

Case report

See http://www.oxfordjournals.org/our_journals/ndtplus/

Rapid remission of steroid and mycophenolate mofetil (mmf)-resistant minimal change nephrotic syndrome after rituximab therapy

Tom Yang¹, Cynthia C. Nast², Ashley Vo¹ and Stanley C. Jordan¹

¹Department of Medicine, Division of Nephrology and ²Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

Keywords: focal segmental glomerulosclerosis; minimal change disease; nephrotic syndrome; rituximab; steroid resistance

Introduction

Minimal change nephrotic syndrome (MCNS) is the most common cause of nephrotic syndrome (NS) in children. However, this disease also occurs in adults as an idiopathic abnormality, in association with lymphoid and other neoplasms and with administration of therapeutic agents. The pathogenesis of MCNS is not completely understood, but there is now consensus that a glomerular permeability factor in some cases is responsible for the clinical and pathological features of the disease [1–4]. Data to support this include isolation of a permeability factor produced by clonal expansion of T-cells that alters albumin permeability of rat glomerular epithelial cell monolayers [3] and induces proteinuria when injected into rats [4]. Other investigators suggest MCNS is a systemic disorder of T-cell function and cell-mediated immunity [1,2]. However, the role of T-cells and their products in the development of MCNS is not defined.

Until recently, little thought was given to a pathogenic role for B-cells in MCNS. However, serendipitous clinical experiences with the anti-B-cell (anti-CD20) drug rituximab (Rituxan[®], Genentech Inc. Vacaville, CA, USA) in the treatment of B-cell lymphomas or immune thrombocytopenic purpura (ITP) in paediatric transplant recipients, who also had recurrent focal segmental glomerulosclerosis (FSGS) [5–7], showed long-term resolution of NS. This finding suggests that B-cells and/or their products

may be a critical element in FSGS and NS. The role of B lymphocytes in the pathogenesis of MCNS is unclear. While B-cell depletion is a recognized therapy for NS mediated by antibody or immune complexes [8,9], until recently there have been no reports using this approach in treating adult-onset MCNS [10]. Herein, we report an adult with steroid and mycophenolate mofetil-resistant MCNS who subsequently had a rapid and prolonged response to treatment with rituximab.

Case report

A 40-year-old Guatemalan female in excellent health, without significant past medical history and no history of atopic disease, presented in June 2005 at an outside hospital, complaining of increasing bilateral lower extremity oedema and vague abdominal pains. Her serum albumin was 17 g/l and urine analysis showed 4+ proteinuria. Her serum creatinine was 53 µmol/l. The patient was referred to a nephrologist and underwent renal biopsy in July 2005.

Light microscopy of the renal biopsy disclosed glomeruli, tubules, interstitium and vasculature without abnormalities. Immunofluorescence of glomeruli was positive only for minimal segmental mesangial staining for IgM in a granular pattern. Electron microscopy revealed >95% effacement of podocyte foot processes within glomeruli. A diagnosis of minimal change disease was made.

The patient was treated with prednisone 60 mg/day from July to October 2005 with an incomplete clinical response. Repeat urine study in October 2005 revealed 1.48 g protein/creatinine ratio. Attempts to taper steroids resulted in increased proteinuria and she developed steroid complications, including cushingoid appearance, acne, glucose intolerance, easy bruising and obesity. A further attempt to reduce steroids was initiated by adding mycophenolate mofetil (MMF) (CellCept[®], Roche Pharmaceuticals, Nutley, NJ, USA)

Correspondence to: Stanley C. Jordan, MD, Professor of Pediatrics & Medicine, Director, Nephrology & Transplant Immunology, Medical Director, Kidney Transplant Program, Cedars-Sinai Medical Center, 8635 W. 3rd St., Suite 490W, Los Angeles CA 90048, USA. Email: sjordan@cshs.org

at 1g twice daily in November 2005. Despite this, she experienced a complete relapse of her MCNS with proteinuria increasing to 4+ and worsening oedema. Prednisone was increased to 60 mg/day and MMF was discontinued. Other medication at this time included furosemide 40 mg bid, potassium chloride 40 meq/day, losartin potassium 50 mg/day and lansoprazole 30 mg/day.

The patient was referred to our institution in January 2006. At that time, her physical exam revealed a weight of 68.7 kg (dry weight around 61.2 kg), blood pressure 119/58, pulse 69, temperature 36.6 and respiratory rate 20. She displayed cushingoid features, severe acne and 3+ lower extremity pitting oedema. Urine dipstick revealed 4+ protein with 15 g protein/creatinine ratio and a benign sediment. Her serum albumin was 17 g/l, total cholesterol 17.8 mmol/l, LDL 15 mmol/l, triglycerides 3.5 mmol/l and serum creatinine 46 µmol/l. Serologies for hepatitis B, hepatitis C, HIV1/HIV2 and parvovirus B19 PCR were negative.

Prednisone was given at 60 mg/day and MMF restarted at 1 gm/bid. She returned 6 weeks later, was admitted due to lack of clinical response, and underwent repeat renal biopsy to confirm the diagnosis. The renal biopsy showed glomeruli without pathological changes by light microscopy, specifically lacking segmental sclerosis, adhesions or hypercellularity. There was mild interstitial oedema and tubular cells focally displayed acute injury. There was no significant staining of glomeruli for any immune reactants by immunofluorescence. Electron microscopy revealed 75–80% effacement of podocyte foot processes (Figure 1) as the only glomerular abnormality. Tubular cells showed focal mitochondrial swelling. Diagnoses of podocyte foot process effacement, consistent with partially treated minimal change disease and mild acute tubular injury, were made.

At this point, different treatment options were discussed with the patient and included long-term cyclosporin A and oral cyclophosphamide. She was reticent about these choices, due to prior poor response to treatment. We then discussed the possibility of using rituximab, as clinical reports had demonstrated responses in patients with FSGS resistant to other therapies [5]. The patient agreed to this approach and was started on rituximab 375 mg/m²/week for 4 weeks, MMF 1000 mg twice a day and prednisone 40 mg every day with a rapid prednisone taper to 5 mg/day over 1 month. She had a dramatic and to date, prolonged and complete response to rituximab. Following the second rituximab dose, the urinary protein excretion dropped by 25%, and 10 weeks after start of rituximab, the urine protein/creatinine ratio was normal with a serum albumin level of 49 g/l. The patient was last seen more than 1 year after initiation of therapy and remained in complete remission with overall improvement including a weight of 61.7 kg, no oedema and no cushingoid features. She is currently maintained on MMF 250 mg/twice daily and prednisone 5 mg/daily.

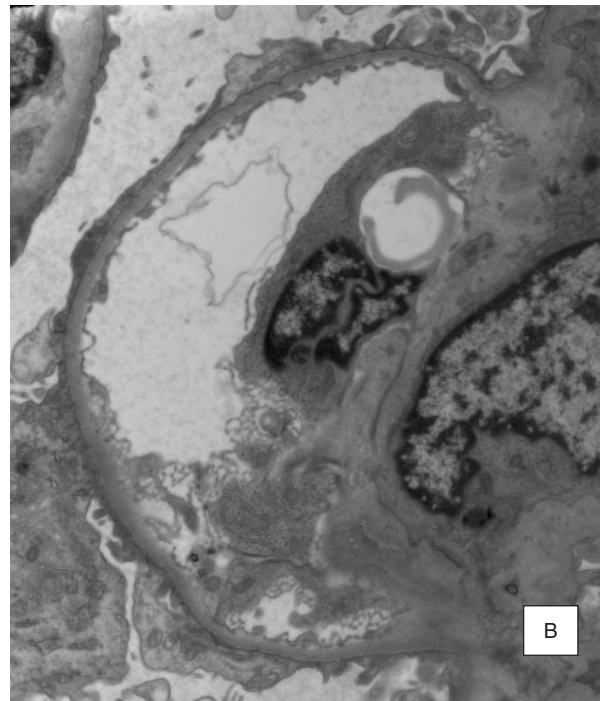
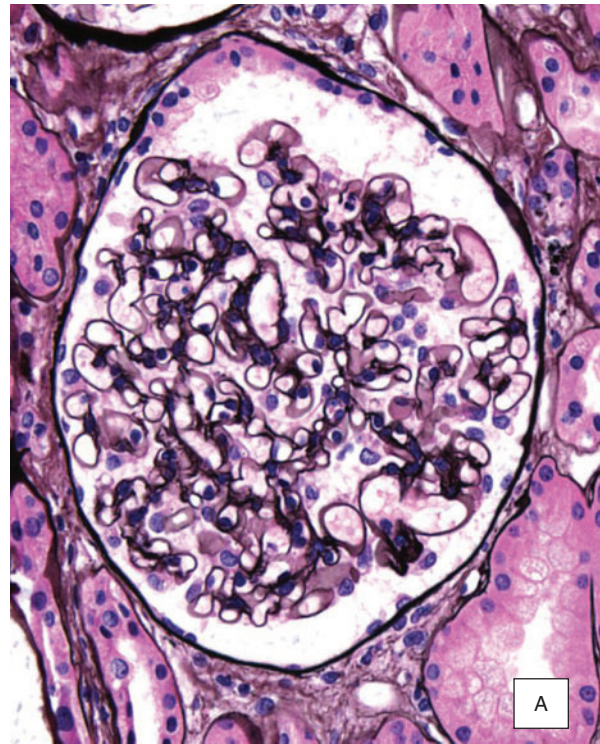


Fig. 1. Second renal biopsy. (A). Normal glomerulus without capillary wall or mesangial abnormalities. Periodic acid-methenamine silver 80×. (B). Electron micrograph of representative glomerulus showing incomplete (80–85%) effacement of podocyte foot process. (10000×).

Discussion

MCNS is the most common cause of NS in children, accounting for 90% of cases under the age of 10 [1]. Adult onset MCNS accounts for ~15% of NS cases in

Table 1. Summary of literature on use of rituximab in treatment of patients with MCNS and FSGS

Reference	MCNS/FSGS	Rituximab dose	Outcome: remission (Y/N)	Side effects (Y/N)
Benz <i>et al.</i> [5]	One patient, SD-FSGS 35 relapses, unresponsive to steroids/cyclophosphamide	375mg/m ² weekly 4×	(Y) >4month	N
Smith [24]	One patient, SD-MCNS, multiple relapses unresponsive to Cyclophosphamide/MMF/Prograf	375mg/m ² 1×	(Y) >8month	N
Hofstra <i>et al.</i> [23]	One patient, SD-MCNS, multiple relapses, unresponsive to cyclophosphamide/MMF/Prograf	1gm i.v. every other week 2×	(Y) partial >4month	N
Gossman <i>et al.</i> [22]	One patient, recurrent FSGS post-transplant resistant to MMF/prograf and plasmapheresis	375mg/m ² 2×	(Y) 12 month	N
Bagga <i>et al.</i> [21]	Five patients (SR-MCNS/FSGS) unresponsive to CSA/cyclophosphamide	375mg/m ² weekly 4×	(Y) complete remission in 3/partial in 2 (longest >58 wks.)	N
Kamar <i>et al.</i> [20]	Two patients (recurrent FSGS post-transplant) resistant to MMF/Prograf, plasmapheresis	375mg/m ² weekly 2× and 375mg/m ² weekly 4×	(Y) one patient complete remission (N) second patient	N
Gilbert <i>et al.</i> [18]	One patient SD-MCNS frequent relapses, unresponsive to cyclophosphamide/CSA/Prograf	375mg/m ² weekly 4×	(Y) 9month Relapse a/w return of B-cells	N
Francois <i>et al.</i> [10]	One patient, SD-MCNS. 30 relapses over 22 years. Resistant to multiple therapies	375mg/m ² weekly 4×	(Y) complete remission after 22 years of frequent relapses (3 years)	N
Pescovitz <i>et al.</i> [7]	One patient post-transplant with recurrent FSGS and PTLD	375mg/m ² weekly 4×	(Y) complete remission of PTLD and FSGS	N
Nozu <i>et al.</i> [6]	One patient post-transplant with recurrent FSGS and PTLD	375mg/m ² weekly 4×	(Y) complete remission of PTLD and FSGS	N

PTLD, post-transplant lymphoproliferative disorder; 1×, one treatment; 2×, two treatment; 4×, four treatment.

adults of all ages [11]. The long term prognosis of adult onset MCNS is debatable but appears comparable to childhood MCNS [11]. Despite much effort, the pathogenic mechanisms responsible for MCNS are not clearly understood [1–4,12–15], although most data suggest that MCNS is a systemic immunological condition of T-cell dysfunction [1–2]. Permeability factors produced by T-cells have been suggested as the cause of capillary wall permeability [16]. Our group has shown that IL-13 appears to be an important cytokine associated with proteinuria and possibly MCNS, as levels are elevated with relapse of MCNS and disappear with remission. In addition, overexpression of IL-13 in rats results in proteinuria, foot process effacement and other features of MCNS [12–15].

Until recently, there has been little regard for a role of B-cells in the pathogenesis of MCNS. However, when rituximab, a chimeric anti-CD20 antibody, was used to treat ITP concurrent with NS and post-transplant lymphoproliferative disorder, in transplant recipients with recurrent FSGS and NS, there were unexpected remissions of NS [5–7]. This initiated interest in pathogenic pathways involving B-cells that could be responsible for NS. Most recently, Pescovitz *et al.* [7] successfully used rituximab in the treatment of FSGS, an entity that may progress from MCNS and shares podocyte injury and foot process effacement.

The effect of B-cell depletion on T-cell function is unknown, but appears to be minimal. However, one study demonstrated increased numbers of T-regulatory cells after rituximab therapy in SLE patients [17].

Thus, the alleged permeability factor responsible for NS in some patients could be produced by B-cells or T-cells through pathways regulated or stimulated by B-cells. The former seems likely since Gilbert *et al.* [18] recently reported using rituximab to treat a child with steroid-dependent MCNS with resulting long-term remission, despite failure of multiple other therapies. The child remained in remission, while the CD19 (B-cell) counts were undetectable, but relapsed after 9 months when CD19 (+) cells returned. Francois *et al.* [10] demonstrated the efficacy of rituximab in a patient with MCNS diagnosed at age 6 and treated with rituximab at age 30 after frequent relapses and treatment failures with other agents. Thus, chronic childhood MCNS persisting into the adult-years may respond to rituximab and sustained remissions with rituximab are possible despite long-term disease and treatment failures. This article and our case suggest that B-cells play an important role in the pathogenesis of MCNS and represent a reasonable therapeutic target. This is in contrast to the long-held ideas of the primacy of T-cells in the mediation of MCNS [16,19]. Clearly, our findings and those of others suggests that B-cells and/or their products may be central to the pathogenesis of MCNS [18–24]. Table 1 represents a summary of the published case reports of the use of rituximab in MCNS and FSGS, usually steroid-resistant lesions. These reports, although uncontrolled, show that patients may have dramatic and sustained responses with complete or partial remissions to rituximab alone, despite prolonged

courses of steroids, cytotoxic drugs, MMF and calcineurin inhibitors without good response prior to initiation of rituximab.

In conclusion, rituximab therapy in an adult with refractory MCNS resulted in a rapid and sustained remission. This dramatic response to rituximab after months of steroid dependency and resistance suggests that B-cell depletion may be an important new approach to management of MCNS in children and adults.

Conflict of interest statement. Dr. Jordan has grant support from Genentech Inc.

References

1. Van den Berg J, Weening JJ. Role of the immune system in the pathogenesis of the idiopathic nephrotic syndrome. *Clin Sci* 2004; 107: 125–136
2. Mansour H, Cheval L, Elalouf JM *et al.* T-cell transcriptome analysis points up a thymic disorder in idiopathic nephrotic syndrome. *Kidney Int* 2005; 67: 2168–2177
3. Pegoraro AA, Singh AK, Arruda JA, Dunea G, Bakir AA. A simple method to detect an albumin permeability factor in the idiopathic nephritic syndrome. *Kidney Int* 2000; 58: 1342–1345
4. Koyama A, Fujisaki M, Kobayashi M, Igarashi M, Narita M. A glomerular permeability factor produced by human T cell hybridomas. *Kidney Int* 1991; 40: 453–460
5. Benz K, Dotsch J, Rascher W, Stachel D. Change in the course of steroid-dependent nephrotic syndrome after rituximab therapy. *Pediatr Nephrol* 2004; 7: 794–97
6. Nozu K, Iijima K, Fujisawa M, Nakagawa A, Yoshikawa N, Matsuo M. Rituximab treatment for posttransplant lymphoproliferative disorder induces complete remission of recurrent nephrotic syndrome. *Pediatr Nephrol* 2005; 20: 1660–1663
7. Pescovitz MD, Book BK, Sidner RA. Resolution of recurrent focal segmental glomerulosclerosis proteinuria after rituximab treatment. *N Engl J Med* 1963; 354: 1961–1963
8. Remuzzi G, Chiurciu C, Abbate M, Brusegan V, Bontempelli M, Ruggenti P. Rituximab for idiopathic membranous nephropathy. *Lancet* 2002; 360: 923–924
9. Kamar N, Rostaing L, Alric L. Treatment of hepatitis C-virus-related glomerulonephritis. *Kidney Int* 2006; 69: 436–439
10. Francois H, Daugas E, Bensman A, Ronco P. Unexpected efficacy of rituximab in multirelapsing minimal change nephritic syndrome in the adult: first case report and pathophysiological considerations. *Am J Kidney Dis* 2007; 49: 158–161
11. Tse KC, Lam MF, Yip PS *et al.* Idiopathic minimal change nephrotic syndrome in older adults: steroid responsiveness and pattern of relapses. *Nephrol Dial Transplant* 2003; 18: 1316–20
12. Wei CL, Cheung W, Heng CK *et al.* Interleukin-13 genetic polymorphisms in Singapore Chinese children correlate with long-term outcome of minimal-change disease. *Nephrol Dial Transplant* 2005; 20: 728–34
13. Cheung W, Wei CL, Seah CC, Jordan SC, Yap HK. Atopy, serum IgE, and interleukin-13 in steroid-responsive nephrotic syndrome. *Pediatr Nephrol* 2004; 19: 627–32
14. Yap HK, Cheung W, Murugasu B, Sim SK, Seah CC, Jordan SC. Th1 and Th2 cytokine mRNA profiles in childhood nephrotic syndrome: evidence for increased IL-13 mRNA expression in relapse. *J Am Soc Nephrol* 1999; 10: 529–37
15. Lai K-W, Wei C-L, Tan L-K *et al.* Overexpression of interleukin 13 induces minimal change nephropathy in rats. *J Am Soc Nephrol* 2007; 18: 1476–1485
16. Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. *Lancet* 1974; 7; 2: 556–560
17. Sfikakis PP, Boletis JN, Lionaki S *et al.* Remission of proliferative lupus nephritis following B cell depletion therapy is preceded by down-regulation of the T cell costimulatory molecule CD40 ligand: An open-label trial. *Arthritis Rheum* 2005; 52: 501–513
18. Gilbert R, Hulse E, Rigden S. Rituximab therapy for steroid-dependent minimal change nephrotic syndrome. *Pediatr Nephrol* 2006; 21: 1698–1700
19. Araya CE, Wasserfall CH, Brusko TM *et al.* A case of unfulfilled expectations. Cytokines in idiopathic minimal lesion nephrotic syndrome. *Pediatr Nephrol* 2006; 21: 603–610
20. Kamar N, Faguer S, Esposito L *et al.* Treatment of focal segmental glomerular sclerosis with rituximab: 2 case reports. *Clin Nephrol* 2007; 67: 250–254
21. Bagga A, Sinha A, Moudgil A. Rituximab in patients with the steroid-resistant nephrotic syndrome. *N Engl J Med* 2007; 356: 2751–2752
22. Gossman J, Scheuermann EH, Porubsky S, Kachel HG, Geiger H, Hauser IA. Abrogation of nephrotic proteinuria by rituximab treatment in a renal transplant patient with relapsed focal segmental glomerulosclerosis. *Transpl Int* 2007; 20: 558–62
23. Hofstra JM, Deegens JK, Wetzels JF. Rituximab: effective treatment for severe steroid-dependent minimal change nephrotic syndrome? *Nephrol Dial Transplant* 2007; 22: 2100–2102
24. Smith GC. Is there a role for rituximab in the treatment of idiopathic childhood nephrotic syndrome? *Pediatr Nephrol* 2007; 22: 893–98

Received for publication: 26.6.07

Accepted in revised form: 2.8.07