Case Report

IgE DEPOSITS IN GLOMERULI WITH MEMBRANOUS NEPHROPATHY AND MARKED ASTHMATIC PREDISPOSITION IN HUMANS*

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Described herein is a patient in whom membranous nephropathy appeared to be associated with a strong family history of bronchial asthma. IgE was demonstrated in the glomerular capillary walls in a diffuse granular pattern.

RECENTLY IgE was found to be localized in the bronchial mucosa of patients with asthma,¹ in the thyroid of patients with Graves disease,² in the glomeruli of patients with certain forms of nephrotic syndrome³ and in many renal arterioles of patients with malignant nephrosclerosis.⁴

Whether or not IgE plays a definite role in the pathogenesis of these diseases has been investigated.

Nephrotic syndrome with inhaled allergens⁵ or with atopic dermatitis⁶ is reported herein.

Cameron⁷ made a study of four patients with specific pollen sensitivity, but definite proof of IgE in the glomeruli was not demonstrated.

The following case does however suggest the role of IgE in the pathogenesis of certain forms of the membranous nephropathy.

CASE REPORT

The patient is presently a laborer aged 42.

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A sore throat and tonsillitis were often present when he was 14 and 15 years old.

In the Spring of 1970, he felt a palpitation in his heart plus dyspnea. At that time, he was occupied in electro-plating and was considerably exposed to chromium, the dyspnea and cough seemed to become progressively worse.

In December of 1970, he consulted to a doctor and was diagnosed as a case of bronchial asthma. No specific therapy was given.

In January of 1971, a routine urinalysis revealed a proteinuria but again specific therapy was not administered.

In February of 1971, he had an attack of precordial oppression accompanied by pain which lasted for one hour. He visited general practitioner who recommended a complete physical check-up in light of the proteinuria and abnormal ECG.

He had admitted to hospital for three months, during which time he was treated for a nephritis.

The proteinuria was however unalleviated and he was re-admitted twice to hospital before the admission to Kyoto University Hospital.

A Family history is summarized in Fig.1. A strong family history of bronchial asthma is present.

Fig.1.

Fig.2. Portion of glomerulus from renal biopsy: thickening of the glomerular capillary wall (hematoxylin-eosin, original magnification 140).

The physical examination in January 1972 was unremarkable except for a slight ankle and pretibial edema. Blood pressure was 132/86 mmHg.

Laboratory data: hemoglobin, 15.8 g/100 ml; hematocrit, 47% W.B.C. 7200/cumm, with 47% neutrophils, 43%, lymphocytes, 5% monocytes and 5% eosinophils.

Serum electrophoresis disclosed a total protein of 4.1 g, albumin 1.9 g, alpha₁ globulin 0.36 g, alpha₂ globulin 0.62 g, beta globulin 0.53 g and gamma globulin 0.68 g/100 ml. Test results for LE cells, rheumatoid factor and nuclear anti-

bodies were negative.

Group A streptococci was not revealed in the throat culture. Repeated urine culture was negative.

Urine protein level was 4.5 gm/24 hr and creatinine clearance was 117 ml/min. The urine sediment contained 5 to 7 R.B.C. per high-power field (HPF), several W.B.C. per HPF, and occasional waxy casts.

A biopsy of the kidney was done on February 14, 1972. The fresh tissue was fixed in 10% formalin, embedded in paraffin, serially sectioned, and stained with hematoxylin and eosin.

Fig.3. There is a widening of the capillary basement membrane with great variation in density. The dense granular deposits are more prominent toward epithelial surface. The membranous transformation is remarkable and epithelial foot processes are fused. (Electron microscopy; magnification, 17000).

Fig.4. Immunofluorescent photomicrograph of glomerules; diffuse finely granular deposits of IgG are seen along the basement membrane (original magnification 160).

Fig.5. Immunofluorescent photomicrograph of glomerulus; finely granular deposits of complement all along the basement membrane (original magnification 160).

Fig.6. Immunofluorescent photomicrograph of glomerulus; glomerulus diffusely stained along the basement membrane with antihuman IgE (original magnification 160).

For electron microscopic study tissue sample was immediately fixed in cold buffered glutaraldehyde, post-fixed in osmium tetroxide, and embedded in Epon. Ultrathin sections were stained with a combination of uranyl acetate and lead citrate.

For an immunohistochemical study, the tissue was quick frozen in isopentane which was precooled in a mixture of dry ice and acetone. The tissue was transferred from isopentane into a test tube of acetone precooled to -60°C . and the specimen was substituted in acetone for 14 days,

according to the technique of Post.¹⁵

The tissue was then embedded in paraffin. Consecutive paraffin sections, four microns in thickness, were treated with commercially obtained fluorescein-isothiocyanate (FITC) conjugated rabbit antisera against human IgG, IgM, IgA, Beta-1C/Beta-1A globulin and Fibrinogen (Behringwerke AG.).

Localization of IgE was performed by double-layer immunofluorescence with anti-human rabbit IgE and FITC conjugated anti-rabbit goat IgG (Behringwerke AG.). The specificity of each antiserum was established by immunoelectrophoresis. Reactions of antiserum fluorescence were specifically blocked by an unconjugated sample of the same antiserum obtained from the same source. The anti-IgE specificity was further tested by indirect immunofluorescence staining with antinuclear antibody of a known immunoglobulin class.

The sera that had antinuclear antibody titer of 2300 when tested with anti-IgG conjugate had no antinuclear antibody titer when tested with anti-IgE.

IgG (Fig.4), beta-1C/1A-globulin (Fig.5), IgE (Fig.6) and, to lesser extent, IgM, Fibrinogen were deposited in a granular pattern along the glomerular basement membrane (GBM).

There was no stain with antihuman IgA sera.

Electron microscopy revealed numerous electron-dense deposits along the epithelial side of the GBM (Fig.3).

Fig.2 illustrates the glomerular histology of this case under light microscopy. There is a diffuse thickening of the GBM and epithelial fatty degeneration in the proximal convoluted tubule.

DISCUSSION

In 1966, *Ishizaka et al.* identified a unique immunoglobulin, IgE, as the carrier of reaginic antibody activity.^{8,9}

The role of IgE in the mediation of immediate hypersensitivity reactions and its association with asthma and other atopic diseases has been established.⁹⁻¹¹

Several authors suggest that reaginic antibody (IgE) plays a role in the development of renal disease, especially in relation to the allergic diseases.^{3,5,12,13}

J. Hardwicke et al. reported on interesting case where recurrent attacks of the nephrotic syndrome were over a 7 year period related to the patient's hypersensitivity to pollens.¹²

The patient observed by the authors is a case of association of nephrotic syndrome with a predisposition to asthma.

Five cases of membranous nephropathy for IgE deposits were studied and moderate to minimal deposits of IgE in the glomerular capillary walls were observed. In addition, three out of the five cases did have a predisposition to asthma and one of the five had an eczematous dermatitis (unpublished data). It appears feasible that certain membranous nephropathies are related to an allergy, in which elevated levels of IgE are present.

IgE-mediated responses, with release of vasoactive substances, may be one of the mechanisms responsible for the permeability of protein from the glomerular basement membrane.

Dixon et al. succeeded in producing a membranous glomerulonephritis by immunization with the autologous renal tubular antigen in rats.¹⁴

Allergic diseases may in some way be related to the autoimmune diseases. Three possibilities for the role of IgE in the pathogenesis of glomerulonephritis are proposed:

- 1) IgE-reaginic antibody, may play a certain role in the early stage of pathogenesis as the mediator of immediate hypersensitivity reactions.
- 2) When glomerulonephritis is simultaneously present with an allergic disease and the serum IgE is elevated, then IgE may play a certain role in the pathogenesis of all stages as do other immunoglobulins.
- 3) A combination of the above factors.

Further studies are in progress to elucidate the pathogenetic role of IgE in glomerulonephritis.

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