Tohoku J. Exp. Med., 2002, **196**, 293-298

*Case Report*

# Subsequent Progression to Membranous Glomerulonephritis Following Exacerbation of Urticarial Rash in Systemic Lupus Erythematosus: Report of 2 Cases

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Suzuki, K., Tanaka, H., Nakahata, T., Fukuyama, Y., Ito, E. and Waga, S. *Subsequent Progression to Membranous Glomerluronephritis Following Exacerbation of Urticarial Rash in Systemic Lupus Erythematosus: Report of 2 Cases.* Tohoku J. Exp. Med., 2002, **196** (4), 293-298 —— Two Japanese female adolescents with systemic lupus erythematosus (SLE), known cases of urinary tract involvements: one with biopsy-proven class II lupus nephritis and the other one with lupus cystitis without overt glomerulonephritis (silent lupus), who after more than 4 years' observation presented with subsequent progression to membranous glomerulonephritis (MGN) following exacerbation of urticarial rash. Although it is well known that lupus nephritis shows histological transformation with time, the late progression to MGN from another World Health Organization histologic pattern has been reported to be less common in pediatric-onset SLE. Although pathogenesis of their MGN remains speculative, these clinical observation might suggest that a possible association between exacerbation of urticarial rash and subsequent progression to MGN in the selected patients with SLE. ——
membranous glomerulonephritis; systemic lupus erythematosus; subsequent progression; urticarial rash


Glomerulonephritis is an hallmark of patients with systemic lupus erythematosus (SLE) (Cameron 1994; Le Thi Huong et al. 1999). The World Health Organization (WHO) classification of histologic subtypes of lupus nephritis is usually used to determine the histologic pattern. The incidence of class V: membranous glomerulonephritis (MGN) has

Received January 31, 2002; revision accepted for publication April 15, 2002.
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generally been reported as 10-20% (Cameron 1994; Le Thi Huong et al. 1999; Iitaka et al. 2001), and less common in children compared to adults (Cameron 1994; Iitaka et al 2001). Interestingly, some pediatric patients may develop overt SLE several years later after the emergence of MGN (Libit et al. 1976; Kallen et al. 1977). However, to our knowledge, subsequent progression to MGN from another WHO histologic pattern has been reported to be relatively rare. We report 2 adolescent SLE patients, who presented with subsequent progression to MGN after over 4 years' close observation.

## Case Reports

*Patient 1*

A Japanese adolescent aged 18.5 years with a 4-year history of SLE with biopsy-proven class II lupus nephritis (Fig. 1a), which was in clinical remission under prednisolone (PSL) therapy, presented in early 2000 with clinical flare of SLE, associated with significant proteinuria, urticarial rash on the whole body with malar rash, and hypocomplementemia. She had been treated with oral PSL, 12.5 mg daily combined with azathioprine (AZP), 75 mg daily. Since July 1999, she had been suffering from refractory rash mimicking urticaria on the whole body associated with a significant hypocomplementemia (C3 56 mg/100 ml, C4 less than 10 mg/100 ml), and had been treated with steroidal ointment at a dermatologist.

In January 2000, when massive proteinuria of 560 mg/100 ml appeared, she transferred to us. On admission, the rash was still occurring on the abdomen, back and lower extremities. Physical examination was unremarkable except for the rash. Malar rash was noted. Blood pressure was 110/70 mmHg. Laboratory tests revealed serum total protein 5.5 g/100 ml, albumin 2.4 g/100 ml, urea nitrogen 16 mg/100 ml, creatinine 0.6 mg/100 ml, cholesterol 260 mg/100 ml, IgG 1350 mg/100 ml, IgA 516 mg/100 ml, IgM 167 mg/100 ml, C3 44 mg/100 ml (normal 79-152 mg/100 ml), C4 less than 10 mg/100 ml (normal 16-38 mg/100 ml), and hemolytic complement activity less than 10 U/ml (normal 23-46 U/ml). The results of immunological examinations were as follows; anti-nuclear antibody (ANA) 1 : 1280 with a speckled pattern, anti-double stranded (anti-ds) DNA antibody 91.9 IU/ml by enzyme-linked immunosorbent assay (normal $<$ 10 IU/ml), anti-Sm antibody positive, anti-SS-A/Ro antobody by enzyme immunoassay (EIA) 103.0 EU/ml (normal $<$ 15.0 EU/ml), anti-SS-B/La antibody by EIA negative and circulating immunocomplex (CIC) by C1q binding assay (normal $<$ 3.0 $\mu$g/ml) 5.9 $\mu$g/ml. Peripheral blood count was unremarkable. Daily urine protein excretion ranged from 3.3 to 4.8 g. Occult blood in urine was 2+.

A percutaneous renal biopsy on hospital day 7. By light microscopy, all of the 13 glomeruli showed mild mesangial hypercellurality with diffuse capillary loop widening (Fig. 1b). The interstitium was intact. Immunofluorescence revealed 2+ of IgG, and C3, 1+ of IgA, IgM and C1q deposits in a granular pattern with capillary and mesangial distribution (Fig. 1c). Electron microscopy showed mesangial deposits, dense massive subendothelial and intramembranous deposits. The overall pathology was that of stage II MGN. Then she was treated with oral PSL, 40 mg daily combined with monthly intravenous cyclophosphamide pulse (1 g) therapy (iv-CPA). The dosage of PSL was tapered. Although her refractory skin rash, hypocomplementemia and high titer of serum anti-DNA antibody gradually subsided, proteinuria (daily urine protein excretion, approximately more than 2 g) persisted. After 3-course of iv-CPA, ciclosporin (2.5 mg/kg, daily) was replaced as an immunosuppressant. Her proteinuria gradually decreased thereafter.

*Patient 2*

A Japanese adolescent aged 16.5 years with

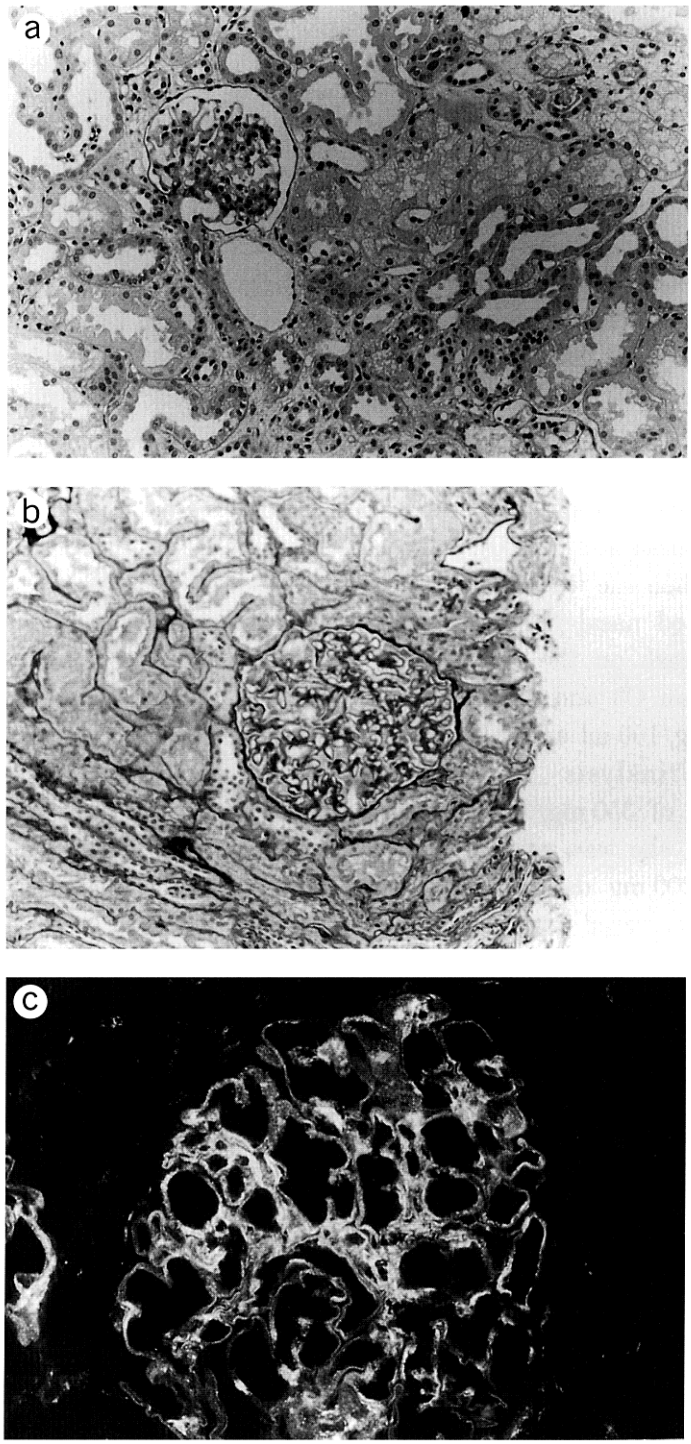


Fig. 1. a: First renal biopsy at the age of 14 years showing mild mesangial proliferation without tubulointerstitial changes (periodic acid-Schiff stain, ×200). b: Second renal biospy at the age of 18 years showing mild mesangial hypercellularity with diffuse thickness of glomerular capillary basement membrane (PAS, ×200). c: IgG deposits along the glomerular capillary walls and in the mesangium (×400).

a 4.5-year history of SLE complicated with thrombocytopenia, intestitial cystitis and paralytic ileus (Tanaka et al. 2000) was referred to our hospital because of significant proteinuria and hypocomplementemia. She had been treated with oral PSL, 25 mg daily and monthly iv-CPA (700 mg) at a regional hospital, and the therapy proved effective. When a total of 6 times of iv-CPA had been done, she developed persistent nausea and a mild liver dysfunction, and then refused taking iv-CPA. No overt glomerulonephritis had occurred during the clinical course of "lupus cystitis", and her clinical picture of initial presentation has been reported previously (Tanaka et al. 2000).

In March 2000, when she was on PSL 17.5 mg daily, she developed nasal mucocutaneous ulceration, urticarial rash on the whole body and malar rash. Serum C3 and C4 decreased significantly to 31.0 mg/100 ml and 2.0 mg/100 ml, respectively. Urinalysis revealed a significant proteinuria of 350 mg/100 ml without hematuria. Then, she was given PSL, 60 mg and mizoribine, 200 mg daily. Although the therapy resulted in a rapid improvement of the nasal ulcer and skin rash, proteinuria remained. The dosage of PSL was reduced to 22.5 mg daily on a gradual basis.

On admission, she was not in a serious condition. Physical examination was unremarkable. Blood pressure was 122/72 mmHg. Laboratory tests revealed serum total protein 5.8 g/100 ml, albumin 3.4 g/100 ml, urea nitrogen 17 mg/100 ml, creatinine 0.5 mg/100 ml, cholesterol 244 mg/100 ml, IgG 935 mg/100 ml, IgA 172 mg/100 ml, IgM 142 mg/100 ml, C3 20 mg/100 ml, C4 3 mg/100 ml and hemolytic complement activity less than 10 U/ml. The results of immunological examinations were follows: ANA 1 : 160 with a speckled pattern, Anti-ds DNA antibody 12 IU/ml, anti-SS-A/Ro antibody 20.0 EU/ml and CIC 4.6 $\mu$g/ml. Anti-Sm antibody and anti-SS-B/La antibody were absent. Platelet count decreased to 82 000/$\mu$l. Daily urine protein excretion ranged from 1.0 to 1.7 g without hematuria. Neither lower urinary tract manifestations nor abdominal complaints were seen. Intravenous pyelography disclosed complete resolution of the hydrouretor with hydronephrosis due to lupus cystitis (Tanaka et al. 2000).

A percutaneous renal biopsy revealed MGN

TABLE 1. *Clinical characteristics of two patients with SLE who showed subsequent progression to membranous glomerulonephritis as a late sequel*

| | Patient 1 | Patient 2 |
|---|---|---|
| Age at the onset of SLE | 14.2 years | 11.5 years |
| Clinical manifestations at the onset of SLE | Fever, Malar rash, Mild proteinuria (<50 mg/100 ml) | Thrombocytopenia, Hemolytic anemia, Paralytic ileus, Interstitial cystitis |
| Initial renal involvement | WHO class II | Silent lupus |
| Time interval from the onset of SLE to progression to MGN | 4 years | 4.5 years |
| Serological status at the onset of MGN | ANA 1280×, CH50 <10 U/ml, CIC 5.9 $\mu$g/ml, SS-A/Ro 103.0 EU/ml | ANA 160×, CH50 <10 U/ml, CIC 4.6 $\mu$g/ml, SS-A/Ro 20.0 EU/ml |

SLE, systemic lupus erythematosus; MGN, membranous glomerulonephritis; WHO, world health organization; ANA, anti-nuclear antibody; CH50, complement hemolytic activity (normal 23-46 U/ml); CIC, circulating immune complex (normal<3.0 $\mu$g/ml; SS-A/Ro, anti-SS/Ro antibody (normal<15.0 EU/ml).

with a mild mesangial hypercellularity of 26 glomeruli without tubulointerstitial changes. Immunofluorescence revealed 2+ of IgG and IgA, 1+ of IgM, C3 and C1q deposits in a granular pattern with capillary and mesangial distribution. An electron-microscopic study revealed numerous deposits of varying size within and adjacent to the epithelial side of glomerular basement membrane and mesangial area.

Although ciclosporin (2.5 mg/kg, daily) combined with PSL (40 mg, daily) was started following the diagnosis of MGN, her proteinuria remained still.

Summary of current case reports is depicted in Table 1.

## DISCUSSION

It is well known that lupus nephritis shows histological transformation with time (Cameron 1994; Le Thi Huong et al. 1999). The most frequent transformation has been reported as from focal: class III WHO histologic pattern to diffuse proliferative: class IV, and from diffuse proliferative to chronic screlosing glomerulonephritis: class VI (Le Thi Huong et al. 1999). Sorof et al. (1998) reported recently that they found an increasing incidence of childhood class V lupus nephritis at their institution, and that the transformation to class V lupus nephritis occurred in 19% of patients having repeat biopsies. However, a transformation from focal proliferative to MGN has generally been reported to be less common (Cameron 1994; Le Thi Huong et al. 1999; Khajedehi et al. 1999; Iitaka et al. 2001). Actually, Iitaka et al. (2001) reported that a subsequent progression to MGN occurred only 1 SLE patient (2.8%) out of 36 at their institution. Also, we have experienced 26 SLE patients with nephritis in our hospital during past 12 years. Although most of them received repeat renal biopsies during the clinical courses, we found only 2 patients (7.7%) described here showing a subsequent progression to MGN.

Interestingly, both of our patients developed MGN as a late sequel following exacerbation of urticarial rash associated with a significant hypocomplementemia. Although that possible association may occur on the basis of chance, we think that their clinical courses described above are attractive.

Patient 1 showed class II lupus nephritis at the onset of SLE. She had received successful immunosuppressive therapy, and a clinical remission was achieved for over 3.5 years. While, Patient 2 showed unique association of interstitial cystitis and paralytic ileus without overt nephritis at the onset of SLE. Despite an aggressive immunosuppressive treatment, she had been suffering from refractory "lupus cystitis." However, no evidence of glomerulonephritis was seen during a 4.5-year clinical course. When MGN occurred "lupus cystitis" completely disappeared. These clinical observation might suggest that the autoimmune targeting in the patient goes beyond the antigenic determinants of the blood vessels in the bladder and the intestine. Thereafter, MGN developed as the new immunological target as a late sequel.

Although pathogenesis of the transition in the patients remains speculative, exacerbation of urticarial rash associated with a significant hypocomplementemia seemed to contribute to subsequent progression to MGN. Regarding association of urticarial rash and glomerulonephritis with membranous features in rheumatic diseases, some recent reports described occurrence of MGN or membranous proliferative glomerulonephritis in hypocomplementemic urticarial vasculitis (Kobayashi et al. 1994; Cadnapaphornchai et al. 2000). Since cutaneous lesion of hypocomplementemic urticarial vasculitis is thought to be overlapping with that of a proportion of SLE patients, an autoimmune interaction between skin and preexisting glomerular changes due to hypocomplementemic rheumatic diseases which favors an immune reaction in the subepithelial space

might be attributable to the pathogenesis. However, it is difficult to draw a definite conclusion from our present findings because of only speculative information is represented, and no further evidence regarding the relationship between exacerbation of uriticarial rash and subsequent progression to MGN is documented. We therefore think that further studies should be required to explain the relationship in the future.

Since SLE is a multi-system disease, its clinical manifestations varies, and may show the transformation with time (Cameron 1994). Accordingly, SLE patients show great variation in the clinical expression of disease. However, it may be interesting to consider that a proportion of patients with lupus nephritis who develop acute exacerbation of urticarial rash have a risk for subsequent progression to MGN.

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