

CASE REPORT

Takayasu arteritis presenting as embolic stroke

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SUMMARY

A 52-year-old Caucasian woman presented to the emergency department with symptoms of acute ischaemic stroke (right-side weakness, confusion and aphasia) that resolved completely after administration of tissue plasminogen activator. During stroke work-up, she was found to have an enhancing infiltrate of the aorta at the level of the take-off of the great vessels, most consistent with early Takayasu arteritis. After being discharged home on steroids and dual antiplatelet therapy, she returned 2 days later with re-presentation of weakness and aphasia. Further work-up revealed two intraluminal clots in the left common carotid and left internal carotid arteries that had not been discovered during previous testing. This case illustrates the need to screen for sources of embolic stroke in patients with Takayasu arteritis, especially those with recurring symptoms.

BACKGROUND

Takayasu arteritis (TA) is a rare granulomatous vasculitis of large and medium arteries typically affecting the aorta, subclavian and carotid arteries. The incidence of TA worldwide is only 1–2 per million people, predominantly affecting Asians and women in their 20s.¹ The signs and symptoms of TA are due to both systemic inflammation as well as local damage to the vasculature. The presentation of TA can be quite variable, ranging from diminished pulses to ischaemic stroke. While stroke is a rare presenting symptom of TA, it can occur in 5%–17% of patients with TA.^{2–4} Ischaemic strokes can be either occlusive, from external compression of arteries, or embolic, from stasis caused by poor flow through stenotic areas. Guidelines for the work-up of TA are unclear as it is such a rare

disease; here we present a case of TA where the source of emboli causing ischaemic stroke was not discovered during initial work-up.

CASE PRESENTATION

A 52-year-old woman presented to the emergency department with less than 1 hour of sudden onset of weakness, mild confusion and complete aphasia. On physical exam, her stroke manifestations included aphasia, mild confusion, weakness and right-sided pronator drift. During admission, a blood pressure difference between the arms was found, with the right arm 115/73 and left arm 99/62. There were no appreciable carotid bruits and pulses were palpable in all four extremities. CT of the head showed a hyperdense middle cerebral artery (MCA) sign involving the distal M1 segment of the left MCA with questionable extension into an M2 branch. CT angiography (CTA) of the head showed asymmetry of the distal internal carotid arteries, left smaller than the right, and an abrupt occlusion of the distal M1 branch of the left MCA artery. Later, MRI of the brain showed an acute infarct involving the left temporal insular and peri-insular region. The patient's symptoms resolved completely an hour after tissue plasminogen activator (tPA) administration.

Due to the patient's age and lack of significant risk factors for stroke,⁵ work-up was carried further. The asymmetry of the distal internal carotid arteries seen on the CTA of the head prompted a CTA of the neck. This revealed soft tissue thickening with inflammatory stranding involving the proximal aortic arch with extension into the great vessels and involvement of the carotid system, concerning for an inflammatory vasculitis. Additionally, severe stenosis was present with near-occlusion of the left common carotid artery. Additional areas of inflammatory changes and wall thickening involving the mid and distal left common carotid artery extending into the left internal and external carotid arteries were also observed (figure 1). Echocardiogram was normal. CTA of the chest showed an enhancing infiltrative mass around the proximal great vessels and aortic arch at the level of the great vessel take-offs, measuring approximately 8 mm in thickness, most consistent with early TA (figure 2 and 3). At this time no further imaging was pursued due to the radiologically apparent disease on CTA of the chest and neck (sensitivity and specificity for the diagnosis of TA are 95% and 100%, respectively¹). Rheumatological screening showed sedimentation rate of 36 mm/hour, C reactive protein (CRP) of 12 mg/L and positive antinuclear antibody.

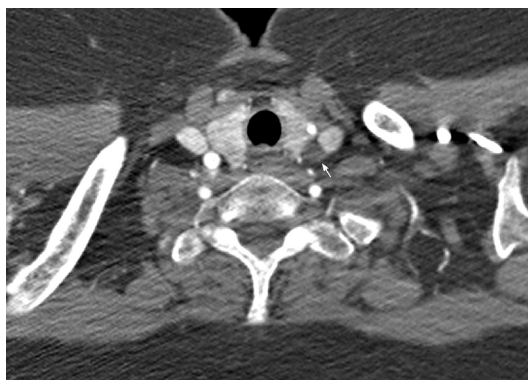


Figure 1 Axial CT angiography of the neck demonstrating occlusion of the left common carotid artery.



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Figure 2 Axial CT angiography of the chest demonstrating an enhancing infiltrative mass around the aortic arch.

A diagnosis of TA was made based on the difference in blood pressure, elevated erythrocyte sedimentation rate (ESR) and characteristic radiographical findings involving the aorta and common carotid.⁶ The patient was released on high-dose daily prednisone, aspirin and clopidogrel. Unfortunately, she re-presented 2 days after discharge complaining of similar symptoms, namely aphasia, right-side leg weakness and leg cramping. At this time, tPA administration was not pursued due to recent administration during previous admission, in accordance with standard guidelines.⁷ Symptoms resolved without further intervention. MRI revealed interval extension of infarct in the left subinsular and insular region, with a new infarct in the inferior insular

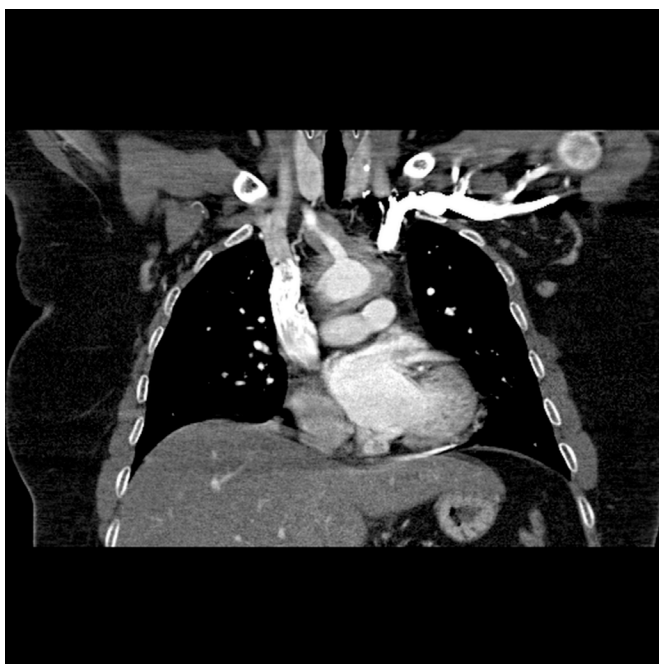


Figure 3 Coronal CT angiography of the chest demonstrating an enhancing infiltrative mass around the proximal great vessels, aortic arch, at the level of the great vessel take-offs approximately 8 mm thick, most consistent with Takayasu arteritis.

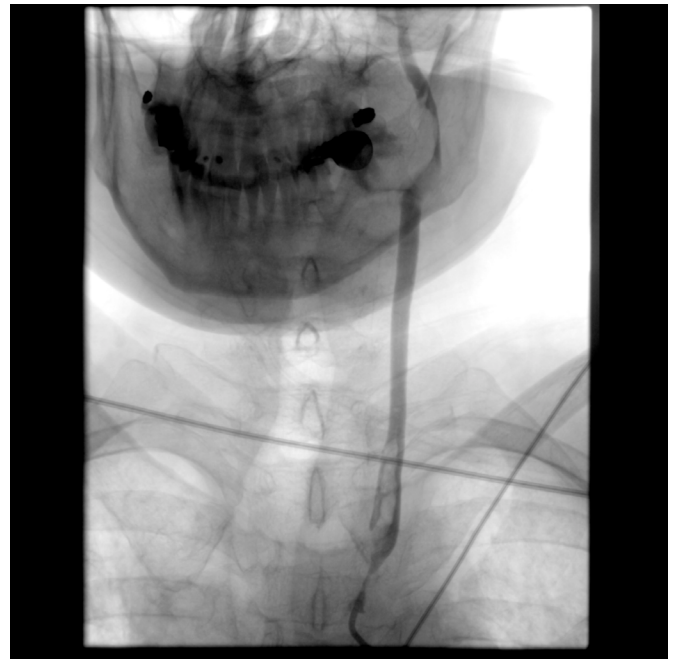


Figure 4 Interventional radiology (IR) cerebral angiogram obtained at second admission, demonstrating the left common carotid and two intraluminal clots.

cortex and in the periaxial white matter on the left. Further work-up at this admission included an interventional radiology cerebral angiogram with catheter placement in the internal carotid. Conventional angiography revealed severe left common carotid artery stenosis at origin, resulting in stasis of blood and leading to the development of a large positional thrombus of the left common carotid artery. A second large intraluminal thrombus was found in the proximal left internal carotid artery (figure 4). Perfusion of the left internal carotid artery above the level of this thrombus showed distinct delay. At this time vascular surgery was consulted for possible thrombectomy. This was deferred due to concern related to the friability of the vessel in the setting of severe inflammation. Thrombophilia work-up returned negative, and the clots were felt to be due to arterial stasis secondary to compression of the vessels from vasculitis. At this time, clopidogrel was discontinued. The patient was therapeutically anticoagulated with warfarin. Aspirin was continued. Methotrexate was added for further management of the arteritis and in hopes of being able to reduce the dose of prednisone once inflammation was better controlled.

DIFFERENTIAL DIAGNOSIS

TA is a difficult disease to diagnose given that it is relatively rare and the differential diagnosis is wide; the differential diagnosis for causes of ischaemic stroke is narrower but can be equally difficult to diagnose.

The differential diagnosis for TA includes other large-vessel vasculitides such as giant cell arteritis (GCA), systemic lupus erythematosus, syphilis, tuberculosis and Kawasaki disease, and congenital connective tissue disorders such as Marfan's syndrome, as well as several other disorders and pathologies. These can be difficult to distinguish from TA and are typically differentiated by epidemiological characteristics, complications and appearance on imaging.^{1 8} Angiography is considered the gold standard diagnostic imaging for TA with a sensitivity and specificity of 100%. CT is considered to be a reliable alternative

to angiography. However, neither of these two tests offer much clinical utility in evaluating the early disease processes associated with TA. Positron emission tomography (PET) scan is considered to be the most sensitive test for detecting early inflammatory stigmata of TA. PET scan offers some additional benefits in being able to evaluate disease recurrence and response to treatment.¹ PET scan was not used in our patient during initial work-up as it was not felt to add any further information in light of characteristic lesions on CTA.

The aetiology of ischaemic stroke in TA is occlusive or embolic, from compression of arteries or from clot formation. Guidelines for the work-up of ischaemic stroke in TA are unclear. In our case, we initially attributed the patient's stroke symptoms to occlusion—the symptoms resolved with tPA administration, and the aetiology was felt to be related to compression of arteries from the underlying vasculitis. Pursuing further work-up was deferred until the patient re-presented with similar stroke symptoms. At this point, interventional radiology (IR)-guided catheter placement revealed the presence of two large intraluminal thrombi that were likely the source of emboli.

The wide differential underscores the difficulty in arriving at the diagnosis of TA, especially if the patient does not fit the typical demographics. In our case, the characteristic imaging findings of large-vessel aortitis and the suspicion of the diagnosing radiologist helped to narrow the differential. Once the carotid thrombi were discovered, these were felt to be the most likely aetiology of the patient's stroke and treated accordingly.

TREATMENT

There are no meta-analyses available for the treatment of TA, but expert consensus and a few clinical trials outline the treatment strategies used today. Treatment can be pharmacological or surgical, with pharmacological therapy being the predominant modality in one survey (75.2% pharmacological vs 13.3% surgical⁹).

Pharmacological therapy aims at controlling the dysregulated inflammatory process in TA. Corticosteroids are the mainstay of treatment. Adjuvant immunosuppressants are often added with higher, difficult-to-control levels of inflammation, as well as when attempts to taper steroid therapy are made.⁴ High-dose corticosteroids (1 mg/kg/day) are used initially to treat TA. Weaning steroids has proven to be difficult in patients with TA. Immunosuppressants such as cyclophosphamide, azathioprine, methotrexate and mycophenolate can be used when attempting to taper steroid therapy. With the initiation of immunosuppression, the disease takes a stable course in the majority of patients.¹⁰ Biological agents such as anti-tumour necrosis factor therapy, infliximab and etanercept also have a role in steroid dose reduction and control of inflammation.¹

Surgical interventions are less commonly employed and include endovascular surgery and surgical revascularisation. Surgical intervention is aimed at reducing complications that can reduce life expectancy, namely stroke, myocardial infarction, renal failure and aneurysmal rupture. Although a seemingly good option for treatment, restenosis after transluminal angioplasty and stent-graft placement occur in up to two-thirds of patients and are only recommended in certain cases. Indications for surgery include severe renovascular stenosis, severe myocardial ischaemia, extreme claudication, critical cerebral ischaemia or stenosis of three or more cerebral vessels, severe aortic stenosis, thoracic or abdominal aneurysms >5 cm with a tendency to rupture, and severe aortic coarctation.¹

In those patients who have thrombus formation secondary to stenosis, appropriate administration of anticoagulation therapy is necessary. In patients with embolic stroke without TA, short-term anticoagulation (3–6 months) is used for acute symptomatic occlusion.^{11 12} To the best of the authors' knowledge, no guidelines on how to approach anticoagulation for thrombus formation in TA exist. The thrombus formation can be presumed to be provoked by the state of inflammation from TA; however, the risk of further clot formation from ongoing inflammation will be dependent on disease control and will need to be tailored to each individual patient. Thus in these cases, the typical short course of anticoagulation may not be sufficient.

OUTCOME

After the patient was discharged, she returned for follow-up with rheumatology 6 weeks later with no other stroke events. She was stable with methotrexate 15 mg weekly, prednisone 60 mg daily, folate and warfarin. Her international normalised ratio remained therapeutic with subsequent testing demonstrating decrease in CRP and ESR to within normal limits. At this point, the patient elected to move care to a different hospital system and was lost to follow-up.

DISCUSSION

TA is a rare large-vessel systemic vascular arteritis usually affecting the aorta and the main branches.^{1 2} The pathogenesis of TA continues to remain largely unknown. Neither inflammatory markers nor clinical exam is reliable in determining disease course or response to treatment. As such imaging remains an essential part of disease monitoring. Due to the significant sequelae associated with TA, early diagnosis and treatment are important for reducing the overall morbidity and mortality of the disease. TA has a wide differential and can be particularly difficult to diagnosis. There are two distinct phases of TA, active inflammatory phase and late chronic phase. The early active phase is characterised by general symptoms such as malaise, fever, night sweats, arthralgias, headaches and rashes. During the late chronic phase, vessel involvement is apparent. Those in the late chronic phase tend to experience more specific symptoms including but not limited to renovascular hypertension, acute mesenteric ischaemia, retinopathy, amaurosis fugax, transient ischaemic attacks and strokes.¹ In a single-institution study, 13% of 45 patients with TA initially presented with stroke.¹³ Emboli arise from involved vessels due to thickening, stenosis, dilation and/or aneurysmal formation.

Overall incidence of stroke in this subset of patients has been cited anywhere from 10% to 20%¹⁴; stroke as initial manifestation is even more rare.^{15–17} In a single-institution retrospective study, the prevalence of stroke in patients already diagnosed with TA was 15%.² Other than embolism, occlusive lesions from stenosis, hypertension and cerebral hypoflow are all possible aetiologies. The rarity of the disease in the setting of this atypical presentation can cause delay of diagnosis.¹⁵ Ultimately when patients with neurological deficit present in the setting of systemic symptoms, TA should rise in the differential.^{10 16}

Although our patient had low suspicion for TA based on physical exam and lack of systemic symptoms of inflammation, the diagnosis was ultimately made due to her signs and symptoms of unequal blood pressures in both arms, limb claudication and abnormal imaging. She had another stroke 2 days after discharge and was placed on anticoagulation therapy after discovery of intraluminal thrombi. Although biopsy and thrombectomy were initially considered, neither was pursued due to the limited

utility of biopsy¹ and because of concern about the friability of the left common carotid with any surgical manipulation.

There are case reports in the literature of TA presenting with ischaemic stroke,^{3 14 18} but identifying embolic stroke is rare and not well-described.¹⁹ Specific guidelines for evaluating for thrombi in areas of stenosis do not exist. This case demonstrates the need for maintaining a high suspicion for embolism as the aetiology for ischaemic stroke, especially in those patients who re-present with stroke symptoms. The discovery of two intraluminal thrombi in this patient led to the initiation of anticoagulation, and the patient suffered from no additional stroke events after adequate anticoagulation. Initial discovery of the thrombi during our patient's first admission may have prevented the second stroke and progression of ischaemia; however, as no guidelines exist, investigation of thrombi in areas of stenosis was not thought to be cost-effective in management during work-up for our patient. The rarity of this presentation underscores the difficulty of knowing when to pursue further testing. We suggest considering the patient's degree of stenosis and using this as a guide to the risk of thrombosis; in our patient, near-complete occlusion led to arterial stasis. Further description of such cases in the literature is needed to develop guidelines for distinguishing emboli as the cause of ischaemic stroke in TA.

Learning points

- ▶ Cryptogenic stroke in young patients should include Takayasu arteritis in the differential.
- ▶ High suspicion for embolism as source of ischaemic stroke in new diagnosis of Takayasu arteritis must be maintained.
- ▶ Prompt initiation of anticoagulation therapy for those with Takayasu arteritis and thrombi is necessary to prevent embolic stroke.

Contributors KF was instrumental in the conception and design, acquisition of data or analysis, and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version published. LG was instrumental in the conception and design, acquisition of data or analysis, and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version published. KB was instrumental in the conception and design, acquisition of data, or analysis and interpretation of data; drafting the article; and final approval of the version published. . BH was instrumental in the conception and design, acquisition of data, or analysis and

interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version published. All authors agree to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

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