A Case of Immune Complex Glomerulonephritis Associated with Pulmonary Cryptococcosis

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Dear Sir,

We describe a case of immune complex glomerulonephritis (ICGN) associated with pulmonary cryptococcosis (PC). An 80-year-old woman presented with a 1-month history of general fatigue and peripheral edema. A diagnosis of nephrotic syndrome (NS) was made on the basis of physical and laboratory examinations, and she was admitted to evaluate the etiology of the NS. Laboratory parameters included hemoglobin 15.0 g/dl, WBC 5700/mm³, total protein 5.7 g/dl, albumin 2.7 g/dl, total cholesterol 303 mg/dl, triglyceride 174 mg/dl, BUN 15 mg/dl, creatinine 0.7 mg/dl, glucose 100 mg/dl, and erythrocyte sedimentation rate 93 mm/h. Complement components and circulating immune complexes (IC) were almost normal. Antinuclear antibody, rheumatoid factor, HBsAg, antibody to hepatitis C virus antistreptolysin-O, and antistreptokinase were negative. Creatinine clearance was 72.0 ml/min. In view of her age and clinical course, an underlying malignancy was suspected. However, chest X-ray, gastrointestinal series, abdominal ultrasonography, and thoracoabdominal computed tomography (CT) revealed no evidence of malignancy. Three weeks after admission, a bilateral pulmonary infiltrate appeared on the chest X-ray, and progressed gradually (fig. 1). Urinary protein excretion was increased with slight exacerbation of respiratory state. CT also revealed the bilateral interstitial infiltrate, together with lymphadenopathy. Transbronchial lung biopsy and brushing cytology revealed histiocytic giant cells and fungi positive for PAS and Grocott staining. *Cryptococcus neoformans* was identified by culture. Serum cryptococcal antigen was positive at 1:64 (serodirect method). Treatment with Fulconazole 200 mg/day was begun, and urinary protein excretion decreased to the physiological level within a week. After 6 months, the infiltrate on the chest X-ray and serum antigen had disappeared. Renal biopsy was then performed. A low-power electron microscopy view showed minor glomerular abnormalities. A magnified view revealed the formation of subepithelial humps in some loops, but no immune deposits in mesangial areas (fig. 2). Immunofluorescence microscopy using antisera against human immunoglobulins and complement components revealed no reaction in the glomerular capillary walls or mesangial areas, despite repeated trials. The clinical course is shown in figure 3.

It has been described that circulating ICs formed from cationic antigens or low-avidity antibodies become trapped in the subepithelial spaces [1, 2]. However, several lines of evidence have

indicated that subepithelial immune deposits are not derived from the circulation but are formed locally [3]. The mechanism may involve either insoluble fixed renal antigens or soluble extrarenal antigens. It is proposed that the formation of IC, especially in the case of 'planted' exogenous antigens, involves a charge-dependent or charge-independent mechanism [4, 5]. Subepithelial deposits are typically observed in post-streptococcal-type glomerulonephritis with formation of humps as a self-limiting form. However, no study has proved the presence of streptococcal antigens in the

Fig. 1. Chest X-ray showed the interstitial infiltrate in the bilateral lower lung fields. subepithelial ICs. This may be because streptococcal antigens probably react in the pre-re-nal stage. These ICs then produce other antigens, and secondary ICs (without streptococcal antigenicity) are deposited in the glomerular subepithelial spaces; ICs which compose the humps are completely saturated, and have no more capacity for reactivity with detectable antibody such as FITC. In the glomeruli of the present patient, we did not detect cryptococcal antigens, nor was there any reactivity for immunoglobulins such as IgG. The mechanism was therefore probably similar to that of poststreptococcal-type glomerulonephritis. Moreover, the timing of renal biopsy may have been too late.

Cases of ICGN associated with fungal infections including Candida [6] and Asper-

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1992Month	3	4	5	6	7	8	9	10	11
Event	Admission	TBLB	Renal biopsy		Discharge				
WBC, /mm ³	5,700	9,000	6,200	5,600	7,300				
(eosinophil %)	(17)	(22)	(3)	(2)	(2)				
CRP, mg/dl	0.3	4.0	0.2	0.2	0.1				
ESR, mm/h	93	127	55	51	26				
Crypto. Ag.	× 64	× 32	× 16	× 8	× 1	0			

Fig. 2. a Low-power electron microscopy revealed only minor glomerular abnormalities (bar = 50 µm). b A magnified view revealed formation of the humps in the sub-epithelial space (bold bar = 1 µm).

Fig. 3. Clinical course and its relationship to therapy. TBLB = Transbronchial lung biopsy and brushing cytology; FCZ = Fulconazole; d.i. = drip infusion; p.o. = peroral; Crypto. Ag. = Cryptococcal antigen.

gillus [7] have been reported previously. The renal histopathological findings in these cases were different, including membranoproliferative glomerulonephritis and crescentic glomerulonephritis. It is proposed that the differences are dependent on each of the characteristics of the ICs, as mentioned above.

There have been several reports of NS complicated with PC [8,9]. All of the affected patients were on prednisone or immunosuppressant for the treatment of NS, and no case of ICGN caused by PC has been described. During the clinical course, Fulconazole improved dramatically both PC and proteinuria without the need for steroids, and we did not find any solid tumor for 6 months. We concluded that this was a case of ICGN associated with PC.

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