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Case Report

Atypical childhood Takayasu arteritis – A case report

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ABSTRACT

Childhood Takayasu arteritis is one of the most common vasculitis in paediatric age group. It predominantly involves the greater vessels such as aorta and its branches, leading to granulomatous inflammation. The process of inflammation gives rise to the symptoms based on thrombotic or aneurysmal phenomena. This is a case report of a 11-year-old girl diagnosed in an urban tertiary care centre in India with childhood Takayasu arteritis. The said child had first presented with non-specific symptoms such as leg ache, back ache and fever. Over the course of illness, the child developed hypertension and had also suffered from PRES (posterior reversible encephalopathy syndrome). Clinical examination was consistent with Takayasu arteritis, however with predominant medium-sized vessel involvement on imaging. Since this is a relatively atypical presentation, it was mandatory to rule out other causes of medium-vessel arteritis, especially DADA2 (deficiency of ADA2).

1. Introduction

Takayasu Arteritis is the most common cause of granulomatous inflammation of large arteries and the third most common cause of vasculitis in the paediatric age group.[1] It is characterized by granulomatous inflammation of the aorta and its major branches. Symptoms result from systemic inflammation, local inflammatory processes, and organ dysfunction secondary to ischemia.[2] There is an overall female preponderance of the disease and is around 2.5:1 for the paediatric population. The peak age of onset in children is around 12 years, although infancy-onset Takayasu arteritis have also been described.[3] The disease results from an attack by the body's own immune system, causing inflammation in the vasa varosum layer of the vessel wall with giant cells and granulomas. Persistent inflammation leads to blood vessel dilatation and aneurysms ultimately leading to stenotic or occluded vessels.[4] Common early signs and symptoms are weakness, malaise, and fever. Other than early-stage constitutional symptoms, vascular complications such as stroke, myocardial infarction, resistant hypertension, and heart failure can emerge after arterial wall thickening, stenosis, occlusion, aneurysm, or thrombosis formation due to progressive inflammation.[5] However, the onset which is characterized by an acute inflammatory phase with non-specific systemic symptoms may contribute to the diagnostic delay. Treatment modalities include both medical and surgical, based on the presentation of the patient. The aim of the present report was to describe a case of paediatric Takayasu arteritis seen in an Indian tertiary care centre, with a relatively atypical presentation, predominantly involving the medium-sized vessels.

2. Discussion

11-year-old female child, born out of third-degree consanguineous marriage presented with complaints of

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bilateral symmetrical leg pain, predominantly in the thighs and calves, dull-aching type, with no diurnal variation and not associated with morning stiffness or claudication, back ache and neck ache 9 months back for 2-3 weeks. On enquiry, there was history of low-grade fever, intermittent in nature, maximum recorded temperature of 38.5 degree Celsius, without diurnal variation, not associated with nigh-sweats. The parents had also noticed that the child wasn't gaining adequate weight during this period of illness. Patient was investigated for the above complaints. MRI spine was done with suspicion of spinal Kochs but was within normal limits. Baseline haematological and autoimmune workup revealed no significant findings except for nutritional anaemia. The child was started on symptomatic treatment with NSAIDS for pain and supplements (calcium, iron and multivitamins) after which the child had brief symptomatic relief. 7 months later, child presented to the health facility with convulsions in the form of generalized tonic-clonic convulsion secondary to hypertension, recorded blood pressure at the time of acute event being 200/100mm hg on right upper limb. However, the hypertensive reading was noted only in the right arm. There was a 4-limb discrepancy of blood pressure along with inequality in the pulses felt at different arterial markings. Patient was started on antihypertensives and was stabilized. During the course of illness, the child also developed haematuria and proteinuria. An extensive set of workups was organized to reach a final diagnosis.

Doppler studies showed the following results: Upper limb doppler – left subclavian circumferential thickening. Left brachial, radial and ulnar arteries showing dampened flow velocity with monophasic waveform. Lower limb doppler – right common femoral arterial intimomedial thickening with normal triphasic waveform. Left saphenous artery: long segment circumferential thickening extending into left superficial femoral artery. Left superficial femoral artery involved in its entire length. Collaterals formed and profunda enlarged.

CT aortogram was suggestive of: Circumferential wall thickening involving mid and distal arch of aorta. Left proximal subclavian artery causing its complete stenosis with rest of the left subclavian artery opacified from left vertebral artery suggestive of subclavian steal phenomenon.

1. Anterior and lateral aorta and the level of origin of celiac and SMA shows wall thickening
2. Diffuse circumferential wall thickening of celiac axis causing significant luminal narrowing (>90% stenosis) with severely attenuated proximal and mid part of splenic artery with reformation of distal splenic artery.
3. Non-visualization of proximal portion of SMA with rest of SMA reformed via prominent collaterals mainly from IMA and partially from pancreaticoduodenal arcade.
4. Severely attenuated right accessory renal artery in its proximal portion with resultant renal infarct in mid and lower pole of right kidney.
5. Left common femoral artery shows diffuse circumferential wall thickening causing subtle luminal narrowing < 20%. Above features suggestive of atypical Takayasu's aortoarteritis (type V) – due to lack of significant aortic involvement and predominant involvement of celiac axis and SMA.

2D echocardiography showed features of hypertensive disease with concentric LVH with preserved left ventricular function.

FDG-PET failed to reveal significant uptake and ADA2 levels were within normal limits. Inflammatory markers such as ESR and CRP were raised. The child was started on cyclical immunomodulator cyclophosphamide for 6 doses; monthly once, under steroid- coverage along with continuation of anti-hypertensive medications and nutritional supplements.

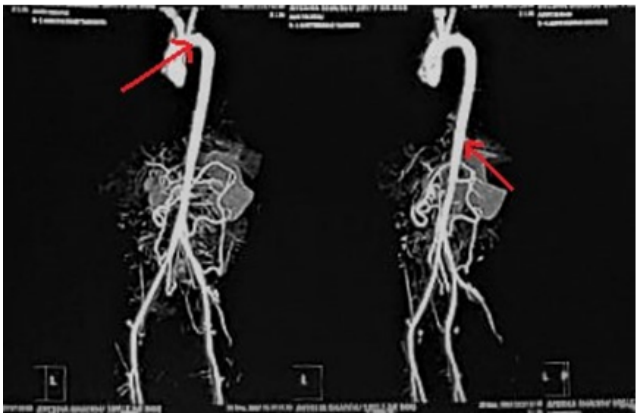

Fig. 1: CTaortogram showing (a) complete stenosis of LSA, (b) narrowing of celiac axis

Subsequently during the course of illness, the patient developed new onset microscopic haematuria as well as proteinuria. Repeat doppler studies were done, which was suggestive of right renal artery involvement. Left renal vessels were normal in calibre.

EULAR/PRINTO/PRES criteria is used for diagnosis of childhood Takayasu arteritis. It includes:

Angiographic abnormalities (conventional, CT, or magnetic resonance angiography) of the aorta or its main branches and at least 1 of the following criteria:

1. Decreased peripheral artery pulse(s and/or claudication of extremities.
2. Blood pressure difference between arms or legs of >10 mm Hg.
3. Bruits over the aorta and/or its major branches.
4. Hypertension (defined by childhood normative data.

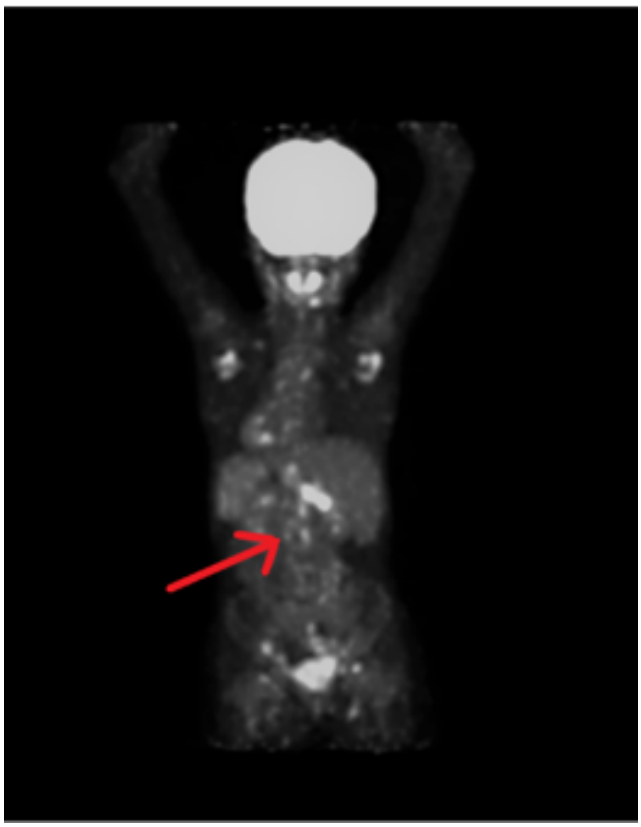

Fig. 2: FDG-PET showing lack of uptake in greater vessels

5. Elevated acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein.[6]

The above criteria was fulfilled by our patient, hence confirming the diagnosis. Conventionally, glucocorticoids are the mainstay of therapy, typically starting with high doses (1-2 mg/kg/day of prednisone or methylprednisolone IV) followed by gradual dosage tapering. When disease progresses or recurs, steroid-sparing therapy is often required, usually involving methotrexate or azathioprine. Cyclophosphamide is reserved for severe or refractory disease. Results of small case series also suggest that mycophenolate mofetil or anti-TNF-a therapy may be beneficial in select patients. Anti-IL-6 therapy with tocilizumab has shown promising results in a small case series of children with TA.[7] Antihypertensive medications are often necessary to control blood pressure caused by renovascular disease. Although ACE inhibitors have potency in reducing organ remodelling and proteinuria, it would be detrimental to use it here in a case of unilateral renal ischemia since this is an ongoing disease which has a propensity to involve the contralateral side in future. According to Cavoli et al, there is frequent involvement of renal arteries, usually with renovascular hypertension. The incidence ranges from 24% to 68%.[8] The renal artery involvement is often bilateral and frequently ostial and proximal, usually with coexistent stenosis of the perirenal aorta. Stenotic phenomena are more common than aneurysmal phenomena in younger age group, leading to renal ischemia and symptoms like haematuria and proteinuria, both of them seen in our case.

Hence, a low-dose calcium channel inhibitor was continued for our patient. Before starting immunomodulatory agents and steroids, it is also mandatory to rule out tuberculosis, especially in an Indian setup, since it has a propensity to flare-up during immunosuppression. There have also been evidences of tuberculosis being the etiological factor for the development of Takayasu disease.[9] Treatment modalities in such cases include initiation of appropriate anti-tubercular regimen followed by immunomodulation. After effectively ruling out tuberculosis, our patient was started on a pulse steroid therapy for 3 days, followed by 6 cycles of cyclophosphamide under steroid coverage. The child was followed up 2-weekly to assess progression of the illness. The child has not had any significant adverse effect during therapy.

However, it was seen that the patient had a predominant involvement of medium-sized vessels. This is a characteristic finding in the disease DADA2, i.e., deficiency of ADA2 which is a monogenic vasculitis syndrome. In this disease there is extensive vasculopathy ranging from livedo reticularis to polyarteritis nodosa (PAN) and life-threatening ischemic and/or haemorrhagic stroke. Vasculitis and inflammation affects many organs, which explains the intestinal, hepatological, neurological, cutaneous and renal manifestations. DADA2 should be primarily considered in patients with early-onset fevers, rashes, and strokes even in the absence of positive family history. Along with vascular involvement, haematological manifestations such as hypogammaglobulinemia, although pure red cell aplasia (PRCA), immune thrombocytopenia, and neutropenia are also frequently seen.[10] Diagnosis is made on the basis of ADA2 enzyme activity in patients' serum. Although immunomodulators and steroid are the mainstay of management, as a more definitive treatment, HSCT has been reported to control both the immunological, the haematological, and the vascular phenotype of DADA2.[11]

In our case, a total of 4 samples were tested to rule out DADA2- the patient, her parents and an unrelated control sample were sent to a CLIA certified laboratory. We have a documented normal ADA2 enzyme activity with adequate control samples in our case, hence ruling out DADA2.

3. Conclusion

Takayasu arteritis is one of the most common large vessel arteritis seen in children. It commonly presents with 4-limb pulse and blood pressure discrepancy and is diagnosed on radiological imaging. In case of atypical presentation such as predominant medium vessel involvement, it is

important to rule out other diseases like DADA2 since the treatment modalities are different. Takayasu arteritis is treated with immunosuppression and anti-hypertensives. A routine follow-up is to be carried out to monitor the patient.

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5. Conflict of Interest

None.

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