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A Case of Aortitis Syndrome and IgA Nephropathy: Possible Role of Human Leukocyte Antigens in Both Diseases

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ABSTRACT

A 51-year-old woman, who had both aortitis syndrome (Takayasu arteritis) and IgA nephropathy, presented with hypertension, fever, a high erythrocyte sedimentation rate, high C-reactive protein and serum IgG levels, proteinuria, and renal dysfunction. Renal arteriography showed stenosis and poststenotic dilatation at the origin of the right renal artery, as well as tortuosity of the left renal artery branches and marked atrophy of the left kidney. Renal biopsy showed IgA nephropathy with deposits of IgA, C3, and fibrinogen in the glomeruli and arteriolosclerosis. The present patient had human leukocyte antigen (HLA)-B 52, which is reported to be related to the aortitis syndrome, as well as HLA-DR 4, which is possibly related to IgA nephropathy, suggesting that HLA status may be involved in the pathogenesis of both diseases.

Key words: *Aortitis syndrome (Takayasu arteritis), Immunoglobulin A nephropathy, Human leukocyte antigen*

The aortitis syndrome is a type of vasculitis characterized by localized lesions in the arteries of the trunk, especially the aorta and the pulmonary arteries[9,10]. The main lesion found in IgA nephropathy is proliferation of the glomerular mesangium, and immunological abnormalities appear to be involved in the onset of this disease[12]. Since about ten years ago, the relationship between the aortitis syndrome and IgA nephropathy has attracted attention[10,11]. Here we report a patient with hypertension, proteinuria and renal dysfunction, who had both the aortitis syndrome and IgA nephropathy. This case suggested a possible relationship between human leukocyte antigen (HLA) status and both these diseases.

CASE REPORT

The patient was a 51-year-old woman who was diagnosed as having hypertension without proteinuria in 1989. She was prescribed a calcium antagonist, but stopped taking it after 2 weeks because of headache. She was found to have proteinuria, hematuria, and hypertension during a routine medical examination in 1992, but was not treated at that time. In 1993, proteinuria, hematuria, hypertension, anemia, and renal dysfunction were noted and she was admitted to Onomichi General Hospital on November 11 for further investigation. On admission, the blood pressure was 180/120 mmHg in the right arm and 210/120 mmHg in the left arm, and it showed a marked difference at every subsequent time of measurement. The body temperature was 37.2°C. There were no heart murmurs and no abdominal bruit. Funduscopic examination revealed marked arteriolar attenuation and sclerosis.

Routine laboratory tests showed proteinuria and hematuria, with total protein excretion of 0.7g/day. She also had normochromic, normocytic anemia and a high erythrocyte sedimentation rate. Blood samples for the measurement of plasma renin activity and aldosterone concentration were taken in the fasting state while the patient was resting in the morning, without antihypertensive therapy and with a daily salt intake of 7g. The plasma renin activity and aldosterone concentration were high. Renal function tests showed that the BUN, creatinine, and uric acid levels were high, while the creatinine clearance was low. The serum IgG and C-reactive protein levels were

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Table 1. Laboratory Data on Admission

1) Urinalysis		TG	96 mg/dl
Albumin	(+)	BS	100 mg/dl
Glucose	(–)	renin	27.9ng/ml/hr
Occult blood	(2+)	aldosterone	343pg/ml
Sediment		6) Serological tests	
RBC	7~8/HPF	CRP	10.26 mg/dl
WBC	1~2/HPF	RF	LT21.3 IU/ml
Cast	(+)	7) Renal function tests	
Daily Urinary Protein	0.7g/day	BUN	50.7 mg/dl
2) CBC		Creatinine	2.5 mg/dl
WBC	7000/mm^3	UA	9.2 mg/dl
RBC	268×10^4/mm^3	Na	141 mEq/liter
Hb	7.9 g/dl	K	4.4 mEq/liter
Ht	23.6%	Cl	105 mEq/liter
Plt	25.8×104/mm^3	Ca	4.0 mEq/liter
3) ESR	160mm/h	P	4.1 mg/dl
4) Coagulation tests		Ccr	25.6 ml/min
PT	80%	8) Immunological tests	
aPTT	24.7 sec	IgG	2620 mg/dl
Fbg	728 mg/dl	IgA	401 mg/dl
5) Biochemistry tests		IgM	112 mg/dl
TP	8.1 g/dl	C3	112.0 mg/dl
Alb	51.5%	C4	46.4 mg/dl
α1-gl	2.6%	CH50	49.8 U/ml
α2-gl	11.1%	DNA	3IU/ml
β-gl	11.1%	ANA	×20
γ-gl	23.7%	C-ANCA	(–)
T-Bil	0.30 mg/dl	P-ANCA	(–)
GOT	14 IU/liter	anti-GBMAb	(–)
GPT	6 IU/liter	9) HLA analysis	
LDH	401 IU/liter	HLA-A	(24, 26)
ALP	168 IU/liter	HLA-B	(52, 62)
LAP	32 IU/liter	HLA-C	(W1, W3)
ZTT	14.0 KU	HLA-DR	(4, 2)
ChE	5130 IU/liter	10) ECG	W.N.L.
TC	218 mg/dl	11) Chest X-ray	CTR 53%

high. The chest X-ray film revealed a cardiothoracic ratio of 53%, but electrocardiography showed no abnormalities. HLA analysis showed HLA-A24, A26, B52, B62, CW1, CW3, DR4, and DR2 (Table 1). Although low-grade fever of around 37°C persisted after admission, various tests were not able to reveal the cause of the fever. Renal biopsy was performed on November 24, 1993 to determine the cause of her proteinuria and hematuria, and six glomeruli were obtained. One showed hyalinization, and another showed segmental sclerosis, while slightly mesangial cell proliferation was seen in the remaining four glomeruli (Fig. 1). Moreover, interstitial fibrosis and cellular infiltration were observed, and arteriolosclerosis was also noted. Because there were no glomeruli in the cryosections taken for fluorescent antibody staining, an indirect enzyme antibody method was used to stain paraffin sections. IgA deposits were found in the mesangial region and some of the capillary walls (Fig. 2). Deposits of C3 and fibrinogen were also seen. Based on these findings, IgA nephropathy associated with arteriolosclerosis was diagnosed.

Abdominal CT scanning performed on December

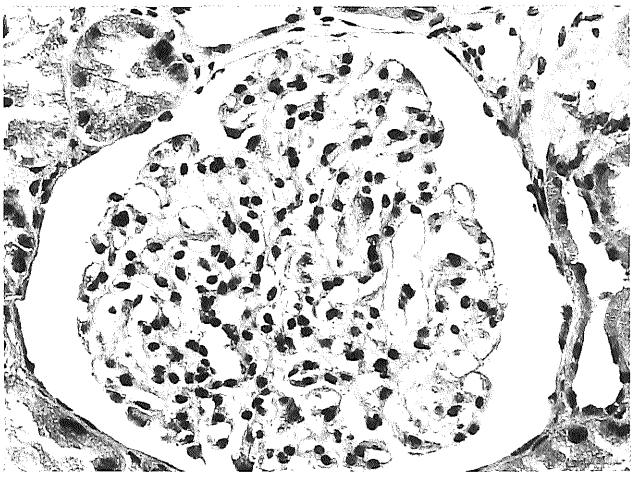


Fig. 1. Light micrograph of the renal biopsy specimen.
Slight mesangial cell proliferation was seen in the glomerulus (HE×140).

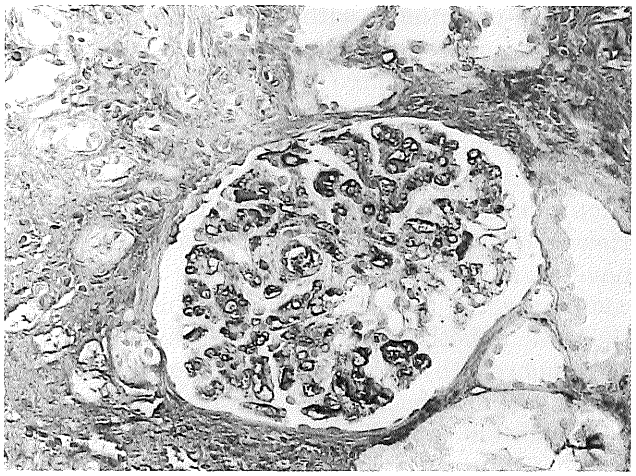


Fig. 2. Indirect enzyme antibody staining of the renal biopsy specimen.
IgA deposits can be seen in the mesangial region and in some of the capillary walls (×140).

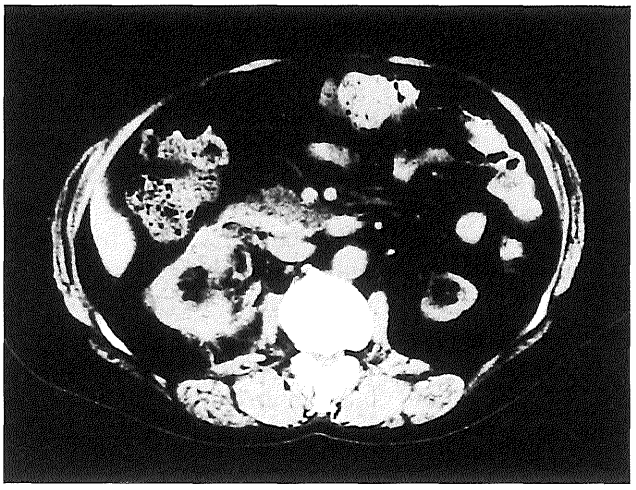


Fig. 3. Abdominal CT scan.
There is atrophy of both kidneys, but it is more marked on the left side.

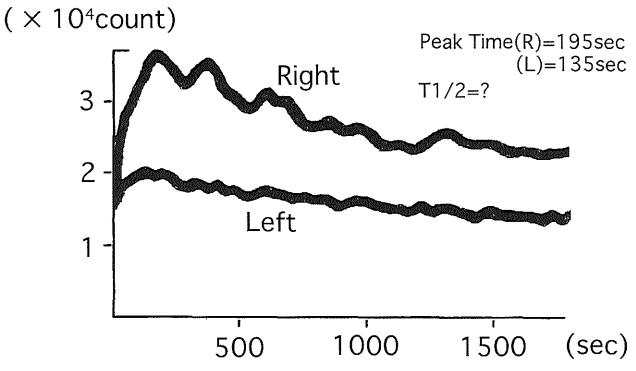
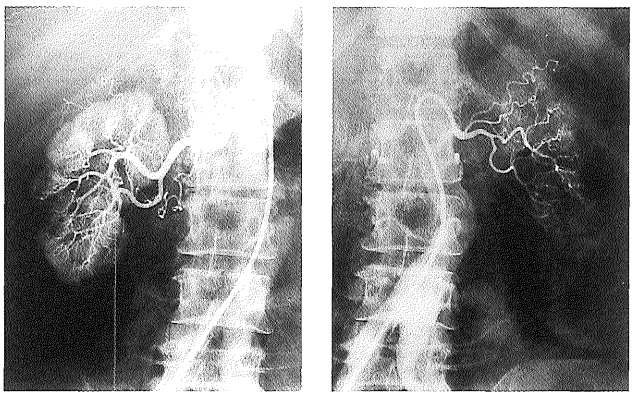


Fig. 4. Renogram obtained with ^{123}I-orthoiodohippurate.
There is dysfunction of both kidneys, especially on the left side.



5-a **5-b**

Fig. 5. Renal arteriography findings.
(a) Right renal arteriography shows stenosis and poststenotic dilatation at the origin of the right renal artery.
(b) Left renal arteriography shows tortuosity and irregularity of the branch vessels as well as atrophy of the left kidney.

5 showed atrophy of both kidneys, especially the left kidney (Fig. 3). A subsequent renogram showed dysfunction of both kidneys, especially on the left side (Fig. 4). The patient requested discharge from hospital on December 8, 1993. Since the aortitis syndrome was suspected, she was readmitted on February 28, 1994 for aortography. Aortography revealed tortuosity of the abdominal aorta and the common iliac arteries, with about 60% stenosis at the origin of the right renal artery. Right renal arteriography showed stenosis and poststenotic dilatation at the origin of the right renal artery (Fig. 5-a), while left renal arteriography showed tortuosity and irregularity of the branch vessels as well as atrophy of the left kidney (Fig. 5-b). The amount of contrast medium that could be used was limited by her renal dysfunction, so the thoracic aorta was not examined.

The aortitis syndrome was diagnosed from the high erythrocyte sedimentation rate, C-reactive protein, and serum IgG levels, together with the arteriography data and the blood pressure difference between the left and right arms.

Clinical course: The blood pressure was controlled with an α-blocker (doxazosin mesilate, 4mg /day), and proteinuria almost disappeared when the blood pressure was controlled. Prednisolone was started at a dose of 30 mg/day on March 7, 1994. Her fever resolved and C-reactive protein, erythrocyte sedimentation rate and serum IgG level became normal (Fig. 6). Percutaneous angioplasty was attempted for the stenosis at the origin of the right renal artery, but it failed because the lesion could not be crossed with the guide wire.

DISCUSSION

The aortitis syndrome is characterized by localized lesions of the arteries of the trunk, mainly the

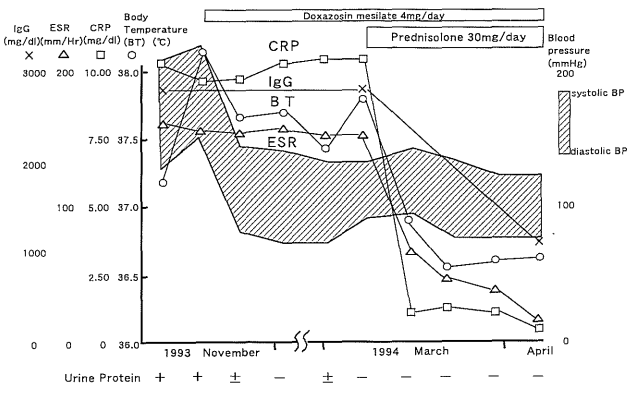


Fig. 6. Clinical course of the patient.

aorta and the pulmonary arteries, and its histological features are vasculitis associated with infiltration of inflammatory cells in the media[9,10]. It is not rare for the lesions to also involve the coronary and renal arteries, but the more peripheral arteries are usually spared. Therefore, patients with proteinuria and renal dysfunction are uncommon.

From about ten years ago, there have been reports of the aortitis syndrome in patients with glomerular diseases such as IgA nephropathy, focal glomerulonephritis, amyloid kidney[10,11] and crescentic glomerulonephritis[1]. In the present case, IgA deposits were seen in the glomeruli on renal biopsy, indicating that the aortitis syndrome was associated with IgA nephropathy. Despite the presence of IgA nephropathy, we speculated that our patient's hypertension was largely caused by the aortitis syndrome underlying the essential hypertension based on the past history. In addition, hypertension secondary to IgA nephropathy should have developed after the onset of proteinuria and hematuria and there should have been more marked mesangial matrix expansion if the hypertension was of renal origin. Thus, both the stenosis of the right renal artery and the extremely low blood flow in the left kidney were perhaps related to hypertension. Moreover, it seemed that the hypertension caused arteriolosclerosis in the kidneys and this worsened the high blood pressure. However, the genesis of the hypertension could not be definitely determined because we could not measure renin activity in the bilateral renal veins. Evidence of the involvement of an immunological mechanism in the aortitis syndrome includes circulating immune complexes in the blood[8], high levels of immunoglobulins[9], a response to steroids and immunosuppressants[9], and the detection of antiaortic antibodies, although there is no general agreement on this issue[6]. IgA nephropathy is an immune complex type of nephritis in which immune complexes are deposited in the glomerular mesangium[12], and it appears possible that a common immunological mechanism could damage the arteries and glomeruli of patients with both of these diseases. Recently Cavatorta et al[2] reported a case of IgA nephropathy associated with Takayasu arteritis and they proposed that both diseases may arise from a common immunological mechanism. In the present case, both diseases might have developed simultaneously in 1992, although this is not clear. However, these diseases would not necessarily have a simultaneous onset, because the antigens composing the immune complexes might not be the same in both cases. The aortitis syndrome and IgA nephropathy are relatively common in Japan, and the genetic background is considered to make an important contribution to the two diseases. Nishimura et al[7] investigated the HLA status of 64 Japanese patients with the aortitis syndrome. They found that susceptibility to the syndrome was determined by HLA B52 and HLA B39 among class I genes and by the haplotype HLA-DRB1*1502-DRB5*0102-DQA1*0103-DQB1*0601-DPA1*02- DPB1*0901 among class II genes, while HLA-B51, HLA-B54, and HLA-DRB1*0405-DRB4-0101-DQA1*0301-DQB1*0401 determined resistance to the syndrome. In the case of IgA nephropathy, a relationship with HLA-DR4 has been strongly suggested in Japan[3-5]. The present patient had both HLA-B52 (possibly related to the aortitis syndrome) and HLA-DR4 (possibly related to IgA nephropathy). In patients who have the aortitis syndrome combined with IgA nephropathy, HLA status may be involved in the pathogenesis of both diseases.

In conclusion, the association between the aortitis syndrome and IgA nephropathy may be of interest in helping to clarify the pathogenesis of these two diseases.

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