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Myeloperoxidase Antineutrophil Cytoplasmic Autoantibody –associated Glomerulonephritis in a Very Elderly Patient with Generalized Vasculitis at Autopsy

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ABSTRACT

An 86-year-old woman was admitted with hemoptysis and rapid deterioration of renal function. Renal biopsy disclosed necrotizing crescentic glomerulonephritis. Based on positivity for serum myeloperoxidase antineutrophil cytoplasmic autoantibody (MPO-ANCA), MPO-ANCA-associated glomerulonephritis was diagnosed. Steroid pulse therapy was performed, but the patient died after the second course. Autopsy revealed renal vasculitis with fibrinoid necrosis extending to the level of the arcuate arteries. Vasculitis was also observed in the liver, adrenal gland, uterus, and spleen, suggesting the presence of microscopic polyarteritis. This case demonstrates the broad spectrum of MPO-ANCA-positive vasculitis and suggests the need for a more effective therapy suitable for very elderly patients.

Key words: *Crescentic glomerulonephritis, Microscopic polyarteritis, MPO-ANCA, Steroid therapy*

Antineutrophil cytoplasmic autoantibody (ANCA) is often detected in diseases causing renal vasculitis[6)]. Myeloperoxidase (MPO)-ANCA is frequently detected in patients with microscopic polyarteritis and idiopathic necrotizing crescentic glomerulonephritis, which is thought to be a form of vasculitis limited to the glomerular capillary vessels[6,13)]. We recently encountered a very elderly patient with MPO-ANCA-associated nephritis and observed evidence of widespread microscopic polyarteritis at autopsy.

CASE REPORT

The patient was an 86-year-old woman who developed facial and leg edema associated with decreased urine output. She had been healthy and had not experienced renal dysfunction previously, although she suffered from pneumonia at the age of 40 years. In early June 1996, she complained of a cough followed by severe headache and anorexia, for which she visited a local doctor. Based on the presence of leukocytosis, an increase of C-reactive protein, and infiltration in the right middle lung field on the chest X-ray film, pneumonia was diagnosed and an antibiotic was prescribed. Subsequently, her fever persisted, and she had a modest hemoptysis in mid-June. Her blood urea nitrogen (BUN) was 49.5 mg/dl and serum creatinine was 3.3 mg/dl on June 11, but her urine output decreased gradually with the development of edema. On June 23, she was referred to Kure National Hospital. Since severe renal dysfunction was indicated by a BUN of 162 mg/dl, a serum creatinine of 12.6 mg/dl, and a potassium of 7.4 mEq/liter, the patient was admitted with a diagnosis of acute renal failure.

Physical examination findings: The patient was 150 cm tall and weighed 55 kg. Her temperature was 36.8 °C the pulse rate was 70/min and regular, the blood pressure was 130/54 mmHg, and the respiration rate was 16/min. Moderate disorientation was noted. She had edema of the face, arms and legs, both calves, and the dorsum of both feet. In addition, moist rales were heard in the left lower lung field.

Laboratory findings (Table 1): Urinalysis detected proteinuria, hematuria, and casts, with a total urinary protein excretion of 370 mg/day.

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Table 1. Laboratory data on admission

Urinalysis		Uric acid	7.6 mg/dl
pH	6.5	Total protein	5.7 g/dl
Urobilinogen	N+	Albumin	2.5 g/dl
protein	(+)	α1-globulin	8.0%
Occult	(3+)	α2-globulin	10.8%
Glucose	(–)	β-globulin	7.2%
Sediment		γ-globulin	37.5%
Red blood cells	50–60 /HPF	Total cholesterol	98 mg/dl
White blood cells	5–6 /HPF	Triglycerides	194 mg/dl
Casts	(+)	Na	137 mEq/liter
Crystals	(+)	K	7.4 mEq/liter
Total daily urinary protein	0.37 g/day	Cl	102 mEq/liter
Complete blood count		Ca	7.8 mg/dl
Red blood cell count	340×10^4 /μl	P	7.1 mg/dl
Hemoglobin	10.3 g/dl	C-reactive protein	12.2 mg/dl
Hematocrit	29.5%	Serum parameters	
White blood cell count	23700 /μl	Immunoglobulin G	2290 mg/dl
band	1.0%	Immunoglobulin A	448 mg/dl
seg	88.0%	Immunoglobulin M	231 mg/dl
eosino	4.0%	Complement 3	46 mg/dl
mono	0.0%	Complement 4	39 mg/dl
lympho	7.0%	Serum complement	15.1 U/ml
Platelets	40.7×10^4 /μl	Anti nuclear antibody	×80
Coagulation studies		C-ANCA*	<10 EU
Prothrombin activity	63%	P-ANCA**	401 EU
aPTT	30.4 sec	Anti-glomerular basement membrane antibody	(–)
Fibrinogen	444.3 mg/dl		
FDP	10 μg/ml	HBs antigen	(–)
Biochemistry tests		HCV antibody	(+)
Total bilirubin	1.4 mg/dl	Renal function test	
Aspartate aminotransferase	16 IU/liter	Creatinine clearance	1.1 ml/min
Alanine aminotransferase	2 IU/liter	Osmotic pressure	
Lactate dehydrogenase	490 IU/liter	Plasma	319 mOsm/liter
Cholinesterase	752 IU/liter	Urine	296 mOsm/liter
Alkaline phosphatase	294 IU/liter	Blood gas analysis	
Leucine aminopeptidase	45 IU/liter	PH	7.322
γ-Glutamyltranspeptidase	30 IU/liter	PCO_2	26.0 mmHg
Zinc turbidity test	19.2 KU	PO_2	67.2 mmHg
Blood urea nitrogen	162 mg/dl	HCO_3^-	16.4 mmol/liter
Creatinine	12.6 mg/dl	BE	–10.2 mmol/liter

*: Cytoplasmic antineutrophil cytoplasmic antibody

**: Perinuclear antineutrophil cytoplasmic antibody

The complete blood count revealed leukocytosis with a shift to the left and normochromic normocytic anemia. There was prolongation of the prothrombin time and an increase of fibrinogen. Biochemistry tests showed a marked increase of BUN, creatinine, potassium, phosphate, and C-reactive protein as well as a decrease of total protein, albumin, and total cholesterol. Other studies revealed polyclonal hyper-γ-globulinemia, positivity for anti-nuclear antibodies, and a

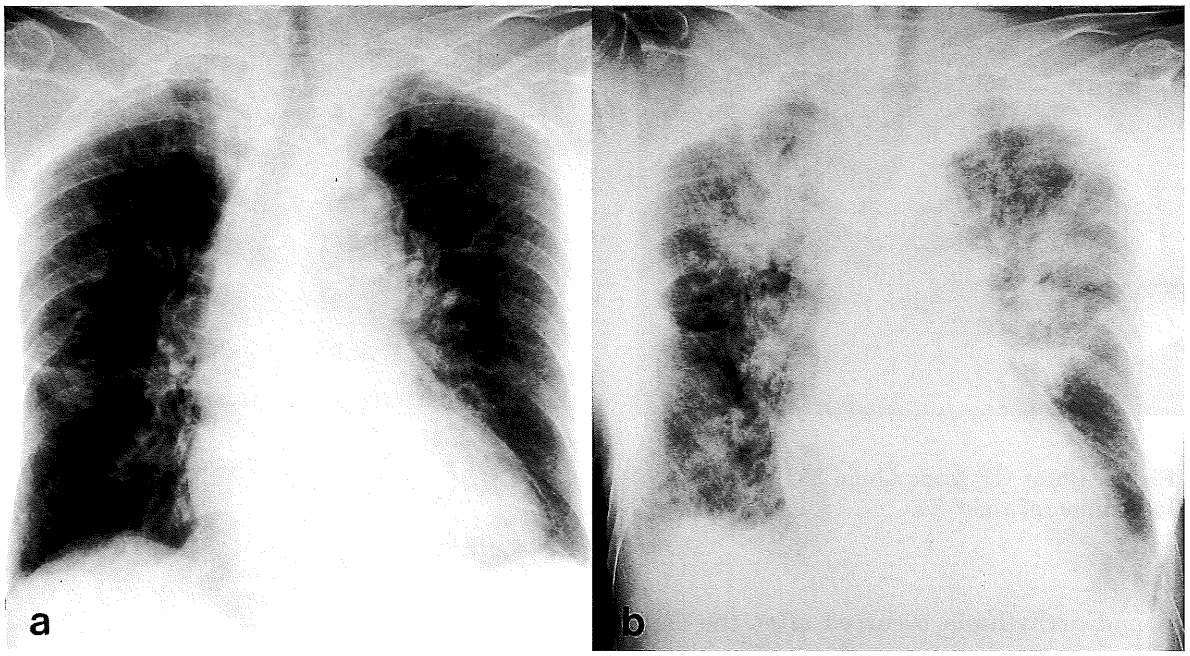

Fig. 1a) Chest X-ray film (June 22, 1996).
Increased pulmonary vascular markings and infiltration in the right middle lung field suggest the presence of pneumonia.
Fig. 1b) Chest X-ray film (July 12, 1996).
Cardiac dilatation, increased pulmonary vascular markings, and bilateral pleural effusion are noted. Severe hemorrhage can be seen in both lungs.

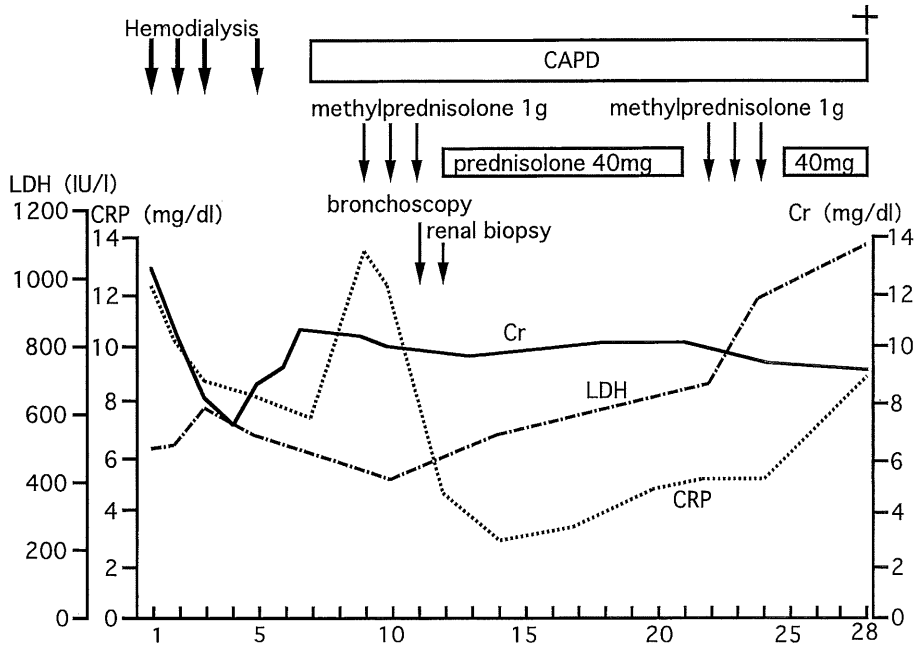

Fig. 2. Clinical course

decrease of serum complement. The patient was also positive for HCV antibodies. Her creatinine clearance was severely decreased. Blood gas studies indicated metabolic acidosis with hypoxemia. The admission chest X-ray film showed cardiac dilatation (cardiothoracic ratio: 63.0%) and slightly increased pulmonary vascular markings as well as infiltration of the right middle lung field (Fig. 1a).

Clinical course (Fig. 2): Based on the admission laboratory data, acute renal failure was diagnosed and hemodialysis was started. Since hypo-

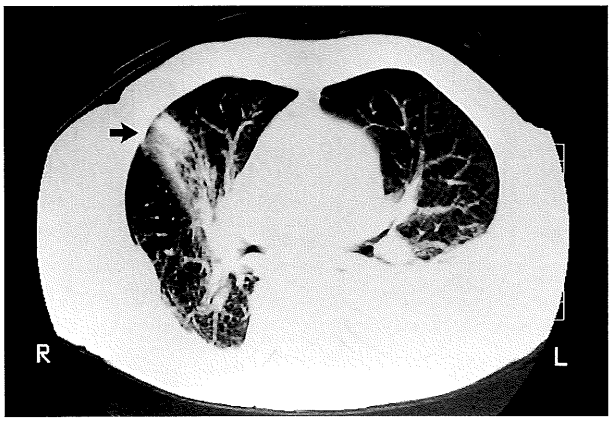

Fig. 3. Chest CT scans (June 28, 1996)
Infiltration of right S4.

tension and arrhythmia occurred after the third hemodialysis session, she was changed to continuous ambulatory peritoneal dialysis from hospital day 7. As a result, the serum creatinine level was controlled at around 9 mg/dl and BUN at around 80 mg/dl. Although oliguria persisted, her level of consciousness improved slightly. Chest CT scans (Fig. 3) revealed infiltration in the right S4 region and bilateral pleural effusions. Since bronchoscopy showed bronchial mucosal bleeding and the bronchoalveolar lavage fluid was bloody, alveolar hemorrhage was diagnosed. She was negative for cytoplasmic ANCA and anti-glomerular basement antibodies, whereas her MPO-ANCA titer was a high 401 EU, suggesting MPO-ANCA-associated glomerulonephritis. Steroid pulse therapy was started on hospital day 9. Renal biopsy performed on day 12 revealed glomeruli with crescent formation and marked interstitial cellular infiltration. Since fluorescent antibody staining showed no deposits of immunoglobulin and complement, necrotizing crescentic glomerulonephritis arising from MPO-ANCA-associated renal disease was diagnosed. After the first course of steroid pulse therapy, the C-reactive protein level decreased to 2.9 mg/dl and her respiratory status improved transiently. Subsequently, the C-reactive protein level increased again with deterioration of her respiratory status accompanied by the onset of wheezing. The second course of steroid pulse therapy was started on hospital day 22, but the infiltrative changes on her chest X-ray films became more dense, suggesting alveolar hemorrhage (Fig. 1b). On day 28, respiratory arrest occurred abruptly and the patient died.

Autopsy findings (Fig. 4, 5): At autopsy, the kidneys showed crescent formation in the glomeruli and cellular infiltration in the stroma. Vasculitis with fibrinoid necrosis was observed extending from the interlobular arteries to the afferent arterioles. Similar changes were also seen even at the arcuate artery level. The lungs showed bilateral pleural effusions and intraalveolar hemorrhage as well as clots, although the bleeding was slight.

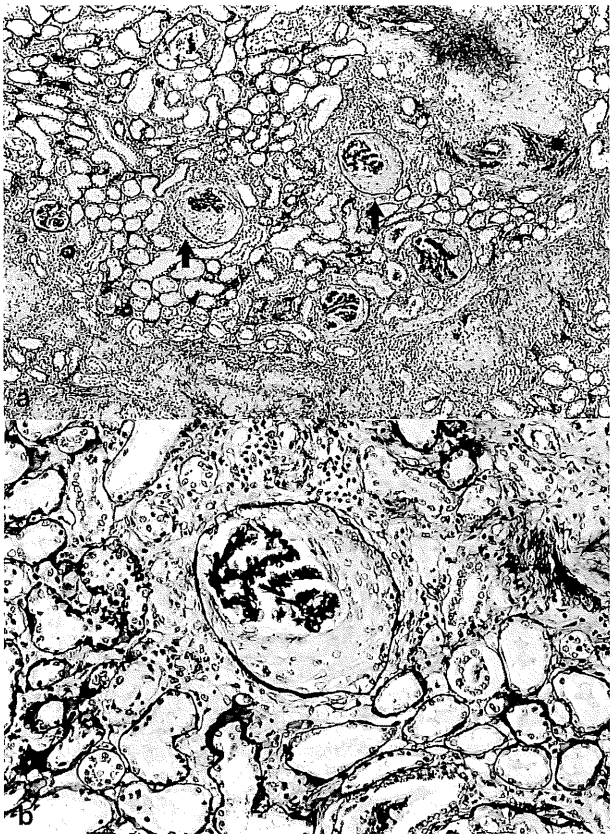

Fig. 4. Renal biopsy
a) There are crescentic glomeruli and marked cellular infiltration in the stroma (×48, PAM stain).
b) A high-power image of the cresentic glomeruli shown on the upper figure. (×150, PAM stain)

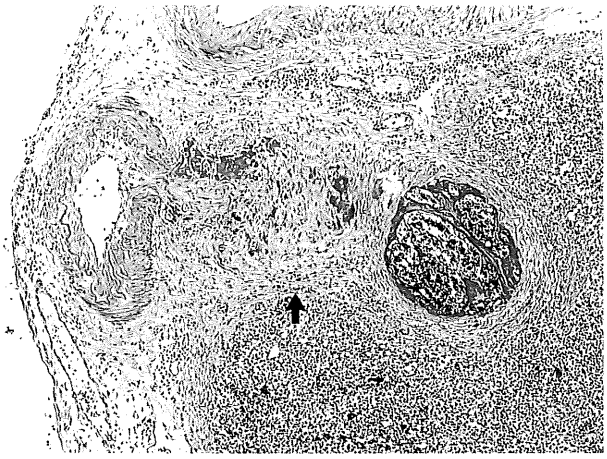

Fig. 5. Histological findings in the spleen at autopsy. There is vasculitis with fibrinoid necrosis. (×60, HE stain)

Features of vasculitis with fibrinoid necrosis were also observed in the arterioles of the liver, adrenal gland, uterus, spleen, and bone marrow.

DISCUSSION

In 1982, ANCA was first detected by Davies et al in a patient with focal necrotizing nephritis[4]. Subsequent studies showed that there are several types of ANCA depending on the identity of the target antigen. Cytoplasmic ANCA (C-ANCA) is frequently detected in patients with Wegener's granulomatosis and can be used as an indicator of disease activity[14]. ANCA with MPO as the antigen (MPO-ANCA) is one type of perinuclear ANCA and it can be detected in various types of vasculitis, including microscopic polyarteritis, idiopathic necrotizing crescentic glomerulonephritis, and allergic granulomatous vasculitis[7,12]. The histopathological features of renal MPO-ANCA include vasculitis with fibrinoid necrosis of the arterioles and the pauci-immune type of necrotizing glomerulonephritis with crescent formation[8]. Most patients with ANCA-associated glomerulonephritis show rapidly-progressive glomerulonephritis and their renal function deteriorates over several weeks to several months. In the present patient, MPO-ANCA-associated glomerulonephritis was diagnosed because her serum MPO-ANCA titer was very high (401 EU) and renal biopsy detected pauci-immune necrotizing crescentic glomerulonephritis. It has been reported that the MPO-ANCA antigen titer is correlated with disease activity[1,12], so our patient may have had active disease based on her high antibody titer.

MPO-ANCA-associated glomerulonephritis usually occurs in relatively elderly patients, with the mean age of onset being 56.7 years. There is a slight female predominance. Our patient was 86 years old, offering an interesting implication for the relationship between MPO-ANCA production and age-related immune response. Renal biopsy was carried out to make the diagnosis although the patient was very old. There is no definitive age limit for renal biopsy, and the incidence of complications is reported to be 2.2–9.8%[11]. Bleeding into the retroperitoneum, pneumothorax, and vomiting have been reported as complications of renal biopsy, although all patients recovered without sequelae[11].

Common renal diseases in the elderly include membranous nephropathy, proliferative glomerulonephritis, amyloidosis, ischemic sclerosis, and nodular periarteritis, a different profile from that of renal disease in the young[5,10]. In elderly patients, renal disease can often only be identified by renal biopsy. Therefore, biopsy should probably be carried out without hesitation even in elderly patients to identify the disease.

For treatment of MPO-ANCA-associated glomerulonephritis, steroid pulse therapy and immunosuppressive therapy as well as plasmapheresis are usually employed[2,3,9]. In the present case, steroid pulse therapy alone was used without an immunosuppressant because the patient was very old. However, steroid therapy alone proved unable to control pulmonary hemorrhage and renal inflammation. Whether immunosuppressive therapy is appropriate for treatment of such elderly patients requires investigation in consideration of the increase in the very elderly population.

MPO-ANCA-associated fibrinoid necrosis is usually linked with vasculitis of arteries smaller than the interlobular arteries, as represented by the glomerular capillaries in the kidneys. In the present patient, vasculitis with fibrinoid necrosis was observed even at the level of the arcuate arteries, and this was also the case in the liver, adrenal gland, spleen, uterus, and bone marrow. Therefore, vessels as thin as those which are affected in relatively classical polyarteritis were damaged in the present patient. This appears to be a rare finding among patients clinically diagnosed as having MPO-ANCA-positive microscopic polyarteritis, and provides interesting implications for a better understanding of the pathogenesis of MPO-ANCA-associated vasculitis.

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