

# Recurrent stroke in a patient of lung cancer without pulmonary mass

## A case report

Lisha Wang, MD, Yan Xu, PhD\*, Minghui Tuo, MD, Lei Zhang, PhD, Hong Zhang, PhD, Jing Wang, PhD

### Abstract

**Rationale:** Repeated occurring stroke in short intervals with hypercoagulability is unusual so in such cases the conventional vascular risk factors might not be the causes of stroke.

**Patient concerns:** We have presented a case of 60-year-old male presenting with recurrent stroke due to thrombophilia.

**Diagnoses:** Lung cancer was detected by superficial lymph nodes ultrasound and further pathological examination.

**Interventions:** The patient suffered a recurrent stroke and he had persistently high level of D-dimer which suggested the diagnosis of thrombophilia, thus, he was treated with low-molecular-weight heparin. Unfortunately, the treatment was not effective for the patient and he died before any other treatments could be administered.

**Outcomes:** Despite anticoagulant therapy, the patient suffered multiple episodes of stroke and ultimately died.

**Lessons:** This case of recurrent stroke with coagulation disorders without evidence of cancer in imaging and blood test is rare. So in a stroke patient, we should consider malignancy or metastasis as a differential diagnosis as it may be the first manifestation of active cancer elsewhere.

**Abbreviations:** ADC = apparent diffusion coefficient, CT = computed tomography, DWI = diffusion-weighted imaging, MRA, MRV = magnetic resonance angiography and venography, MRI = magnetic resonance imaging, PT-INR = prothrombin time-international normalized ratio, SWI = susceptibility-weighted imaging, TF = tissue factor.

**Keywords:** lung cancer, radiological features, recurrent stroke, thrombophilia

## 1. Introduction

Stroke is the second most common cause of death and major cause of disability worldwide.<sup>[1]</sup> Referring to etiologies of stroke, over 150 potential causes have been listed.<sup>[2]</sup> Apart from conventional vascular risk factors, cancer could play an important role in patients' vulnerability to stroke. Previous study has demonstrated that stroke in cancer patients is not rare during its clinical course, presenting in up to 15% of patients.<sup>[3]</sup> In addition, about 20% to 40% of cancer patients suffering from cerebral infarction lack conventional stroke risk factors.<sup>[4]</sup> Lung cancer is the most common type of cancer, with the highest incidence of cerebral

infarction. Furthermore, the incidence of cerebral infarction in lung cancer is 1.43 times higher than it is in normal population.<sup>[4]</sup> However, as a primary manifestation in a tumor patient, stroke is rare and is difficult to be identified in clinical practice, especially for those patients without visible mass. Here we report a rare case of recurrent stroke with lung cancer without visible solid mass in lung.

## 2. Case report

A 60-year-old male was brought to the emergency department of a local hospital for a sudden onset of vertigo, blurred vision, and left-hand disability. A brain computed tomography (CT) scan was advised and admitted in the hospital. No abnormality was detected in the CT scan and the patient was diagnosed as acute cerebral infarction and treated with conventional cerebral vascular therapy. The symptoms had completely resolved with treatment so the patient was discharged from the hospital. However, these symptoms reoccurred twice after 7 days and 10 days, respectively. On the 13th days, the symptoms reappeared along with vision impairment and headache. Additionally, his repeat brain CT scan showed bilateral cerebellum hemorrhagic infarction. The patient was then referred to our hospital. Our neurological evaluation revealed vague and dysmetria to the right side in finger-nose test. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) exhibited multiple acute infarctions and a mixed signal in the left-occipital lobe. Susceptibility-weighted imaging (SWI) showed hemorrhagic infarcts in the left-occipital lobe and small hemorrhage lesions in bilateral corona radiata. MRI T2 FLAIR shows old lesions in the right-frontal lobe and new lesions in bilateral occipital lobe and corona radiata. Whereas magnetic resonance angiography and venography (MRA, MRV) displayed no abnormality (Fig. 1).

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Department of Neurology, Zhongnan Hospital of Wuhan University, Wuchang District, Wuhan City, Hubei Province, People's Republic of China.

\* Correspondence: Yan Xu, Department of Neurology, Zhongnan Hospital of Wuhan University, No.169 Donghu Road, Wuchang District, Wuhan City, Hubei Province, People's Republic of China, 430071 (e-mail: shennei@outlook.com).

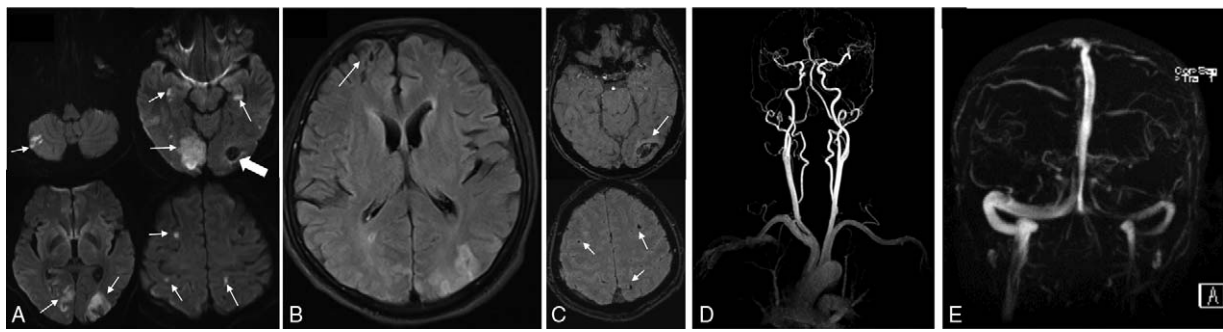
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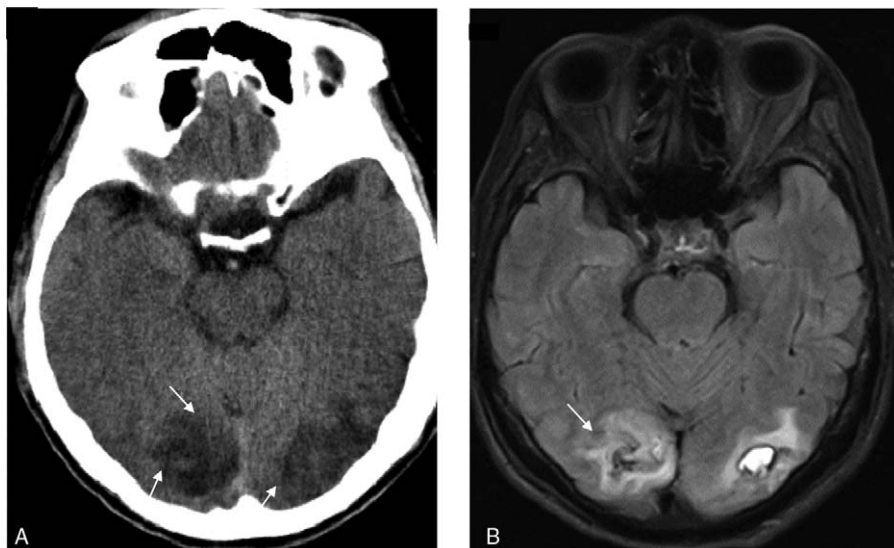


**Figure 1.** (A) MRI diffusion-weighted imaging sequence shows hyperintensity in the right cerebellum, bilateral hippocampus, occipital lobes, frontal and parietal lobes (thin arrow), a mixed signal in the left-occipital lobe (coarse arrow). (B) MRI T2/fluid-attenuated inversion recovery shows hypointensity in the right-frontal lobe (arrow). (C) MRI susceptibility-weighted imaging sequence shows hypointensity in the left-occipital lobe, bilateral frontal, and parietal lobes (arrow). (D) Magnetic resonance angiography (MRA) shows normal arteries. (E) Magnetic resonance venography (MRV) shows normal veins. MRA=magnetic resonance angiography, MRI=magnetic resonance imaging, MRV=magnetic resonance venography.

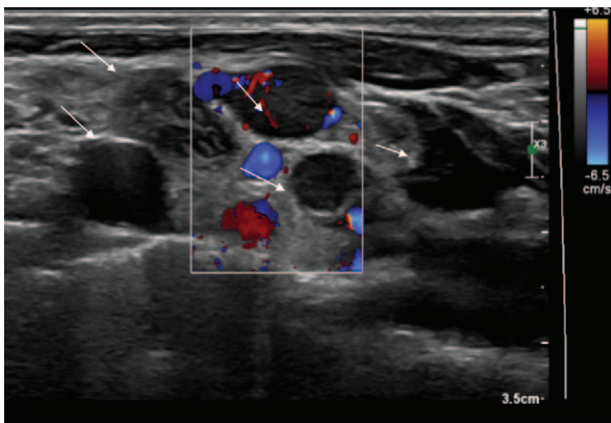
In magnetic resonance imaging (MRI), new and old lesions were seen in the involved cerebral portion along multiple vascular territories in both the anterior and posterior circulation. There was no past history of common vascular risk factors and heart diseases, especially atrial fibrillation. Based on these findings, we considered emboli to be etiology of recurrent stroke. At the same time, blood tests showed coagulation disorders with evaluated prothrombin time-international normalized ratio (PT-INR) (1.45), evaluated D-dimer (2522 ng/mL), reduced antithrombin (73%), and evaluated fibrin/fibrinogen degradation products (45.75  $\mu\text{g/mL}$ ), which suggested thrombophilia. The patient was given symptomatic treatment including mannitol dehydrate therapy and removal of oxygen free radicals, and low-molecular-weight heparin was added for thrombophilia. Regardless the treatment, the abnormal clotting and recurrent stroke continued. The patient's condition got worse and had paroxysmal aggravating left-limbs disability. The left-limbs disability was partially relieved after half an hour. An emergency brain CT performed showed suspicious hemorrhagic infarcts in bilateral

occipital lobe. A repeated MRI showed increase in size of hemorrhagic infarction in the right-occipital lobe (Fig. 2).

Since, cardiac embolism is the most common cause for cerebral embolism, we performed echocardiography, holter monitor, and foaming experiment to screen for underlying heart diseases (endocarditis, arrhythmia, particularly atrial fibrillation, and patent foramen ovale) which may induce the formation of embolus but all these tests were normal. Vascular ultrasound was done to rule out deep vein thrombosis of lower extremities and thrombus was not found in lower extremity vessel. Therefore, we supposed thrombophilia to be the reason of embolism while its pathogenesis of was unclear. Due to multiple etiology of thrombophilia, likely systemic diseases such as connective tissue disorder and cancer were taken into account. The laboratory workup for tumor markers, immune disorders, and infectious diseases were within normal limits. Additionally, there was no family history of hypercoagulability, so thrombophilia due to connective tissue diseases or inherited thrombophilia was unlikely. Cancers usually accompanies abnormalities in coagulation,

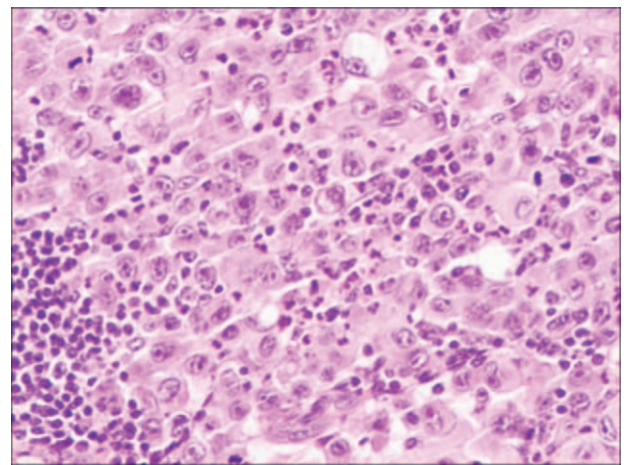


**Figure 2.** (A) The brain CT scan shows suspicious hyperdense zones in bilateral occipital lobe. (B) Repeated MRI T2/fluid-attenuated inversion recovery shows an increasing mixed signal in the right-occipital lobe (arrow). CT=computed tomography, MRI=magnetic resonance imaging.



**Figure 3.** (A) Superficial lymph nodes ultrasound shows swollen lymph nodes (arrow).

so, although with normal tumor markers, further examination were carried out to rule out the diagnosis of malignancy. Bone marrow aspiration was done to screen for hematological cancer. Simultaneously, thoracic and abdominal CT scan, along with prostate ultrasound was also done. These test results were normal. As evident, though a primary mass could not be located, tumor cell may spread via the lymphatic system. So, superficial lymph nodes ultrasound performed revealed enlarged lymph nodes in bilateral cervical, axillary, and inguinal region (Fig. 3A). Unfortunately, when the lymph node biopsy was planned, the patient had a new episode of stroke and he was completely blinded and his left limbs were paralyzed. Along with that he had frequent episodes of nausea and vomiting. The repeat enhanced MRI revealed new infarction in bilateral occipital lobe and parietal lobe and there was no obvious enhanced signal intensity (Fig. 4). Once the patient was stable, lymph node biopsy was done and the result stated supraclavicular lymph node with metastatic carcinoma. Immunohistochemistry results of tumor cell were: CD117 (-), CD20 (-), CDX2 (-), CK7 (+), NapsinA (+), OCT3/4 (-), PLAP (-), SALL4 (-), TTF-1 (+), VILLIN (-), a-inhibin (-), Ki-67 (positive rate 60%), all of which suggested lung cancer (Fig. 5). In conclusion, it was the occult lung cancer

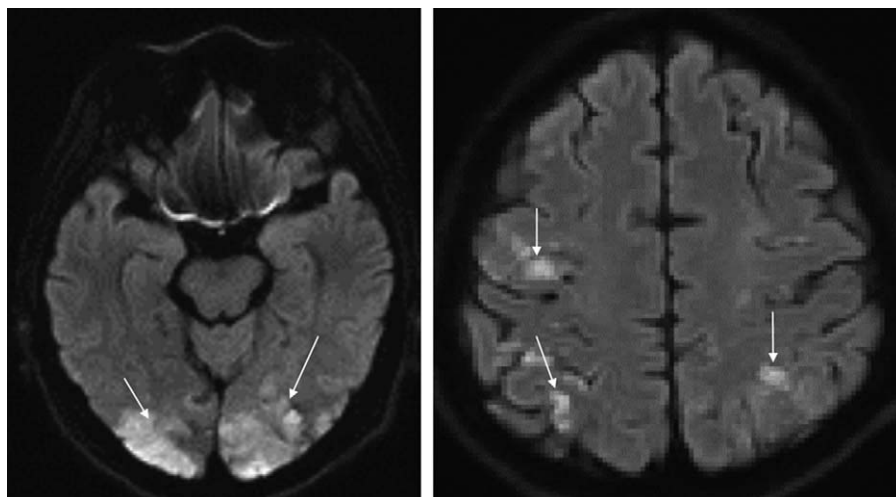


**Figure 5.** Lymph node biopsy shows tumor cells are similar in size, the nucleus is round or oval, much of the nuclear chromatin is deeply stained (high magnification, hematoxylin, and eosin stain).

that induced the recurrent stroke. The patient again had sudden headache, nausea and vomiting and was agitated. His brain CT scan showed an extensive cerebral hemorrhage (Fig. 6). The patient died after 1 week.

### 3. Discussion

We illustrated a case of recurrent stroke with thrombophilia caused by lung cancer, which was diagnosed by pathological examination, without any evidence in blood tests or chest CT scan. The brain MRI showed lesions involving multiple vascular territories in both the anterior and posterior circulation (bilateral middle cerebral artery and bilateral posterior cerebral artery, posterior inferior cerebellar artery) with co-existing new and old lesions. Based on these points, we considered embolism to be the cause of recurrent stroke. Cardiac causes tumors and coagulation disorders because thrombophilia are common reasons of embolism. Thrombophilia has an inherited or acquired predisposition to thrombosis. Thrombophilia is not a disease itself, but may be associated with other diseases (e.g., cancer), drug



**Figure 4.** The second repeated MRI diffusion-weighted imaging sequence shows hyperintensity in bilateral occipital lobe, frontal, and parietal lobes (arrow). MRI = magnetic resonance imaging



**Figure 6.** The repeated CT scan shows hyperdense zone in the right-medial temporal lobe. CT=computed tomography.

exposure (e.g., oral contraceptives) or other conditions (e.g., pregnancy or postpartum), and is known as acquired thrombophilia. Meanwhile, genetic defect in coagulation function may also cause thrombophilia.<sup>[5]</sup> Considering the variety of etiology of thrombophilia, we should conduct a comprehensive examination for determining its etiology. Cancer patient usually have concurrent thrombophilia. Both clinical and laboratory findings indicate that 90% of all metastatic cancers are accompanied by abnormalities in coagulation variables, for example, circulating D-dimers, thrombin-antithrombin complexes, tissue factor (TF), and other changes.<sup>[6]</sup> Cui et al<sup>[7]</sup> have shown that tumor cells could impair the balance of coagulation, anticoagulant, and fibrinolytic system through multiple mechanisms, which leads to prethrombotic state. Therefore, cancer patients are vulnerable to stroke. However, Taccone et al<sup>[3]</sup> retrospectively reviewed 5106 ischemic stroke patients between 1991 and 2004, and identified that a group of 24 patients (0.4%) had an underlying malignancy. Furthermore, tumor cell early can spread via the lymphatic system without visible primary mass, which increases the difficulty of its diagnosis. Therein, the first-ever stroke revealing an undiagnosed underlying malignancy is a very rare event. Also screening for lymph node metastases should not be ignored in diagnosing cancer. A study indicates that higher D-dimer levels can be a prediction of cancer-related stroke.<sup>[8]</sup> In addition, Nam et al<sup>[9]</sup> reported that D-dimer levels may predict 30-day mortality

in acute ischemic stroke patients with active cancer. For cancer patients with venous thromboembolism, treatment with low-molecular-weight heparin is the preferred agent based on the findings of large clinical trials.<sup>[10,11]</sup> Similarly, Jang et al<sup>[12]</sup> have reported that in patients with cancer-associated stroke, the D-dimer levels and the risk of recurrence decreased with enoxaparin administration. On the contrary, D-dimer levels and recurrent stroke were not prevented in spite of giving low-molecular-weight heparin in our case, which was unusual. Persistently high level of D-dimer indicates that the recurrent stroke may be related to tumor emboli and not the thrombus. As for ultimate extensive intracranial hemorrhage, which might be related to the metastatic tumors damaging vessel walls or abnormal clotting, the cause is unclear as autopsy was not done.

#### 4. Conclusions

Our case highlighted that recurrent stroke may be the first clinical manifestation for patients with metastatic tumor even without visible mass entity, particularly without conventional vascular risks factors. Tumor screening such as PET scan and lymph node examination are essential especially in the absence of solid tumor.

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