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Case Report

A rare case of refractory active antibody mediated rejection who had recurrence of immunoglobulin a nephropathy in the form of crescentic glomerulonephritis

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ABSTRACT

Immunoglobulin A nephropathy is one of the most common recurrent glomerulonephritis after kidney transplantation. Recurrence rate is around 30% at 10 years after transplant. Rarely, rapid deterioration of renal function may occur suggestive of presence of crescents. Presence of donor specific antibodies can predict poor transplant outcomes. Compliance to immunosuppressive medications will prevent development of donor specific antibodies and prolong allograft survival. Authors hereby report a case of refractory active antibody mediated rejection who developed recurrent Immunoglobulin A nephropathy 3 years after renal transplantation.

Keywords: Cyclophosphamide, Crescentic glomerulonephritis, Refractory active antibody mediated rejection, Recurrent Ig A nephropathy, Steroid

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common form of glomerulonephritis worldwide. There is mesangial proliferation and diffuse deposition of IgA.[1] There is progression to end stage kidney disease (ESKD) in around 25% of the patients within 10 years of diagnosis.[2] Around 9–61% of the patients with primary IgAN can recur post renal transplantation.[3] Mostly, IgAN recur after 3 years of renal transplantation.[4] With recurrence of IgAN, the risk of graft loss increases by twofold.[5] Usual presentations are persistent haematuria and low-grade proteinuria. Rarely, there can be a rapid deterioration of renal function which can be suggestive of presence of crescents.[6] We hereby report a case of refractory active ABMR who developed recurrent IgAN 3 years after renal transplantation in the form of crescentic glomerulonephritis.

CASE REPORT

Patient was hypertensive from 2020 for which he was on tablet Amlodipine 5 mg once daily dosage. He was found to be hepatitis B reactive in 2020 for which he was started on Entecavir. With a basic disease of chronic glomerulonephritis, patient was declared ESRD in January, 2022. Live related renal transplant was done on 19 April 2022. Pre transplant donor specific antibody (DSA) class 1 titre was >1000 pre-transplant. Thymoglobulin was given as induction. Immediate post-transplant period was uneventful. He was on triple maintenance immunosuppression (Prednisolone+ Tacrolimus+ Mycophenolate sodium). Nadir Creatinine was around 1 mg/dl. He lost to follow up from December, 2023 to December, 2024. Compliance to immunosuppression during this time is doubtful. He had asymptomatic rise in creatinine to 1.39 mg/dl on

22.1.2025. Tac level was 1.99 ug/l in January, 2025. Graft biopsy showed 5/7 glomeruli segmental sclerosis, interstitial fibrosis and tubular atrophy (IFTA)-20-25%, ci1, ct1, cv2, ah3, ptc2, ctg1, diffuse c4d staining with immunofluorescence showing Ig A 1+ AND C3 1+ suggestive of active antibody mediated rejection (ABMR) with evidence of moderate chronicity. Baseline proteinuria was 10.2 gm in February, 2025. DSA titres against class II HLA were 8674 MFI (Mean fluorescence intensity). Immunosuppression was augmented. He was given pulse steroids followed by high dose oral steroids. He received a total of 100 gm intravenous immunoglobulin (IVIG) over 5 days with 5 sessions of plasmapheresis. 24 hours urine protein was 5.83 gm on 9.3.2025. DSA titres against class II HLA were 4252 MFI on 25.3.2025. Serum creatinine was 2.2 mg/dl. He was given another 5 sessions of plasmapheresis and injection Rituximab 1gm in April, 2025.

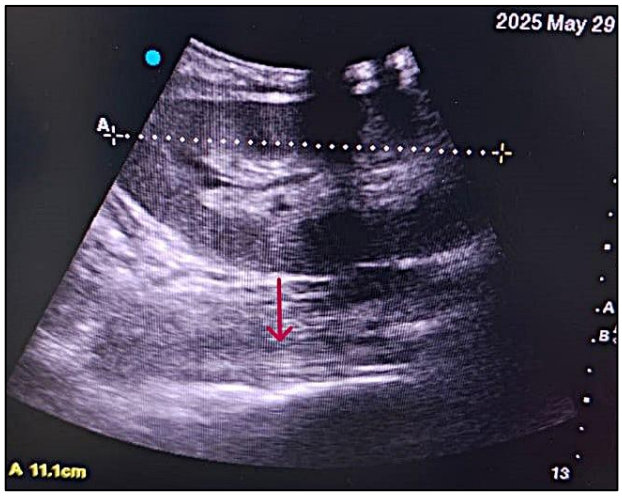

Figure 1: Graft kidney, 11.1 cm in size and slightly raised echogenicity.

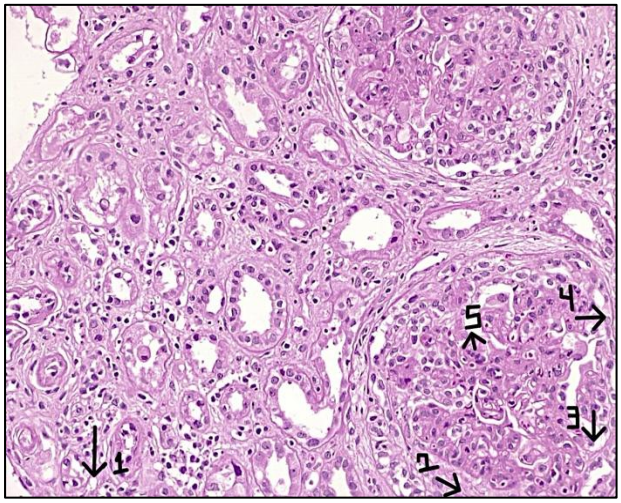

Figure 2: Renal biopsy light microscopy H&E stain 40X magnification. 1. Peritubular capillaritis, 2. Cellular crescent, 3. Endocapillary hypercellularity, 4. Mesangial expansion, 5. Mesangial hypercellularity.

He presented with uremic gastritis and lower limb oedema with a rapid rise of creatinine from 2.2 to 7.8 mg/dl within a span of 2 weeks in May, 2025. Table 1 shows the investigations at presentation. Ultrasound (USG) Doppler showed normal sized graft kidney with slightly raised echogenicity and resistive index (RI) of 0.6-0.7 with no evidence of graft stenosis, thrombosis and hydronephrosis. Figure 1 shows the USG image of the graft kidney. Haemodialysis was initiated in view of fluid overload. DSA titres against class II HLA were 4113 MFI on 31.5.25. Tac level was kept around 5 ug/l.

Cytomegalovirus (CMV) DNA, Epstein bar virus (EBV) DNA, BK virus DNA and hepatitis B DNA were negative in May, 2025. Graft biopsy showed 1/10 glomeruli global sclerosis, crescents in all glomeruli, IFTA-20-25%, ct1, ci1, ti2, cv2, ah1, ptc1, c4d+ staining with severe acute tubular injury. Immunofluorescence showed Ig a-3+ and c3-1+. This was suggestive active antibody mediated rejection with moderate chronicity with crescentic Ig A Nephropathy. Figure 2 shows the graft biopsy light microscopy H and E stain image. He was given pulse methylprednisolone 500 mg followed by oral prednisolone 1 mg/kg/day dose. He was given IV IG a total dose of 100 gm over 5 days. Intravenous cyclophosphamide 750 mg was given as per CYCLOPS regime. He was managed as a case of crescentic glomerulonephritis.

Table 1: Investigations at presentation.

Parameters (units)	Patient values	Reference range
Haemoglobin (gm/dl)	10.3	12-15 gm/dl
TLC ($\times10^3$/ul)	5.35	4-11$\times10^3$/ul
Platelet count ($\times10^3$/ul)	231	150-400$\times10^3$/ul
Urea (mg/dl)	90	17-43 mg/dl
Creatinine (mg/dl)	7.8	0.55-1.02 mg/dl
Serum albumin (gm/dl)	2.8	3.5-5.2 gm/dl
24-hour urine protein (gm/day)	7.4	0.04-0.15 gm/day

DISCUSSION

Crescentic IgAN is estimated to account for 3–5% of IgAN.[7] Recurrence rate is around 30% at 10 years after transplant and around 50% in biopsied patients.[8-11] In this case, there was recurrence of IgAN within 3 years of renal transplantation. Median time to recurrence was found to be 3.4 years as per TANGO study.[12] TANGO study also found that the presence of pre-transplant donor-specific antibodies (DSAs) and post-transplant de novo DSAs increased IgAN recurrence risk.[12] In this case, pre transplant DSAs were present. Clinical factors associated with a higher risk of IgAN recurrence include a rapidly progressive course of disease in native kidneys, crescents

on the native kidney biopsy, male gender, younger age at transplantation, early steroid withdrawal, living related donor and lower donor–recipient HLA mismatch.[13-17] Circulating under-galactosylated or galactose deficient (Gd) IgA1 and the subsequent generation of anti-GdIgA1 IgG (IgA) play central roles in the pathogenesis of IgAN.[18] Suzuki et al, found that serum IgA levels were closely associated with disease activity in native Ig AN.[19] Serum IgA was an independent risk factor for IgAN recurrence as per Julian's group.[20]

Donor was wife with 3/12 HLA match in this case. There was no early steroid avoidance. Thymoglobulin was given as an induction agent in this case. Mousson et al, speculated that the presence of crescentic IgAN in native kidneys may be associated with the recurrence of crescents in the allograft.[11] Native kidney biopsy is not available in this case. Tang et al, suggested that establishment of mycophenolate mofetil therapy in cases whose immunosuppressive regimen consisted of Prednisolone Calcineurin inhibitor Azathioprine may prevent the formation of crescents.[21] But patients on MMF still can have crescentic IgAN recurrence.[11] This case also had crescentic IgAN recurrence although he was on Mycophenolate sodium as maintenance immunosuppression agent. Radhakrishnan et al reported a case who achieved remission with pulse steroids and six-monthly doses of intravenous cyclophosphamide. Steroids were tapered over 3 months. Intravenous cyclophosphamide is recommended for crescentic IgAN in native kidneys by KDIGO guidelines with low quality of evidence, but it is not an established treatment in allograft recurrence.[22]

Sensitization can occur in cases of organ transplant, pregnancy or blood transfusion.[23,24] Presence of DSA, either preformed or de novo can predict poor transplant outcomes which include high incidence of antibody-mediated rejection, graft dysfunction and inferior graft survival. The risk factors for de novo DSA include high HLA mismatches (especially DQ mismatches), inadequate immunosuppression and nonadherence and graft inflammation, such as viral infection, cellular rejection or ischemia injury, which can increase graft immunogenicity.[25-27]

In this case, patient was non-compliant to immunosuppressive medications for which he had such high levels of DSA's that were refractory to therapies given for ABMR in the form of high dose steroids, intravenous immunoglobulin, plasmapheresis and rituximab. There are no approved therapeutics for refractory chronic ABMR.[28] As per Degner et al patients with c-ABMR were treated with IVIG, corticosteroids and rituximab. Persistent rejection after each biopsy was treated primarily with IVIG and corticosteroids. There was reduction in circulating levels of class II and total DSA. There was no change in the overall kidney function in the first year of diagnosis.[28] Patients in this study later demonstrated persistent allograft inflammation but eventually had modest histologic improvement.[28] In this case, DSA were persistently elevated and biopsy showed evidence of active antibody mediated rejection with moderate chronicity. Thus, IV IG and pulse steroids followed by oral steroids were given again.

CONCLUSION

Recurrence of basic disease can present as crescentic glomerulonephritis that can lead to rapid deterioration of renal function. Compliance to immunosuppressive medications will prevent development of DSA and prolong allograft survival.

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