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

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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 manifestations 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

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.
patients\(^{17}\). 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).
The DIC panel disclosed highly elevated FDP level (160,000-320,000 µg/L, normal range < 5000 µg/L), D-dimers level (3970 µg/L, normal range < 250 µg/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 µg/L, D-dimer around 5980 µg/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 para-cava 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 µg/L) and D-dimers (3670 µg/L). Unfortunately, left hemiplegia and consciousness distur-
bance developed about 8 days later in spite of oral anti-
coagulant treatment, and repeated brain CT scans dis-
closed 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 sud-
denly. Brain CT scans without contrast medium were
done within 12 hours after the onset of symptoms, and
revealed hypodense lesions mainly confined to the cor-
tex 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 inves-
tigations fail to demonstrate any evidence of cardioenic
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 confirmed of the
abnormally activated hemostatic system in cancer
patients. The hemostatic system can be altered signifi-
cantly by malignancy. For example, abnormal hemosta-
sis 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 include increased fib-
rinogen 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 sys-
temic circulation(6,7). Myeloproliferative syndromes, para-
protein disorders, and the malignant tumors of lung,
colon, gallbladder, stomach, ovary, and pancreas are
most commonly associated with thrombosis(6,7).

DIC, a common hematologic abnormality in patients
with cancer, may complicate the the clinical picture any
time during the course of the malignancy, either when the
malignancy is still occult(8), or when it is widely dissemi-
nated(9). The altered intravascular coagulation status may
be so mild that it can be detected only by abnormal labo-
rary 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, emboliza-
tion, 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 paraneo-
plastic cerebrovascular events are high, and thus effec-
tive 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\textsuperscript{(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\textsuperscript{(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\textsuperscript{(14,15,16,17)}. The three cases in this report all suffered from unusual cerebrovascular events with multiple cerebral arteries occlusion and chronic 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 established a combination of antineoplastic and antithrombotic therapy should be given immediately.

REFERENCES