

Angiosarcoma at the site of nonfunctioning arteriovenous fistula in a kidney transplant recipient

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Angiosarcoma is a rare malignant neoplasm of the endothelial cells of blood vessels or lymphatics. We report a case of a 46-year-old male patient with a kidney transplant who developed epithelioid angiosarcoma at the site of a nonfunctioning arteriovenous fistula in the antecubital fossa 3 years after renal transplantation. The patient had skin, soft tissue, and bone metastasis on presentation. He died of systemic metastasis with respiratory failure. (J Vasc Surg Cases 2016;2:53-5.)

Angiosarcoma, a rare malignant neoplasm of the endothelial cells of blood vessels or lymphatics, accounts for <2% of all sarcomas with a predilection to soft tissues and skin. Epithelioid angiosarcoma is a subtype of angiosarcoma in which the malignant endothelial cells are epithelioid in appearance. Renal transplant recipients may rarely develop angiosarcoma at the site of arteriovenous (AV) fistulas.¹⁻¹³ The survival of these patients is usually very poor. We report a case of an epithelioid angiosarcoma at the site of a nonfunctioning AV fistula in a kidney transplant recipient. Because of the rarity of the disease, clinicians should be aware of this malignant neoplasm as an early diagnosis and intervention may affect the patient's outcome. A written consent was obtained from the patient for photography and publication.

CASE REPORT

A 46-year-old man with a background history of hypertension and atrial fibrillation receiving chronic anticoagulation developed end-stage renal disease of unknown cause and was started on hemodialysis through a right-sided brachiocephalic AV fistula. Three years before presentation to our center, he underwent a living related kidney transplantation from his son. He had been maintained on mycophenolate mofetil, tacrolimus, and prednisone. In November 2013, he presented to our hospital with pain and swelling of the right upper extremity. On examination, there was a 3- × 2-cm irregular, rubbery, maroon lesion over the right antecubital fossa close to

the site of the AV anastomosis (Fig 1, A). There was no bruit or thrill appreciated over the fistula. There was swelling of the right forearm extending from the elbow all the way down to the fingers. He had several bluish to black plaques and nodules over the right fingers and palm of variable sizes up to 1 cm in diameter (Fig 1, B). Plain films of the right upper extremity showed extensive lytic lesions involving all the bones up to the distal humerus (Fig 2). Magnetic resonance imaging scan showed the bone destruction at the area of the main mass in the antecubital fossa and extending distally down to the radius, ulna, and hand bones. The laboratory tests revealed normal kidney allograft function with a serum creatinine concentration of 1.0 mg/dL (0.4-1.4). Serum calcium concentration was 8.2 mg/dL (8.7-10.2), serum intact parathyroid hormone level was 51.6 pg/mL (14-72), and parathyroid hormone-related peptide level was 0.3 pmol/L (<2.0). The result of a serum test for human herpesvirus 8 viral DNA by polymerase chain reaction was negative.

A biopsy of one of the palmar lesions showed superficial and deep dermal proliferation of anastomosing vascular channels lined by atypical cells with large hyperchromatic nuclei with frequent mitoses. The vascular channels were surrounded by abundant hemorrhage and extravasated red blood cells as well as hemosiderin deposition. The infiltrating tumor cells showed areas of epithelioid cells and other areas of spindle cells, some with open cytoplasmic lumina. Perineural invasion was noted. The tumor extended to the subcutaneous fat and fascia (Fig 3, A).

Biopsy from the AV fistula site showed dilated thrombosed venous blood vessels surrounded by cells similar to those seen in the former biopsy with hemorrhage, necrosis, and vascular invasion (Fig 3, B).

Immunohistochemical staining with CD31, AE2/AE3 keratin, CK7, and vimentin was positive, whereas staining with melan-A, S100, HMB-45, CD34, CK20, and actin was negative. These pathologic changes confirmed the diagnosis of epithelioid angiosarcoma.

Staging workup with computed tomography showed metastatic disease in both lungs represented by multiple lesions. Despite the pulmonary involvement, the patient had no pulmonary symptoms.

After the diagnosis was made, the immunosuppressive regimen was modified to sirolimus and prednisone, and he was started on systemic paclitaxel. Restaging with computed tomography scan of the chest after four cycles showed almost complete resolution of the pulmonary lesions. Three of the hand lesions dried up and fell

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Fig 1. **A**, Right antecubital fossa showing swelling with purple discoloration of the skin at the site of the arteriovenous (AV) fistula. **B**, Multiple bluish fungating nodules and plaques on the palmar side of the right hand and right-hand fingers.

off eventually. There was minor regression of the lesion in the antecubital fossa. Paclitaxel was replaced by sunitinib after five cycles because of toxicity and lack of further response. The response of the lung lesions was excellent; however, he continued to have severe pain in the extremity with further weakness, rendering the limb completely nonfunctional. Despite our attempt to control his pain with local and systemic measures, it continued to be a major problem, leading to poor quality of life. In March 2014, he underwent an above-elbow amputation for intractable pain. Unfortunately, 2 months after the amputation, he developed progression of his metastatic pulmonary disease and succumbed to respiratory failure 6 months after diagnosis.

DISCUSSION

Our patient developed angiosarcoma at the site of an old, nonfunctioning AV fistula and presented with systemic metastatic disease involving the lungs, most likely as the result of systemic hematogenous spread. The presentation of the multiple scattered lesions in the skin, subcutaneous tissue, and bones of the forearm most likely represented hematogenous spread downstream from the AV fistula site.

Angiosarcoma is a malignant neoplasm of the endothelial cells of blood vessels or lymphatics accounting for <2% of all sarcomas with a predilection to soft tissue or skin; 50% of angiosarcomas arise in the head and neck region. AV fistulas are the sites of development of angiosarcomas in renal transplant patients.¹⁻¹³ Angiosarcoma also developed at the site of AV fistulas of hemodialysis patients who did not



Fig 2. Plain film of the right upper extremity showing extensive lytic lesions.

undergo renal transplantation.^{14,15} The malignant neoplasm developed between 3 and 20 years after the creation of the fistulas.¹⁻¹⁵

Epithelioid angiosarcoma is a subtype of angiosarcoma in which almost all malignant endothelial cells are epithelioid in appearance. Fifty-four percent of the angiosarcomas arising in dialysis AV fistulas had the histologic features of epithelioid angiosarcomas.¹⁻⁸

On histopathologic evaluation, the tumor presents as multinodular masses with cystic degeneration, hemorrhage, and scarce or absent vascular spaces. The malignant epithelioid endothelial cells are the hallmark of the epithelioid angiosarcomas. Mitoses, nuclear atypia, and necrosis are common features. The tumor cells are immunoreactive for vimentin and for the vascular markers factor VIII, CD31, and CD34 in 40% to 100% of cases. They are negative for S100 and melan-A. The histologic differential diagnosis includes malignant peripheral nerve sheath tumor, epithelioid sarcoma, malignant melanoma, anaplastic large cell lymphoma, and epithelioid hemangioendothelioma.¹⁶

The aggressive nature of the disease is reflected in the high mortality rate in a period of 7 to 18 months. Systemic chemotherapy is the only proven option that may prolong survival in patients with metastatic angiosarcomas. These tumors are found to be sensitive to taxanes in few retrospective case series.^{1,17}

Several theories have explained the development of angiosarcomas at the site of AV fistulas. Proliferation of

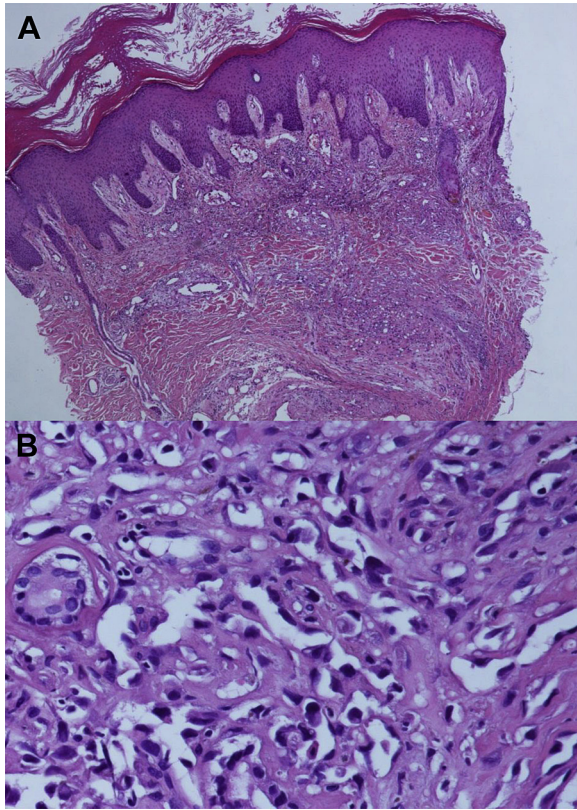


Fig 3. **A**, Superficial and deep dermal proliferation of anastomosing vascular channels surrounded by abundant hemorrhage and extravasated red blood cells as well as hemosiderin deposition (hematoxylin and eosin $\times 20$). **B**, The infiltrating tumor cells showing areas of solid epithelioid cells and other areas of spindle cells, some with open cytoplasmic lumina (hematoxylin and eosin $\times 100$).

the endothelial cells within the fistula may be triggered by the shear forces and oscillatory flow that upregulates the vascular adhesion molecules, which stimulates endothelial cell proliferation.¹⁸ Oscillatory flows were also found to trigger the overproduction of matrix metalloproteinase 9, leading to vascular remodeling and increased metastatic potential in soft tissue sarcomas.¹⁹

Immune suppression acts as an additive factor by suppressing the immune surveillance, enhancing the action of oncogenic viruses and facilitating production of vascular endothelial growth factors that promote angiogenesis.²⁰ Local ischemia at the site of an intact AV fistula may enhance the local toxic effect of immunosuppression. In addition, increased venous pressure at the AV fistula leads to reduction of lymphatic drainage, which may lead to impairment of local immune surveillance.⁶ Recently, *MYC* gene amplification was found in an angiosarcoma arising from a clotted AV graft site.¹³

CONCLUSIONS

Angiosarcomas arising at AV fistulas are very rare tumors and may present with unusual manifestation. Regular surveillance of AV fistulas in renal transplant recipients should be

part of the routine physical examination. Any suspicious lesion at the site of AV fistulas should alert the clinician to perform skin biopsy to make the diagnosis in a timely manner.

REFERENCES

1. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. *Lancet Oncol* 2010;11:983-91.
2. Conlon PJ, Daly T, Doyle G, Carmody M. Angiosarcoma at the site of a ligated arteriovenous fistula in a renal transplant recipient. *Nephrol Dial Transplant* 1993;8:259-62.
3. Parrott NR, Scott PD, Freemont AJ, Johnson RW. Angiosarcoma in an arteriovenous fistula following successful renal transplantation—a case report. *Transplantation* 1993;55:676-7.
4. Bessis D, Sotto A, Roubert P, Chabrier PE, Mourad G, Guilhou J. Endothelin-secreting angiosarcoma occurring at the site of an arteriovenous fistula for haemodialysis in a renal transplant recipient. *Br J Dermatol* 1998;138:361-3.
5. Wehrli BM, Janzen DL, Shokeir O, Masri BA, Byrne SK, O'Connell JX. Epithelioid angiosarcoma arising in a surgically constructed arteriovenous fistula: a rare complication of chronic immunosuppression in the setting of renal transplantation. *Am J Surg Pathol* 1998;22:1154-9.
6. Webster P, Wujanto L, Fisher C, Walker M, Ramakrishnan R, Naresh K, et al. Malignancies confined to disused arteriovenous fistulae in renal transplant patients: an important differential diagnosis. *Am J Nephrol* 2011;34:4-8.
7. Farag R, Schulak JA, Abdul-Karim FW, Wasman JK. Angiosarcoma arising in an arteriovenous fistula site in a renal transplant patient: a case report and literature review. *Clin Nephrol* 2005;63:408-12.
8. Qureshi YA, Strauss DC, Thway K, Fisher C, Thomas JM. Angiosarcoma developing in a non-functioning arteriovenous fistula post-renal transplant. *J Surg Oncol* 2010;101:520-3.
9. Byers RJ, McMahon RF, Freemont AJ, Parrott NR, Newstead CG. Epithelioid angiosarcoma arising in an arteriovenous fistula. *Histopathology* 1992;21:87-9.
10. Byers RJ, McMahon RF, Freemont AJ, Parrott NR, Newstead CS. Angiosarcoma at the site of a ligated arteriovenous fistula in a renal transplant recipient. *Nephrol Dial Transplant* 1994;9:112.
11. Medioni LD, Costes V, Leray H, Chammas M, Durand L, Baldet P. Angiosarcoma arising from an arterio-venous fistula in a renal transplant recipient. An unusual complication. *Ann Pathol* 1996;16:200-2.
12. Ahmed I, Hamacher KL. Angiosarcoma in a chronically immunosuppressed renal transplant recipient: report of a case and review of the literature. *Am J Dermatopathol* 2002;24:330-5.
13. Paral KM, Raca G, Krausz T. *Myc* amplification in angiosarcoma arising from an arteriovenous graft site. *Case Rep Pathol* 2015;2015:537297.
14. Chanyaputhipong J, Hock DL, Sebastian MG. Disseminated angiosarcoma of the dialysis fistula in 2 patients without kidney transplants. *Am J Kidney Dis* 2011;57:917-20.
15. Demey K, Reyns LM, Schepers S. Angiosarcoma arising in an arteriovenous fistula in a patient without kidney transplant. *Acta Chir Belg* 2014;114:75-8.
16. Fletcher CD, Beham A, Bekir S, Clarke AM, Marley NJ. Epithelioid angiosarcoma of deep soft tissue: a distinctive tumor readily mistaken for an epithelial neoplasm. *Am J Surg Pathol* 1991;15:915-24.
17. Abraham JA, Hornicek FJ, Kaufman AM, Harmon DC, Springfield DS, Raskin KA, et al. Treatment and outcome of 82 patients with angiosarcoma. *Ann Surg Oncol* 2007;14:1953-67.
18. Chappell DC, Varner SE, Nerem RM, Medford RM, Alexander RW. Oscillatory shear stress stimulates adhesion molecule expression in cultured human endothelium. *Circ Res* 1998;82:532-9.
19. Benassi MS, Gamberi G, Magagnoli G, Molendini L, Ragazzini P, Merli M, et al. Metalloproteinase expression and prognosis in soft tissue sarcomas. *Ann Oncol* 2001;12:75-80.
20. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. *Transplantation* 2004;77:1777-82.

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