



## Is Pre-Pulseless Takayasu's Arteritis Always Treatable?

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### Abstract

TA is a rare large vessel vasculitis of unknown etiology, which is difficult to treat. Its natural history is marked by the absence of response to most therapies. The nonspecific nature of the symptoms at presentation and the absence of physical signs result in delayed diagnosis so that many cases progress to vessel stenosis before recognition. It is a common belief that early diagnosis, now possible with the development of PET scans, is imperative to limit inflammation before damage occurs in the form of pulse loss. The unique findings in our case challenge this common belief. We present a case diagnosed before any vascular deformation whose disease progressed despite aggressive therapy. TA is a rare large vessel vasculitis of unknown etiology; its natural history is marked by the absence of response to most therapies.

### Introduction

The management of TA remains a complex clinical challenge from the onset. The nonspecific nature of the symptoms at presentation and the absence of physical signs result in delayed diagnosis in at least 20% of cases [1]. Once vessel stenosis occurs, abnormal hemodynamics from altered blood flow lead to further damage to the vessel wall. Damage begets more damage, which can eventually culminate in complete occlusion of the vessel due to fibrosis, intimal plaques and thrombi. A large majority of patients continue to remain minimally symptomatic; they manifest only when the precarious blood supply from collateral vessels is compromised due to dehydration or other factors. It is commonly believed that early diagnosis is essential to allow therapy to limit inflammation before damage occurs in the form of pulse loss [2]. The unique findings in our case challenge the concept that this is always successful.

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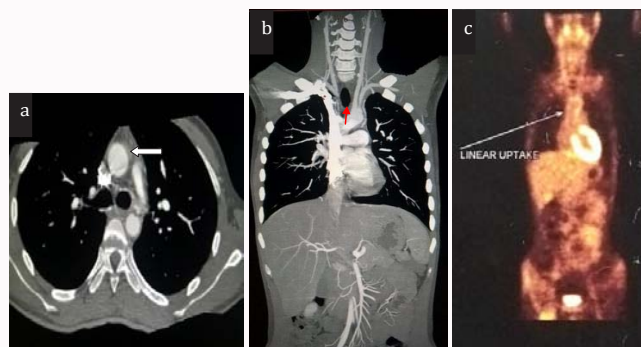
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### Case Presentation

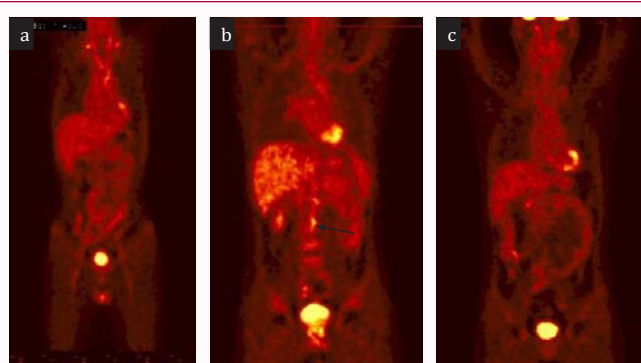
An 18-year-old boy presented to the Clinical Immunology department with complaints of high-grade fever for past 2 months plus 14 kg weight loss. He had undergone extensive workup elsewhere for pyrexia of unknown origin (PUO) without much avail. His investigations consistently showed raised acute phase reactants (APR), with normal hemogram and serum chemistry. Cultures and autoantibody screen were non-contributory. Meanwhile, he had been treated with various antibiotics without relief. He also complained of new onset precordial pain, which was constricting in nature, brought on by exertion and relieved with NSAIDs. Computerized Tomography (CT) of the chest, embarked upon to find the causative focus of PUO, revealed thickening of the wall of the arch and ascending aorta (Figure 1). This raised suspicion of an underlying large vessel vasculitis. FDG PET scan confirmed diffuse uptake in the arch and ascending aorta, along with bilateral common carotid arteries, more so on the left side (Figure 1c). The uptake was higher than the liver, and amounted to SUV<sub>max</sub> 2.3 in the ascending aorta. The absence of any mass or peri-aortic tissue essentially ruled out IgG4 related disease.

Cardiovascular examination was reviewed again but was found to be normal. All peripheral pulses were felt and no bruit could be appreciated. The boy, now three months into the illness, was labeled with a diagnosis of 'pre-pulseless' Takayasu's arteritis and initiated on 1 mg/kg Prednisolone plus Azathioprine, to which the fever responded. He was also found to have hypertension at this time, and ECG as well as Echocardiography bore the stigmata of this in the form of left ventricular hypertrophy. Doppler scan of the renal arteries was normal.

Despite the initial good response, the systemic symptoms resurfaced over the next month, and the patient developed a bruit in the left Subclavian Artery (SCA). CT angiography showed new involvement of the left SCA, seen as thickening of the vessel wall at the ostium. It also confirmed



**Figure 1:** (a) CT Angiogram at 3 months of symptoms: Axial image shows diffuse circumferential wall thickening of the arch of aorta (thick white arrow). (b) Coronal image at the same time shows diffuse circumferential wall thickening of bilateral common carotid artery (red arrow) without significant luminal narrowing. (c)  $^{18}\text{F}$ FDG PET image at 3 months of symptom onset shows circumferential and linear uptake (thin white arrow) in these areas suggestive of inflammatory process involving the large vessel walls possibly large vessel vasculitis; CT- Computerized tomography, FDG PET- fluoro-D-glucose positron emission tomography.



**Figure 2:** (a)  $^{18}\text{F}$ FDG PET scan one year later, after Cyclophosphamide and Methotrexate trial shows persistent uptake in the arch, descending aorta and bilateral common carotid artery (thick white arrow) (b) New focus of uptake is seen in descending abdominal aorta (black arrow) after eight months of monthly Tocilizumab infusion (c) No uptake is seen in subsequent scan done after four years of the illness (suggesting lack of active disease); FDG PET- fluoro-D-glucose positron emission tomography.

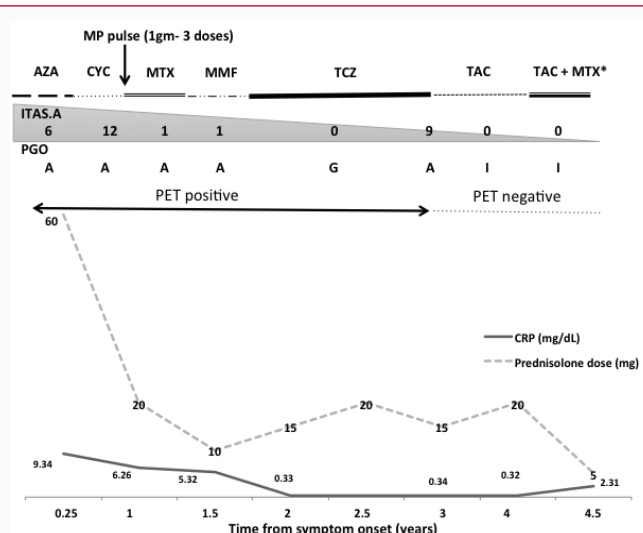
the previous findings of isolated wall thickening at the ascending aorta and the arch, plus the right Common Carotid Artery (CCA) just distal to the origin.

Cyclophosphamide monthly infusions were then initiated but were halted after three doses when the patient developed low-grade fever with pleural thickening, which was initially attributed to tuberculosis. When all workup was negative, the fever was deemed to be due to Takayasu arteritis activity and he was pulsed with three doses of 1gram methyl prednisolone. This time the patient chose to take Methotrexate (MTX) instead, although fever persisted for three months despite full dose (25 mg/week) of MTX and split prednisolone dosing (15 and 5 mg respectively). APRs were elevated and repeat PET scan showed uptake as before (Figure 2a).

He was subsequently treated with Mycophenolate Mofetil 3 grams per day, plus prednisolone 20 mg per day, for 3 months before it was stopped due to diarrhoea and rash. He was subsequently given tocilizumab monthly infusions (8 mg/kg) for 8 months, to which he responded briefly, with negative APRs for the first time in the course of his illness. At that time, however, PET scan continued to show disease activity. This follow up PET scan revealed new focus of uptake in the



**Figure 3:** MR angiogram after three years into the disease, shows moderate narrowing of the left CCA (white arrow) and mild narrowing of right CCA & left SCA (white arrowhead), suggestive of damage; MR- Magnetic resonance, CCA- common carotid artery, SCA- subclavian artery.



**Figure 4:** Timeline of events.

\* ITAS A=Indian Takayasu's Arteritis Activity Score, PGO- Physician's Global Assessment (A= Active, G=Grumbling, I-Inactive), AZA= Azathioprine, CYC= Cyclophosphamide, MP= Methyl Prednisolone, MTX= Methotrexate, MMF= Mycophenolate Mofetil, TCZ = Tocilizumab, TAC= Tacrolimus, CRP= C-reactive protein.

descending aorta as well ( $\text{SUV}_{\text{max}}$  4.1), although previous foci had become inactive (Figure 2b), and soon thereafter his clinical disease resurfaced despite ongoing therapy. He had accrued damage in the form of left subclavian stenosis and symptoms of vertebro-basilar insufficiency. He also sustained a Transient Ischemic Attack (TIA) due to hypoperfusion in the left MCA territory from his underlying carotid disease. He was then switched to tacrolimus (TAC) (1 mg/day) and prednisolone (15 mg per day) with clinical benefit. The last PET scan while on TAC was negative (Figure 2c), even though stenosis in the carotids has been progressive on follow up CTA. He has bilateral CCA and left SCA long segment stenosis (5 and 7 cm long respectively) along with intramural plaques visualised in the entire upper aorta and descending aorta close to the renal arteries on MRI (Figure 3).

After 6 months of tacrolimus, he again had precordial pain and

accelerated hypertension. He did not have fever this time, although CRP was elevated but PET scan continued to be negative. Trough serum Tacrolimus levels were normal so MTX was added, but the symptoms subsided within a month's time.

## Discussion

The need for early diagnosis of Takayasu's arteritis is widely accepted among rheumatologists and cardiologists alike. Novel imaging methods such as  $^{18}\text{F}$ -FDG-PET, Doppler US, or MR angiography can identify early vessel wall inflammation before stenosis occurs. The era of FDG PET in the workup of PUO has improved case detection rates [2]. Its impact on the survival rates in TA are not clear [3] but it is believed that early diagnosis and institution of treatment can prevent damage accrual. Our case highlights the shortcoming of the present immunosuppressive therapy (including biologics such as Tocilizumab), in preventing vascular obstruction even if instituted at the pre-pulseless stage.

This case defines clearly the natural history of the disease. The patient manifested with systemic symptoms with elevated APRs plus positive vessel inflammation on PET and only later went on to vessel stenosis with claudication. This highlights the sensitivity of FDG PET in early diagnosis, before changes are appreciated on angiography.

Interestingly, the patient developed progressive disease despite initiation of therapy - including steroids, immunosuppressants and biologics - early in the course (Figure 4). The failure to respond to multiple therapies is even more surprising. The patient had high disease activity as scored on ITAS.A at symptoms onset, though scores were much lower on follow up as persistent disease is not recorded PET findings often remain positive even after initiation of treatment [4]. The lack of a comparative clinical gold standard of disease activity makes it difficult to comment on the utility of PET in the follow up of patients [2]. However, persistent PET positivity while on treatment is consistent with findings of persistent inflammation in post mortem studies on patients without clinical symptoms of activity [5]. It is known that Th17 responses dominate in the active phase of the disease before autonomous activity from vascular smooth muscle cells is triggered [6]. It is not very clear, though, as to how late in the disease pathogenesis, these changes occur.

The findings from this case may lead us to believe that the autonomous activity is triggered as early as 3 months into the disease. This indicates that we need to think about disease progression as a much more complex process than current dogma about the benefits of early diagnosis suggests. The role of immunosuppression in altering the disease course remains dubious at best. Restenosis after intervention is the best model for treatment efficacy in Takayasu's. It has been clearly shown that restenosis rates are lower in cases that undergo intervention only after receiving immuno-suppressants [7]. However attempts to control systemic as well as vascular inflammation in this patient failed miserably at all times.

The only time our patient felt clinically better was while on Tocilizumab, but never-the-less vascular progression continued. The patient did stabilize eventually on Tacrolimus (clinically and on PET scan), which suggests that T cell responses are important in the pathogenesis. TA is a granulomatous inflammatory disease and T cells are important for granuloma formation; hence there is rationale for using T-cell directed therapies in TA. However, the reported failure of other T cell targeted therapies like abatacept in TA may lead us to think otherwise [8]. Failure of Cyclosporine in Takayasu's has been

reported in previous studies, though two Japanese cases benefitted with Tacrolimus [9-11]. Although both TAC and cyclosporine antagonize calcineurin and cytokine production, the former in addition inhibits the expression of high affinity IL-7 receptor on immune cells. It also prevents IL-2 mediated IL-5 production by CD4+T cells [12]. Thus it is more efficacious at reducing IL-2 producing T cells in renal transplant patients. It is plausible to suggest that such additional immunosuppressive actions of Tacrolimus have a role to play in as yet undiscovered pathogenic pathways of this intriguing disease.

Fever and chest pain in the last episode subsided within a month of adding MTX to TAC, when drug effectiveness was not expected to take over. Similarly, in clinical practice, it is not unusual to find patients who present with stenosis without ever having had systemic symptoms of the pre-pulseless phase. This could possibly suggest that intermittent inflammation in TA starts and ceases on its own, consequent to factors that are still unknown. The course of TA is highly variable from being a monophasic inflammatory illness in some but a progressive obstructive vascular lesion at one or more sites in others. Our case illustrates the substantial problems in controlling such progressive disease despite early diagnosis with initiation of active therapy in the pre-pulseless phase.

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