bradford L, Swartz K, Rose S (2010) Primary angiosarcoma of the ovary complicated by hemoperitoneum: a case report and review of the literature. Arch Gynecol Obstet 281:145–150
31. Serrano C, García A, Brana I et al (2010) Angiosarcoma of the ovary: is it always a lethal disease? J Clin Oncol 28(33):e675–e677
32. Cambruzzi E, Pegas KL, Milani DM et al (2010) Angiosarcoma arising in an ovarian fibroma: a case report. Pathol Res Int 2010:842592
33. Kiesel H, Muller AM, Schmitt-Graeff A et al (2009) Dramatic and durable efficacy of imatinib in an advanced angiosarcoma without detectable KIT and PDGFRA mutations. Cancer Biol Ther 8:319–321