Delayed Graft Function Complicated by Anuria in a Kidney Transplant Patient

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Case Description
A 45-year-old woman with chronic IgA nephropathy had undergone deceased-donor kidney transplantation with rabbit anti-thymocyte globulin induction, after continuous ambulatory peritoneal dialysis for about 4 years. Warm ischemia time was prolonged (35 minutes) due to the multiorgan harvesting procedure. Cold ischemia time was around 3 hours. The patient developed delayed graft function (DGF). Doppler study was normal. Initial graft biopsy specimen from postsurgery day 3 showed mild acute tubular injury. She was continued on corticosteroids and mycophenolate mofetil. Because she remained anuric, repeat Doppler was performed on postsurgery day 8, which showed loss of diastolic flow with raised resistive index (0.98) (Figure 1A). An allograft biopsy specimen showed widespread areas of patchy cortical necrosis in the background of significant acute tubular injury (Figure 1B). Immunohistochemistry showed mild circumferential positivity for C4d in peritubular capillaries (<10%) (Figure 1C). Donor-specific antibodies against HLA class 1 were positive, confirming superimposed antibody-mediated rejection. Retrospectively, we found that the recipient of another kidney from the same donor also had DGF, and his biopsy specimen showed severe acute tubular injury. Our patient remained dialysis dependent after 4 weeks and was continued on continuous ambulatory peritoneal dialysis with close follow-up.

The common causes of acute cortical necrosis (ACN) are severe and prolonged ischemia or hypotension, vascular insults (thromboembolism, inflammatory, and structural), disseminated intravascular coagulation, infections (sepsis; coronavirus disease 2019; angioinvasive infections, such as Aspergillus and Mucor), immunologic causes (SLE and antiphospholipid antibody syndrome), envenomation (snake bite), drugs and poisonings, acute pancreatitis, burns, and postpartum and post-transplant injury (ischemia-reperfusion injury, severe rejection, vascular thrombosis, and thrombotic microangiopathy). ACN is associated with complete necrosis, identified by only ghost outlines (washout appearance with no nuclear details) of glomeruli and tubules in the areas involved. It is irreversible and heals with fibrosis and then calcification. If it is diffuse and bilateral, it leads to graft loss. Bilateral ACN is a marker of the generalized Shwartzman reaction. In contrast, acute tubular necrosis is actually a misnomer, and is usually associated with subtle tubular injury rather than necrosis. Injury may vary from loss of brush border, vacuolization, and flattening with dilated lumina to completely denuded epithelium, but the basement membrane is intact, which leads to regeneration after a few weeks.

Ischemia-reperfusion injury, especially in deceased-donor transplantation, can result in DGF (commonly acute tubular injury). If it is severe, it can lead to ACN as illustrated in our case (1). Sometimes, it may require graft nephrectomy, especially in the presence of vascular thrombosis. The incidence of post-transplant ACN appears to be declining due to better immunologic evaluation, screening for prothrombotic states in patients who are high risk (multiple arteriovenous graft failures, miscarriages, spontaneous or recurrent deep vein thrombosis/embolism), advances in surgical techniques, and better deceased-donor management. Ischemia-reperfusion injury can also trigger alloimmune injury precipitating rejection. The identification of associated rejection has prognostic and therapeutic implications. The presence of tissue injury with C4d deposits and HLA donor-specific antibodies confirms the diagnosis of associated active antibody-mediated rejection in our case. Severe forms of rejection, including antibody-mediated rejection, can also result in ACN (2). Thrombotic microangiopathy can be an associated finding in these cases. Our patient illustrates the grave prognosis associated with ACN, and its inter-relationship with ischemia-reperfusion injury and antibody-mediated rejection.

Teaching Points
- Ischemia-reperfusion injury, especially associated with deceased-donor transplantation, can lead to ACN, which is usually associated with irreversible graft injury and graft loss.
- Ischemia-reperfusion injury can also trigger alloimmune injury, precipitating rejection.
- Loss of diastolic flow with raised resistive index on Doppler is a nonspecific finding, but indicates a poor prognosis with higher risk of graft loss.

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ACN can be a manifestation of severe rejection, including antibody-mediated rejection.

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Author Contributions
P.K. Etta conceptualized the study, wrote the original draft, reviewed and edited the manuscript, provided supervision, and was responsible for formal analysis, investigation, methodology, software, validation, and visualization.

References

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Figure 1. Doppler and allograft biopsy showing features of ischerial-reperfusion injury triggering rejection. (A) The Doppler waveform pattern of segmental and interlobar arteries of kidney allograft shows loss of diastolic flow with raised resistive index (0.98), indicating marked parenchymal injury. (B) Light microscopy examination of the kidney allograft biopsy specimen (hematoxylin and eosin) showing widespread areas of patchy cortical necrosis with ghost outlines of necrotic tubules (arrows). The intervening areas show significant acute tubular injury with vacuolization, flattening, and denudation of the epithelium lining of tubules (arrow heads). Original magnification, ×10. (C) Immunohistochemistry examination for C4d deposits in the kidney allograft biopsy specimen shows mild circumferential C4d positivity in peritubular capillaries (<10%; arrows), indicating a possibility of antibody-mediated rejection (hematoxylin and eosin). Original magnification, ×20. AT, acceleration time; AI, acceleration index; EDV, end diastolic velocity; HR, heart rate; MDV, mean diastolic velocity; PSV, peak systolic velocity; PI, pulsatility index; RI, resistive index; S/D, systolic/diastolic ratio; TAPV, time averaged peak velocity.