

Case Report

Uterine Angiosarcoma: A Case Report and Literature Review

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Summary: Uterine angiosarcoma is a rare, extremely malignant vascular tumor. Here, we report a case of giant uterine angiosarcoma in a 56-yr-old woman. The tumor was diagnosed as an epithelioid uterine angiosarcoma based on histopathologic findings. The tumor cells showed vascular differentiation; they were positive for the vascular endothelial markers CD31, CD34, and was negative for lymphatic endothelial marker D2-40. In addition, the tumor cells showed overexpression of cell-cycle regulatory protein cyclin D1 and were positive for epithelial-mesenchymal transition marker vimentin. Although it was reported previously that there was breakage in *YWHAE*, *NUTM2A* (*FAM22A*), and *NUTM2B* (*FAM22B*) in a case of uterine angiosarcoma, no breakage in these loci was detected by fluorescence *in situ* hybridization in the present case. **Key Words:** Uterine angiosarcoma—Immunohistochemistry—Histogenesis—CD34—D2-40.

Angiosarcoma is a type of highly malignant tumor, which arises from the inner lining cells of vasculature in the skin or superficial soft tissue. Angiosarcoma can occur in various organs, such as ovary, oral cavity, small intestine, thyroid, pleura, lung, testis, and parotid, as summarized by Lin et al. (1).

Uterine angiosarcoma occurs predominately in perimenopausal and postmenopausal women. The mean age of the patients is 57 yr (range, 17–81 yr), and 5-yr overall survival of the patients is about 27% (2,3). Patients with uterine angiosarcoma usually

present with heavy vaginal bleeding, anemia, body weight loss, and/or a pelvic mass. The diagnosis of angiosarcoma is mainly based on morphologic examination and immunohistochemical (IHC) staining. The tumor is typically poorly differentiated and comprised of epithelioid to spindle-shaped cells with poorly formed vascular spaces and intracytoplasmic vacuolation. Most tumor cells are positive for endothelial markers, such as CD31, CD34, and factor VIII (4–7). The pathogenesis of angiosarcoma is still obscure. Patients with uterine angiosarcoma usually have poor prognosis. Elucidation of pathogenesis and histogenesis of uterine angiosarcoma could contribute to the clinical diagnosis and treatment. However, only a few cases have been reported in the literature (4,8,9).

Here, we present a case of uterine angiosarcoma and a review of the previously reported cases. The relationship between genetics and histogenesis of uterine angiosarcoma is also discussed.

CLINICAL SUMMARY

A 56-yr-old postmenopausal woman sought medical advice because of lower abdominal pain, anemia,

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and pelvic mass. The patient had a history of uterine leiomyoma for 14 yr. She had no history of surgery, malignant tumors, radiation therapy, or chemical exposure.

Preoperative laboratory examination revealed that this patient had anemia (hemoglobin, 2.4 g/dL; hematocrit, 7.4%). The serum level of ovarian cancer antigen CA-125 was 142.80 U/mL, which was significantly elevated compared with the normal level (<35 U/mL). Other tumor markers including α -fetoprotein, carcinoembryonic antigen, CA-153, and CA-199 in serum were within the normal limits. The preoperative diagnosis suggested uterine malignancy.

Intraoperative Findings

There were several masses in the uterus, and the biggest one was in antetheca of the uterine fundus. Multiple metastases masses were found in the abdominal-pelvic cavity; the right fallopian tube, peritoneum, retroperitoneum, right round ligament, small bowel, and greater omentum were involved. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were subsequently performed.

MATERIALS AND METHODS

Histopathologic and IHC Examination

The excised tissue was fixed in 10% buffered formalin and embedded in paraffin. Sections (4 μ m thick) were prepared for hematoxylin and eosin staining and IHC staining. Antibodies against the following antigens were used in IHC staining: CD10, CD31, CD34, factor VIII, vimentin, cyclin D1, α -smooth muscle actin, and D2-40. All of these antibodies were purchased from Santa Cruz, Japan.

Fluorescence *In Situ* Hybridization (FISH) Analysis

According to the protocol of a previous study (2,10), FISH probes flanking *YWHAE*, *NUTM2A* (also named as *FAM22A*), and *NUTM2B* (also named as *FAM22B*) genes were prepared from the Bacterial Artificial Chromosome library (10). The FISH procedure was performed as previously reported (11,12). The chromosomal positions of the probes were shown in Figure 3A.

Hybridization was performed on 4- μ m-thick sections using a standard pretreatment and hybridization protocol. The cut-off value of >10% in tumor cell nuclei showing a split signal was considered positive for the rearrangement of the flanked gene.

RESULTS

Pathologic Findings of the Uterine Angiosarcoma

As shown in Figure 1A, the uterine cavity was filled with tumor mass, which was 11 \times 8 \times 7 cm in size and gray-red in color. Tumor also involved the cervix and fallopian tubes.

Histologic examination revealed deep infiltration of the myometrium by the epithelioid tumor cells with involvement of the uterine serosa (Fig. 1B). These cells displayed marked pleomorphism and hyperchromatic nuclei with frequent mitotic figures (Fig. 1C). In addition, malignant cells were found in both omental biopsies and peritoneal lavage fluid (data not shown).

IHC Findings of the Uterine Angiosarcoma

IHC staining data were presented in Figure 2. For the vascular endothelial markers, the tumor cells were diffusely positive for CD31 and focally positive for CD34 (Fig. 2), but negative for factor VIII (data not shown). Moreover, the tumor cells showed increased expression of cyclin D1, a key protein for regulation of cell proliferation, and also positive for vimentin, a hallmark of epithelial-mesenchymal transition. In contrast, smooth muscle marker α -smooth muscle actin, lymphatic marker D2-40, and endometrial stromal marker CD10 were negative in tumor cells (data not shown). The surgical margin of the vagina was free of malignancy.

FISH Analysis of the Uterine Angiosarcoma

The pathogenesis of uterine angiosarcoma is still obscure. Recently, Suzuki et al. (10) reported a case of uterine angiosarcoma with breakages at 3 loci, *YWHAE* (17p13), *NUTM2A* (*FAM22A*) (10q23), and *NUTM2B* (*FAM22B*) (10q22). Here, FISH with probes flanking *YWHAE*, *NUTM2A*, and *NUTM2B* genes were performed (Fig. 3A). The FISH with 2 probes flanking the *YWHAE* were shown as yellow (overlapping) signals (Fig. 3B), which indicated that there was no genetic rearrangement involving *YWHAE*. In addition, the FISH with probes for detecting fusion of *YWHAE* and *NUTM2A* (Fig. 3C) or *YWHAE* and *NUTM2B* (Fig. 3D) were presented as separate signals (orange and green), which suggested that there was not fusion on these genes.

DISCUSSION

Uterine angiosarcoma is a very rare tumor. As reviewed in Table 1 (13), there were only 12 cases of

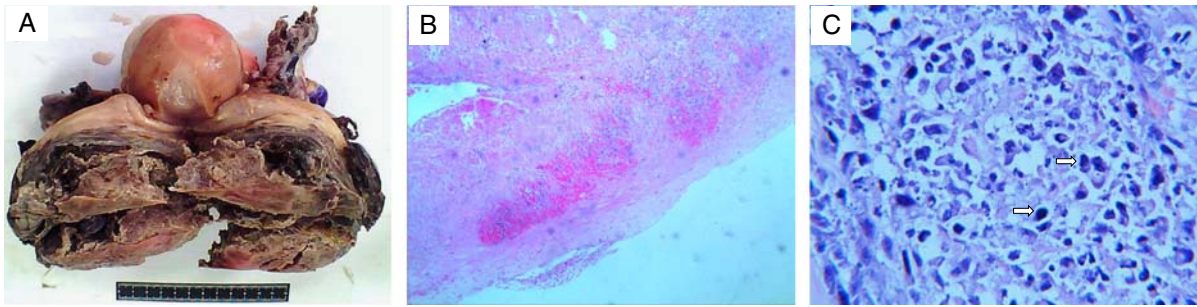


FIG. 1. Pathologic findings of the uterine angiosarcoma. (A) Gross view of the surgical specimen. The uterine cavity has a spongy hemorrhagic appearance with necrotic tissue, a benign smooth muscle proliferation, and the right fallopian tube with necrotic tissue. (B) Hematoxylin and eosin (H&E) staining of cross-sections shows the tumor infiltrated deeply from myometrium to serosal surface of the uterine fundus (magnification: 40 ×). (C) H&E staining shows epithelioid tumor cells, some of which exhibit vesicular nuclei (arrow) (magnification: 400 ×).

uterine angiosarcoma reported in the medical literature in the past 20 yr. Here, we reported an additional case with giant uterine angiosarcoma. These case reports not only

provided information regarding the clinical features, pathologic descriptions, and therapeutic regimen, but also suggested possible pathogenesis.

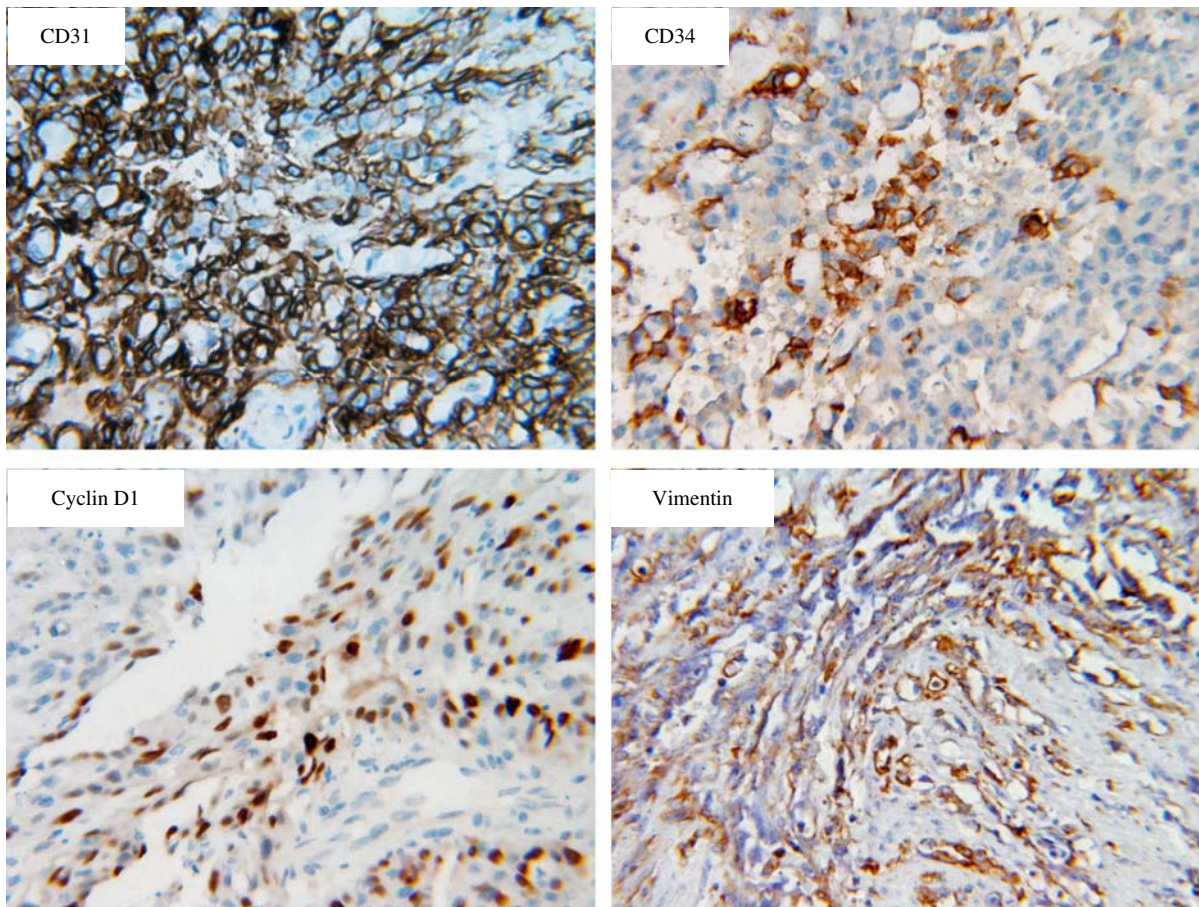


FIG. 2. Immunohistochemical findings. The tumor cells are strongly positive for vascular endothelial marker CD31 and cell-cycle regulatory protein cyclin D1, focally positive for vascular endothelial marker CD34, and epithelial-mesenchymal transition marker vimentin (magnification: 400 ×).

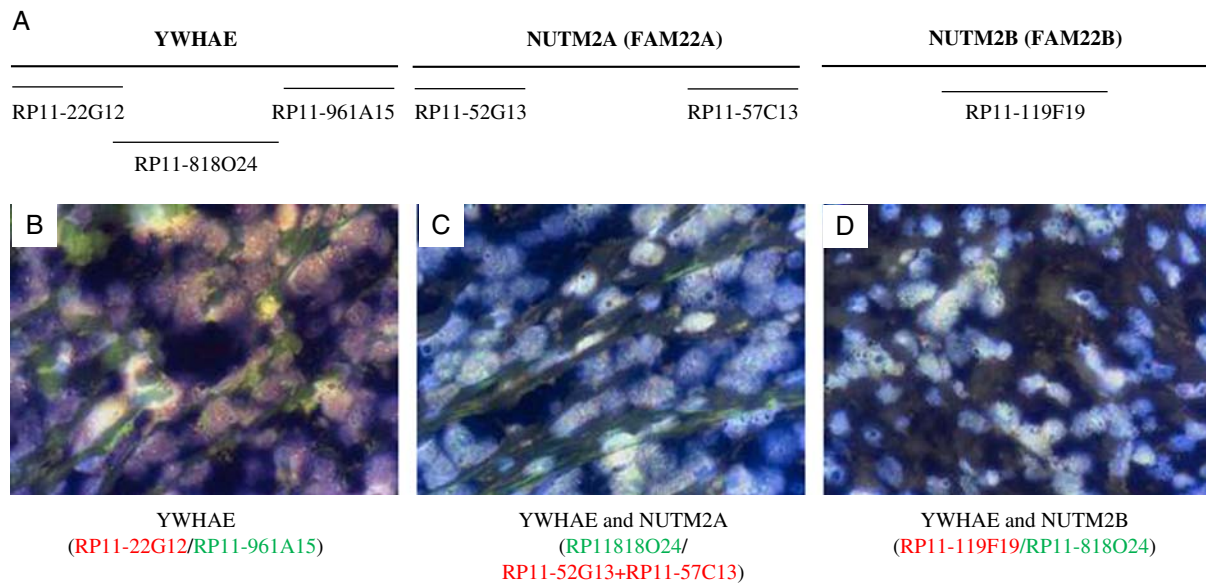


FIG. 3. (A) The chromosomal positions of FISH probes flanking 3 interest genes: *YWHAЕ*, *NUTM2A* (*FAM22A*), and *NUTM2B* (*FAM22B*). (B–D) Representative findings of the uterine angiosarcoma by FISH. The probes at the locations flanking the *YWHAЕ* locus (B) are shown as overlapped signals (yellow). The probes flanking the *YWHAЕ* and *NUTM2A* loci (C) and the probes flanking the *YWHAЕ* and *NUTM2B* (D) were presented as separate signals (green and orange). FISH indicates fluorescence *in situ* hybridization.

Several endothelial markers have been used for assisting the diagnosis of uterine angiosarcoma in previous reports, such as CD31, CD34, and factor VIII. In our case, both CD31 and CD34 were positive, but expression of factor VIII was absent.

Notably, the tumor cells were negative for the lymphatic marker D2-40. It was reported that cutaneous angiosarcoma can be divided into vascular type, mixed type, and lymphatic type, based on the data of IHC staining with CD34 and D2-40.

TABLE 1. Summary of reported cases of uterine angiosarcomas between 1994 and 2014

References	No. cases	Age (yr)	Presenting symptoms	Macroscopic features	Surgery	Therapy	Follow-up/survival
Drachenberg et al. (13)	1	58	Bleeding, anemia	12-cm uterus		Chemo and RT	Died at 2 mo
Schammel and Tavassoli (7)	4	49	Mass, anemia, weight loss	29 × 29 × 19 cm mass	Pathology—research and practice	None	Died at 3 mo
		58	Vaginal bleeding, anemia	12 cm	TAH/BSO	Chemo and RT	Died at 2 mo
		70	Bleeding	5 × 2.5 × 3 cm polyp	TAH/BSO	None	NED at 37 mo
		75	Bleeding	6.3 × 6 × 4.5 cm mass	TAH/BSO	None	Died at 7 mo
Mendez et al. (4)	1	59	Bleeding, pelvic	12-wk-size uterus	TAH/BSO, lymph node biopsies	None	Vaginal mass at 5 wk postoperative
Konishi et al. (8)	1	62	Anemia	17 × 15 × 7.5 cm	TAH/BSO	Chemo	NED at 2 mo after surgery
Cardinale et al. (5)	2	81	Abdominal pain, anemia	8 × 7 × 4.5 cm	Not mentioned	None	Died at 6 mo
		35	Short of breath, dry cough, gastrointestinal reflux	25-cm mass	Not mentioned	None	Died shortly
Olawaiye et al. (6)	1	54	Pelvic mass	11 × 6 cm	TAH/BSO	Chemo and RT	Died at 12 mo
Hwang and Lim (2)	1	61	Vaginal bleeding, abdominal pain	12 × 10 × 9 cm	TAH/BSO, para-aortic lymph node dissection	RT	Not mentioned
Suzuki et al. (10)	1	64	Vaginal bleeding	7.5 × 5.5 × 3.5 cm	Pathology—research and practice	None	Died at 50 mo
This study	1	56	Pelvic mass, anemia	11 × 8 × 7 cm	TAH/BSO	None	Withdrew

TAH/BSO, total abdominal hysterectomy/bilateral salpingo-oophorectomy; RT, radiation treatment; NED, no evidence of disease.

According to this, histogenesis of uterine angiosarcoma probably also be divided into vascular type (both CD34⁺ and D2-40⁻), mixed type (CD34⁺ and D2-40⁺), and lymphatic type (both CD34⁻ and D2-40⁺). The current case should be vascular-type angiosarcoma. However, there were no data of D2-40 in most of the uterine angiosarcoma cases reported previously (Table 1). IHC staining with CD34 and D2-40 should be considered in pathologic examination, which may contribute to our understanding and classification of uterine angiosarcoma. The high expression of cyclin D1 protein suggested active proliferation of the tumor cells.

Recently, the breakages at *YWHAE*, *NUTM2A*, and *NUTM2B* loci were detected in a case of uterine angiosarcoma. These genetic changes may contribute to the pathogenesis of uterine angiosarcoma. However, neither breakage nor fusion of these genes was detected in tumor cells of the current case. This genetic difference may be due to different histogenesis of the 2 cases: the one with breakages at *YWHAE*, *NUTM2A*, and *NUTM2B* loci is lymphatic type (CD34⁻ D2-40⁺), whereas the current case is vascular type. More cases are needed to discuss the relationship between genetics and histogenesis of uterine angiosarcoma.

In addition, although the apparent histogenic origin (vascular vs. lymphatic) of cutaneous angiosarcoma was not related with prognosis, it probably contributes to selection of antiangiogenic agents (14). Further studies focusing on the histogenesis of uterine angiosarcoma in relation to clinical diagnosis and treatment should be performed.

Currently, surgical resection is the only treatment modality for uterine angiosarcoma. It has a poor prognosis due to local and distant recurrence (15). The patients with tumor <5 cm in size have a better prognosis (Table 1). Although the combination chemotherapy was adopted in some cases (10,12,16,17), the effect of chemotherapy is limited. Unfortunately, the patient in this report withdrew from further treatment and was discharged against medical advice.

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