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A case of resistant Membranous Nephropathy with venous thrombosis treated with Rituximab presenting with a relapse Response to a second course of Rituximab

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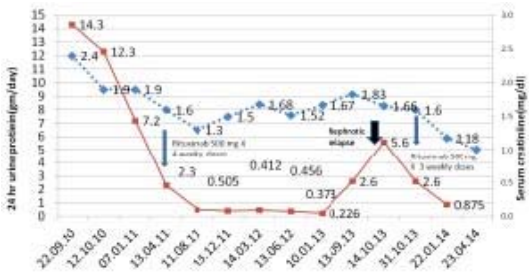
Abstract :
A 54 year old gentleman with no previous co-morbidities, with nephrotic syndrome, normal renal function complicated by deep vein thrombosis (DVT) in lower limbs with renal biopsy showing Membranous nephropathy was treated with Steroid and cyclophosphamide and later with Tacrolimus and steroids with no response in proteinuria and worsening renal function. His investigation revealed a protein of 3 and no active urine sediments and a 24 hr urinary protein of 14.3gmday, serum albumin of 2.0gmdl, hypercholesterolemia and serum creatinine was 1.9 mgdl. In view of poor response to Endoxan and worsening renal function to prednisolone and Tacrolimus, function he was advised for Rituximab .He was given Rituximab 500 mg per dose IV as an infusion for a total of four weekly doses and the follow up showed a good response with no symptoms and a urine analysis negative for protein and 24 hr urine protein of 505 mgday serum creatinine of 1.3 mgdl and the serum albumin of 4.1 gmdl, normal fasting lipid profile. After duration of two and half years in remission there was an increase in proteinuria to 5.6 gmday. He was given second course of Rituximab of three doses at 375 mg1.73 m2 per dose was given at weekly intervals. There were no adverse events during the infusion. After the second course of the Rituximab he improved symptomatically and with a reduction in 24 hr urine protein to 875 mgday and serum creatinine came down to 1.13mgdl. Conclusion A third of MN patients relentlessly progress to end stage renal disease and in this subset of patients rituximab has shown good promise in achieving remissions for prolonged intervals. Some of these cases, which subsequently relapse, can be treated with a second course of Rituximab successfully with no apparent side effects attributable to rituximab. There was a sustained remission and improvement in the GFR.

Keyword : Nephrotic Syndrome, proteinuria, Membranous nephropathy, Relapse, Rituximab



Graph representing the 24 hr urine protein and Serum creatinine in mg/dl over the follow up period of three years and the time of Nephrotic relapse (broad arrow) and administration of the rituximab(thin arrows)

A 54 year old gentleman with no previous comorbidities, with progressive edema in both lower limbs since March 2009, had to be admitted with bilateral lower limb cellulites. On evaluation at a local hospital he was diagnosed with nephrotic syndrome with a normal renal function. There was deep vein thrombosis (DVT) in the both lower limbs. He underwent CT-guided renal biopsy which was suggestive of Membranous nephropathy. He received Endoxan for 3 months. He was started on warfarin for DVT and diuretics were given for reduction of edema. Steroids were not prescribed for reasons not specified. After three months of treatment, there was no improvement in symptoms. Subsequently in December 2009 he was initiated on Tacrolimus and prednisolone in view of non response to initial regimen. By March 2010 proteinuria was persistent with worsening of renal function with a S. Creatinine of 2mg/dl. At this point of time, Tacrolimus was stopped and was referred to our hospital.

His investigation revealed a protein of 3+ and no active urine sediments and a 24 hr urinary protein of 14.3gm/day, hypoalbuminemia with a serum albumin of 2.0gm/dl, hypercholesterolemia and haemoglobin of 10.1 gm%. The serum creatinine was 1.9 mg/dl. C3 AND C4 were normal. Screening of the Hepatitis B and C and HIV were negative. The colour Doppler was showing features of chronic right DVT of the lower limb. His anti-coagulation was stopped and his bleeding parameters were normalized following which he underwent an ultrasound guided renal biopsy on 7/10/2010. His biopsy shows diffuse, uniform thickening of glomerular capillary walls and mild matrix expansion. The Immunofluorescence shows Contiguous, granular IgG (3+) C3 (2+) on capillary walls suggestive of Membranous nephropathy. There was mild interstitial infiltration. In view of past history of poor response to Endoxan alone and worsening renal function to prednisolone and Tacrolimus he was advised for prednisolone and oral Endoxan for three months. The oral anticoagulation was restarted in view of chronic DVT in the lower limbs. The RAAS inhibition was optimised with Losartan. He came for review after three months of Endoxan and Prednisolone with persistent symptoms. The evaluation revealed a serum creatinine of 1.9 mg/dl and serum albumin was 2.9 mg/dl and the haemoglobin of 8.1 mg/dl. There was persistent proteinuria with bland urine sediment and a 24 hr urine protein of 7.2 gm/day.Since there was no symptomatic improvement with Endoxan and prior use of Tacrolimus was associated with worsening of renal function, he was advised for Rituximab after ruling out infection which included a screening for tuberculosis with a chest x-ray

and sputum for AFB. He was given Rituximab 500 mg per dose IV as an infusion for a total of four weekly doses and the follow up showed a good response with increased serum albumin at 3.3 gm/dl with disease in partial remission at three months with a 24 hr urine protein of 2.3 gm/day which further reduced to 1.4gm/day over the next month with a serum albumin of 3.8gm/dl. He was advised for a review after three months during which he was on prednisolone of 20 mg on alternate days and oral anticoagulation for chronic DVT. During the subsequent visit he was completely free of his symptoms and investigation revealed a urine analysis negative for protein and 24 hr urine protein of 505 mg/day serum creatinine of 1.3 mg/dl and the serum albumin of 4.1 gm/dl, normal fasting lipid profile. During this visit he was advised for a gradual taper of the steroid dose over the next three months. The renal function remained stable and proteinuria improved to remission. The trends in the 24 hr urine protein and creatinine over the next three years are represented in **fig 1**. After a duration of two and half years in September 2013 there was an increase in proteinuria to an urine protein creatinine ratio of 2.82 with a 24 hr urine protein of 2.6 gm/day and serum albumin was 2.7 gm/dl and serum creatinine of 1.83mg/dl. The proteinuria increased to 5.6 gm/day over the next month with further reduction serum albumin to 2.2 gm/dl. Serum creatinine remained stable. There was a dilutional hyponatremia which improved with fluid restriction. He was explained about the relapse and the options of reinitiation of the immunosuppression were also discussed. A thorough examination and evaluation for the focus of any potential malignancy and chronic infection, including a bone marrow smear and biopsy were negative. An evaluation for the EBV and a quantitative PCR for CMV were negative and he was advised for a second course of Rituximab of three doses at 375 mg/1.73 m2 per dose was given at weekly intervals. There were no adverse events during the infusion. Prednisolone was restarted at 1 mg /kg on alternate days was advised to continue for three months. After the second course of three weekly doses of Rituximab he improved symptomatically and the serum creatinine came down to 1.13mg/dl. There was an increase in serum albumin to 3.2 gm/dl with a reduction in 24 hr urine protein to 875 mg/day. After this he was advised for a steroid taper over the next three months. He continued to be on Optimum RAAS blockade and oral anticoagulation as there was an evidence of chronic deep venous thrombosis.

DISCUSSION:

Membranous nephropathy (MN) is most common aetiology for nephrotic syndrome after 50 yrs of age. An immune complex mediated disease, in which podocyte antigens or similar antigens in circulation are targeted by circulating IgG4 antibodies resulting in formation of either circulating immune complexes which either cross the glomerular basement membrane or form in situ as sub-epithelial deposits resulting in stimulation of the complement cascade resulting in non fatal podocyte injury and breach of the filtration barrier manifesting as nephrotic range proteinuria. Recent literature supports the pathogenic role of an autoantibody against the Mtype isoform of the phospholipase A2 receptor (PLA2R) with a good correlation between titres of this antibody and nephrotic range proteinuria or posttransplant recurrence of idiopathic membranous nephropathy[7] .The other possible antigen targets

proposed are neutral endopeptidase, aldose reductase, superoxide dismutase 2 and enolase. There are several studies which have demonstrated show a decline in the titre of antiPLA2R antibodies and remission of proteinuria after treatment of Membranous nephropathy [7]. The secondary causes of Membranous nephropathy include autoimmune diseases like SLE,IgG4related autoimmune disease, infections like the Hepatitis B and C, Schistosomiasis and malignancies which include the breast and prostate malignancies. Several medications and the chemical molecules have been implicated as causative for Membranous Nephropathy[8]. The natural history of the Membranous nephropathy which, shows a spontaneous remission rate of around 30 % has encouraged an initial expectant management with the optimal RAAS blockade and blood pressure control for 3 – 6 months except when such a management is punctuated with life threatening complications like sepsis secondary to severe hypoalbuminemia, debilitating nephrotic illness impairing the quality of life or thrombo-embolic events which immediately warrant a more specific therapy with immunosuppressives. The available therapies for induction of remission in Membranous nephropathy are the prednisolone administered along with either an alkylating agents like cyclophosphamide or Calcineurin Inhibitors The remission rates achieved are around 50-90 %. About a third of patients with Membranous Nephropathy will not achieve remission despite the use of the standard regimens and progress to end stage renal disease over a period of time. Therapeutic role of Rituximab has been well contemplated in several anecdotal reports and later with well controlled trials in Membranous nephropathy resistant to the conventional immunosuppressive therapy and optimal RAAS blockade.

Rituximab in Membranous nephropathy:

Rituximab is a chimerical monoclonal antibody with human constant region and murine variable region against CD20; an antigen expressed during most stages of Bcell development except their stem cell precursors was approved for the use in haematological malignancies like non Hodgkin's lymphoma and chronic lymphocytic leukaemia. Subsequently it use has been extended to autoimmune diseases like the SLE and the vasculitis. [9] Rituximab was first reported to induce remission of nephrotic syndrome in a boy aged 16 years who was treated for coexisting idiopathic thrombocytopenic purpura. A systemic review of data from 21 studies including 69 patients with membranous Nephropathy complete and partial response rates were around 15-20% and 35-40% with many of these patient being non responsive to the initial standard treatment. In a subsequent study with a prospective cohort of 100 consecutive patients with membranous nephropathy given 1–4 doses of Rituximab, with an median follow up of 2.5 years complete and partial remission occurred in 27 and 38 patients, respectively, with a range 3.2–12.0 months duration for remission. About a third of patients in this study had no response to previous therapy with other medications. Remission was seen in 47 of 68 (69.1%) patients given Rituximab as the primary immunosuppressive agent, and in 18 of 32 (56.3%) patients who received Rituximab as a second line agent after failure to achieve remission to the first line immunosuppressives. The proportion of patients with achieving complete and partial remission increases over time, indicating a delayed response and remission is

sustained after Bcell recovery. These may reflect a lag in regaining the structural integrity of the glomerular filtration barrier including the clearance of sub-epithelial immune complexes. Although these patients might relapse, retreatment with rituximab is effective in inducing further remission.[17] Studies indicating an improvement in glomerular filtration rate (GFR) increased in patients with complete remission. [17]

Mechanism of action of Rituximab in Nephrotic syndrome:

reactions or increased risk of infection. This is a rare case in which adult membranous nephropathy was successfully treated with a second course of Rituximab without any adverse effects. Predictors of a lack of response to Rituximab therapy in patients with membranous Nephropathy include a high tubulointerstitial score and tubular atrophy and interstitial fibrosis in kidney biopsy samples and impaired renal function at baseline.[17] Serum levels of rituximab were lower in patients with membranous nephropathy with substantial proteinuria than in those given rituximab during remission, or in patients with rheumatoid arthritis. The loss of drug in proteinuric patients has been considered as a speculative mechanism for the lower level of the drug in nephrotic syndrome. Decreased efficacy of Rituximab in patients with proteinuria in the nephrotic range has been proposed in other studies, which suggests that rituximab should be administered in multiple doses to achieve good therapeutic efficacy and the use of RAAS blockade for reduction in the proteinuria might help in the augmentation of the therapeutic effect of the drug. Most studies of patients with nephrotic syndrome have used a Rituximab dose of 375 mg/m2 once a week for 1–4 weeks, which is adapted from the standard regimen for lymphoma.

Side effect profile after Drug administration:

It has been a relatively safe drug with few side effects which predominantly consists of infusion reactions that can be avoided with premedication with antihistaminics and hydrocortisone. The other adverse effects are increased susceptibility to infections like the BK nephropathy, herpes group of viruses. Rarely Acute lung injury and CNS gliomas have been reported' **Conclusion:** The natural history of membranous nephropathy though, demonstrates a spontaneous resolution in around a third of patients; with current standard immunosuppressive regimens significant remission rates are being achieved. But still around a third of these patients relentlessly progress to end stage renal disease and in this subset of patients rituximab has shown good promise in achieving remissions for prolonged intervals. Some of these cases, which subsequently relapse, can be treated with a second course of Rituximab successfully as demonstrated in our case. There was an improvement in the GFR as demonstrated by the decline in serum creatinine with no side effects attributable to the drug. There was no evidence of infection despite a thorough evaluation prior to the second course. The final take on the definite immunosuppression for MN will need further evolution of the current concepts in terms of causation of the disease and pathogenesis. Until then Rituximab provides a safe alternative for the patients with resistant MN and its consequent complications like the thromoembolic events and sepsis.

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