

Case Report

The development of membranous lupus nephritis during treatment with mycophenolate mofetil for proliferative renal disease

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Abstract

The transformation of lupus nephritis from one histologic pattern to another is well described. We report a case of a patient who initially presented with diffuse proliferative glomerulonephritis and was treated with prednisone and mycophenolate mofetil (MMF). She initially responded well to therapy, but later developed high-grade proteinuria while still on MMF and low-dose steroids. A repeat biopsy performed after the increase in proteinuria demonstrated that she had focal proliferative disease but that she had also developed membranous lupus nephritis. Our case is unique in that we report a patient who developed membranous lupus nephritis while receiving MMF.

Keywords: membranous lupus nephritis; mycophenolate mofetil; transformation

Background

Renal involvement is common in patients with systemic lupus erythematosus, but there is great patient-to-patient variability in the course of the renal disease. Given the variable clinical course of lupus nephritis, pathologic grading systems have been developed in order to identify which patients are most likely to benefit from aggressive immunosuppressive therapy. In addition to variation between patients, individual patients may have disease flares and spontaneous remissions and the renal disease may transform from one histologic class to another over time. The most common histologic transformation seems to be a progression from focal to diffuse proliferative nephritis or from proliferative to sclerotic disease [1–3]. Although less common, transformation from proliferative disease to a membranous pattern of injury has also been described [2,4,5]. Here, we present a case of a patient with lupus who initially presented with diffuse proliferative disease, but who developed a membranous pattern of injury while being treated with mycophenolate mofetil (MMF) and prednisone.

Case report

A 29-year-old female was diagnosed with lupus in 1999. She was treated with leflunomide, plaquenil and methotrexate. These medications were discontinued in 2005, but she periodically received pulsed prednisone to control joint swelling and pain. Haematuria and proteinuria were incidentally found on urinalysis in late 2006. At that time, her serum creatinine was 1.0 mg/dL (88.4 µmol/L), C3 level was 36 mg/dL (90–180 mg/dL), C4 level was 3 mg/dL (16–47 mg/dL) and 24-h urine collection contained 3.87 g of protein. She was empirically treated with corticosteroids. Her proteinuria rapidly improved and the serum creatinine fell to 0.8 mg/dL (70.7 µmol/L). Shortly thereafter, she underwent a renal biopsy which revealed diffuse proliferative glomerulonephritis (Figure 1A; all 16 glomeruli showed involvement) with areas of necrosis and crescents (2 out of 16 glomeruli). Electron microscopy demonstrated subendothelial and mesangial deposits (Figure 1B).

In April 2007, she began receiving MMF at a dose of 500 mg twice daily and, eventually, the dose was increased to 1500 mg twice daily. Her protein/creatinine ratio remained below 0.5 on this regimen (Figure 2) and her creatinine ranged from 0.8 to 1.0 mg/dL (70.7–88.4 µmol/L). By April of 2009, she remained on MMF and her prednisone dose had been reduced to 7 mg/day. A urine sample at that time demonstrated a protein/creatinine ratio of >2.0. The prednisone was increased to 60 mg/day without improvement in the degree of proteinuria, although the serum creatinine decreased slightly in the following weeks. The C3 level was 133 mg/dL (90–180 mg/dL) and the C4 level was 19 mg/dL (16–47 mg/dL).

In August of 2009, she underwent a second renal biopsy which demonstrated focal proliferative changes (Figure 1C; 3 of 29 glomeruli affected) without crescents or necrosis. The capillary loops appeared thickened, although a Jones methenamine silver stain was not available. Electron microscopy from this biopsy demonstrated extensive subepithelial and intramembranous deposits (Figure 1D). Electron-dense deposits were also noted in the mesangium, but subendothelial deposits were not identified.

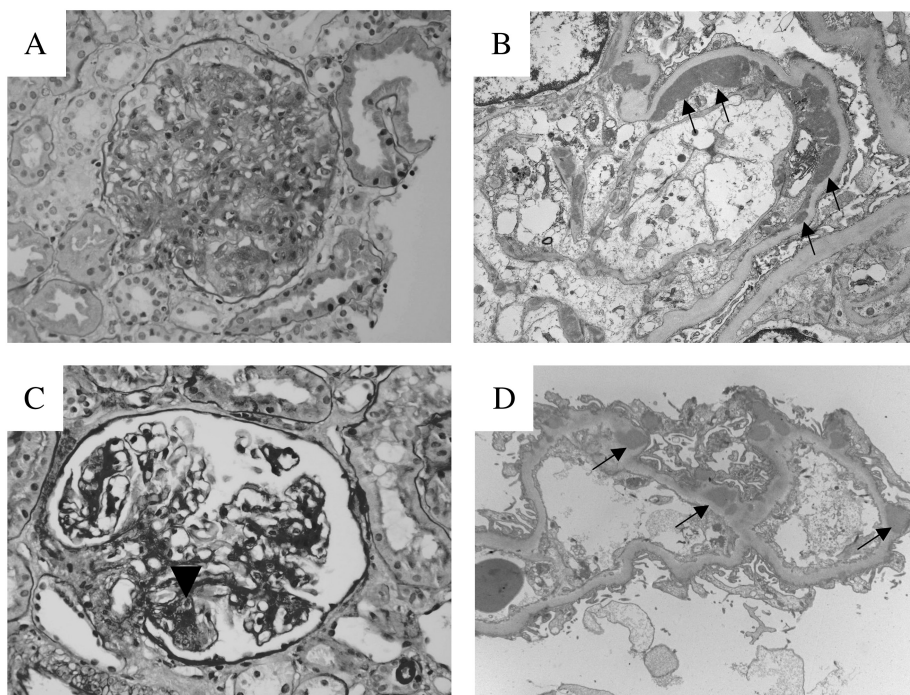


Fig. 1. Renal biopsies obtained before and after treatment with MMF and steroids. **(A)** Light microscopy of the patient's first renal biopsy demonstrated diffuse proliferative changes. **(B)** Electron microscopy demonstrated extensive immune deposits in the subendothelial space (indicated with arrows) and in the mesangium. Immune complexes were not identified in the subepithelial space. **(C)** Light microscopy from the second biopsy demonstrated mesangial hypercellularity and focal proliferative changes (arrowhead) (3 of 29 glomeruli affected) without crescents or necrosis. **(D)** Electron microscopy from this biopsy demonstrated extensive subepithelial (indicated with arrows) and intramembranous deposits. Electron-dense deposits were noted in the mesangium, but subendothelial deposits were not identified. A and C are stained with periodic acid Schiff. Original magnification $\times 400$.

Discussion

The clinical course of lupus nephritis varies from patient to patient. Even for an individual, the nature of the renal involvement can change over time or in response to therapy. For example, Mahajan *et al.* evaluated 41 patients with lupus nephritis who had undergone two renal biopsies at least 3 months apart [2]. In their series, 10 of 15 patients who presented with focal proliferative disease subsequent-

ly developed either diffuse proliferative disease or membranous disease. Other studies have also shown that proliferative disease can transform into a membranous pattern, although such transformations appear to be rare [1,4,6].

The significance of the current case is that the transformation between disease classes occurred despite immunosuppressive treatment with MMF. Lentz *et al.* described transformation from proliferative to membranous nephropathy in a patient who had received more than 30 months of therapy with corticosteroids [4]. Another patient was reported to have developed membranous lupus nephritis after receiving a renal transplant after her native kidneys were destroyed by proliferative lupus nephritis [5]. This transformation occurred while the patient was being treated with cyclosporine, azathioprine and steroids. Our patient was treated with MMF and steroids at doses similar to those used in recent large trials [7]. Although the patient had initially appeared to respond to this regimen, the repeat biopsy showed that she had persistent proliferative disease and she had developed subepithelial deposits and thickened basement membranes while on this therapy. Mycophenolic acid levels were not measured, and compliance with therapy during the treatment period cannot be verified. This leaves open the possibility that this case actually represents a recurrence of disease while on inadequate therapy with transformation of the histology rather than a transformation while on treatment doses of MMF.

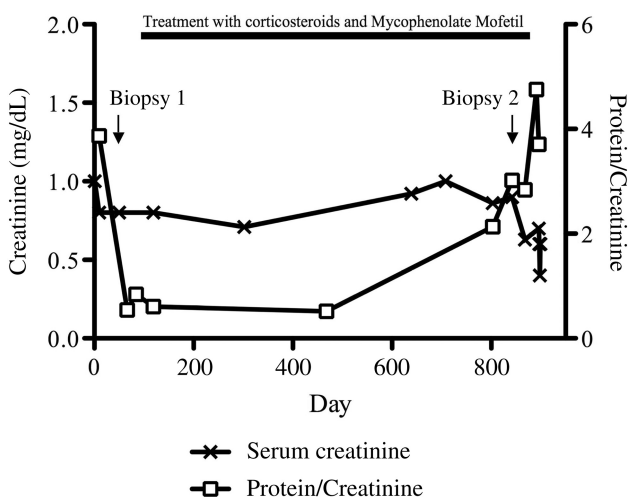


Fig. 2. Serum creatinine and urine protein/creatinine ratio. Treatment was started around the time of the patient's first renal biopsy.

Most large trials that have studied the effects of treatment on membranous lupus nephritis also included patients with proliferative disease or with mixed patterns of disease, so the specific effects of immunosuppression on the membranous process are difficult to discern. Case series and retrospective analyses have suggested that several immunosuppressive agents may be beneficial, including azathioprine, chlorambucil, cyclophosphamide and calcineurin inhibitors [8]. Austin *et al.* recently demonstrated that adjunctive therapy with cyclosporine or cyclophosphamide were more effective than prednisone alone in inducing remission and preventing relapse of the nephrotic syndrome [9].

Although the efficacy of MMF for the treatment of lupus membranous nephritis is uncertain, many authors include it as a reasonable treatment choice. Furthermore, for patients with both proliferative and membranous patterns of disease, the treatment is usually dictated by the proliferative component. Could treatment of this patient with MMF have contributed to the development of a membranous lesion, or was it merely inadequate treatment for the lesion as it developed? It has been proposed that different types of autoantibodies can cause different patterns of renal injury [10]. It is possible that immunosuppression changes the nature of the autoantibodies, thereby changing their physicochemical properties and/or their ability to fix complement. Even if this transformation was induced by treatment with MMF, the rarity of such reports makes this unlikely to be a general response to the agent. The continued widespread use of MMF for the treatment of lupus nephritis, however, should provide future insight into whether MMF is as effective for the process causing membranous lupus nephritis as it is for proliferative disease.

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Conflict of interest statement. The results presented in this paper have not been published previously in whole or part. J.M.T. is a stockholder in and consultant for Taligen Therapeutics, Inc.

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