Takayasu's Arteritis as a Rare Cause of Group 4 Pulmonary Hypertension

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Takayasu's arteritis (TA) is chronic granulomatous pan-arteritis of the great vessels that affects large arteries, preferentially affecting the aorta, its main branches, and the pulmonary arteries.[1-3] It is a rare idiopathic systemic inflammatory disease.[4] TA usually affects women <40 years of age, with a mean age at diagnosis between 25 and 30 years old,with female gender predominance reported between 75%, and 97% of cases.[1,5] In the United States (US), the estimated incidence is 2-3 cases per million per year.[6] TA causes inflammatory lesions characterized by thickening of the arterial wall, leading to arterial lumen remodeling after proliferation of myofibroblasts.[4-7] Inflammation has been observed in the media and adventitia as well, with the presence of mononuclear cells and giant cells during active inflammation, progressing to fibrosis, and dense scarring of the arterial wall leading to stenosis.

In contrast, destruction of the elastic lamina, and the media can lead to aneurysm formation.[1,8,9] Symptoms vary from non−specific constitutional symptoms to those attributable to arterial stenosis, aneurysm, and occlusion and depend on the vascular bed being affected, severity, and

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duration of vascular involvement. The initial phases of TA present with non−specific symptoms, such as fever, fatigue, and chest pain.[10,11] The active phase can remit spontaneously in about 3 months. It can progress insidiously over months to years toward the chronic phase when vascular involvement is evident. The late occlusive phase is characterized by inflammatory and obliterative changes typically found in the aorta and its branches.

The incidence of pulmonary arteritis (PA) in patients with TA varies significantly between studies.[2,3] According to autopsy reports, PA occurs in 20%-56% of patients with TA.[12] An incidence of PA between 33% and 86% has been reported.[13,14] A Chinese study found that PA occurred in up to 6.3% of TA patients.[2] Mechanical obstruction of the pulmonary circulation is the primary mechanism of which pulmonary hypertension (PH) developes in PA associated with TA.[13]

Here in, we report a case of TA with severe involvement of the pulmonary vasculature and its main branches, resulting in significant PH.

Case Description

A 45-year-old female with a history of systemic hypertension and diabetes mellitus was admitted to the Rheumatology in-patient service in 2015 due to dyspnea on medium exertion, non−productive cough and hemoptysis (100 mL/day). Due to a decrease in the intensity of the bilateral carotid pulse and the absence of a right radial pulse, a CT angiography of the chest was performed, which revealed diffuse thickening of the aorta with stenosis of the great vessels of the neck, and chest. Magnetic resonance imaging (MRI) was also performed, reporting vasculitis of the great vessels (TA), with significant involvement of the aorta from its origin to the descending thoracic segment (AP) and its branches (Fig 1A-B). The patient was discharged with prednisone 50 mg every 24 hours.

Follow-up was lost for 5 years. In February 2021, the patient was hospitalized due to syncope with severe head trauma and seizures. In March 2021, progressively worse dyspnea was reported with an increase in oxygenation requirements, and mild edema in the pelvic limbs, for which hospitalization was decided. On physical examination, the patient had obesity, a round face, hirsutism, short and wide neck, carotid pulses decreased in amplitude bilaterally, and absence of a right radial pulse. The chest had decreased respiratory sounds without crackles. Rhythmic heart with increased heart sounds, a high-pitched grade II/VI holosystolic murmur and regurgitant timbre was heard in the tricuspid focus, which increased with the Rivero-Carvallo manoeuvre. Abdomen with increased

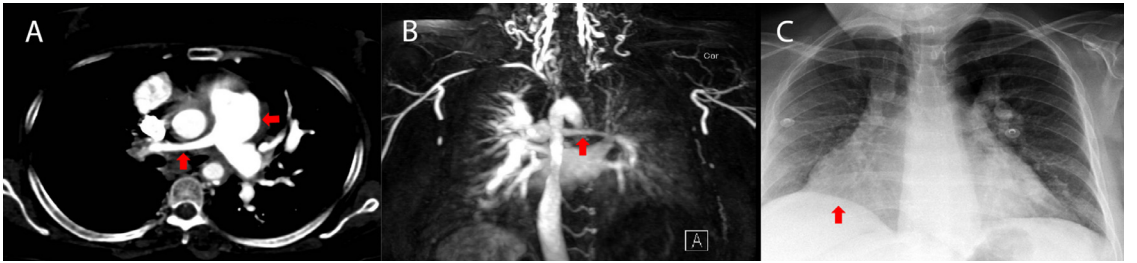


FIG 1. (A) Chest CT angiography with right main pulmonary artery stenosis and dilation of the pulmonary artery trunk (red arrows). (B) The right pulmonary artery branch is thinned, and the left pulmonary arterial tree alternates between areas of stenosis with posterior dilation of the main branches (red arrow). (C) Cardiomegaly with a prominent right heart profile (red arrow) (Color version of the figure is available online.)

volume due to adipose panicle. Bilateral lower extremities with diminished pulses and bimalleolar edema.

Laboratories were remarkable for an hemoglobin (Hb) 10.2 g/dL, hematocrit 32.4%, platelets 249 × 10e3/uL. procalcitonin 0.19, creatinine 0.41 mg/dL, lactic dehydrogenase 285u/L, erythrocyte sedimentation rate (ESR) 93 mm/hr, C-reactive protein (CRP) 428 mg/L, D-dimer (DD) 2349 ug/L. brain natriuretic peptide (BNP) 175.2 pg/mL. Arterial blood gases with PaO2 54.7mm / Hg, SO2 87.1%, PaCO2 32.4 mm Hg. 12-lead surface electrocardiogram showed sinus tachycardia, with data of right atrial enlargement, without acute ischemic data or lesion. Chest radiograph showed cardiomegaly with prominend right sided heart enlargement, and a prominent left pulmonary artery (Fig 1C).

Transthoracic echocardiogram reported free wall of the right ventricle (RV) 8 mm, tricuspid annulus systolic excursion (TAPSE) 24cm, RV fractional area change 41%, dilated right atrium (RA) with an indexed volume of 38 mL/m^2, a maximum speed of tricuspid regurgitation of 470 cm/sec, estimated pulmonary artery systolic pressure (PASP) of 108 mm Hg. Left ventricular function was reported normal. Lung perfusion scintigraphy showed a perfusion defect of the right upper lobe (Fig 2A).

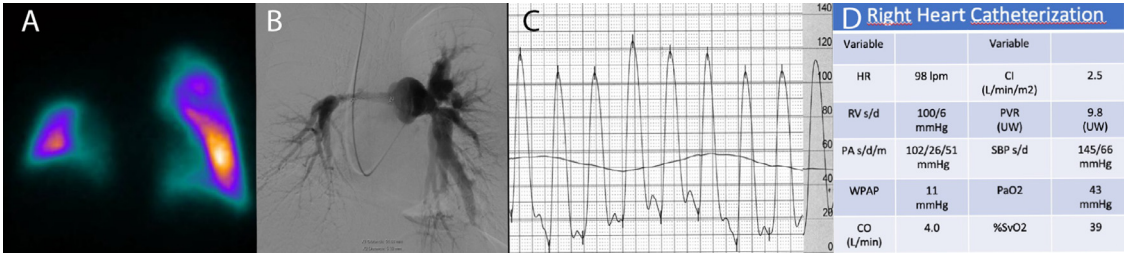
Right heart catheterization (RHC) showed right atrial pressure (RAP) of 7 mm Hg, mean pulmonary artery pressure (mPAP) 51 mm Hg, mean pulmonary artery occlusion pressure (mPAOP) of 11 mm Hg, pulmonary vascular resistance (PVR) 9.8 Wood Units (WU), concluding severe precapillary PH (Fig 2C-D).

Based on the findings of CT angiography and MRI of the chest (Fig. 1A-B), which showed a decrease in the calibre of the right pulmonary artery (6mm), it was decided to perform digital subtraction pulmonary angiography (Fig 2B), revealing a significant stenosis 5.1 cm in length with a diameter <5.3 mm (at the distal level) and a diameter > 11.1 mm (at the proximal level).

Discussion

TA is the third commonest vasculitis in childhood worldwide but is relatively uncommon in the US. In 1990, the Japanese government added TA to the list of intractable diseases, with 5000 cases added over the subsequent decade.[1] A study in Minnesota found the incidence to be 2.6 cases per million each year.[14] The true extent of the disease in the western countries is not well known.

The etiology of TA remains unknown; however Tuberculosis infection was proposed as a predisposing factor. Patients with TA were found to



D Right Heart Catheterization

Variable		Variable	
HR	98 lpm	CI (L/min/m2)	2.5
RV s/d	100/6 mmHg	PVR (UW)	9.8 (UW)
PA s/d/m	102/26/51 mmHg	SBP s/d	145/66 mmHg
WPAP	11 mmHg	PaO2	43 mmHg
CO (L/min)	4.0	%SvO2	39

FIG 2. (A) Perfusion lung scan showing right upper lobe perfusion defects. (B) Pulmonary angiography with the absence of pulmonary vasculature in the right upper lobe. (C) Righ heart catheterization tracing of pulmonary artery pressure. (D) Cardiopulmonary hemodynamic data during right heart catheterization.

have higher immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA) titers against the M tuberculosis extract than control patients.[15] A recent study reported CD3+ T cells and IgG antibodies reactive to circulating antimycobacterial heat shock protein 65 (mHSP65) antibodies and its human homologue, hHSP60. However, these data appear to be in contradiction with other observations. In a series of 17 children, none had active tubercular lesions.[16] Cutaneous hypersensitivity to tubercular protein was seen in only 35.2% of cases. Various other mechanisms such as autoimmunity and genetic predisposition have been proposed. Both cellular and humoral factors are probably involved. Autoimmunity appears to be the most plausible mechanism. Defective T lymphocyte regulation and anti−endothelial, anticardiolipin, and antiaorta antibodies have been suggested to play a role in the aetiology of the disease.[17] The precise nature of the antigens needs to be identified.

The American College of Rheumatology (ACR) included arteriogram abnormalities in its diagnostic criteria of TA. Angiography is the gold standard for evaluating vascular lesions; in particular; panangiography allows a correct assessment of the extension of the disease, which correlates with its severity. Some authors underline the high incidence of coronary involvement in Takayasu's arteritis (15%) and recommend performing a coronagraphic exam. Assessment of pulmonary vasculature by angiography is not universally recommended for patients with PH symptoms.[18] However, non−invasive techniques (eg lung perfusion scan) have demonstrated lung perfusion abnormalities in about two-thirds of asymptomatic patients.[19] Angiography allows a topographic classification that correlates anatomical involvement, clinical manifestations, and prognosis. However, angiography is an invasive method; it cannot differentiate active from burned-out lesions and exposes the patients to risks connected with radiation and the contrast medium. In the early phase of Takayasu's arteritis, the thickening of the vascular wall of the aorta or pulmonary artery can be detected by CT or MRI. CT, combined with injection of contrast medium (the so-called angio-CT), allows studying wall inflammation. However, it has a low spatial resolution, and cannot evaluate medium-size arteries.[19]

A diagnosis of TA requires that at least 3 of 6 criteria be met as outlined by the ACR (Table 1). The presence of 3 or more of these 6 criteria demonstrates a sensitivity of 90.5% and a specificity of 97.8%.[20] Our patients fulfilled ACR criteria, considering she was a female; her age at presentation was <40 years old and had decreased or absent pulses in various places. The laboratory criteria showing active inflammation with elevated ESR and CRP, as well as her characteristic CT, MRI, and

TABLE 1. The *American college of rheumatology* 1990 criteria for the diagnosis of Takayasu's arteritis[17]

Criterion	Definition
• Age at disease onset less than 40 y.	Development of symptoms or findings related to Takayasu's arteritis at age.
• Claudication of limbs.	Development and worsening of fatigue and discomfort in muscles of 1 or more limbs while in use, especially the arms.
• Decreased brachial arterial pulse.	Decreased pulsation of one or both brachial arteries.
• Blood pressure difference of greater than ten mmHg.	Difference of more than ten mmHg in systolic blood pressure between arms.
• Bruit over subclavian arteries or aorta.	Bruits audible on auscultation over 1 or both subclavian arteries and/or abdominal aorta.
• Arteriographic abnormalities	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal limbs are not caused by arteriosclerosis, fibromuscular dysplasia, or similar causes, changes usually focal or focal segmental.

conventional pulmonary angiographic findings. The prognosis of the disease is affected by the clinical classification[21] (Table 2). The 5-year survival rate from diagnosis is 100% for those in groups 1 and 2a and 70%-80% for those in groups 2b and 3. The leading cause of death is congestive heart failure due to hypertension or severe aortic regurgitation.[22]

Pulmonary Vascular Involvement in Takayasu Arteritis and Associated PH

Chronic obstruction of pulmonary arteries can be due to various diseases, including chronic thromboembolic disease, fibrosing mediastinitis,

TABLE 2. Clinical classification of Takayasu's disease as described by Ishikawa[20]

Group	Clinical features
Group 1	Uncomplicated disease with or without the involvement of the pulmonary arteries.
Group 2a	Mild to moderate disease with one of the following complications: retinopathy; secondary hypertension; aortic regurgitation; aortic or arterial aneurysm.
Group 2b	Severe disease with one of the following complications: retinopathy; secondary hypertension; aortic regurgitation; aortic or arterial aneurysm.
Group 3	Two or more complications present

or neoplasia. Large vessel vasculitis like TA is an unusual cause of pulmonary artery obstruction and can be challenging to diagnose.

The precise diagnosis of pulmonary arterial involvement almost always depends on imaging modalities since clinical manifestations and laboratory test results are often non−specific. Typical manifestations of pulmonary arterial involvement on CT include thickening and enhancing the arterial wall in the early stages of the disease and luminal stenosis or occlusion in chronic stages. Although pulmonary arterial involvement is common, most lesions are found in segmental or subsegmental arteries, and primary PA involvement represents only 5% of PA stenoses.[7] PH is an essential complication in the course of PA associated with TA.[13] PH occurs in 12%-13% of patients with TA and 42.2% of patients with PA.[2,23] PH leads to right heart dysfunction, which seriously affects the prognosis of patients with TA. PH is a late manifestation of PA that indicates a weaker response to treatment and a poor prognosis.[2,13]

According to Toledano and colleagues, the mortality rate was 20.5% in patients with intra-abdominal hypertension and 33.3% among patients with PH.[13] It is well known that right heart catheterization (RHC) is the gold standard for diagnosing PH, although a transthoracic echocardiogram should be performed initially when PH is suspected.[23] There are many options for treating pulmonary arteritis, such as corticosteroids, percutaneous transluminal pulmonary balloon angioplasty (PTPA), and surgery.[24] The Il-6 receptor antagonist tocilizumab is a relatively effective drug for controlling pulmonary artery lesions.[5] PTPA and stenting have been described in patients with severe proximal pulmonary artery stenosis.[23,24] When the response to these treatment options is limited, adding drugs specified for PH may represent an attractive option. The existing literature on the treatment of PH in TA is limited to case series where, because it belongs to group 4 of the WHO PH classification, riociguat could be an option. However, bosentan, and sildenafil are options described in the literature on patients with PH and TA.[23,24] PTPA currently represents a relatively safe and effective endovascular therapeutic technique for symptomatic chronic thromboembolic pulmonary hypertension with acceptable mortality. In a 29-month follow-up study, Dong and colleagues observed that both subjective symptoms and sustained improved pulmonary hemodynamics after PTPA in patients with pulmonary arterial stenoses in TA.[25] In our patient, due to a 5 cm stenosis of the right pulmonary artery and the high risk of pulmonary artery rupture and complications, we considered that she was not an ideal candidate for PTPA.[8]

Conclusion

The investigation and management of TA can prove challenging. The initial symptoms and signs are non−specific, and a high index of suspicion is needed if the diagnosis is to be made. The clinical manifestations of TA, particularly in the clinical scenario of pulmonary vascular involvement involving are non−specific, making this condition subject to misdiagnosis and significant delay in its diagnosis. PH often complicates TA and is associated with poor prognosis. Early clinical features such as repeated fever, chest pain, hemoptysis with or without dyspnea, and recurrence of subpleural wedge-shaped shadows on chest CT should arouse suspicion for PH in patients with TA and prompt further vascular imaging investigations. This may allow TA with pulmonary vascular involvement to be diagnosed early, before the occurrence of irreversible stenotic, and fibrotic vascular lesions.

Author Contributions

Every single coauthor designed, performed research, helped in writing, crafting, editing, and critically reviewing key elements of the manuscript. All coauthors read and approved the final version of the manuscript.

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