Case Report

Adenovirus-Associated Thrombotic Microangiopathy and Necrotizing Interstitial Nephritis in a Renal Transplant Recipient: A Case Report and Review

Abstract

Adenoviral infections, though rare, may be a source of significant morbidity and mortality in the early post renal transplant period. We present a case of fever and graft dysfunction in a deceased donor renal transplant recipient whose initial post-operative period was complicated by vascular thrombosis and ureteric necrosis. He had received induction immunosuppression with Rabbit-Anti Thymocyte Globulin. Graft biopsy was suggestive of Thrombotic Microangiopathy (TMA) accompanied by intense interstitial inflammation, hemorrhage, necrosis, WBC casts and tubular injury. Viral cytopathic changes were discernible on light microscopy, leading to suspicion of adenoviral infection. This was confirmed with immunohistochemical demonstration of adenoviral antigens in the graft biopsy. He was treated with a step down of immunosuppression and intravenous Immunoglobulin. However, the patient's general condition deteriorated rapidly, and he succumbed to his illness. We highlight this association of TMA and necrotizing tubulo-interstitial nephritis with adenoviral infection of the renal allograft.

Keywords: *Adenovirus, graft dysfunction, necrotising interstitial nephritis, renal transplant, thrombotic microangiopathy*

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Introduction

Adenoviral necrotising interstitial nephritis of the renal allograft is a rare cause of early graft dysfunction that is associated with significant morbidity and mortality. We present a case with coexistent thrombotic microangiopathy (TMA) and interstitial nephritis related to adenoviral disease. Our report seeks to highlight this association and discusses how to diagnose this complex entity. We also examine treatment modalities and introspect on early and effective therapy.

Case History

A 45-year-old man with chronic kidney disease stage 5, on maintenance hemodialysis, underwent deceased donor renal transplantation. His native kidney disease was unknown and pre transplant immunological workup included negative complement-dependent cytotoxicity and flow cytometry crossmatch. Transplant surgery was prolonged and complicated by significant intra-operative hemorrhage as the patient had prior stab injury to the lower abdomen, necessitating adhesiolysis. The allocated kidney had two renal arteries, which were anastomosed to the recipient's left external and internal Iliac arteries. Double J (DJ) stent was placed in situ. Induction immunosuppression consisted of a single dose of 50 mg of rabbit Anti-Thymocyte Globulin and 1 g of Methylprednisolone given intra-operatively, as per unit protocol. Maintenance immunosuppression included Mycophenolate Mofetil (MMF) 1 g per day, Tacrolimus 0.1 mg/kg per day and Prednisolone 0.5 mg/kg per day.

Patient was hypotensive in the immediate post-operative period requiring blood transfusions, inotropic support, and broad spectrum antibiotics (Piperacillin-Tazobactam). Hemodynamics stabilized by the third post-operative day. Blood cultures and perfusion fluid cultures yielded no growth.

The patient, however, remained anuric, requiring hemodialysis. Renal Doppler-ultrasound showed normal flow

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in both arteries and no evidence of urinary obstruction. Post-operative tacrolimus trough (C0) levels were in acceptable range (day #4 post-transplant – 9 ng/ml; day #10 -8 ng/ml). In view of delayed graft function, renal allograft biopsy was done on the sixth post-operative day which showed acute tubular injury; diuresis began by day #10.

On day #16, patient developed features of urinary leak evidenced by high drain output. Patient was taken up for re-exploration, where the accessory renal artery was found to be thrombosed with necrosis of the distal ureter at the vesico-ureteric junction. The native ureter was mobilized and anastomosed with the graft renal pelvis. The necrosed ureter and thrombosed artery were ligated and excised. New DJ stent was inserted. Biopsy of the excised tissue showed necrosis and no evidence of rejection. Urine output was maintained post-operatively.

However, by day #28, the patient developed fever spikes with worsening graft dysfunction. Tacrolimus trough levels, complete blood counts, peripheral smear and LDH levels were not contributory. He was treated with broad spectrum antibiotics (Meropenem). Urinalysis showed microscopic hematuria and ultrasound/Doppler of the graft was unremarkable. Urine culture was sterile and aerobic, anaerobic and fungal blood cultures showed no growth. There was no clinical evidence of focus of infection elsewhere. The possibility of graft pyelonephritis or antibody mediated rejection was considered, and patient was subjected to a repeat allograft biopsy on day #34.

The tissue was stained with Hematoxylin, Eosin and special stains including Periodic acid-Schiff, Silver and Trichrome were applied. Ten glomeruli were seen in the biopsy. Fibrin thrombi were noted within the capillaries of one glomerulus on Masson's trichrome [Figure 1], suggestive of TMA. There were sheets of neutrophils, macrophages and lymphocytes throughout the core with micro-abscess formation, and destruction of tubules [Figure 2]. What stood out were hyperchromatic, smudged nuclei seen in occasional tubular epithelial cells [Figure 3] with focal areas of cortical necrosis and large areas of interstitial hemorrhage in the absence of vascular inflammation, leading us to suspect adenoviral infection. C4d staining was negative.

Strongly positive immunohistochemical (IHC) staining for adenovirus in the tubules, confirmed the diagnosis of adenoviral interstitial nephritis [Figure 4]. Peripheral blood qualitative PCR for adenoviral DNA was positive. Immuno-peroxidase staining for SV40 T antigen for BK/Polyoma virus on the graft biopsy was negative. Plasma PCR testing for BK virus and Cytomegalovirus were also negative. Donor specific antibody was not present by Luminex single antigen bead testing. The patient was treated with a step down of immunosuppression and broad-spectrum antibiotics for secondary bacterial infection.

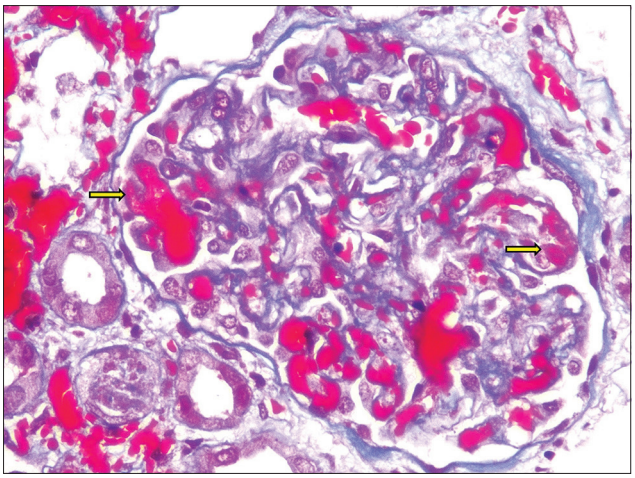

Figure 1: Massons trichrome stain confirms the presence of fibrin in the glomerular capillaries (arrow) ×400

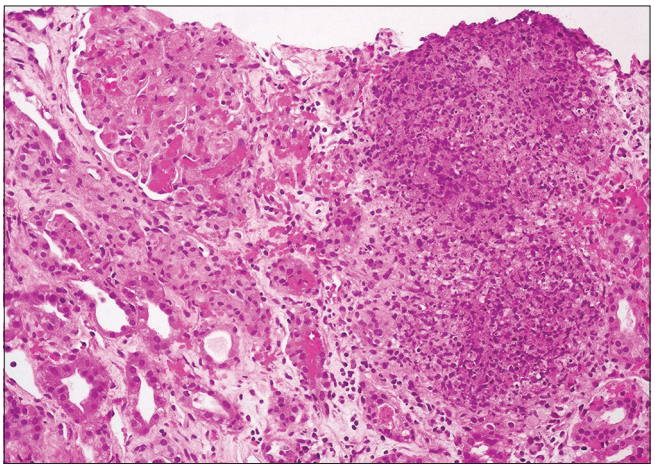

Figure 2: Dense neutrophilic infiltrate is seen in some areas in the interstitium. They invade and destroy some of the tubules H and E ×200

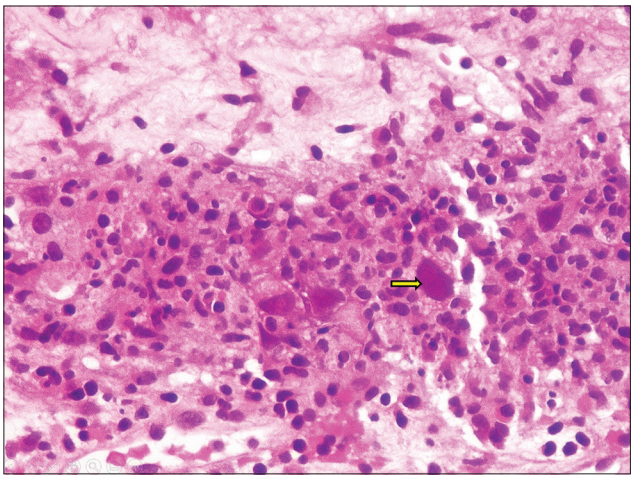

Figure 3: Rare tubular epithelial cells had a 'smudged out' nucleus (arrow) H and E ×400

DJ stent was removed. As he continued to clinically worsen, both Tacrolimus and MMF were completely withdrawn, low-dose steroids continued and intravenous

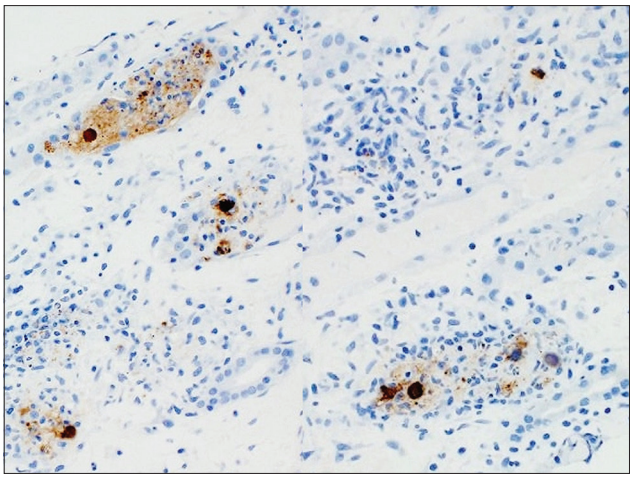

Figure 4: IHC stain for Adenovirus is positive over some of the tubular epithelial cells

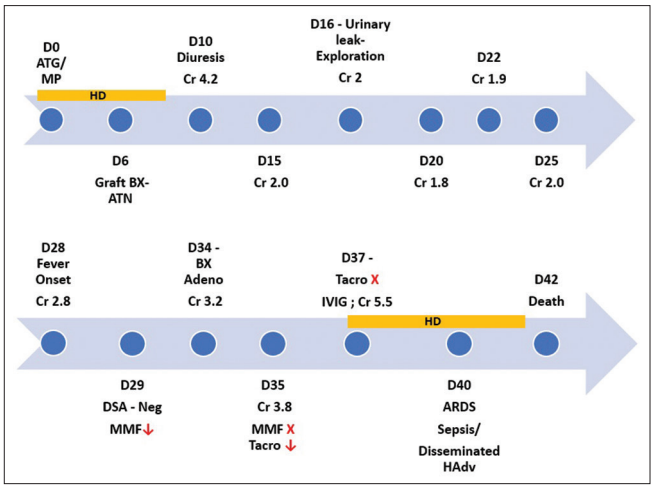

Figure 5: Timeline of events

Immunoglobulin (0.4 g/kg per day) initiated [Figure 5]. Anti-viral therapy was contemplated; however, his general condition deteriorated rapidly with development of acute respiratory distress syndrome, related to underlying graft adenoviral infection and sepsis. The patient succumbed to his illness, shortly thereafter.

Discussion

This report describes a fatal case of TMA and necrotizing tubulo-interstitial allograft nephritis due to adenovirus in a deceased donor kidney transplant recipient.

Adenoviruses are double-stranded DNA viruses that usually cause self-limiting respiratory, gastrointestinal, conjunctival and other illnesses. Most of these infections occur in childhood after which they establish latency in lymphoid tissue. In the immunocompromised host, the latent virus can activate to disastrous outcomes.[1] Adenoviruses have cytolytic and immunomodulatory properties. The concern, therefore, is of direct infection, graft dysfunction and predisposition to rejection.[2]

Infection can occur due to reactivation of the latent virus, de-novo infection post-transplant and even transmission through the graft.[3] In a study of 92 renal transplant recipients, adenoviral viremia was relatively common (6.5%) in the first year post-transplant, though clinical disease per se was rare. Several other case reports have, however, highlighted significant morbidity and mortality related to adenoviral infections in the renal transplant setting.[4] The most common manifestation is asymptomatic viremia that is detected in programs that carry out routine viral screening. Symptomatic disease may present as macro-hematuria, dysuria and fever. The classical combination of hemorrhagic cystitis and graft dysfunction may be an important pointer to adenoviral infection.[5] Major organ involvement is rare, but when it occurs, acute allograft dysfunction is the most common manifestation and may progress to involve the gastro-intestinal tract, testes, lung, liver and culminate in overwhelming sepsis, as in our patient.

The largest case series of adenoviral infections in renal transplant recipients from Thailand, suggests that most patients (76.5%) are diagnosed in the early post-transplant period (<3 months) with a mean time to presentation of 5 weeks post-transplant. This is understandable, considering the heightened net immunosuppression during this period.[6]

A graft biopsy is instrumental in differentiating rejection or pyelonephritis from an adenoviral nephritis. Pathological changes associated with adenoviral infection in the renal allograft include tubular cell necrosis with viral cytopathic effects like nuclear enlargement, hyperchromatic nuclei and basophilic nuclear inclusions representing viral particles. This is usually accompanied by severe interstitial inflammation comprising of macrophages, neutrophils and even granulomas have been described.[7] The distal nephron is primarily affected with maximum inflammation in the medulla and cortico-medullary junction. These cytopathic changes may, however, be subtle or focal and need a high level of suspicion and the keen eye of a discerning pathologist for swift recognition. BK Virus nephropathy may be a close differential as these features may be common to both viruses. However, necrotizing inflammation, granuloma formation and interstitial hemorrhage are usually seen in adenoviral disease and not with other viruses. BK virus nephropathy may also be associated with more chronic interstitial changes reflecting the indolent nature of the disease.[8,9]

It is important to note that the intense inflammatory exudate, WBC casts and tubular injury seen in this disease may mimic a graft pyelonephritis. Presence of significant necrosis, interstitial hemorrhage and cytopathic changes should alert the pathologist to something more sinister, as in our case. Adenoviral interstitial nephritis may mimic rejection, and the absence of vascular inflammation in the glomerulus and other blood vessels with c4d negativity

would support a diagnosis of the former.[7] Electron microscopy, if done, shows the typical 70–80 nm diameter adenoviral particles within the nuclei and cytoplasm of tubular epithelial cells.

To confirm the diagnosis, the pathologist must demonstrate the presence of adenovirus particles in the graft biopsy by IHC staining or *in situ* hybridization for adenoviral antigens. This will show tubular nuclear staining and possibly weaker cytoplasmic staining for the virus. In our patient, pertinent cytopathic changes with intense interstitial inflammation, characteristic hemorrhage and necrosis alerted us to the likelihood of adenoviral nephritis, which we confirmed with IHC staining.

Adenoviruses have been implicated in virus-associated TMAs and the proposed mechanism by which endothelial damage occurs may be modulation of endothelial intracellular factors that increase natural killer cell-mediated cytotoxicity.[10] This is the first case report of acute adenoviral graft nephritis associated with TMA that we could find in our literature search.

Our patient also presented with vascular complications and ureteric necrosis that was encountered in the early post-transplant period, preceding the onset of fever. Surgical/technical complication is the most likely cause for such an occurrence. The biopsy of the vessel and ureter only demonstrated necrosis and did not show features of rejection or viral cytopathic changes.

Polymerase chain reaction testing from peripheral blood for adenovirus DNA is a sensitive test to detect viremia, as in our patient. However, the Valganciclovir solid organ transplant study group demonstrated that the mere presence of viremia does not suggest disease and in most cases may lead to benign outcomes.[4] This testing may provide contributory evidence in a patient with histopathological changes and the viral load has been demonstrated to be associated with worse clinical outcomes in other studies.[6] Urinary testing is not encouraged as it may be a result of late shedding of the virus with no clinical consequence whatsoever.

Management is to be tailored to the specific patient as there are no clear guidelines or large trials in adenoviral infections. In 29 cases of disseminated human adenoviral (HAdV) infections described so far in renal transplant patients, adverse outcome was encountered in 20%, which included four deaths and two allograft losses. These statistics therefore exhort a swift therapeutic response to disseminated adenoviral disease. Disseminated disease is defined in a patient with HAdV viremia and involvement of two or more organ systems.[11]

The first recommended step in the treatment of adenoviral infection is reduction of net immuno-suppression, which is deemed sufficient in more than 60% of the cases according to the large series from Thailand.[6] But a closer look at 29 patients with disseminated disease reported worldwide till 2017 reveals that 3 out of 4 patients who died, did not receive specific anti-viral therapy. This is in comparison to the rest (25 of 29) who survived, the majority of whom received specific anti-viral therapy.[11] The anti-viral armamentarium shown to be effective against adenoviruses includes Cidofovir, Ganciclovir, and Brincidofovir with adjunctive intravenous Human Immunoglobulin. Cidofovir is pan serotypic and has demonstrated best efficacy among all the available agents. Its main drawbacks include dose limiting nephrotoxicity, and cost. Brincidofovir, an oral lipid ester of cidofovir has been touted to be less nephrotoxic but is not yet available in the market. Ganciclovir has limited activity against adenovirus *in vitro* but has been used successfully in some case reports. Ribavarin is not recommended as it has no consistent activity against adenovirus in vitro. Pooled intravenous human immunoglobulin has been utilized as adjunctive immunotherapy and has shown promise especially in patients with a hematopoietic stem cell transplant.[1,12-14]

It is prudent to understand that what may seem as focal allograft disease may quickly progress to overwhelming sepsis, as in our patient. Our decision to scale down immunosuppression was quick, however we did not initiate specific anti-viral as initial disease did not appear disseminated and Cidofovir was not immediately available at our center. We initiated IVIG when the patient deteriorated, however, the downhill turn was quickly, fatal.

Conclusion

Necrotizing adenoviral tubulo-interstitial nephritis is a potentially fatal infectious complication that should be kept in mind in the early post kidney-transplant period. Cytopathic changes in renal allograft biopsies may provide clues to an underlying adenoviral etiology, which can be confirmed with IHC testing. This infection deserves a swift response by reducing net immunosuppression. It may be prudent to initiate anti-viral agents and IVIG early in disseminated disease. Our association of adenoviral interstitial graft nephritis with TMA has been highlighted.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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