Angiosarcoma in arteriovenous fistula after kidney transplantation

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ABSTRACT

Angiosarcoma is a rare complication of both functioning and nonfunctioning fistulas. It is an aggressive soft tissue sarcoma arising from vascular or lymphatic endothelial cells. We report a case of angiosarcoma from a nonfunctional fistula in a kidney transplantation patient receiving immunosuppressive drugs. The patient had presented with arm pain mimicking a thrombosed arteriovenous fistula. (J Vasc Surg Cases and Innovative Techniques 2021;7:142-7.)

Keywords: Angiosarcoma; Arteriovenous fistula; Epithelioid tumor; Renal transplant; Vascular access

Angiosarcoma is a rare aggressive soft-tissue sarcoma characterized by rapidly proliferating and extensively infiltrating anaplastic cells, which derives from blood vessels and lining of irregular blood-filled spaces.[1] It is a rare complication of arteriovenous fistulas.[2] In renal transplant recipients, angiosarcoma is an extremely rare type of cancer, accounting for <1% of all cancers and 2% of localized soft tissue cancer.[3] Because of its rarity, most clinicians are unaware of this condition, resulting in a delayed diagnosis and treatment. The institutional review board and ethics committee approved the present study, and a retrospective analysis of the medical records was conducted. The related reported data were also reviewed.

CASE REPORT

A 58-year-old man had presented with right arm pain at a brachiocephalic arteriovenous fistula (BCAVF). He had end-stage renal disease and had begun hemodialysis via a right BCAVF 5 years earlier. After 1 year of hemodialysis, he had undergone living related kidney transplantation (KT). He had been receiving immunosuppression therapy with prednisolone, mycophenolate mofetil, and tacrolimus. His baseline creatinine was 0.6 mg/dL. Later, he had complained of right arm pain, and a partially thrombosed AVF was diagnosed. After 6 months of conservative treatment, his pain and weakness had become severe. Also, paresthesia in his right arm and bleeding erosion from the BCAVF were observed. The diagnosis was impending rupture of an AVF aneurysm. He subsequently underwent aneurysmal resection. Preoperative chest radiograph showed a right lung mass. During the intraoperative period, no mass in the intraluminal cephalic vein could be identified (Fig 1). However, his severe arm pain had persisted postoperatively, and a radiograph showed multiple osteolytic lesions in the right humeral shaft, proximal ulna, and radius (Fig 2). Chest computed tomography revealed a 2-cm, lobulated pulmonary nodule in the right upper lung. Therefore, we suspected primary lung cancer with bone metastases. Fifteen days later, he had returned with acute limb ischemia of the right arm. Computed tomography angiography showed no contrast filling in the proximal radial and ulnar arteries at the distal brachial to brachial bifurcation. An eccentric filling defect was seen at the right brachial artery (Fig 3). Intraoperatively, soft tan-brown tissue was recovered by brachial arterial embolectomy. Cytologic examination of the blood clot showed atypical cells. In addition, pathologic examination of the tissue revealed epithelioid angiosarcoma. Examination of a bone biopsy specimen from the right humerus revealed angiosarcoma. At 3 months after aneurysm resection, the patient underwent right shoulder disarticulation. Histopathologic examination of the right shoulder disarticulation revealed

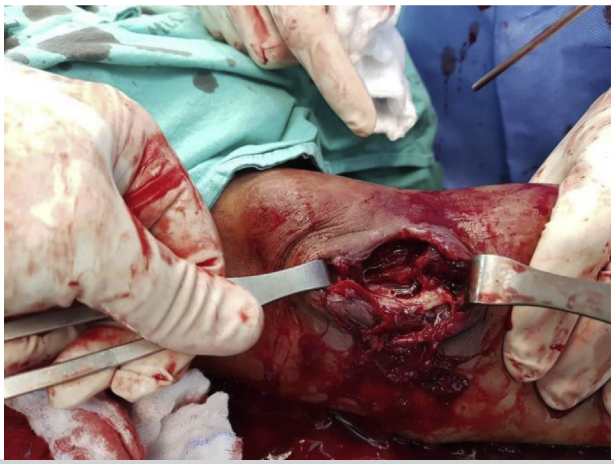

Fig 1. Thrombosis of cephalic vein found intraoperatively. After removal of the clot, no mass and no abnormality was found in the cephalic vein.

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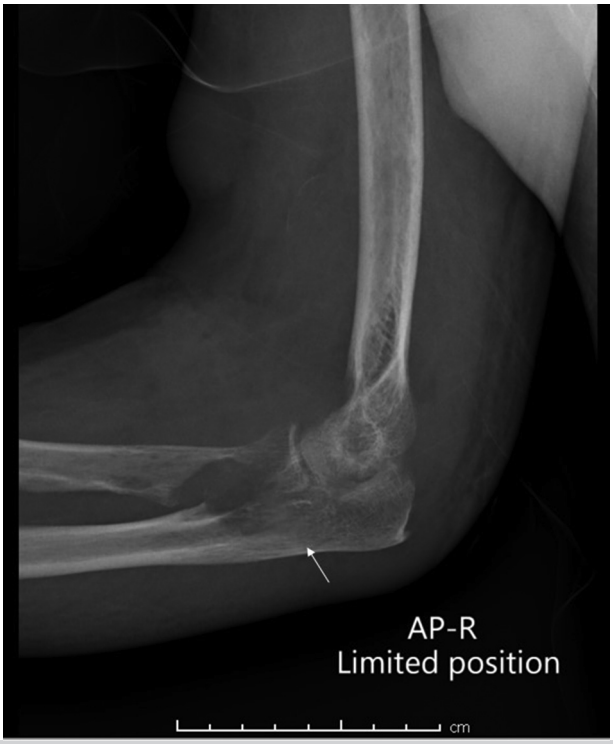

Fig 2. Radiograph of the right elbow showing an osteolytic lesion at the ulna (*white arrow*).

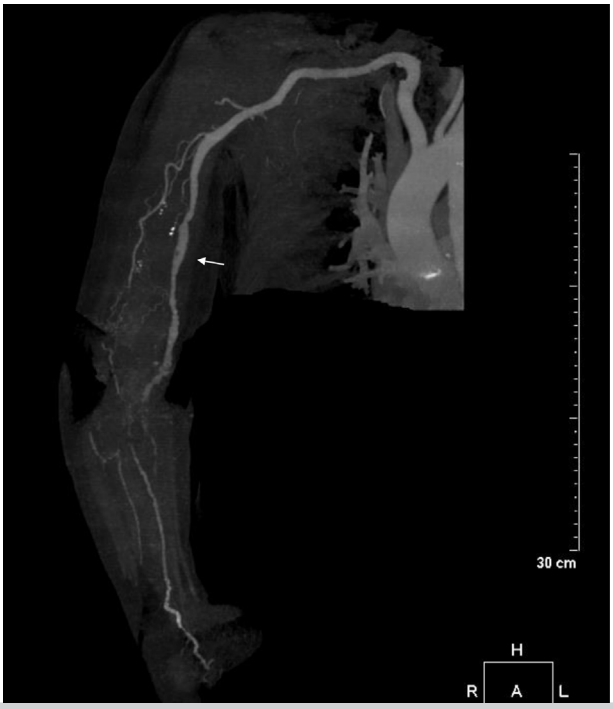

Fig 3. Computed tomography angiogram showing total thrombosis of the cephalic vein of the brachiocephalic arteriovenous fistula. No contrast filling had occurred in the proximal radial and ulnar arteries at the distal brachial to brachial bifurcation. An eccentric filling defect was seen at the right brachial artery (*white arrow*).

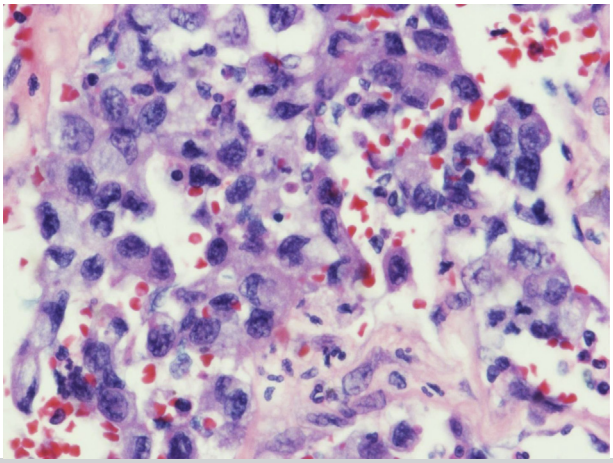

Fig 4. High-grade pleomorphic epithelioid cells with amphophilic cytoplasm and vasoformative growth.

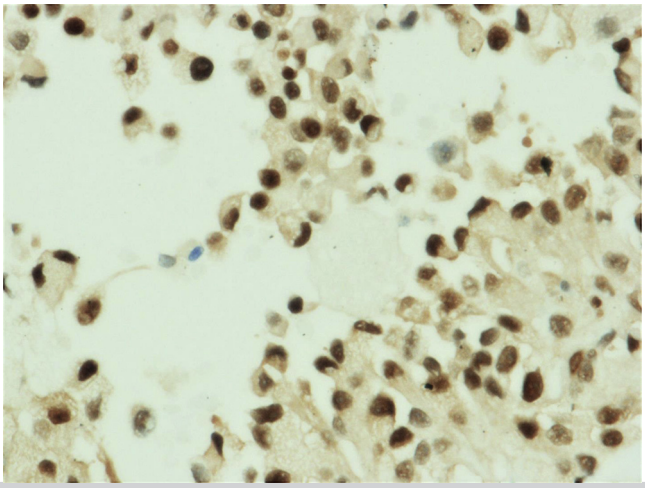

Fig 5. Positivity to ERG immunohistochemistry and other vascular markers such as FLI1, CD31, and CD34 (data not shown) confirmed the diagnosis of angiosarcoma.

angiosarcoma involving the AVF, soft tissue of the cubital fossa, and proximal humerus (Figs 4 and 5). The final diagnosis was angiosarcoma at the AVF with bone and pulmonary metastasis. Therefore, we planned palliative chemotherapy with paclitaxel (Taxol; Bristol-Myers Squibb, New York, NY) weekly. However, the patient developed hemoptysis. He died of massive hemothorax 10 months after symptom onset and 1 month after diagnosis. Because the patient had died and we were unable to contact his relatives, consent could not be obtained from the patient or his family.

DISCUSSION

According to our review of the reported data[4-23] (Table), 23 cases of angiosarcoma occurring from vascular access had been described in 20 English language reports. Most of the patients were men (83.3%), and their mean age was 52.7 ± 15.2 years. The most often used vascular

Table. Summary of reported cases of angiosarcoma at arteriovenous fistula sites

Investigator	Sex; age, years	Vascular access	AVF status	Transplantation		IST	Presentation
				Type	Status		
Byers et al,[4] 1992; Parrott et al,[5] 1993	M; 36	RC-AVF	Functional	DDKT	Functional	Azathioprine, cyclosporine, prednisolone	Swelling
Wehrli et al,[6] 1998	M; 64	RC-AVF	Thrombosed	DDKT	Functional	Azathioprine, cyclosporine, prednisone	Swelling, pain
Álvarez et al,[3] 2013	F; 47	AVF	Thrombosed	DDKT	Functional	Cyclosporine, MMF	Nail-bed splinter lesions, pain, hand retraction
Conlon et al,[7] 1993	M; 40	BC-AVF	Thrombosed (ligated aneurysm)	First DDKT Second DDKT	Rejection Functional	Treated for rejection Prednisolone, azathioprine, prednisone	Pain and swelling
Keane et al,[8] 1993	M; 11	AVF	Thrombosed (ligated aneurysm)	First DDKT Second DDKT	Rejection Functional	Treated for rejection Corticosteroids, azathioprine	Mass, induration arising from AVF
Bessis et al,[9] 1998	M; 61	BC-AVF	Thrombosed	DDKT	Functional	Azathioprine, cyclosporine, prednisolone	Pain, swelling, tenderness
Farag et al,[10] 2005	M; 26	AVF	Thrombosed (ligated aneurysm)	First DDKT plus PT Second DDKT	Not functional Functional	NA Azathioprine, cyclosporine, prednisolone	Mass
Webster et al,[11] 2011	M; 59	BC-AVF	Thrombosed	LRKT	Functional	Rituximab daclizumab, tacrolimus	Pain, swelling
Webster et al,[11] 2011	F; 41	BC-AVF	Thrombosed	LRKT	Functional	Alemtuzumab, prednisolone, tacrolimus	Pain
Webster et al,[11] 2011	M; 44	BC-AVF	NR	DDKT	Functional	Prednisolone, tacrolimus, MMF	Pain, mass
Demey et al,[12] 2014	M; 80	AVF	Functional	No KT	No KT	No KT	Pain, swelling
Roy et al,[13] 2018	M; 63	AVF	Thrombosed (ligated aneurysm)	KT	Functional	MMF, tacrolimus	Mass
Aldaabil et al,[14] 2016	M; 46	BC-AVF	Thrombosed	LRKT	Functional	MMF, tacrolimus, prednisone	Pain, swelling
Qureshi et al,[15] 2010	M; 48	AVF	Functional	First KT Second LRKT	Not functional Functional	NA Prednisolone, MMF, rituximab, IVIG, tacrolimus	Pain
Costa et al,[16] 2017	F; 70	BC-AVF	Thrombosed (ligated aneurysm)	KT	Functional	Tacrolimus, MMF, prednisolone	Dyspnea
Chanyaputhipong et al,[17] 2011	M; 57	RC-AVF	Thrombosed (ligated aneurysm)	DDKT	Rejection	None	Pain, mass
Chanyaputhipong et al,[17] 2011	M; 63	BC-AVF	Thrombosed (aneurysm)	No KT	No KT	No KT	Pain, mass with bleeding
Gale et al,[18] 2017	M; 44	RC-AVF	Functional	DDKT	NR	NR	Necrotic fingers
Kakisis et al,[19] 2019	M; 60	RC-AVF	Thrombosed	DDKT	Functional	Prednisolone, cyclosporine, MMF	Bleeding from AVF
Jansen et al,[20] 2013	M; 58	NR	NR	DDKT	Functional	Yes (NR)	Nodule, pain, hand dysfunction
Kleman et al,[21] 2016	M; 71	AVF	NR	LRKT	Functional	Alemtuzumab, tacrolimus, MMF	Edema, erythema, non-PTH hypercalcemia
Andre et al,[22] 2012	M; 62	AVF	Functional	First KT Second KT	Not functional Functional	NR Prednisone, tacrolimus, MMF	Nonhealed wound at AVF removal site
Figueiredo et al,[23] 2019	F; 55	AVG	Thrombosed (ligated aneurysm)	KT	Functional	Tacrolimus, prednisolone, MMF	Mass
Present case, 2020	M; 58	BC-AVF	Thrombosed	LRKT	Functional	Prednisolone, tacrolimus, MMF	Pain

AS, Angiosarcoma; *AVF*, arteriovenous fistula; *BC*, brachiocephalic; *CMT*, chemotherapy; *DDKT*, deceased donor kidney transplantation; *Dx*, diagnosis; *F*, female; *IST*, immunosuppressive therapy; *KT*, kidney transplantation; *LRKT*, living related kidney transplantation; *M*, male; *MMF*, mycophenolate mofetil; *NA*, not applicable; *NR*, not reported; *PT*, pancreatic transplantation; *PTH*, parathyroid hormone; *RC*, radiocephalic; *RT*, radiation therapy; *Tx*, treatment; *VA*, vascular access.

Table. Continued.

Initial Dx	Interval to Dx (weeks)	Interval (years) from		Metastasis before Tx	Tx	Recurrence	Survival
		VA to AS	KT to AS				
Thrombotic VA, infection	20	12	8	No	Above elbow amputation	Postnasal space, lung and axillary lymph node metastasis	1 Year
Thrombotic VA	4	10	7	No	RT, followed by below elbow amputation	Local and lung metastasis	Alive 6 months after amputation
Thrombotic or aneurysmal VA	12	14	8	Bone, lung	CMT	NR	2 Months
NA	4	40	16 7	No	Skeletalization of anterior compartment of arm; RT	Local recurrence and lung metastasis	5 Months
NA	8	NR	NR 7	No	Wide excision, RT	Local recurrence, lung and brain metastasis	8 Months
Thrombotic or aneurysmal VA	NR (>6)	7	5	No	Above elbow amputation	Lung metastasis	7 Months
Thrombotic or aneurysmal VA	NR	13	NR 11	Lung	CMT	Local recurrence	11 Months
Thrombotic and infection VA	NR	3	2	No	Above elbow amputation	No	Survived
Thrombotic VA	4	NR	NR	NR	NR	Lung metastasis	4 Months
NR	12	13	8	NR	NR	Lung metastasis	6 Months
Aneurysmal VA	36	4.5	No KT	Bone	Supportive care	NR	1 Month
Mass	NR	NR	6	Lung	NR	NR	10 Days
NR	NR	NR	3	Lung, bone	CMT, above elbow amputation	NR	6 Months
Infection	NR	3	NR 2	No	"High" above elbow amputation	No recurrence or metastasis	9 Months
Pneumonia	NR	11	9	Lung	NR	NR	NR
Granuloma, infection	8	17	NR	NR	Wide excision, RT, CMT	Local recurrence, lung and bone metastasis	11 Months
AVF malformation or AS	3	9	No KT	No	Wide excision, RT, CMT	Lung metastasis	9.5 Months
Hand ischemia	NR	6	NR	No	Forequarter amputation	NR	NR
NR	NR	11	6	No	Above elbow amputation	Lung metastasis	6 Months
NR	NR	NR	NR	NR	NR	NR	NR
Cancer	NR	NR	NR	No	AVF resection, RT, CMT	NR	NR
NR	NR	NR	NR NR	Lung	RT, CMT	NR	NR
NR	8	NR	15	Lung	Palliative care, CMT	NR	4 Months
Thrombotic VA	24	5	4	Lung, bone	Shoulder disarticulation, CMT	NR	1 Month

access was the AVF (95.6%). Of the 20 patients, 13 (65%) had undergone deceased donor KT, 5 (25%) had undergone living related KT, and 2 (10%) had not undergone KT. Of the 23 kidney grafts, 20 (93%) were functional. Only five patients had received a second KT.

The pathophysiology of angiosarcoma at an AVF after KT remains unclear. The possible mechanisms include the following[11]: (1) impairment of local immune response caused by the increased lymphatic workload and decreased lymphatic drainage from the increased venous pressure at the AVF site[24]; (2) turbulent blood flow in the AVF associated with the increased production of reactive oxygen species and matrix metalloproteinase-9, which results in a proliferative response and leads to vascular remodeling[25]; and (3) a large hypoxic area of the tumor caused by rapid cell proliferation exceeding the capacity of the oxygen supply. These mechanisms induce T-cell suppression, which leads to a diminished immune response.[26] Furthermore, KT patients have a three- to fivefold increased risk of any cancer.[27] Also, prolonged immunosuppression therapy has been associated with an increased cancer risk.[28]

According to our review, the most common clinical presentations were nonspecific pain (58.3%), swelling (29.2%), and a mass (29.2%). The initial diagnosis for pain at the AVF included a thrombosed AVF (44%), aneurysm (25%), infection (25%), and cancer (6.3%). Therefore, conservative treatment, including antibiotics and ligation without biopsy, was commonly implemented. These treatments usually led to a delayed diagnosis. The median interval from presentation to diagnosis was 10.8 weeks (range, 4-12 weeks). Thus, a high index of suspicion for angiosarcoma is required.

In our patient who had undergone brachial arterial embolectomy, we sent the clot and tissue for histopathologic examination. Cytologic examination of the blood clot showed atypical cells, and pathologic examination of the tissue showed epithelioid angiosarcoma. Pathologic examination of the shoulder disarticulation showed extensive tumor invasion; however, the origin of the tumor could not be identified. It might be that the origin of angiosarcoma came from the arterial side. Thus, we believe that any patient who has undergone KT and presents with pain or aneurysmal changes should have the blood clot from the aneurysm of an AVF examined cytologically and the tissue examined pathologically.

The tumor histologic features in angiosarcoma have varied widely from well to poorly differentiated. Abnormal, pleomorphic, and malignant endothelium are hallmarks of angiosarcoma. The cell appearance can be rounded, polygonal, fusiform, and, possibly, epithelioid.[2] Epithelioid angiosarcoma is a variant of angiosarcoma composed of neoplastic cells with an epithelioid appearance. The most sensitive and specific marker for endothelial differentiation is CD31, which indicates platelet–endothelial cell adhesion molecule expression.[29] From our review, all the patients were positive for CD31 expression. For our patient, the pathologic findings showed that the tumor was composed of high-grade pleomorphic epithelioid cells with positivity to ERG using immunohistochemistry and other vascular markers such as FLI1, CD31, and CD34.

Angiosarcoma behaves aggressively, recurs locally, and spreads widely. Moreover, it has a high rate of lymph node and systemic metastases. Our review showed that nearly one half of the patients had had metastases at diagnosis. Also, 85% of the patients had experienced recurrence, with 7.75% in the bone and 76.95% in the lungs. The mean survival period was 24.2 $\pm$ 14.4 weeks. Therefore, the tumor-related death rate is considerably high.

The ideal primary treatment is radical surgery with complete resection. However, difficulties ensue with wide excision owing to the tumor size and location, which will result in functional impairment and difficulty in wound reconstruction. Because of the high local recurrence rate, adjuvant radiotherapy has been recommended. Angiosarcoma spreads mainly through hematogenously, and the most common metastatic site has been the lungs. Chemotherapy is the primary option for metastatic angiosarcoma. Biologic therapies, in particular, antiangiogenic therapies, are considered interesting options for angiosarcoma-specific treatment.

CONCLUSION

Angiosarcoma at vascular access sites can occur in both KT and non-KT patients. Because the presentation is not specific, a high index of suspicion is required to prevent a delayed diagnosis. Angiosarcoma has aggressive behavior and high local recurrence and metastatic rates. The primary treatment of angiosarcoma is radical surgery with complete resection. Chemotherapy is the primary treatment of metastatic angiosarcoma, with radiotherapy for local recurrence prevention. However, despite multimodal treatment, the prognosis of these patients has remained poor.

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