A rare case of transition to membranous lupus nephritis from diffuse proliferative lupus nephritis

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Abstract

Lupus nephritis is an important complication of systemic lupus erythematosus (SLE) that affects the prognosis. A rare type of lupus nephritis, class V, shows histological findings resembling those of membranous nephropathy. While most diffuse proliferative lupus nephritis is associated with other SLE disease activity, class V lupus nephritis can occur without systemic activity. Furthermore, Class V is less responsive to steroid therapy than other forms of lupus nephritis. We treated a young woman with class IV lupus nephritis who developed class V and showed severe proteinuria and lesions resembling those of membranous nephropathy in spite of favorable response to treatment of SLE including diffuse proliferative lupus nephritis. Analysis of immunoglobulin G subtypes deposited in glomeruli disclosed that the deposits were mainly IgG1, leading to a diagnosis of secondary membranous nephropathy associated with SLE. Nevertheless the patient has been treated with steroids, complete remission has not yet been achieved after 1 year, thus immunosuppressants have been added. Renal function has been maintained. To our knowledge, SLE patient with transition to membranous lupus nephritis from diffuse proliferative lupus nephritis is quite rare.

Key words: SLE, membranous lupus nephritis

Introduction

Lupus nephritis is an important complication affecting the prognosis of patients with systemic lupus erythematosus (SLE). Among children with SLE, approximately 90% of them develop nephritis. Children with SLE or lupus nephritis show higher disease activity than adults. Nephritis activity frequently correlates with that of SLE. In diffuse proliferative lupus nephritis (DPLN), disease activity of SLE is high. Severe proteinuria often manifests as nephrotic syndrome. On the other hand, class V is a relatively rare type of lupus nephritis that can develop without other SLE activity such as hypocomplementemia and elevation of anti-double-stranded DNA (dsDNA) antibodies.

We report a patient who showed nephrotic syndrome and lesions resembling those of membranous nephropathy, despite successful suppression of other SLE disease activity.

Patient presentation

A 24-year-old woman presented with nephrotic syndrome. At the age of 10, she developed a butterfly rash on the face, purpura in all 4 extremities, and hypocomplementemia, and a strongly positive antinuclear antibody test led to a diagnosis of SLE. Proteinuria was present, and renal biopsy was performed. Histological examination indicated a diagnosis of DPLN (Figure 1). Steroid therapy decreased disease activity, but relapse occurred repeatedly when the dose
was reduced. Cyclosporine (3 mg/kg/day), mizoribine (150 mg/day), and mycophenolate mofetil (500 mg/day) were also given. During therapy, additional renal biopsies were performed, with specimens showing the finding of DPLN. Subsequently, treatment with betamethasone (1 mg/day), mizoribine (150 mg/day), and tacrolimus (3 mg/day) improved clinical symptoms including amelioration of urinary protein and hematuria, as well as activity parameters such as anti-dsDNA antibodies and circulating immune complexes as evaluated by the C1q method. However, increased urinary protein associated with hypoalbuminemia indicated the development of nephrotic syndrome. The patient was admitted for renal biopsy and reassessment of treatment strategy.

On admission, she was 151 cm tall and weight- ed 47 kg, body temperature was 36.9°C and blood pressure was 106/66 mmHg. A butterfly rash was present on the face and eyelids; distal limbs were edematous. The patient showed no abnormal respiratory, cardiac, or neurologic findings. Urine examination on admission showed proteinuria (3.07 g/day) but no hematuria. Hematologic examination disclosed leu- kocytosis (5700 cells/μL), a normal lymphocyte count (1200 cells/ μL), and normal hemoglobin concentration (11.3 g/dL). Blood chemistry examination showed a total protein concentration of 5.4 g/dL and an albumin concentration of 2.3 g/dL, both indicating hypoproteinemia; together with a high cholesterol concentration of 335 mg/dL; these laboratory findings were consistent with nephrotic syndrome. The blood urea nitrogen (BUN) concentration was 12 mg/dL, the serum creatinine concentration was 0.38 mg/dL, and the creatinine clearance was 101.5 mL/min/1.73 m², showing no decrease in renal function. Among serum complement components, C3 and C4 titers were 71 mg/dL and 15 mg/dL, respectively, and the CH₅₀ titer was 36.3 U/mL, indicating no hypocomplementemia. The anti-dsDNA antibody concentration was 36 IU/mL, and the circulating immune complex concentration by the C1q method was 2.6 μg/mL; both of these which showed slight elevations. Laboratory findings on admission are shown in Table 1. SLE disease activity index score² was 6 points.

The renal biopsy specimen obtained after admission contained 18 glomeruli. Although some residual DPLN lesions were present, diffuse thickening and spike formation were observed in the glomerular capillary walls, while parts of these walls showed a double contour and a chain-like pattern of the basement membrane, characteristic of membranous nephropath-

![Fig. 1](image1.png)

**Fig. 1** Histologic findings at the first admission at age 10. Diffuse mesangial cell proliferation and thickening of the glomerular basement membrane represented diffuse proliferative lupus nephritis.

![Fig. 2](image2.png)

**Fig. 2** Renal findings on the most recent admission at age 24. Light microscopy showed residual mild mesangial cell proliferation but also a double contour duplication of the glomerular basement membrane, a finding characteristic of membranous nephropathy (arrows). (Panel a, periodic acid-Schiff stain, ×400; b, methenamine silver stain, ×1000). Fluorescent antibody examination detected granular complement C3 deposition, mostly in the basement membrane (c, original magnification, ×200). Electron microscopy showed electron-dense deposits in the glomerular basement membrane (d, original magnification, ×5,000).
y (Figure 2a, b). By fluorescent antibody examination, granular immunoglobulin (Ig) G, C1q, and C3 deposition were demonstrated (Figure 2c) in the glomerular capillary wall and mesangial region. Electron microscopy showed deposits with high electron density in the subepithelial area and also subendothelial area of the glomerular basement membrane and within the membrane, a characteristic finding of membranous nephropathy (Figure 2d). By IgG subclass staining, IgG1 immunoreactivity was present mainly in the glomerular basement membrane (Figure 3a), but IgG4 reactivity was absent (Figure 3b). On this basis, a diagnosis of membranous lupus nephritis, i.e., lupus nephritis class V, was made.

Treatment with prednisolone (40 mg/day), tacrolimus (3 mg/day), an angiotensin-converting enzyme inhibitor (5 mg/day), and an angiotensin receptor antagonist (4 mg/day) was initiated. After 4 weeks, urinary protein decreased (0.5 g/day) (Figure 4). However, complete remission has not yet been achieved, and therapy is being continued.

Discussion

Lupus nephritis includes various histological types, with DPLN being most common form. Membranous lupus nephritis has been reported to constitute about 15% of all cases of lupus nephritis. When a diagnosis of SLE is made, lupus nephritis often is present already. Membranous lupus nephritis manifests as chance proteinuria or sometimes nephrotic syndrome, sometimes lacking the diagnostic criteria of SLE. In addition, unlike DPLN, membranous lupus nephritis correlate poorly with disease activity markers such as hypocomplementemia or elevation in the anti-dsDNA antibody titer. Decreased renal function is infrequent, and hematuria is often mild. Before the onset of membranous lupus nephritis in our patient, urinary findings showed correlation with SLE activity. Membranous lupus nephritis, which later developed in our patient, showed previously reported characteristics as above this disorder.

IgG-subclass deposition patterns in glomeruli differ between primary and secondary membranous nephropathy. Primary membranous nephropathy is characterized by IgG4 deposition. In this patient, however, IgG1 deposition was predominant, as seen in secondary membranous nephropathy associated with SLE.

In the onset of membranous lupus nephritis in recognition of a characteristic unlike DPLN, underlying immunological abnormalities apart from anti-dsDNA antibodies are suspected. Antigens implicated in such occurrences include
M-type phospholipase A2 receptor (PLA2R) and superoxide dimutase 2 (SOD2). The same antigens are suspected in idiopathic membranous nephropathy (antibody prevalence, 70% to 80%). Recently, PLA2R, a glycoprotein expressed on renal glomerular epithelial cells, has been also reported in patients with membranous lupus nephritis. We need to test for involvement of this antigen to investigate the complication of membranous nephropathy in the present patient in future study.

To our knowledge, transition to membranous lupus nephritis from diffuse proliferative lupus nephritis is very rare, however, the precise reason for this transition in our patient remains unclear. Complete remission has not been achieved in our patient. Membranous lupus nephritis tends to respond to steroids less than other nephritides such as DPLN. Considering that remission may not occur until after a year or more, we intend to continue steroids and immunosuppressants while carefully observing the patient’s course. In addition, from a point of the insurance adaptation of the drug in Japan and the preservation of fertility, we employed Tacrolimus as an immunosuppressant drug.

Conflict of Interest and Consent Issues

We have no conflicts of interest affecting the present study. We obtained consent from the patient’s parents for use of the patient’s kidney biopsy specimens.

References