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Case Report

Takayasu's arteritis: Is it a reversible disease? Case Report and Literature Review

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Abstract

Background: Takayasu's arteritis (TA) is a rare and potentially devastating condition leading to prolonged morbidity and even death.

Case Description: We report an 18-year-old female presenting with an acute ischemic stroke treated with intravenous thrombolysis and subsequent endovascular therapy (ET) with excellent results followed by chronic treatment with immunosuppressants after a formal diagnosis of TA. Following immunosupression, improvement was noted in critical stenoses of the extracranial large vessels.

Conclusion: These observations underscore the importance of early initiation of therapy to halt or even reverse vascular pathology, though frequent follow up is mandatory as relapse is common. In this article we provide brief review of the current literature on TA related to pathophysiology, criterion for diagnosis, therapy, and follow up.

Key Words: Acute stroke, endovascular treatment, reversibility, stenosis, Takayasu's arteritis

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BACKGROUND

Takayasu's Arteritis, (TA) also known as pulseless disease, is an idiopathic large vessel vasculitis affecting the aorta and its major branches. Although most commonly seen in Asia, TA is reported in the United States with an incidence of 2.6 cases per million annually[7] Typical presentation is seen in people aged between 20 and 40 years old, though cases diagnosed in late adulthood or in childhood are not rare. There is marked variation in the incidence, gender, prevalence, and mortality from country to country raising the question of genetic, social, and environmental factors. For example, male to female prevalence is 1:1.3 in India though 1:9 in Japan.[4] Mortality also varies between countries and may be attributable to differences in severity of disease expression, medical therapy, and access to surgical intervention. In India, mortality is 17%[8] whereas in Korea, 5-year mortality is 7.1% and 10 year mortality is 12.8%.[17] Early clinical stages may present subtly with malaise or fever. However as the disease progresses unexplained hypertension, acute neurological deficits

or claudication of the extremities are more common. Treatment typically involves immunosuppression and longitudinal follow up is mandatory. We describe in this case report, an eighteen year old female who presented with an acute ischemic stroke, treated with intravenous tissue plasminogen activator (t-PA), endovascular therapy (ET) and chronically with immunosuppressants showing improvement of the previous critical stenotic lesions in the extracranial large vessels. This underscores the importance of early initiation of therapy, which may potentially halt or even reverse the vascular pathology.

CASE REPORT

An 18-year-old Hispanic female with no significant past medical history presented with acute onset left side weakness, left hemi neglect, and an national institutes of health stroke scale (NIHSS) stroke scale of 15. The admission computed tomography (CT) angiogram (CTA) of head and neck revealed hyper dense right middle cerebral artery (MCA) with intraluminal clot in the right internal carotid artery (ICA) at the level of the ophthalmic artery extending into the M1 and M2 segment of the MCA. Also observed was near-total stenosis of the right common carotid artery (CCA) [Figures 1 and 2]. Additionally the left CCA demonstrated significant stenosis and bilateral CCA thickening circumferentially. On CT Perfusion there was delayed time to peak (TTP), increased mean transit time (MTT), reduced cerebral blood flow (CBF), and preserved cerebral blood volume (CBV) in the right MCA distribution suggestive of a large at-risk penumbra. The patient received intravenous tissue plasminogen activator (t-PA) within 90 minutes of symptom onset. Patient was taken to interventional suite for cerebral angiogram directly after intravenous t-PA based on pre t-PA imaging and persistence of symptoms. The femoral puncture time was 2 hours and 25 minutes after the onset of her symptoms. Percutaneous transluminal balloon angioplasty of the right CCA and ICA followed by mechanical thrombectomy of the right ICA and MCA was performed. Immediately post procedure, she was moving her previously plegic left hemibody. There were no post procedure complications. Magnetic resonance (MR) of the brain revealed a small area of completed infarct in the right MCA territory. She was discharged home after 3 days with a modified Rankin score (m-RS) of 1.

She was electively readmitted shortly after discharge for evaluation of her underlying large vessel occlusions and stenoses. This included acute phase reactants and CTA of the chest to inspect the aorta and its branches. ESR (83) and CRP (28) were elevated.

CTA of the aortic arch [Figures 3 and 4] showed soft tissue thickening around the aortic arch extending into the great vessel origins. The soft tissue swelling extended superiorly into the right brachiocephalic artery and into the right CCA with significant narrowing to less than 2 mm. No flow was evident in the proximal aspect of the left CCA. At the origin of the right subclavian artery there was a 1 cm segmental occlusion with distal reconstitution. There was no evidence for aneurysm or dissection of the thoracic aorta. The celiac, superior mesenteric, and renal arteries appeared normal.

According to the recent criteria for large vessel vasculitis;[18] a diagnosis of TA was made and the patient was initiated on combination therapy of steroids and azathioprine. Two weeks later she began etarnecept therapy. She had repeat blood work and CTA of the chest 6 months after the initial

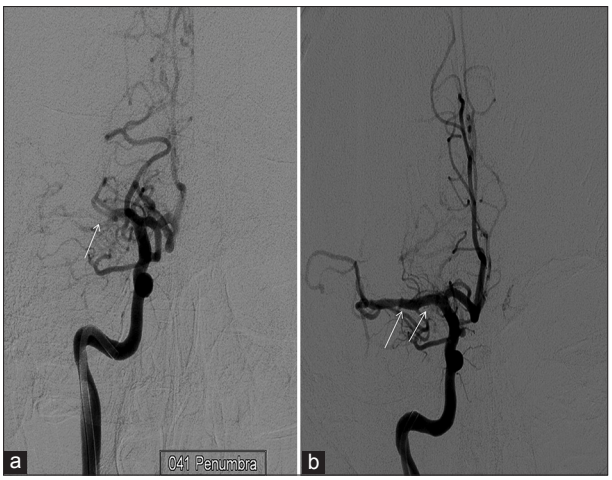

Figure 1: Pre and Post t-PA/Angioplasty Middle cerebral artery (MCA). (a) There is an acute thrombus (arrow) in the M1 MCA segment (right).The intravenous t-PA has dissolved the supraclinoid ICA thrombus, but no effect on the MCA thrombosis which warranted mechanical endovascular therapy. (b) Postpenumbra device and angioplasty there is TIMI 3 flow in the MCA (left)

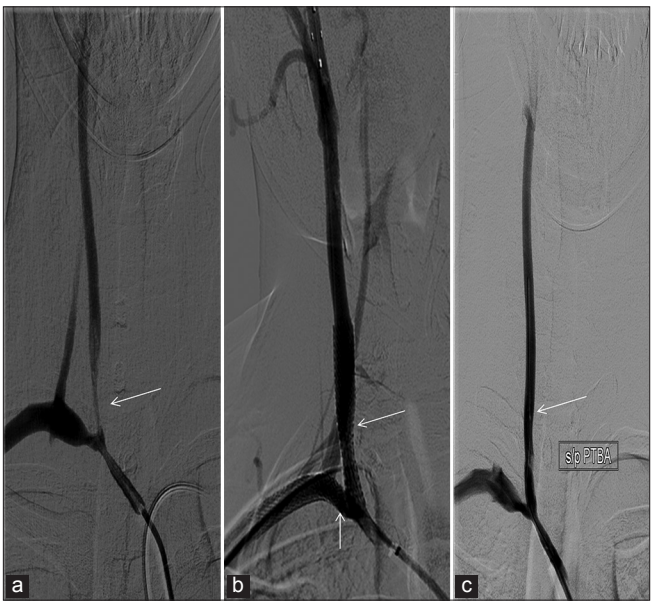

Figure 2: Pre and Post t-PA/Angioplasty Common carotid artery (CCA). (a) Severe stenosis in the CCA at the origin (Arrows). (b) Temporary stents in the CCA and subclavian artery (Arrows). (c) Postangioplasty CCA

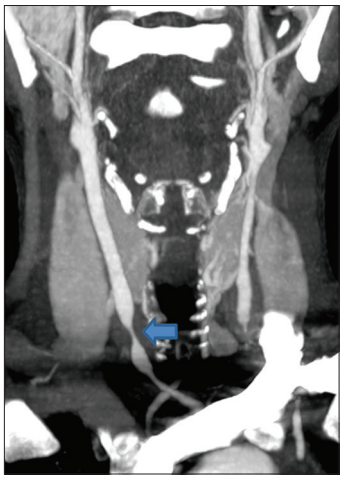

Figure 3: CTA NECK: Patient's CTA neck showing significant narrowing of the right CCA pretreatment

event at which time ESR and CRP were normal. Repeat imaging [Figures 5] revealed significant improvement in the degree of soft tissue thickening around the aortic arch and the proximal brachiocephalic vessels. There was improvement in the luminal diameter of the right brachiocephalic artery extending into the right CCA. Where it had appeared that the proximal right subclavian artery was completely occluded, there was now a small lumen visible. Additionally, where prior CTA showed no flow in the left common carotid artery, now there was a very small lumen present. The left subclavian and vertebral arteries were patent. The remainder of the ascending and descending thoracic aorta was patent. She did not show any new neurological deterioration when last seen 3 months after stroke. Last rheumatology clinic follow up (17 months from her first presentation) reinforces symptom stability

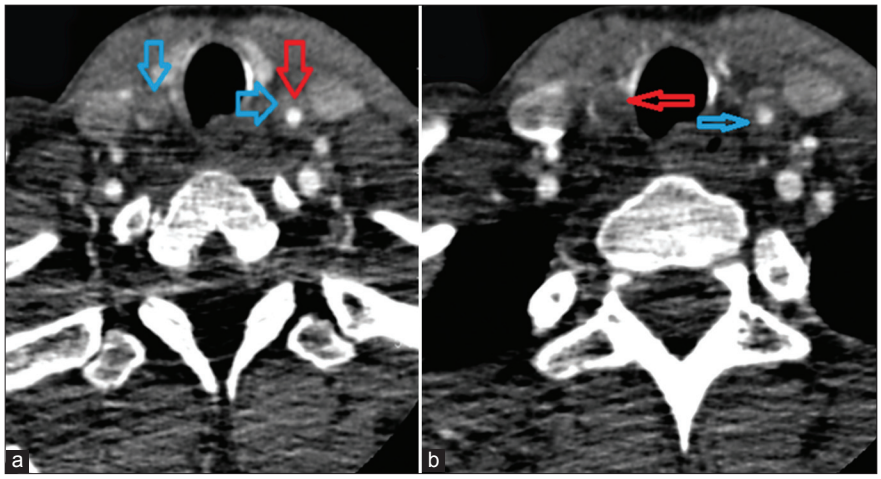

Figure 4: Pretreatment/Post ET CTA of the neck (axial view). (a) CTA axial view show nearly occluded right CCA (thin blue arrow) with minimal cresenteric flow and extensive soft tissue thickening (thick blue arrow) in and around the wall of the vessel. Also seen is the left CCA (thick red arrow). (b) Right (red) and Left (blue) CCA

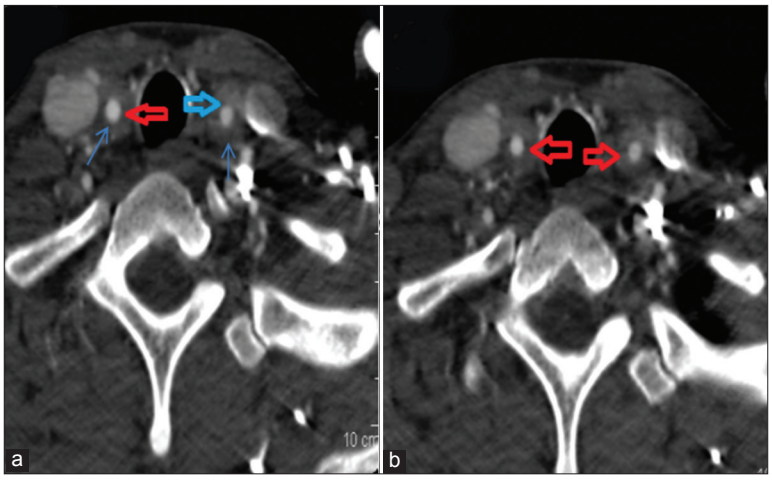

Figure 5: Posttreatment CTA of the neck (axial view). (a) CTA showing improvement in the caliber and soft tissue deposition of the CCA. Thin blue arrow: improvement in the soft tissue thickening in the wall. Thick red and blue arrows denote Right and Left CCA, respectively. (b) Again shown is the reduced soft tissue deposition in the vessel wall. Arrow denotes Right and Left CCA

and an ESR of 15. Medical therapy with infliximab, solumedrol pulse and daily prednisone continues.

DISCUSSION

TA is an idiopathic chronic arteritis with predilection for the aorta and its major branches. Pathophysiology of TA can be divided into early, intermediate and chronic stages for clinical purposes.

In the early stage, there is mononuclear cell infiltration[1] via vasa vasorum, subsequently migrating to the macro luminal intima causing local destruction of elastin and arterial smooth muscle cells. Aggressive treatment at this stage is likely crucial to halt or even reverse the disease. As the disease process progresses, there is irreversible damage.

In the Intermediate stage, there is secondary deposition of mucopolysaccharides, and fibroblasts along with smooth muscle cell proliferation.[21] TNF-alpha plays a prominent role in smooth muscle cell proliferation particularly as it relates to pathological proliferation in the development of the vascular lesion. As such, inhibition of TNF-alpha pathways has been shown to decrease smooth muscle cell proliferation[11] with retrospective data suggesting clinical benefit via this mechanism.[16] As such, timely initiation of TNF-alpha inhibitor therapy may modulate the intermediate stage of disease.

Finally, in the chronic stage there is further thickening of tunica intima, media, and adventitia along with neovascularization where fibrosis replaces the elastic tissue resulting in luminal narrowing. At this stage, the opportunity for reversibility of vessel pathology is decreased. In this setting, immunomodulators play a role in preventing relapses and new lesions.

Vessel pathology of TA can be varied. Rapid disease progression may lead to aneurysm formation secondary to inadequate fibrosis. Aneurysms may also form secondary to inflammation mediated mural stress. This commonly affects the aorta, subclavian, renal, carotid, and vertebral arteries.[1] A retrospective Italian study on 104 patients showed stenosis as the most common lesion, seen in 93% of TA patients, followed by occlusion seen in over half, dilatation in 16%, and aneurysms in 7% of patients.[22]

Aneurysms are common and clinically significant in the aortic root, where they can cause valvular regurgitation. Hypertension is most often caused by renal artery stenosis, but can also be associated with suprarenal aortic stenosis or a chronically damaged, rigid aorta.

The diagnosis of TA involves combination of clinical, laboratory and imaging features. Various validated criteria have been developed over the years which can help diagnose TA with 91% sensitivity and 98% specificity [Table 1].[2,18]

Imaging modalities such as conventional angiography, MRI, MRA, CT angiography, or ultrasonography can be used in the diagnosis each having advantages and disadvantages. One of the earliest abnormalities in TA is increased vessel wall thickness which can be detected with ultrasonography. Conventional angiography is the gold standard given its sensitivity for detecting aneurysms and local areas of stenosis. The common carotid and proximal subclavian arteries are assessed using non-invasive color duplex high-resolution ultrasound.[18] Another method of visualizing inflammation is delayed gadolinium enhanced MRI, in which TA patients will exhibit hyper enhancement in their aortic walls, particularly in the early phase. In recent years, Gadolinium and Iodine enhanced MRA or CTA have become popular modalities both due to their non-invasiveness and for their ability to visualize the entire aorta and its branches. 18F-fluorodeoxyglucose positron emission tomography (FDG PET) scans are highly sensitive for vascular inflammation. Areas of increased inflammation will show increased FDG uptake. In TA patients' post-treatment, decreased FDG uptake is often detected.[14]

Both medical and surgical modalities play an important role in disease management [Table 2]. Though corticosteroids remain mainstay, newer immunosuppressant medications have shown promise. Prednisone is typically prescribed at 0.5-1 mg/kg/day for 1-3 months, followed by a slow taper. This therapy allows for 67% remission, but up to 50% treated individuals will relapse – most often when daily dose of oral corticosteroid is under 20 mg. Often, relapses are treated with either increasing corticosteroid dose or the addition of a corticosteroid sparing immunosuppressant

Table 1: Diagnostic criteria for Takayasu's arteritis

American College of Rheumatology criteria need at least 3 out of the following 6 features.	Pediatric Rheumatology International Trials Organization
• Age < 40 years; • Claudication of extremities; • Decreased upper extremity pulse, • Difference of at least 10 mmHg in systolic BP measurement between 2 arms; • Angiographic stenosis or occlusion of aorta and its major branches; • Bruit heard over major blood vessels.	Mandatory criteria: Angiographic abnormalities of the aorta or its main branches and pulmonary arteries showing aneurysm/ dilatation with one of the five minor criteria: • Pulse deficit or claudication • Four limbs BP discrepancy • Bruits • Hypertension • Acute phase reactant

Table 2: Disease modifying drugs in Takayasu's arteritis*

Prednisone (0.5–1 mg/kg/day for 1–3 months) followed by slow taper with or without steroid sparing agents.
Methotrexate (up to 20 mg/week)
Azathioprine 2 mg/kg/day
Cyclophosphamide 2 mg/kg/day
Mycophenolate mofetil 2 g/day
Anti-TNF therapy(Infliximab, Etanercept)
Intereukin-6 receptor inhibitor (Tocilizumab)

*Common clinical practice is to start with Glucocorticoids and add steroid sparing agents; steroid later is reduced (or stopped) to minimal possible dose to maintain the remission phase.

Table: 3 Key points

- Usually occurs in young (<40 years) and more common in women.
- Can present as acute stroke in the young.
- Idiopathic chronic pan arteritis with predilection for aorta and its major branches.
- Pathology is sometimes reversible if treatment is initiated early.
- At least 6 months of clinical and biochemical stability before it is called "sustained remission".
- Steroids play an important role.
- Newer immunosuppressants have helped in the long-term outlook of this disease and in avoiding long-term effects of steroids.
- Long-term follow up is mandatory as relapse is very common.

such as methotrexate.

There have been several studies looking at various immunosuppressants such as Cyclophosphamide, methotrexate, mycophenolate mofetil, and Azathioprine. However, no cytotoxic drug has been shown to have superior efficacy; thus treatment choice depends on weighing each patient's ability to tolerate side effect profiles of particular drugs.[9]

Recently anti-TNF therapy and Intereukin-6 receptor inhibitor (Tocilizumab) have been tried especially in patient refractory to standard therapy. Following treatment with an anti-TNF agent steroid-free remission was seen. In one study, patients treated with anti-TNF therapy for 28 months resulted in prednisone-free remission in 60% patients with 28% patients achieving remission with daily prednisone therapy <10 mg/day.[16]

Early surgical intervention in conjunction with institution of appropriate immunosuppressive therapy is key in the management. However, if inflammation is not in remission outcomes maybe less favorable.[14] Traditionally, hemodynamically significant areas of stenosis and occlusion have been treated surgically with either revascularization or angioplasty. The surgical intervention is advised in cases of cardiac ischemia with coronary artery involvement, moderate to severe aortic regurgitation, cerebrovascular ischemia with coronary artery involvement, ADL limiting extremity claudication, and hypertension with stenosis of the renal artery.[9] Surgical bypass may be achieved in endovascular or open formats with the use of synthetic or autologous grafts.[6] If surgical intervention is well tolerated, 20 year survival rates are73.5%. However, long-term surgical follow- up is necessary due to the long-term complication of anastomotic aneurysm in 13.8% patients.[15] Percutaneous transluminal renal angioplasty (PTRA) has been shown to have less favorable outcomes than bypass surgery. In 8 months post surgery, researchers found restenosis of 21% after PTRA.[19,20] Comparing PTRA to bypass, another study found that patients in the bypass group experienced 35% restenosis over 168 months, while patients in the angioplasty group experienced 57% restenosis over 72 months.[12] Bypass graft surgery for the thoracic aortic arch critical stenosis has been found to be a protective factor against future stroke and experts recommend that critical stenosis of the thoracic aortic arch be corrected despite presence of adequate collateral blood flow.[5]

Various clinical and diagnostic factors will be taken into consideration while monitoring the disease activity.[3,10,13] The Commonly used criteria includes: 1) presence of clinical features and elevated acute phase reactants not attributable to another medical condition, 2) clinical features suggesting vascular insufficiency, 3) new vascular lesion(s) in previously unaffected vascular territories, and 4) biopsy of affected vessels showing inflammatory changes. A remission of at least 6 months is required to consider it sustained. Also, multi-systemic clinical assessment tools, like "Disease extent index for takayasu's arteritis" (DEI.Tak) and "Indian takayasu's arteritis score" (ITAS), assist in monitoring disease activity.

The sequelae of TA which includes aortic regurgitation, Cardiomyopathy, left ventricular systolic dysfunction, uncontrolled HTN, renal failure, myocarditis, and central nervous manifestations are the principal causes of severe morbidity and mortality. Mortality ranges from 3%-35% at 5 years follow-up depending on the severity of the disease, patient demographics, and geographical distribution.

In summary, See Table 3 Takayasu's arteritis is a chronic pan-arterirtis, often presenting with an acute neurological problem. A high degree of suspicion is required to diagnose this condition in young (<40 years) patients presenting with ischemic stroke and pulse asymmetry. The early diagnosis and initiation of therapy using new diagnostic criteria may potentially reverse vessel pathology. Emerging immunosuppression therapy is showing great promise and is helpful in steroid sparing. Endovascular therapy and other surgical options have a role but caution must be exercised as outcomes are less favorable in patients with active disease.

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