Familial Membranous Lupus Nephritis in Brothers

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Dear Sir,

Although the etiology of systemic lupus erythematosus (SLE) is thought to be multi-factorial, genetic factors have long been suspected to be involved in its pathogenesis [1]. Studies of the familial occurrence of SLE [1, 2] and of the abnormal serologic patterns in relatives of patients with SLE [2, 3] suggest hereditary factors in its origin. Here we report on 2 brothers, both of whom developed familial membranous lupus nephritis (MLN) as an another supporting case.

A 15-year-old boy with erythematous maculopapular skin rash on nearly the whole body with malar rash and photosensitivity was admitted to Chungnam National University Hospital in August 1989. His laboratory values were as follows: hematocrit 34.2%, WBC 5,700/mm³, platelet count 106,900/mm³, albumin 34 g/l, and creatinine 53 µmol/l. The amount of 24-hour urinary protein excretion was 970 mg and microscopic hematuria was also noted. ANA was positive (1:40) as a speckled pattern and anti-dsDNA antibody was also positive (qualitative examination). Serum levels of C3 and C4 were 450 and 80 mg/l, respectively. Serum levels of immunoglobulins were normal and serum cryoglobulin, VDRL, ASO, and rheumatoid factor (RF) test were negative. Renal biopsy was performed; Light microscopy (LM) showed that the glomeruli revealed segmentally hypercellular mesangium and diffuse thickening of the capillary basement membrane without remarkable tubulointerstitial and vascular changes: immunofluorescence (IF) studies showed extended granular 3+ staining of IgG and 1+ staining of C3 along the capillary wall; ultrastructural examination disclosed diffuse numerous subepithelial deposits involving with multiple spike and dome formations. Therapy of daily oral prednisolone was prescribed and the dosage modified according to the serum levels of C3 and C4. In November 1994, clinical features of full-blown nephrotic syndrome appeared suddenly after an episode of a flu-like syndrome. We prescribed again a high dose of oral prednisolone. However, the patient showed only partial remission of the nephrotic syndrome. His 15-year-old younger brother was admitted to Chungbuk National University Hospital in December 1993 with a rash on the whole body with photosensitivity. In the previous year the rash had waxed and waned on his face and hands. On physical examination, fever (38.4°C), conjunctival injections, malar rash, oral ulcer, and both cervical lymphadenopathies were noted. Initial laboratory data revealed: hematocrit 33.4%, platelet count 113,000/µl, WBC

count $2,100/\text{mm}^3$, creatinine $106 \mu\text{mol/l}$, and albumin 30 g/l . In serologic findings, the following determinations were negative or within normal limits: ASO, RF, VDRL, lupus anticoagulant, and antiplatelet antibody. ANA was positive (1:20) as a speckled pattern and anti-dsDNA antibody (45.6 IU/ml) and anti-Sm antibody were also positive. Complement levels were all depressed and revealed: C3 190 mg/l , C4 60 mg/l , Clq 8 mg/l , and CH 50 18.5% . Urinalysis revealed protein-uria, 4+. A renal biopsy was carried out: LM showed that all eight glomeruli revealed diffuse thickening of the capillary wall and slightly widened mesangial spaces without remarkable tubulointerstitial changes; IF studies showed positive staining for IgA, C3, and IgG along the capillary wall; electron microscopy showed numerous epithelial and intramembranous electron dense deposits. His lupus was controlled by prednisolone (60 mg , 1.7 mg/kg/day) and proteinuria was diminished. During the 2-year follow-up period, prednisolone was changed to deflazacort because of steroid-induced diabetes mellitus, he experienced one episode of hy-perbilirubinemic hepatopathy (unknown etiology), and he had been managed with deflazacort according to the levels of complements and anti-dsDNA antibody and the amount of proteinuria. We performed HLA typing for class I and II molecules in the 2 siblings. HLA typing of the elder brother was: HLA-A24, -A31, HLA-B51, -B58, HLA-DR3, -DR53, and -DQ8, and those of the younger brother was: HLA-A2, -A24, HLA-B51, HLA-DR9, -DR53, and DQ8. Urinalysis and ANA test were performed in the other family members, father, mother, and sister, and revealed normal findings. The genetic component to the etiology of SLE has been suggested by the familial incidence [1-3], healthy relatives with ANA and other autoantibodies [2, 4], associations with the major histocompatibility complex [3, 5-7], and differential racial incidences [3, 8]. The occurrence of multiple cases in the same family does not absolutely prove the existence of genetic linkage, because it could also be possible due to common environmental

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factors. Nevertheless, and in the view of the accumulating experience with familial cases, the significance and nature of these hypothetical environmental factors remain undefined. From the occurrence of SLE in families in a frequency greater than anticipated, various investigations of HLA associations with this disease have been done. However, their results of HLA profiles were so variable depending on the authors or race investigated [1, 3, 5, 6]. Variability does exist between races with HLA-A1 being found more in black SLE patients and HLA-A8 appearing more frequently in white SLE patients [5, 6]. And HLA-DR2 and/or DR3, together with their highly linked DQ antigens have been found in excess in Caucasians with SLE [7]. Our results of HLA typings are not the commonly reported findings. Moreover, there have been no reliable data on HLA results in Korean SLE. Therefore, we cannot estimate the significance of our HLA results.

In conclusion, because MLN, familial incidence, and male occurrence are uncommon in lupus, separately, our case of MLN in brothers seems to be very rare in combination. Moreover, this report may be the first case of familial lupus in brothers having the renal pathology of membranous type from the review of the related articles which have been

reported. Further studies are necessary in order to reveal the pathophysiologic interrelations in lupus between genetic factors, familial occurrence, brother occurrence, and MLN.

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