Hyperimmunoglobulin E Syndrome Associated with Nephrotic Syndrome

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A 21-year-old man was admitted to Kure National Hospital with nephrotic syndrome in September 1996. He had suffered from an intractable pruritic skin rash and recurrent subcutaneous abscesses caused by the hyperimmunoglobulin E syndrome since the age of 18 months. Renal biopsy gave a diagnosis of membranoproliferative glomerulonephritis. Steroid therapy decreased urinary protein loss and hypoproteinemia, and his pruritic skin rash was improved. Patients with hyperimmunoglobulin E syndrome have a defective immune response, especially to Staphylococcus aureus infection. Continuous antigen stimulation may have caused this patient’s renal histological damage as in immune complex glomerulonephritis.

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Key words: membranoproliferative glomerulonephritis, immune complex glomerulonephritis, steroid responsiveness, Staphylococcus aureus infection

Introduction

Hyperimmunoglobulin E (hyper-IgE) syndrome is characterized by a chronic pruritic skin rash, recurrent pyogenic infection with Staphylococcus aureus (S. aureus), and high immunoglobulin (Ig) E levels from infancy, and is usually associated with depressed neutrophil chemotaxis (1-3). In this syndrome, T cell dysfunction has been described and is thought to cause overproduction of IgE (4, 5). Renal disease is rarely associated with this syndrome. However, we encountered an unusual patient who had the hyper-IgE syndrome complicated by nephrotic syndrome and this case is reported here.

Case Report

The patient, a 21-year-old man, had no significant family history. Since the age of 18 months he had suffered from intractable pruritic skin eruptions and an elevated IgE level (3,100 U/ml), and had been repeatedly admitted to hospital because of recurrent subcutaneous abscesses, phlegmon, muscle abscesses, and myelitis caused by S. aureus. A diagnosis of hyper-IgE syndrome was made at the age of 13 years. In 1993, at age 18, proteinuria was first detected at a routine school medical examination, and he went to Kure National Hospital for assessment. At that time, renal function was normal with a urinary protein excretion of 0.9 g/day. In August 1994, the patient underwent renal biopsy at another hospital for the examination of poteinuria. Only minor glomerular abnormalities were detected, so he was left untreated (Fig. 1A). In mid September 1996, his pruritic skin rash became worse and abdominal distension as well as generalized edema developed. On September 24, he was diagnosed as having nephrotic syndrome at Kure National Hospital and was admitted on September 25.

Status on admission

The patient was 170.7 cm tall and weighed 71.5 kg. The temperature was 36.7°C, and the blood pressure was 144/88 mmHg. A skin rash with desquamation was observed on the face, trunk, and extremities. There was pitting edema of all four extremities, but no ascites or pleural effusion. Urinalysis revealed protein (3+), occult blood (1+), and oval fat bodies. The daily urinary protein excretion was 16.7 g. Hematology tests disclosed eosinophilia (915/µL), and biochemistry tests revealed marked hypoalbuminemia (1.5 g/dl), hypercholesterolemia (296 mg/dl), and an increase of α2-globulin. There was also a decrease in IgG and an increase in IgE, with a high level of soluble cluster of differentiation 23 (CD23). There were no abnormalities of autoantibodies, and 50% hemolytic unit of From *the Department of Internal Medicine, Kure National Hospital, Kure, **the Second Department of Internal Medicine, Hiroshima University School of Medicine, Hiroshima and ***the Second Department of Pathology, Nagasaki University School of Medicine, Nagasaki, *^Present address: the Second Department of Internal Medicine, Hiroshima University School of Medicine, Hiroshima

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complement was slightly decreased (27.7 U/ml) (Table 1). Renal function was normal (24-hr creatinine clearance was 143.5 ml/min, blood urea nitrogen was 7 mg/dl, and serum creatinine was 0.6 mg/dl) and there were no abnormalities detected on bone marrow examination.

**Clinical course (Fig. 2)**

Laboratory findings indicated a diagnosis of hyper-IgE syndrome associated with the nephrotic syndrome. Rest and oral furosemide (40 mg/day) reduced his weight to 58.5 kg on hospital day 24. Renal biopsy revealed hyalinization of 2 out of 11 glomeruli, while the remaining glomeruli showed mesangial cell proliferation and matrix expansion leading to prominent focal sclerosis in some areas. Some glomeruli showed small crescents and adhesions of Bowman’s capsule. The basement membrane was thickened (Fig. 1B), and showed duplication (Fig. 1C), as well as apparent subendothelial deposits. The interstitium showed diffuse severe fibrosis and cellular infiltration, and foam cells were present in some areas. Immunofluorescence detected deposits of IgG, IgM, complement 3, and complement 4, mainly in the basement membrane with a fringe pattern (Fig. 1D), while IgA and fibrinogen were negative. Electron microscopy could not be done because the specimens prepared for study contained no glomeruli. These findings indicated a diagnosis of membra noproliferative glomerulonephritis according to the World Health Organization classification. On hospital day 29, prednisolone (40 mg/day), dilazep hydrochloride (300 mg/day), and warfarin (1 mg/day) were commenced. On day 48, the daily urinary protein excretion was decreased to 4.0 g, total protein was increased to 4.3 g/dl, and
serum albumin was increased to 2.5 g/dl. In addition, his skin rash showed improvement and the eosinophil count had decreased. On day 106, serum IgE was reduced to 2,300 U/ml. On day 133, at the time of discharge, his hypoproteinemia had improved, with a total protein level of 5.6 g/dl and an albumin level of 3.7 g/dl. In September 1997, one year after discharge, the patient was still taking prednisolone at 17.5 mg/day. The total protein level was 6.0 g/dl, serum albumin was 4.1 g/dl, serum IgE was 950 U/ml, and soluble CD23 was 303 U/ml, indicating that his condition was stable.

Discussion

Hyper-IgE syndrome was initially reported by Buckley et al (6). It is an immunodeficiency syndrome characterized by repeated pyogenic infections caused by S. aureus, intractable pruritic eczema, high IgE levels, depressed neutrophil chemotaxis, and T lymphocyte dysfunction (1). Some investigators have reported that the pathogenesis of hyper-IgE syndrome and the mechanism underlying the high IgE levels involve suppressor T cell defects (5, 7). The increase of IgE has been suggested to be caused by decreased activity of Th1 cells that produce interferon-γ and interleukin (IL)-2, combined with hyperactivity of Th2 cells that generate IL-4, IL-5, and IL-13, i.e., an imbalance between Th1 and Th2 activity. In patients with this syndrome, a specific IgE antibody to S. aureus has been detected in the serum (8), and the high incidence of S. aureus infection has been suggested to be related to a defective immune response (9).

Methylprednisolone and interferon-γ are reported to inhibit FcεR2 (CD 23) expression at the mRNA and protein levels
Tanji et al.

In the present patient, the serum IgE level decreased along with clinical improvement and thus appeared to be a useful index of disease activity. Steroid therapy may have improved the balance between cytokine secretion, CD23 expression, and serum IgE production.

Kimura’s disease (angiolympoid hyperplasia with eosinophilia) is also associated with high IgE levels and hypereosinophilia complicating nephrotic syndrome. Patients with this disease have subcutaneous granulomas of the head and neck. However, our patient had no subcutaneous granulomas and no associated features of this disease.

Immune complex glomerulonephritis has been reported in association with staphylococcal infections, including bacterial endocarditis, ventriculoatrial shunt infections, pneumonia, and visceral abscesses with or without septicemia (11, 12). The histopathological features are reported to be diffuse glomerular proliferation and exudation, mesangial proliferation, mild to moderate interstitial cellular infiltrate, infrequent crescent formation, and membranoproliferative features (12). When staphylococcal infection causes glomerulonephritis, S. aureus antigens are directly deposited within the glomeruli (13), leading to immune complex formation. A cationic staphylococcal protein has recently been reported to play a role in acute glomerulonephritis following S. aureus infection in rats (14). In our patient, S. aureus antigens or immune complexes composed of these antigens may have been deposited in the glomeruli, leading to the production of various cytokines, an increase of the extracellular matrix, and glomerular damage. Patients with hyper-IgE syndrome are immunodeficient, especially in relation to S. aureus, and thus immune complex glomerulonephritis may have a tendency to develop secondary to S. aureus infection. Also, IgE itself stimulates mast cells to secrete vasoactive mediators, which increase capillary permeability and induce protein leakage. Thus, continuous antigenic stimulation may have caused the renal histological damage noted in our patient.

References