The significance of necrosis (karyorrhexis), among the most characteristic findings in lupus nephritis, was evaluated by studying the correlation between the existence of necrosis in renal biopsy specimens and laboratory findings. The subjects were 54 patients with diffuse proliferative lupus nephritis and 6 patients with focal proliferative lupus nephritis selected from 143 patients with lupus nephritis. We also compared the clinical course of oral prednisolone and intravenous methylprednisolone pulse therapies after steroid administration. Compared with the non-necrosis group, the necrosis group had significantly lower CH50 levels and more proteinuria. Patients with necrosis were effectively treated with repeated pulse therapy judging by immunological activity and the decrease in proteinuria at an early stage, but responded poorly to oral steroid therapy. As the presence of necrosis in cases of lupus nephritis means high immunological activity of the lesion and there is responsiveness to a large dose of steroids, extensive immunosuppressive therapy including methylprednisolone pulse therapy should be applied to these patients.

Key words: systemic lupus erythematosus, karyorrhexis, steroid pulse therapy, complement, anti-nuclear factor, proteinuria

Introduction

Renal involvement is an important factor that influences the prognosis of systemic lupus erythematosus (SLE) (1). Lupus nephritis, which presents various clinical pictures, is generally classified histologically according to the Classification of World Health Organization (WHO) (2), as indices of active lesions of lupus nephritis, necrosis (karyorrhexis), hematoxylin bodies, wire-loops, hyaline thrombi, and cellular crescents are known. Of these lesions, karyorrhexis is characteristic of lupus nephritis and seen frequently in this condition. This necrosis is commonly found in focal proliferative lupus nephritis (FPLN), or type III by WHO Classification, and diffuse proliferative lupus nephritis (DPLN), or type IV by WHO Classification. In this study, we first examined the correlation between the presence of necrosis and laboratory findings in cases of FPLN and DPLN to clarify the significance of necrosis in lupus nephritis, and then assessed the effects of steroid therapy including methylprednisolone pulse therapy in the necrosis group and the non-necrosis group.
grade 1 (speckled), grade 2 (speckled-diffuse), grade 3 (diffuse), grade 4 (diffuse-shaggy), and grade 5 (shaggy).

As indices of renal abnormalities, hematuria, proteinuria, and total protein in serum were used. For hematuria, urinary sediment was observed under a 400-power microscope and classified into grade 0 (4 or less red cells), grade 1 (5–10 cells), grade 2 (11–50 cells), and grade 3 (51 or more cells). The levels of anti-DNA antibody, ANF, and hematuria were statistically analyzed using 2xn table and chi square test for the difference between the two groups; the levels of CH50, proteinuria, and total protein in serum were analyzed using Wilcoxon rank sum test.

Then the effects of steroids were retrospectively compared between the necrosis group and the non-necrosis group. Of the 60 cases, the clinical course of 45 could be followed for 6 months and evaluated. Eight cases in the necrosis group and 9 cases in the non-necrosis group were treated with repeated steroid pulse therapy, and 14 cases in the necrosis group and 14 cases in the non-necrosis group were treated with conventional oral steroid therapy for comparison.

One course of the pulse therapy consisted of intravenous drip infusion of methylprednisolone, 1,000 mg, dissolved in 500 ml of 5% glucose given over 2 hours for 3 consecutive days. This course was repeated at least twice and followed by oral administration of prednisolone that was started at 30–40 mg/day and then tapered. The conventional oral steroid therapy consisted of prednisolone that was started at 30–50 mg/day and then tapered. In both groups the initial dose of prednisolone was administered for 4 to 8 weeks and then decreased to approximately 90% of the previous dosage according to the immunoserological activities such as CH50 and anti-DNA antibody. The effects of the repeated pulse therapy and conventional oral steroid therapy in the non-necrosis group and the necrosis group were assessed using CH50, ANF, proteinuria, and hematuria as indices. The data were statistically analyzed by analysis of variance and Welch t-test.

## Results

The laboratory findings from pretreatment renal biopsy were compared between the non-necrosis group and the necrosis group. In immunoserologic tests, serum complement levels were significantly lower in the necrosis group, although anti-DNA antibodies and ANF were not significantly different (Table 1). While the findings of hematuria and serum total protein levels were similar in the two groups, the amount of proteinuria was significantly higher in the necrosis group (Table 2).

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<tr>
<th>Table 1. Comparison of Immuno-serological Data between Non-Necrosis and Necrosis Groups in Patients with Lupus Nephritis</th>
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Mean±SEM, *p<0.05, **anti-DNA antibody grade (RIA) 0: ≤25, 1: 26–60, 2: 61–100, 3: >101, ***ANF (antinuclear factor) grade 1: speckled, 2: speckled-diffuse, 3: diffuse, 4: diffuse-shaggy, 5: shaggy.

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<th>Table 2. Comparison of Urinalysis and Serum Total Protein between Necrosis and Non-Necrosis Groups in Patients with Lupus Nephritis</th>
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Mean±SEM, *p<0.025, **hematuria grade 0: RBC ≤4/HPF, 1: RBC 5–10/ HPF, 2: RBC 11–50/HPF, 3: RBC ≥51/HPF.
Necrosis in Lupus Nephritis

Repeated Pulse Therapy Group

A) CH50

B) ANF

C) Proteinuria

D) Hematuria

Oral Steroid Group

Fig. 2. Movement of CH50 (A), antinuclear factor (ANF) (B), proteinuria (C), and hematuria (D) after repeated pulse therapy or conventional oral steroid administration in non-necrosis and necrosis groups. ●●: non-necrosis group after repeated pulse therapy, ○○: necrosis group after repeated pulse therapy, ▣▪: non-necrosis group after oral steroid, □□: necrosis group after oral steroid.
The necrosis group showed a better response to repeated pulse therapy or conventional oral steroid therapy, showing an earlier increase in the CH50 level than the non-necrosis group, though the difference was not statistically significant (Fig. 2A). Repeated pulse therapy increased the CH50 level earlier than oral steroid therapy.

After the repeated pulse therapy, the necrosis group showed an improving tendency in ANF. But this group did not show sufficient improvement in ANF following oral steroid therapy. In the non-necrosis group, there were slow improvements in ANF both following repeated pulse therapy and the conventional therapy (Fig. 2B). Repeated pulse therapy was more effective in improving ANF compared with oral steroid therapy.

Proteinuria was massive in the necrosis group compared to the non-necrosis group. Urinary protein excretion before treatment in the necrosis group was significantly more in those receiving pulse therapy than in those receiving oral steroid therapy. The necrosis group was more responsive to repeated pulse therapy: proteinuria began to decrease at 8 weeks after repeated pulse therapy and at 10 weeks after oral steroid therapy in contrast to the non-necrosis group who responded poorly to steroid therapy (Fig. 2C).

The degree of hematuria was more severe in those receiving repeated pulse therapy compared with those receiving oral steroid. Hematuria decreased in both the necrosis and non-necrosis groups after repeated pulse therapy, however the effect was transient and the degree of hematuria returned to close to the starting range after 6 months. Effect of therapy on hematuria was slow following conventional oral steroid therapy (Fig. 2D). Repeated pulse therapy in the necrosis group brought about prompt improvement in CH50, ANF, proteinuria and hematuria.

Discussion

Methodical studies of the histological types or histological activity of lupus nephritis was initiated by Pollak and associates (5) and, through Baldwin and associates’ study (6), were compiled into the WHO histological classification by Churg and Sobin (2). The WHO Classification, which is generally used now, classifies the condition in two ways, i.e. morphologic classification in terms of morphology and histological activity.

Karyorrhexis (necrosis) is seen in type III-a (FPLN with active necrotizing lesions) and type IV-b (DPLN with active necrotizing lesions), and type IV-c (DPLN with active and sclerosing lesions). Necrosis is observed also in rapidly progressive glomerulonephritis and nephritis with active periarteritis nodosa. Although the exact mechanism of necrosis in lupus nephritis has not yet been fully elucidated, deposition of the immune complex of DNA-anti-DNA antibody in the glomerulus is thought to initiate lupus nephritis. This is followed by complement activation and thus neutrophil infiltration. Phagocytosis of the immune complex might lead to karyorrhexis of neutrophils. Release of chemical mediators from neutrophils damage the glomerulus.

The present study showed that, in the cases of DPLN and FPLN, the necrosis group had higher immunological activity and proteinuria. Hill and colleagues (7) reported similar findings in a clinicopathological study in 59 patients with lupus nephritis: the group with necrosis or crescents had lower levels of C3 and higher anti-DNA antibody levels than the group without. They found no difference in ANF and in proteinuria, though the incidence of hematuria was higher in the necrosis group than in the non-necrosis group. Austin and colleagues (8) studied the relation between active lesion, chronic lesion, and scored indices of them (activity index and chronicity index) and their outcome. Presence or absence of necrosis was not reflected in the outcome, whereas activity indices and chronicity indices were reflected.

The principle of treatment of lupus nephritis is immunosuppressive therapy mainly with steroids. Since Cathcart and colleagues reported the effectiveness of pulse therapy in rapidly progressive DPLN (9), it has been the primary treatment of DPLN (10–12).

The present study of steroid therapy in necrosis and non-necrosis groups suggested that, in terms of fluctuations in complement levels, necrosis might be a good index of responsiveness to steroids. Both ANF and proteinuria responded differently to different therapies. The necrosis group responded earlier to repeated pulse therapy than the non-necrosis group, while responding poorly to oral steroid therapy. In this context, the presence of necrosis in renal lesions implies responsiveness to steroids. Since oral steroid therapy is insufficient for the necrosis group, more effective therapy such as methylprednisolone pulse therapy would be necessary for this group. The present results are consistent with our earlier studies on the effect of pulse therapy as assessed by WHO morphologic classification (12, 13) and other investigators’ findings (9). In conclusion, the presence of necrosis in cases of lupus nephritis means high immunoserological activity of the lesion, implies responsiveness to steroids, and suggests the applicability of extensive immunosuppressant therapy including methylprednisolone pulse therapy.

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References

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