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Case Report

Fatal hemorrhage from rupture of metastatic tumors rapidly developed after optimal primary surgery for ovarian angiosarcoma arising from a mature cystic teratoma

U Chul Ju[1], **Woo Dae Kang**[1], **Seok Mo Kim**[1]

[1]*Department of Obstetrics and Gynecology, Chonnam National University Medical School, Gwangju, Republic of Korea*

Summary

Background: Primary ovarian angiosarcoma arising from a mature cystic teratoma is a very rare tumor, known to be very aggressive and respond poorly to chemotherapy. However, little information exists regarding the treatment of this disease. *Case:* Here, we report the first case of a teenage girl diagnosed with primary ovarian angiosarcoma arising from a mature cystic teratoma. The patient received no adjuvant treatment after primary surgery. Despite stage I disease, the patient presented with metastatic tumors within two months postoperatively. She died of a fatal hemorrhage presumed to occur in metastatic tumors after receiving delayed chemotherapy. *Conclusion:* Because primary ovarian angiosarcoma arising from a mature cystic teratoma can be found in young women, early diagnosis and proper treatment are essential. The tumors grow rapidly and are fragile enough to rupture, so it is reasonable to prescribe early adjuvant treatments after optimal debulking surgery before progression or recurrence. Treatment of the recurrent or metastatic tumors should be performed with caution because complications, such as severe bleeding, may arise from the hemorrhagic tumors.

Key words: Primary ovarian angiosarcoma; Mature cystic teratoma; Young woman; Hemorrhage.

Introduction

Mature cystic teratoma of the ovary is the most common germ cell tumor, accounting for approximately 27% of the ovarian tumors, and is most commonly found in teenage women [1]. Their components derive from the ectoderm, endoderm, and mesoderm that undergo malignant transformations in 0.2 – 2% of the cases [1]. The most common histologic type of malignant transformation is squamous carcinoma, whereas adenocarcinoma, basal cell carcinoma, melanoma, thyroid carcinoma, sarcoma, and angiosarcoma are rare [2].

Primary ovarian angiosarcoma is very rare, with only 29 cases reported in the English literature [3]. As mentioned previously, some primary ovarian angiosarcomas arise from mature cystic teratomas. Primary ovarian angiosarcoma arising from a mature cystic teratoma is often a unilateral tumor 2 – 29 cm in diameter and represents a fragile hemorrhagic tumor [1, 2]. Ruptured, progressive, or metastatic tumors may result in uncontrollable bleeding [4].

Here, we report the first case of a teenage girl who was diagnosed with primary ovarian angiosarcoma arising from a mature cystic teratoma after surgery, which resulted in the patient's death due to hypovolemic shock secondary to sudden fatal hemorrhage from the rupture of metastatic tumors.

Case report

An 18-year-old woman (G0P0) was admitted to our department (Chonnam National University Hospital) in November 2017, presenting with a week-long history of abdominal pain. Seven years earlier (in 2010), she underwent a bilateral ovarian cystectomy for mature cystic teratomas. Abdominal masses were palpated under the umbilicus level. Transabdominal ultrasonography showed two cystic tumors of 15 cm and 7 cm. Her vital signs were stable. Laboratory findings revealed mild anemia (hemoglobin, 9.7 g/dL) and mild leukocytosis (11,200/uL). Cancer antigen (CA) 125 and CA 19-9 tumor markers were elevated at 394.9 units/mL (normal range, 0 – 35) and 348.0 units/mL (normal range, 0 – 37), respectively. Human epididymis protein 4 (HE4) and the risk of ovarian malignancy algorithm (ROMA) were within the normal ranges. Pelvic magnetic resonance imaging (MRI) showed two multiloculated cystic tumors of mixed composition, measuring 16 × 15 × 10 cm in the left ovary and 8 × 7 × 7 cm in the right ovary. The scan revealed a small amount of hemoperitoneum from a focal rupture of the left ovarian tumor. There was no lymphadenopathy or abnormal findings in other organs.

The laparotomy showed a focally ruptured, 15 cm left ovarian tumor with a necrotic surface and an 8 cm right ovarian tumor with a smooth wall with 100 ml of hematoma in the Douglas pouch (Figure 1). The other abdominal organs had normal appearances and no enlarged lymph nodes were palpated. Analysis of the intraoperative frozen section of the left ovarian tumor revealed a mature cystic teratoma. These findings and the patient's young age indicated limited surgical procedures, including left salpingo-

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Table 1. — *Primary ovarian angiosarcomas arising from mature cystic teratomas in articles published in the English literature*

Articles	Age	Tumor size (cm)	FIGO stage	Additional pathology	Adjuvant therapy	OS (months)
Nielsen et al. [5] (2 cases)	20	6	III	n/a	n/a	15
	32	13	III	-	n/a	30
Devouassoux-Shisheboran et al. [6]	40	n/a	IV	n/a	n/a	n/a
den Bakker et al. [7]	30	n/a	IIIC	Cutaneous type angiosarcoma	Bleomycin + etoposide + cisplatin	9
Contreras et al. [2]	32	n/a	n/a	-	Ifosfamide + doxorubicin	29
Takahashi et al. [8]	59	16 × 12 × 4.5	n/a	Clear cell carcinoma	Paclitaxel	n/a
Albertin et al. [9]	64	19.8 × 17.8 × 14	IIIC	-	Paclitaxel	1.5
Kudela et al. [1]	44	8 and 6	IV	-	None	2
The current case	18	16 × 15 × 10	IC	-	None	2.5

FIGO, the International Federation of Gynecology and Obstetrics; OS, overall survival

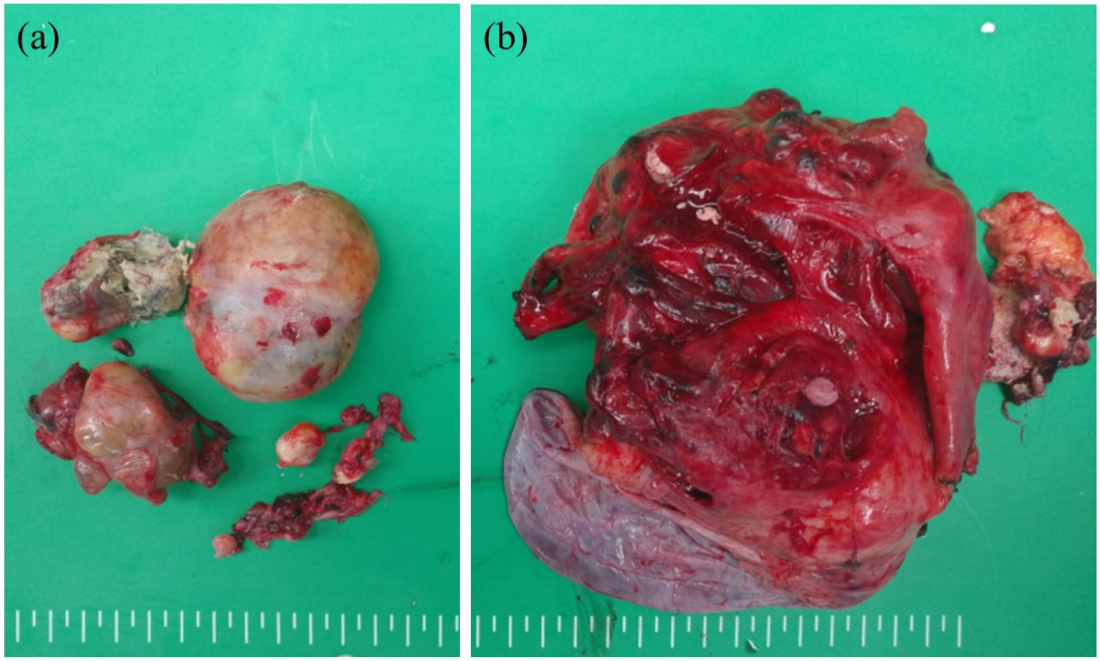

Figure 1. — Right ovarian tumors after ovarian cystectomy. (a) and left ovarian tumor after salpingo-oophorectomy (b). The right ovarian tumors appeared pinkish-red with a smooth surface, containing sebum, hair, fat, and cartilage. The left ovarian tumor was entirely replaced by a dark, necrotic tumor with a ragged surface, measuring 15 × 12 × 9 cm and weighing 621 g. The tumor contained sebum, hair, yellowish-white gelatin, cartilage, and necrotic and hemorrhagic foci on the cut section.

oophorectomy, right ovarian cystectomy, infracolic omentectomy, and cytology. The patient recovered well and was discharged to home on the fifth postoperative day. However, the final pathology report confirmed primary ovarian angiosarcoma arising from a mature cystic teratoma of the left ovary, staged IC3 by the International Federation of Gynecology and Obstetrics (FIGO) system, and mature cystic teratoma of the right ovary. We recommended adjuvant chemotherapy to the patient and her parents, who choose to go to another hospital to continue treatment. The patient received oriental medical treatment without adjuvant chemotherapy after discharge.

Two months later, the patient was admitted to the emergency room with complaints of dyspnea, vomiting, and abdominal pain. Contrast-enhanced computed tomography (CT) of the abdomen and chest showed a large volume of ascites and multiple metastatic lesions in the abdominal cavity and pleural effusion in both lungs (Figure 2). Discussion at our tumor board recommended chemotherapy consisting of 75 mg/m^2 doxorubicin plus 15 mg/kg olaratumab per day every three weeks. Two days after the initiation of chemotherapy, she presented with cold sweats, dizziness, worsening shortness of breath, and persistent abdominal pain. She was hypotensive and severely anemic with a hemoglobin of 5.1 g/dL. Despite transfusions of packed red blood cells, she was not hemodynamically stable and

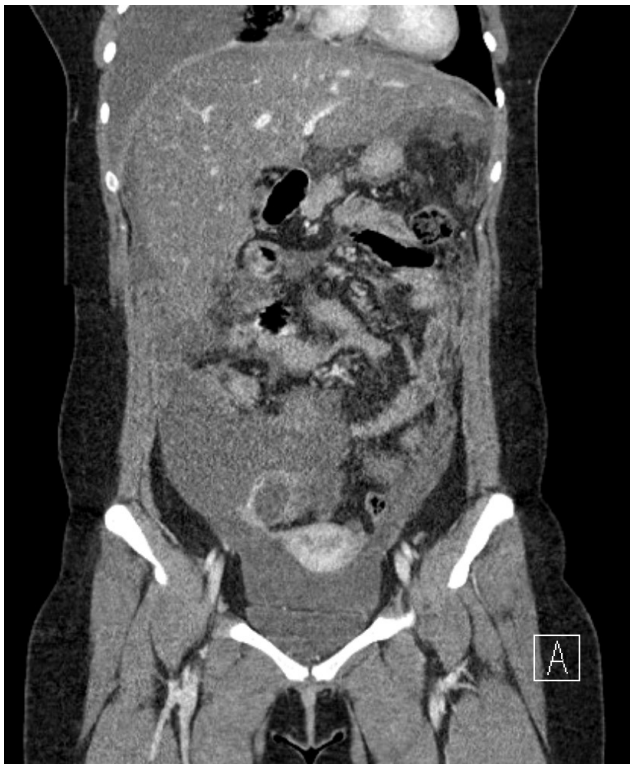

Figure 2. — Contrast-enhanced computed tomography image showing multiple metastatic lesions in the abdominal cavity with malignant ascites and pleural effusion.

died of cardiac arrest within four hours. Her parents decided not to proceed with a post-mortem examination. The cause of her death was presumed to be hypovolemic shock secondary to sudden fatal hemorrhage from the rupture of metastatic tumors.

Discussion

Only eight cases of primary ovarian angiosarcoma arising from mature cystic teratoma have been reported in the English literature (Table) [1, 2, 5-9]. The age at diagnosis in the reports ranged from 20 to 64 years. Even with surgery and adjuvant treatment, the average overall survival for this cancer is only 11.4 months and ranges from 1.5 to 29 months. The tumors are commonly detected in advanced stages of the disease and this late diagnosis leads to poor prognosis. In the current report, the disease was diagnosed as early-stage (FIGO stage IC3) in a teenage woman. Nevertheless, the disease showed a very rapid recurrence and progression within two months postoperatively.

Angiosarcomas are composed of vasoform and solid histologic patterns. The histologic features of primary ovarian angiosarcoma have been described by the presence of interlacing vascular spaces with endothelial cells demonstrating nuclear pleomorphism and mitotic activity. Immunohistochemical staining, especially for the vascular markers CD34 and CD31, assists in the diagnosis [7]. Endothelial cell markers, including Factor VIII-related antigen and vimentin, also help to support a diagnosis [10].

The proper management of primary ovarian angiosarcomas has not yet been established due to the rarity of the disease. Nevertheless, adjuvant chemotherapy after optimal debulking surgery is commonly used for the treatment of primary ovarian angiosarcomas [1]. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN guidelines®) lists paclitaxel, docetaxel, vinorelbine, sorafenib, sunitinib, and bevacizumab with activity against angiosarcomas [11]. A previous meta-analysis reported that adjuvant chemotherapy improved local control and disease-free survival but provided no survival advantage for patients with ovarian angiosarcomas [12]. Although radiotherapy can achieve 80% local control in the early stages, radiotherapy does not improve survival because ovarian angiosarcomas are frequently detected in the late stages [13]. Ravi et al. reported a good response to pazopanib in a patient with angiosarcoma with an increase in vascular endothelial growth factor receptor (VEGFR) [14]. Further research on appropriate chemotherapy and targeted therapies is needed for the management of primary ovarian angiosarcoma.

Primary ovarian angiosarcomas are very aggressive and the metastatic tumors are very rapidly growing tumors. Angiosarcomas are also very fragile tumors with highly developed vascular structures. Because of these features, angiosarcomas, especially recurrent or metastatic tumors, are easily ruptured. Bradford at al. reported fatal hemorrhage complications from progressive and metastatic angiosarcoma sites [4]. The present report also showed rapid, progressive metastatic lesions after primary surgery. In addition, this report related a patient's death due to sudden fatal hemorrhage presumed to have occurred in metastatic tumors after receiving delayed chemotherapy. In contrast, a previous study reported a good prognosis for patients without remnant or recurrent tumors after optimal debulking surgery who received early adjuvant chemotherapy [2]. These results suggest that patients who undergo surgical treatments for primary ovarian angiosarcoma should receive early adjuvant chemotherapy before the disease progresses or recurs. This attempt might slow disease recurrence or progression and also reduce complications, such as hemorrhage in rapidly growing metastatic tumors.

In conclusion, primary ovarian angiosarcoma arising from a mature cystic teratoma is extremely rare. The tumor can be found in young women, so early and accurate diagnosis is critical. Optimal debulking surgery is important in the initial treatment of primary ovarian angiosarcoma. Although the role of adjuvant chemotherapy in a patient's survival is still uncertain, it is reasonable to prescribe early adjuvant chemotherapy in an attempt to reduce the risk of complications from progression or recurrence. Treatments to prevent recurrence or metastasis should be performed with caution because of the complications, such as severe bleeding, that may occur from fragile hemorrhagic tumors.

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Conflict of interest

The authors declare no conflicts of interest.

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References

[1] Kudela E., Nachajova M., Biringer K., Slavik P., Plank L., Danko J.: "Bilateral ovarian angiosarcoma arising from the mature – A case re-port and review of the literature". *Int. J. Surg. Case, Rep*., 2018, 42, 90.

[2] Contreras A.L., Malpica A.: "Angiosarcoma arising in mature cystic teratoma of the ovary: a case report and review of the literature". *Int. J. Gynecol. Pathol*., 2009, 28, 453.

[3] Kruse A.J., Sep S., Slangen B.F., Vandevijver N.M., Van Gorp T., Kruitwagen R.F., Van de Vijver K.K.: "Angiosarcomas of primary gynecologic origin: a clinicopathologic review and quantitative analysis of survival". *Int. J. Gynecol. Cancer*, 2014, 24, 4.

[4] Bradford L., Swartz K., Rose S.: "Primary angiosarcoma of the ovary complicated by hemoperitoneum: a case report and review of the literature". *Arch. Gynecol. Obstet.*, 2010, 281, 145.

[5] Nielsen G.P., Young R.H., Prat J., Scully R.E.: "Primary angiosarcoma of the ovary: a report of seven cases and review of the literature". *Int. J. Gynecol. Pathol*., 1997, 16, 378.

[6] Devouassoux-Shisheboran M., Vortmeyer A.O., Silver S.A., Zhuang Z., Tavassoli F.A.: "Teratomous genotype detected in malignancies of a non-germ cell phenotype". *Lab. Invest*., 2000, 80, 81.

[7] den Bakker M.A., Ansink A.C., Ewing-Graham P.C.: "Cutaneous-type" angiosarcoma arising in a mature cystic teratoma of the ovary". *J. Clin. Pathol*., 2006, 59, 658.

[8] Takahashi H., Chaopotong P., Kajita S., Hashimura M., Yamazaki H., Saegusa M.: "Mixed angiosarcoma, clear cell adenocarcinoma and mature teratoma elements in an ovarian tumor: a case report and lit-erature review". *Pathol. Int*., 2012, 62, 538.

[9] Albertin C., Johnson K.A., Connor J.P., Al-Niaimi A.N.: "Angiosarcoma originating from an ovarian mature teratoma, a rare disease with complex treatment modalities". *Gynecol. Oncol. Case Rep*., 2013, 5, 31.

[10] Quesenberry C.D., Li C., Chen A.H., Zweizig S.L., Ball H.G. 3rd: "Primary angiosarcoma of the ovary: a case report of stage I disease". *Gynecol. Oncol*., 2005, 99, 218.

[11] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guideline®) Soft Tissue Sarcoma. Available at: https://www.nccn.org/professionals/physiciangls/pdf/sarcoma.pdf. Version 1. 2018.

[12] Budd G.T.: "Management of angiosarcoma". *Curr. Oncol. Rep.*, 2002, 4, 515.

[13] Mark R.J., Poen J.C., Tran L.M., Fu Y.S., Juillard G.F.: "Angiosarcoma. A report of 67 patients and a review of the literature". *Cancer*, 1996, 77, 2400.

[14] Ravi V., Sanford E.M., Wang W.L., Ross J.S., Ramesh N., Futreal A., et al.: "Antitumor response of VEGFR2- and VEGFR3-Amplified angiosarcoma to pazopanib". *J. Natl. Compr. Canc. Netw*., 2016, 14, 499.

Corresponding Author:
SEOK MO KIM, M.D., Ph.D.
Department of Obstetrics and Gynecology, Chonnam National University Medical School, 8 Hakdong, Dong-gu, Gwangju (Republic of Korea)
e-mail: seokmo2001@hanmail.net