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Glomerular IgA deposition in pulmonary diseases

YUZO ENDO and MITSURU HARA

Departments of Immunology and Pathology, Toranomon Hospital, Tokyo, Japan

Glomerular IgA deposition in pulmonary diseases. Glomerular changes of 70 cases of pulmonary diseases and 25 control cases among 1100 consecutive autopsy cases were studied by light, immunofluorescence, and electron microscopy. These pulmonary diseases consisted of 11 cases of chronic obstructive bronchiolitis (COB), 15 cases of bronchopneumonia, 4 cases of acute interstitial pneumonia, 22 cases of idiopathic interstitial pneumonia (IIP), and 18 cases of lung cancer free from IIP. Bacteriological examination of the lung was performed in these cases including control cases on autopsy. Mesangial IgA deposition was predominant in 25 out of the 70 study cases (36%) frequently accompanied by C3, whereas slight mesangial IgA deposition was observed in one of the control cases. Incidence of IgA deposition was 64% in IIP, 54.5% in COB, 13.3% in bronchopneumonia, 16.7% in lung cancer and 25% in acute interstitial pneumonia. The results of the present study suggest that recurrence or persistence of inflammatory processes of the lung leads to IgA-mediated immune abnormalities and to mild mesangial changes with predominant IgA deposition, which are similar to the immunopathologic features of IgA nephropathy.

In IgA nephropathy, upper respiratory tract infections are frequently accompanied by recurrent hematuria [1]. Upper respiratory tract infections are thought to play an important role in the pathogenesis of IgA nephropathy. Mucous membranes of the upper respiratory tract may act as defense mechanisms against foreign substances present in inhaled air. However, not only upper respiratory tract, but also the lung or lower respiratory tract is a mucosal site protected by IgA as well as IgM and cellular immunity [2–4]. These mucous membranes are exposed to a number of microorganisms and/or other antigenic substances, which are blocked by cooperation between physical nonspecific defense mechanisms such as ciliary movement and acquired specific immune defense mechanisms [5]. Therefore, it may be possible that lower respiratory tract infections as well are closely related to the pathogenesis of IgA nephropathy. However, little attention has been given to this possibility in the literature. The present study is undertaken to investigate these glomerular changes in pulmonary diseases.

Methods

Ninety-five autopsy cases (male, 67; female, 28) of pulmonary inflammatory diseases, lung cancer, and control cases were obtained out of 1100 consecutive autopsy cases examined at the Department of Pathology, Toranomon Hospital in Tokyo, Japan, between May 1979 and December 1984. Almost all the cases studied were examined within 4 hr after death. Seventy out of the 95 cases were classified into six groups according to the following pulmonary changes: 11 cases of chronic obstructive diseases of small airways [6] or chronic obstructive bronchiolitis which corresponds to a disease commonly called diffuse panbronchiolitis in Japan [7], 15 cases of bronchopneumonia related closely to the direct cause of death, 4 cases of acute interstitial pneumonia caused by Bleomycin or pneumocystis carinii, 13 cases of idiopathic interstitial pneumonia (IIP) without lung cancer, 9 cases of IIP associated with lung cancer, and 18 cases of lung cancer free from IIP. The reason why the cases of IIP were subdivided into two groups pertaining to the presence or absence of lung cancer was to study the influence of lung cancer on glomerular changes. Twenty-five control cases consisted of myocardial infarction, subarachnoidal hemorrhage, acute heart failure due to hypokalemia, and others without fatal pulmonary changes. None of the cases studied had any evidence to suggest such diseases as systemic lupus erythematosus, rheumatoid arthritis, overt diabetes mellitus, malignant hypertension, generalized amyloidosis, pneumoconiosis, hepatitis B virus antigenemia, chronic hepatitis, and liver cirrhosis.

Light microscopy

Kidney tissue samples were fixed in 10% formalin, embedded in paraffin, cut at 1 to 2 μ and stained with hematoxylin and eosin (H & E), periodic acid-Schiff (PAS), Mallory's Azan, Weigert's elastica-van Gieson, and periodic acid methenamine silver stain with H & E counterstain (PAM).

Immunofluorescence microscopy

Kidney tissue samples were snapfrozen in dry ice and acetone mixture and stored in a Levco deep freezer at −70°C until use. Frozen sections were cut at 3 to 4 μ by a Damon/IEC cryostat at −20°C. After fixation in acetone, the sections were incubated with fluorescein isothiocyanate (FITC) conjugated rabbit antiserum to human IgG, IgA, IgM, Clq, C3, C4, or secretory component (SC) (Fuji Zoki, Japan), respectively, in a moist chamber at 37°C for 30 min. F/P ratio of each antiserum used was between 2 and 3. Monospecificity of each antiserum was checked by Ouchterlony double immunodiffusion method. The sections were examined under a magnification ×200 with a fluorescence microscope (Olympus, Japan) equipped with optimal excitation and barrier filter for FITC. The degree of fluorescence was graded as − (negative), ± (mild), 1+ (moderate), and 2+ (marked).

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Table 1. Glomerular immunoglobulin, complement, secretory component (SC), and electron dense deposits (EDD) in the 70 study and 25 control cases

Pulmonary changes	Number of cases	IgG		IgA		IgM		C1q		C3		C4		SC		EDD	
		L	M	L	M	L	M	L	M	L	M	L	M	L	M	L	M
Chronic obstructive bronchiolitis	11	1[m]	2	—	6[b]	—	3	—	1	1[m]	5[a]	—	2	—	—	1	5
Bronchopneumonia	15	—	—	—	2	—	2	—	—	—	—	—	1	—	—	0	2
Acute interstitial pneumonia	4	—	—	—	1	—	1	—	—	—	—	—	—	—	—	0	1
IIP	13	—	1	—	8[b]	—	5[b]	—	1	—	7[b]	—	—	—	—	0	7
IIP with lung cancer	9	—	—	—	6[b]	—	4[b]	—	—	—	4[a]	—	1	—	—	0	5
Lung cancer	18	—	—	—	3	—	3	—	2	—	3	—	1	—	—	0	2
Control	25	—	—	—	1	—	—	—	—	—	1	—	1	—	—	0	0
Total	*95*																

Abbreviations: L, glomerular capillary loop; M, mesangium; m, fine granular immunofluorescence along glomerular capillary loop; IIP, idiopathic interstitial pneumonia.

Statistically significant compared with control cases in χ^2 test:

[a] $P < 0.05$.

[b] $P < 0.01$.

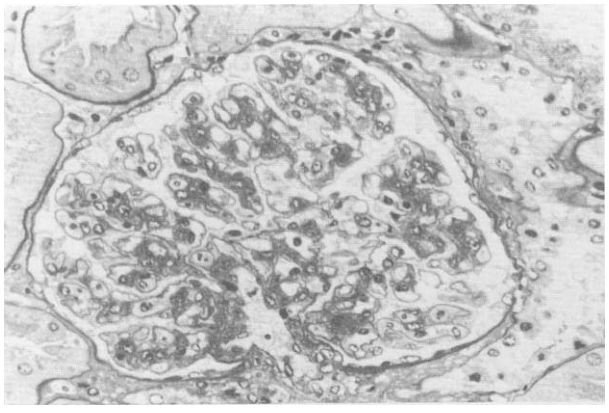

Fig. 1. *Glomerular changes of a 63-year-old female with chronic obstructive bronchiolitis.* Histological changes are confined to the mesangium with a mild increase in the matrix. Hypercellularity in the mesangium is minimal. The capillary wall of the glomerulus is normal. (Periodic acid-Schiff staining; ×250)

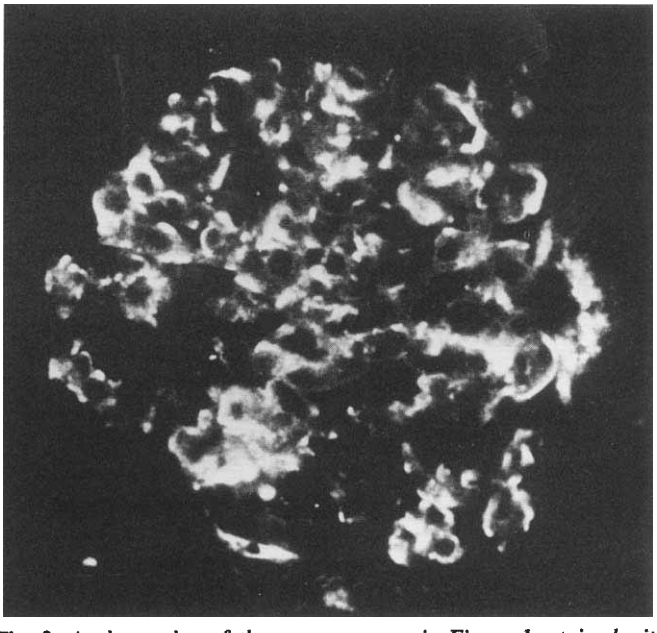

Fig. 2. *A glomerulus of the same case as in Figure 1, stained with FITC-labeled rabbit antiserum to human IgA.* IgA is diffusely present in the mesangium. (×200)

Electron microscopy

Kidney tissue samples were fixed in 2.5% glutaraldehyde, buffered with 0.1 M phosphate (pH 7.2), and postfixed in 1% osmium tetroxide. After being embedded in epoxy resin (Epon 812), sections were cut by a ultramicrotome (Porter-Blum). Ultrathin sections were stained with uranyl acetate and lead citrate, and examined with an electron microscope (Hitachi HU-12).

Bacteriological examination

Five milliliters of blood were obtained on autopsy from the right and left atrium by a sterile syringe and injected into the blood culture broth (Eiken, Japan). Four spots of the pleural surface of bilateral lungs were sterilized by a heated spatula, and cut by a sterile knife to insert a calibrated inoculating loop into the lung. Liquid samples taken by this loop were streaked on culture media, which were incubated at 37°C for more than a week. The number of bacteria was evaluated by semiquantitative analysis of bacterial colony formation as follows: negative, 1+, 2+, and 3+ in accordance with occupying areas of colonies on the culture medium. Culture media used were blood agar

Table 2. Data of the 11 cases of chronic obstructive bronchiolitis[a]

Case	Age	Sex	Serum IgG	Serum IgA	Serum IgM	Mild proteinuria	IgG L	IgG M	IgA L	IgA M	IgM L	IgM M	C1q L	C1q M	C3 L	C3 M	C4 L	C4 M	EDD L	EDD M
1	63	F	2600	1048	188	+	−	±	−	++	−	−	−	±	−	++	−	−	−	+
2	63	F	2820	648	134	+	−	−	−	+	−	−	−	−	−	+	−	−	−	−
3	57	F	2320	784	172	+	+[m]	−	−	±	−	+	−	−	+[m]	+	−	−	+	+
4	48	M	2360	708	120	−	−	−	−	±	−	−	−	−	−	−	−	−	−	+
5	60	F	ND	ND	ND	−	−	±	−	+	−	±	−	−	−	+	−	±	−	+
6	46	F	ND	ND	ND	−	−	−	−	±	−	±	−	−	−	±	−	±	−	+
7	60	F	ND	ND	ND	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
8	57	F	1380	256	158	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
9	68	M	1571	349	100	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
10	69	F	840	507	83	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
11	76	M	ND	ND	ND	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

Abbreviations: L, glomerular capillary loop; M, mesangium; m, fine granular immunofluorescence along glomerular capillary loop; ND, not determined.

[a] Normal ranges of Immunoglobulins: IgG, 820 to 2290 mg/dl; IgA, 130 to 380 mg/dl; IgM, 60 to 380 mg/dl.

Table 3. Data of the 22 cases of idiopathic interstitial pneumonia with and without lung cancer[a]

Case	Age	Sex	Lung cancer	Serum IgG	Serum IgA	Serum IgM	Mild proteinuria[b]	IgG L	IgG M	IgA L	IgA M	IgM L	IgM M	C1q L	C1q M	C3 L	C3 M	C4 L	C4 M	EDD L	EDD M
1	71	M	−	2560	518	172	+	−	+	−	+	−	−	−	+	−	±	−	−	−	+
2	59	M	−	1880	532	138	+	−	−	−	+	−	−	−	−	−	±	−	−	−	+
3	71	M	−	1846	693	127	−	−	−	−	+	−	−	−	−	−	+	−	−	−	+
4	58	M	−	1995	630	171	−	−	−	−	±	−	−	−	−	−	±	−	−	−	+
5	85	M	−	ND	ND	ND	−	−	−	−	±	−	−	−	−	−	±	−	−	−	+
6	67	M	−	3097	423	197	−	−	−	−	±	−	±	−	−	−	+	−	−	−	+
7	67	M	−	2760	388	132	−	−	−	−	±	−	−	−	−	−	−	−	−	−	−
8	66	M	−	ND	ND	ND	−	−	−	−	±	−	−	−	−	−	−	−	−	−	−
9	71	M	−	2760	910	239	−	−	−	−	−	−	±	−	−	−	±	−	−	−	+
10	51	F	−	2800	504	264	−	−	−	−	−	−	±	−	−	−	−	−	−	−	−
11	77	F	−	1677	225	224	−	−	−	−	−	−	±	−	−	−	−	−	−	−	−
12	75	M	−	1134	433	102	−	−	−	−	−	−	±	−	−	−	−	−	−	−	−
13	62	M	−	1336	398	67	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
14	63	M	+	1760	292	246	+	−	−	−	±	−	−	−	−	−	±	−	−	−	+
15	85	M	+	ND	ND	ND	+	−	−	−	+	−	±	−	−	−	−	−	−	−	+
16	48	M	+	ND	ND	ND	−	−	−	−	±	−	−	−	−	−	±	−	−	−	+
17	62	M	+	1533	300	134	−	−	−	−	+	−	±	−	−	−	±	−	−	−	+
18	62	M	+	1582	328	219	−	−	−	−	±	−	±	−	−	−	±	−	±	−	+
19	64	M	+	ND	ND	ND	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−
20	65	M	+	ND	ND	ND	−	−	−	−	−	−	±	−	−	−	−	−	−	−	−
21	61	M	+	1280	192	77	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
22	70	M	+	ND	ND	ND	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

Abbreviations: L, glomerular capillary loop; M, mesangium; ND, not determined.

[a] Normal ranges of immunoglobulins: IgG, 820 to 2290 mg/dl; IgA, 130 to 380 mg/dl; IgM, 60 to 380 mg/dl.

[b] Mild proteinuria was less than 1.0 g/day.

medium (BBL, USA), chocolate agar medium (BBL, USA), modified Drigalski agar medium (Eiken, Japan) and Sabouraud agar with chloromycetin (Eiken, Japan).

Clinical observations

Age, sex, respiratory function test, radiological examination, urinalysis, blood laboratory data, bacteriological data of sputum and blood, serum immunoglobulin quantification (Laser Nephelometry, Hoechst), rheumatoid factor, antinuclear antibody, Coombs and cold hemagglutinin test were recorded from the clinical files of Toranomon Hospital.

Results

Light microscopy

Glomeruli of the 70 study cases were almost normal or showed a mild increase in mesangial matrix with or without mild hypercellularity (Fig. 1). These mild mesangial changes were observed in 4 cases consisting of 2 out of the 11 cases of chronic obstructive bronchiolitis, one of the 22 cases of IIP with or without lung cancer, and one of the 18 cases of lung cancer free from IIP. Focal or segmental changes of glomeruli were hardly observed. Double contour of the tuft capillary wall was also rare. Membranous glomerulonephritis with spike formation was observed in one case of chronic obstructive bronchiolitis.

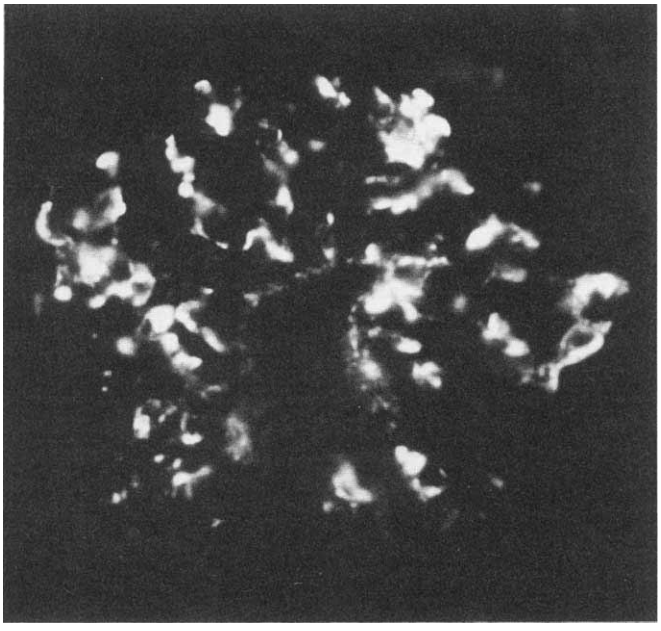

Fig. 3. *A glomerulus of the same case as in Figure 1, stained with FITC-labeled rabbit antiserum to human C3.* Deposition pattern of C3 is similar to that of IgA. (×200)

There was no crescent formation in the glomeruli of the cases studied.

Immunofluorescence microscopy

IgA deposition was predominant in 25 out of the 70 study cases (36%), whereas slight IgA deposition was observed in one of the control cases (Table 1). The pattern of IgA deposition in the glomeruli was predominantly mesangial (Fig. 2). As shown in Tables 1, 2, and 3 the incidence of IgA deposition was 54.5% (6/11) in chronic obstructive bronchiolitis, 61.5% (8/13) in IIP without lung cancer, 66.7% (6/9) in IIP associated with lung cancer, respectively. Each incidence of them was statistically significant compared with that of the control cases (χ^2 test, $P < 0.001$). On the other hand, the incidence of the IgA deposition was 13.3% (2/15) in bronchopneumonia, 25% (1/4) in acute interstitial pneumonia and 16.7% (3/18) in lung cancer free from IIP. The degree of fluorescence intensity of IgA in the glomeruli was rather weak as compared with that of typical IgA nephropathy. However, fluorescence intensity of IgA was strong enough in nine cases studied to be diagnosed as IgA nephropathy and four cases of them histologically showed mild mesangial widening. IgA was frequently accompanied by IgM, but less frequently accompanied by IgG in the cases of IIP (Table 3). One of the cases of chronic obstructive bronchiolitis showed fine granular deposition of IgG along the glomerular capillary walls associated with IgA and IgM deposition scattered sparsely in the mesangium. The deposition pattern of complement components in the glomeruli was predominantly mesangial (Fig. 3), except for the one case of membranous glomerulonephritis, which showed granular deposition of C3 associated with IgG along the tuft capillary wall. As shown in Tables 2 and 3, the incidence of C3 deposition was 45.4% (5/11) in chronic obstructive bronchiolitis, 53.8% (7/13) in IIP and 44.4% (4/9) in IIP associated with lung cancer. Accordingly, neither IgA nor C3 showed any significant difference between IIP with and without lung cancer concerning the incidence of deposition in the glomeruli. The incidence of C3 in the cases of IIP with or without lung cancer was statistically significant compared with that of the control cases (χ^2 test, $P < 0.05$ or < 0.01). A secretory component was not detected in all the cases studied.

Electron microscopy

Ultrastructural examination was performed in the cases positive for immunofluorescence microscopy. As shown in Tables 1, 2, and 3 electron dense deposits were observed in 5 cases of chronic obstructive bronchiolitis, 12 cases of IIP with or without lung cancer, 2 cases of bronchopneumonia, and 2 cases of lung cancer. Although the deposits tended to be small in size, one case of chronic obstructive bronchiolitis showed large electron dense deposits in the mesangium as shown in Figure 4. Each case of chronic obstructive bronchiolitis and IIP without lung cancer showed subepithelial fine deposits scattered along the glomerular basement membrane associated with electron dense deposits in the mesangium.

Bacteriological examinations (Table 4)

In the cases of chronic obstructive bronchiolitis, *Pseudomonas aeruginosa* and its mucoid type were detected in 63.6% (7/11), whereas in the cases of bronchopneumonia and lung cancer, various species such as *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Enterobacter, Candida albicans,* and so forth, were commonly positive in addition to *Pseudomonas aeruginosa*. In the cases of IIP, the incidence of positive bacterial culture was rather less than that detected in chronic obstructive bronchiolitis: bacteria species detected were *Pseudomonas aeruginosa, Streptococcus faecalis, Klebsiella pneumoniae, Enterobacter, Nocardia species,* and so forth. *Pseudomonas* infection was frequently coincident with glomerular IgA deposition in the cases of chronic obstructive bronchiolitis, whereas this tendency was not seen in the cases of IIP or other pulmonary diseases positive for glomerular IgA deposition.

Clinical observations

The age of the study cases ranged from 38 to 85 years and that of the control cases was almost the same (29 to 84 years of age). The age of the 25 cases positive for glomerular IgA deposition ranged from 48 to 85 years of age (male, 21; female 4). Chronic alcoholism was not represented. As shown in Tables 2 and 3, mild proteinuria (less than 1.0 g/day) was observed in 3 cases of chronic obstructive bronchiolitis, 2 cases of IIP without lung cancer, and 2 cases of lung cancer free from IIP. There was no case associated with hematuria. Serum IgA tended to be higher than 500 mg/dl in chronic obstructive bronchiolitis and IIP with or without lung cancer. Initial symptoms of chronic obstructive bronchiolitis were dyspnea on exertion, cough, and sputum. Chest x-ray films showed fine nodular shadows diffusely distributed in the hyperinflated lungs. Sputum culture yielded *Hemophilus influenzae, Streptococcus pneumoniae,* or *Klebsiella pneumoniae* and most frequently *Pseudomonas aeruginosa* at the terminal stage. The time of suffering from this disease in the cases studied was longer than 7 years. Severe dyspnea was treated by long-term administration of corticosteroid and antibiotics. Initial symptoms of IIP were usually dyspnea on exertion and cough. In almost all the IIP cases, chest x-ray films

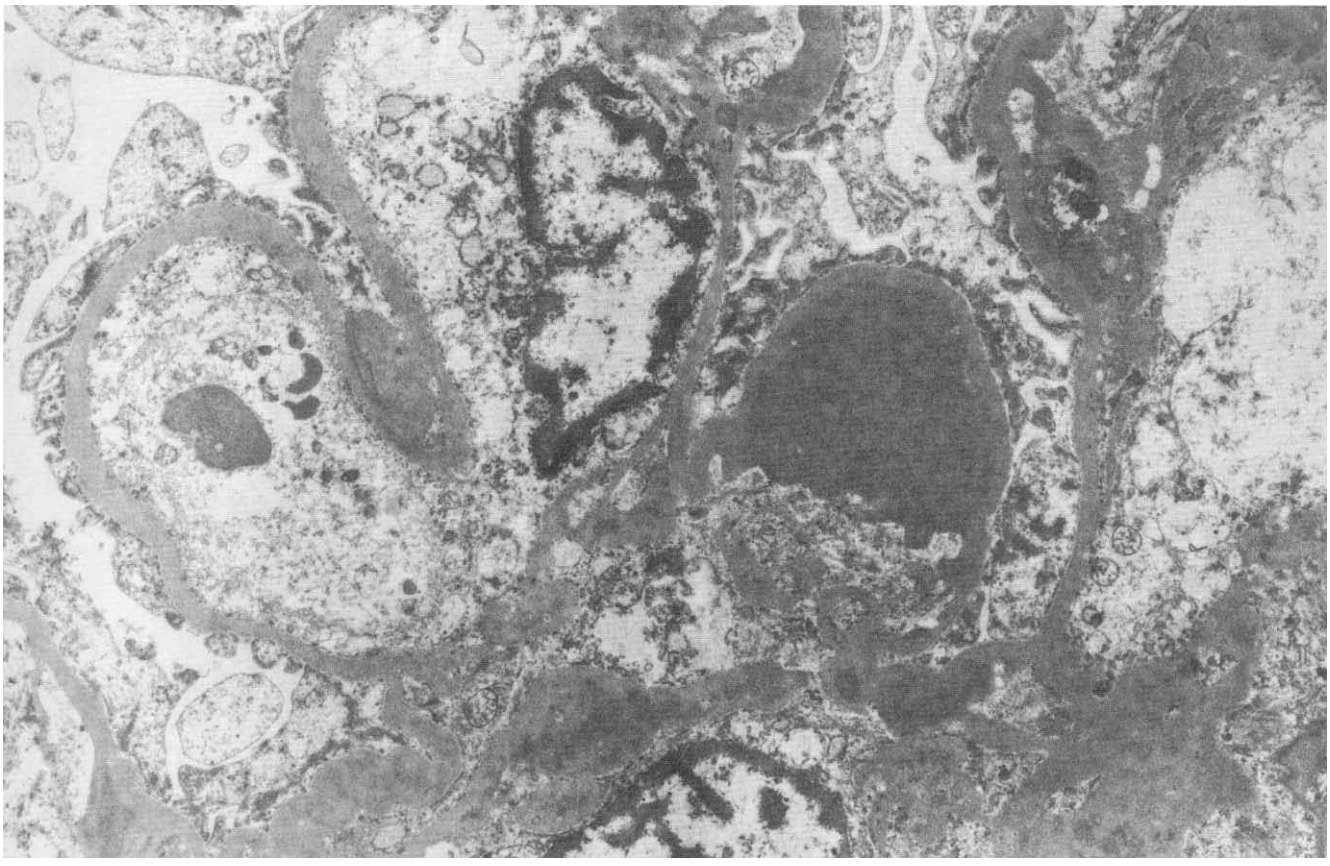

Fig. 4. *Electron micrograph of the glomerular changes of the same case as in Figure 1.* Electron dense deposits are present in the mesangium. (×7,200)

showed elevation of the diaphragm and reticulonodular or small ring-like shadows on the lower lung field at the first consultation in Toranomon Hospital. Acute exacerbation of IIP was often recurrent and treated by corticosteroid and antibiotics. The disease duration ranged from 2 to 8 years.

Discussion

Because IgA nephropathy is frequently preceded by upper respiratory tract infections, mucosa of the upper respiratory tract including tonsils may be an important site of antigenic entry which presumably leads to IgA nephropathy. Recently, viral etiology in IgA nephropathy is postulated by Tomino et al [8] on the basis of of cross-reactivity of IgA antibodies between renal mesangial areas and nuclei of tonsillar cells. The present study, however, revealed that chronic inflammatory processes of the lung such as chronic obstructive bronchiolitis and IIP are closely related to the predominant IgA deposition in the mesangium associated with deposition of C3, which is similar to the immunopathologic features of IgA nephropathy originally described by Berger [1]. In addition, lung cancer has been shown not to be concerned in the glomerular IgA deposition. Under normal conditions, the lung or lower respiratory tract is a mucosal site protected by IgA as well as IgM and cellular immunity [2, 4] which prevent entry of antigens into the systemic circulation more effectively than the physical integrity of mucous membrane, mucous layer [9], and ciliary movement. In general, acute infection of the lung is often caused by bacteria and easily cured by antibiotics. However, in chronic obstructive bronchiolitis and IIP, infection and inflammation were persistent or recurrent and bacterial flora varied in accordance with antibiotics administered. It is noticeable that the incidence of *Pseudomonas* infection was prevalent in the cases of chronic obstructive bronchiolitis in the present study. This microorganism was substituted for other bacteria or persisted despite intensive chemotherapies in the long course of the disease. In IIP, however, bacteria detected on autopsy were not always *Pseudomonas aeruginosa* but of various species even in the terminal stage under treatment of antibiotics and/or corticosteroid. Nonetheless, the incidence of glomerular IgA deposition in chronic obstructive bronchiolitis and IIP was so high that infections of various microorganisms including *Pseudomonas aeruginosa* in the lower respiratory tract may play an important role in the pathogenesis of glomerular IgA deposition. As IgA antibodies binding specifically to peptidoglycan of various bacterial cell wall can be detected in human sera [10, 11], it is likely that recurrent infections of various bacteria in the lung stimulate IgA-mediated immune mechanisms. IgA in respiratory secretions blocks antigen uptake on mucous membranes effectively [12] and appears to form complexes with antigens [13] or to activate antibody (IgA)-dependent monocyte or lymphocyte-mediated killing of bacteria [12, 14]. Chronic inflammation in the lung may alter mucosal permeability and enhance uptake of immunologically unrelated macromolecules [15, 16]. The results of the present study suggest that recurrence

Table 4. Bacterial species identified from the lungs on autopsy (study cases, 70; control cases, 25)

	COB	Broncho-pneu-monia	Acute interstitial pneumonia	IIP	Lung can-cer	Con-trol
Number of cases	11	15	4	22	18	25
Staphylococcus aureus		2			1	1
Streptococcus epidemicus		1				1
α-Streptococcus		1	1	2	1	2
Streptococcus faecalis		1		2	2	
Escherichia coli		2			1	
Klebsiella pneumoniae		4	1	1		
Enterococcus		4		1		
Enterobacter		4	1	2		
Serratia		1		2	1	
Citrobacter		2			2	
Proteus		2				
Hemophilus influenzae					1	
Pseudomonas aeruginosa	7	2	1	5	3	
Pseudomonas aeruginosa (Mucoid)	5					
Pseudomonas cepacia					1	
Acinetobacter		1		2		
Nocardia species				2		
Candida albicans		3		1	3	1
Others				4	6	3
Gram (+) rods						
Micrococcus						
etc.						

Abbreviations: COB, chronic obstructive bronchiolitis; IIP, idiopathic interstitial pneumonia with and without lung cancer.

or persistence of inflammatory processes of the lung leads to IgA-mediated immune abnormalities and to mild mesangial changes with predominant IgA deposition, which are similar to the immunopathologic features of IgA nephropathy.

Reprint requests to Dr. Y. Endo, Department of Immunology, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, 105 Tokyo, Japan

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