Pearls & Oy-sters: Primary Cerebral Buerger Disease

A Rare Differential Diagnosis of Stroke in Young Adults

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Pearls

- Buerger disease (thromboangiitis obliterans [TAO]) typically occurs in men younger than 40–45 years who have a history of heavy tobacco use.
- The involvement of small and medium-sized vessels with normal proximal arteries and corkscrew-like collaterals in proximity to occluded arteries are angiographic features of TAO.
- Cessation of tobacco use is mandatory to stop disease progression and recurrent strokes.

Oy-sters

- Other causes of distal emboli and occlusions must be excluded for diagnosis of TAO.
- The corkscrew-like collaterals may be missed or misinterpreted on CT or magnetic resonance angiography.
- A primary cerebrovascular manifestation without peripheral vascular ischemic complications is rare but possible.

A 41-year-old man presented with acute left upper motor neuron facial palsy and dysarthria. He had a medical history of recurrent ischemic strokes at ages 26 and 35 years with residual minor right hemiparesis and coordination deficits. Previous strokes were classified as embolic stroke of undetermined source and secondary prevention with acetylsalicylic acid was initiated. The patient had no vascular risk factors except being a heavy smoker (>20 cigarettes/day) for 25 years. Besides occasional marijuana smoking, he did not have any illicit drug abuse. He had no family history of stroke, autoimmune conditions, or cancer.

Diffusion-weighted and fluid-attenuated inversion recovery MRI revealed acute infarction in the right and chronic infarction in the left middle cerebral artery territory (figure). We performed a comprehensive etiologic workup including serologic screening for coagulopathies and Fabry disease, drug screening, duplex ultrasound of extracranial and intracranial arteries, cardiac workup including Holter electrocardiogram for 72 hours, and transthoracic and transesophageal echocardiography, which were all unremarkable and particularly ruled out patent foramen ovale as potential cardioembolic stroke mechanism.

As time-of-flight (TOF) angiography showed no occlusion of proximal arteries but prominent small vessels in the right anterior cerebral artery territory (figure) suggesting arteriovenous malformation (AVM), we decided to perform digital subtraction angiography (DSA), which ruled out AVM but revealed multiple stenoses and occlusions of distal cerebral arteries surrounded by corkscrew-like collateral vessels (figure). In retrospect, these corkscrew-like

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(A) Diffusion-weighted imaging of the brain. Arrows indicate acute infarction in the right middle cerebral artery territory (rostral insular and operculum). (B) Fluid-attenuated inversion recovery imaging of the brain. Arrows indicate chronic infarction in the left middle cerebral artery territory (frontal region). (C) Time-of-flight angiography of the cerebral arteries. The label indicates prominent vessels originating from the right anterior cerebral artery. (D) Maximum intensity projection images of 3D rotational angiography. The magnification indicates corkscrew-like collateral vessels in the proximity to an occluded branch of the right anterior cerebral artery. (E, F) Cerebral angiograms of the anterior and left middle cerebral arteries (E) and the posterior cerebral arteries (F). Arrowheads and magnification indicate corkscrew-like collateral vessels next to occluded vessels.

collaterals originating from the right anterior cerebral artery could already be seen on the TOF images (figure).

With the suspicion of cerebral vasculitis, we performed antibody screening for systemic vasculitis including anti-neutrophil cytoplasmic (ANCA), antinuclear (ANA), and extractable nuclear antigens (ENA-A), cardiolipin, and anti-double stranded DNA antibodies (anti-dsDNA), with negative results. CSF analysis was unremarkable (cell count 3 MPt/L [reference <5], protein level 388 mg/L [150–450 mg/L], glucose 3.56 mmol/L [2.8–4.4 mmol/L], lactate 1.66 mmol/L [1.3–2.4 mmol/L]), including antigen tests for Lyme disease, neurosyphilis, and herpes simplex virus and

varicella-zoster virus PCR. We further discussed leptomeningeal biopsy, which was declined by the patient.

Based on the absence of other stroke etiologies, DSA results, age, and smoking status, we suspected Buerger disease (TAO) as stroke etiology. Consistently, Doppler ultrasound of lower extremities showed clinically asymptomatic occlusions of crural arteries bilaterally, which were confirmed by DSA. The patient did not report any Raynaud phenomenon, extremity pain, or ischemia. Antibody testing showed G-protein receptor autoantibodies directed against $\alpha 1$ receptor and endothelin A receptor. Levels of erythrocyte sedimentation rate (4 mm/1 hour [reference <15 mm/1 hour]) and

C-reactive protein (0.7 mg/L [<5.0 mg/L]) were within normal limits.

With the diagnosis of TAO, we strongly recommended cessation of tobacco and cannabis use. The patient received oral varenicline medication and was referred to our smoking cessation outpatient clinic and stroke follow-up program. At discharge, the patient had recovered from facial palsy and dysarthria. The patient reduced (<5 cigarettes/day) but did not quit smoking after 3 months of follow-up. During this time course, he had no further cerebral or peripheral vascular ischemic complications.

Discussion

Buerger disease, first described in 1879 and allocated to its current denotation in 1908, is a nonatherosclerotic segmental inflammatory disease affecting small to medium-sized arteries and veins, most commonly of the lower and upper extremities.^{1,2} Involvement of other vascular territories has also been reported.³ Cerebrovascular involvement in Buerger disease is infrequent but clinical, angiographic, and pathologic demonstration has been reported.^{4,6} Historical neuropathologic data proposed two types of cerebral TAO: type 1 associated with large artery changes and type 2 associated with medium and small artery changes.⁶

TAO typically occurs in men younger than 40–45 years who have a history of chronic and substantial smoking.⁷ The involvement of small and medium-sized vessels with normal proximal arteries and corkscrew-like collaterals in the proximity to occluded arteries are angiographic features of TAO.³ These features and exclusion of other causes for distal embolization or occlusion are the major diagnostic criteria of TAO.^{3,7} Histology is the gold standard to establish a definitive diagnosis but is seldom used in clinical practice due to the risk associated with biopsy.⁸ A biopsy is rarely needed for diagnosis unless the patient presents with unusual characteristics.³

The pathogenesis of TAO is unclear. There is strong evidence that smoking is crucial for onset and progression of the disease.^{3,8} An underlying immune-mediated mechanism is discussed. In detail, immunocompetent cells, elevated pro- and anti-inflammatory cytokines, and various kinds of autoantibodies including antiendothelial antibodies, antibodies directed against vessel wall structures such as elastin and collagen, anticardiolipin antibodies, and antineutrophil cytoplasmic antibodies have been identified in patients with TAO.^{3,8,9}

Although they are widely used, there is no proven evidence for the use of steroids or platelet function inhibitors such as acetylsalicylic acid in TAO.^{9,10} Recently, agonistic autoantibodies directed against G-protein-coupled receptors associated with prolonged vasoconstriction were found in 9 out of 11 patients with TAO and preliminary studies of immunoadsorption treatment showed promising therapeutic results in advanced disease.^{8,9} In line with these data, $\alpha 1$ receptor and

endothelin A receptor autoantibodies were identified in our patient and we discussed an immunoadsorption therapy. However, immunoadsorption was deferred as the patient struggled with smoking abstinence, which should be a precondition for this costly off-label therapy. Randomized controlled trials assessing the effectiveness of immunoadsorption and pharmacologic agents are needed.¹⁰ The risk of vascular events and limb amputation is significantly higher in patients who continue smoking, whereas the only proven treatment strategy to prevent progression of the disease is complete discontinuation.^{3,9} We found no studies investigating long-term outcome of TAO with cerebrovascular involvement. In a previous case report of cerebral TAO, the patient stopped smoking and was free of symptoms during 1 year of follow-up.⁴

This case report should raise awareness for TAO as a rare etiology of stroke in young adults. TAO should be considered in young patients with stroke with a significant history of smoking. A primary cerebrovascular manifestation without peripheral vascular ischemic complications is rare but possible. Cessation of tobacco use is mandatory to stop disease progression and recurrent strokes. There is no evidence-based causative therapy.

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Name	Location	Contribution
Daniel Kaiser, MD	University Hospital Carl Gustav Carus, Dresden, Germany	Described the case and drafted the manuscript, had a major role in data acquisition and analysis, performed literature review
Georg K. Leonhardt, MD	University Hospital Carl Gustav Carus, Dresden, Germany	Contributed to the analysis of the data, revised the manuscript for intellectual content
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