Cerebrovascular Complications in Patients with Malignancy: Report of Three Cases and Review of the Literature

Poh-Shiow Yeh and Huey-Juan Lin

Abstract- A cerebrovascular thromboembolic event may precede the identification of cancer, and be the first clinical evidence of an underlying malignancy. The malignancy can cause either nonbacterial thrombotic endocarditis or hypercoagulable state, both of which may have clinical manifestions such as thrombotic or embolic occlusion of multiple major cerebral vessels. We present three cases with unusual cerebrovascular events. The first case is a 62-year-old woman who was admitted due to acute left limbs weakness and consciousness disturbance. Brain computed tomographic (CT) scan showed right middle cerebral artery (MCA) and posterior cerebral artery (PCA) infarctions with uncal herniation. The second case is a 44-year-old woman who was hospitalized due to acute bilateral limb weakness and consciousness disturbance. Bilateral MCA, left PCA, anterior cerebral artery (ACA) infarctions and deep vein thrombosis in the left leg were diagnosed. The third case is a 63-year-old man who developed sudden onset of right hemiplegia and consciousness disturbance. Brain CT scan showed bilateral MCA and left ACA infarction. The results of a series of examinations including biochemistry, lipid profile, carotid duplex, and transthoracic and transesophageal echocardiography were unremarkable. All patients had positive disseminated intravascular coagulation (DIC) tests with elevated D-dimers and fibrinogen degradation products (FDP). Further systemic evaluation for malignancy revealed ovarian cancer in the first patient, endometrial carcinoma in the second patient, and adenocarcinoma of lung in the third patient. They all died of the underlying malignancy. Because the hemostatic system can be altered by malignancy, intravascular coagulation abnormalities of these malignancy-related strokes may be disclosed by laboratory assays of hemostasis.

Key Words: Malignancy, Disseminated intravascular coagulation (DIC), Hypercoagulable state

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INTRODUCTION

Cerebrovascular events may be the first clinical manifestations in patients with underlying malignancy[1,2]. Malignancy-related hypercoagulability unaccompanied by nonbacterial thrombotic endocarditis (NBTE) may cause cerebral infarction by thrombotic occlusion of cerebral vessels. Graves et al found intravascular coagulation to be the second most common cause of symptomatic cerebral infarction in cancer

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patients[3]. In stroke of unknown etiology, a paraneoplastic process should always be kept in mind. With a clinical suspicion of cerebrovascular complication related to cancer, we should try to detect the hypercoagulable state which may be associated with the underlying malignancy. Here we present three cases suffering from cerebral vascular events and also malignancies. The unusual clinical presentations and abnormal findings on disseminated intravascular coagulation (DIC) profiles unveil hypercoagulability states which may be related to the underlying malignancies. Antineoplastic treatment was initiated as soon as the pre-existing cancers were found and confirmed by further studies in these patients.

CASE PRESENTATION

A 62 year-old female patient was admitted because of leftlimb weakness and consciousness disturbance. Brain computed tomography (CT) scan showed infarction in the right middle cerebral artery (MCA) and left posterior cerebral artery (PCA) territories (Fig. 1). There was no history of major systemic diseases, such as hypertension, diabetes mellitus and hypercholesterolemia, and she is anonsmoker. Laboratory examinations revealed normal biochemistry, lipid profile, complete blood counts and platelet counts, prothrombin time (PT) and activated partial thromboplastin time (aPTT).

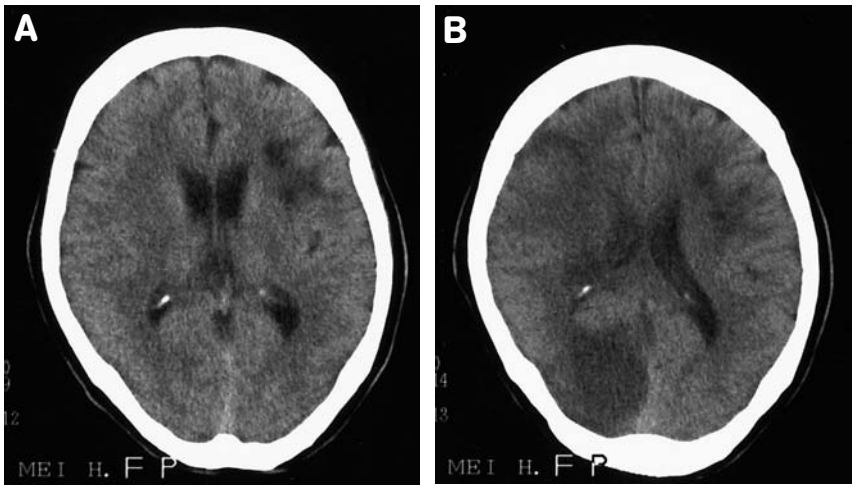

Figure 1. (A) Left frontotemporl subcortical hypodensity was seen on the first day of stroke. (B) Right frontotemporal infarcts (right MCA territory) and right occipital infarcts (right PCA territory) in evolution on the third day of stroke.

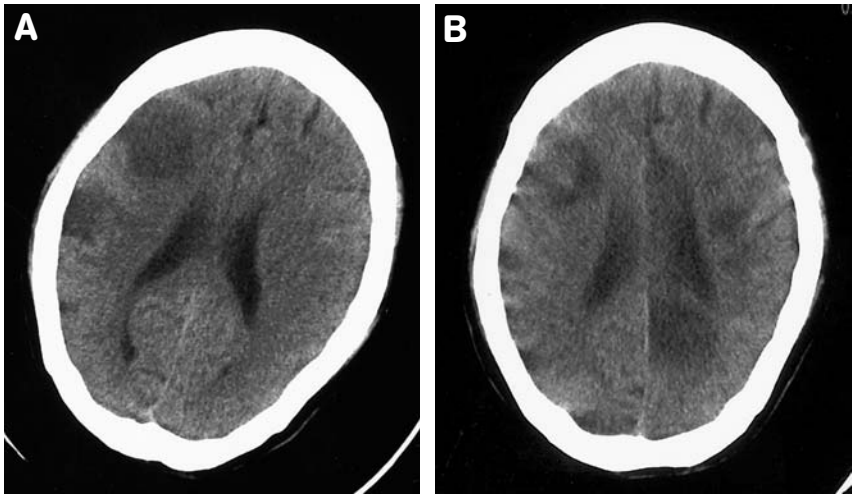

Figure 2. (A) Right perisylvian and frontal infarcts (right MCA territory). (B) Infarcts in the territories of bilateral MCA, left ACA, and left PCA.

The DIC panel disclosed highly elevated FDP level (160,000-320,000 ug/L, normal range < 5000 ug/L), D-dimers level (3970 ug/L, normal range < 250 ug/L), and normal fibrinogen level (399 mg/dL, normal range 200-400 mg/dL). The carotid duplex study revealed normal findings. There was no valve or chamber abnormality in transthoracic echocardiography (TTC) and transesophageal echocardiography (TEE) examinations. Because tumor marker studies revealed elevated CA 125 (372.1 U/ml, normal range < 35 U/ml), a paraneoplastic process related chronic DIC status was highly suspected. Abdominal CT scan showed an ovarian tumor, which was proved to be a malignancy with intestinal, mesenteric, and peritoneal seeding after surgical intervention. She died of the underlying malignancy one month after the onset of cerebral infarction.

The second patient was a 44 year-old female who was hospitalized due to acute onset of bilateral limb weakness and obtunded consciousness. Emergent brain CT scans showed multiple infarctions on bilateral MCA, left PCA and anterior cerebral artery (ACA) territories (Fig. 2). She was also noted to have deep vein thrombosis in the left lower limb later (Fig. 3). There is no past history of cardiac or any other major systemic diseases. Routine laboratory examinations including biochemistry, lipid profile, complete blood counts and platelet counts, PT and aPTT were all normal. The electrocardiography (EKG), TTE and TEE findings were also unremarkable. However, the DIC panel showed abnormal findings with much elevated FDP level around 160,000-320,000 ug/L, D-dimer around 5980 ug/L, and fibrinogen level at 492 mg/dL. Further tumor marker studies showed high level of CA 199 (>500 U/mL, normal rage < 37 U/mL) and CA-125 (277 U/mL, normal range < 35 U/mL). Abdominal sonography revealed a hepatic tumor, and needle biopsy disclosed an endometrioid carcinoma with liver metastasis. Despite antithrombotic treatment, her condition declined quickly and she died before any anti-neoplastic therapy was given.

The third patient was a 63 year-old male who suffered from sudden onset of right hemiplegia and speech difficulty. The first brain CT scan showed recent infarction in the left perisylvian area, possibly supplied by the MCA. Routine biochemistry and hematology laboratory tests were all normal. EKG, TTE and TEE studies also disclosed no abnormalities. However, there is a mass-like lesion near the right hilum in plain chest X-ray, and chest CT revealed a right hilar mass with right pleural effusion and lymphadenopathy in the retrocava and paracava space. Lung cancer was thus highly suspected. The DIC panel showed a chronic DIC status with normal PT, aPTT, and fibrinogen level, but highly elevated FDP (320,000-640-000 ug/L) and D-dimers (3670 ug/L). Unfortunately, left hemiplegia and consciousness distur-

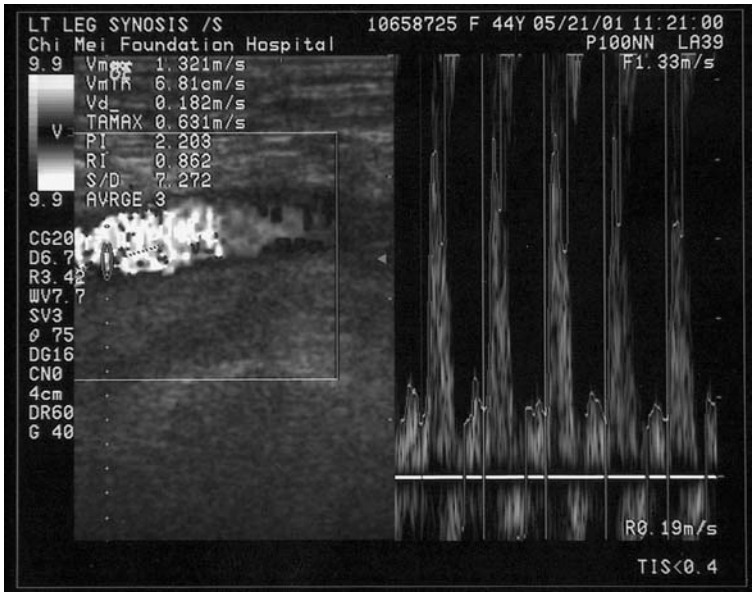

Figure 3. Increased peak systolic velocity and aliasing phenomenon in the left common femoral artery revealed by Doppler sonography.

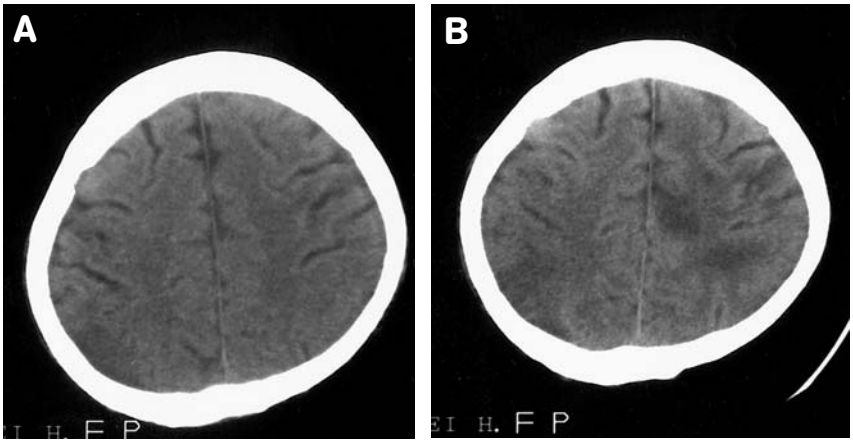

Figure 4. (A) Right occpitoparietal infarct (right MCA territory) on the first day of stroke. (B) Left parasagittal and frontoparietal infarcts (left ACA and MCA territories) on the fifth day of stroke.

bance developed about 8 days later in spite of oral anticoagulant treatment, and repeated brain CT scans disclosed new cerebral infarctions in the right MCA and left ACA territories (Fig. 4). He died of poor neurologic condition.

DISCUSSION

In all 3 cases the clinical symptoms developed suddenly. Brain CT scans without contrast medium were done within 12 hours after the onset of symptoms, and revealed hypodense lesions mainly confined to the cortex and major arterial territories, suggesting cerebral infarction rather than brain metastasis. These cases had recurrent cerebral infarctions involving the territories of more than one major artery, but series of clinical investigations fail to demonstrate any evidence of cardiogenic embolization or artery-to-artery embolism, suggesting cerebrovascular diseases related to unusual etiology.

Since the first description of the association between deep vein thrombosis and pancreatic malignancy by Trousseau in 1865[4], many studies have confirmedof the abnormally activated hemostatic system in cancer patients. The hemostatic system can be altered significantly by malignancy. For example, abnormal hemostasis assay is detectable in 50% of the patients with cancer, and even up to 95% of those with metastasis[5]. The changes of hemostatic system may includeincreased fibrinogen and platelet catabolism, unusually elevated titers of coagulation factors V, VIII, IX, X, fibrinogen, peptide A, peptide B, FDP, and D-dimers[6,7]. These laboratory findings vividly imply the existence of consumptive coagulation processes. It is also reported that many malignant tissues can release procoagulant materials, and sometimes also fibrinolytic materials, into the systemic circulation[6,7]. Myeloproliferative syndromes, paraprotein disorders, and the malignant tumors of lung, colon, gallbladder, stomach, ovary, and pancreas are most commonly associated with thrombosis[7].

DIC, a common hematologic abnormality in patients with cancer, may complicate the the clinical picture any time during the course of the malignacy, either when the malignancy is still occult[8], or when it is widely disseminated[9]. The altered intravascular coagulation status may be so mild that it can be detected only by abnormal laboratory tests, such as elevated levels of FDP, D-dimers, fibrinopeptides A and B, and so on. On the other hand, abnormalities in intravascular coagulation may proceed to more than just a laboratory phenomenon, and become clinically manifest by localized thrombosis, embolization, or systemic disseminated intravascular coagulation. The brain could be involved in about 70% of the patients with malignancy-related DIC, followed in order by the heart, kidney and spleen[10,11]. Nearly 25% of brain infarcts in cancer patients occurred as consequences of DIC[12].

The morbidity and mortality rates of these paraneoplastic cerebrovascular events are high, and thus effective therapy of DIC in such patients represent a major clinical challenge. These patients are notoriously resis-

tant to anticoagulant therapy, and thromboembolic events usually continue after initiation of antithrombotic remedies[13]. The first and most essential therapeutic modality should be directed to the treatment of the underlying malignancy which is the trigger of the procoagulant process. Antineoplastic therapy is often associated with significant improvement or cessation of DIC[14,15]. The treated patients are less susceptible to thrombosis and thromboembolism after correction of the abnormal hemostasis status.

A paraneoplastic process should always be kept in mind in stroke of unknown etiology, although there has been no standard or pathognomonic laboratory tests for malignancy-related DIC. These patients usually have highly elevated FDP and D-dimers, indicating that a widespread clotting process has occurred and the fibrinolysis is active[1,16,17]. The three cases in this report all suffered from unusual cerebrovascular events with multiple cerebral arteries occlusion and chornic DIC, and were all proved to have malignancies with the treatment diverted to antineoplastic modalities accordingly.

In conclusion, coagulopathy and thrombotic occlusion of the cerebral vessels in the absence of NBTE is one of the common causes of cerebral infarction in patients with cancer. Clinical neurologist shall keep in mind that cerebrovascular event could sometimes be the first clinical manifestation of paraneoplastic syndromes. The cerebrovascular event usually results from hypercoagulable state and is a presentation of chronic form of DIC. Investigation with appropriate hematological tests may help to diagnose the unusual hypercoagulable state. When the diagnosis of malignancy is establisheda combination of antineoplastic and antithrombotic therapy should be given immediately.

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