Membranous Glomerulopathy Associated with Rheumatoid Arthritis May Respond to Rituximab

Bryan J Wolf MD[1], John S Pixley MD FACP[1,2], William M O'Neill Jr MD[3]

[1]University of Nevada School of Medicine; [2]Reno Veterans Administration; [3]Sierra Nevada Nephrology

Abstract

Membranous glomerulonephritis is an uncommon extra-articular manifestation of rheumatoid arthritis, which need not be associated with prior DMARD (disease-modifying antirheumatic drug) therapies (Clin Rheum 1996, 15, 385). We observed a patient with an 8-year history of seropositive erosive rheumatoid arthritis complicated by the development of refractory nephrotic syndrome secondary to biopsy-proven membranous glomerulonephritis. Signs and symptoms of his disabling kidney disease included renal insufficiency, massive proteinuria (25 grams), edema and a hypercoaguable state (deep venous thrombosis and pulmonary emboli). Alkylating agents, antimetabolites and glucocorticoids were ineffective in reducing his proteinuria over a 2 year period. The patient subsequently received 2 courses (1 gram twice over a 2 week period) of rituximab (a monoclonal antibody to CD20 that specifically depletes B cells), 6 months apart. Serum albumin at initial treatment was 2.0 gm/dl and normalized (3.7 gm/dl) one month after the second course of therapy. This was accompanied by a corresponding decrease of urinary protein (22 grams to 7.4 grams/24 hours) and a reduction in diuretic requirements. B cell directed therapy may prove useful in treating membranous glomerulopathies.

Background

Renal complications of rheumatoid arthritis include membranous glomerulonephritis, secondary amyloidosis, a focal, mesangial proliferative glomerulonephritis (GN), rheumatoid vasculitis, and analgesic nephropathy[1, 2, 3].

Historically, membranous GN in patients with rheumatoid arthritis was commonly due to disease modifying treatment (gold and penicillamine) [1, 2, 3, 4, 5].

However as early as 1977, it was suggested that the development of membranous GN could also be a consequence of rheumatoid arthritis [4, 5].

Membranous changes are a consequence of subepithelial immune complexes (immunoglobulin and complement) depositing in the glomerular basement membrane resulting in the development of nephrotic range proteinuria [1, 3].

Clinical Summary

1995: X, a 39yo male construction worker, presents to his PCP with c/o bilateral hand arthralgias. Over the next 2 years he develops arthralgias in his feet, is diagnosed with polyarthritis, and started on prednisone.
1997: X is diagnosed with Rheumatoid Arthritis. Methotrexate is added to his prednisone.
1999: Symptoms have not responded well to treatment. Methotrexate is discontinued and Leflunomide is started.
2001: Symptoms now include arthralgias in the neck and shoulders. X is referred to Dr John Pixley, UNR Rheumatology. The diagnosis of RA is confirmed by plane films **(fig 1)**, clinical criteria (eg. rheumatoid nodule overlying right 4th metatarsalphalangeal joint), and serologic criteria (rheumatoid factor elevated at 304).
2002: Plaquenil is added to Prednisone and Leflunomide.
2003: X now develops HTN and is started on Diovan. His Prednisone is discontinued and Etanercept is started. His rheumatoid factor is still elevated at 206.
Early 2004: X states that arthralgias are now well controlled, but he develops lower extremity edema and has a 50 lb weight gain to 274 lbs. Lasix is started. Albumin level decreases to 1.7g/dL (3.5 – 5.5) and urine protein is 18,920mg/24hr (30 – 150).
Late 2004: A renal biopsy is performed and shows Membranous Nephropathy **(fig. 2)**. Serologic studies fail to show evidence of other connective tissue diseases: ANA is negative, complement levels are normal, ANCA panel is negative, antiglomerular basement Ab is negative. Patient is hospitalized with bilateral pulmonary emboli. Plaquenil, Leflunomide, and Etanercept are discontinued. Prednisone and Chlorambucil are started.
Early 2005: Creatinine has increased to 3.1mg/dL (0.5 – 1.5) and urine protein is 24,804mg/24hr. Chlorambucil is discontinued and Mycophenolate is started. Patient is still on Prednisone.
Late 2005: Patient is hospitalized with acute-on-chronic renal failure. Creatinine is 6.1mg/dL. Patient requires 3 hemodialysis sessions. Patient is placed on the renal transplant list at UC Davis. Prednisone and Mycophenolate are discontinued. Zaroxolyn is added to high-dose Lasix.
Early 2006: X receives first course of Rituximab. Azathioprine and low-dose Prednisone are started. Albumin increases to 2.9g/dL, creatinine decreases to 2.5mg/dL, and urine protein decreases to 9,296mg/24hr. Patient is removed from Renal Transplant List.
Late 2006: X receives second course of Rituximab. Azathioprine is discontinued. Albumin is now normal at 3.7g/dL and weight is down to 193 lbs.
Early 2007: X is now only on Prednisone 5mg QD, Lasix 40mg QD, and Zaroxolyn PRN. Arthralgias continue to be well controlled, edema is resolved, weight is stable at 195 lbs, creatinine is 2.1mg/dL, and albumin is 3.6g/dL.

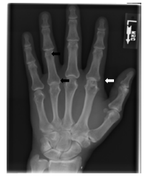

Fig 1. ES's left hand film. Black arrows show metacarpophalangeal and proximal interphalangeal joint space narrowing; white arrow shows periarticular bone demineralization. Note lack of distal interphalangeal joint involvement.

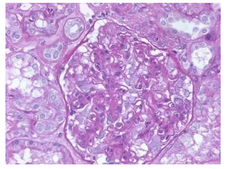

Fig 2. ES's renal biopsy.

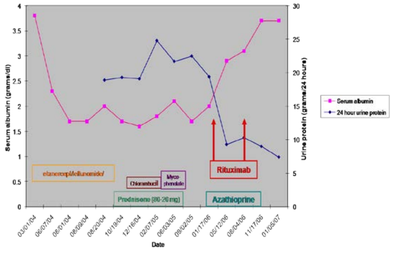

Fig 3. Graph showing albumin and 24-hr urine protein levels over time. Colored boxes show the time frame over which that medication was administered. There is a marked improvement in levels after administration of Rituximab.

Table 1

CD19+ Lymphs	0/uL (394-2235)
CD5+ Lymphs	89/uL (394-2235)
CD19+5+ Lymphs	1/uL (0-132)
CD20+ Lymphs	1/uL (0-559)
Alpha-1 Globulin	0.3g/dL (0.1-0.4)
Alpha-2 Globulin	0.8g/dL (0.4-1.2)
Beta Globulin	0.8g/dL (0.6-1.3)
Gamma Globulin	0.3g/dL (0.5-1.6)
IgG	334mg/dL (700-1600)
IgA	139mg/dL (70-400)
IgM	<1mg/dL (40-230)

Peripheral blood levels of lymphocytes and immunoglobulins 49 weeks after second Rituximab course.

Treatment Rationale

Rituximab is a chimeric (murine/human) monoclonal antibody that binds CD20 (human B-lymphocyte-restricted antigen), depletes the circulation of B lymphocytes for a prolonged period (6-9 months) and reduces circulating immunoglobulin levels.

It is effective in rheumatoid arthritis implicating B lymphocytes and or their products in part in mediating rheumatoid synovitis.

Immune complexes that deposit in the basement membrane in membranous GN contain immunoglobulins (IgM, IgG, and IgA).

We hypothesize that it may be effective in secondary membranous GN by inhibiting the deposition of new immune complexes in the basement membrane, allowing the removal of existing immune complexes and the repairing of the basement membrane.

Conclusions

Rituximab therapy was associated with low levels of circulating serum immunoglobulins (IgM & IgG) and CD19 and CD20 surface bearing lymphocytes 16 weeks after final treatment **(table 1)**.

Rituximab therapy was associated with reversal of 2 years of refractory nephrotic syndrome **(fig 3)**.

B cell directed therapies may be useful in treating secondary forms of membranous glomerulonephritis.

References

1. Kumar, Robbins and Cotran: Pathologic Basis of Disease, 7th edition, Saunders, Philadelphia, PA (2005)
2. Harris: Kelley's Textbook of Rheumatology, 7th edition, Sunders, Philadelphia, PA (2005)
3. UpToDate Online 15.1
4. Samuels B, Lee JC, Engleman EP, Hopper J. Membranous nephropathy in patients with rheumatoid arthritis: Relationship to gold therapy. Medicine. 57: 319-327 (1978).
5. Zarza LP, Sanchez EN, Acin PA, Ara JM, Banos JG. Membranous glomerulonephritis in rheumatoid arthritis unrelated to gold, d-penicillamine or other connective tissue disease. Clinical Rheumatology 15: (4) 385-388 (1996).