Takayasu arteritis in a 4-year-old girl: case report and brief overview of the pediatric literature

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Takayasu arteritis (TA) is a large vessel vasculitis that involves the aorta, its major branches and pulmonary arteries. Diagnosis of TA during childhood remains challenging due to the non-specific symptoms. We report a four-year-old girl presenting with fever, fatigue, weight loss, and elbow pain who was later diagnosed as childhood TA. On admission, she had fever, hypertension, decreased pulses, bruits, hepatosplenomegaly, and increased erythrocyte sedimentation rate and C-reactive protein level. Computed tomography angiography showed luminal narrowing and wall thickening in ascending aorta, brachiocephalic, left common carotid and left vertebral arteries and descending aorta. Oral corticosteroid (prednisone, 2 mg/kg/day) was instituted, later followed by oral methotrexate (12.5 mg/m^2/week). TA is rare in children; however, childhood TA must be considered in children who present with non-specific systemic symptoms, hypertension and increased acute phase reactants.

Key words: Takayasu arteritis, vasculitis, hypertension, children.

Takayasu arteritis (TA) is a rare large vessel vasculitis that involves the aorta, its branches and pulmonary arteries. Vessel wall inflammation leads to concentric wall thickening, fibrosis and thrombus formation, producing a variety of ischemic symptoms. The disease is associated with a high incidence of morbidity and a significant risk of early death[1-6].

Takayasu arteritis (TA) is predominantly a disease of young adults in the second and third decades of life [2]. The onset of illness may be earlier, including childhood, and rarely, infancy[1,3-6]. The clinical manifestations in children are less specific than in adults, and children usually present with fever, headaches, hypertension, weight loss, and arthritis[6]. Diagnosis of TA during childhood remains challenging due to the non-specific symptoms. To date, few studies on childhood TA (c-TA) have been published[1,3-6]. In Kerr et al.'s study [2], pediatric patients represented 30% of their study population, and they reported an incidence in all ages of 2.6/1,000,000.

We report a four-year-old girl who presented with fever, fatigue, weight loss, and elbow pain who was later diagnosed as c-TA.

Case Report

The patient was a four-year-old girl. She was admitted with complaints of fever, fatigue, weight loss, and left elbow pain starting one month ago. Her medical history was unremarkable. On physical examination, her body weight was 14.5 kg (10-25th percentile) and height was 96 cm (10-25th percentile). Her blood pressures were 150/80 mmHg and 70/40 mmHg in the left and right upper extremities, respectively, and 110/60 mmHg in both lower extremities. Pulse deficits were present between right and left brachial and radial pulses. 4/6 grade systolic ejection murmur (bruits) was noted over the mesocardiac area and carotid arteries. The liver and spleen were palpable 5 cm below the costal margin. The neurologic examination was unremarkable.

Laboratory parameters were as follows: White blood cell count: 22600/mm^3, hemoglobin: 11.4 g/dl, platelet count: 319000/mm^3, erythrocyte sedimentation rate: 96 mm/h (0-20), serum C-reactive protein level: 151 mg/L (0-5), and antistreptolysin O titer: 109 IU/ml. Serum electrolytes, liver and kidney function tests, thyroid function tests, urinalysis, rheumatoid factor, and procoagulant markers including serum factor levels were normal. Viral markers were negative for hepatitis B and C virus (HBV, HCV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Peripheral blood smear was normal. Blood cultures revealed *Brucella melitensis*. Rose Bengal and Gruber Widal tests and Brucella IgM and IgG, antinuclear antibody, antineutrophil cytoplasmic antibodies, and antiphospholipid and anticardiolipin antibodies were negative. Investigations for tuberculosis revealed negative results. Ophthalmological examination excluded retinopathy and iridocyclitis.

Chest radiographs revealed atelectasis in the left lower lobe. Abdominal ultrasonography showed hepatosplenomegaly and normal kidneys. Thorax computed tomography (CT) demonstrated small atelectatic areas in both lungs. Doppler sonography excluded bilateral renal artery stenosis.

Oral rifampicin and trimethoprim-sulfamethoxazole (TMP-SMX) were started for brucella infection, and intravenous streptomycin and ceftriaxone were instituted later. Follow-up blood cultures did not yield *B. melitensis*. Transthoracic echocardiography showed segmental narrowing in the aortic arch and its branches and abnormal flow pattern in the ascending, transverse and descending aorta. Computed tomography angiography (CTA) showed irregular narrowing in the arcus aorta, ascending aorta, brachiocephalic, left common carotid, and left vertebral arteries, and descending aorta (Fig. 1). The patient's clinical findings and results of noninvasive imaging studies were compatible with the diagnosis of c-TA according to the final EULAR/PRINTO/PRES (European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society) c-TA criteria[5]. Oral corticosteroid treatment (prednisone, 2 mg/kg/day) and acetyl-salicylic acid (3 mg/kg/day, p.o.) were instituted. Blood pressure was controlled with oral amlodipine (5 mg/day). No surgical interventions were performed. As the disease was limited to the upper side of the diaphragm without pulmonary involvement, oral methotrexate (12.5 mg/m^2/week) was added[7]. Cranial magnetic resonance imaging (MRI) excluded cerebral aneurysms. Within one month, she became afebrile and acute phase reactants were normalized; oral prednisone was tapered to 0.5 mg/kg/day.

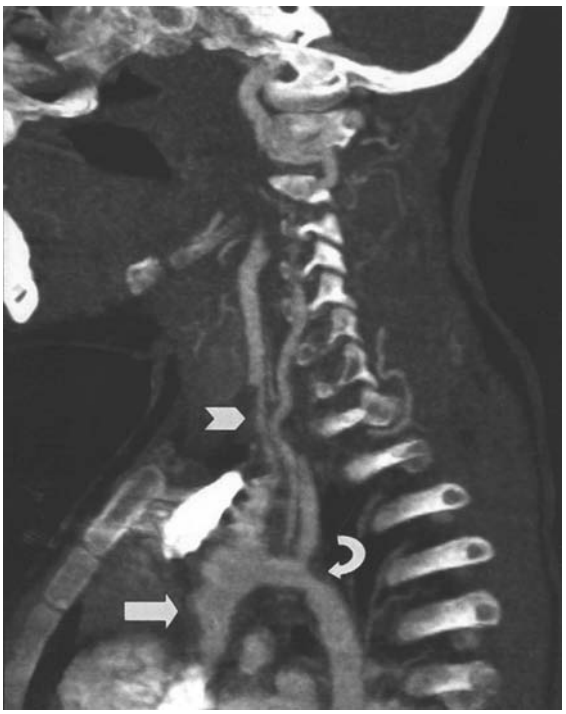

Figure 1. CT angiography subvolume maximum-intensity-projection (MIP) image shows luminal narrowing and wall thickening in ascending aorta (arrow), common carotid artery (arrowhead) and descending proximal portion of aorta distal to the left subclavian artery (curved arrow).

Discussion

The etiology and precise pathogenesis of TA are still unknown. Since large vessel biopsies are most often not possible, diagnosis of TA depends on a history of constitutional symptoms suggestive of a systemic illness, clinical findings, typical angiographic morphology, and the differential diagnosis of other conditions causing aortitis[8]. In 2008, EULAR/PRINTO/PRES proposed final validated classification criteria for Henoch-Schönlein

purpura, childhood polyarteritis nodosa (c-PAN), c-Wegener granulomatosis (c-WG), and c-TA[5]. Diagnosis of our patient was based on these final criteria and the characteristic angiographic findings.

The most common presenting features in adults with TA are hypertension and bruits[2]. In a review of 241 pediatric cases of TA, the most frequent presentation was hypertension (83%), followed by headaches (31%), fever (29%), dyspnea (23%), weight loss (22%), vomiting (20%), abdominal pain (17%), and musculoskeletal symptoms (14%) [6]. Adult patients with TA rarely present with arthritis or arthralgia[2]. However, arthritis is common in c-TA[6]. In a recent series of 87 children with TA, all children had angiographic abnormalities (100%). Abnormal acute phase reactants (87%), decreased peripheral artery pulses (71%), hypertension (63%), discrepancy of four-limb blood pressures (62%), bruits (57%), and claudication (38%) were the commonly observed features[5].

Our patient is relatively younger than the previously reported patients with TA. She presented with fever, weight loss and arthralgia. Clinical investigations revealed hypertension, decreased pulses, discrepancy of four-limb blood pressures >10 mmHg, bruits, and angiographic evidence of involvement of the aorta and its main branches. Brucella species rarely cause aortitis and have been implicated in a few cases[8-10]. Culture, when positive, provides the definitive diagnosis and is considered the gold standard in the laboratory diagnosis of brucellosis, as confirmed in our patient. Rarely, some patients with brucellosis will have a positive blood culture in the absence of positive serology. Brucellosis can cause infective endocarditis (IE), but infective aneurysms of the aorta are extremely rare, often reported as case reports[9,10]. Most reported infected aneurysms were peripheral arterial aneurysms, which were secondary complications of IE. In TA, aortic involvement, aortic aneurysms and branch vessel disease of the subclavian, innominate, renal, common carotid, vertebral, and mesenteric arteries are highly prevalent[8]. In our patient, echocardiographic study did not show vegetations but demonstrated segmental narrowing in the aortic arch and its branches and abnormal flow pattern in the ascending, transverse and descending aorta, which were in favor of a TA diagnosis. The patient possibly had a pre-existing aortic wall pathology due to TA, and it may be speculated that the brucellosis contributed to the inflammation. However, we are not able to present substantial data for this suggestion. TA is very rarely manifested by hepatosplenomegaly in its pre-pulseless stage, but in our patient, hepatosplenomegaly was considered as a clinical feature of brucellosis[11].

A combination of imaging modalities is required for the diagnosis and monitoring of TA in children. Vascular imaging is accomplished by conventional angiography, MR angiography (MRA), CTA, or Doppler ultrasound[6]. Angiography has traditionally been the gold standard, but it is invasive, and acute intramural inflammation or chronic wall fibrosis cannot be distinguished. MRA is preferred for long-term follow-up, as it visualizes vessel wall inflammation and mural thickening, shows edema representing active inflammation, and provides information relating to activity of the disease. CTA provides similar information to MRA, albeit with high radiation. Sonography might help to establish the early stage of TA in a pre-stenotic phase in the extracranial vessels. Corticosteroids are still the mainstay of treatment in c-TA[6]. Remission is achieved in 60% of patients treated with glucocorticoids alone, although relapses occur with dosage reduction[6,7]. Cyclophosphamide and methotrexate can be added, if the patient is unresponsive to glucocorticoids alone[7]. Despite the extent and severity of vascular lesions, patients can benefit from surgical interventions, which include bypass surgery, the use of interposition grafts and percutaneous transluminal angioplasty[2,6,12]. The outcome of TA depends on the vessel involvement and severity of hypertension. The mortality rate in children was reported to be as high as 35-40% by five years[1].

To conclude, we reported herein a four-year-old girl presenting with fever, weight loss and arthralgia who was later diagnosed as c-TA. Although rare, c-TA must be considered in children who present with non-specific systemic symptoms, hypertension and increased acute phase reactants.

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