Successful induction of granulomatosis with polyangiitis with tacrolimus

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ABSTRACT

We report a 50-year-old female who presented with inflammatory arthritis, upper respiratory tract symptoms, and microscopic hematuria with nephrotic range proteinuria. Antineutrophil cytoplasmic antibodies (ANCA) were detectable and kidney biopsy showed pauci-immune focal necrotizing crescentic glomerulonephritis. She was treated with pulse intravenous cyclophosphamide (CYC) and prednisolone. Patient developed severe leucopenia after the first dose and subsequently had leucopenia to low dose CYC, mycophenolate mofetil and azathioprine were also tried. However, patient developed leukopenia with all the above agents. Initiation of tacrolimus (TAC) was followed by dramatic response: Proteinuria decreased, serum albumin normalized and C-ANCA and anti-PR3 ANCA assays became negative. This is the first successful case of TAC as an induction agent in a patient with GPA (ANCA associated vasculitis with renal involvement).

Key words: Antineutrophil cytoplasmic antibodies, associated vasculitis, granulomatosis with polyangiitis

Introduction

Granulomatosis with polyangiitis (GPA) is one of the anti neutrophil cytoplasmic antibody-associated vasculitis (AAV) with multisystemic involvement.[1] Renal manifestations are variable, ranging from asymptomatic microscopic hematuria to advanced renal failure. Overall, 50-95% of patients develop clinical evidence of renal impairment during the course of the disease.[2] Pulse intravenous cyclophosphamide (CYC) and steroids are the induction agent of choice in AAV with renal involvement.[2,3] Mycophenolate mofetil (MMF) and rituximab are alternative induction agents.[4,5] Until now, there are no reported cases for the use of calcineurin inhibitors as induction agents in the management of generalized AAV.[6]

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Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.136885

Case Report

A 50-year-old female presented with symmetrical small and large joint arthralgia with early morning stiffness, upper respiratory symptoms in the form of intermittent nasal stuffiness, dry cough, epistaxis, together with pedal edema. Patient was evaluated initially by her primary health care physician for these presenting complaints. Upon investigation, she was found to have dipstick positive proteinuria.

On examination, her blood pressure was160/80 mm Hg. There was no pallor, icterus, cyanosis or clubbing. She had bilateral pitting pedal edema with tenderness of the small joints of the hands. Upper respiratory tract examination revealed mucosal edema with secretions in both nasal cavities. Indirect laryngoscopy was done, which identified oropharyngeal mucosal erythema. Laryngopharynx were unremarkable. Examinations of the cardiovascular, respiratory, abdominal, and neurological systems were unremarkable.

Urine analysis revealed 2 + albuminuria with a 24-h urine protein of 3.8 g and 30-40 red blood cells/high power field. Renal function tests were deranged with a serum creatinine of 1.5 mg/dl and blood urea of 40 mg/dl. Hematological evaluation showed hemoglobin of 12 g/dl, total leukocyte count (TLC) of 4900/cu mm, platelet count of 180 × 10^3/cu mm and an erythrocyte sedimentation

rate of 50 mm/h. Cytoplasmic-antineutrophil cytoplasmic antibodies (C-ANCA) (3 + by indirect immunofluorescence, [IF]) and anti-proteinase3 (PR3) ANCA (14 U/ml by enzyme linked immunosorbent assay (ELISA); reference range <1.3 U/ml) were positive. Antinuclear factor was negative, and complement levels were within normal range (C3-109 mg/dl; reference range 90-207 mg/dl, C4-17 mg/dl; reference range 10-40 mg/dl). She tested negative for hepatitis B surface antigen, antibody to hepatitis C virus and HIV I and II. High-resolution computerized tomography of the chest identified no abnormalities. With a provisional diagnosis of nephrotic syndrome with GPA (renal and upper respiratory tract involvement), a kidney biopsy was performed.

Kidney biopsy showed 10 glomeruli, four of which showed cellular crescents. One of the glomeruli showed the presence of tuft necrosis ([Figure 1], periodic acid-Schiff stain, ×400). The tubulointerstitial compartment revealed acute changes predominantly with patchy areas of sclerosis and atrophy (10% of cortical area). Blood vessels were unremarkable with no evidence of vasculitis. Immune deposits were absent on IF and electron microscopy. A diagnosis of pauci-immune necrotizing crescentic glomerulonephritis was made.

Patient was started on pulse intravenous CYC (750 mg/m^2) and pulse methyl prednisolone (15 mg/kg) daily for 3 days, followed by oral prednisolone (1 mg/kg/day). After 15 days of pulse CYC therapy, she developed leucopenia (TLC-2700). Subsequently, CYC was therefore withheld for 2 weeks. Total counts improved to 4500, and the next dose of intravenous pulse CYC (375 mg/m^2) was given. Unfortunately, 2 weeks later, she developed leucopenia again (TLC-1400/cu mm). Her 24-h urine protein, serum albumin and creatinine were 2.9 g, 2.9 g/dl and 1.4 mg/dl, respectively. In response to the severe leukopenia, CYC treatment was withheld, and she was advised rituximab therapy. However, patient refused to consent for biological agents citing adverse reactions in her family members.

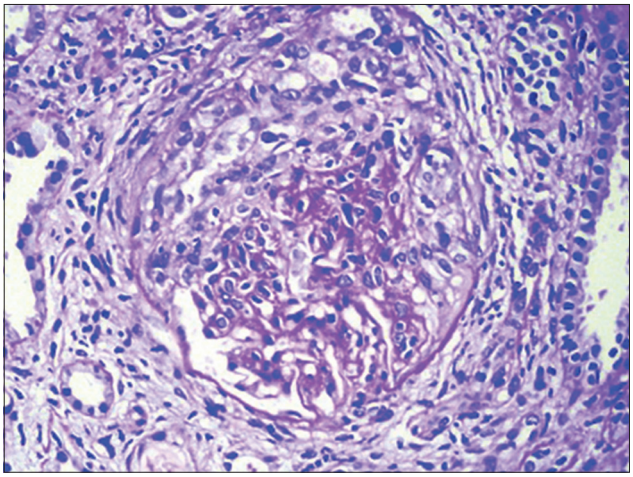

Figure 1: A glomerulus showing cellular crescent. The underlying glomerular tuft shows segmental necrosis with fibrin exudation and presence of few karyorrhectic debris (periodic acid-Schiff stain, ×400)

Consequently, she was then started on MMF (1.5 g/day). Ten days after starting MMF, her TLC declined to 1500/cu mm. MMF was therefore also withheld and following improvement of her TLC, azathioprine (AZA) therapy was started. Patient's 24-h urine protein, serum albumin and creatinine were 2.4 g, 3.2 g/dl, and 1.2 mg/dl, respectively at the time of stopping MMF. Patient developed severe leukopenia (TLC 1800/cu mm) 15 days after initiating AZA. C-ANCA (3+) and anti-PR3 (12 U/ml) were repeated, all of which were still positive with persistent upper respiratory tract symptoms and arthralgia.

In view of the severe leukopenia with CYC, MMF and AZA, the patient was counseled and started on tacrolimus (TAC) (trough levels 8.9 ng/ml) therapy. At the time of the initiation of TAC, 24-h urine protein was 4.7 g; serum creatinine 1.4 mg/dl and serum albumin was 2.9 g/dl. Six months after starting TAC therapy, her upper respiratory tract symptoms and arthralgia subsided, 24-h urine protein excretion reduced to 0.89 g/day with serum albumin of 3.4 g/dl and serum creatinine of 0.9 mg/dl. C-ANCA and anti-PR3 were repeated, which were negative (C-ANCA was not detected by IIF and anti-PR3 was <1.3 U/ml by ELISA) and TLC throughout therapy was maintained between 5000 and 7000 cells/cu mm. Patient's TAC dose was reduced after 6 months to maintain a trough level of 5 ng/ml. At present, 12 months postinitiation of TAC therapy, the 24 h urine protein is 0.8 g; creatinine of 1 mg/dl and albumin of 3.7 g/dl [Figure 2].

Discussion

The clinical presentation (upper respiratory tract symptoms, inflammatory arthritis and renal involvement), laboratory parameters (ANCA positive by both IF and ELISA) and the kidney biopsy of our patient were consistent with active GPA. The patient received sequential induction with CYC, MMF and AZA. However, due to the development of leucopenia with all these agents, she was started on TAC therapy, to which she responded very well.

Granulomatosis with polyangiitis and microscopic polyangiitis are two types of associated vasculitis (AAV), which have been sub classified by European Vasculitis Study group according to the severity and extent of

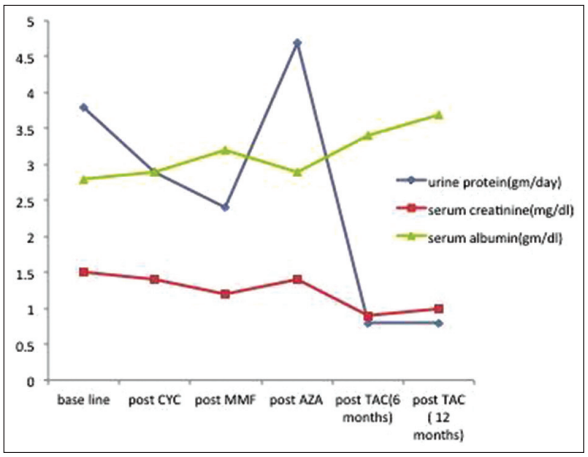

Figure 2: Course of the illness and successful response to tacrolimus

organ involvement, ranging from localized to severe organ threatening or life-threatening disease, to guide appropriate treatment decisions.[6] Initial studies in the management of AAV with renal involvement have shown favorable results with CYC as an induction agent with a remission rate between 75% and 80%, respectively.[2,3] A small randomized trial was conducted, comparing MMF and CYC in AAV with renal involvement, which showed MMF was better in inducing remission when compared to CYC.[4] Rituximab in vasculitis trial compared rituximab with CYC based regimens in AAV with renal involvement and found similar rates of remission (76% with rituximab vs. 82% with CYC; $P > 0.05$) between rituximab and CYC based regimens.[5]

Tacrolimus has been used as an induction agent in systemic lupus erythematosus with renal involvement, and has a remission rate of 75-89% in patients with active lupus nephritis.[7,8] Until now, no case report has shown a beneficial effect of TAC in patients with AAV with renal manifestations. This is the first case in which TAC was used in a patient who was intolerant to standard therapy and showed a positive response. T-cell targeted agents were used in some studies, which led to remissions in refractory AAV disease.[9,10] These results have confirmed a pathogenic role for T-cell and the potential for T-cell depletion to produce sustained remissions. Mechanism by which TAC achieved remission in our patient would probably be due to T-cell regulatory properties of the drug.

In our patient, we initially used pulse CYC (750 mg/m^2) and oral steroids for induction. She developed leucopenia with the first dose of pulse CYC. Second dose of pulse CYC (375 mg/m^2) was given after the counts had returned to normal range. However, she developed leucopenia even after receiving reduced dose of CYC. MMF and AZA were tried in a sequential manner, but patient developed severe leukopenia with these agents too. CYC induced leukopenia develops in 20-30% of patients, whereas 20-40% of patients with MMF and 25% of patients with AZA develop leucopenia.[11-13] However, no data is available on development of leukopenia due to all three drugs in a single patient. The repeat ANCA and clinical features were suggestive of active disease and thus the patient needed further immunosuppression for the management of AAV. She was started on TAC based on successful outcomes of TAC being used as an induction agent in the management of lupus nephritis and reduction in the recurrence of ANCA vasculitis postrenal transplant in patients treated with TAC.[7,8,14] After 6 months of therapy with TAC and steroids, she achieved negative ANCA status, improvement in upper respiratory tract symptoms, arthralgia and partial remission in proteinuria. The clinical remission and negative ANCA status was maintained at 1 year of therapy. Persistence of some proteinuria at 1 year is probably due to residual chronicity changes left after healing of crescentic glomerulonephritis.

Conclusion

This is the first successful use of TAC as an induction agent in the management of GPA with renal involvement. Although TAC has shown good results in the above patient, randomized control trials comparing TAC with the standard immunosuppression agents will be needed to introduce TAC as an induction agent in AAV with renal involvement.

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How to cite this article: Ramachandran R, Tiwana S, Prabhakar D, Gowda K, Nada R, Kumar V, *et al*. Successful induction of granulomatosis with polyangiitis with tacrolimus. Indian J Nephrol 2015;25:46-9.

Source of Support: Nil, **Conflict of Interest:** None declared.