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CASE REPORT

Familial Takayasu's arteritis in female siblings

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Abstract Takayasu's arteritis (TA) is a rare chronic vasculitis of the aorta and its main branches. Infectious agents or autoimmunity are thought to influence the pathophysiology. Ethnic preponderance in East Asia and usually affects young Asian women suggesting a possible role of genetic factor in the etiology. We present a rare case of familial TA in female siblings with the involvement of the main branches of aortic arch and renal arteries described by three-dimensional computed tomography (3D-CT). This case is rare familial TA in female siblings with CT angiography, which is feasible in diagnosis and informative for the stage of TA.

Keywords Takayasu's arteritis · Familial · Sibling · 3D-CT · Etiology

Introduction

Takayasu's arteritis (TA) is a rare, large-vessel vasculitis that mainly affects the aorta and its main branches [1]. The most common changes of TA are mural thickening and luminal narrowing of the aorta. The branches of the aorta often reveal localized stenosis or occlusion, which interferes with blood flow and causes pulseless when affecting the subclavian arteries [2].

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The etiology of TA is still obscure. It can be a multifactorial or be correlated with infectious agents and autoimmunity. Tuberculosis has been considered in view of the high prevalence of infection in TA patients [3]. More recently, viral infection is being implicated as a trigger of vasculitis [4]. Infiltrating cells in the aortic tissue are consisted of gamma-delta T cells, natural killer cells, cytotoxic T cells, T helper cells, and macrophages, suggesting a role for autoimmunity in the physiopathology of the TA [5].

TA has been recognized worldwide in both sexes and usually affects young Asian women [1]. Most cases of TA have been reported in Japan, South East Asia, India and Mexico [1]. There is strong female predominance, with a female to male ratio of 9:1 [6]. Familial occurrence of TA was reported for 21 families in Japan, 3 in Brazil, 1 in Taiwan, and 2 in India [7–10]. Ethnic differences and familial occurrences suggest a role of genetic factors in its pathogenesis.

We report a familial TA in female siblings with three-dimensional computed tomography (3D-CT) angiography.

Case report

Case 1

A 46-year-old woman visited hospital with a month history of dysarthria and dysphagia. She has been hypertensive and had a medical history of angina pectoris for 13 years. At the age of 43 years, TA was diagnosed and it was associated with renovascular hypertension, angina, and subclavian artery stenosis. Before 2 months, she suffered from right side weakness by left striatocapsular infarction. Her blood pressure was 150/110 mmHg in the right arm, whereas 130/100 mmHg in the left side. On neurologic examination, she

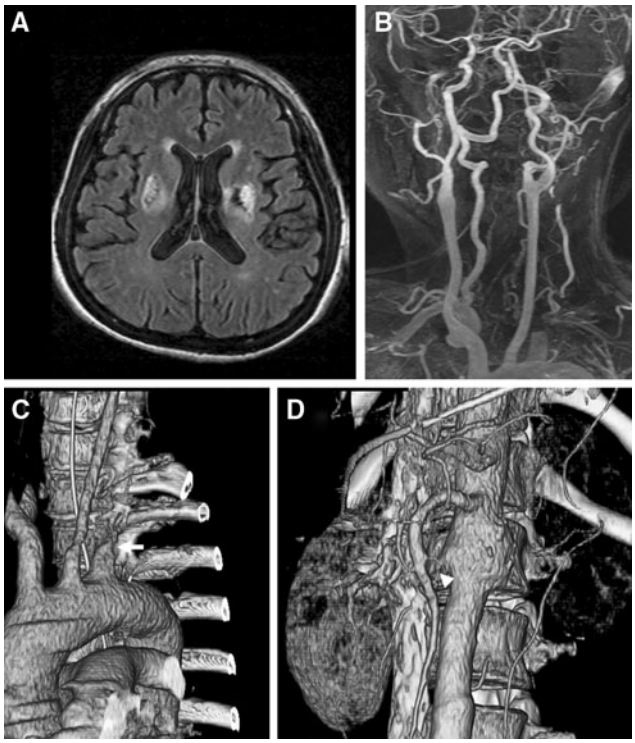

Fig. 1 Case 1: magnetic resonance imaging (**a**, **b**) and three-dimensional computed tomography (**c**, **d**). FLAIR image and MRA reveal high-signal intensity at bilateral basal ganglia (**a**) and total obstruction of left subclavian artery (**b**). 3-D CT angiography showing total occlusion of left subclavian artery (**c** *arrow*), left renal artery and narrowing of right renal artery (*arrow head*) with mild aneurismal dilatation of abdominal aorta (**d**)

showed severe dysarthria, dysphagia and motor weakness of MRC grade IV at four extremities. Brain magnetic resonance imaging revealed acute infarction in the right basal ganglia (BG) and chronic infarction in the left BG and left periventricular area (Fig. 1a). Magnetic resonance angiography and three-dimensional CT angiography illustrated total occlusion of left subclavian and left renal artery with luminal narrowing of right renal artery (Fig. 1b–d). Mild aneurismal dilatation of abdominal aorta below superior mesenteric artery level was also shown (Fig. 1d). Thoracic and abdominal CT images showed no thickening of aortic wall (Fig. 2). In complete blood counts and chemistry, white blood cell (WBC 5.46×0^3 per μl) count and erythrocyte sedimentation rate (ESR 9 mm/h) were normal. Mild elevation of C-reactive protein (CRP 1.68 mg/dl) was observed. Combined antiplatelet (aspirin plus clopidogrel) therapy was administered. Bulbar symptoms such as dysarthria and dysphagia gradually improved and she was discharged in 2 months.

Case 2

A 33-year-old woman who is younger sister of Case 1 presented with total occlusion of left common carotid artery (CCA) and thickened wall of right CCA incidentally found. Before, 16 years, she was diagnosed as having TA with renovascular hypertension, narrowing of both renal arteries and abdominal aorta at the level of second lumbar vertebral body. Before 7 months, she complained of both upper

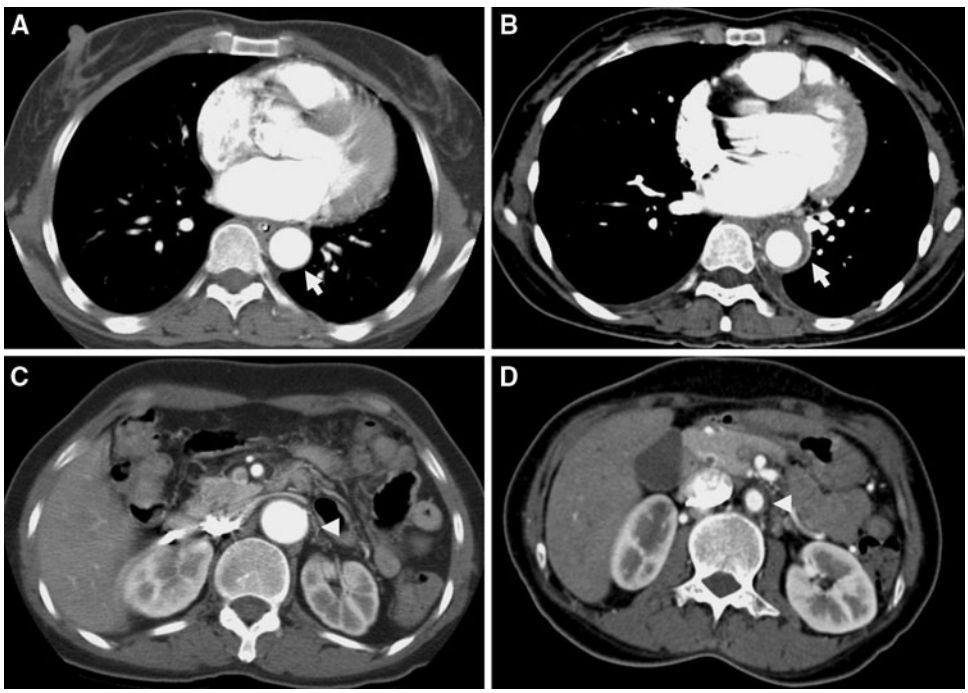

Fig. 2 Contrast-enhanced computed tomography of Case 1 (**a**, **c**) and Case 2 (**b**, **d**). Thoracic CT images showing the descending aorta with normal appearance (**a** *arrow*) and concentric thickening (**b** *arrow*). Abdominal CT image of Case 1 shows normal wall thickness of abdominal aorta (**c** *arrow head*) and that of Case 1 demonstrates enhancement of thickened abdominal aorta with concentric stenosis (**d** *arrow head*)

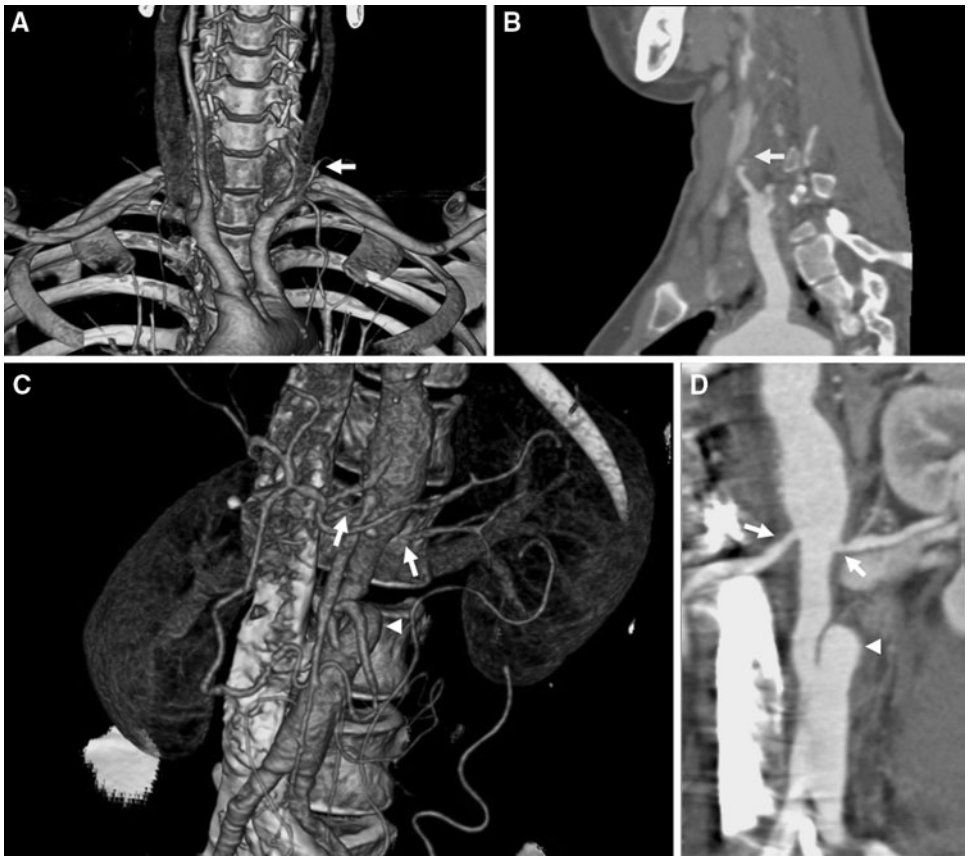

Fig. 3 Case 1: three-dimensional computed tomography of aortic arch and abdominal aorta. **a**, **b** 3D-CT angiography showing occlusion of left common carotid artery (*arrow*). **c**, **d** Stenosis of both renal artery (*arrows*) and focal dissecting aneurysm in the infrarenal abdominal aorta (*arrow head*) by 3D-CT angiography

extremities paresthesia. CT angiography demonstrated occlusion of left CCA, wall thickening of right CCA, stenosis of both renal arteries and focal dissecting aneurysm in the infrarenal abdominal aorta (Figs. 2, 3). ESR and CRP were elevated at 70 mm/h and 3.28 mg/dl. WBC count was within normal limit. No intervention was performed, and she was discharged with adding antiplatelet drug (aspirin).

Family history

Father of these patients died of cerebral infarction at his fifties, but their mother has been healthy except for hypertension. Four male siblings of the patients and four children of the two patients are all healthy.

Discussion

Here, we reported a rare cases of familial TA with their clinical manifestation and laboratory findings. There was no report for comparisons between the familial and the sporadic TA. TA can be classified into five types according to the angiogram. A study about the clinical characteristics of 108 sporadic TA patients in Korea showed that type I was the most common, followed by types V and IV [11]. Our two cases belong to types IV and V, respectively, at the time of diagnosis. It is unknown whether types V or IV has more likely to be associated with familial occurrence or not. However, referring to other reported familial cases, the classification would not implicate a genetic etiology [8, 12]. The clinical spectrums between countries are different. Korean and Indian patients frequently showed involvement of the abdominal aorta, whereas Japanese patients more often revealed involvement of the aortic arch and its branches [13]. To further determine these difference between the familial versus sporadic, more cases need to be collected.

The age of onset of our patients were 33 and 16 years old, which is not different from sporadic cases previously reported in Korea (mean age; 29.5 ± 12.0 years ranging from 5 to 57 years old) [11]. Other characteristic manifestations of TA, such as malaise, dizziness, vascular bruit, blood pressure difference and elevated ESR were also accompanied in our patients [11].

Recent studies have illustrated an association between TA and different human leukocyte antigen (HLA) alleles [1, 14]. In Japan and Korea, clear association with the extended haplotype is reported: HLA B*52, DRB1*1502, DRB5*0102, DQA1*0103, DQB1*0601, DPA1*02-DPB1*0901 [14]. Moreover, HLA gene analysis performed in 38 members of the 21 affected Japanese families revealed that 29 of these patients carried the HLA B52 antigen (77 vs. 23%) [7]. However, recent study that investigated

the functional single-nucleotide polymorphism of PTPN22 gene encoding the lymphoid-specific protein tyrosine phosphatase failed to find any association with TA susceptibility, angiographic type, vascular involvement or prognosis [15]. Although we did not perform genetic analysis, the possibility of genetic etiology in these female siblings could be presumed.

It is unknown whether there is characteristic radiological findings that may be frequent in familial cases. Conventional angiography is used for diagnosis of TA. Inflammation of vessel wall can be assessed by Doppler ultrasound [1]. CT determines the phase of the disease by wall thickness and enhancement. Because aortic wall thickening is characteristic of arteritis, a decrease in mural thickening may reflect the effect of treatment [16]. In Case 1, there was no enhancement or thickening in abdominal and descending aorta, suggesting the late phase of TA. Although CRP was mildly elevated, the ESR was normal. In Case 1, wall thickening and subtle enhancement were observed in abdominal and descending aorta showing the early and the active phase of TA, with the elevation of ESR and CRP. Similarly, Nishimoto et al. [17] reported that thickening of the aortic vessels on CT were reduced by anti-IL-6 receptor antibody. Although our two cases were from same etiology, radiologic or laboratory findings can be different depending on the stage of TA. Therefore, it may not be inferred from genetic pathogenesis only from radiologic or inflammatory signs. However, CT angiography is feasible in diagnosis and in vivo monitoring of the disease.

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References

1. Johnston SL, Lock RJ, Gompels MM (2002) Takayasu arteritis: a review. J Clin Pathol 55:481–486
2. Rubin E, Gorstein F, Rubin R, Schwarting R, Strayer D (2005) Rubin's pathology: clinicopathologic foundations of medicine, 4th edn. Lippincott Williams & Wilkins, Philadelphia, p 508
3. Subramanyan R, Joy J, Balakrishnan KG (1989) Natural history of aortoarteritis (Takayasu's arteritis). Circulation 80:429–437
4. Numano F (2000) Vasa vasoritis, vasculitis and atherosclerosis. Int J Cardiol 75:S1–S8
5. Seko Y, Minota S, Kawasaki A et al (1994) Perforin-secreting killer cell infiltration and expression of a 65-kD heat-shock protein in aortic tissue of patients with Takayasu's arteritis. J Clin Invest 93(2):750–758
6. Vanoli M, Bacchiani G, Origg L, Scorza R (2001) Takayasu's arteritis: a changing disease. J Nephrol 14:497–505
7. Numano F, Kobayashi Y (1996) Takayasu arteritis: clinical characteristics and the role of genetic factors in its pathogenesis. Vasc Med 1:227–233
8. Sato E (1998) Demographic, clinical and angiographic data of patients of Takayasu arteritis in Brazil. Int J Cardiol 66:67–70
9. Tsai MJ, Lin SC, Wang JK, Chou CC, Chiang BL (1998) A patient with familial Takayasu's arteritis presenting with fever of unknown origin. J Formos Med Assoc 97(5):351–353
10. Naik N, Kothari SS, Sharma S (1999) Familial Takayasu's aortoarteritis in two sisters. Indian Heart J 51(1):75–76
11. Park MC, Lee SW, Park YB, Chung NS, Lee SK (2005) Clinical characteristics and outcomes of Takayasu's arteritis: analysis of 108 patients using standardized criteria for diagnosis, activity assessment, and angiographic classification. Scand J Rheumatol 34:284–292
12. Kodama K, Kida O, Morotomi Y et al (1986) Male siblings with Takayasu's arteritis suggest genetic etiology. Heart Vessels 2:51–54
13. Numano F, Kobayashi Y (1999) Takayasu arteritis-beyond pulselessness. Intern Med 38(3):226–232
14. Salazar M, Varela A, Ramirez LA et al (2000) Association of HLA-DRB1*1602 and DRB1*1001 with Takayasu arteritis in Colombian mestizos as markers of Amerindian ancestry. Int J Cardiol 75:S113–S116
15. Sahin N, Aksu K, Kamali S et al (2008) PTPN22 gene polymorphism in Takayasu's arteritis. Rheumatology 47(5):634–635
16. Paul JF, Fiessinger JN, Sapoval M et al (2001) Follow-up electron beam ct for the management of early phase Takayasu arteritis. J Comput Assist Tomogr 25(6):924–931
17. Nishimoto N, Nakahara H, Yoshio-Hoshino N, Mima T (2008) Successful treatment of a patient with Takayasu arteritis using a humanized anti-interleukin-6 receptor antibody. Arthritis Rheum 58(4):1197–1200