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. It is a rare complication of arteriovenous fistulas. 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. 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

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Fig 1. Thrombosis of cephalic vein found intraoperatively. After removal of the clot, no mass and no abnormality was found in the cephalic vein.
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 (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 |
|---------------------------------------|-----------------|-----------------|------------|-----------------|-----|--------------|
| Byers et al. 1992, Parrott et al. 1993 | M, 36           | RC-AVF          | Functional | DDKT            | Azathioprine, cyclosporine, prednisolone | Swelling |
| Wehrli et al. 1998                    | M, 64           | RC-AVF          | Thrombosed | DDKT            | Azathioprine, cyclosporine, prednisolone | Swelling, pain |
| Alvarez et al. 2013                   | F, 47           | AVF             | Thrombosed | DDKT            | Cyclosporine, MMF | Nail-bed splinter lesions, pain, hand retraction |
| Conlon et al. 1993                    | M, 40           | BC-AVF          | Thrombosed (ligated aneurysm) | First DDKT Second DDKT | Treated for rejection | Pain and swelling |
| Keane et al. 1993                     | M, 11           | AVF             | Thrombosed (ligated aneurysm) | First DDKT Second DDKT | Treated for rejection | Mass, induration arising from AVF |
| Bessis et al. 1998                    | M, 61           | BC-AVF          | Thrombosed | DDKT            | Azathioprine, cyclosporine, prednisolone | Pain, swelling, tenderness |
| Farag et al. 2005                     | M, 26           | AVF             | Thrombosed (ligated aneurysm) | First DDKT plus PT Second DDKT | NA | Mass |
| Webster et al. 2011                   | M, 59           | BC-AVF          | Thrombosed | LRKT            | Rituximab daclizumab, tacrolimus | Pain, swelling |
| Webster et al. 2011                   | F, 41           | BC-AVF          | Thrombosed | LRKT            | Alemtuzumab, prednisolone, tacrolimus | Pain |
| Webster et al. 2011                   | M, 44           | BC-AVF          | NR         | DDKT            | Prednisolone, tacrolimus, MMF | Pain, mass |
| Derney et al. 2014                    | M, 80           | AVF             | Functional | No KT           | No KT | No KT | Pain, swelling |
| Roy et al. 2018                       | M, 63           | AVF             | Thrombosed (ligated aneurysm) | KT             | MMF, tacrolimus | Mass |
| Alidaabib et al. 2016                 | M, 46           | BC-AVF          | Thrombosed | LRKT            | MMF, tacrolimus, prednisolone | Pain, swelling |
| Qureshi et al. 2010                   | M, 48           | AVF             | Functional | First KT Second LRKT | NA | Prednisolone, MMF, rituximab, IVIG, tacrolimus | Pain |
| Costa et al. 2017                     | F, 70           | BC-AVF          | Thrombosed (ligated aneurysm) | KT             | Tacrolimus, MMF, prednisolone | Dyspnea |
| Chanyaputhipong et al. 2011           | M, 57           | RC-AVF          | Thrombosed (ligated aneurysm) | DDKT            | None | Pain, mass |
| Chanyaputhipong et al. 2011           | M, 63           | BC-AVF          | Thrombosed (aneurysm) | No KT           | No KT | No KT | Pain, mass with bleeding |
| Gale et al. 2017                      | M, 44           | RC-AVF          | Functional | DDKT            | NR | NR | Necrotic fingers |
| Kakisis et al. 2019                   | M, 60           | RC-AVF          | Thrombosed | DDKT            | Prednisolone, cyclosporine, MMF | Bleeding from AVF |
| Jansen et al. 2013                    | M, 58           | NR              | NR         | DDKT            | Yes (NR) | Nodule, pain, hand dysfunction |
| Klemens et al. 2016                   | M, 71           | AVF             | NR         | LRKT            | Alemtuzumab, tacrolimus, MMF | Edema, erythema, non-PTH hypercalcemia |
| Andre et al. 2012                     | M, 62           | AVF             | Functional | First KT Second KT | NR | Prednisolone, tacrolimus, MMF | Nonhealed wound at AVF removal site |
| Figueiredo et al. 2019                 | F, 55           | AVG             | Thrombosed (ligated aneurysm) | KT             | Tacrolimus, prednisolone, MMF | Mass |
| Present case, 2020                    | M, 58           | BC-AVF          | Thrombosed | LRKT            | 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.
| Initial Dx | Interval to Dx (weeks) | Interval (years) from VA to AS | Interval to AS | Metastasis before Tx | Tx | Recurrence | Survival |
|------------|------------------------|-------------------------------|---------------|----------------------|----|------------|----------|
| 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 | NR | NR | NR | NR | NR | NR |
| Cancer | NR | NR | NR | No | AVF resection, RT, CMT | 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: (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; (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; 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. Moreover, KT patients have a three- to fivefold increased risk of any cancer. Also, prolonged immunosuppression therapy has been associated with an increased cancer risk.

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 (63%). 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. 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. 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 ± 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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REFERENCES
1. Rouhani P, Fletcher CD, Devesa SS, Toro Jr. Cutaneous soft tissue sarcoma incidence patterns in the U.S.: an analysis of 12,114 cases. Cancer 2008;113:616-27.
2. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. Lancet Oncol 2010;11:983-91.
3. Álvarez CL, García-Cosmes P, Fraile P, Del Carmen Martínez S, Tabernero JM. Angiosarcoma in vascular access after transplantation. Clin Kidney J 2013;6:549-50.
4. Byers RJ, McMahon RF, Freemont AJ, Parrott NR, Newstead CG. Epithelioid angiosarcoma arising in an arteriovenous fistula. Histopathology 1992;21:87-9.
5. 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.

6. 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.

7. 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.

8. Keane MM, Carney DN. Angiosarcoma arising from a dialysis arteriovenous fistula site of a ligated arteriovenous fistula. J Urol 1993;149:364-5.

9. Bessis D, Sotto A, Roubert P, Chabrier PE, Mourad G, Guilhou JJ. 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.

10. Farag R, Schulak JA, Abdul-Karim FW, Wasman JK. Angiosarcoma arising in an arteriovenous fistula in a renal transplant patient: a case report and literature review. Clin Nephrol 2005;63:408-12.

11. Webster P, Wujanto L, Fisher C, Walker M, Ramakrishnan R, Watters K. Angiosarcoma in an arteriovenous site of a nonfunctioning arteriovenous fistula. J Vasc Surg 2004;40:520-3.

12. 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.

13. Roy SF, Ghazawi FM, Alsarheed A, Lach KD, Watters K, O’Brien E. Angiosarcoma arising within a nonfunctioning arteriovenous fistula. Int J Dermatol 2018;57:1513-5.

14. Aidaabiil RA, Alkhunaizi AM, Al-Dawarsi NA, Dawamneh MF, Rabah R. Angiosarcoma at the site of nonfunctioning arteriovenous fistula in a kidney transplant recipient. J Vasc Surg Cases Innov Tech 2016;2:53-5.

15. 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.

16. Costa BNL, Rivera CF, Rodriguez MC, Romero TH, Muniz AL, Hermida TF, et al. Angiosarcoma developing in an arteriovenous fistula after kidney transplantation. Case Rep Transplant 2017;2017:2426859.

17. Chanyaphithipong 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.

18. Gale AL, Marco RAW, Liberman SR, Zavlin D, Echo A. Case report: angiosarcoma in the upper extremity related to a nonfunctioning arteriovenous fistula. Hand (N Y) 2017;12:NP132-N135.

19. Kakisis JD, Antonopoulos C, Moulakakis K, Taliadoros A, Rontogianni D, Brountzos E, et al. Angiosarcoma of a thrombosed arteriovenous fistula in a renal transplant recipient. Ann Vasc Surg 2019;56:357.e1-4.

20. Jansen R, McHargue C. Angiosarcoma in a condensed sporotrichoid distribution arising at an arteriovenous fistula site: case report. J Am Acad Dermatol 2013;68:AB157.

21. Klemm M, Bermudez C, Gray J. Angiosarcoma in an unused arteriovenous fistula of a renal transplant patient. Am J Kidney Dis 2016;67:A63.

22. Andre J, Parsikia A, Minimo C, Khanmoradi K, Campos S, Zaki R, et al. Soft tissue sarcoma at a dialysis access site in a transplant recipient. Exp Clin Transplant 2012;10:410-5.

23. Figueiredo AC, Leal R, Rodrigues L, Romãozinho C, Escada L, Sá H, et al. Arteriovenous graft in kidney transplant patients: look out for the rare but fearsome angiosarcoma. J Vasc Access 2020;21:1049-52.

24. Bordea C, Cortina-Borja M, Wojnarowska F, Morris PJ. Distribution of upper limb skin cancers in relation to arteriovenous fistula side in renal transplant recipients. Transplantation 2001;71:143-5.

25. Castier Y, Ramkhelawon B, Riou S, Tedgui A, Lehoux S. Role of NF-kappaB in flow-induced vascular remodeling. Antioxid Redox Signal 2009;11:1641-9.

26. Doedens AL, Stockmann C, Rubinstein MP, Liao D, Zhang N, DeNardo DG, et al. Macrophage expression of hypoxia-inducible factor-1 alpha suppresses T-cell function and promotes tumor progression. Cancer Res 2010;70:7465-75.

27. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370:529-67.

28. Wong G, Chapman JR. Cancers after renal transplantation. Transplant Rev (Orlando) 2008;22:141-9.

29. Ohsawa M, Naka N, Tomita Y, Kawamori D, Kanno H, Aozasa K. Use of immunohistochemical procedures in diagnosing angiosarcoma: evaluation of 98 cases. Cancer 1995;75:2867-74.

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