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

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Angiosarcoma is a rarely 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.1-4 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 forearm 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 forearm. He presented to our hospital with pain and swelling of the right forearm. There was swelling of the right forearm extending from the elbow all the way down to the fingers. He had several bluish 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 the site of the AV anastomosis (Fig 1, A). There was no bruise 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 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.

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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. Angiosarcoma also developed at the site of AV fistulas of hemodialysis patients who did not undergo renal transplantation. The malignant neoplasm developed between 3 and 20 years after the creation of the fistulas.

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.

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.

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.

Several theories have explained the development of angiosarcomas at the site of AV fistulas. Proliferation of...
Angiosarcomas arising from a clotted AV graft site.13

Some with open cytoplasmic lumina (hematoxylin and eosin showing areas of solid epithelioid cells and other areas of spindle cells, MYC gene amplification was found in an angiosarcoma arising in an arteriovenous fistula in a renal transplant recipient. 

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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.

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