CASE REPORTS

Resolution of IgM Nephropathy After Rituximab Treatment

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Immunoglobulin M (IgM) nephropathy is an idiopathic glomerulonephritis characterized by mesangial deposits of IgM. IgM nephropathy presenting with proteinuria, especially nephrotic syndrome, frequently is steroid dependent or steroid resistant and associated with reaching end-stage renal disease after a 15-year follow-up. Because no long-term effective treatment is known for patients with IgM nephropathy, there is a clear need for therapeutic alternatives. We describe a patient who reached end-stage renal disease 20 years after IgM nephropathy was diagnosed at the age of 3 years. IgM nephropathy recurred after kidney transplantation, leading to microscopic hematuria and proteinuria. High-dose steroid therapy was not effective, and kidney function slowly decreased. Three years after transplantation, 2 doses of rituximab were administered, leading to complete remission of the IgM nephropathy. One year after rituximab treatment, the patient has stable kidney function, normal urinary sediment, and no proteinuria. Rituximab may be a valuable novel therapeutic drug for the treatment of patients with IgM nephropathy.
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INDEX WORDS: Immunoglobulin M (IgM) nephropathy; rituximab; anti-CD20; transplantation; nephrotic syndrome.

Immunoglobulin M (IgM) nephropathy is an idiopathic glomerulonephritis characterized by immunofluorescence IgM deposits within the mesangium, which can be recognized as electron-dense deposits by using electron microscopy.[1] IgM deposition often is associated with complement C3. Light microscopy shows variable features of normal glomeruli to mesangial hypercellularity and extracellular matrix accumulation with or without a varying degree of segmental or global sclerosis. This translates to a wide spectrum of clinical presentation, varying from isolated hematuria to overt nephrotic syndrome. The disease may affect both pediatric and adult patients, and the overall long-term prognosis is favorable for patients with isolated hematuria. Patients presenting with proteinuria and specifically nephrotic syndrome have an increased risk of developing end-stage renal disease.[1] Although the proteinuria may respond to steroid treatment, steroid dependency is frequent.[1-3] Long-term remission of proteinuria was achieved in only 14% of patients, indicating the need for a more effective treatment.[1,2] We report the case of a 26-year-old man who presented with recurrence of IgM nephropathy after transplantation and responded with complete remission of proteinuria after rituximab treatment.

CASE REPORT

Clinical History

Severe nephrotic syndrome was first diagnosed in the patient at the age of 3 years. Complete remission of proteinuria initially was achieved with steroid therapy. However, frequent relapses occurred during the years, leading to steroid-dependent and, in later years, steroid-resistant nephrotic syndrome. A kidney biopsy performed at age 14 years showed 20 glomeruli with similar histological changes. In all glomeruli, modest mesangial hypercellularity was observed (Fig 1A) without areas of sclerosis. The tubulointerstitial compartment showed no abnormalities. Immunofluorescence was negative for IgG, IgA, and complement, but deposits of IgM were present in a granular mesangial pattern (Fig 1D). Based on these findings, IgM nephropathy was diagnosed. Serum IgM levels were within normal range.

As a consequence of prednisone treatment, the patient developed a short stature and aseptic osteonecrosis of the femur. Additional treatments with cyclophosphamide and cyclosporine were ineffective, and kidney function gradually decreased, reaching end-stage renal disease at the age of 22 years. After 2 years of peritoneal dialysis therapy (he became anuric after 1 year of dialysis), he received a kidney transplant from a living related donor with 2 HLA-AB mismatches and 1 HLA-DR mismatch. Panel-reactive antibodies were 0% before transplantation. Immunosuppressive

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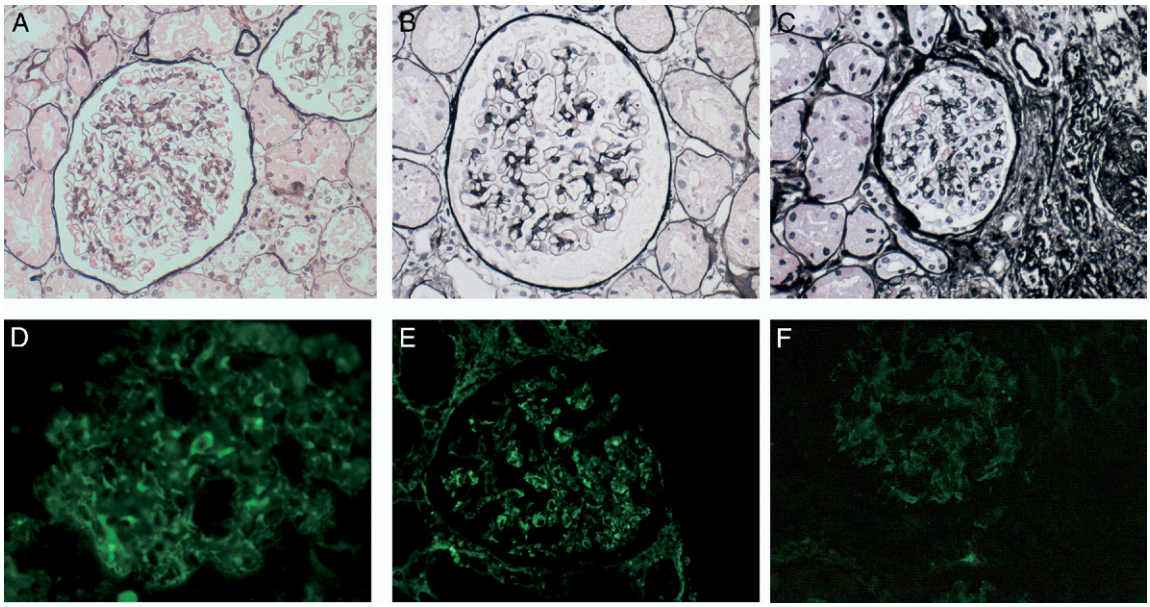

Figure 1. Light microscopy of sections from kidney biopsies of the (A, D) native kidney and (B, C, E, F) transplant kidney (B, E) before and (C, F) after treatment with rituximab. (Top panel) Light microscopy of Jones silver-stained sections of glomeruli and (bottom panel) immunofluorescence of glomeruli stained with anti–immunoglobulin M (IgM) antibody. The glomerulus from the native kidney has (A) increased mesangial cellularity with (D) granular mesangial deposition of IgM, whereas the glomerulus from the transplant kidney before rituximab treatment shows (B) normal architecture with (E) diffuse to granular mesangial deposition of IgM. Six months after rituximab treatment, the kidney biopsy specimen showed many sclerosed glomeruli with thickened Bowman capsules in the viable glomeruli, but no mesangial deposition of IgM.

medication consisted of tacrolimus, prednisone, and mycophenolate mofetil. Excellent kidney function was acquired initially, with an estimated glomerular filtration rate (according to the Cockcroft-Gault formula[4]) of 122 mL/min and protein-creatinine ratio of 0.12 (Fig 2). However, persistent microscopic hematuria was detected within the first week after transplantation, which was soon followed by progressive proteinuria and decreasing estimated glomerular filtration rate.

The kidney biopsy specimen showed 32 glomeruli, with 2 globally sclerosed. Glomeruli showed normal architecture

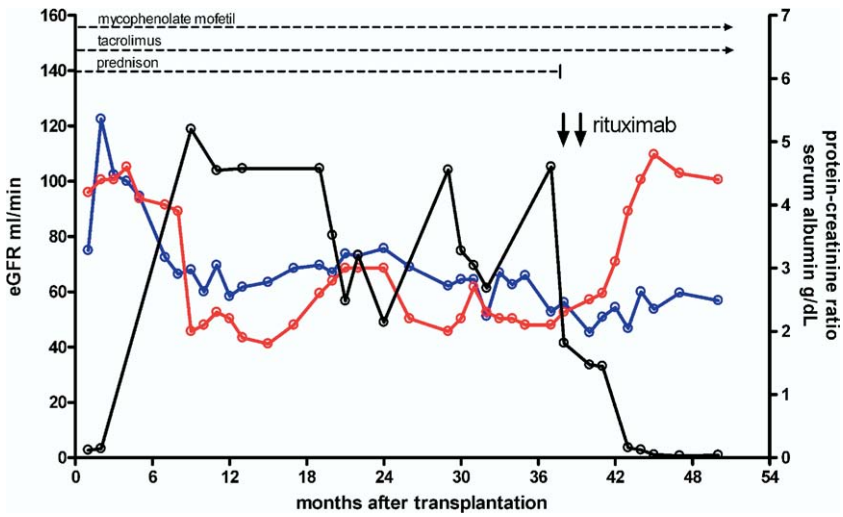

Figure 2. Estimated glomerular filtration rate (eGFR; left y-axis, red line) according to the Cockcroft-Gault formula,[4] serum albumin concentration (g/dL; right y-axis, blue line), and urine protein-creatinine ratio (right y-axis, black line) after kidney transplantation. On the x-axis, time after transplantation in months is shown.