III. Lupus Erythematosus (2) Pathogenesis and Treatment of Lupus Nephritis

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The pathogenetic mechanism of lupus nephritis is considered to be mainly immunological disorder caused by the deposition of the circulating immune complexes in the renal glomerulus and intrarenal coagulopathy may play some role in the tissue damage of lupus nephritis. In this study the pathogenesis of lupus nephritis is to be discussed in the following points; 1) the effect of the nature of immune complexes on the development of lupus nephritis and 2) the role of blood coagulation process in lupus nephritis. On these points of view, we discussed the treatment of lupus nephritis, especially steroid, including pulse therapy, immunosuppressive and anticoagulant therapy.

I) Pathogenesis of Lupus Nephritis

Lupus nephritis closely resembles experimental serum sickness nephritis mediated by antigen-antibody complexes. A characteristic feature of lupus nephritis is the multiplicity of the forms the renal lesions may taken.

On the other hand, in experimental serum sickness nephritis, the valency of antigens and individual variations in the immune response of the host, especially antibody affinity, play an important role in the localization of the complexes and in the development and fate of glomerulonephritis.

In the present study, we investigated at first, the factors determining the localization of antigen-antibody complexes in the glomerulus in passive serum sickness

nephritis. Various types of soluble antigen-antibody complexes composed of antigens and rabbit antibodies with different immunochemical properties were infused into normal C57BL mice, and the pattern of localization of the complexes in these mice were studied by light, immunofluorescent, and electron microscopy.

The following results were noted: (1) Antibody affinity for antigens has a profound effect on the pattern of complexes localization: the complexes composed of high affinity antibodies tended to be localized in the mesangial stalk region, whereas those composed of moderate affinity antibodies were found localized in the peripheral capillary walls as well as in the mesangium. The complexes formed out of extremely low affinity antibodies failed to be deposited in the glomeruli. (2) The valence of the antigen and the antigen to antibody (Ag/Ab) ratio also had important effects on the patterns of localization of the immune complexes: Complexes composed of high valency antigens tended to be localized in the mesangial stalk region. Complexes composed of low valency antigen with a low Ag/Ab ratio were localized in peripheral capillary walls, whereas those composed of low valency antigens but with a high Ag/Ab ratio could not be detected at all in the glomerulus. It was concluded that the molecular size of soluble complexes, being determined by immunochemical properties of either antigens or antibodies, influences the pattern of their localization in the glomerulus.

Based on these results, next we investigated the relationship between the antibody avidity and the histological activity of lupus nephritis by measuring the antibody avidity for native DNA.

The avidity for native DNA was almost less than 40%. The avidity and histological activity of lupus nephritis were correlated: The antibody of active group sera was higher than that of the inactive group sera and the group without urinary abnormalities. In the group with antibodies of relatively high avidity, the complexes were deposited mainly in the subendothelial side of glomerular basement membrane and mesangium. On the other hand, in the group with low avidity antibodies, the complexes were localized in the subepithelial side of GBM. If the native DNA-antinative DNA system is the mechanism basic to lupus nephritis, the differences in immune response of the host, namely the degree of antibody avidity may greatly affect complexes formation and influence the histological activity and nephritogenicity of lupus nephritis.

Another pathogenetic mechanism of lupus nephritis is considered to be intrarenal coagulation and fibrinolytic system. As one of the parameters of intrarenal coagulation and fibrinolytic mechanism is the excretion of urinary fibrin-fibrinogen degradation products (U-FDP). We measured urinary plasmin activity (U-plasmin) as a new parameter as well as FDP. The levels of U-plasmin and FDP were obtained by radiocaseinolytic assay and solid state binding radioassay respectively.

Both U-plasmin and FDP were elevated in rapidly progressive glomerulonephritis, focal glomerular sclerosis, membranoproliferative glomerulonephritis and active lupus nephritis. Both of them were low in minimal change, fixed stage of chronic glomerulonephritis and inactive lupus nephritis. And low U-plasmin with high FDP was noted in some cases of membranous nephropathy. These results suggest that in the cases with high U-plasmin and FDP,

intrarenal coagulation may take place. In the cases with low plasmin and FDP, intrarenal coagulation may not take place. In the cases with low plasmin and high FDP, the U-FDP may be caused by the low selectivity of GBM and partly tubular dysfunction. It was concluded that in active lupus nephritis, intrarenal coagulation may be also one of the important pathogenetic mechanisms and excretion of U-plasmin is valuable as a indicator for the presence of intrarenal coagulation and reliable to determin the indication and to moniter anticoagulant therapy.

II) Treatment of Lupus Nephritis

Steroid therapy is considered to be primary in the treatment of lupus nephritis. Especially high-dose steroid therapy favors a good prognosis in lupus nephritis in comparison with other primary renal diseases. In addition to it, immunosuppressive therapy may give some place especially in steroid resistant lupus nephritis. Our treatment is based on these two well established therapies in the standpoint of its pathogenesis. There is no significant difference in the levels immune complexes assayed by Clq binding test between lupus nephritis and without nephritis. And remarkable decrease in the circulating immune complexes was detected in the two cases with steroid pulse therapy and in other two cases with high dose steroid therapy. On the other hand, avidity for native DNA was elevated in the cases which altered membranous lupus nephritis to diffuse proliferative lupus nephritis. From these experience, it offers some important data in the treatment of lupus nephritis and determination of its prognosis to measure anti-DNA antibody, avidity for native DNA and circulating immune complexes.

Our data suggestive of markedly increased coagulation activity in the lupus kidney. Anticoagulation therapy is indicated in this situation. This is the result of anticoagulant therapy in 14 cases of renal disease including 4 cases of lupus

nephritis. It was effective in 6 cases (43%) and half of them were from lupus nephritis. There was significant improvement in renal function in 3 cases of lupus nephritis out of the 4 cases. Anticoagulant therapy was started in the early stage from the onset and warfarin after heparin was administered more than 6 months in these

successful cases. From our standpoint of view, it is effective to start anticoagulant therapy in the early stage of lupus nephritis. It is helpful to maintain the kidney function and to protect the kidney from the tissue damage. Lupus nephritis is a kind disease which benefits by anticoagulant therapy.

III. Lupus Erythematosus (Supplementary) Treatment and Prognosis of Lupus Nephritis

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The purpose of this work is (1) to study the long-term prognosis of SLE patients who received renal biopsies and who started therapy with various types of treatment, and (2) to try to set up a therapeutic regimen for lupus nephritis. It also discusses whether the treatments alter the natural course of lupus nephritis or not.

MATERIAL AND METHOD

Renal tissue from 110 SLE patients diagnosed as having satisfied ARA criteria for SLE were examined histologically. They were classified into 6 types; 1. minimal change (MC) (42 cases), 2. focal proliferative GN (FGN) (15 cases), 3. diffuse proliferative GN (DPGN) (16 cases), 4. membranous GN (MGN) (15 cases), 5. membranoproliferative GN (MPGN) (18 cases), 6. advanced stage (4 cases). The types of treatment were classified as follows: 1. low doses of steroids, 2. high doses of steroids, 3. combined therapy of steroids

and cytostatics. SLE patients treated with high doses of steroids included the patients with MC and FGN treated with over 30 mg/day of prednisone, and the patients with DPGN, MGN and advanced stage treated with over 40 mg/day. Cyclophosphamide, azathioprine and 6 mercaptoprine were used as cytostatics. Survivalship of lupus nephritis after starting therapy with these types of treatment was evaluated by the life table method. The differences of the responses of steroids for clinical and immunological findings among the histological types of nephritis after the start of treatment with 40 mg/day were studied. In SLE patients with DPGN, MGN and MPGN, the changes in clinical and immunological findings during the treatment were also studied. Relationship between the treatment and transformation of glomerular lesion of lupus nephritis using rebiopsy or autopsy specimen was studied.