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CASE REPORT

Gemcitabine-based regimen for primary ovarian angiosarcoma with *MYC* amplification

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ABSTRACT

Angiosarcoma is a rare and aggressive type of sarcoma, and primary angiosarcoma of the ovary is extremely rare. We report the case of a 29-year-old woman who was diagnosed with ovarian angiosarcoma and possible bone metastases. We treated this patient with a gemcitabine-based regimen as postoperative adjuvant chemotherapy, after which she achieved at least 7 years of progression-free survival, an extremely long duration given the aggressive features of this tumour. We retrospectively performed immunohistochemical analyses and fluorescence *in situ* hybridization to make a pathology diagnosis and to investigate the tumour features. *MYC* amplification and c-Myc protein overexpression were positively detected. It might be possible to correlate the effectiveness of the gemcitabine-based chemotherapeutic regimen with *MYC* gene amplification and c-Myc protein overexpression.

KEY WORDS

Angiosarcoma, mucinous cystadenoma, surgical resection, chemotherapy, gemcitabine, *MYC*

1. INTRODUCTION

Angiosarcoma, an aggressive soft-tissue neoplastic disease, is rare, having an annual incidence of less than 1 per million population[1]. Angiosarcomas arise at various sites; in elderly people, these tumours commonly arise in the scalp and face[2]. Primary angiosarcoma of the ovary is extremely rare[3], with only 35 cases being reported to date (Table I). The median overall survival of patients with metastatic angiosarcoma is generally less than 11 months[30], and the median overall survival of patients with angiosarcoma of the ovary is 6–7 months[17]. Systemic chemotherapy for patients presenting with unresectable disease is therefore generally considered palliative.

Our patient presented with advanced ovarian angiosarcoma and bone metastases and still achieved 7 years of progression-free survival after treatment with a gemcitabine-based regimen. Recently, *MYC* amplification was proposed to occur in a proportion of primary[31] and radiation-induced angiosarcomas[32]. Enhanced expression of c-Myc is an important mediator leading to disease development[33]. We therefore report our case and the results of retrospective *MYC* gene amplification and c-Myc protein expression analyses, discuss the relevance of those factors in terms of therapy and prognosis, and review the related literature.

2. CASE DESCRIPTION

A 29-year-old woman was admitted to the emergency room with abdominal pain and fever. Abdominal palpation revealed rebound tenderness. Transvaginal ultrasonography revealed a cystic mass of approximately 9 cm in the right pelvis, within which several solid masses existed. The masses were recognized as blood clots or other artefacts unrelated to the tumour component. A small amount of ascites in the Douglas pouch was also observed.

Laboratory data revealed a white blood cell count of $9320\times10^3/\mu L$, with 85.6% neutrophils, and 2.30 mg/dL serum C-reactive protein. On the following day, serum C-reactive protein increased to 11.22 mg/dL, indicating a level of inflammation.

Clinically, a rupture or torsion of the right ovarian tumour with acute peritonitis was suspected. Intravenous administration of ceftriaxone sodium hydrate 2 g daily was initiated and continued for 3 days.

Magnetic resonance imaging revealed a cystic right ovarian tumour whose cystic portion contained a fluid or blood component [Figure 1(A,B)]. Computed tomography revealed low-density areas in several bones, suggestive of osteolytic bone metastases [Figure 2(A)]. We also examined the tumour markers cancer antigen 125, carbohydrate antigen 19-9, and carcinoembryonic antigen, whose

TABLE I Primary angiosarcoma of the ovary reported in the literature

Reference	*Case ID*	*Age (years)*	*Clinical manifestations*	*Stage*	*Histology*	*Treatment*		*Follow-up*
						Primary	*Adjuvant*	
Ongkasuwan *et al.,* 1982[4]	1	77	Abdominal distention	III	Mucinous cyst adenoma and angiosarcoma	Right salpingo-oophorectomy	None	Died of disease (2 months)
Patel *et al.,* 1991[5]	2	42	Abdominal pain	IV	Angiosarcoma	Right salpingo-oophorectomy	None	Died of disease (18 days)
Cunningham *et al.,* 1994[6]	3	19	Abdominal discomfort	IV	Angiosarcoma	Left salpingo-oophorectomy, omentectomy, and para-aortic lymph node biopsy	Ifosfamide, doxorubicin	Died of disease (7 months)
Nara *et al.,* 1996[7]	4	33	Hemoptysis	IV	Angiosarcoma	Lung biopsy	None	Died of disease (2 months)
Nielsen *et al.,* 1997[8]	5	20–32	Abdominal pain	I	Angiosarcoma	Not available	Not available	No evidence of disease (5.5 years)
	6		Abdominal pain	I	Angiosarcoma	Not available	Not available	No evidence of disease (9 years)
	7		Abdominal pain	I	Angiosarcoma	Not available	Not available	Not available
	8		Abdominal pain	I	Angiosarcoma	Not available	Not available	Not available
	9		Abdominal pain	III	Angiosarcoma	Not available	Not available	Died of disease (2 months)
	10		Abdominal pain	III	Dermoid cyst and angiosarcoma	Not available	Not available	Died of disease (15 months)
	11		Abdominal pain	III	Dermoid cyst and angiosarcoma	Not available	Not available	Died of disease (30 months)
Furihata *et al.,* 1998[9]	12	46	Abdominal mass and discomfort	I	Angiosarcoma	Total abdominal hysterectomy bilateral salpingo-oophorectomy, and pelvic lymphadenectomy	Cisplatin, para-aortic radiation therapy	Died of disease (9 months)
Lifschnitz–Mercer *et al.,* 1998[10]	13	25	Abdominal pain	III	Angiosarcoma	Left salpingo-oophorectomy,	Ifosfamide, doxorubicin	Recurrent disease (18 months)
Nucci *et al.* 1998[11]	14	35	Palpable ovarian mass	IV	Angiosarcoma	Salpingo-oophorectomy	None	Died of disease ("quickly")
	15	25	Abdominal pain	III	Angiosarcoma	Left salpingo-oophorectomy,	Chemotherapy	No evidence of disease (3 months)
	16	42	Hemoperitoneum	I	Angiosarcoma	Salpingo-oophorectomy	None	Died of disease (2 years)
	17	27	Abdominal pain	I	Angiosarcoma	Right salpingo-oophorectomy,	None	No evidence of disease (14 months)

TABLE I Continued

Reference	*Case ID*	*Age (years)*	*Clinical manifestations*	*Stage*	*Histology*	*Treatment*		*Follow-up*
						Primary	*Adjuvant*	
Jylling *et al.,* 1999[12]	18	37	Cyst	I	Mucinous cystadenocarcinoma and angiosarcoma	Right oophorectomy	Not available	Not available
Platt *et al.,* 1999[13]	19	40	Abdominal pain	IV	Angiosarcoma	Optimal debulking	Mesna, doxorubicin, ifosfamide, dacarbazine	No evidence of disease (2 months)
Twu *et al.,* 1999[14]	20	38	Hemoptysis	IV	Angiosarcoma	Full staging, debulking	Ifosfamide, doxorubicin	Died of disease (7 months)
Pillay *et al.,* 2001[15]	21	45	Abdominal distention	IV	Borderline serous cystadenocarcinoma and angiosarcoma	Suboptimal debulking	None	Died of disease (3 months)
Davidson and Abeler, 2005[16]	22	19	Abdominal pain	III	Angiosarcoma	Left ovariectomy	Doxorubicin, ifosfamide, explorative laparotomy, radiation therapy	Died of disease (1 year)
Quesenberry *et al.,* 2005[17]	23	31	Abdominal distention	IC	Angiosarcoma	Full staging	Mesna, doxorubicin, ifosfamide, dacarbazine	No evidence of disease (10 months)
Jha *et al.,* 2005[18]	24	28	Abdominal pain	I	Angiosarcoma	Right salpingo-oophorectomy,	Complete re-debulking, ifosfamide, doxorubicin	No evidence of disease (6 years)
den Bakker *et al.,* 2006[19]	25	30	Abdominal pain	III	Dermoid cyst and angiosarcoma	Left salpingo-oophorectomy, staging, and subtotal omentectomy	Chemotherapy, debulking	Died of disease (9 months)
Contreras and Malpica, 2009[20]	26	32	Bloating, abdominal pain	IV	Dermoid cyst and angiosarcoma	Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and appendectomy	Ifosfamide, doxorubicin	Died of disease (29 months)
Bradford *et al.,* 2010[21]	27	67	Bloating, fatigue, abdominal pain	IIIC	Angiosarcoma	Full staging, debulking	None	Died of disease (1 month)
Cambruzzi *et al.,* 2010[22]	28	65	Sensation of heaviness in the hypogastrium	I	Ovarian fibroma and angiosarcoma	Exploratory laparotomy	Chemotherapy	No evidence of disease (2 months)
Serrano *et al.,* 2010[23]	29	23	Abdominal pain	IIIC	Angiosarcoma	Optimal debulking	Epirubicin, ifosfamide	No evidence of disease (12 months)
Iljazovic *et al.,* 2011[24]	30	11	Left hip pain	IIA	Angiosarcoma	Tumourectomy, bilateral salpingo-oophorectomy, and partial omentectomy	Ifosfamide, actinomycin, vincristine, omentectomy, and lymphadenectomy	No evidence of disease (10 months)
Aragon *et al.,* 2011[25]	31	39	Abdominal girth	IV	Mucinous cyst adenoma and angiosarcoma	Total abdominal hysterectomy, bilateral salpingo-oophorectomy,	None	Died of disease (3 months)
Bosmuller *et al.,* 2011[26]	32	81	Abdominal pain and distention	I	Angiosarcoma	Total abdominal hysterectomy, right salpingo-oophorectomy,	Doxorubicin	No evidence of disease (5 months)

TABLE I Continued

Reference	Case ID	Age (years)	Clinical manifestations	Stage	Histology	Treatment		Follow-up
						Primary	Adjuvant	
Takahashi *et al.*, 2012[27]	33	59	Acute abdominopelvic pain	Not available	Clear cell carcinoma, dermoid cyst, and angiosarcoma	Total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy	Paclitaxel, platinum	Not available
Guseh *et al.*, 2013[28]	34	40	Fatigue and nausea	IIIC	Angiosarcoma	Total abdominal hysterectomy, bilateral salpingo-oophorectomy,	Ifosfamide, doxorubicin	Recurrent disease
Yaqoob *et al.*, 2014[29]	35	41	Abdominal pain and vaginal bleeding	IA	Angiosarcoma	Left salpingo-oophorectomy, incisional biopsy of right ovary	None	Not available

FIGURE 1 *Magnetic resonance image of patient's pelvis at admission. A right adnexal cystic mass, 9.8×9.1×6.0 cm, containing fluid or bloody components (arrow) and a solid tumour (arrow head), 4.5×3.5×3 cm, in the cyst is suggestive of malignancy (A) T1-weighted image. (B) T2-weighted image.*

values were 40.3 IU/mL (reference range: 0–35 IU/mL), 1349.0 IU/mL (reference range: 0–37 IU/mL), and 48.6 ng/mL (reference range: 0–5 ng/mL) respectively. In other words, all values exceeded their reference range. We considered that the right ovarian tumour was malignant in nature.

Given the patient's wish to preserve fertility, a right salpingo-oophorectomy was performed. Bloody ascites was observed, and the right ovarian tumour was found to ooze from a minute surface rupture. We re-examined the tumour markers at 13 days post-surgery and found normalized levels (cancer antigen 125, 26.5 IU/mL; carbohydrate antigen 19–9, 14.0 IU/mL; carcinoembryonic antigen, 1.2 ng/mL). We continued to evaluate those markers for 7 years post-surgery, and the values never rose above their reference range.

The resected specimen revealed a cystic tumour with a maximum diameter of approximately 9 cm and

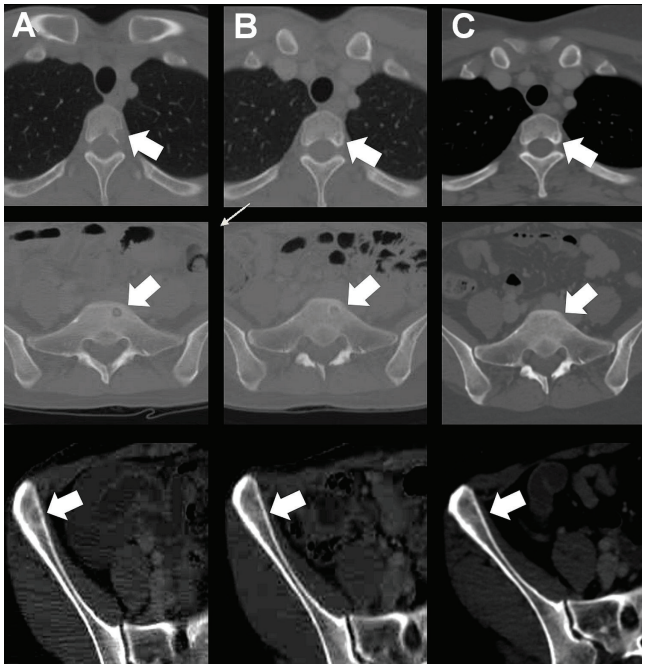

FIGURE 2 *Systemic computed tomography showing the long-term response of bone metastases in T3, sacral bone, and right ilium. (A) Initial admission (baseline). (B) Immediately after 6 courses of chemotherapy. (C) After 7 years of chemotherapy. Low-density areas were ossified from peripheral areas at time B and remained ossified at time C, suggesting that the regimen was effective in treating the metastatic angiosarcoma; the patient experienced 7 years of progression-free survival.*

a solid portion measuring 4.5×3.5×3 cm. The cystic portion contained mucinous material and large blood clots [Figure 3(A)]. Histologic examination of the tumour revealed that the solid portion had originated from the cyst wall [Figure 3(B)]. The cystic portion consisted of a mucinous epithelium overlying a cyst wall that was almost flat and showed no nuclear pseudostratification, weak nuclear irregularity, and non-prominent nucleoli. Those findings were consistent with mucinous cystadenoma [Figure 3(C)]. However, the solid portion exhibited an anastomosing vascular structure with atypical endothelial cells consistent with angiosarcoma [Figure 3(D)]. By immunohistochemistry, the atypical endothelial cells were found to be positive for CD31 [Figure 3(D), inset], CD34, and factor VIII–related antigen. A diagnosis of ovarian angiosarcoma arising from a mucinous cystadenoma was made.

Retrospective immunohistochemistry and fluorescence *in situ* hybridization performed 7 years after the initial diagnosis revealed diffuse c-Myc–positive angiosarcoma cells [Figure 3(E)] and nuclear *MYC* (8q24) amplification [Figure 3(F)] respectively. Using fluorescence *in situ* hybridization, red (*MYC* probe) and green signals (chromosome 8 centromere) were counted in 50 cells. Of those cells, 18 (36%) had copy numbers of 3 or 4, 31 (62%) had copy numbers of 5 or

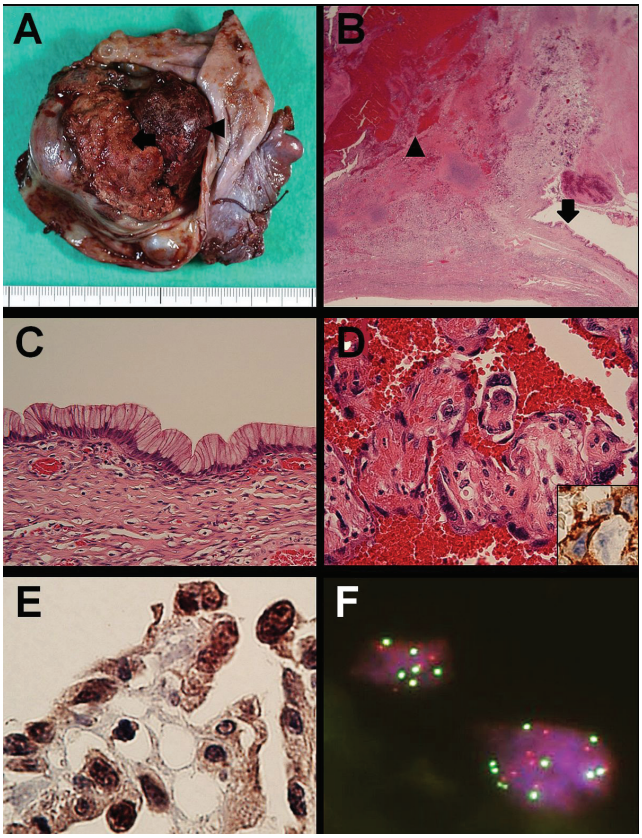

FIGURE 3 *Pathology observations. (A) The cystic tumour has a hemorrhagic mural nodule (arrow) containing mucinous material and a large blood clot (arrowhead). (B) A low-power view shows the cyst wall, comprising mucinous epithelium (arrow) and an abrupt transition to the hemorrhagic nodule (arrowhead). Hematoxylin and eosin (HE) stain; 12.5× original magnification. (C) In a high-power view of the mucinous epithelium, no significant atypia is seen. HE stain; 400× original magnification. (D) In a high-power view of the hemorrhagic nodule, vascular channels are seen to be covered with highly atypical endothelial cells. HE stain; 400× original magnification. Inset, shows atypical endothelial cells positive for CD31. Immunostain; 400× original magnification. (E) Highly atypical endothelial cells are strongly reactive for c-Myc. Immunostain; 400× original magnification. (F) Fluorescence* in situ *hybridization reveals* MYC *amplification, as indicated by red (*MYC *probe) and green (chromosome 8 centromere probe) signals, which were almost equal in number and often exceeded 5 in number. 1000× original magnification.*

more, and 1 (2%) had a copy number of more than 15 for both probes, thus confirming *MYC* amplification.

A diagnosis of primary angiosarcoma of the ovary with bone metastases (stage IV, T1cN0M1) was clinically appropriate. Although no evidence-based chemotherapeutic regimen was available at the time, gemcitabine-based chemotherapy had been reported to be efficacious in a few angiosarcoma cases[34,35]. We therefore administered gemcitabine-based therapy in combination with cisplatin, which is frequently used for ovarian cancers. The patient received intravenous

gemcitabine 1000 mg/m^2 on days 1 and 8 and intravenous cisplatin 70 mg/m^2 on day 1 every 28 days for 6 cycles. No significant adverse events were observed during chemotherapy; however, grade 1 neutropenia and grade 2 nausea were identified according to the *Common Terminology Criteria for Adverse Events* (version 3.0).

The patient's status was repeatedly monitored using tumour markers and computed tomography, without suggestion of tumour recurrence. Notably, immediately after the 6 chemotherapy courses, computed tomography revealed low-density areas of ossification in several bones [Figure 2(B)]. Those areas remained ossified for 7 years after chemotherapy initiation [Figure 2(C)], reflecting progression-free survival of at least 7 years' duration.

During the follow-up period, to the time of writing, the patient had not achieved pregnancy—not for organic reasons, but likely because of side effects from the chemotherapeutic agents.

3. DISCUSSION

Table I summarizes the 35 previously reported primary angiosarcomas. As mentioned earlier, few ovarian angiosarcomas have been treated with adjuvant chemotherapy, and the associated effects have been poorly characterized. However, several regimens have been reported to effectively treat angiosarcoma, regardless of origin. Combination therapy with anthracyclines and ifosfamide has been proved to be effective for the treatment of metastatic soft-tissue sarcoma, including angiosarcoma[23]. Doxorubicin-based and weekly paclitaxel regimens have demonstrated similar efficacy ranges for metastatic angiosarcomas[30]. However, we selected gemcitabine in the present case because several publications had reported its efficacy in angiosarcoma treatment[34,35]. After we initiated chemotherapy for our patient, gemcitabine monotherapy was reported to effectively treat advanced angiosarcoma[36]. Although the clinical diagnosis of bone metastases in our case was not definitive because no bone biopsy was conducted for histologic confirmation, the patient's clinical outcome is consistent with reports proposing that gemcitabine-based chemotherapy regimens could be considered effective for angiosarcomas, including advanced disease.

After surgery, serum levels of the tumour markers cancer antigen 125, carbohydrate antigen 19–9, and carcinoembryonic antigen promptly declined to within their reference ranges, even before chemotherapy for angiosarcoma control was introduced. Those levels remained normal for 7 years. Mucinous cystadenomas are known to elevate levels of those markers above their normal range[37,38]. Assuming that bone metastases were truly present, the initially elevated tumour marker levels might have been primarily a result of the mucinous cystadenoma component of the tumour rather than the angiosarcoma component.

To the best of our knowledge, this report is the fourth of an ovarian angiosarcoma arising from a mucinous cystadenoma[4,12,25] and the first to be treated with postoperative chemotherapy. In our retrospective analysis, the mural nodule of the mucinous cystadenoma was identified as angiosarcoma with *MYC* gene amplification and c-Myc protein overexpression. This case is therefore also extremely rare pathologically, because ovarian mucinous tumours are rarely associated with mural nodules reflecting any type of sarcoma-like (benign) disease, sarcoma, or carcinoma[39,40]. The features as described suggest that the primary ovarian angiosarcoma in this case developed sequentially as a mural nodule from the mucinous cystadenoma. During angiosarcoma formation, which appears to have been prompted by a mucinous cystadenoma, alterations in the molecular signatures similar to those observed in secondary angiosarcomas might have occurred. One such similarity might have been the observed *MYC* amplification in the present case[32].

The c-Myc protein regulates numerous processes, including cell cycle progression, epithelial–mesenchymal transition, stem-cell progression, and angiogenesis, thereby facilitating tumour initiation and progression. Gong *et al.* showed that gemcitabine downregulates *MYC* gene expression and induces apoptosis in HL-60 cells[37], a finding that might partly explain that agent's therapeutic efficacy in this case. Also, reduced *MYC* expression in tumour cells was recently proposed to induce sensitivity to DNA-damaging reagents such as cisplatin by stimulating *BIN1* transcription and disrupting PARP1 activity[41]. Therefore, gemcitabine administration might also have facilitated the antitumour efficacy of cisplatin.

In the present case, a gemcitabine based-regimen treated a primary ovarian angiosarcoma with *MYC* gene amplification and c-Myc protein overexpression extremely effectively. Although further studies with more enrolled cases are needed to statistically prove the effectiveness of this gemcitabine-based regimen and the correlation between *MYC* status and clinical outcomes, this remarkable case suggests that gemcitabine-based regimens could be a therapeutic option and even a first-line chemotherapy for the treatment of angiosarcomas.

4. SUMMARY

The patient reported here experienced 7 years of progression-free survival after treatment with a gemcitabine-based regimen for a primary ovarian angiosarcoma with *MYC* gene amplification. *MYC* amplification and the effectiveness of gemcitabine-based regimens in primary angiosarcomas should be addressed in future analyses and studies.

5. CONFLICT OF INTEREST DISCLOSURES

The authors declare that they have no financial conflicts of interest.

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