Slow Rise in Serum Creatinine Level in a Kidney Transplant Recipient 3 Years Post-Transplant

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Introduction
For most American Society of Nephrology (ASN) Kidney Week attendees, case-based clinical nephrology talks are one of the most exciting venues. The Nephrology Quiz and Questionnaire (NQQ) is the essence of clinical nephrology and represents what drew all of us into the field of nephrology. This year’s NQQ in surprisingly temperate Chicago, with full-house attendance, was no exception. The expert discussants prepared vignettes of puzzling cases, which illustrated some topical, challenging, or controversial aspect of the diagnosis or management of key clinical areas of nephrology. These eight interesting patients were presented and eloquently discussed by our four expert ASN faculty. Subsequently, each discussant prepared a manuscript summarizing his or her case discussions, which serves as the main text of this article (Mark A. Perazella and Michael Choi, comoderators).

Patient
A 58-year-old man presents for an office visit approximately 3 years after a deceased donor transplant and is noted to have a slowly increasing serum creatinine level over the last 3 months (Figure 1).

The patient received a deceased donor kidney transplant over 3 years ago for ESRD secondary to hypertension after 4 years on hemodialysis. He was mismatched at the B, DR, and DQ loci, and his panel reactive antibody, reflecting preformed anti-HLA antibodies, was zero. Medical issues included hypertension, colitis treated with mesalamine, secondary hyperparathyroidism, and gastric esophageal reflux disease.

After transplant, there was a slow return of kidney function, with a nadir serum creatinine of 1.7 mg/dl reached at 6 weeks. Immunosuppression included induction therapy with solumedrol and alemtuzumab followed by maintenance with mycophenolate mofetil 1000 mg twice daily, tacrolimus (dosed to maintain levels of 5–7 ng/ml), and prednisone 5 mg daily. He was cytomegalovirus (CMV) and Epstein–Barr virus IgG positive before transplant and received 3 months of CMV prophylaxis with valganciclovir.

After the second post-transplant year, the patient cancelled several follow-up appointments. Tacrolimus levels, which had been persistently 6–8 ng/ml, became more erratic, with several levels below 5 ng/ml (Figure 1). However, a recent level was 8 ng/ml. Serum creatinine started to rise from a baseline of 1.7–1.8 to 2.2 mg/dl and then, 2.4 mg/dl. In the office, he denied gastrointestinal symptoms, weight change, fever, chills, or dysuria but did complain of fatigue. Medications were tacrolimus 2 mg twice daily, mycophenolate 1000 mg twice daily, prednisone 5 mg daily, amlodipine 10 mg daily, metoprolol 100 mg twice daily, and mesalamine 400 mg twice daily.

BP was 140/90 mmHg. A rash of chronic folliculitis was on his neck. The kidney transplant area was not tender; 2+ pretibial edema was present. Blood test results showed serum creatinine level 2.4 mg/dl, bicarbonate 19 mEq/L, potassium 5.5 mEq/L, hemoglobin 11 g/dl, hematocrit 35%, and white blood cell count normal. Most recent tacrolimus level was 5 ng/ml. A kidney ultrasound shows no obstruction. Urinalysis was 1+ protein, 4–6 white blood cells/high powered field, 1–2 red blood cells/high powered field, and leukocyte esterase negative.

Question 1
After discussion with the transplant center, which is the best management for the slow rise in serum creatinine?

A. Lower tacrolimus dose to 1 mg twice daily and repeat serum creatinine
B. Hold mesalamine and repeat serum creatinine
C. Switch from tacrolimus to sirolimus to decrease calcineurin nephrotoxicity
D. Arrange for kidney biopsy

Discussion of Question 1
The correct answer is D: arrange for a kidney biopsy. A persistent increase in serum creatinine is worrisome for acute rejection, a diagnosis that can only be confirmed with a kidney biopsy. Although a recent tacrolimus level of 8 ng/ml was above his usual range, lowering tacrolimus dose would not be appropriate, because serum creatinine continued to rise even with a lower subsequent tacrolimus level (Figure 1). Although mesalamine is a known cause of interstitial nephritis, this would be unusual in this patient who had been stable on this drug for years.
Switching from tacrolimus to sirolimus, done frequently in the first post-transplant year, is an important consideration. In the absence of varying trough levels or drugs that affect tacrolimus metabolism, tacrolimus trough levels should be quite stable. Marked variation in the levels is a pattern reported to be associated with chronic rejection and worse graft outcomes thought to be due to nonadherence (1). Missed and canceled clinic visits raise additional concerns for nonadherence in this patient.

Additional Course

Kidney biopsy showed a borderline acute cellular rejection. Ten percent of the interstitium was scarred, and interstitial fibrosis/tubular atrophy was grade 1; blood vessels were normal, and there was no evidence for transplant glomerulopathy. Immunofluorescence with SV40 staining for BK virus and C4d staining, a finding associated with antibody-mediated rejection, were negative. The patient received three doses of solumedrol at 500 mg per dose. Additional testing revealed that the patient had developed de novo donor-specific antibodies (dnDSAs) not present pretransplant. A Luminex-based assay, in which single beads are coated with individual HLA antigens and read as mean fluorescent intensity (MFI), showed that he had developed an MFI of 13,000 against HLA DQ7 (considered high in our laboratory) and an MFI of 6400 against HLA DQ8 (considered moderate). An MFI of 1000 is the cutoff for positive detection. Thus, he had developed dnDSAs against donor HLA class 2 antigens.

Question 2

Which is the most important reason for kidney allograft dysfunction and loss over time?

A. Calcineurin nephrotoxicity
B. Antibody-mediated immune injury
C. Recurrent disease
D. Cytokine damage from viral infections (CMV or BK)

Discussion of Question 2

The correct answer is B: antibody-mediated immune injury. This represents a shift in thinking from beliefs held a decade ago. In 2003, a major study by Nankivell et al. (2) provided data that interstitial scarring and atrophy from calcineurin nephrotoxicity and immunologic factors were a major reason for long-term allograft loss. However, in that study, there was no staining for C4d in biopsies, a marker for complement-mediated antibody injury, and donor-specific antibodies (DSAs) were not measured. On the basis of a belief that chronic calcineurin inhibitor (CNI) nephrotoxicity contributed to reduced long-term graft survival, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines from 2009 suggested that the lowest dose of calcineurin inhibitor be used in 2–4 months after transplant in the absence of rejection (3). However, subsequent studies failed to establish CNI nephrotoxicity as a major player alone. In the Deterioration of Kidney Allograft Function Study of 173 transplant patients with for-cause biopsies, patients with evidence for antibody-mediated activity (positive DSA and C4d staining) had the worst outcomes, and patients with calcineurin-mediated damage alone had the best prognoses (4). Subsequent studies have verified the importance of chronic rejection and not calcineurin nephrotoxicity as the most prominent cause for long-term graft loss, with humoral injury having a major role (5,6).

Although recurrent glomerular disease occurs in the allograft (most notably IgA nephropathy, FSGS, membranous glomerulopathy, and dense deposit disease), it accounts for <25% of allograft loss (5,6). Similarly, although CMV viremia can be associated with an increased risk of rejection and BK nephropathy can contribute to graft loss, they are not, in and of themselves, as common a cause of graft loss as chronic rejection.

Circulating DSAs are directed primarily against HLA molecules on endothelial cells. The development of dnDSAs is a risk factor for antibody-mediated injury and has been reported to occur in 15%–25% of patients over 5–10 years (7,8). Although many patients can have DSAs with stable graft function for years (8), the appearance of dnDSAs, especially those directed against the DQ epitope, has been associated with poor graft outcomes (7,9,10). Although young age, deceased donor transplant, and HLA mismatch at DQ locus have been identified as risk factors (9), low levels of immunosuppression (either iatrogenic or due to poor patient adherence) are thought to be major contributors to this phenomenon (5,8–10). DSAs are often reported at MFI with varying thresholds for what is considered positive depending on the program. Routine monitoring of DSAs is not yet advocated due to variation in assays and lack of sufficient data as to the cost and context in which this test should be used in all patients as a screening tool (11).

Adequate dosing with calcineurin inhibitors is thought to be important in preventing the formation of DSAs (9,10). In the few calcineurin conversion trials in which dnDSAs have been measured, an increase has been seen when calcineurin inhibitor is switched to a mammalian target of rapamycin inhibitor (12). In contrast to mammalian target of rapamycin inhibitors, immunosuppression with belatacept seems to be associated with a lower formation of dnDSAs than cyclosporin (13). Thus, studies advocating for
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have better tools to characterize a patient (14). Clearly, not all patients are at the same risk of light of the potential for such practices to be associated with dnDSA appearance and subsequent long-term graft loss (14). Clearly, not all patients are at the same risk of developing dnDSAs and losing their grafts, but until we have better tools to characterize a patient’s individual immunologic risk, the need for adequate calcineurin inhibitor dosing needs to be appreciated.

There is no proven effective therapy for chronic anti-body-mediated injury and rejection in which proteinuria due to transplant glomerulopathy is seen. Therefore, it becomes imperative to prevent its occurrence. Avoidance of the practice of reducing calcineurin doses too low and attention to patient nonadherence are important factors to consider here (5,9,10). Patient nonadherence is common post-transplant (15) and was shown to account for over 40% of long-term graft loss (5). Low or varying tacrolimus levels as well as missed visits may be clues to poor patient adherence and require attention by the nephrologist, often with the help of a social worker. Reasons for patient nonadherence are multiple and include patient attitudes, support systems, and insurance coverage as well as number and side effects of medications. Simplifying and clarifying the medical regimen, fostering relationships and good communication, increasing visit frequency if needed, and stressing patient understanding are all helpful but of course, require more time.

In our patient, he denied nonadherence, although there were clues that made us believe otherwise. He was also mismatched at the DR/DQ loci, another risk factor for dnDSA formation. His rise in creatinine level responded to pulse steroids, and his creatinine has remained stable at 2 mg/dl. Although his borderline rejection showed no evidence for humoral injury, cellular rejection has been associated with development of dnDSAs (8), perhaps because both can be the result of nonadherence with the immunosuppressive regimen. He will be followed closely, because he is at risk for antibody-mediated injury in his allograft.

In summary, chronic antibody-mediated injury is a common feature of later allograft loss, and thus, this entity should be kept in mind in patients with worsening allograft function. Current evidence suggests that maintaining optimal doses of immunosuppressive drugs, such as calcineurin inhibitors, and encouraging patient adherence with these drugs may be critical in preventing the development of dnDSAs and the resulting humoral injury that can occur. Nephrologists who care for transplant patients can play a major role in this regard.

Disclosures

None.

References


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