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Metastatic angiosarcoma arising in a patient with long-standing treatment-refractory hemangioma

Angiosarcomas are malignant tumors of the vascular endothelium and are typically idiopathic. These tumors comprise 2% of all soft tissue sarcomas and have an estimated incidence of 2 per million.[1,2] Known causes of angiosarcoma include genetic syndromes—such as von Hippel-Lindau, Chuvash polycythemia, Bannayan-Riley-Ruvalcaba, Cowden, and hamartomatous polyposis syndromes—chronic lymphedema, and exposure to radiation.[3] Vinyl chloride, arsenicals, and thorotrast are known to increase the incidence of angiosarcoma of the liver.[4]

Malignant transformation of hemangioma is rare. We describe metastatic angiosarcoma in a patient with a large, long-term treatment-resistant subcutaneous hemangioma, illustrating such a possibility. We review similar cases and discuss the value of determining pathogenesis in such patients.

CASE PRESENTATION AND SUMMARY

A 55-year-old female with a long-standing childhood hemangioma of the left lower extremity was referred to Ochsner Medical Center for tissue diagnosis of new pulmonary nodules. Her medical history included a 7 pack-year smoking history; she had quit 3 years prior. Her family history included a sister who died from breast cancer. The patient initially had a progressive, intermittently bleeding tumor in the left foot at age 7. She was diagnosed with hemangioma in her twenties. At that point, her tumor began to involve the posterior calf and femur, causing deformity. She had multiple surgical resections but reportedly all pathology demonstrated benign hemangioma. She received radiation for pain, a routine treatment at the time, but developed a focus of progression in the heel. Above-knee amputation was considered but could not be performed when hemangioma was discovered in the hip area. She was lost to follow-up between 2001 and 2015. Lower extremity magnetic resonance imaging in 2015 was stable with imaging prior to 2001. A repeat biopsy in 2016 demonstrated hemangioma. The patient then received radiation to a wider field, including the femur, with minimal response. She completed a course of steroids as well. Bevacizumab was started in 2017 and improved foot deformity. She also briefly trialed pazopanib for 4 weeks in 2018 in an attempt to switch to oral medications. Despite partial response, she discontinued both agents in July 2018 because of toxicity and the burden of recurrent infusions.

Four months later, she presented with 2 months of intermittent hemoptysis and 18 months of metallic odors. Additionally, she lost 25 pounds in 3 months, which she attributed to a diet plan. At this visit, her left lower extremity exhibited multiple subcutaneous tumors and nodules.

Computed tomography (CT) with contrast demonstrated innumerable pulmonary nodules, the largest measuring 2.2 cm in the right lower lobe superior segment. Positron emission tomography (PET)/CT revealed 2 nodules with mild hypermetabolic activity; the largest nod-

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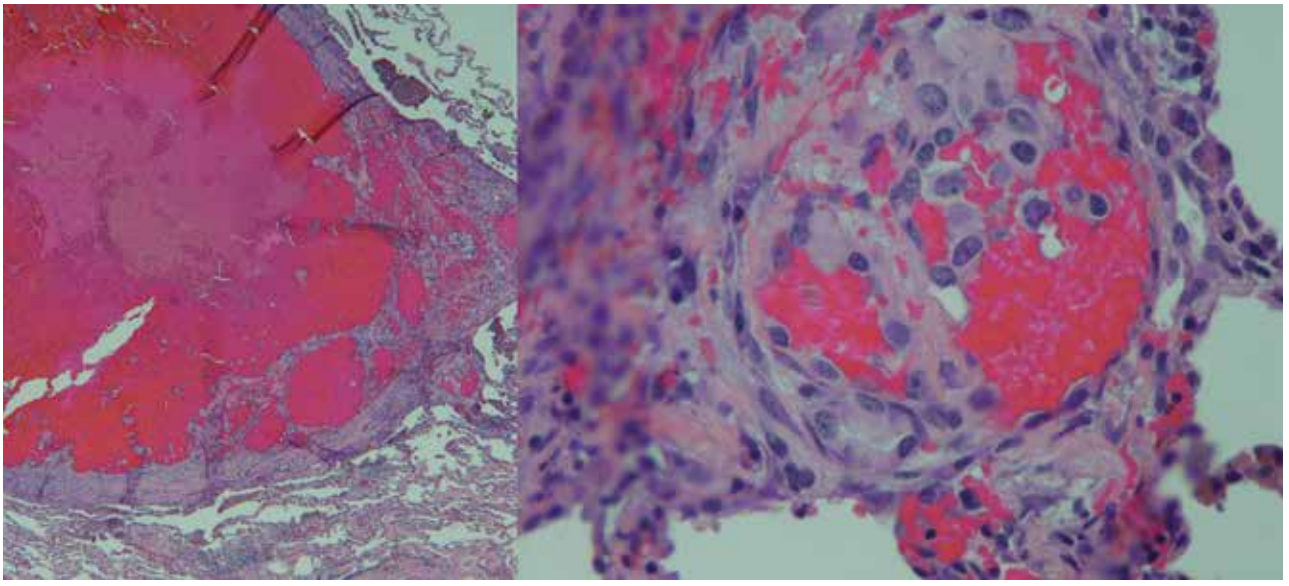

FIGURE 1. Areas of angiosarcoma under 10x (left) and 40x (right) magnification with dilated blood-filled spaces, fresh red blood cells, and intraluminal invasion. Cells demonstrate hyperchromasia with irregular nuclear contours and prominent nucleoli. Mitoses were present.

› DETERMINING ETIOLOGY MAY BENEFIT PATIENTS FOR PROGNOSTICATION AND POSSIBLY INFORM FUTURE SELECTION OF TREATMENT MODALITIES.

ule had a maximum standardized uptake value of 2.7. Bronchoalveolar lavage studies showed intra-alveolar hemorrhage with hemosiderin-laden macrophages. No malignancy, granuloma, or dysplasia was found in transbronchial needle aspirate of the largest nodule. The patient had no lymphadenopathy.

At this hospital, surgical resection by video-assisted thoracoscopic surgery confirmed multifocal malignant epithelioid neoplasm suspicious for angiosarcoma. Multiple areas showed proliferation of atypical epithelioid-to-spindle cells. There were prominent associated hemosiderin-laden macrophages, fresh red blood cells, and dilated blood-filled spaces. Cells demonstrated hyperchromasia with irregular nuclear contours, prominent nucleoli, and mitoses (**FIGURE 1**). Additionally, there were areas of focal organizing pneumonia. For atypical cells, staining was CD31-positive and CD34-negative. Staining was strongly positive for ERG. There was increased Ki-67 with retained *INI* expression and patchy weak reactivity for Fli-1.

Next-generation sequencing was performed. Specimen tumor content was 15%. Genomic findings included *IDH1* p.R132C mutation, with variant allele frequency <10%. Testing was inconclusive for *MSI* and *TMB* mutations. PD-L1 assessment could not be performed. Unfortunately, the patient did not qualify for any clinical trials, as there were no matching alterations. This patient was lost to follow-up.

DISCUSSION

Angiosarcoma accounts for 2% of soft tissue sarcomas.[1] Cutaneous angiosarcomas most commonly occur in the face and scalp of the elderly, or in sites of chronic lymphedema. Angiosarcoma also develops following radiation therapy.[5] For breast cancers and tumors of the head and neck, irradiation has <1% risk of inducing secondary malignancy, including angiosarcoma.[6]

This patient had a new diagnosis of angiosarcoma in the setting of long-standing benign hemangioma with history of radiation treatment. Thus, it is unclear whether this angiosarcoma was primary, radiation-induced, or secondary to transformation from the preexisting vascular tumor. Post-irradiation sarcoma carries a less favorable prognosis compared to de novo sarcoma; however, reports conflict on whether this holds for angiosarcoma subtypes.[6] Determining etiology may

TABLE 1 Cases with malignant disease progression in patients with benign vascular disease

	Authors	Year	Age	Sex	Dx 1	Location	Rad	Sx	Dx 2	Latency	Extent	IHC
Adult	Mandahl	1990	90	M	HA	Face	/	NS	AS	Cc	Local	VIII+
	McRae	1990	24	F	HA	Larynx	/	5y	AS	5y	Local	N/A
	Tohme	1991	36	F	HA	Liver	N/A	N/A	AS	Cc	Local	N/A
	Chalet	1993	32	F	HA	Heart	/	12y	AS	12y	Local	VIII+
	Obana	1996	44	F	HA	Vertebra	80Gy	2y	AS	2y	Local	N/A
	Tsukagoshi	1998	46	F	HA	Liver	/	1y	a	Cc	Spleen	CD31+,CD34+,VIII+
	Fukuroku	1999	55	M	HE	UE	N/A	N/A	HE, AS	N/A	Distant	N/A
	Yamamoto	2001	71	M	HA	LE	Bomb	5mo	AS	Cc	Local	VIII+
	Rossi	2002	73	M	HA/VM	LE	/	9mo	AS	Cc	Local	b
	Rossi	2002	65	M	HA/VM	Parotid	/	1y	AS	Cc	Local	b
	Rossi	2002	61	F	HA/VM	LE	/	NS	AS	Cc	Local	b
	Rossi	2002	69	F	HA/VM	Vertebra	/	2y	AS	Cc	Local	b
	Antosz	2010	44	F	DHE	LE	/	5y	AS	18mo	Distant	CD34+,VIII+
	Nathenson	2014	40	F	HA	LE	/	10y	EHE, AS	Cc	Local	CD31+
	Huerta-Orozco	2015	41	M	HA	Liver	/	/	AS	6mo	Distant	CD31+,CD34+
Pediatric	McCarthy	1950	15	F	HA	LE	Yes	N/A	AS	18y	Local	N/A
	Pedlashuk	1972	2	F	HA	Cheek	48Gy	N/A	AS	12y	Local	N/A
	Ward	1977	5mo	M	HA	Scalp	10Gy	N/A	AS	18y	Local	N/A
	Bennett	1978	1	M	HA	Cheek	Yes	N/A	AS	30y	Local	N/A
	Kim	1978	7	M	HA	LE	71Gy	NS	AS	30y	NS	N/A
	Sarrat	1980	N/A	N/A	HA	N/A	N/A	N/A	AS	N/A	N/A	N/A
	Strate	1984	3mo	M	HE	Liver	N/A	N/A	AS	4y	N/A	N/A
	Davidson	1985	N/A	N/A	HA	N/A	N/A	N/A	AS	N/A	N/A	N/A
	Handfield-Jones	1988	Cg	F	AL	Face	26Gy	24y	AS	23y	Local	VIII+
	Sironi	1988	2	N/A	HA	UE	Needles	N/A	AS	14y	N/A	N/A
	Costello	1990	3	N/A	HA	LE	8Gy	N/A	AS	33y	Local	N/A
	Cancellieri	1991	Cg	F	AL	Chest	Yes	NS	AS	22y	Local	VIII+
	Cancellieri	1991	Cg	F	AL	Scapula	15Gy	NS	AS	16y	Local	VIII+
	Caldwell	1995	Cg	F	HA	LE	55Gy	15y	AS	29y	Local	VIII+

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benefit patients for prognostication and possibly inform future selection of treatment modalities.

The mutational signature in radiation-associated sarcomas differs from that of sporadic sarcomas. First, radiation-associated sarcomas demonstrate more frequent small deletions and balanced translocations. *TP53* mutations are found in up to 1/3 of radiation-associated sarcomas and are more often due to small deletions than in sporadic sarcomas.[7] High-level *MYC* amplification occurs in 54%-100% of secondary angiosarcomas, compared to 0-7% in sporadic angiosarcomas. Co-amplification of *FLT4* occurs

TABLE 1 Cases with malignant disease progression in patients with benign vascular disease *Cont'd*

	Authors	Year	Age	Sex	Dx 1	Location	Rad	Sx	Dx 2	Latency	Extent	IHC
Pediatric	Quecedo	1996	Cg	M	HA	LE	/	18y	DHE	18y	Local	CD34+,VIII-
	Cabo	1998	Cg	M	HA	Cheek	Yes	10y	AS	54y	Local	CD31+,VIII+
	Damiani	2004	14	F	HA	Parotid	/	8y	AS	8y	Local	CD31+,CD34+
	Drager	2005	NS	F	HA	UE	Yes	NS	AS	NS	Local	CD31+,CD34+
	Nazir, Pervez	2006	Cg	F	HE	Back, scalp, liver	/	/	No bx	Cc	Distant	No bx
	Jeng	2014	5mo	M	HA	Skin, lung, liver	/	/	AS	45mo	Distant	NS
	Kamath	2015	2	M	HE	Liver	/	/	AS	1mo	Distant	CD34+
	Present Study	2019	7	F	HA	LE	Yes	48y	AS	48y	Distant	CD31+,CD34-

a - Sarcomatoid changes not otherwise specified
b - Cases were positive for 2 of 3 markers
AL = angiomatous lesion, AS = angiosarcoma, Bomb = atomic weapon explosion, Bx = biopsy, Cc = concurrent, Cg = congenital, DHE = Dabska hemangioendothelioma, Dx = diagnosis, EHE = epithelioid hemangioendothelioma, Gy = gray, HA = hemangioma, HE = hemangioendothelioma, IHC = immunohistochemistry, LE = lower extremity, N/A = article not available, NS = not stated, Rad = radiation, Sx = duration of symptomatic disease, UE = upper extremity, VM = venous malformation, / = None

in 11%-25% of secondary angiosarcomas.[8] Additionally, transcriptome analysis revealed differential expression of a 135-gene signature compared to non-radiation-induced sarcomas.[7] Although this patient was not specifically analyzed for such alterations, such tests may differentiate post-irradiation angiosarcoma from sporadic etiologies.

In this patient, the R132C *IDH1* mutation was identified and may be the first reported case in angiosarcoma. Typically, this mutation occurs in chondrosarcoma, myeloid neoplasms, gliomas, and cholangiocarcinomas. It is also found in spindle cell hemangiomas but not in other vascular tumors.[9] The clinical significance of this mutation is uncertain at this time.

There are approximately 36 reported cases of malignant disease arising in patients with less aggressive vascular tumors (**TABLE 1**). Of these, 25 of 36 involve angiosarcoma arising in patients with hemangioma. Four cases of angiosarcoma were reported in patients with hemangioendothelioma, 1 case of hemangioendothelioma in a patient with hemangioma, 1 case of Dabska tumor in a patient with hemangioma, and 1 case of angiosarcoma in a patient with Dabska tumor. Fifteen cases involved initial disease with adult onset and 21 involved initial disease with pediatric onset, suggesting even distribution. Malignant disease mostly occurred in adulthood, in 26 out of 33 cases. Latency to malignancy ranged from concurrent discovery to 54 years. Mean latency, excluding cases with concurrent discovery, was shorter with adult-onset initial disease, at 4.2 years, compared to 16 years among patients with onset of initial disease in childhood. Longer latency in the pediatric-onset population correlated with longer latent periods for radiation-induced angiosarcoma following benign disease, which is reported to average 23 years.[10] Thirteen of 19 cases with pediatric onset disease had a history of radiotherapy, while 2 of 13 cases with adult onset disease did. Sixteen cases involved tumor in the bone and soft tissue, as in this patient. Notably, 4 of these cases involved long-standing hemangioma for 10 years or more, as in this patient, suggesting a possible correlation between long-standing vascular tumors and malignant transformation. Angiosarcoma arising in non-irradiated patients suggests that malignant transformation and de novo transformation may compete with radiation-induced mutation in tumorigenesis. Further, 8 cases involved angiosarcoma growing within another vascular tumor, demonstrating the possibility of

malignant transformation. Dehner and Ishak described a histological model for quantifying such a risk; a validated model may be particularly useful in patients with long-standing hemangioma.[11]

Etiology of tumorigenesis in cases of angiosarcoma arising in patients with a history of benign hemangioma may benefit prognostication and inform treatment selection in the future. Owing to long latent periods, radiation-associated angiosarcoma incidence may rise, as radiation therapy for benign hemangioma was recently routine. Future research may provide insight into disease progression and possibly predict the risk of angiosarcoma in patients with long-standing benign disease. **TSJ**

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› **LONGER LATENCY IN THE PEDIATRIC-ONSET POPULATION CORRELATED WITH LONGER LATENT PERIODS FOR RADIATION-INDUCED ANGIOSARCOMA FOLLOWING BENIGN DISEASE.**