Nephrology Quiz and Questionnaire: Transplantation

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Summary
Presentation of the Nephrology Quiz and Questionnaire (NQQ) has become an annual “tradition” at the meetings of the American Society of Nephrology. It is a very popular session judged by consistently large attendance. Members of the audience test their knowledge and judgment on a series of case-oriented questions prepared and discussed by experts. They can also compare their answers in real time, using audience response devices, to those of program directors of nephrology training programs in the United States, acquired through an Internet-based questionnaire. Topics presented here include transplantation issues. These cases, along with single best answer questions, were prepared by Dr. Hricik. After the audience responses, the “correct” and “incorrect” answers were then briefly discussed and the results of the questionnaire were displayed. This article aims to recapitulate the session and reproduce its educational value for a larger audience—that of the readers of the Clinical Journal of the American Society of Nephrology. Have fun.


Case 1: Donald E. Hricik (Discussant)
A 53-year-old man with ESRD secondary to IgA nephropathy received a kidney transplant from a deceased donor 6 months ago. The patient received induction antibody therapy with rabbit antithymocyte globulin. Serum creatinine concentrations ranged between 1.3 and 1.6 mg/dl during the previous 4 months. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisone. Other medications include metoprolol, trimethoprim-sulfamethoxazole, omeprazole, and ergocalciferol. One week earlier, a serum creatinine concentration was 1.8 mg/dl and a repeat level was 2.0 mg/dl. Results on surveillance blood PCR for BK polyoma virus were negative 3 months after transplantation but now show a viral level of 5000 copies/mL. The patient is entirely asymptomatic. On examination, his body temperature is 37.2°C and his BP is 138/88 mmHg. There is no allo- graft tenderness. Doppler ultrasonography of the transplanted kidney shows no hydronephrosis and mildly increased resistive indices. A biopsy of the transplanted kidney is performed. The pathologist reviews the light microscopic findings and notes lymphocytic infiltrates in 20% of the core, as well as mild tubulitis. Findings are Banff grade “suspicious” for acute rejection. No glomerular abnormalities are present.

Discussion of Case 1 (Question 1A)
The best choice is C. The detection of BK polyoma viremia in a kidney transplant recipient with an increasing serum creatinine concentration raises a serious concern for BK polyoma virus nephropathy. Transplant renal biopsy represents the gold standard for diagnosis of BK polyoma virus nephropathy. However, in the early stages of this disorder, classic cytopathic changes in epithelial cells may be minimal, and interstitial inflammation, including tubulitis, can be confused with acute cellular rejection (1,2).

The polyoma viruses are a group of species-specific small-DNA viruses that include human pathogens (BK and JC viruses) and the primate pathogen (SV40) (1). The BK virus shares 70% of DNA sequence homology with SV40, and immunostaining against the latter virus forms the basis for the immunohistochemical diagnosis of BK polyoma nephropathy. Antibodies to BK polyoma virus can be detected in approximately 80% of adults. Viral infection typically occurs in childhood and is then followed by a latent state with viral presence in the uroepithelium, lymphoid tissues, and brain (3). In the first year after transplantation, 10%–20% of kidney transplant recipients develop BK viremia. Reduction of immunosuppression is the mainstay of therapy (4). With aggressive surveillance protocols, aimed to detect viremia before the development of impaired kidney function, graft loss now occurs in less than 5% of viremic patients. The risk for graft loss is related to histologic stage, starting with mild inflammation (tubulitis), increasing to cytopathic changes in tubular epithelial cells, and followed by progressive fibrosis.

Immunostaining for IgA and C3 would be of some interest in this patient with underlying IgA nephropathy. However, the absence of glomerular abnormalities rules against recurrent IgA nephropathy.
Furthermore, recurrence of the original disease would probably not account for marked interstitial inflammation noted on light microscopy. The detection of C4d deposits in peritubular capillaries represents the histopathologic hallmark of acute humoral rejection (5). Unless the pathologist noted peritubular capillaritis on light microscopy, acute humoral rejection would not be a serious concern in this case at this point. The presence of BK viremia, with or without overt nephropathy, is generally believed to reflect overimmunosuppression (4), in which concurrent cellular or humoral rejection would be distinctly unusual.

**Case 1, continued**

Tacrolimus treatment was discontinued and the dose of mycophenolate mofetil was reduced by 25%. One month later, results of blood PCR for BK polyoma virus were negative and the serum creatinine level decreased slightly to 1.7 mg/dl. Two months later, routine laboratory testing revealed a serum creatinine concentration of 3.2 mg/dl. Repeat biopsy showed acute humoral rejection with positive staining for C4d. Two donor-specific antibodies were detectable in high titers. Tacrolimus treatment was renewed. Despite a trial of pulse steroid therapy, plasmapheresis, and intravenous immunoglobulin, the patient exhibited progressive renal dysfunction and returned to dialysis treatment 6 months later. One month later, the patient tells you that a friend from his church wishes to be evaluated as a possible living donor (Figure 2). He continues to receive tacrolimus and prednisone.

**Question 1B**

What is your BEST advice regarding re-transplantation with a living unrelated donor?

A. The first transplanted kidney is a reservoir for BK polyoma virus and must be removed before a second transplant.
B. Deceased-donor transplantation is preferred because the risk for recurrent BK polyoma virus nephropathy is lower than that with a related donor.
C. Repeat BK polyoma blood PCR should be performed. If result is negative, he should continue current immunosuppression until the second transplantation is performed.

D. Irrespective of the current BK viral load, tacrolimus must be weaned and discontinued before a second transplant.

**Discussion of Case 1 (Question 1B)**

The best choice is C. The clinical predicament presented by this case brings up two controversial management issues: (1) the role of transplant nephrectomy before retransplantation in a patient with a previous graft loss due to BK polyoma nephropathy and (2) general management of a patient with a previously failed allograft.

Because BK polyoma virus can become latent in uroepithelial tissues, there is a logical concern that retention of the failed allograft will create a reservoir for re-infection of a new graft. However, there is some evidence that BK present in the donor kidney may serve as the source of the infection in the recipient, at least in the first year after transplantation (3). Moreover, clinical experience has suggested that the risk for BK polyoma nephropathy in a second transplant is not influenced by removal of a previous allograft (6,7). In a recent retrospective study of 31 patients undergoing retransplantation within a median of 6 months after graft failure from BK nephropathy, 35% developed recurrent BK viremia but only 6% developed overt nephropathy (7). Clearance of previous BK viremia was the only factor associated with lack of recurrence, and the effects of prior nephrectomy were not significant.

Controversies regarding the general management of the patient with a failed graft focus on practices for weaning immunosuppression and on the role of transplant nephrectomy (8). It is generally recognized that complete weaning of immunosuppression can lead to increased generation of anti-HLA antibodies that may limit opportunities for retransplantation. However, for patients requiring long waiting times for deceased-donor kidney transplantation, continued immunosuppression will increase the risk for infection. Retrospective studies suggest that removal of a failed allograft and discontinuation of immunosuppression may decrease mortality rates and increase the chances of retransplantation (9). One theory behind these observations is that the allograft tissue acts as a source of inflammation. However, such studies are fundamentally flawed by retrospective designs that fail to consider important biases in the selection of patients for transplant nephrectomy (10). Moreover, other studies suggest that removal of the allograft actually increases the circulating levels of anti-HLA antibodies (11). The theory here is that the allograft tissue acts as a "sponge" for circulating antibodies. There is no consensus about the optimal timing of nephrectomy and weaning of immunosuppression after graft failure. However, in this case, the availability of a live donor will allow for relatively rapid retransplantation, and one can make a strong argument to continue immunosuppression to prevent HLA sensitization, so long as BK viremia is under control. Donor source (i.e., living versus deceased donor) has not been identified as a risk factor for BK polyoma viremia after kidney retransplantation (12).

**Case 2: Donald E. Hricik (Discussant)**

A 65-year-old man with ESRD due to chronic GN (of unknown nature) had a previous kidney transplant that failed 3 years ago. He then began receiving long-term hemodialysis and was on the waiting list for another kidney transplant. He continued to work full-time as an attorney. Two years ago, he was hospitalized for an upper gastrointestinal hemorrhage resulting from gastric erosions and received 6 units of packed red blood cells. He is now highly sensitized against HLA antigens; recent flow cytometry–measured panel-reactive antibody levels were 92% for class I antigens.

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**Table 1. Criteria for defining an expanded-criteria donor**

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<td>1. Deceased donor age &gt; 60 yr OR</td>
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<td>2. Deceased donor age 50–59 yr with ≥2 of the following:</td>
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<td>history of hypertension</td>
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<td>terminal serum creatinine concentration &gt;1.5 mg/dl</td>
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<td>death from cerebral vascular accident</td>
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and 94% for class II antigens. He had previously signed a consent form agreeing to consider an expanded-criteria donor (ECD). The patient has been allocated a kidney allograft from a donor after cardiac death (DCD), a 49-year-old male drowning victim (Figure 3).

Question 2

The patient’s concerns about accepting this allograft would BEST be allayed by which ONE of the following facts?

A. Kidneys from DCD donors exhibit rates of allograft survival equivalent to those from ECDs.

B. Kidneys from DCD donors exhibit rates of delayed graft function similar to those from standard-criteria donors (SCDs).

C. Kidneys from DCD donors exhibit allograft survival rates equivalent to those from SCDs.

D. Kidneys from DCD donors exhibit rates of primary non-function lower than those from ECDs.

Discussion of Case 2 (Question 2)

The correct choice is C, given data from the Scientific Registry for Transplant Recipients. The definition of an ECD (Table 1) was derived from a large multivariate analysis that sought to identify risk factors that collectively posed a 70% increase in the relative risk for graft loss compared with relatively healthy, younger donors, also known as SCDs (13). DCDs are donors with terminal illnesses but intact brain function. Organs from DCDs are harvested quickly after declaration of asystole. Because varying degrees of warm ischemia are involved in the harvesting of DCD organs, it is no surprise that recipients of these organs experience relatively high rates of delayed graft function or even primary nonfunction (14). However, long-term follow-up of patients receiving kidneys from DCDs indicate that both patient and graft survival are similar to those achieved with brain-dead donors (15) (Figure 4), whereas graft survival of DCD recipients is actually superior to that of ECD recipients (15).

Disclosures

None.

References


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