RENAL BIOPSY TEACHING CASE

A Novel Etiology of Renal Allograft Dysfunction

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COMMON CAUSES of renal allograft dysfunction include acute rejection, cyclosporine or FK506 toxicity, acute tubular necrosis, and chronic allograft nephropathy. Important but less frequent causes are recurrent and de novo diseases in the allograft. We report the case of a 66-year-old man who developed renal insufficiency 8 months posttransplantation. A novel cause of renal allograft dysfunction was identified.

CASE REPORT

A 66-year-old Hispanic man received a cadaveric renal transplant on January 24, 2000. The cause of end-stage renal disease in the native kidney was presumed to be malignant hypertension, although no native renal biopsy had been performed. The patient had been on hemodialysis for 5 years before transplantation. On preoperative evaluation, an echocardiogram revealed severe left ventricular hypertrophy with an ejection fraction of 44%, and a dobutamine stress test found no evidence of ischemic changes. Serologic evaluation included positive cytomegalovirus and Epstein-Barr virus titers, negative human immunodeficiency virus (HIV), negative hepatitis B surface antigen, negative hepatitis C virus antibody, and negative rapid plasma reagin.

A postoperative delay in graft function was treated empirically with antihuman thymocyte immunoglobulin (Thymoglobulin) for 7 days. Then, cyclosporine therapy was initiated, and high-dose prednisone was tapered to 5 mg daily. The patient was maintained on cyclosporine, 325 mg daily, and mycophenolate mofetil, 1000 mg twice a day. By 4 weeks post-transplantation, the patient had a baseline serum creatinine of 1.5 to 1.7 mg/dL. After an episode of epigastric pain at 3 weeks post-transplantation, serum amylase rose to 557 U/L, and buffy coat and urine cultures were positive for cytomegalovirus. A 3-week course of intravenous ganciclovir was initiated, and mycophenolate mofetil was discontinued. A 3-month course of oral ganciclovir followed, and mycophenolate mofetil was restarted at 500 mg twice a day.

Three months after transplantation, the patient had a serum creatinine of 2.2 mg/dL. Renal biopsy revealed isometric tubular vacuolization, consistent with cyclosporine toxicity. After the biopsy, cyclosporine dose was lowered to 250 mg daily. One month later, the patient's serum creatinine returned to 1.5 mg/dL.

Four months later, serum creatinine rose to 2.5 mg/dL, prompting a second renal biopsy, which revealed mild acute rejection (Banff grade 1A, CCTT grade 1) and mild chronic allograft nephropathy. The patient was treated with a 3-day course of intravenous methylprednisolone (Solu-Medrol); cyclosporine and mycophenolate mofetil were discontinued; and the patient was started on FK506, 1 mg twice a day, and sirolimus, 2 mg daily. Renal function did not improve, and 18 days later creatinine remained elevated at 2.5 mg/dL, prompting a third renal biopsy.

Biopsy Findings

The third renal biopsy was processed entirely for light microscopy and consisted of two cores of renal cortex. One core was infiltrated extensively by a neoplastic proliferation of spindle cells with moderate-to-high cellularity that formed vascular spaces containing red blood cells (Fig 1A, B). In most fields, the tumor cells were elongated and pleomorphic with hyperchro-

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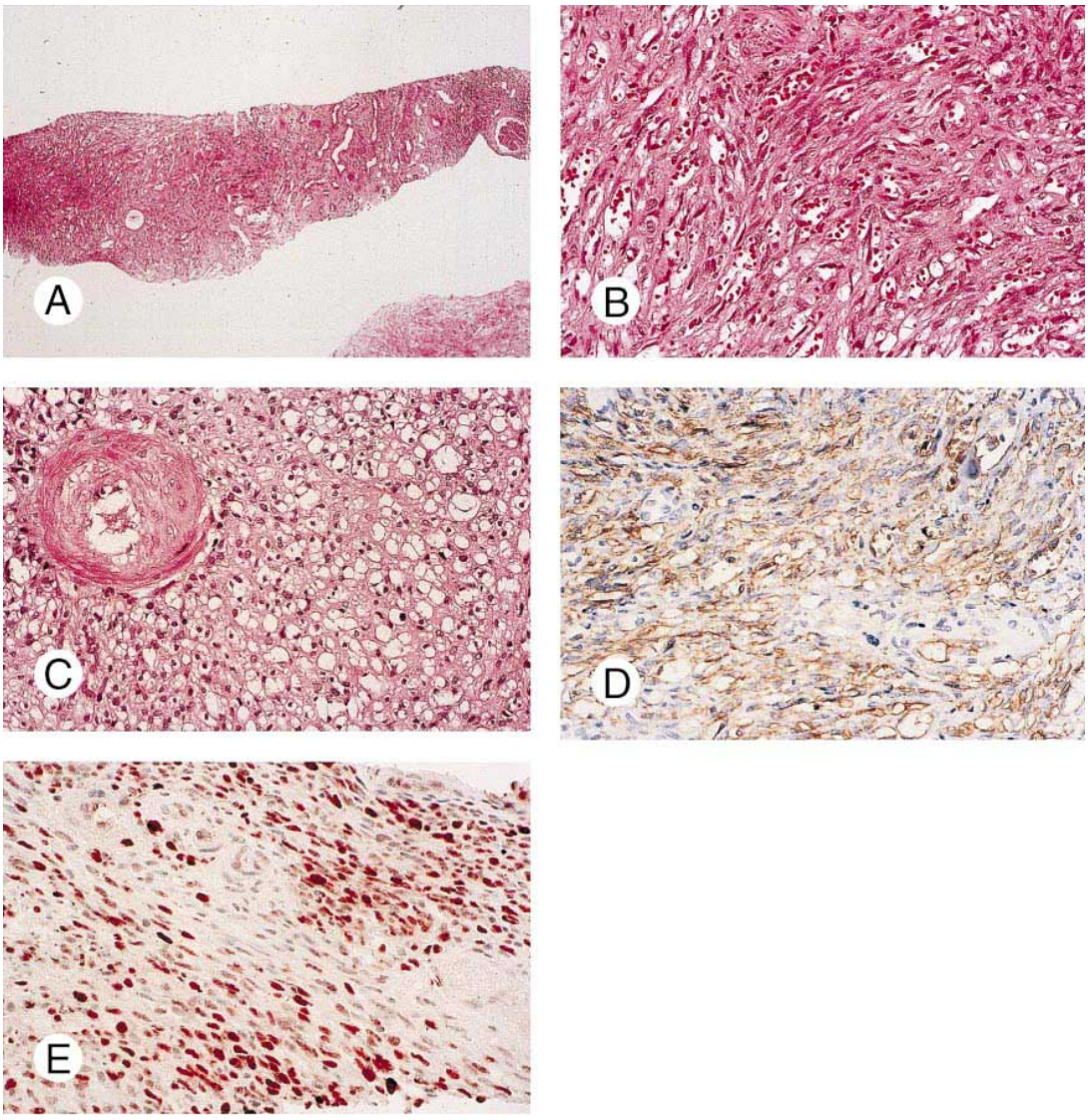

Fig 1. (A) Low-power view shows extensive replacement of the renal parenchyma by a poorly circumscribed cellular neoplasm. A single glomerulus can be seen at the periphery. (H&E, original magnification ×40.) (B) The neoplasm is composed of spindle cells that form numerous small vascular channels containing erythrocytes. (H&E, original magnification ×250.) (C) In some areas, the tumor displays an epithelioid pattern with rounded cells containing more abundant cytoplasm. (H&E, original magnification ×250.) (D) Immunohistochemical staining for endothelial marker CD34 highlights the numerous elongated vascular channels within the tumor. (Original magnification ×250.) (E) Immunohistochemical staining for latency associated nuclear antigen 1 (LANA1) shows strong and diffuse nuclear positivity. (Original magnification ×250.)

matic nuclei and focal mitotic figures. In some areas, the neoplastic cells appeared epithelioid with more abundant cytoplasm (Fig 1C).

Immunohistochemical staining of the spindle cell neoplasm was positive for endothelial markers CD31 and CD34 (Fig 1D). In contrast, staining was negative for S100, cytokeratin, desmin, smooth muscle actin, HMB45 (a marker of melanocytes also present in renal angiomyolipomas), and EBER. These findings confirmed the vascular origin of the tumor and provided evidence against spindle cell renal cell carcinoma; angiomyolipoma; and tumors of smooth muscle, fibroblast, or neural origin. The tumor stained posi-

tively for latency associated nuclear antigen 1 (LANA1) (Fig 1E), a marker of Kaposi's sarcoma herpes virus (KSHV) that is constitutively expressed in KSHV-infected cells.[1,2]

Sections of residual, nontumoral renal cortex contained 23 glomeruli, 9 of which were globally sclerotic. Most of the globally sclerotic glomeruli were clustered in the subcapsular cortex in an area representing a probable old cortical scar. The remaining glomeruli were unremarkable except for mild ischemic-type wrinkling of the glomerular basement membrane. There was diffuse moderate-to-severe tubular atrophy and interstitial fibrosis. There was patchy mild-to-moderate interstitial inflammation composed mainly of lymphocytes with rare eosinophils. There was minimal tubulitis (no more than one infiltrating leukocyte per tubular cross-section). Vessels displayed moderate nonspecific arteriosclerosis.

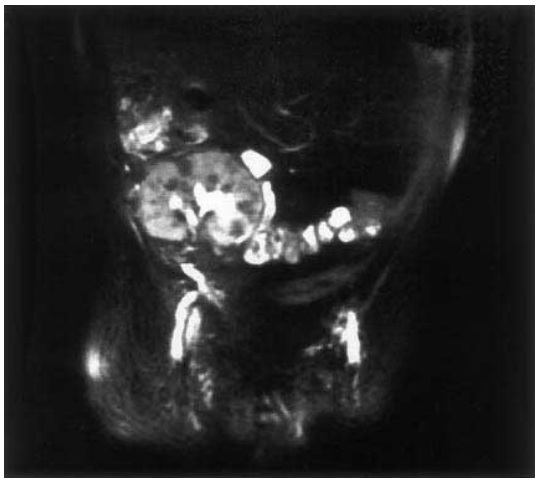

Fig 2. T2-weighted coronal magnetic resonance imaging scan with fat saturation shows multiple low-attenuation lesions throughout the parenchyma of the renal allograft.

Pathologic Diagnosis

The major finding was a spindle cell neoplasm that stained positively for endothelial cell markers CD34 and CD31 as well as LANA1, a specific marker of KSHV infection. The combined growth pattern and cytologic features of the tumor together with the immunohistochemical results were diagnostic of Kaposi's sarcoma (KS). The main finding in the non-neoplastic tissue was moderate chronic allograft nephropathy. The extent to which each process was contributing to the patient's renal insufficiency was unclear. The scattered foci of minimal tubulitis were insufficient to diagnose borderline or mild acute rejection by either the BANFF 1997 or CCTT criteria.

Clinical Follow-Up

After the biopsy, a workup for possible systemic involvement by KS was performed. Magnetic resonance imaging (MRI) of the allograft revealed numerous rounded lesions throughout the cortex and medulla that measured up to 9 mm in diameter (Fig 2). A chest wall skin lesion was identified, and biopsy confirmed the presence of KS. Abdominal computed tomography scan was unremarkable (including the native kidneys). Chest radiograph revealed reticular opacities in both lung zones, suggestive of KS. Bronchoscopy revealed multiple hemorrhagic pulmonary nodules typical of KS; however, bronchoscopic biopsy was deferred because of risk of bleeding.

The patient was treated with doxorubicin, 20 mg/m^2 every 3 weeks for 5 months. FK506 dosage was decreased to 1 mg daily, prednisone was maintained at 5 mg daily, and sirolimus was discontinued. Five months later, serum creatinine remained stable at 1.8 mg/dL, and repeat MRI of the renal allograft revealed an interval reduction in the number and size of the intraparenchymal nodules. The improvement in renal function after reduction in immunosuppression and treatment with doxorubicin strongly suggests that KS was the major cause of renal allograft dysfunction.

Because of the relationship between KSHV infection and the development of KS, the patient's serum was retrieved for further study. An indirect immunohistochemical assay for antibody against LANA1 revealed pretransplant seronegativity; however, post-transplantation serum taken at the time of diagnosis of KS showed the patient to have converted to KSHV seropositivity. The only information available on the donor is that she was a 50-year-old Alaskan woman with history of ethanol abuse who died from intracerebral bleeding and uncal herniation after head trauma. Donor serum was not available for study. Other recipients of organs from this donor included a 55-year-old woman who

died 3 months after renal transplant as a result of disseminated aspergillosis, with no evidence of KS on postmortem examination, and a 49-year-old woman who is alive and well 1 year after liver transplant, without clinical evidence of KS. The latter patient's serum was not available for testing.

DISCUSSION

Kaposi's sarcoma is a tumor of probable endothelial origin that has been linked causatively to infection with KSHV.[3] KS is most common in geographic regions where KSHV is endemic, such as Africa and the Mediterranean region, and in immunosuppressed hosts, such as patients with HIV infection.[3] KS may develop in organ transplant recipients who are treated with immunosuppressive therapy. The incidence of KS in the transplant population is variable but usually reflects the prevalence of KSHV infection in the geographic region.

The largest source of information on KS in organ transplant recipients in the United States is the Cincinnati Transplant Tumor Registry (CTTR),[4] which has compiled data on 356 patients with post-transplant KS. When nonmelanomatous skin cancers were excluded, KS accounted for 5.7% of post-transplant tumors in the United States, a 100- to 500-fold greater incidence than in the general population.[4] The risk of developing post-transplantation KS was highest in adult male patients following renal transplantation, and in patients of Arab, African American, Italian, Jewish, or Greek descent.[4] Almost half of cases of KS occurred within the first year post-transplantation, although the mean time course from transplantation to KS detection was 21 months.[4] Post-transplantation KS was seen more commonly with cyclosporine-based than azathioprine-based immunosuppressive regimens.[5] In approximately 60% of patients, KS was confined to the skin and mucous membranes, whereas in the remaining 40%, there was visceral involvement, usually in association with cutaneous disease. Therapies directed toward KS in this population included surgical excision, radiation, chemotherapy, reduction or cessation of immunosuppressive therapy, and combined therapies. The prognosis for post-transplantation KS is poor, although complete remission is more common after nonvisceral than visceral disease (53% versus 27%).[6] In the CTTR, 57% of patients with visceral KS died, mainly as a direct result of KS, whereas only 23% of patients with nonvisceral KS died, typically as a result of either infection or rejection.[6]

Saudi Arabia has the highest reported incidence of post-transplantation KS worldwide, affecting 26 of 630 (4.1%) transplant patients in one center.[7] This incidence is substantially greater than the estimated incidence of 0.4% in the United States,[8] 0.2% in Australia and New Zealand,[9] 1.1% in Turkey,[10] and 1.6% in Italy.[11] Within the cohort from Saudi Arabia, only 12 patients developed other tumors. Thus, KS accounted for 70.3% of all post-transplant tumors in Saudi Arabia, in contrast to 5.7% in the CTTR.[7] The higher incidence of post-transplantation KS in Saudi Arabia parallels the higher seroprevalence of KSHV in this population.

The immunosuppressive regimen required for organ transplantation provides a permissive environment for the development of KS. Compared with a KSHV-seropositive nontransplant control population, renal transplant recipients with KSHV infection have higher titers of anti-KSHV antibodies and may have detectable viral DNA within peripheral blood.[12] The role of immunosuppression in the development and maintenance of KS is underscored by observations that reduction in immunosuppression promotes shrinkage or disappearance of the tumor[11,13,14] and that recurrences of KS often follow reintroduction of immunosuppression.[6]

KSHV infection may be donor-transmitted, latent in the recipient, or acquired de novo after transplantation. In an Italian population, 26 of 175 (14.9%) patients were KSHV seropositive before renal transplantation, and of these 26 patients, 6 (23.1%) developed post-transplantation KS.[15] After transplantation, 14 of 88 (15.9%) patients seroconverted, although only 1 (1.1%) patient developed clinical evidence of KS.[15] In a Swiss population of 220 renal transplant recipients, 14 patients (6.4%) were KSHV seropositive before transplantation, but 39 (17.7%) were found to be seropositive 1 year later.[16] In six patients who seroconverted, donor serum was available for testing, and in five of six patients, anti-KSHV

antibody was detected, indicating donor-transmitted infection.[16]

Although KS is common in renal transplant recipients, KS rarely has been identified within the renal allograft and has never been implicated as a cause of renal insufficiency.[17-20] The case reported herein is unique in that the renal insufficiency was due to extensive renal allograft involvement by KS (as documented by MRI). This conclusion is supported by the finding that reduction in immunosuppression and treatment with doxorubicin led to simultaneous shrinkage of the tumor and improvement in renal function. To our knowledge, this is the first report of renal allograft dysfunction directly attributable to renal parenchymal infiltration by KS.

The role of pretransplantation screening for KSHV infection has not been defined. In one study from France, a group of 32 seropositive transplant recipients were found to have a graft survival of 72% and an incidence of KS of 28% at 3 years of follow-up.[21] These data confirm that pretransplant KSHV seropositivity is associated with a significant risk of post-transplantation KS and raise important issues regarding identification of populations at risk and how they should be managed: Is there a role for widespread screening for KSHV infection in organ transplant recipients similar to screening in use for cytomegalovirus, Epstein-Barr virus, and HIV? If so, how should this information be used? Should an attempt be made to match seropositive donors with seropositive recipients? Should prophylactic antiviral therapy be offered to KSHV-positive recipients? Given the data that ganciclovir is effective in reducing the incidence of KS in HIV-positive patients,[22] a prospective trial of prophylactic ganciclovir in KSHV-seropositive patients may be warranted.

REFERENCES

1. Dupin N, Fisher C, Kellam P, Ariad S, Tulliez, M, Franck N, van Marck E, Salmon D, Gorin I, Escande JP, Weiss RA, Alitalo K, Boshoff C: Distribution of human herpesvirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. Proc Natl Acad Sci U S A 96:4546-4551, 1999

2. Parravicini C, Chandran B, Corbellino M, Berti E, Paulli M, Moore PS, Chang Y: Differential viral protein expression in Kaposi's sarcoma-associated herpesvirus-infected diseases. Am J Pathol 156:743-749, 2000

3. Antman K, Chang Y: Kaposi's sarcoma. N Engl J Med 342:1027-1038, 2000

4. Penn I: Kaposi's sarcoma in transplant recipients. Transplantation 64:669-673, 1997

5. Penn I: Cancers in cyclosporine-treated vs azathioprine-treated patients. Transplant Proc 28:876-878, 1996

6. Penn I: Sarcomas in organ allograft recipients. Transplantation 60:1485-1491, 1995

7. Qunibi WY, Barri Y, Al-Furayh O, Almeshari K, Khan B, Taher S, Sheth K: Kaposi's sarcoma in renal transplant recipients: A report on 26 cases from a single institution. Transplant Proc 25:1402-1405, 1993

8. Odajnyk C, Muggia FM: Treatment of Kaposi's sarcoma: Overview and analysis by clinical setting. J Clin Oncol 3:1277-1285, 1985

9. Sheil AGR, Disney APS, Mathew TH, Amiss N: De novo malignancy emerges as a major cause of morbidity and late failure in renal transplantation. Transplant Proc 25:1383-1384, 1993

10. Arican A, Karakayali H, Bilgin N, Haberal M: Results of treatment in renal transplant patients with Kaposi sarcoma: One center's experience. Transplant Proc 32:626-628, 2000

11. Montagnino G, Bencini PL, Tarantino A, Caputo R, Ponticelli C: Clinical features and course of Kaposi's sarcoma in kidney transplant patients: Report of 13 cases. Am J Nephrol 14:121-126, 1994

12. Hudnall SD, Rady PL, Tyring SK, Fish JC: Serologic and molecular evidence of human herpesvirus 8 activation in renal transplant recipients. J Infect Dis 178:1791-1794, 1998

13. Qunibi W, Akhtar M, Sheth K, Ginn HE, Al-Furayh O, DeVol EB, Taher S: Kaposi's sarcoma: The most common tumor after renal transplantation in Saudi Arabia. Am J Med 84:225-232, 1988

14. Nagy S, Gyulai R, Kemeny L, Szenohradszky P, Dobozy A: Iatrogenic Kaposi's sarcoma: HHV8 positivity persists but the tumors regress almost completely without immunosuppressive therapy. Transplantation 69:2230-2231, 2000

15. Cattani P, Nanni G, Graffeo R, Capuano M, Cerimele F, La Parola IL, Diociaiuti A, Pozzetto U, Cerimele D, Fadda G, Castagneto M: Pretransplantation human herpes virus 8 seropositivity as a risk factor for Kaposi's sarcoma in kidney transplant recipients. Transplant Proc 32:526-527, 2000

16. Regamey N, Tamm M, Wernli M, Witschi A, Thiel G, Cathomas G, Erb P: Transmission of human herpes virus 8 infection from renal-transplant donors to recipients. N Engl J Med 339:1358-1363, 1998

17. Butkus DE, Kirchner KA, Neill J, Raju S: Kaposi's sarcoma in a transplanted kidney. Transplantation 48:146-149, 1989

18. Foulet A, Bendjaballah F, Manganella-Meduri G, Paradis V, Hiesse C, Benoit G, Vieillefond A: Multivisceral Kaposi's sarcoma and encrusted pyelitis after renal transplantation. Ann Pathol 16:453-456, 1996

19. Diaz-Candamio MJ, Pombo F, Lorenzo MJ,

Alonso A: Kaposi's sarcoma involving a transplanted kidney: CT findings. AJR Am J Roentgenol 171:1073-1074, 1998

20. Mansy H, Al-Harbi A, Somorin A, El-Shadly M, Jaber K: Kaposi's sarcoma and cold abscess of the graft in a renal transplant recipient. Nephrol Dial Transplant 13:789-791, 1998

21. Frances C, Mouquet C, Marcelin AG, Barete S, Agher R, Charron D, Benalia H, Dupin N, Piette JC, Bitker MO, Calvez V: Outcome of kidney transplant recipients with previous human herpesvirus-8 infection. Transplantation 69: 1776-1779, 2000

22. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA: Oral gancyclovir for patients with cytomegalovirus retinitis treated with a gangcyclovir implant. N Engl J Med 340:1063-1070, 1999