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IgE Associated Nephropathy in a Patient with Subcutaneous Eosinophilic Lymphoid Granuloma (Kimura's Disease)

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Summary. A patient with subcutaneous eosinophilic lymphoid granuloma (Kimura's disease) associated with a high serum IgE level and a marked blood eosinophilia, had a glomerulonephritis with electron dense deposits in mesangial, paramesangial, subendothelial, intramembranous and epimembranous areas. By immunofluorescence, all the glomeruli showed predominant depositions of IgE and IgG along the paramesangial areas and capillary walls together with complement components. The germinal centers in the lymph follicles formed in both the subcutaneous granuloma and the kidney interstitium also contained mainly IgE and IgG but no complement components. These features of this disease suggest that the glomerular lesion is one of the systemic manifestations of Kimura's disease.

Key words: Granuloma – Eosinophilia – IgE – Glomerulonephritis

Introduction

Kimura et al. (1948) reported a disease characterized by the formation of subcutaneous granuloma in soft tissues with lymph follicle hyperplasia and a marked infiltration of eosinophils (Reed and Terazakis 1972). As additional characteristics, marked eosinophilia (Iizuka 1959), mast cell infiltration in the granuloma, elevated serum IgE level, appearance of IgE antibodies against Candida albicans and localization of IgE in the germinal centers of lymph follicles (Takenaka et al. 1976) have been reported.

We describe here a patient with typical Kimura's disease who also had a renal disease with glomerular deposition of IgE, IgG, IgM and complement components.

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Clinical History

A 31 year old man was admitted to Kyoto University Hospital on November 27, 1979, for evaluation of proteinuria and haematuria. His medical history included nephritis when he was 3 years old but the details were unknown. Subcutaneous tumors were first noted on his right elbow at 12 years of age and on the left elbow at 15. These tumors were surgically excised on each occasion. Approximately 18 months prior to admission, he had an influenza-like illness associated with oedema on his face and legs, proteinuria and haematuria. Several months later, subcutaneous tumors appeared on his left and right thighs. The family history was non-contributory.

The subcutaneous tumors were hard, mobile, smooth-surfaced and painless. Lymph nodes in the left inguinal region were swollen.

The tumors on his thighs were excised on December 26, 1979 and a percutaneous kidney biopsy was performed one month after the tumor excision. The postoperative course was uneventful.

Laboratory Findings

Blood Counts. Hb 12.8 g%, Leucocytes 7,800/mm^3 with eosinophilia up to 31%.

Serum Chemistry. Total protein 6.5 g%, Albumin 4.17 g% IgG 9.62 mg/ml, IgA 1.69 mg/ml, IgM 0.91 mg/ml, IgE over 4,000 U/ml, Urea-N 22 mg%, Anti-streptolysin 0 titer less than 1:20.

Urine Analysis. Proteinuria up to 0.6 g/24 h.

Renal Function Tests. STS clearance 103 ml/min/1.48 m^2, PAH-clearance 568 ml/min/1.48 m^2.

A Bone Marrow Aspirate. A marked eosinophilia.

Skin Test. Mantoux Reaction: 25 mm × 15 mm (erythema with induration), Candida albicans: 8 mm × 5 mm (induration)/8 mm × 5 mm (erythema), Buckwheat: negative, Saline control: negative.

Materials and Methods

Light Microscopy. Tissues were fixed in 10 per cent formalin Zenker's solution and embedded in paraffin. The following stains were used for 4 μm sections: haematoxylin and eosin, periodic acid-Schiff's haematoxylin, Azan Mallory and elastic van Gieson. Acridine-orange fluorescent staining was also applied to detect mast cells (Jagatic and Weiscopf 1966).

Electron Microscopy. Small blocks of the renal biopsy specimen were fixed in 2% glutaraldehyde and embedded in epon. After thin sectioning, the tissues were stained with uranyl acetate and lead citrate and studied under a Hitachi Electron Microscope.

Immunofluorescence. Tissues were rapidly frozen in dry-ice acetone. Cryostat sections at 2 μm were air-dried and washed 3 times in isotonic phosphate-buffered saline (pH 7.2) for 15 min each without fixation, followed by staining for 30 min at room temperature with fluorescein-labeled antisera monospecific to each alpha, gamma, mu and epsilon chains, Clq, C4, C3, C5, properdin and albumin (Behringwerke, AG, West Germany, Medical Biological Company, Japan and Kent Laboratory, USA). Intensity of the fluorescence was graded from 0 to 3+. Specificity of the reaction was examined by both blocking and absorption tests. The specificity of the IgE staining was confirmed by the following observations: 1) On immunoelectrophoresis IgE myeloma serum gave a single line of precipitation against the anti-IgE serum used: normal serum failed to give a line of precipitation. 2) Absorption of the antiserum with normal human serum had no effect on the staining of the structures comtaining IgE. 3) Pre-treatment of the sections with unconjugated anti-IgE serum abolished the following direct fluorescent staining of the structures with fluorescein-labeled anti-IgE. 4) Staining of the structures containing IgE did not occur when the fluorescein-labeled antiserum was absorbed with IgE myeloma serum.

Results

Under the light microscope, the subcutaneous tumors are characterized by the formation of numerous lymph follicles with well-developed germinal centers with a marked diffuse infiltration of eosinophils around the lymph follicles.

Table 1. Immunofluorescence findings in germinal centers in the subcutaneous granuloma.

Immunoglubulin and Complement	Incidence in fluorescence positive germinal centers	
	Granuloma No. positive/No. tested (%)	Control[a] No. positive/No. tested (%)
IgG	101/138 (73.1%)	28/90 (31.1%)
IgA	12/134 (8.9%)	33/86 (38.1%)
IgM	61/133 (45.8%)	24/91 (26.3%)
IgE	105/133 (78.9%)	0/90 (0%)
C3	0/134 (0%)	0/88 (0%)

[a] Tonsil of a patient with IgA nephropathy

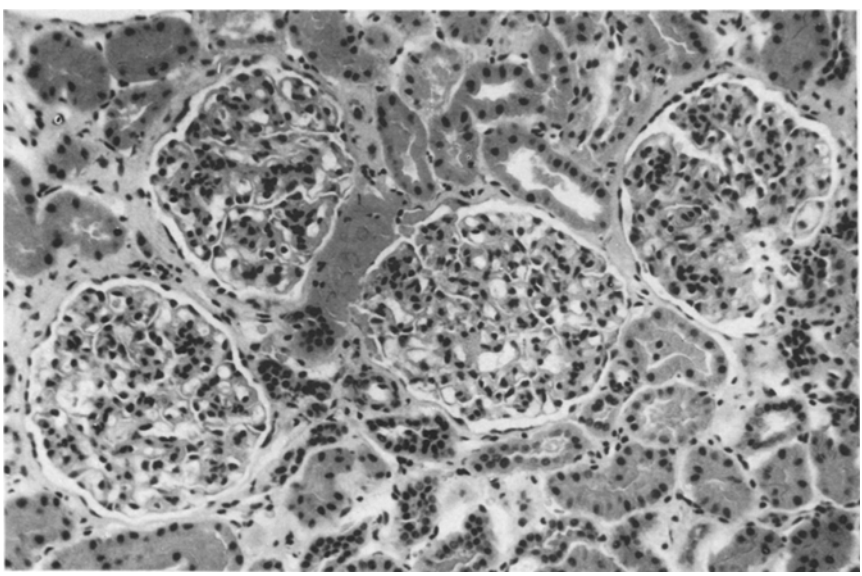

Fig. 1. Light microscopy of glomeruli. H&E stain. ×100

A number of mast cells is also seen among these eosinophils. Plasma cells are scattered in inter-lymphfollicular spaces but not found in the germinal centers. Another predominant feature in the tumor tissue is the proliferation of small vessels. The histological diagnosis is Kimura's disease (Takenaka et al. 1976; Wells and Whimster 1969). Immunofluorescent studies reveal the localization of IgE, IgG and IgM in the germinal centers in reticular pattern. Absorption studies using non-fluorescein-labeled antisera confirm the specificity of the immunoglobulin localization in the germinal centers. Albumin and the complement components are not detected in the germinal centers. Eosinophils are also stained with all fluorescin-labeled antibodies, however, both the absorption and blocking tests fail to abolish the staining of eosinophils (Fuerst and Jannach 1965).

The ratio of fluorescence positive to the total number of germinal centers in one section is calculated for each immunoglubulin staining (Table 1). Fluores-

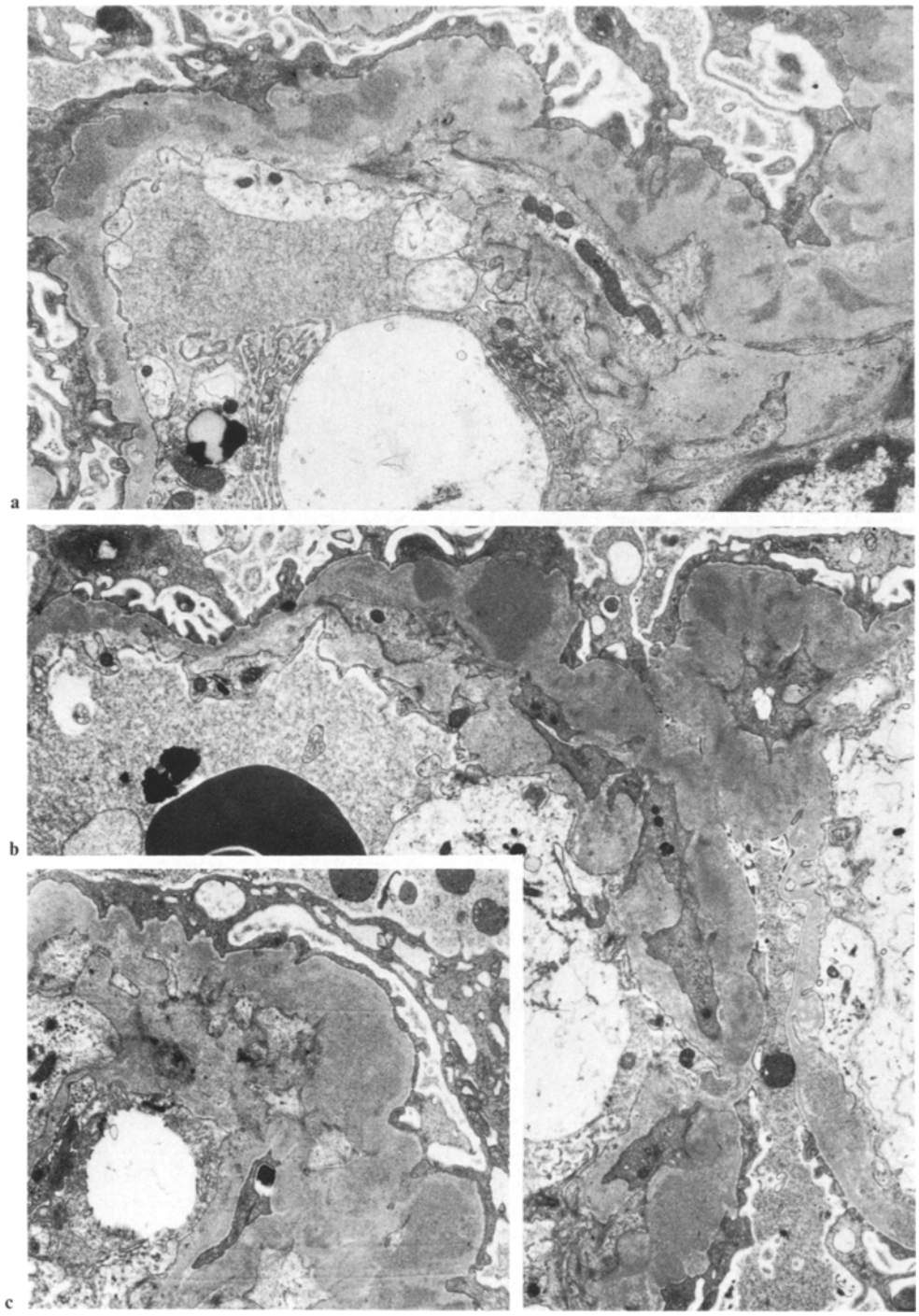

Fig. 2a–c. Electron micrograph of glomeruli. **a** Paramesangial and intramembranous deposits. ×8,300. **b** Epimembranous deposits and partial attenuation of basement membrane. ×5,000. **c** Subendothelial deposits and subendothelial extension of mesangium. ×3,000

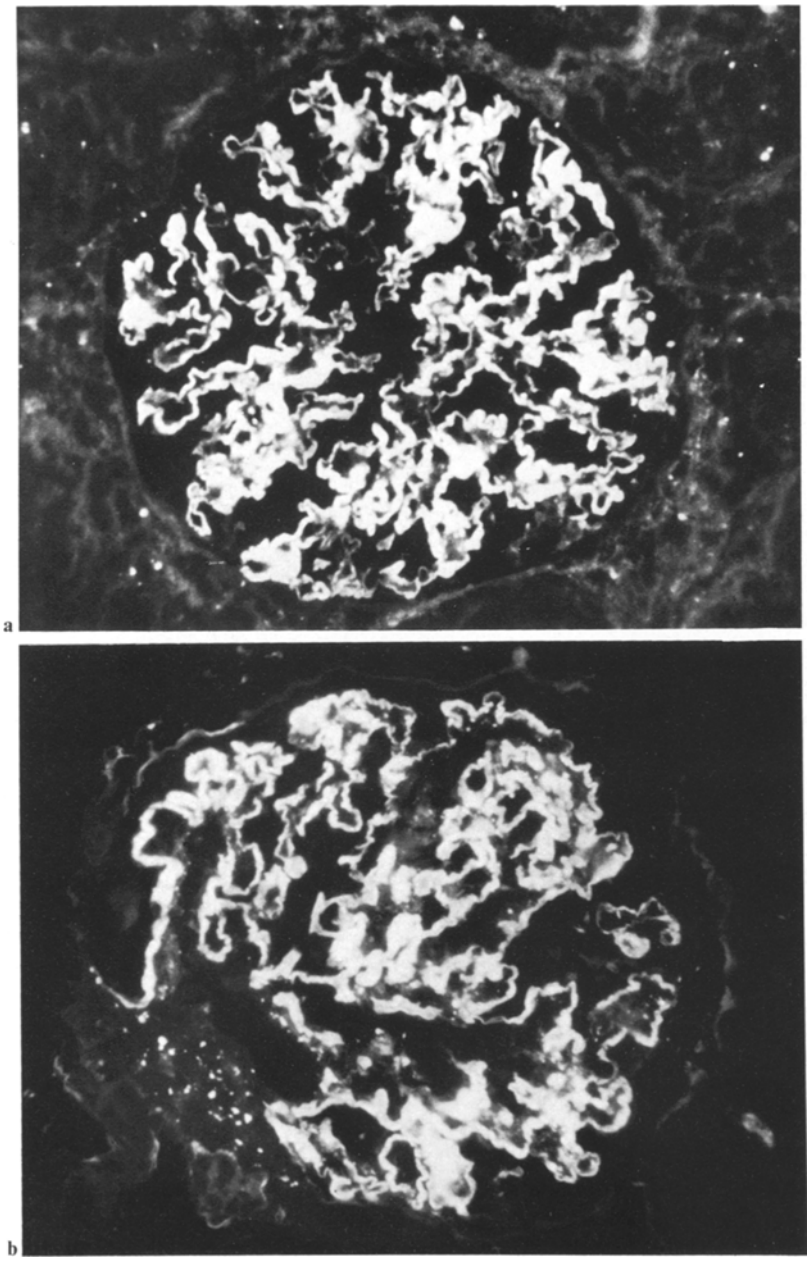

Fig. 3a, b. Immunofluorescence microscopy. Paramesangial and capillary wall deposition of IgG (**a**) and IgE (**b**). ×200

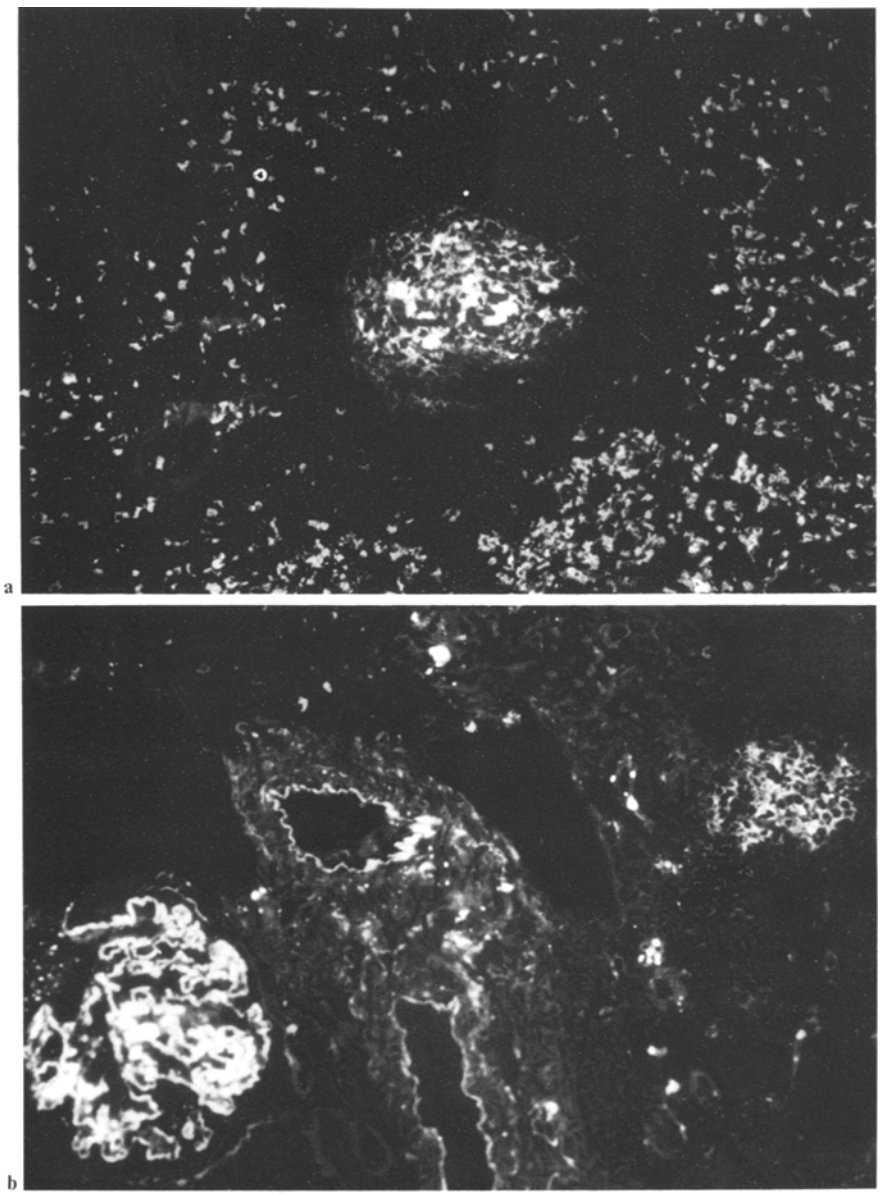

Fig. 4a, b. Immunofluorescence microscopy. IgE in germinal center in granuloma (**a**) and in renal tissue (**b**), a glomerulus with IgE deposits (**b**) and nonspecific fluorescence of eosinophils around the lymph follicle (**a**). ×100

cence of IgE and IgG is more intense than that of IgM and IgA. These findings are in keeping with the observations of Takenaka et al. (1976).

In light microscopic examination of the kidney biopsy tissue, the glomeruli show a diffuse proliferation of endocapillary cells and particularly mesangial cells, with irregular thickening of capillary walls. Although sclerosis is evident

in some glomeruli, there are no capsular adhesion or crescent formation (Fig. 1). Red blood cell casts are seen in the tubular lumens. There are eosinophil infiltrates and the formation of some lymph follicles in the interstitium. Electron microscopic examination reveals an increase of mesangial matrix, narrowing of some capillary lumens and vacuolization of the endothelial cells. Glomerular basement membranes are thickened but partially attenuated. Electron dense deposits are observed in paramesangial and mesangial areas and epimembranous, intramembranous and subendothelial areas of basement membranes. Some subendothelial extension of mesangium and fusion of foot processes are also seen (Fig. 2a–c). In addition to these findings, there are a few hump-like deposits in epimembranous areas. Immunofluorescence shows a bright diffuse deposition of IgG (3+) (Fig. 3a), IgE (3+) (Fig. 3b), IgM (1+), C3 (1+), C5 (1+) and properdin (1+) along the paramesangial areas and the capillary walls. Staining for IgA, Clq and C4 are all negative. In addition, localization of IgE, IgG and IgM is also observed in the germinal centers of the lymph follicles in the kidney interstitium in the same pattern as those in the subcutaneous granuloma (Fig. 4a and b). No complement components are found in the germinal centers.

Discussion

Accumulating evidence has suggested that the subcutaneous eosinophilic lymphoid granuloma, Kimura's disease, is an atopic disease due to bacterial, viral or parasitic allergens (Iizuka 1959). Takenaka et al. (1976) reported that the majority of the patients with Kimura's disease showed immediate skin reactions to Candida allergen extract and had elevated levels of anti-Candida IgE antibodies. However, these authors and Iizuka (1959) could not demonstrate Candida organisms in the diseased tissues. Itkin and Dennis (1966) reported that atopic fungus allergy is evoked by soluble Candida extract. All these findings may lead to the postulate that a certain type of allergy to a soluble Candida substance is involved in the pathogenesis of Kimura's disease. If so, one would expect the occurrence of systemic manifestations in this disease. In fact, a systemic lymphadenopathy occurs frequently in this disease (Takenaka et al. 1976). In the present case, we found the formation of some lymph follicles in the kidney, with localization of IgE in well-developed germinal centers. The presence of IgE deposits in the diseased glomeruli strongly suggests that the glomerular disorder is also one of the systemic manifestations of Kimura's disease, although there have apparently been no reports documenting renal involvement in this disease.

The present case appeared to be distinct from the several previously described renal diseases associated with glomerular IgE deposits: minimal change nephrotic syndrome, membranous nephropathy, acute poststreptococcal glomerulonephritis, systemic lupus erythematosus (SLE) nephropathy and IgA nephropathy (Gerber and Paronetto 1971; Robertson et al. 1976; MacPhaul et al. 1974). The present case is distinguishable from minimal change nephrotic syndrome and membranous nephropathy by the electron microscopic findings. Mesangial IgA deposit is absent in this case. Although some morphological similarities exist between the present case and acute poststreptoccoccal glomerulonephritis,

such as the presence of "hump", there were no clinical and laboratory findings of streptococcal infection. SLE can be excluded by the lack of clinical manifestations shown in ARA criteria.

To elucidate the pathogenesis of the glomerular disorder in Kimura's disease it will be necessary to demonstrate the presence of anti-Candida antibodies in the kidney eluates.

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