Case reports

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Male siblings with Takayasu's arteritis suggest genetic etiology

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Summary. Takayasu's arteritis is a nonspecific arteritis involving the aorta and its major branches. The disease mainly affects young females and familial incidence is uncommon. In this paper, two rare cases of male siblings with Takayasu's arteritis and the results of their HLA typing are described. The HLA haplotype of the two cases was completely identical—A2-B40-Cwl and A24(9)-Bw59-Cwl, DR2, and DR4. It is reported that Bw52(5) is strongly associated with the disease. However, in our cases, Bw52(5) was not found, while DR2 and DR4, which have been reported in association with several autoimmune disease, were detected. Accordingly, in these cases, genetic factors might be associated with the pathogenesis of the disease through an autoimmune mechanism.

Key words: Takayasu's arterits – Familial cases – HLA typing

Since the first description of Takayasu's arteritis in 1908 [1], it has been known as a specific disease. The disease mainly affects young females and has been reported primarily in Asia [2], so racial factors have been suggested as being of pathogenetic importance. Although the etiology of Takayasu's arteritis has been extensively investigated, it remains unknown. Recently, genetic factors of the disease have been reported [3–5], especially in association with HLA. A familial incidence of Takayasu's arteritis is rarely seen. In Japan, only 16 families with this disease have been reported [6]. We report male sibling cases and the results of HLA typing of their families.

Case reports

Case 1

A 47-year-old man visited our clinic with complaints of a weak pulse in the right radial artery and hypertension. He had been diagnosed as having hypertension at age 20. At age 43, he underwent a left partial nephrectomy because of nephrolithiasis.

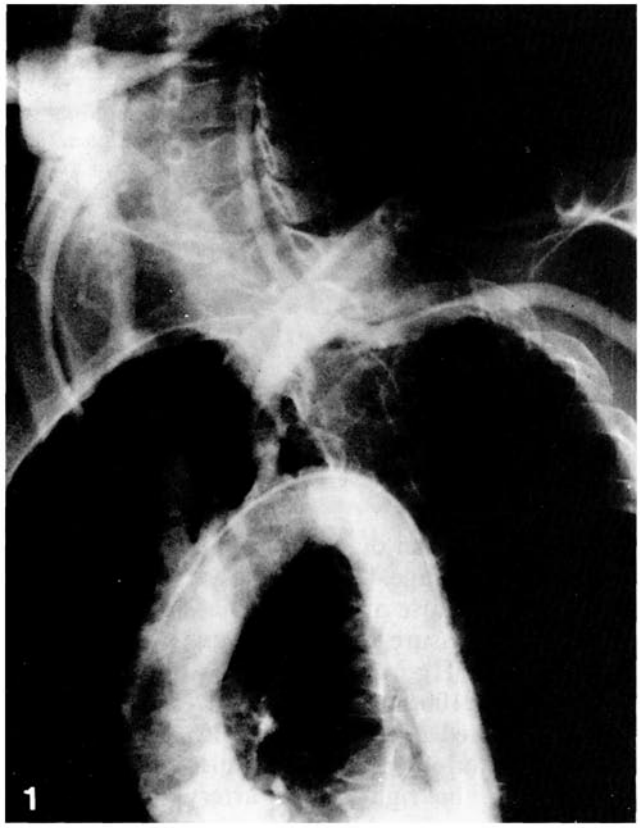
His blood pressure was 224/92 mmHg in the left arm, 100/82 mmHg in the right, 98/80 mmHg in the left thigh, and 100/80 mmHg in the right. Systolic bruits were noted over the bilateral carotid arteries, sternum, and abdomen. Reduced pulsation amplitude was noted in the right radial artery and bilateral dorsal pedis arteries. No cardiac murmur or rales were audible. Funduscopic examination showed moderate arteriolar narrowing.

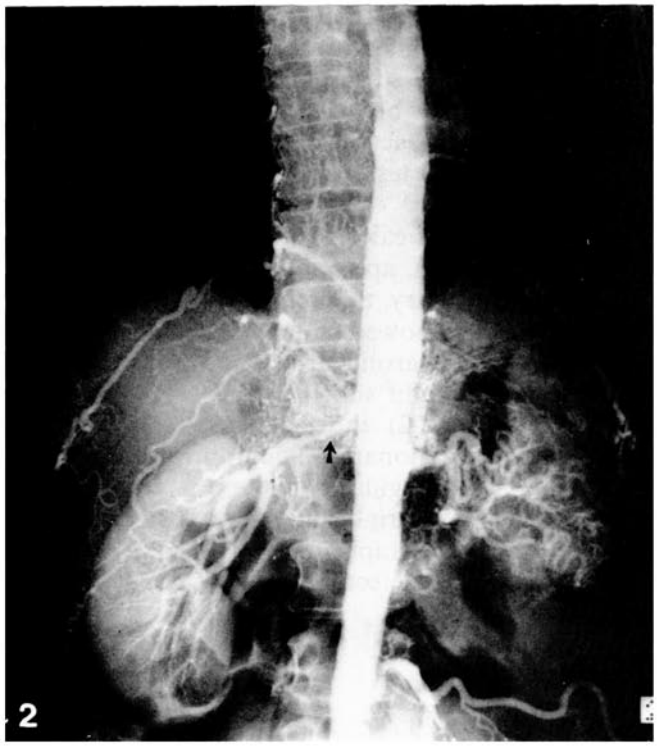
The erythrocyte sedimentation rate (ESR) was 5 mm/h. The white blood cell (WBC) count was 8000/mm^3 and C-reactive protein (CRP) was negative. The tuberculin test was negative. Renal function tests were normal.

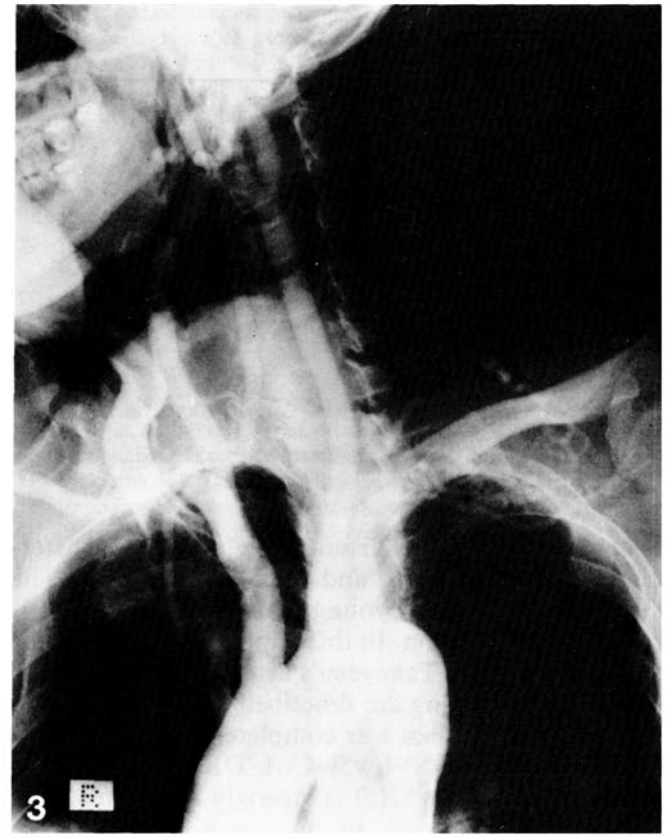
A chest X-ray revealed several calcifications in the fields of both lungs, apparently due to an old infection with pulmonary tuberculosis. Thoracic aortography (Fig. 1) showed a tented occlusion in the origin of the left carotid artery and an aneurysmal occlusion of the right subclavian artery. Abdominal aortography (Fig. 2) showed stenoses of bilateral renal arteries. Pulmonary angiography showed mild stenosis and wall irregularity in the superior and anterior branches of the right pulmonary artery. Pulmonary perfusion scintigraphy using ^{99m}Tc-MAA showed multiple perfusion defects. ECG revealed left ventricular hypertrophy.

Case 2

This is a 43-year-old man and the younger brother of case 1. At age 20, he was admitted for 6 months because of pulmonary tuberculosis and was diagnosed as having hypertension at age 22. At age 39, he suffered from mild hemiparesis in the right upper and lower extremities which healed spontaneously within a week. Thereafter, high blood pressure and weak pulse in the left radial artery were noted. At age 43, he







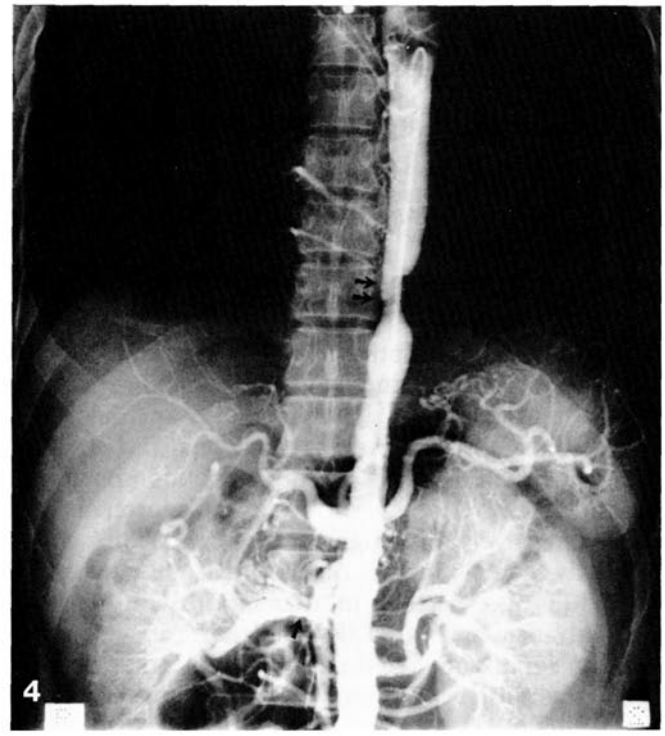


Fig. 1. Thoracic aortogram in case 1. Tented occlusion in the origin of the left carotid artery and aneurysmal occlusion of the right subclavian artery

Fig. 2. Abdominal aortogram in case 1. Stenoses of bilateral renal arteries (*arrow*) and irregularity of the aortic wall with mild narrowing in the distal portion are seen

Fig. 3. Thoracic aortogram in case 2. Obstruction of the left subclavian artery is seen in the portion 4–5 cm distal to the origin

Fig. 4. Abdominal aortogram in case 2. Atypical coarctation of the abdominal aorta at the level of the diaphragm (*double arrows*) and stenosis of the right renal artery (*arrow*) are seen

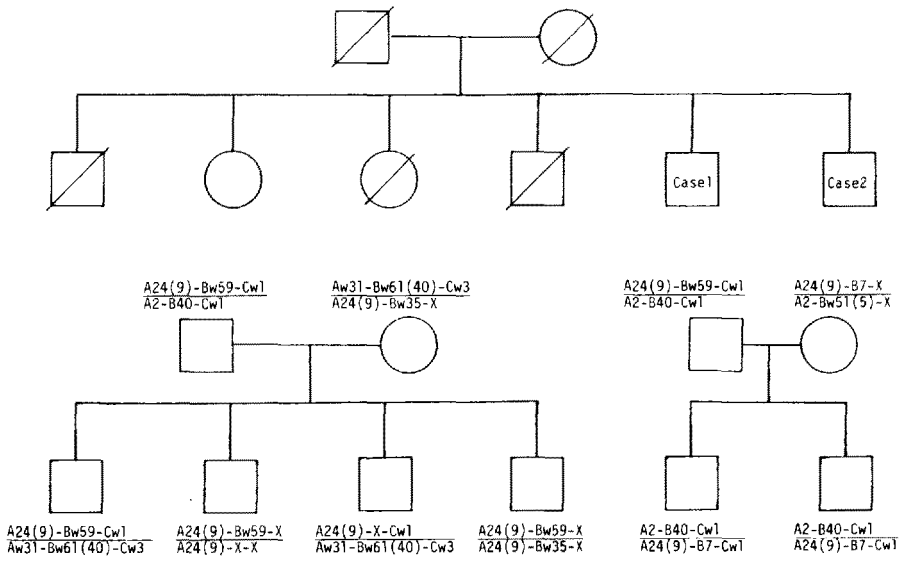


Fig. 5. Pedigree and genotypes of the family. × represents undetected locus, □ male, ○ female, / death

visited a clinic because of headache and was referred to our clinic for further examination. His blood pressure was 180/102 mmHg in the right arm, 120/94 mmHg in the left, 120/84 mmHg in the right thigh, and not measurable in the left. Extensive systolic bruits were noted over the epigastric region and back. No cardiac murmur or rales were audible. Mild numbness was present in the right foot. Funduscopic examination showed mild arteriolar narrowing and arteriolar-venous crossing.

ESR was 3 mm/h. WBC was 8400/mm^3 and CRP was negative. The tuberculin test was positive. No other findings suggesting active inflammatory processes were present. Renal function tests were normal.

A chest X-ray revealed dullness of the left costophrenic angle and pleural adhesion. Thoracic aortography (Fig. 3) showed obstruction of the left subclavian artery in the portion 4–5 cm distal to the origin and mild stenosis of the descending aorta. Abdominal aortography (Fig. 4) showed atypical coarctation of the abdominal aorta at the level of the diaphragm and stenosis of the right renal artery. ECG revealed left ventricular hypertrophy.

HLA typing of family

HLA typing as determined by the Terasaki-NIH standard method [7] was performed for four major loci (A, B, C, and DR) which were serologically defined (Fig. 5). In both cases, HLA haplotype for the A, B, and C loci was identical—A2-B40-Cwl and A24(9)-Bw59-Cwl.

HLA typing for the DR locus was performed only in cases 1 and 2. In both cases, DR2 and DR4 were detected.

Family history

A brief pedigree of the family is shown in fig. 5. The father of the two patients died of unknown etiology at age 52; the mother died of cerebral infarction at age 82. One of two other brothers died of pulmonary tuberculosis at age 32 and the other of unknown etiology at age 1. One sister died of pulmonary tuberculosis at age 21. The remaining sister is healthy. All six children of the two patients are healthy.

Discussion

Familial cases of Takayasu's arteritis are infrequent. Two Japanese brothers are presented with Takayasu's arteritis, which was clinically diagnosed according to symptoms and angiography. They had no symptoms and findings which suggested active inflammation. Weakness of pulse and hypertension, possibly associated with renal artery stenosis, were considered to be a consequence of prior inflammation from Takayasu's arteritis. In case 1, the blood pressure in bilateral lower thighs was apparently lower than that in the left arm. This suggests the possibility of stenosis distal to the abdominal aorta as shown in Fig. 2.

We have found only one previous description of male siblings with Takayasu's arteritis [8]. Although the etiology of this disease has been extensively investigated, it has not been clarified. Hypotheses for the etiology include an autoimmune theory [9–11] and a genetically related factor [3–5]. In recent years, numerous studies on the possible association of histocompatibility antigen with various diseases have been carried out. A close relationship between some antigens and Takayasu's arteritis has been reported. Isohisa et al. [5] reported that patients with Takayasu's arteritis had a statistically significant high frequency of the haplotype of Bw52 compared with healthy Japanese. In our cases, however, Bw52 was not found. Volkman et al. [12] reported that the Bw52 antigen was found in only one of their 11 patients,

while DR4 was found in seven of ten patients. Moreover, Moriuchi et al. [4] reported that not only Bw52 but also DR2 and MB1 antigens were significantly increased in their 47 patients. Although the HLA antigens were identical in our two cases, no specific haplotype was detected for the A, B, or C loci. Both DR2 and DR4 are associated with several autoimmune diseases [13–15]. Since DR2 and DR4 were found in our two cases, a genetic factor might be associated with the pathogenesis of the disease through an autoimmune mechanism.

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