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CASE REPORT

Malignant hemangiosarcoma in a renal allograft: diagnostic difficulties and clinical course after nephrectomy and immunostimulation

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The authors of this manuscript have no conflict of interest to disclose.

*Dedicated to the memory of Majida Tufail Hanel who sadly deceased on November 22, 2013.

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Summary

Hemangiosarcomas are rare tumors of endothelial cell origin. To date, only 20 cases of hemangiosarcoma have been described after renal transplantation, occurring mostly in the skin or in a dialysis fistula. We report a primary metastasizing hemangiosarcoma arising from a renal allograft. The patient was treated with transplant nephrectomy, discontinuation of immunosuppression, and immunostimulation with pegylated interferon-α-2a and has now been in complete remission for 3 years.

Background

Hemangiosarcomas are rare malignant soft tissue tumors of endothelial cell origin representing 2% of all sarcomas [1]. Most hemangiosarcomas develop in the absence of precursor lesions, and some cases have been reported to arise from dialysis fistulas [2]. Spreading occurs hematogenously, most commonly to the lungs, liver, bone, soft tissue structures, and lymph nodes [2]. Hemangiosarcomas have rarely been described after renal transplantation [1,3–5]. We present a case of primary metastasizing hemangiosarcoma arising from a transplant kidney that was successfully treated by transplant nephrectomy, immunosuppression discontinuation, and immunostimulation with pegylated interferon-α 2a.

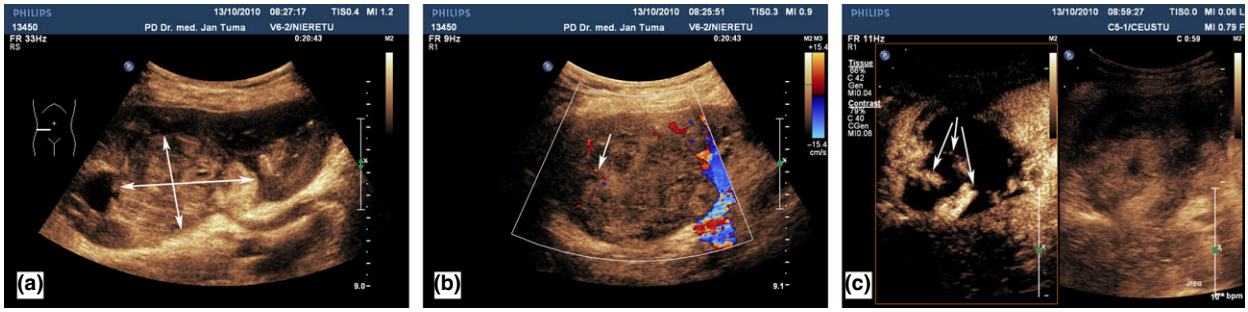

Figure 1 (a–c) Ultrasound images. (a) Hyperechoic inhomogeneous lesion 5.1 × 6.9 × 6.3 cm. (b) Color Doppler showing only minimal perfusion on the border of the lesion (arrow). (c) Contrast-enhanced ultrasound (CEUS) showing more perfused parts of the tumor (arrows).

Case report

A 63-year-old patient from Serbia with end-stage renal failure due to suspected Balkan nephropathy received a living donor transplant from his HLA-identical, dizygotic twin brother in 1987. In 2004, nephrectomy of the left kidney was performed because of severe urothelial dysplasia. Immunosuppressed with relatively low doses of cyclosporine alone (cyclosporine trough levels 60–100 ng/ml), graft function remained stable with a serum creatinine around 150–200 μM until June 2006, when a sudden increase to 300 μM was noted. Ultrasound of the transplant kidney then was unremarkable. A renal biopsy in June 2006 showed calcineurin-related damage, which prompted cyclosporine dose minimization and addition of azathioprine to the regimen. Concurrently, the patient complained of bloody sputum occurring each morning. A workup including sputum analysis, chest X-ray, pulmonary lung function tests, and bronchoscopy in June 2006 did not reveal the source of bleeding; however, hemoptysis continued over the next months, fortunately without major bleeding.

After changing the immunosuppressive regime, creatinine levels dropped to 250 μM, but rose again to 350 μM in 09/2010. Renal ultrasound then showed a hyperechogenic 5.1 × 6.9 × 6.3 cm lesion with minimal perfusion by color duplex and contrast-enhanced ultrasound, interpreted as a nonmalignant lesion (Fig. 1). A contrast-enhanced abdominal CT scan confirmed a 7.6 × 5.9 × 5.4 cm, partly nodular enhancing mass in the transplant kidney 10/2010 (Fig. 2), compatible with renal cell cancer. To clarify this discrepancy, a renal biopsy of the mass was performed in 10/2010, which contained sparse infiltrates of atypical cells adjacent to intact renal parenchyma and a large area of tumor necrosis. The tumor cells showed a partly epithelioid, partly spindle cell morphology with high-grade nuclear atypia. Immunohistochemistry was positive for CD31 (Fig. 3d), CD34, and vimentin. Tests for cytokeratins, lymphoma markers, and human herpes virus

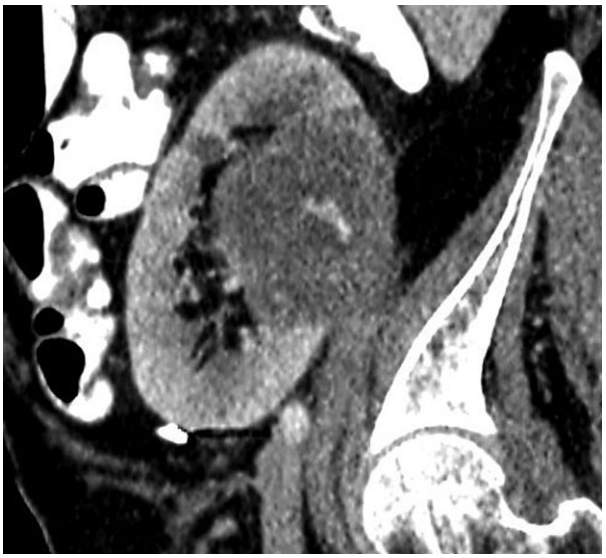

Figure 2 Contrast-enhanced abdominal CT scan showing a 7.6 × 5.9 × 5.4 cm mass with partially nodular aspect in the transplant kidney in 10/2011.

8 returned negative. A diagnosis of high-grade sarcoma, most likely a hemangiosarcoma, was assigned.

Thereupon, transplant nephrectomy was performed in 11/2010 and hemodialysis treatment started. Macroscopically, the tumor had a diameter of 60 × 50 × 40 mm and contained widespread hemorrhagic necrosis (Fig. 3e). The viable tumor showed the same features seen in the biopsy with a high rate of proliferation (Fig. 3f), resulting in the final diagnosis of a high-grade hemangiosarcoma. There was no spread to the resected local lymph nodes.

Immunosuppression was stopped the day after nephrectomy. A contrast-enhanced staging CT of the chest 8 days postoperative showed left-sided ground-glass infiltrates (Fig. 4a), an area in the left lingula with a nodular aspect (Fig. 5a), and several right-sided subpleural nodules. Considering the unremarkable pulmonary workup that had

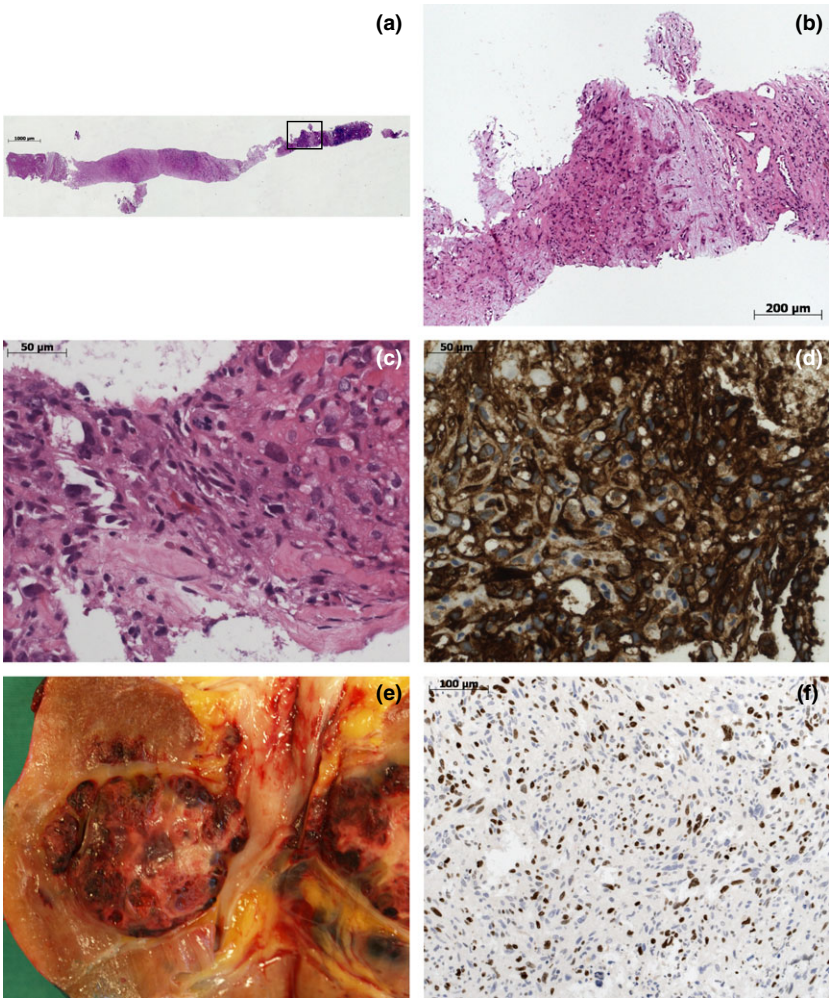

Figure 3 (a–d) Renal allograft biopsy. (a) Low-power magnification shows widespread necrosis (left-hand side), a small rim of viable tumor cells (box), and adjacent renal parenchyma (right-hand side) (b, c). Higher magnification reveals a high-grade tumor with immunohistochemical CD31 expression (d), consistent with an angiosarcoma in the renal allograft. (e) Macroscopic section through the explanted transplant kidney demonstrates a mostly hemorrhagic tumor within the parenchyma. (f) A high number of sarcoma nuclei stain for the proliferation marker Mib-1, indicating a high proliferation rate. (a–c) H&E stain. (d, f) Immunohistochemistry.

excluded alternative causes of hemoptysis 3 months earlier, bleeding from intrapulmonary metastases of this vascular tumor was assumed, and in 01/2011, a 16-week course of peginterferon-α 2a (135 µg weekly) was started in an attempt to enhance the immunologic antitumor response. Over the course of this therapy, hemoptysis stopped. A follow-up CT scan in 08/2011 showed progressive normalization of the left lung (Fig. 4b), including complete disappearance of the nodule in the left lingula (Fig. 5b). The right-sided nodules remained stable in size, showed no uptake by PET CT scan, and were shown to contain only scar tissue in a thoracoscopic wedge biopsy performed 9 days after the CT scan. After 3 years of regular CT scan follow-up, the patient has remained in complete remission and clinically asymptomatic.

The donor was examined after diagnosis of the hemangiosarcoma. There were no clinical signs of malignancy and no history of any cancer.

Discussion

Hemangiosarcomas are rare tumors accounting for <0.2 ‰ of all cancers in the United States. They occur mostly in skin and superficial soft tissue [2]. A current PubMed search using the terms "renal" or "kidney" and "angiosarcoma" revealed 34 case reports of primary hemangiosarcoma. Twenty of these cases occurred after renal transplantation, most of the time either in the skin [3,4], or associated with an arteriovenous dialysis fistula [1,3,6,7]. Only three reported hemangiosarcomas

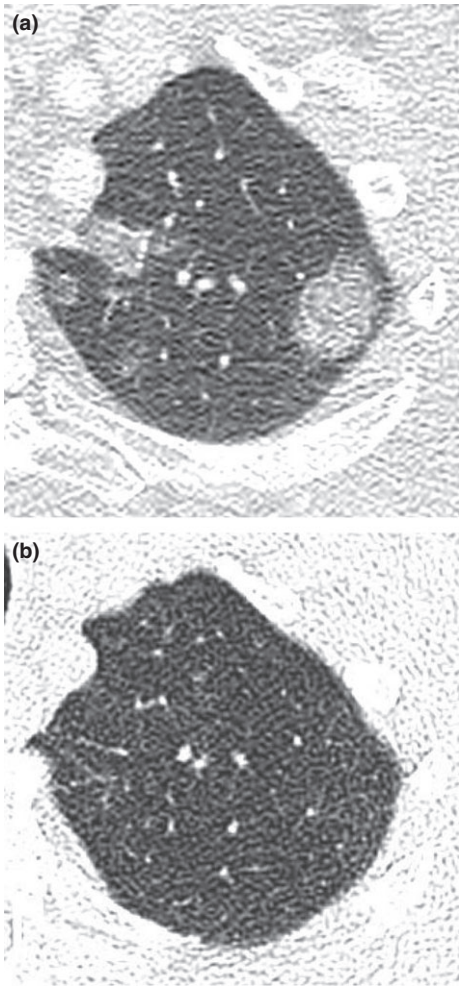

Figure 4 CT scan with ground-glass infiltrate in the left-sided upper pulmonary lobe in 11/2010 (a) and successive normalization after therapy in 07/2011 (b).

involved a kidney allograft [5,8]; in two, it remains unclear whether they originated from the allograft or from the tissue adjacent to it. One case report describes the donor tumor transmission to renal transplant recipients [5]. In the present case, the extremely rapid tumor growth 23 years after transplantation and the excellent health of the kidney's living donor 23 years after donation make donor-to-recipient transmission extremely unlikely. We consider it safe to assume that the tumor developed *de novo* in the immunosuppressed recipient, making this the first report of a hemangiosarcoma arising *de novo* from a renal allograft.

In the present patient, Balkan nephropathy was suspected due to the patient's origin, the clinical picture, and the history of urothelial dysplasia. Patients with Balkan nephropathy are at known risk of urothelial cancer, but no association with vascular tumors such as the present case's hemangiosarcoma has been reported [9].

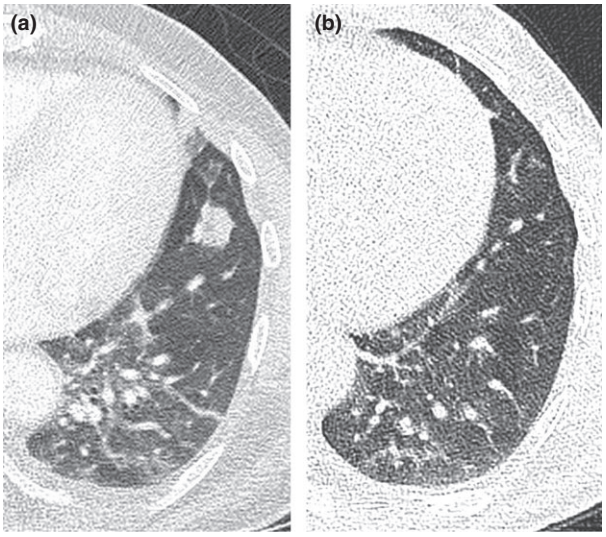

Figure 5 CT scan showing a left-sided nodule in the left lingula in 11/2010 (a) and normalization after therapy in 07/2011 (b).

Imaging findings in hemangiosarcomas, including contrast-enhanced renal ultrasound, may vary, so that it may be challenging to make the correct diagnosis. In animal models, renal hemangiosarcomas—unlike hemangiomas—did not present as vascularized, rapidly contrast-enhancing masses, but rather as nonenhancing nodules during the early arterial and late corticomedullary phase [10]. In our case, this presentation was initially misinterpreted as being indicative of a nonmalignant lesion. The discrepancy was later explained by the histologic finding of widespread tumor necrosis. Sarcomas may also be indistinguishable from the more common renal cell carcinoma in CT scans, because contrast enhancement may be heterogeneous in both [11]. Therefore, when in doubt, a biopsy of the lesion for histologic evaluation should be obtained.

There are no randomized trials available to guide treatment for hemangiosarcoma [2]. Based on a few prospective studies and case series, complete resection followed by radiotherapy is considered the treatment of choice in localized disease with cure rates of 30–60% [2,4,12]. In disseminated disease, cytotoxic chemotherapies have been tried, but response rates remained poor [13,14], so that to date, no standard treatment regimen has been established [2]. As interferon-α had been successfully used in the treatment malignancies such as renal cell cancer, neuroendocrine tumors, skin melanomas, and certain types of leukemia and lymphomas [15], immunotherapy of hemangiosarcoma with interleukin-2 was studied in a SCID mouse model and found to significantly inhibit tumor growth [16]. In humans, treatment for scalp hemangiosarcoma with interleukin-2 combined with radiotherapy

was reported in a retrospective study of 20 patients, which resulted in prolonged survival when compared to radiotherapy alone (40 vs. 15–18 months) [17]. In other case reports, scalp hemangiosarcoma was treated with interferon-α and either chemotherapy or radiotherapy, resulting in complete clinical remission over a follow-up of up to 2 years [18,19].

The reported post-transplant hemangiosarcomas were primarily treated with excision or amputation, mostly followed by irradiation, with or without chemotherapy using anthracyclines and taxanes [1,4]. Unlike in the present case, immunosuppression was continued with the exception of one patient [5]. With continued immunosuppression, outcome was extremely poor with 100% mortality within 1–12 months after diagnosis [1,4]. In contrast, remissions in response to a reduction or cessation of immunosuppression have been reported to occur in approximately sixty percent of post-transplant Kaposi's sarcoma cases, another tumor of vascular origin arising in the context of immunosuppression. Administration of α-interferon or chemotherapy is recommended in these cases, when needed [8].

Although the presence of lung metastases was not histologically proven, pulmonary ground-glass infiltrates, which are typical findings in metastatic hemangiosarcoma [20] and the negative pulmonary workup for other reasons of hemoptysis, led us to assume pulmonary metastasis and to commence immunostimulation with pegylated interferon-α 2a after nephrectomy and the stop of immunosuppression. This led to the subsequent cessation of hemoptysis and normalization of the pulmonary lesions. So the clinical course was consistent with a response to the withdrawal of immunosuppression and the addition of immunostimulation. In view of the otherwise bleak prognosis, we suggest to attempt this treatment in similar cases.

Authorship

DK: wrote the paper. MTH, AB and TK: contributed to writing the paper, scientific discussion. HY: evaluated the pathological slides. JT: performed the ultrasound examination and CEUS, scientific discussion. HH: evaluated the pathological slides, contributed to writing the paper, scientific discussion. OS: read the CT scans, scientific discussion.

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References

1. 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.
2. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. *Lancet Oncol* 2010; **11**: 983.
3. 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.
4. Urun Y, Dogan I, Kiremitc S, Akbulut H, Icli F. Angiosarcoma related to immunosuppressive therapy 8 years after renal transplantation. *Ann Transplant* 2011; **16**: 138.
5. Thoning J, Liu Y, Bistrup C, *et al.* Transmission of angiosarcomas from a common multiorgan donor to four transplant recipients. *Am J Transplant* 2013; **13**: 167.
6. 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.
7. 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.
8. Penn I. Sarcomas in organ allograft recipients. *Transplantation* 1995; **60**: 1485.
9. Zivcic-Cosic S, Grzetic M, Valencic M, *et al.* Urothelial cancer in patients with Endemic Balkan Nephropathy (EN) after renal transplantation. *Ren Fail* 2007; **29**: 861.
10. Haers H, Vignoli M, Paes G, *et al.* Contrast harmonic ultrasonographic appearance of focal space-occupying renal lesions. *Vet Radiol Ultrasound* 2010; **51**: 516.
11. Katabathina VS, Vikram R, Nagar AM, Tamboli P, Menias CO, Prasad SR. Mesenchymal neoplasms of the kidney in adults: imaging spectrum with radiologic-pathologic correlation. *Radiographics* 2010; **30**: 1525.
12. Abraham JA, Hornicek FJ, Kaufman AM, *et al.* Treatment and outcome of 82 patients with angiosarcoma. *Ann Surg Oncol* 2007; **14**: 1953.
13. Penel N, Bui BN, Bay JO, *et al.* Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol* 2008; **26**: 5269.
14. Agulnik M, Okuno S, Von Mehren M, *et al.* An open-label multicenter phase II study of bevacizumab for the treatment of angiosarcoma. *J Clin Oncol* 2009; **27**: 15s : Abstract 10522.
15. Radesi-Sarghi S, Arbion F, Dartigeas C, *et al.* Interferon alpha with or without rituximab achieves a high response rate and durable responses in relapsed FL: 17 years' experience in a single centre. *Ann Hematol* 2014; **93**: 147.
16. Masuzawa M, Mochida N, Amano T, *et al.* Evaluation of recombinant interleukin-2 immunotherapy for human hemangiosarcoma in a SCID mice model (WB-SCID). *J Dermatol Sci* 2001; **27**: 88.

17. Ohguri T, Imada H, Nomoto S, *et al.* Angiosarcoma of the scalp treated with curative radiotherapy plus recombinant interleukin-2 immunotherapy. *Int J Radiat Oncol Biol Phys* 2005; **61**: 1446.
18. Bong AB, Bonnekoh B, Schon MP, Gollnick H. Treatment of scalp angiosarcoma by controlled perfusion of A. carotis externa with pegylated liposomal doxorubicin and intralesional application of pegylated interferon alfa. *J Am Acad Dermatol* 2005; **52**: 20.
19. Burns B, Blakey S, Harris W. Complete response of metastatic angiosarcoma to liposomal doxorubicin and interferon-α2a. *Proc Am Soc Clin Oncol* 2002; **21**: Abstract 2939.
20. Tateishi U, Hasegawa T, Kusumoto M, *et al.* Metastatic angiosarcoma of the lung: spectrum of CT findings. *AJR Am J Roentgenol* 2003; **180**: 1671.