A Case of Late Kidney Allograft Failure: A Clinical Pathological Conference from American Society of Nephrology Kidney Week 2011

Parmjeet Randhawa* and Roslyn B. Mannon†


Introduction

With the advent of more potent immunosuppression, early outcomes after kidney transplantation have been excellent. However, long-term graft survival has improved at a slower pace and does not reflect the substantial gains made in the early post-transplant period (1). Identification of the failing kidney allograft is based on the detection of alteration in GFR, using serum creatinine as the primary surveillance tool. About half of late graft failure is associated with specific pathology within the kidney allograft and allograft biopsy is a key tool to manage and diagnose late injury (2). In the following clinical case presentation from Kidney Week 2011, we present a case of late allograft failure after an initial early acute rejection and a period of apparent clinical stability. The case is instructive in identifying the causes of late kidney injury and demonstrates the role of allograft biopsy in assisting in the critical management of recipients with declining kidney function. Proper intervention even in the late post-transplant period may alter the course and ameliorate the decline in allograft function.

Case History

A 45-year-old male patient underwent kidney transplantation for ESRD due to IgA nephropathy. After 5 years on dialysis, he received a deceased donor 3 antigen-matched kidney allograft. His panel reactive antibody was 5%. The cold ischemia time was 27 hours. Immunosuppression was provided based on the transplant center’s current standard of care. It initially consisted of induction therapy with corticosteroids and rabbit antithymocyte globulin, and included maintenance therapy of 14 mg of tacrolimus daily, 1 g of mycophenolate mofetil twice daily, and 50 mg of prednisone four times daily that was subsequently tapered. The patient was cytomegalovirus seronegative as was the donor; antiviral prophylaxis consisted of 200 mg of acyclovir once daily.

The serum creatinine fell to 2.5 mg/dl postoperatively, but rose to 2.9 mg/dl by day 10 postoperatively. An allograft biopsy was performed. This showed a Banff 1A acute cellular rejection that was treated with pulse corticosteroids. A post-treatment biopsy on day 23 was interpreted as showing borderline changes suspicious for acute rejection by Banff criteria. In addition, the presence of mild tubular vacuolization was noted. No further therapeutic intervention was performed. At this time, the serum creatinine was 1.7 mg/dl.

The patient did well until 18 months post-transplant, when a serum creatinine of 2.1 mg/dl prompted another allograft biopsy. This again showed borderline changes suspicious for acute rejection. In addition, there was now mild to moderate interstitial fibrosis (IF) and tubular atrophy (TA). No treatment was given and the patient continued on his maintenance immunosuppressive medications.

At month 19.5, the patient developed a brownish discoloration of the urine with microscopic hematuria on urinalysis. A cystoscopy was performed. Urine cytology showed red blood cells, neutrophils, and bland urothelial cells. SV40 staining was negative. The patient was then treated with a course of ciprofloxacin as empirical therapy for a urinary tract infection. A urine culture was negative. No significant improvement occurred after treatment with ciprofloxacin. Repeat examination of the urine a week later showed persistent red blood cells and neutrophils with a few atypical urothelial cells. Urine protein excretion was <300 mg a day. Allograft ultrasonography did not show hydronephrosis or other infiltrative lesion.

At this point, the serum creatinine began to rise to 3.1 mg/dl and an allograft biopsy was again performed. This revealed a Banff grade 1B acute cellular rejection and only mild IF/TA. In addition, there was no mesangial proliferation, glomerulitis, peritubular capillaritis, or chronic transplant glomerulopathy. Pulse steroid therapy was initiated empirically and did not result in any improvement.

Due to persistent allograft dysfunction, a repeat biopsy was performed 10 days later (month 20). This showed worsening of mononuclear inflammation, persistent tubulitis (grade 3), and again a few atypical tubular epithelial cells. No C4d staining or immunofluorescence examination was performed. Electron microscopy did not show recurrent IgA nephropathy. A cytomegalovirus antigenemia assay was performed and was negative. The serum was positive for antihepatitis B surface antibody
but negative for antibodies to hepatitis C virus. Urine culture was again obtained but was negative for bacteria and fungi. The patient was afebrile and there were no systemic symptoms. Liver function tests were within reference limits. Further diagnostic testing was performed.

Clinical Differential

This is an illustrative case of a failing kidney allograft in a recipient of relatively low immunologic risk. It is the first renal transplant, with no other history of sensitizing events such as blood transfusions or pregnancies. The panel reactive antibody was <5%, meaning that the recipient had antibodies to <5% of the HLA proteins of the potential donor pool, allowing for a high likelihood of negative cross-match against the majority of possible donors. In this case, the HLA mismatch was three of six HLA proteins measured. With the potency of current immunosuppression, however, the effects of matching on outcome have been diminished with similar 1-, 3-, and 5-year graft survivals to those with fewer mismatches (3). Finally, cold ischemic time in this donor kidney was 27 hours and, in the absence of mechanical pump perfusion (4), may be associated with delayed graft function, the need for dialysis support, and worse long-term transplant outcomes (5).

Although improvements in short-term graft function and survival in the current era of immunosuppression are outstanding, survival rates in the late post-transplant period have improved but less impressively (1,6). Both immunologic and nonimmunologic events need to be considered in late allograft failure [i.e., failing kidney function >1 year after transplantation (7,8)]. About half of kidney transplants are lost due to recipient death with a functioning graft from cardiovascular disease, infection, or malignancy (8). The remaining graft losses are due to failing function. We will thus focus on the causes of failing allograft function.

In the past, late kidney allograft failure was referred to as chronic rejection and subsequently as chronic allograft nephropathy (CAN) (9). This term relates to the characteristic histologic features of IF and TA but became a disease entity and used as a cause of late graft failure even in the absence of tissue for histologic diagnosis. Consequently, in current clinical practice, the term CAN has been eliminated and specific pathologic investigation into the cause of IF/TA and functional failure are emphasized (10). More recent studies suggest that failing allografts have specific diagnoses of injury and that specific treatments may be available to ameliorate declining function (2). In this single center study of >1300 kidney transplant recipients, graft failure occurred in 153 recipients. The causes included glomerular disease such as recurrent disease, transplant glomerulopathy, and de novo disease in 37%, acute rejection in 16%, other medical/surgical conditions in 16%, and IF/TA in 31% of failed grafts. In this latter group, an etiology could be identified 81% of the time.

In recent cross-sectional analysis of failing kidney allografts from seven transplant centers in North America, the presence of IF/TA changes alone did not predict graft failure (11). Moreover, allografts labeled as calcineurin inhibitor toxicity fared no worse than other grafts in the absence of this diagnosis (11). The preponderance of abnormalities in this study featured immunologic injury including acute rejection (12) and antibody-mediated injury (13). Moreover, the presence of inflammation in the allograft, in areas of fibrosis and TA, was an independent negative feature of allograft failure (14). Thus, IF/TA is not an idiopathic and independent feature of a large proportion of failing allografts but identification of coincident pathology is important in defining outcome.

In review of this patient’s course, an initial rejection episode was detected in the early post-transplant course on day 10. This seems somewhat surprising, in the context of current immunosuppressive strategies, in which acute rejection rates in the first year after transplantation are <10% (3). However, early acute rejection may not necessarily have a lasting effect on allograft function (15), particularly if the episode is steroid responsive and there is a return to baseline renal function. In this recipient, serum creatinine was back to baseline by day 23. Moreover, there was apparent clinical stability on only two maintenance agents (something that is not commonly done in US transplant programs) until month 18. At that time, the serum creatinine began to rise, and an allograft biopsy demonstrated Banff borderline rejection and mild-moderate IF/TA. In interpreting this biopsy, the presence of borderline inflammatory changes is not considered rejection by Banff criteria unless other causes of graft dysfunction have been reasonably excluded (9). The IF/TA present is significant and may be a result of a past rejection episode. There are no comments here about other inflammation such as glomerulitis or evidence of antibody-mediated injury; hence, we can only presume that these are nonspecific changes, and perhaps renal function changed due to prerenal issues or drug effects.

However, the recipient developed gross hematuria about a month after biopsy. Because the hemogram is not commented on, the severity is not clear. In a recipient, sources of gross blood include native kidneys, the bladder (hemorrhagic cystitis), and the allograft. Because the timing is after the allograft biopsy, obtaining a transplant ultrasound with Doppler studies would be appropriate to rule out an arteriovenous malformation. Other possibilities include renal masses or tumors, nephrolithiasis, and hemorrhage related to inflammation of the bladder (cystitis) or kidneys (nephritis) as seen in viral, fungal, or bacterial infections. Finally, hematuria could represent recurrent IgA nephropathy. Initial work-up should include ultrasonography of native and transplanted kidneys, cystoscopy with culture, and cytology. Cystoscopy was not noted to show a source of bleeding or abnormality of the bladder mucosa. The obtained cytology shows some inflammatory cells, but no evidence of malignant cells or abnormal uroepithelial cells. The rationale for the course of ciprofloxacin is not clear; this likely represents empirical antibacterial treatment. Renal ultrasonography of the transplant was not remarkable either and there was minimal urine protein, making IgA recurrence less likely. Repeated examination of urine ultimately showed atypical uroepithelial cells. In the absence of malignancy, this would suggest a viral infection of the uroepithelium. Pathogens include cytomegalovirus, BK, or adenovirus, all known causes of hemorrhagic cystitis (16,17).

Because of worsening allograft function, another biopsy was obtained demonstrating significant tubulitis, without
other findings of antibody-mediated injury or IgA nephropathy. Steroid therapy, indicated for acute cellular rejection, had no effect on function. This suggests either a steroid unresponsive rejection or alternatively, interstitial nephritis, viral nephritis, or bacterial pyelonephritis (18). However, there were no reported new medications used in this recipient. Assays for cytomegalovirus and hepatitis B and C were also negative, as was a urine culture. Repeat biopsy demonstrated histologic features of tubulitis and atypical epithelial cells, which are the hallmark of a viral cytopathic process. Moreover, this type of process fits clinically because there was an absence of systemic symptoms such as fever. Further diagnostic studies should include nucleic acid testing for BK polyomavirus as well as adenovirus in the serum coupled with immunostaining of the biopsy for BK or adenovirus viral proteins. Further management would be delineated based on the identification of the viral pathogen but typically would include immunosuppression reduction, which is the opposite of treatment, antirejection therapies. Thus, the most logical clinical diagnosis is a viral nephritis, with associated late declining kidney allograft function.

Pathologic Discussion

The biopsy performed 20 months post-transplant is the most relevant to this case discussion (Figure 1). It showed a diffuse and primarily mononuclear infiltrate but scattered eosinophils were also present. There was extensive tubular disruption with grade 3 tubulitis, which is a lesion most commonly seen in Banff type 1B T cell-mediated rejection. Enlarged and hyperchromatic nuclei were seen in tubular epithelial cells (Figure 2). These nuclei contained intranuclear masses of basophilic material that resulted in peripheral margination of the cellular chromatin. These were interpreted as probable viral cytopathic effects. The glomeruli were essentially normal. Immunohistochemistry for cytomegalovirus, herpesvirus, and polyomavirus were negative, but an antibody to adenovirus highlighted scattered tubular epithelial cells (Figure 3). Electron microscopy showed no mesangial or glomerular basement membrane electron dense deposits to suggest recurrence of IgA nephropathy within the allograft. However, tubular epithelial cells containing intranuclear viral particles measuring approximately 70 nm in diameter (Figure 4). A diagnosis of adenovirus interstitial nephritis was made based on viral cytopathic effects by light microscopy, presence of viral antigens by immunohistochemistry, in situ hybridization for viral DNA, and demonstration of 70-nm particles by electron microscopy. The diagnosis was further confirmed by a urine viral culture.

Differential Diagnosis of the Allograft Biopsy

If consulted by a physician about an apparently compliant patient with refractory rejection, the pathologist should suggest that pharmacokinetic issues such as poor absorption, increased metabolism, or a drug interaction be excluded before entertaining the possibility of steroid-resistant T cell–mediated rejection or antibody-mediated rejection. The next consideration should include the possibility of medication-induced interstitial nephritis or invasive viral infection mimicking T cell–mediated rejection. It is important to remember that both of these conditions can result in tubulitis, which is typically grade 1 or grade 2, but can also be more severe. Recognizing both of these entities is key to the appropriate management of the recipient with graft dysfunction because one requires additional immunosuppression, whereas the other requires reduction in immunosuppression.

The list of drugs that can cause interstitial nephritis is long and includes commonly used agents such as antibiotics, cholesterol lowering compounds, and antihypertensive, antidiabetic, and antiviral agents. The key to diagnosis is not any specific pathologic lesion, but a review of the clinical course. It is necessary to show that the drug was given in a dose and time frame consistent with the onset and progression of allograft dysfunction. Ideally, a prior history of sensitization might be available, and discontinuation of the offending agent will demonstrate a fall in the serum creatinine. Eosinophils are not required for the diagnosis because they only occur
in type I, and not in types II, III, or IV, hypersensitivity reactions (19). Conversely, the most common cause of eosinophilic infiltration in an allograft biopsy is T cell–mediated rejection (20). Thus, eosinophils are neither required nor sufficient for a diagnosis of a drug hypersensitivity reaction.

Another critical consideration when reviewing a biopsy with tubulitis is an allograft infection. A common entity is bacterial pyelonephritis, and the associated pathology is quite distinctive with the inflammatory infiltrate more pronounced in the medulla, with resulting neutrophilic tubulitis, intratubular neutrophil clusters, and microabscess formation (21). These histologic findings were not observed in the patient discussed in this case. Nevertheless, urine cultures are in general important in the work-up of cases with refractory acute rejection. In addition to common bacteria (Escherichia coli, Klebsiella, Proteus), the clinician should give due consideration to less common microbes such as Mycobacteria, anaerobes, Gardnerella, Ureaplasma, Eikenella, Chlamydia, and Mycoplasma, fungi, and parasites. Some of these infectious agents require specialized culture conditions and prolonged incubation before a negative result can be finalized.

In a predominantly lymphocytic interstitial nephritis similar to that seen in the current case, the commonest infectious cause is a viral infection. Polyomavirus BK (and rarely JC or SV40) accounts for most of these cases (22). A simple strategy for diagnosis before biopsy is PCR assay for detection of the large T cell antigen in serum or urine. In this case, this was not done, but biopsy immunohistochemistry and in situ hybridization for polyomavirus were negative, effectively ruling out this diagnosis. Cytomegalovirus infection within the kidney has been reported in the past, but in the era of valganciclovir prophylaxis presents primarily as viremia or gastroenteritis and is rarely seen clinically (23).

Adenoviral infection of the kidney is more common after hematopoietic stem cell transplant recipients with native kidney infection (24). Typical presentation is AKI accompanied by microscopic hematuria but gross hematuria may also occur. More recently, adenoviral infection of the transplanted kidney may also be seen similarly presenting with microscopic or gross hematuria (17,25). In this context, a study of the transplant and native kidneys to evaluate for structural lesions that may incite hematuria, such as calculi or tumors, is necessary. In this recipient, allograft ultrasonography was unremarkable.

Other viral infections of the kidney transplant may include the herpes viruses as well as parvovirus. In this context, diagnosis is based on the appropriate extrarenal clinical presentation, the use of PCR to detect viral genome in serum or urine, serology, or culture. Parvovirus B19 may also cause pure red cell aplasia as well as a distinctive pathology characterized by thrombotic microangiopathy or collapsing FSGS (26). In the latter presentation, allograft dysfunction is accompanied by substantial proteinuria that may be in the nephrotic range.

There are other uncommon causes of interstitial nephritis that may be misinterpreted as T cell–mediated rejection. These include autoimmune diseases such as systemic lupus erythematosus, mixed connective tissue disease and Sjögren’s syndrome, inflammation secondary to GN or arterionephrosclerosis, obstructive uropathy, cystinosis, light chain deposition, gout, and adenine phosphoribosyl transferase deficiency resulting in deposition of 2,8 di-hydroxy-adenine crystals, which may provoke interstitial inflammation.

Diagnosis of Adenovirus Nephritis

This case illustrates the most commonly recognized scenario of adenovirus infection in a kidney transplant recipient (27). Frequently, these individuals present as a refractory rejection and the biopsy shows a lymphocytic, neutrophilic, or granulomatous interstitial nephritis. Neutrophils and granulomas are focal and not always seen. Vascular compromise may lead to infarction and result in confusion with thrombotic microangiopathy or antibody-mediated rejection. Information on the distribution of adenovirus in different compartments of the kidney is limited. Both cortex and medulla were involved in the case presented, although infection limited to the medulla
Diagnosis may be established by urine examination showing white cell casts and decoy cells (viral inclusion cells; Figure 5). PCR on the urine tests is positive for viral DNA. Monitoring of serum viral loads may be useful in showing white cell casts and decoy cells (viral inclusion cells; Figure 5). PCR on the urine tests is positive for viral DNA. Monitoring of serum viral loads may be useful in showing white cell casts and decoy cells (viral inclusion cells; Figure 5).

Clinical Epilogue

After the diagnosis of adenovirus nephritis, the dose of tacrolimus was reduced by 50% and mycophenolate mofetil was discontinued. No antiviral treatment was given. Serum creatinine fell to 2.3 mg/dl over a period of 1 month and to 1.5 mg/dl over the ensuing year. The most recently available serum creatinine 13 years post-transplant is 1.8 mg/dl.

The clinical course in this patient demonstrates resolution of infection and excellent prognosis as is seen in many cases with adenovirus nephritis after kidney transplantation (27). In many cases, it is sufficient to reduce the immunosuppression, allowing the host immune system to recoup and mount a successful antiviral response (31,32). However, fatal cases of disseminated adenovirus disease are reported in the literature typically in the immunocompromised host such as after bone marrow transplantation (33). In the setting of serious disease, cidofovir is the drug of choice although it is not approved by the US Food and Drug Administration for this indication (34). Dosages reported in the literature vary from 1 mg/kg thrice a week to 5 mg/kg every 1–2 weeks (35). Coadministration of probenecid inhibits tubular secretion of the drug and promotes higher levels of cidofovir in the plasma. Ribavirin and vidarabine have also been used anecdotally as antiaadenovirus compounds (36,37).

Acknowledgments

This work was supported in part by grants from the National Institute of Allergy and Infectious Diseases and the National Institutes of Health to R.B.M. (U01AI084150 and U19A1070119) and to P.R. (RO1AI51227 and RO1AI063360).

Disclosures

None.

References


Published online ahead of print. Publication date available at www.csanj.org.