CASE REPORT

Takayasu's arteritis and primary antiphospholipid syndrome presenting as hypertensive urgency

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SUMMARY

A 33-year-old Caucasian man was admitted to the hospital with chest pain and hypertensive urgency. Physical examination revealed widespread arterial bruits and marked difference in blood pressure between the upper limbs. Vascular imaging showed widespread narrowing in multiple vascular territories. He met the established American College of Rheumatology criteria for Takayasu's arteritis. His resistant hypertension was considered to be a consequence of bilateral renal artery stenosis and he subsequently underwent sequential stenting of his renal arteries leading to improvement in blood pressure and reduction in the number of antihypertensive medications. Subsequent imaging revealed progression of aortic thrombus in the setting of an elevated erythrocyte sedimentation rate, and persistently elevated antiphospholipid antibodies fulfilling diagnostic criteria for primary antiphospholipid syndrome, requiring initiation of immunosuppression and anticoagulation.

BACKGROUND

This case is a presentation of Takayasu's arteritis and primary antiphospholipid syndrome as hypertensive urgency refractory to medical management in a young Caucasian man with widespread stenoses in multiple vascular territories including bilateral renal stenoses.

CASE PRESENTATION

We present a case of a 33-year-old Caucasian man who sought medical attention following an injury to his right hand, and who was incidentally found to have hypertension with a documented blood pressure of 210/110 mm Hg. Follow-up with his family physician was recommended but he was not started on pharmacotherapy. Two weeks later, he had left arm numbness while driving and felt generally unwell, so he went to the emergency department, where it was noted that his blood pressure was 200/110 mm Hg; he was prescribed labetalol, an α/β -blocker. There was an improvement in his symptoms and the patient stopped taking the medications. He was seen in the emergency room 2 weeks later with chest pain with no associated troponin release. His blood pressure was 220/120 mm Hg, for which he was hospitalised and initiated on hydralazine.

Telmisartan, amlodipine, clonidine and spironolactone were sequentially introduced. Despite maximal therapeutic dosage of the medications, his blood pressure failed to improve and there was a persistent difference of 15–20 mm Hg between

both arms, with average readings in the range of 150–180 mm Hg systolic. He self-reported a 16-pack-year history of smoking and there was paternal history of hypertension. He worked as a farm labourer and was accustomed to carrying weights of up to 100 pounds for 200 feet with no symptoms of either upper or lower limb claudication. He denied any symptoms of Raynaud's, visual impairment, syncopal episodes, vertigo and abdominal pain after eating. There was no prior history of arthralgias, myalgias, weight loss, mouth ulcers, night sweats and skin lesions consistent with erythema nodosum or pyoderma gangrenosum. On examination, there were bilateral subclavian, renal, iliac and femoral artery bruits. Owing to asymmetric upper limb blood pressures and arterial bruits, the patient underwent a CT scan of the aortic arch, which showed widespread narrowing in multiple vascular territories including coeliac, superior and inferior mesentery and bilateral renal artery stenosis. Despite no troponin release, chest pain was thought to be cardiac in nature, and cardiology was consulted. Transthoracic echocardiogram revealed no regional wall abnormalities, and it was their clinical opinion not to pursue cardiac catheterisation.

INVESTIGATIONS

In a young man, secondary causes of hypertension were investigated and the results were the following: 24 h urine for catecholamines was within the normal range. Thyroid-stimulating hormone was 1.38 mIU/L (normal 0.45–4.5 mIU/L). Plasma renin was 28 ng/L, and renin/aldosterone ratio was not calculated, as aldosterone levels were undetectable. The patient's lipid panel was normal, and his creatinine was 108 μ mol/L, consistent with his age and muscle mass. Inflammatory markers including rheumatoid factor, erythrocyte sedimentation rate and C reactive protein were, likewise, negative. Testing for antiphospholipid antibodies revealed elevated anticardiolipin IgG: 75 GPL/mL (0–22 GPL/mL) and positive dRVVT: 66 (24–42 s), and elevated Kaolin clotting time ratio was 1.4 (0.0–1.2), suggesting the presence of lupus anticoagulant. Antinuclear antibody was also weakly positive, with a titre of 1:80. Anti-double-stranded DNA was negative, and C3 and C4 were elevated at 2.11 g/L (0.90–1.80 g/L) and 0.45 g/L (0.10–0.40), respectively.

CT angiography revealed occlusion of infra-renal abdominal aorta, right and left common iliac arteries and left external iliac artery. In addition, there were occlusions at the origins of the coeliac axis,

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and superior and inferior mesenteric arteries, and presence of extensive collaterals supplying the bowel. The patient had one left and two right renal arteries with tight stenoses present at the origin of all three renal arteries. Subtle mural thickening with surrounding inflammatory change was also noted involving the aorta and several proximal large aortic branches (figure 1). Further CT imaging of the carotids and circle of Willis revealed ectasia of the ascending aorta and normal carotids, and severe stenosis of the right subclavian artery (figures 2 and 3). Imaging of the aortic arch revealed no stenosis of the three major vessels (figure 4). The CT findings were corroborated by subsequent angiography, and further note was made of extensive collateral vessel formation (figure 5).

DIFFERENTIAL DIAGNOSIS

The differential for patients with multiple large vessel stenoses includes atherosclerotic disease, Buerger's disease and mid-aortic stenosis, in addition to a large-vessel vasculitis such as Takayasu's.

Discussions with radiology regarding the appearance of the stenosis, as well as their distribution, suggested vasculitis as the most likely aetiology. Takayasu's arteritis is a large-vessel vasculitis that manifests with predominantly granulomatous lesions affecting the aorta and its major branches, and is the most common aetiology of aortitis. Based on the American College of Rheumatology classification criteria for Takayasu's arteritis, our patient fulfils four of six classification criteria for Takayasu's arteritis: (1) age at disease onset ≤ 40 years; (2) difference of at least 10 mm Hg in systolic blood pressure between the arms; (3)

bruit over one or both subclavian arteries, or over the abdominal aorta (4) arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or other causes.¹ Our patient did not meet the criteria for: claudication of the extremities and decreased pulsation of one or both brachial arteries. Three of six criteria have a combined sensitivity and specificity of 90.5%, and 97.8%, respectively, making Takayasu's arteritis the most likely cause of his stenotic lesions and secondary hypertension. Unlike giant cell arteritis, this form of arteritis is a chronic condition that mainly affects patients <50 years of age.² The occlusion of the patient's infrarenal aorta, including the iliac vessels could possibly suggest aortoiliac occlusive disease, or Leriche syndrome, a presentation of atherosclerosis usually accompanied by lower limb claudication. While smoking history is a risk factor for the development of Leriche syndrome, lack of atherosclerosis on radiological investigations, lack of claudication, younger age and a normal lipid panel suggest a different aetiology.³

The patient's elevated anticardiolipin antibodies, lack of clinical or laboratory evidence for systemic lupus erythematosus and his arterial lesions are suggestive of primary antiphospholipid syndrome (APS). APS is a prothrombotic autoimmune condition that affects both, the arterial and venous systems, and most commonly presents with deep venous thromboses or strokes.⁴ The diagnosis of primary APS is made with at least one of vascular thrombosis, or pregnancy morbidity, and one of elevated IgG or IgM anticardiolipins, presence of IgG or IgM to

Figure 1 (A) Sagittal reconstruction of abdominal aorta showing infra-renal aortic occlusion, and occlusion at the origins of the coeliac and superior mesenteric artery (arrow). (B, C and F) High-grade stenoses at the origins of both main renal arteries. (D, E and G) Axial CT images showing occlusions at the origins of the coeliac axis, and superior and inferior mesenteric arteries. (H) Axial CT image showing infra-renal aortic occlusion. (I) Occlusion of bilateral common iliac arteries. (J) Patent right and occluded left external iliac artery. (K) Bilateral patent common femoral arteries.

Figure 2 (A) and (B) CT reformatted images of right and left carotid arteries showing no stenoses. (C) Volume rendered image showing bilateral common carotid, internal and external carotid arteries. Arrow indicates high-grade stenosis at the origin of right subclavian artery.

glycoprotein II, or lupus anticoagulant activity on two separate occasions 12 weeks apart.⁵ Aortic involvement in primary APS is a rare presentation, and while a few cases in the literature report patients presenting with hypertension secondary to arterial thrombosis, these are different from the mural thickening and stenotic lesions of our patient.^{6–11} Thus, a diagnosis of primary APS is insufficient as a sole diagnosis.

Thromboangiitis obliterans, also called Buerger's disease, is a non-atherosclerotic, segmental, inflammatory disease that most commonly affects the small-sized to medium-sized arteries and veins of the extremities.¹² Patients are young smokers who present with distal extremity ischaemia, ischaemic digit ulcers or digit gangrene. However, given lack of claudication in either limb, Raynaud's, digital ischaemia and the extent of the patient's large vessel stenosis, we felt Buerger's disease was an unlikely explanation for this patient's condition.

An extremely rare condition that presents with systemic hypertension, aortic involvement and steno-occlusion of the renal and mesenteric arteries, is midaortic syndrome (MAS).¹³ This condition usually presents in the paediatric population, though there are reports in young adults.¹⁴ However, after discussion with the radiologist, the patient's aortic lesion was not considered morphologically similar to that of MAS. The stenosis of MAS is referred to as coarctation of the distal aorta; our patient, however, presented with mural thickening and occlusion of the distal aorta.¹⁴ Thus, though similar in presentation and

location, the appearance of the patient's lesion on vascular imaging is inconsistent with a diagnosis of MAS.

TREATMENT

Initial normal C reactive protein and erythrocyte sedimentation rate suggested lack of an active inflammatory response and therefore no immunosuppressive medications were offered. Lack of clinical symptoms of claudication and the presence of extensive collaterals suggested that lesions were longstanding and did not require invasive management. Data regarding the treatment of hypertension secondary to vascular involvement in Takayasu's arteritis is limited, though the literature shows that percutaneous transluminal angioplasty/endovascular stenting is the preferred treatment, especially for inactive significant stenotic lesions.¹⁵ Given the lack of response to multiple antihypertensive medications, and >90% stenosis of both renal arteries, angioplasty of the origin of the left main renal artery was performed with a 6 mm balloon. Postangioplasty, detection of a mild renal artery dissection was treated with the insertion of a 7 mm×3.9 cm Genesis stent. The readings prior to the stenting averaged between 150 and 170 mm Hg. One week post-stenting, the patient's average ambulatory blood pressure was 149/78 mm Hg. Unfortunately, a few weeks after left renal artery stenting, the control declined, and the patient electively underwent stenting of the right main renal artery (figure 6). The accessory right renal artery was not treated.

Figure 3 (A) Sagittal reformatted CT image and (B and C) volume rendered images demonstrating high-grade stenosis (arrow) at the origin of right subclavian artery. The severe degree of stenosis is better visualised on the volume rendered images. There is focal wall-thickening and luminal narrowing at the origin of right subclavian artery.

Figure 4 (A and B) CT reformatted images and (C) volume rendered image of the aortic arch demonstrating no evidence of stenosis at the origin of the three aortic arch branches.

The patient re-presented a few weeks later with right-sided flank pain, with repeat CT of his abdomen and pelvis showing extension of thrombus in his abdominal aorta in the context of repeat antiphospholipid antibodies revealing elevated anticardiolipin IgG at 80 GPL/mL (0–22 GPL/mL), dRVVT of 96 s (24–42 s) and an erythrocyte sedimentation rate of 44 mm/h (0–15 mm/h). A diagnosis of concurrent primary APS was made, and the patient was started on cyclophosphamide, prednisone and warfarin.

As the patient was asymptomatic with regard to his mesenteric and iliac stenosis, interventional treatment for these was not indicated, and the patient was recommended to follow-up

with vascular surgery to monitor for signs and symptoms of mesenteric ischaemia and claudication.

OUTCOME AND FOLLOW-UP

In follow-up appointments, the patient's average ambulatory readings were in the range of 130 systolic, and he is only taking 2 antihypertensives, suggesting an improvement in his blood pressure.

DISCUSSION

Takayasu's arteritis can present with signs and symptoms as a result of systemic inflammation such as fever, fatigue, weight

Figure 5 (A and B) Grey scale and Doppler images of the origin of right subclavian artery demonstrating focal wall-thickening causing luminal narrowing and significantly increased velocities of 3 m/s with aliasing signifying high-grade stenosis (arrow). (C and D) Positron emission tomography CT images demonstrating no increased activity within the major arteries. (E) Doppler image of right vertebral artery at rest demonstrating mid-systolic deceleration termed as 'bunny ear wave pattern' signifying occult steal. (F) Doppler image of the right vertebral artery post-arm exercise showing biphasic flow confirming partial subclavian steal after arm exercise.

Figure 6 (A) Digital subtraction angiography of abdominal aorta confirming bilateral high-grade renal artery stenoses. (B and C) Pre-angioplasty and post-angioplasty images of left main renal artery showing focal dissection post-angioplasty. (D) Satisfactory flow post left renal stenting is seen. Note the presence of high-grade stenoses in the two right renal arteries (arrow heads). (E and F) Prestenting and post-stenting of right renal artery, performed a few weeks later.

loss and malaise. The symptoms as a consequence of local vascular compromise include abdominal pain, claudication of the upper and lower extremities, arterial bruits and, less frequently, severe hypertension, vision loss, end-stage renal disease and strokes.¹⁶

Imaging is key to the diagnosis and assessment of Takayasu's arteritis, both to determine the presence and progression of stenotic or occlusive lesions, and to evaluate disease activity. Of the imaging modalities, angiography remains the gold standard, though CT angiogram and MR angiogram are useful non-invasive methods of assessing arterial lesions. Ultrasonography has proven useful in initial assessment and follow-up, especially for easily accessible vessels, such as the carotids. It is a high-resolution modality with no radiation; however, its use is limited by ultrasound's lack of penetrance, rendering it ineffective for evaluation of deeper vessels.¹⁷ Fluoro-d-glucose positron emission tomography has also been shown to be useful in the assessment of disease activity in Takayasu's arteritis, even in patients undergoing steroid treatment, thus making it a valuable tool for follow-up.¹⁶

The treatment for Takayasu's arteritis depends on several factors, including the acuity of the patient's arteritis, as well as sequelae of arterial stenosis. For patients with active inflammation, initial therapy with high-dose corticosteroids at a dose of 1 mg/kg/day is indicated. There are case reports of methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporine, tacrolimus, leflunomide and antitumour necrosis factor agents being attempted.¹⁵

For patients who present with sequelae of the disease, such as stenotic or occlusive arterial lesions secondary to chronic disease, treatment focuses on revascularisation of affected organs based on clinical consequences of the stenotic lesions. The two options are surgery and percutaneous endovascular treatment. Choice of treatment depends on the severity and characterisation of the stenosis or occlusion. For short-segment lesions, especially renal artery stenosis, percutaneous interventions, either balloon angioplasty or stenting, are preferred.¹⁷

Antiplatelet therapy consisting of indefinite atrial septal aneurysm and 4 weeks of clopidogrel has been suggested post-treatment to prevent re-stenosis. For long-segment stenosis with extensive fibrotic changes or occlusion, as well as in those patients who present with critical cerebrovascular or coronary ischaemia, extremity claudication, severe renal artery stenosis, progressive aneurysms and severe aortic regurgitation or coarctation, surgical management is indicated, and is associated with superior results and better long-term survival.¹⁵

In a series of 22 patients diagnosed with Takayasu's arteritis, 10 were noted to have persistently positive antiphospholipid antibodies, satisfying diagnostic criteria for concurrent APS. These patients were treated medically for both conditions, in addition to definitive management of vascular lesions.¹⁸ The cornerstone of APS treatment remains anticoagulation with heparin followed by chronic anticoagulation with a vitamin K antagonist targeting an international normalised ratio (INR) of 2–3.^{19–20} Expert opinion suggests a higher INR target of 3–4 or 2–3 with low-dose aspirin for patients who experience recurrent thrombosis on vitamin K antagonist.²¹ With the advent of direct oral anticoagulants, movement is being made towards their adoption for the treatment of APS, which is currently being investigated by the Rivaroxaban in antiphospholipid syndrome study, a prospective randomised controlled trial comparing warfarin and rivaroxaban. Other treatment modalities currently undergoing investigation include hydroxychloroquine, statins, complement inhibition, the adenosine receptor antagonist defibrotide and inhibition of intracellular signalling pathways. Studies have shown some efficacy in the use of rituximab, as well as intravenous immunoglobulins, though further research is necessary.²²

While conventional teaching dictates that Takayasu's arteritis is a disease predominantly affecting young women of east Asian descent, several recent reviews note that the ratio of gender involvement varies widely between ethnicities.^{16–23} In particular, much of the available data originate from the Japanese population, making epidemiological data difficult to apply when considering the likelihood of Takayasu's arteritis.

Learning points

- ▶ Takayasu's disease should be considered in the differential diagnosis for young patients who present with hypertensive urgency, even in male patients of non-Asian descent.
- ▶ CT angiogram and MR angiogram are useful, non-invasive imaging modalities for assessing the extent of arterial lesions.
- ▶ Treatment of the condition depends on the activity of the disease and the clinical sequelae of the stenotic lesions.
- ▶ For renal artery stenosis secondary to Takayasu's arteritis, percutaneous endovascular interventions should be considered in resistant hypertension.
- ▶ Takayasu's arteritis is, rarely, associated with primary antiphospholipid syndrome, requiring concurrent treatment of both conditions.

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