Clinical Case Report

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An overlooked cause in a patient with recurrent ischemic stroke

A case report

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Abstract

Rationale: The majority of ischemic strokes are due to cardioembolism, large vessel atherothromboembolism, small vessel occlusive disease, or other unusual mechanisms. In most clinical settings, many strokes without a well-defined etiology requires a thorough diagnostic evaluation, otherwise the underlying cause might be easily overlooked. Here we report on the rare cause of a patient with recurrent stroke.

Patient concerns: A 50-year-old female patient had a 4-year history of recurrent acute onset of neurological deficits.

Diagnoses: Contrast transcranial Doppler ultrasound detected a typical "curtain" appearance of microbubbles, indicative of a right-to-left shunt. Computed tomography pulmonary angiogram was then initiated and a pulmonary arteriovenous malformation (PAVM) in the left lower lobe was found.

Interventions: The patient underwent percutaneous closure of PAVM. Afterward, warfarin was commenced because of the high risk of further thromboembolic complications in the following weeks to months. Post-treatment computed tomography pulmonary angiogram (CTPA) demonstrated successful closure of PAVM. No microbubble signals were detected on post-treatment contrast transcranial Doppler ultrasound (TCD) study.

Outcomes: The patient suffered no further embolic events during 3-year follow-up. No recanalization or new PAVMs were detected on CT scan.

Lessons: Neurological PAVM-associated risks are common but remain poorly recognized. A strategic protocol is imperative in searching for the etiologies of cryptogenic stroke.

Abbreviations: AF = atrial fibrillation, CTA = computed tomography angiography, CTPA = computed tomography pulmonary angiogram, DWI = diffusion-weighted imaging, ECG = electrocardiogram, FLAIR = fluid-attenuated inversion recovery sequence image, MRI = magnetic resonance imaging, PAVM = pulmonary arteriovenous malformation, TCD = transcranial Doppler ultrasound, TEE = transesophageal echocardiogram.

Keywords: ateriovenous malformation, stroke, transcranial doppler ultrasound

1. Introduction

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification assigns ischemic strokes to five subtypes including large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology. Cryptogenic stroke (or stroke of undetermined origin in TOAST terminology) is defined as brain infarction that is not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac, and serologic evaluation. In most clinical settings, many strokes without a well-defined etiology requires a thorough diagnostic evaluation, otherwise the underlying cause might be easily overlooked. Here we report on the rare cause of a patient with recurrent stroke.

2. Case presentation

A 50-year-old right-handed female was admitted with a 4-year history of recurrent acute onset of neurological deficits. The first attack came up in 2009. She suddenly developed difficulty speaking and referred to a local hospital. Brain magnetic

Editor: N/A.

Declarations: Ethics approval and consent to participate: Ethics Committee of Peking Union Medical College Hospital approved this case report. A written informed consent was obtained from the patient for publication of this case report and any accompanying images.

All authors have read and approved the final manuscript.

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:13(e0146)

Received: 8 January 2018 / Received in final form: 23 February 2018 / Accepted: 26 February 2018

http://dx.doi.org/10.1097/MD.0000000000010146

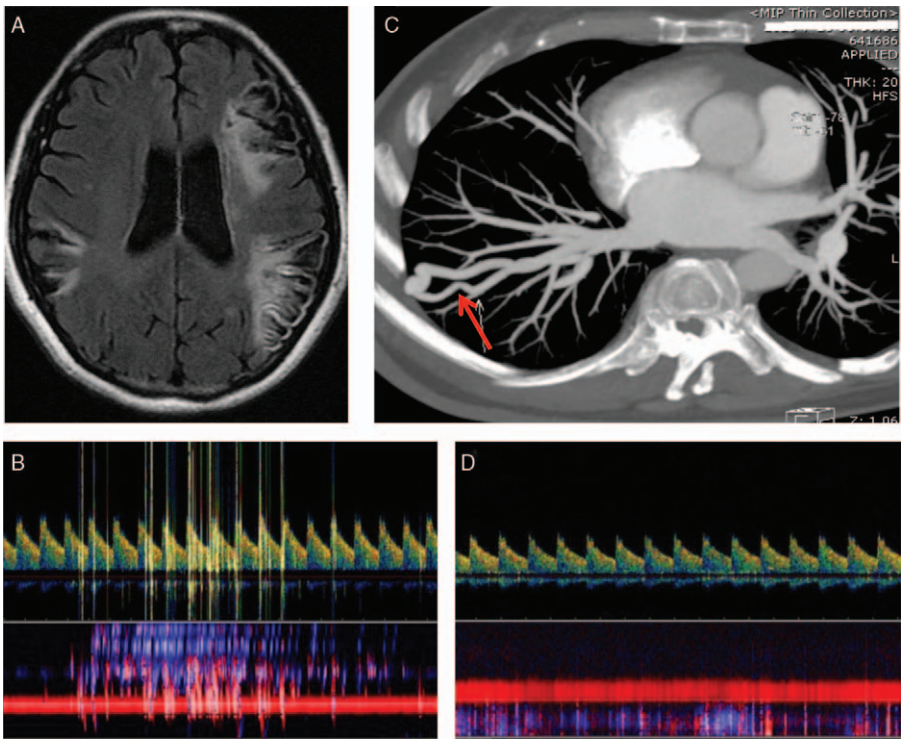

Figure 1. Patient's neuroimagings of particular diagnostic values. (A) Fluid-attenuated inversion recovery sequence in 2011 demonstrating multiple territory infarcts, involving bilateral middle cerebral arteries. (B) Contrast transcranial Doppler ultrasound (TCD) detecting a typical "curtain" appearance of microbubbles, indicating a right-to-left shunt. (C) CT pulmonary angiogram demonstrating demonstrating a moderate-sized pulmonary arteriovenous malformation (PAVM) in the right lower lobe (arrow). (D) Post-treatment contrast TCD study demonstrating complete resolution of previous microbubble signals. PAVM = pulmonary arteriovenous malformation, TCD = contrast transcranial Doppler.

resonance imaging (MRI) demonstrated diffusion-weighted imaging (DWI) hyperintensity in the cortex of left frontal lobe (Fig. 1A). No stenosis of hemodynamical significance was found on brain and neck computed tomography angiography (CTA). Acute cerebral infarction was considered. Aspirin was given but discontinued after a short period of time. The second and third ischemic events followed in 2010 and 2011, respectively, presenting with similar motor and speech deficits. Multiple lesions of fluid-attenuated inversion recovery sequence image (FLAIR) hyperintensities were revealed in the left frontal and parietal lobes and right temporal lobe (Fig. 1A), attributed to the previous several attacks of ischemia. During that time, antiplatelet agent was intermittently used. The latest episode of symptomatic stroke was in May 2013, with sudden onset of expressive dysphasia and right hemiplegia. DWI revealed massive restricted diffusion in the left frontal, parietal, and temporal lobes. Antiplatelet therapy and rehabilitation were given and her symptoms got partial recovery. Brain magnetic resonance angiography disclosed that left anterior cerebral artery and bilateral posterior cerebral artery originated from the communicating arteries (not shown). The patient was then admitted to our hospital for identifying the cause of recurrent stroke.

She had varicose veins in lower extremities for 30 years. She had no history of hypertension, ischemic heart disease, diabetes or hyperlipidemia and had no relevant family history.

On examination, heart rate was 60 beats per minute, blood oxygen saturation was 97% on room air and the respiratory rate was 16 breaths per minute. Neurological examination revealed combined aphasia. Left Babinski sign was present. Cardiovascular examination was unremarkable.

Blood tests including hemoglobin, liver function, cholesterol, homocysteine, and arterial blood gas were within normal ranges. Multiple fresh silent infarcts were demonstrated on brain MRI shortly after admission (not shown).

Thrombophilia screen (proteins C and S, antithrombin, activated protein C resistance assay, factor V Leiden, prothrombin and lupus anticoagulant, antinuclear, and anticardiolipin antibodies) was normal.

Electrocardiogram (ECG) revealed a normal sinus rhythm. Atrial fibrillation was further ruled out at a normal 24-hour Holter ECG. No evidence of patent foramen ovale or other possible cardioembolic phenomena was found on transthoracic and transesophageal echocardiogram (TEE). Aortic CTA was unremarkable. Nonetheless, contrast transcranial Doppler ultrasound (TCD) detected a typical "curtain" appearance of microbubbles, indicative of a right-to-left shunt (Fig. 1B).

Computed tomography pulmonary angiogram (CTPA) was then initiated and a pulmonary arteriovenous malformation (PAVM) in the left lower lobe was found (Fig. 1C). The left PAVM was then confirmed using catheter angiography. Screening Doppler ultrasound of systemic venous system revealed calf muscular venous thrombosis of the right lower limb. The patient underwent percutaneous closure of PAVM. Afterward, warfarin was commenced because of the high risk of further thromboembolic complications in the following weeks to months. Post-treatment CTPA demonstrated successful closure of PAVM. No microbubble signals were detected on post-treatment contrast TCD study (Fig. 1D). Warfarin was maintained with INR between 1.8 and 2.5. The patient suffered no further embolic events during 3-year

follow-up. No recanalization or new PAVMs were detected on CT scan.

3. Discussion

As we know, thrombosis generally refers to local in situ obstruction of an artery, while multiple sites within different vascular territories may be more common in embolism. Given the multiple infarcts within different vascular territory in this patient, negative evaluation for hemodynamically significant carotid or vertebral artery disease, primary diagnostic consideration was given to embolism. Thus, emphasis is placed on investigation of cardiac sources as well as other sources leading to the embolization.

There were no pre-existing conventional vascular risk factors in the patient's medical history. Initial investigations on causes of embolic stroke excluded cardiac embolism secondary to occult paroxysmal atrial fibrillation (AF) and aortic atheromatous disease as well as thrombophilia and substenotic cerebrovascular disease. The diagnosis of undetermined origin stroke might be imprudently made in this clinical setting. However, uncovering the major contributor of thromboembolism is essential to enable the optimal treatment, especially in this patient suffering from several reoccurrences of embolic events. Contrast TCD is a potential alternative to TEE. Recent researches[1,2] indicated that these studies are comparable for the detection of right-to-left shunts, including atrial septal defect, patent foramen ovale, and rare pulmonary arteriovenous malformation. However, TEE could provide anatomic information about the site and size of the shunt, while TCD can only detect a right-to-left shunt, not the location of the shunt. In this patient, transesophageal echocardiogram yielded negative result. Nevertheless, bubble-contrast TCD offered a crucial and valuable clue of occult paradoxical embolism, which prompted further investigation for an extracardiac communication such as a pulmonary arteriovenous malformation. CTPA, which is generally considered the gold standard investigation for diagnosing PAVMs, confirmed the existence of PAVM.

Neurological PAVM-associated risks are common and remain poorly recognized.[3] Even in recent series, the majority of PAVM-induced ischemic strokes or cerebral abscess occurred in patients who had not yet received their diagnosis of PAVM.[4,5] The median delay from cerebral event to PAVM diagnosis was 2 years.[5]

Once the right-to-left shunt is indicated, the source of emboli needs to be considered. When searching for the systemic venous thrombosis in this patient, only calf muscular venous thrombosis of the lower limb was detected. Although it could be the underlying source of paradoxical embolism, the calf muscular venous thrombosis seems less likely to cause large infarction due to its smaller size and lower mobility, compared to that of deep venous thrombosis. Will there be another source of emboli?

According to the definition, PAVM is an abnormal connection between the pulmonary artery and pulmonary vein which lacks that normal capillary component which should exist between the pulmonary arterial and venous circulations of the lung. PAVM may appear macroscopically as a large, single or multilobulated sac or a plexiform mass of dilated vascular channels.[6] Mural thromboses are occasionally seen on pathology of PAVM, which might be a product of the turbulence within the dilated and tortuous anastomosis between an artery and vein. Therefore, we supposed that the PAVM might not only provide the anatomic channel of right-to-left shunt, but also the source of emboli, which were both responsible for the embolic infarction. In this patient, the definite source of emboli was controversial since we did not perform the biopsy of PAVM due to the limitation of catheter occlusion and the pathological evidence of embolus was absent.

PAVM embolization is recommended for the first-line treatment of PAVMs amenable to treatment.[7] In most patients, embolotherapy results in an immediate improvement in the radiographic appearance of PAVMs. Over the long term it also reduces the rate of serious complications especially neurologic events including stroke and cerebral abscess. Surgery is an option for patients who fail repeated embolization as well as for patients whose lesions are suitable for intervention but are deemed not amenable for embolotherapy. In this patient, PAVM was successfully closed by transcatheter embolotherapy, promising an immediate improvement in the radiographic appearance of PAVM and long-term decrement of the rate of neurologic events.

There was no universal recommendation for the duration of anticoagulation following the embolotherapy. Since our patients got a favorable 3-year outcome and tolerated well with Warfarin, the anticoagulative agent was continued.

4. Conclusion

In conclusion, a pulmonary arteriovenous malformation was finally uncovered in this patient with recurrent ischemic stroke, which enabled the optimal treatment. However, neurological PAVM-associated risks are common but remain poorly recognized. A strategic protocol is imperative in searching for the etiologies of cryptogenic stroke.

Author contributions

Conceptualization: J. Ni, M. Liu, S. Gao, X. Yang, Y. Zhu.
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Investigation: J. Ni.
Writing – original draft: X. Yang.
Writing – review & editing: J. Ni, X. Yang, Y. Zhu.

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