FREQUENTLY RECURRENT CEREBRAL INFARCTION AND TROUSSEAU'S SYNDROME

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ABSTRACT

Introduction*: Trousseau's syndrome is a well-known malignancy-associated hypercoagulative state, leading to venous or arterial thrombosis. Stroke may be the first manifestation of the syndrome.*

Materials and methods*: We report a 72-year-old Chinese male developed recurrent cerebral infarction with four events in one month, despite therapy with three kinds of antithrombotics and atorvastatin. Brain magnetic resonance imagine (MRI) showed progressive multiple infarcts, involving the anterior and posterior circulation in two hemispheres of the brain. A whole body positron emission tomography-computed tomography (PET-CT) showed sigmoid carcinoma and tumor metastasis. He was finally diagnosised with sigmoid carcinoma and Trousseau syndrome. Similar medical literatures are reviewed.*

Results*: Ischemic stroke is a common brain lesion in patients with cancer and occasionally is its initial presentation. The widely accepted etiology is related to hypercoagulability though multiple mechanisms are believed to be involved. Elevated plasma levels of D-dimmer have been found in some cancer-related stroke but not all. Low-molecular-weight heparin is considered to be the first-choice agent for controlling thrombosis associated with Trousseau syndrome. Controling over the cancer may help to control the thrombosis.*

Conclusion*: Malignancy should be paid more attention in cryptogenic stroke, particularly in cases of frequently recurrent cerebral infarction. The case of frequent recurrence of cerebral infarction in trousseau has rarely been reported.*

Keywords*: Recurrent stroke, Colon cancer, Cancer hypercoagulability, Treatment.*

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Case Presentation

A 72-year-old Chinese male was admitted to our department because of weakness in the left limbs and slurred speech for 3 days. He has had hypertension for 7 years. His heart rate was 82 beats/min with no atrial fibrillation. Blood pressure was 153/80mmHg (left side) and 156/82mmHg (right side). The neurological examination showed: slurred speech, a shallowing of the nasolabial groove on the left side and the tongue deviated to left. The muscle strength of the left limbs was 4/5. The algesthesia was significantly decreased on the left side. The Babinski and Chaddock signs were positive on the left side. The National Institutes of Health Stroke Scale(NIHSS) was 6. It got 2 scores in the Essen Stroke Risk Score (ERES) and 14 in the Glasgow Coma Score(GCS), while the swallowing function evaluation was normal. Brain magnetic resonance imaging (MRI) showed acute cerebral infarction of the left cerebellum and right frontotemporal lobe (Fig. 1a). The patient was treated with aspirin (100 mg qd) , clopidogrel (75mg qd) and atorvastatin (40mg qn).

On laboratory tests, the blood routine test was normal. The serum of fibrinogen degradation product (FDP) level was negative, and the D-dimer level was 0.40-0.65ug/ml. The tumor marker test results, including CEA, AFP, CA199, CA125, PSA, were within the normal range.

The results of the serum of FT3, FT4, TSH, TPO-Ab, TG-Ab, ANA, ANCA, anti-dsDNA and cardiolipin antibodies were in normal limits. The other tests for this patient including HCY, C-reactive protein, blood glucose level, cholesterol and LDL-C were unremarkable. A more extensive coagulation study(protein C and S, FVIII:C, FIX:CAT-III activity determination) was performed and the result were negative.

After admission, the patient suffered from a series of recurrent strokes regardless of active treatments. On the 11th day, he felt a serious headache. On brain MRI, diffusion-weighted imaging (DWI) showed new lesions in the right cerebellum and cerebrum (Fig. 1b). On the 19th day, His reaction became slowly and the brain MRI showed enlarged lesions (Fig. 1c). On the 34th day, he felt a headache and the muscle strength was further decreased. In the meanwhile, the brain MRI showed new lesions in the left cerebrum (Fig. 1d).

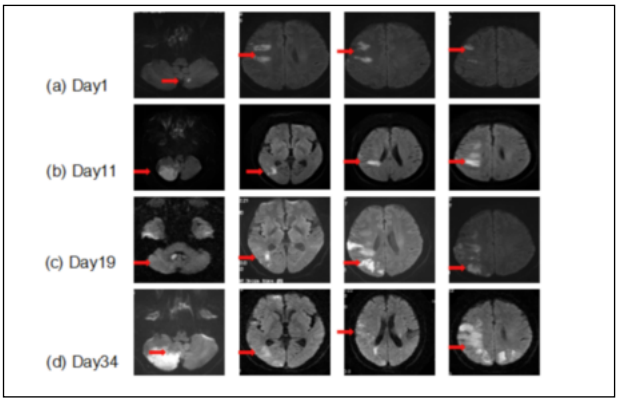

Fig.1. Brain Magnetic Resonance Imaging- Diffusion Weighted Imaging(MRI-DWI) in different timing showed multiple widely spread cerebral infarctions (red arrow) developing over the course of 34 days. Brain MRI in day 1(a), day 11(b), day 19(c) and day 34(d) revealed several new and larger infarctions on both sides of the brain and in the anterior and posterior circulation.

Magnetic resonance angiography (MRA) demonstrated no steno-occlusive changes in cervical and cerebral arteries as well as no obvious aortic plaques. Twenty-four-hours Electro-cardiogram (ECG) monitoring showed sinus rhythm. Transthoracic echocardiography (TEE) was normal. Transcranial doppler (TCD) microembolism monitor and TCD foaming experiment were conducted, but did not reveal any abnormalities.

Finally, a whole body PET-CT (Fig. 2) was conducted, which showed sigmoid colon bowel wall thickening with increased metabolism.

It was considered to be the sigmoid carcinoma, high metabolic lymph nodes, mesenteric root and bilateral adrenal enlargement with high metabolism, which suggested tumor metastasis.

Therefore, he was diagnosed as Trousseau syndrome associated with Sigmoid carcinoma. The patient refused future treatment and was discharged. He died three months later, suffered from other stokes probably.

Discussion

Trousseau syndrome was first described in 1865 by Armand Trousseau[(1)]. Now it refers to all thromboembolic complications related to tumors, including cerebrovascular event, myocardial infarction, peripheral artery occlusion, venous thromboembolism, and hepatic venous occlusive disease, etc. Ischemic stroke is a common brain lesion in patients with cancer and occasionally is its initial presentation. According to a 5-year cohort study, approximately 20% of cryptogenic stroke patients had active cancer at the time of stroke, whereas additional 10 patients (3%) with hidden malignancy[(2)] were identified.

The etiology and pathogenesis is poorly understood, multiple mechanisms are believed to be involved. The widely accepted mechanism is related to hypercoagulability, as cancer often causes a hypercoagulable state. A large autopsy study demonstrated that nonbacterial thrombotic endocarditis (NBTE) is the leading cause of ischemic stroke in patients with cancer, typically occurring in those with disseminated cancer, particularly adenocarcinoma[(3)]. Evidence suggests NBTE arises from cancer-mediated hypercoagulability and consists of sterile, small (5 mm) platelet-fibrin vegetations on normal cardiac valves[(4)].

Furthermore, stroke from NBTE generally often results in diffuse, small- to moderate-size embolic cerebral infarctions. NBTE is the best explanation for the multiple cerebral infarcts in both hemispheres of our patient. And it is interesting that in many cases the cancer is histologically identified as mucin-producing adenocarcinoma[(5)], including gastric, lung, pancreatic and ovarian cancers. Our case was diagnosed as sigmoid carcinoma, histologic type for which is usually adenocarcinoma.

Elevated plasma levels of D-dimmer have been found in cancer-related strokes[(6)]. However, it is unclear whether elevated D-dimer levers are the

result of the cancer or the stroke. A study comparing cancer-related stroke and cancer-free stroke[7] had showed that, higher D-dimer level higher are not sufficient to diagnose cancer-related stroke, as one third of cancer-free stroke patients also had abnormal D-dimer levels. Stroke itself is also associated with increased D-dimer levels, especially the cardioembolic subtype. Furthermore, the D-dimer level does not increase in all thrombosis cases. In our case, the D-dimer level was a little higher, suggesting a trousseau syndrome to a certain extent, while it was not significantly increased, whichmight be helpful to a speedier diagnosis.

Low-molecular-weight heparin is considered to be the first-choice agent for controlling thrombosis associated with Trousseau syndrome[8].The efficacy of warfarin is inferior to heparin. Heparin inhibits the function of cancer-derived mucin, which activates blood platelets, causing microangiopathy[9]. New oral anticoagulants (NOACs) have an additional advantage in that they can be administered orally. But there are no studies, which have assessed the efficacy of NOACs in the treatment of Trousseau syndrome. However, the main mechanism of action of heparin is the inhibition of thrombin and factor Xa, which is more similar to the anticoagulant mechanism of NOACs than warfarin. Therefore, NOACs may be more effective for treatment of the Trousseau syndrome than warfarin[10].

There are many case reports, in which achieving control over the cancer helped to control the thrombosis. But, as it is there is not sufficient evidence to substantiate the claim that controlling the cancer, which is the original illness, is beneficial for controlling the thrombosis[11].

To summarize, acute stroke management in clinical practice should be tailored to the stroke mechanisms in each patient. Malignancy should be considered in cryptogenic stroke, particularly in recurrent cerebral infarction. Identifying hidden malignancy in stroke patients is important for improving prognosis prediction and treatment strategies.

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