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Takayasu arteritis presenting as acute thromboembolic stroke: A case report and literature review

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Abstract

Takayasu arteritis (TAK) is a chronic granulomatous large vessel vasculitis that affects aorta and its main branches. We report a 23 year old lady with no prior medical illness presenting with acute ischemic stroke with right sided hemiparesis and expressive dysphasia. She had no apparent risk factors nor any preceding symptoms. Computed tomography (CT) brain showed left middle cerebral artery (MCA) thrombosis. She was given fibrinolytic therapy with alteplase. Ultrasound carotid doppler revealed extensive left common carotid artery thrombosis along with markedly increased carotid intimal-medial thickness (CIMT) of 0.3 cm consistent with macaroni sign. Magnetic resonance angiography (MRA) of aorta showed right subclavian artery narrowing. Her blood investigation had raised inflammatory markers (ESR/CRP), with normal autoimmune screening. A clinical diagnosis of TAK presenting with thromboembolic stroke was made and patient was treated with anticoagulation (warfarin) and immunosuppressive therapy (prednisolone 1 mg/kg and methotrexate 15 mg/week). The extensive left common carotid artery thrombosis was attributed to vascular inflammation and stasis of blood flow above the level of stenosis.

Patient made good neurological recovery at 3 months of treatment with normalization of speech and significant improvement of motor function. Repeated ultrasound carotid at 6 months of treatment revealed new blood flow within the left common carotid artery with reduction of CIMT to 0.1 cm, suggestive of recanalization and abating vascular inflammation. This case highlights the heterogeneity of TAK which can present de novo as acute ischemic stroke and the utility of carotid doppler ultrasound in its diagnosis.

Keywords

Takayasu; vasculitis; stroke; carotid doppler.

Introduction

Takayasu arteritis (TAK) is a large vessel vasculitis with a variety of clinical presentation including constitutional symptoms, limb claudication, carotidynia, cardiac involvement (angina, myocardial infarction, heart failure, aortic regurgitation), vascular bruit, asymmetrical blood pressure, and diminished pulses. Here we describe a patient presenting with acute ischemic stroke with no apparent risk factors or associated preceding symptoms. Computed tomography (CT) brain showed left middle cerebral artery (MCA) thrombosis. Ultrasound carotid doppler revealed extensive left common carotid artery thrombosis along with markedly increased carotid intimal-medial thickness (CIMT) consistent with macaroni sign. Magnetic resonance angiography (MRA) of aorta showed right subclavian artery narrowing. Clinical diagnosis of TAK presenting with thromboembolic stroke was made and patient was treated with anticoagulation and immunosuppressive therapy and subsequently made good neurological recovery.

Case Presentation

A 23 year old lady of Malay descent with no prior medical illness presented with acute onset of right sided hemiparesis, facial asymmetry and expressive dysphasia. No history of headache, blurring of vision, syncope, seizures or dizziness. No constitutional symptoms of fever, weight loss and night sweats. No history of limb or jaw claudication, no carotidynia and no cardiac failure symptoms. She also did not have symptoms of connective tissue diseases. No prior history miscarriages or vascular thrombosis. She was not on any medication or recreational drug. No family history of stroke or other neurological and autoimmune disorders. Other systemic review was unremarkable. Upon arrival to the emergency department, her GCS was E4 V1 (Expressive dysphasia) M6 =11/15 .Vitals ; normotensive 128/61, pulse 90, oxygenation 100% on room air and afebrile T 37. Her neurological examination revealed right sided hemiparesis with right upper limb power of 0/5 and right lower limb power of 4/5. Pupils were 3 mm equal and reactive. She had right upper motor neuron facial nerve palsy with expressive dysphasia and NIHSS score of 14.

There was no discrepancy of blood pressure between limbs, normal peripheral pulses and no vascular bruit. No hepatosplenomegaly or lymphadenopathy. No vasculitic rash or clinical features of connective tissue disease. Normal optic disc and no evidence of retinal vasculitis. Other examination findings were unremarkable. Blood investigations were within normal parameters apart from raised inflammatory markers (Table 1).

ECG was sinus rhythm without other abnormalities. Echocardiography showed good LV function with EF 67%, no hypokinesia, no vegetation or intracardiac thrombus, normal valves, normal chambers, normal pulmonary pressure, and no congenital shunts.

Urgent CT brain done showed loss of left insular ribbon sign with dense MCA sign in keeping with acute left MCA territory infarct. A neurology consult was obtained and she was given thrombolytic therapy with intravenous alteplase 50 mg according to protocol (3 hours of symptom onset). 2 hours post thrombolysis her NIHSS score improved from 14 to 9.

Table 1: Blood Investigation

Test	Result	Test	Result
WBC	12.99	Creatinine	53 micromol/L
Hb	119gm/L	ANA	Negative
platelets	485	ENA	Negative
Neutrophil	85.5%	dsDNA	Negative
Eosinophil	0%	Lupus anticoagulant	Negative
Lymphocyte	11.9%	Anticardiolipin	Negative
Total protein	86 gm/l	Anti B2 glycoprotein-1	Negative
Albumin	40g/l	C3 (0.9-1.8)	1.9 gm/l
Globulin	46 g/l	C4 (0.1-0.4)	0.4gm/l
Bilirubin	12 micromol/L	ESR	73 mm/hour
AST	28 U/L	CRP (<5)	28.7 mg/L
ALT	13 U/L	HIV/HepB/HepC/VDRL	Nonreactive
Urea	6.3 mmol/L	Fasting glucose	4.8
Na	135 mmol/L	Total cholesterol	5mmol/L
K	4.2mmol/L	Triglyceride	1.05mmol/L

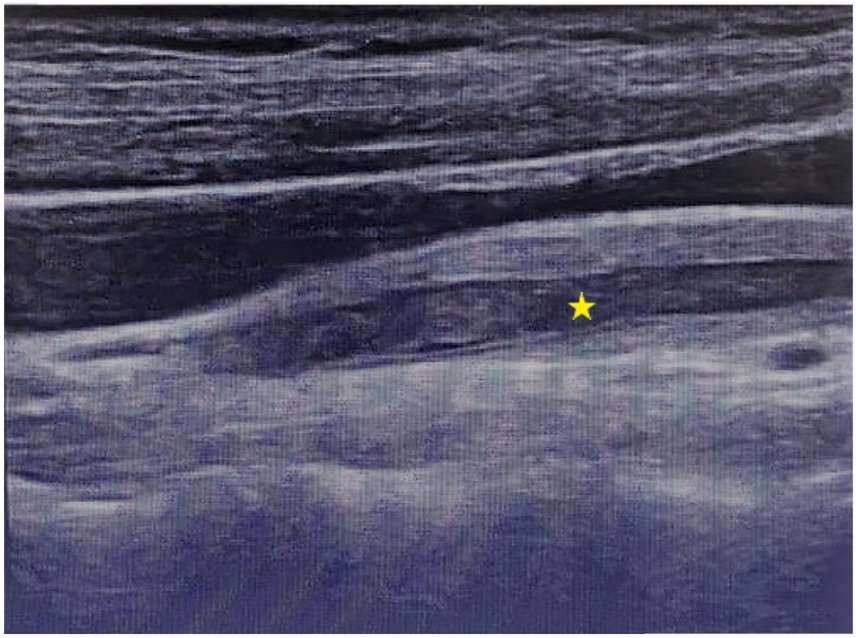

Figure 1: Ultrasound Doppler longitudinal view of the left common carotid artery showing 'macaroni sign' with thrombosis.

Repeated CT scan 24 hours post thrombolysis showed similar distribution of infarct and persistence of dense left MCA sign. MRA brain at 72 hours post thrombolysis showed persistent occlusion of left MCA (distal to M1 segment.)

She had an ultrasound carotid doppler done which showed no color flow or doppler waveform within the left common carotid and left internal carotid arteries. There was a long segment thrombosis invol-

ving left common carotid, left bulb and left internal carotid arteries. The left common carotid intimal wall (CIMT) was thickened at 3 mm (Figure 1). Right sided vessels were normal, with right common carotid artery intimal thickness of 0.07 cm.

CT angiography of carotid and cerebral arteries at day 8 post thrombolysis showed non opacification of left common carotid artery just above its origin until inferior end plate of C4 vertebra suggestive of thrombosis measuring approximately 7.8 cm in length, with reconstitution of contrast beyond this level. The left internal and external carotid arteries were also smaller in caliber compared to the right side, but well opacified until distal branches suggestive of blood flow above the level of thrombosis. The left carotid artery received tributaries from left vertebral artery as collateral. No evidence of calcified carotid arterial wall. Left M2 middle cerebral artery was not opacified in keeping with thrombosis. A further MRA thoracic aorta showed narrowing of the right subclavian artery at the junction between the proximal and middle third.

A clinical diagnosis of Takayasu arteritis (Type 1) presenting with thromboembolic stroke was made and patient was started on prednisolone 1 mg/kg with concurrent methotrexate titrated up to 15 mg/week. She was also started on anticoagulation with warfarin in view of left common carotid artery extensive thrombosis.

At 2 weeks of treatment, patient speech had improved and by week 10, her speech completely normalized with marked improvement of right upper limb power to 4/5 as well as normalization of inflammatory markers. Repeated ultrasound carotid at 6 months of treatment, showed thick echogenic thrombus within the left common carotid artery until the left bulb, however there was now a new demonstrable thin color flow within the left common carotid artery. No color flow within the left internal carotid artery. The other striking finding was the reduction of the left CIMT to 0.1 cm (previously 0.3 cm). Right CIMT was normal 0.07 cm. These changes were suggestive of recanalization and reducing vessel wall inflammation. Patient remained clinically well without recurrence of any new symptom.

Discussion

Takayasu arteritis (TAK) is a chronic granulomatous large vessel vasculitis that affects aorta, its main branches and as well pulmonary and coronary arteries. There are 5 major patterns of vascular involvement based on Takayasu Conference 1994 angiographic classification with subclavian and common carotid arteries being the most frequently affected, especially over the left side. TAK is more prevalent in Asia and has a female preponderance, with a female to male ratio up to 9:1, and generally seen in young patients, ranging 11- 30 years.

The vascular inflammation results in stenosis (> 90% of patients) , occlusion and aneurysms. (25% patients). The vascular occlusions in TAK tend to develop insidiously, thereby allowing development of collateral circulation which is generally not associated with a palpable pulse, yet provides sufficient blood flow to the extremities. This makes distal gangrene rather uncommon in TAK, despite proximal arterial occlusion.

TAK is a heterogenous disease with a triphasic pattern of progression classically described; phase 1: constitutional phase, phase 2: vascular inflammation and phase 3: vascular damage/fibrotic stage. However, in clinical practice, patients can present in any phase or in combination of phases.

In a prospective study involving 275 patients with TAK by Quinn et al [1] analyzing clinical presentation at diagnosis, 8% presented with constitutional symptoms (phase 1), 13-15% patients with carotidynia (phase 2), 43-47% with other vascular symptoms (phase 2), 28-30% with major ischemic event (phase 3) and 2-6% were asymptomatic. The study also found that relapse was most frequent in patients who presented with carotidynia. Among 79 patients who presented with major ischemic event, only 19% (15) had a triphasic pattern of disease, whereas 28% (22) presented de novo without any preceding symptoms.

In a retrospective study by Jing Li et al [2] , involving 411 patients over a span of 24 years, the most common angiographic pattern was Type V 60.8% (250), followed by Type 1 22.1% (91), Type IV 6.3% (26), Type IIa 3.9% (16), Type IIb 3.9% (16) and Type III 2.9% (12). The subclavian (79.8%) and carotid (79.1%) arteries were the most frequently affected vessels. The leading cause of death in this cohort was due to heart failure.

In a similar study by Goel et al [3], involving 40 pediatric onset TAK (age ranging from 1 - 16), the most common angiographic pattern was type V (53%), type IV (25%) and type 1 (10%).

Chung et al [4] evaluated patterns of aortic involvement using CT angiography (n = 85), found that 95% (81) patients had aortic involvement with or without aortic branch involvement. 5% (4) patients had only isolated aortic branch involvement. In terms of aortic branches, the left common carotid (77%) and left subclavian (76%) arteries were most commonly involved. Arterial involvement was contiguous in 81% (69) patients, while skipped lesions were found in 19% (16) patients.

Ultrasound is an emerging modality in the diagnosis of TAK. The 'macaroni sign' refers to the homogenous, mid-echoic, circumferential arterial wall thickening seen in patients with TAK, commonly seen over the common carotid artery. Normal common carotid artery intimal media thickness is approximately 0.7mm +/- 0.1. Maeda et al [5] described 'macaroni sign' in in 19 out of 23 patients (82.6%) with TAK in either one or both sides of the common carotid arteries, while contrast angiography demonstrated carotid lesions in only 13 of 23 (56.5%) patients, suggesting the greater sensitivity of ultrasound in detecting thickened intima-media complex.

Taniguchi et al [6] demonstrated greater sensitivity of ultrasound as compared to angiography in estimating stenotic severity in patients with TAK. 44 carotid arteries of 22 patients were examined. Angiography showed 12 stenotic arteries vs 25 stenotic (18 mild, 7 moderate) arteries in ultrasound. Moreover, ultrasound also detected 6 instances of marginal but definite blood flow that was not revealed by angiography (9 occlusive in angiography vs only 3 true occlusive in ultrasound).

Furthermore, in a study by Svensson et al [7] , patients with clinically active TAK had median CIMT of 2.3 mm (1.7-2.9), stable TAK 1.2 mm (1.1-1.6) vs healthy control 0.5 mm (0.5-0.6). This supports the

possible role of ultrasound as a monitoring tool to assess inflammatory changes and disease activity in TAK. This was also evident in our case where the CIMT had markedly reduced from 30 mm to 10 mm at 6 months of treatment.

In EULAR recommendation of imaging in large vessel vasculitis 2018 [8], MRI is the first imaging of choice to assess mural inflammation and luminal changes. Alternatively, PET, CT and ultrasound may be used. Conventional angiography is not recommended unless patient is also planned for vascular intervention.

(Table 2) highlights 6 cases of TAK presenting with acute ischemic stroke as initial manifestation of the disease, imaging findings and treatment outcome.

In terms of management [15] , patients with established TAK should be started on concurrent glucocorticoids 1 mg/kg (40-60 mg) and conventional synthetic DMARDs due to high rate of relapse (up to 70%) and inability to achieve low dose steroids in many patients. Gradual tapering of glucocorticoids is recommended to reach a dose of ≤15-20 mg within 2-3 months and then to ≤10 mg/day at 1 year. Rapid tapering of glucocorticoids has been associated with higher rate of relapse. Methotrexate demonstrated

Table 2: 6 cases of TAK presenting with acute ischemic stroke as initial manifestation of the disease , imaging findings and treatment outcome.

Case	Presentation	Treatment	Imaging	Outcome
1) 52, Male, NKMI Field et al 2017 [9]	Acute ischemic stroke (right sided hemiparesis, confusion aphasia)	Thrombolysis (tPA) . Prednisolone 60 mg + warfarin + aspirin +Methotrexate 15 mg	CTA brain: MCA thrombosis. CTA neck: severe stenosis / near-occlusion of left common carotid artery, inflammatory changes and wall thickening involving left common carotid artery extending into the left internal and external carotid arteries Conventional angiography: severe left common carotid artery stenosis at origin, stasis of blood and large positional thrombus of the left common carotid artery. A second large intraluminal thrombus in the proximal left internal carotid artery .	Stable at 6 weeks, normalized ESR/CRP. Subsequent lost to follow up
2) 17, Female, NKMI Bejot Y et al 2011 [10]	Acute ischemic stroke (Right hemiplegia and aphasia)	Balloon dilatation of the left common carotid artery + mechanical embolectomy with stenting of both the internal carotid and middle cerebral arteries. Immunosuppressive therapy; not mentioned	MRI: Left MCA territory infarct. Conventional angiography: left internal carotid artery occlusion and thrombus located in the M1 segment of the left middle cerebral artery. Tight stenosis at the origin of the left common carotid artery with unusual collateral vessels and occlusion in the left subclavian artery. 18F-FDG positron emission tomography: increased metabolism in the ascending aorta, aortic arch, and the proximal segment of the cervical arteries .	Not available

3) 18, Female, NKMI V.S.Hedna et al 2012 [11]	Acute Ischemic stroke (Left sided hemiparesis)	Thrombolysis (tPA) Percutaneous transluminal balloon angioplasty of the right CCA and ICA followed by mechanical thrombectomy of the right ICA and MCA performed. Steroids + Azathioprine. Subsequently Etanercept / Infliximab	CTA brain: right MCA thrombosis with intraluminal clot in the right internal carotid artery (ICA). Near-total stenosis of the right common carotid artery (CCA). Left CCA significant stenosis and bilateral CCA thickening circumferentially. CTA aorta : 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 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.	Improvement of soft tissue thickening in CTA at 6 months and normalization of ESR/CRP
4) 28, Male, NKMI M.Silver 2012 [12]	Acute ischemic stroke (right sided hemiplegia and aphasia)	Thrombolysis (alteplase) Interventional thrombectomy, clot retrieval and angioplasty of the left common carotid and MCA thrombus was performed. High dose steroids + methotrexate	CT brain: Left MCA thrombosis. CT angiogram: marked wall thickening involving the left common carotid artery with complete occlusion of the distal left common carotid artery and MCA. Occlusion of the right common carotid and vertebral arteries with extensive collaterals, as well as inflammatory changes surrounding the aorta and subclavian vessels.	Marked clinical improvement and normalization of ESR/CRP
5) 17, Female, NKMI S.W. Cheo 2020 [13]	Acute ischemic stroke (right sided hemiparesis, expressive aphasia)	IV Methylprednisolone 1 gm OD for 3 days. Prednisolone 1 mg/ kg + Methotrexate + aspirin	CT brain: Left MCA thrombosis CTA aorta: thickening of the thoracic aorta, right pulmonary artery and the large and medium size vessels of the abdominal aorta ,causing varying degrees of stenosis, and occlusion of the left common carotid, proximal left subclavian, common hepatic and proximal portion of superior mesentery arteries. Long segment left common carotid artery and ICA thrombosis seen .	Improvement of motor power and speech
6) 25, Female, NKMI N.D.Maravi et al 2017 [14]	Acute Ischemic stroke (right sided hemiparesis and aphasia)	Prednisolone 40 mg + Aspirin 150 mg OD	CT brain: Left MCA thrombosis. Carotid Doppler: circumferential wall thickening of the right common carotid , external and internal carotid arteries causing luminal narrowing. Left common carotid , external and internal carotid arteries thickening causing near total occlusion.	Improvement of motor power and speech at 1 week

efficacy TAK, while other agents like mycophenolate mofetil, azathioprine, leflunomide and cyclophosphamide have limited data. Cyclophosphamide should be reserved in patients where other treatments have failed or not tolerated.

Relapses can occur particularly within the first 5 years of diagnosis. Major relapses should be managed with 40-60 mg of prednisolone, while minor relapses require increment of 5-15 mg from the last stable dose. Tocilizumab has demonstrated efficacy in refractory TAK. In phase 3 TAKT study [16], tocilizumab had steroid sparing effect, improved disease on imaging evaluation and improved well-being without safety concerns. Alternatively, anti-TNF can be considered

Antiplatelet or anticoagulation should not be routinely used in all patients with TAK, unless indicated for other reasons and decision must be individualized. In a retrospective study by W.S de Souza et al [17] involving 48 patients with TAK found that antiplatelet therapy was associated with lower frequency of ischemic events.

The presence of extensive thrombosis in our patient can be explained by two possible mechanisms. Firstly, stenosis causing stasis of blood flow resulting in thrombus formation and secondary embolization to the brain. The other possible mechanism would be de novo thrombus formation precipitated by vascular inflammation. Generally, patients with embolic stroke are managed with anticoagulation, however, in patients with TAK, there are limited consensus on role of anticoagulation and duration of such treatment. Thus, decision for short term anticoagulation while abating vascular inflammation with immunosuppressive therapy should be tailored individually.

Vascular interventions should be performed during stable remission due to increased risk of complications and lower patency rates during active disease. However, such interventions may be considered in cases of dissection, critical ischemia or neurological complications.

Conclusion

TAK is a heterogenous disorder and can present with acute ischemic stroke without preceding symptoms. The diagnosis requires high index of suspicion and meticulous search for etiology for young unexplained stroke. Ultrasound evaluating carotid intimal medial wall thickness (CIMT) is an invaluable tool, aiding in diagnosis and possibly monitoring of vascular inflammation and treatment response.

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