

## CASE REPORT

# Five-day fever: The main presentation of childhood-onset Takayasu arteritis

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## Abstract

In children with a nonspecific constitutional presentation such as prolonged fever, the physician should pay attention to primary vasculitides after ruling out the more common diseases such as infectious diseases, malignancies, and the other rheumatic disorders. The past history of autoimmunity may be a clue for this.

## KEYWORDS

case report, children, primary vasculitis, Takayasu arteritis

## 1 | INTRODUCTION

Takayasu arteritis (TA) is a well-known rare form of large vessel vasculitides characterized by granulomatous inflammatory changes in large arteries, mainly involves the aorta and its major branches. TA typically affects young females under the age of 40. Notably, it is initiated in the second and third decades of life, and it might conceivably be presented by nonspecific symptoms including fever, weight loss, anorexia, profound fatigue, and inability to perform long-term activities. Gradually, with disease progression, the inflammation of large vessel walls leads to stenosis of the lumen, and tightness of the inner-layer of vessels. The symptoms of the disease appear as follows: pain, coldness, or numbness in the lower extremities, diminished or absent of pulse, and blood pressure discrepancy.<sup>1,2</sup>

TA may occur as acute stroke or visual loss in a young person without any prior risk factor.<sup>2,3</sup> Acute-phase reactants are not always precise indicators of inflammatory activity in

the vessel wall.<sup>4</sup> Herein, we reported a teenage girl with TA presented with prolonged fever.

## 2 | CASE REPORT

A 9-year-old Iranian girl, with a short history of high-grade fever, productive cough, palpitation, and chest pain for 5 days, presented to a hospital clinic. Her dull aching chest pain was in the retrosternal and precordium radiating to the back. She appeared comfortable and in less distress in the recumbent position, while sitting, and bending forward, got worse. Deep breathing and coughing worsened the pain.

She had Coombs-positive hemolytic anemia (warm antibody) in 6 months of age. She recovered by supportive care, packed cell transfusion, and taking cyclosporine and prednisolone for about 2 months and folic acid for 1 year. She has been healthy with a normal life and activity till the recent febrile

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illness. Lately, the patient complained of some intermittent dull abdominal pains without any relation to feeding, activity, rest, and any other gastrointestinal manifestations. In physical examination, she was ill and febrile. The patient's blood pressure was normal, and the peripheral pulses were full and symmetric; there were not any other abnormal clinical findings. According to the patient's complete blood count (CBC) report, mild normocytic normochromic anemia was detected. White blood cell and platelet counts were normal. Estimated sedimentation rate (ESR) and C-reactive protein (CRP) were specifically raised (ESR = 110 mm/h, CRP = 89 mg/dL). The liver and renal function tests, coagulation tests, uric acid, lactate dehydrogenase (LDH), creatine kinase MB (CKMB), and troponin revealed no significant abnormality.

Complements, antiphospholipid antibodies along with serum immunoglobulin levels, showed normal and serologic tests for human immunodeficiency virus (HIV), hepatitis B and C virus, Epstein-Barr virus (EBV), Cytomegalovirus (CMV) and parvovirus B19 and blood culture were negative. HLAB5, QuantiFERON, and purified protein derivative (PPD) tests were negative. Electrocardiogram (ECG), echocardiography, and chest X-ray showed a normal pattern. There was no evidence of endocarditis in echocardiography, and left main coronary artery (LMCA) diameter was reported at 3.3 mm. The abdominopelvic ultrasound indicated the following findings: proximal abdominal aorta, superior mesenteric artery (SMA), and the celiac artery were seen with increased wall thickening (up to 2.5 mm) (Figure 1). Spiral multislice thoracoabdominal computed tomography (CT) angiography with intravenous (IV) contrast media revealed the following findings: diffuse wall thickening in thoracic aorta including the origin of common carotid, subclavian and innominate arteries, as well as proximal abdominal aorta involving the celiac axis and superior mesenteric arteries. Furthermore, the thoracic aortic root and ascending aorta and to less extent aortic arch were dilated. The origin of the left main coronary artery was also mildly dilated (Figures 2 and 3).

In the division of infectious disease, she was investigated for endocarditis because of prolonged high fever, raised ESR and CRP. In physical examination and echocardiography, there was no evidence confirming endocarditis. The patient's echocardiography revealed LMCA with 3.3 mm diameter compatible with incomplete Kawasaki disease; hence, she was treated with intravenous immune globulin (IVIG) (2 g/kg) and acetylsalicylic acid (aspirin) (100 mg/kg/d). Furthermore, besides these findings, widening of the root of the aorta was seen in echocardiography. So, consult with pediatric rheumatologist requested.

In the rheumatologic disease ward, the patient underwent abdominopelvic Doppler ultrasound and spiral thoracoabdominal CT Angiography. On the basis of laboratory (high ESR and CRP) and imaging findings, and ruling out infectious diseases such as tuberculosis, according to EULAR/PRINTO/PRES criteria (Table 1), the patient diagnosed as TA.

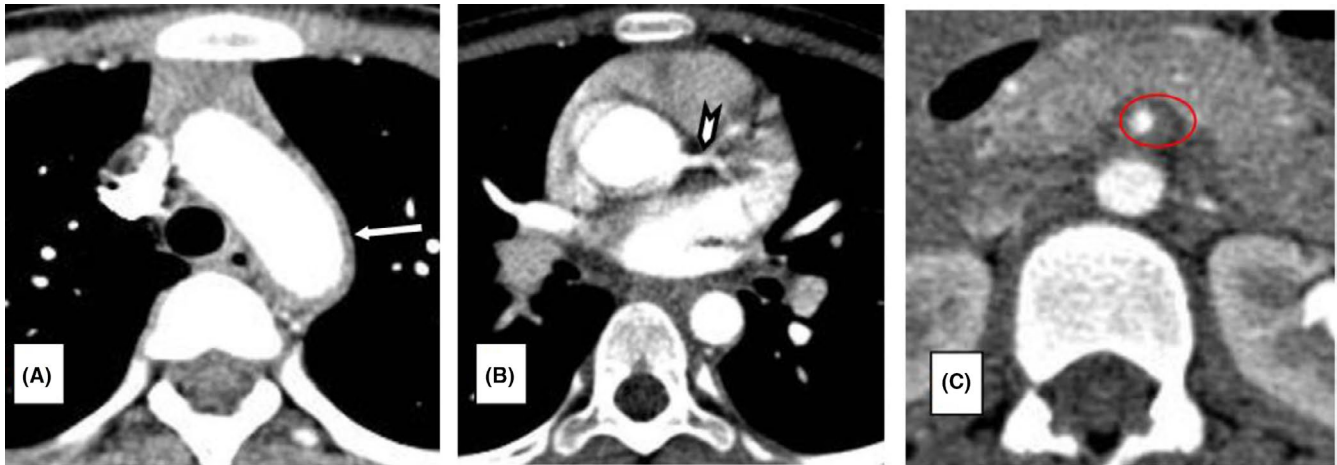
The patient was treated with methylprednisolone pulse, 30 mg/kg/d, for three consecutive days, methotrexate (MTX) (10 mg/m<sup>2</sup>/wk), and aspirin 5 mg/kg/d. From the fourth day onwards, prednisolone 2 mg/kg/d started orally for the patient. Ophthalmology consults revealed vasculitis, so infliximab (IFX) (6 mg/kg) prescribed. After the first pulse of methylprednisolone, the patient's fever ceased, and she discharged on the ninth day of admission. We recommended the patient to have a low-salt diet, relative bed rest, and blood pressure measurements in a regular base. Prednisolone (with 5 mg weekly reduction), MTX, and aspirin with the mentioned dose prescribed.

The patient visited after 2 weeks of treatment. She had not any new complaint and was healthy in physical examination. No abnormal blood pressure in her upper and lower extremities was found; also peripheral pulses were full and symmetric. So low-dose prednisolone tapered gradually. Aspirin and MTX continued.

The patient visited again 2 weeks later with no complaint. CBC, ESR, and CRP were normal. Abdominopelvic



**FIGURE 1** Ultrasonography from upper abdomen reveals thickening of superior mesenteric artery wall in axial (A) and sagittal images (B) white arrow. Thickening of proximal abdominal aorta is noted (C)



**FIGURE 2** Spiral CT angiography of thorax in axial images shows thickening of aortic arch wall (yellow arrow) (A), dilatation of aortic root and left main coronary artery (yellow arrowhead) (B), and thickening of abdominal aorta and superior mesenteric artery wall (red circle) (C)



**FIGURE 3** 3D volume-rendered spiral CT angiography of thorax shows dilatation of aortic root and ascending aorta and to less extent aortic arc

ultrasound revealed no significant abnormality so as for echocardiography. The patient underwent infliximab infusion 6 mg/kg every 4 weeks.

### 3 | DISCUSSION AND CONCLUSION

TA is a rare disease characterized by large vessels vasculitis including the aorta and its main branches. Pathogenesis of the disease is not fully known, but its association with some of the genetic factors has been described. The severity

of the disease is higher in patients with positive HLA B52.<sup>5</sup> Furthermore, the increased prevalence of TA in some races and monozygotic twins suggests the genetic background of the disease. Some studies indicate IL1 gene polymorphism and higher levels of IL-1, IL-6, and anti-TNF- $\alpha$  in TA patients compared to healthy subjects. Our patient had a history of hemolytic anemia (warm antibody) in infancy. This history suggests the patient has a background of autoimmunity, which predisposes her to dysregulation in the acquired immune system (B and T cells) in the future.

Vascular involvement begins with T cells, plasma cells, and macrophage infiltration from vasa vasorum with spreading to the media. Sustained inflammation can lead to the elastic lamina and muscular media damage, proliferation of intima, and ultimately stenosis or vessel obstruction. Subclavian, renal, and carotid arteries are the most common involved branches of the aorta in TA.<sup>6,7</sup> The initial manifestations of the disease are nonspecific and sometimes subtle; so, the diagnosis of the disease can be delayed, and this delay is longer in children than adults.<sup>8</sup> Fatigue and weakness, loss of appetite and weight loss, fever, headache, dizziness, and abdominal pain are the most common early complaints of patients. With the progression of damage to the vessels, late symptoms and signs may occur such as claudication, palpitation, decreased or absent pulse sensations, asymmetric blood pressure, renal failure, Raynaud's phenomenon, heart failure, aortic valve insufficiency, and stroke.<sup>1-3,9</sup> Vascular imaging techniques play a major role in the diagnosis of TA. Although digital subtraction angiography (DSA) is the best method for diagnosis of TA, the use of color Doppler ultrasound, magnetic resonance angiography (MRA), CT angiography, and positron emission tomography (PET) with 18F-fluorodeoxyglucose can show initial vascular changes of vessels including vascular wall thickening or mural inflammation and late changes such as stenosis and aneurysm.<sup>4,9,10</sup>

**TABLE 1** EULAR/PRINTO/PRES criteria and classification definition of Takayasu Arteritis

Mandatory criteria	
Angiographic abnormality	Angiography (conventional, CT, and MRI) of the aorta, its main branches or pulmonary arteries showing aneurysm/dilatation, narrowing, occlusion, or thickened arterial wall, not due to any other causes
Additional criteria (need one of the five)	
(1) Pulse deficit or claudication	Lost/decreased/unequal peripheral artery pulse Symptoms of claudication: focal muscle pain induced by physical activity
(2) Blood pressure discrepancy	Discrepancy of four-limb systolic blood pressure > 10 mm Hg in any limb
(3) Bruits	Audible murmurs or palpable thrills over large arteries
(4) Hypertension	Systolic/diastolic blood pressure > 95th centile for height
(5) Acute-phase reactant	Erythrocyte sedimentation rate (ESR) > 20 mm per hour or C-reactive protein (CRP) above normal

Acute-phase reactants such as CRP and ESR may not match with TA disease activity and severity of vascular involvement.<sup>11</sup> So, close observation, follow-up, and evaluating the disease activity along with clinical symptoms and signs, measuring acute-phase reactants, and vascular imaging seem logical.<sup>9</sup> The use of vascular imaging techniques plays an important role in diagnosing, grading, and disease monitoring as well as evaluating treatment response. Furthermore, in patients with TA, periodic echocardiography is recommended along with an examination of aortic valve insufficiency (AI) and left ventricular hypertrophy (LVH).<sup>9,10</sup>

In TA management, patient and parent training and patient-physician close relationship are very important. Low-salt diet, especially in cases of renal artery involvement, hypertension, and corticosteroid usage is recommended.<sup>12</sup>

The basis of TA management is suppression of systemic and vascular inflammation with corticosteroids (CS). In the active TA disease, the standard treatment is the use of high-dose prednisolone (1–2 mg/kg/d), which usually associates with good response. Side effects of CS or disease recurrence during CS tapering may also occur. At the beginning of treatment with the CS or dose reduction,

concomitant use of other immunosuppressive agents is reasonable.<sup>9,13</sup> Some studies have shown the beneficial effects of MTX (10–15 mg/m<sup>2</sup>/wk) and azathioprine (AZA) (2 mg/kg/d) along with CS in the treatment and control of TA activity.<sup>9</sup> In severe cases, taking cyclophosphamide is useful regarding systemic or life-threatening involvement such as severe aortic valve insufficiency or pulmonary artery involvement.<sup>9</sup>

IL-6 and TNF- $\alpha$  serum levels are higher in TA patients than healthy subjects, as indicated. Case-series studies have shown beneficial effects of IFX, an anti-TNF- $\alpha$  agent, in controlling disease activity and improving the patients' quality of life and life expectancy.<sup>9</sup> These beneficial effects are also reported for tocilizumab, an IL6 monoclonal antibody. In some case series, rituximab has been effective in improving the treatment of TA.<sup>9</sup>

According to high ESR, CRP, and findings of spiral thoracoabdominal CT Angiography with contrast, our patient had type V of TA. She was treated with the protocol previously mentioned (prednisolone, aspirin, MTX, and IFX). The patient visited every month in 6 months after diagnosing with no complaint. CBC, ESR, and CRP were normal. Abdominopelvic ultrasound revealed no significant abnormality so as for echocardiography. After 3-year follow-up, the patient was on remission with low doses of prednisolone, aspirin, and IFX (every 12 weeks).

Primary childhood vasculitides are rare. However, in children with the nonspecific constitutional presentation, the physician should have this group of disorders in mind. Some of these complaints are prolonged fever, fatigue, malaise, and weight loss as well as multi-organ systemic signs and symptoms. After ruling out the more common diseases such as infectious disease, malignancies, the other rheumatic disorders, and drug reactions, the physician should pay attention to this dangerous group of disorders and perform more precise clinical and paraclinical evaluations for finding them.

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We thank the patient and her parents for consent to publish this case study.

## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTION

VJP: served as the main physician and contributed to study concepts, study design, definition of intellectual content, literature research, clinical studies. MJ: contributed to provision of patient information, acquisition of clinical data, literature research, and manuscript writing. KR: contributed to provision of patient information, acquisition of clinical data, literature research. RA: contributed to provision of patient

information, literature research. RS: served as guarantor of integrity of the entire study and edited the manuscript.

## ETHICAL APPROVAL

Not applicable.

## CONSENT STATEMENT

We confirm that the written informed consent form has been provided by the parents to have the case details published. Also, we restate that institutional approval is not required to publish the case details.

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