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Review Article

Post transplant thrombotic microangiopathy

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ARTICLE INFO

Article history:
Received 5 October 2014
Accepted 25 November 2014
Available online 12 December 2014

Keywords:
Eculizumab
Plasma exchange
Post renal transplant thrombotic microangiopathy

ABSTRACT

Thrombotic microangiopathy (TMA) is an uncommon but serious complication in renal transplant recipients. Posttransplant TMA can either be due the recurrence of the pre-transplant disease or it may occur de-novo. Amongst pre-transplant TMA, majority of the atypical HUS usually lead to renal insufficiency and end-stage kidney disease, while the typical or shiga toxin associated HUS has good prognosis. Post-transplant recurrence is <1% in shiga toxin associated HUS, whereas it is around 80–100% in certain forms of atypical HUS. Due to this high recurrence rates, previously the renal transplant was contraindicated in such patients, however, with better understanding of the pathogenesis of disease and progress in genetic analysis, renal transplant may now be possible in some of these patients. In view of the lack of controlled trials, plasma exchange remains the primary modality of treatment, while further options include isolated kidney transplant, liver transplant, combined liver-kidney transplant, prophylactic and therapeutic eculizumab and judicious use of immunosuppressant. In this review, we have discussed various causes of posttransplant TMA, their pathogenesis, outcomes and different therapeutic options.

1. Introduction

Thrombotic microangiopathy (TMA) is a pathological process comprising of microvascular thrombosis, thrombocytopenia and microangiopathic hemolytic anemia, leading to end organ involvement, primarily kidney and brain but may involve other organs also. Historically, TMA with significant central nervous system dysfunction, severe thrombocytopenia and relative renal sparing was labeled as thrombotic thrombocytopenic purpura (TTP) which had characteristic platelet-rich thrombi,[1] while those with predominant renal involvement were termed hemolytic uremic syndrome (HUS) with severe fibrin-rich thrombi.[2] This earlier distinction between TTP and HUS has now been narrowed down to presence or absence of ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) and deficiency of various complement factors.

TMA has been reported to occur in between 3 and 14% of renal transplantation recipients and is associated with an increased risk of graft loss. The first case of de novo HUS in kidney transplant recipient was reported by Leithner et al in 1982.[3] Subsequently other case reports and a cohort study determined that patients of HUS receiving renal transplant had a recurrence rate of 29%, while the incidence of de novo TMA was 0.8%.[4] Since TMA is associated with significant graft loss, it is important to understand its etio-pathogenesis and mange them appropriately. In this review, we will focus on various causes of post renal transplant TMA and their appropriate management.

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http://dx.doi.org/10.1016/j.ijt.2014.11.002

2. Pathogenesis of renal TMA

The most fundamental step in the pathogenesis of TMA is the endothelial cell injury, which triggers a cascade of complement and coagulation system besides abnormal platelet aggregation. Although the cause of predominant involvement of glomerular endothelium is not clear, its fenestrated nature and lack of complement regulators in glomerular basement membrane might make it more susceptible.[5–7] Histopathologically, it is characterized by the presence of fibrin thrombi, endothelial swelling and subendothelial widening with fragmented RBCs in the lumen of arteries, arterioles or glomerular capillaries. Granular C3 deposits can be seen in glomeruli and arterioles in the acute phase, while chronic TMA can have mesangiocapillary pattern with double contoured glomerular basement membrane. The pathology can either be predominantly glomerular, or vascular or mixed type.[8]

3. Classification of post-transplant TMA

In kidney transplant recipients, TMA can either develop de novo or as a result of recurrence of the primary disease (Table 1). Further, it can either be localized or systemic. In a retrospective review, 62% patients had systemic TMA, while 38% had localized TMA.[9] They also noted that while systemic TMA were identified much earlier (21 ± 19 days vs 106 ± 104 days), had greater incidence of dialysis dependent renal failure and early graft loss (38%); localized TMA did not require dialysis or plasma therapy and also did not progress to systemic TMA or graft loss.[9]

3.1. *De novo TMA*

Incidence of de novo TMA varies from 0.8 to 15% of renal transplant recipients and majority occurs within first 3 months post-transplant (53% developed within first month and only 12% after one year of transplant). Calcineurin inhibitor (CNI) toxicity is the most common etiology; other risk factors include female gender, dialysis vintage, sirolimus, donation after cardiac death, delayed graft function, acute rejection, antiphospholipid antibodies and viral infections.[9–11] Nearly 30% patients with diagnosis of de novo TMA had associated mutations in CFH, or CFI and some also had antibodies to ADAMTS 13.[12] This diagnosis should be considered in relatively young patient, who develops severe hypertension with progressive decline in graft function in the early posttransplant period.[13]

Table 1 – Classification of post-transplant TMA.

De novo TMA	Recurrent TMA
Ischemia reperfusion injury Calcineurin inhibitor mTOR inhibitor Viral infections (Influenza, Cytomegalovirus (CMV), BK Virus, Parvo B19) APLA in HCV positive recipients Scleroderma Antibody-mediated rejection Acute vascular rejection	Shiga toxin associated HUS (rare <1%) Atypical HUS - loss of function mutation (Complement Factor H (CFH), Complement Factor I (CFI), Membrane Cofactor Protein (MCP)) - gain of function mutation (Complement Factor B (CFB), C3, thrombomodulin) - genomic rearrangements of CFH & CFHR1-5 (CFH Related Proteins) Second hit by any of the factors for de novo TMA (drugs, pregnancy, rejection, infection)

3.1.1. *CNI associated TMA*

In 1981, Shulman described 3 cases of TMA in bone marrow transplant recipients on cysclosporine (CsA).[14] In 1999, Zarifian et al reported 26 cases of CsA associated TMA over 3 years follow up, where 2 had systemic features.[15] Frequency was higher in recipients who had received micro emulsion cyclosporine A (CsA), possibly because of increased bioavailability and trough levels. Although, mostly a limited disease, it can disseminate to involve organs like lungs, skin, musculoskeletal system or liver.[16]

CsA is directly toxic to endothelial cells; inhibiting the synthesis of prostacyclin and increasing thromboxane A2. It is antiproliferative and pro-apoptotic on endothelial cells and blocks vascular endothelial growth factor (VEGF). High CsA levels is correlated with increased circulating endothelial cells and it also blocks repopulation of allograft vasculature by recipient derived endothelial cells. Biopsy shows thrombi in lumina of arterioles and glomerular capillaries with no significant intimal changes,[17–19] while graft survival was reported to be around 60%.[20] CNI induced TMA usually occurs in first few weeks of transplant when dose of drug is highest and can develop even after a single dose. Though some studies report higher incidence with CsA (5–15%) compare to tacrolimus (1%), others showed no significant difference.[21,22] Mainstay of therapy is withdrawal or reduction of CNI dose and interestingly majority of patients who were subsequently reintroduced to CNI did not have recurrence.

3.1.2. *Sirolimus associated TMA*

Sirolimus blocks mammalian target of rapamycin (mTOR), thereby inhibiting response to cytokines and growth factors, $p70^{s6k}$ activation and progression of cell cycle, preventing proliferation of vascular smooth muscle cells and endothelial cells.[23–25] In the transplant scenario, endothelial cells repair is prevented by antiproliferative action of sirolimus. Though sirolimus was initially considered safe and was used successfully in patients with CNI induced TMA, there were several reports of sirolimus induced TMA, some of which improved after switching to CNI.[26–28] Incidence is as high as 18.1 per 1000 patient years compared to 5per 1000 patient-years for CNI.[4]

3.1.3. *Infection associated post-transplant TMA*

Several infections have been implicated in the posttransplant TMA, including parvovirus B19, cytomegalovirus (CMV), BK polyoma virus (BKV) and hepatitis C virus (HCV). Parvovirus can cause endothelial damage by producing immune complex or by direct invasion of endothelium, as receptor for parvo B19 i.e. P antigen is present on endothelial cells.[29,30]

CMV increases the expression of endothelial adhesion molecules and von-Willebrand factor (vWF). There are