We report a 71-year-old Taiwanese woman with polycythemia vera (PV) presenting with repeated ischemic cerebral infarctions culminating in total occlusion of the right internal carotid artery despite antiplatelet prophylaxis and regular phlebotomy to reduce blood viscosity. Only after the treatment was changed from antiplatelet therapy to anticoagulation for secondary prophylaxis was the chain of recurrent cerebrovascular events broken. JAK2 gene mutation is hypothesized to play a major role in the interaction between blood hyperviscosity and ischemic stroke. Whether it can enhance cascade of coagulopathy resulting susceptibility toward stroke, is still unclear and under close investigation. This report delineates the necessity of using anticoagulant medication to treat PV patients with positive JAK2 mutation. Its complex interplay in hypercoagulopathy and possible thromboembolic event is dicussed.

Cerebrovascular disease often arises from events related to malignancy, although the exact incidence is unknown [1]. Cerebrovascular disease can result from direct tumor embolization; treatment-related complications from chemotherapy, radiation, and hematopoietic stem cell transplantation; and hematological abnormalities such as hypercoagulopathic states in disseminated intravascular coagulation, polycythemia vera from erythropoietin (EPO)-producing tumors, and nonbacterial thrombotic endocarditis. Cestari et al [2] reported that cancer is the most common (30%) primary source of embolic strokes based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Management of ischemic stroke depends on whether the underlying hematological disorder is primary in origin or secondary to malignancy.

CASE REPORT

A 71-year-old Taiwanes woman with a past history of polycythemia vera on regular phlebotomy, peptic ulcer, and hypertension was admitted in March 2005. She suffered from sudden total paralysis of the left extremities with a mild degree of facial palsy on the left side. There was no slurring of the speech, choking on swallowing, eye ball deviation, or spinning sensation.

Other than a transient elevation of blood pressure (201/94 mm Hg) on admission, her physical examination was unremarkable. On neurological examination the patient had good consciousness and orientation with mild left facial palsy of the central type. Muscle power was intact in the right extremities but she was totally paralyzed with a score of 5/0 on the Medical Research Council (MRC) scale in the left extremities.

Brain computed tomography (CT) and magnetic resonance imaging (MRI) on admission showed...
infarctions in the right frontal and parietal lobes. Cervical color-coded duplex study revealed high resistance flow profiles in the bilateral carotid arteries and left vertebral artery with mild plaque formation in the right carotid artery. Transcranial color-coded Doppler study showed only insignificant findings.

The electrocardiogram was normal but echocardiography showed right ventricular enlargement. An abdominal sonogram showed mild splenomegaly without metastatic tumor. Chest roentgenography depicted no lung lesion. No thrombolytic therapy was given except phlebotomy since the patient arrived at the emergency department after the onset of symptoms. The patient’s left limbs partially recovered to muscle power 3/4 on the MRC scale within 2 weeks. She was discharged later with antiplatelet therapy (ticlopidine) for secondary prophylaxis. Regular phlebotomy treatment was discontinued.

One month later in April 2005, the patient was re-admitted with recurrent weakness and dysarthria. Neurological examination revealed muscle strength of 2/4 on the MRC scale for the left limbs with a sensory deficit on the left half of the body. Repeated brain CT showed infarctions involving the right centrum semiovale. She was discharged 2 weeks later with the same antiplatelet therapy on account of poor compliance.

Five months later, in July 2005, the patient was admitted again with recurrent total paralysis (0/0 on the MRC scale) of the left extremities with slight deviation of the mouth, slurring of speech, and urinary incontinence. Neither serum nor cerebrospinal fluid examinations revealed no malignant cells or other abnormalities except slightly elevated CEA (carcinogen embryonic antigen) level. Polycythemia vera was confirmed to be primary by the molecular test for Janus tyrosine kinase 2 (JAK2) gene mutation expression and normal erythropoietin (EPO) level in the blood[3]. Transesophageal echocardiography (TEE) showed no obvious thrombus at the left atrium and atrial appendage. Repeated brain MRI showed multiple lacunar infarctions in the right frontal lobe, parietal lobe, corona radiata, and basal ganglia. Cranial magnetic resonance imaging/angiography showed high-grade stenosis of the right internal carotid artery leading to right side middle cerebral artery infarct (Fig. 1, 2). Vertebral and bilateral common carotid arteriography showed total occlusion of the right internal carotid artery at the supraclinoid segment, hypoplasia of the A1 segment of the left anterior cerebral artery, narrowing of the short segment of the M1 segment of the left middle cerebral artery, and leptomeningeal collaterals from the posterior circulation to the posterior aspect of

Figure 1. Magnetic resonance angiography: high-grade stenosis to total occlusion of the right internal carotid artery and focal stenosis of the left M1 segment four months after the third admission.(arrows)

Figure 2. Diffusion weighted imaging of brain: multiple infarcts in the right frontal lobe, parietal lobe, corona radiata, and basal ganglia. (arrows)
JAK2 gene mutation associated with cerebral infarction

The results of F-18 fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning of the brain were consistent with stroke involving the right hemisphere with crossed cerebellar diaschisis and activation of hematopoiesis of bone secondary to therapy with no evidence of recurrence or metastasis. The laboratory data were indicative of a hypercoagulopathic state with D-dimer >1.0<2.0 μg/ml (normal <0.5 μg/ml) and fibrin degradation product >16<32 μg/ml (normal <8 μg/ml). Anticoagulation (heparin) was initiated and continued with coumadin after discharge for secondary stroke prevention. As a result, the patient had no more recurrence of strokes. Her neurological status improved and regained to a 4/5 on the MRC scale for the left extremities during follow-up visits in December, 2008.

DISCUSSION

Malignancy and hematological disorders such as Polycythemia vera (PV) are well recognized risk factors for coagulation disorders and vascular thrombotic events[1-4]. This patient had the later factor. When she was admitted on the first occasion, it was uncertain whether polycythemia was primary or secondary to malignancy. However on her third admission, polycythemia vera was confirmed to be of primary origin.

Polycythemia vera is a rare and primary myeloproliferative stem cell disorder causing hyperplasia of erythrocyte, leukocyte, and megakaryocyte cell lines in the bone marrow, predominantly erythrocyte cell lines. Somatic point mutation of the tyrosine kinase 2 (JAK2) V617F gene has been described in about 60-70% of polycythemia vera patients[5]. This JAK2 mutation appears to confer a slower rate of disease progression but a higher risk of thrombotic complication[6]. Increased endothelial thickening and injury to intima layer of blood vessel secondary to byproduct of JAK2 mutation might capitulate recurrent pattern in such a short time in our patient.

Thrombotic events of the arterial and venous system are common due to increased blood viscosity[7,8]. Regular phlebotomy to maintain HCT within 50 percent and antiplatelet therapy can reduce the risk of but not totally prevent platelet-mediated microvascular circulation disturbance in polycythemia vera patients due to persistent thrombocythemia[9,10].

The fact that this patient had recurrent strokes leading to total occlusion of the right middle cerebral artery despite antiplatelet therapy and regular phlebotomy highlights the role of hypercoagulopathy from possible PV origin. Although metastasis and non-cancer thrombus were not observed on intensive investigation, the possibility of microembolization could not definitely be excluded unless detection of microembolic signals was performed as was done by Segula et al[11].

Though seldom, the mechanism similar to that of malignancies induced hypercoguloable state such as adenocarcinoma of the colon or cholangiocarcinoma was proposed in medical literature and indeed associated with widespread thromboembolism when cancer cells progress uncontrollably[12]. Kutluhan et al reported a case of cerebral infarction in a patient with colon carcinoma and protein C and S deficiencies who had a response to aspirin and heparinoid[13]. The only abnormal datum was a slight CEA level increase both in the cerebrospinal fluid and the serum testing. Based on PET scanning and lack of clinical tumor recurrence after extensive evaluation it was postulated that the increased CEA level in the

Figure 3. Intracranial arteriography: hypoplasia of the A1 segment of the left anterior cerebral artery, narrowing of the short segment of the M1 segment of the left middle cerebral artery, and leptomeningeal collaterals from the left middle cerebral artery, left anterior cerebral artery, right anterior cerebral artery, and finally the right middle cerebral artery.
cerebrospinal fluid may not be attributed to cancer. A raised cerebrospinal fluid CEA level has been found in patients with metastatic and nonmetastatic neurological disease [14]. So its specificity is equivocal.

When hypercoagulopathy or metastatic emboli is a consideration, the clinical approaches for ischemic stroke in patients with cancer or hematological disorder should be different from that of stroke in patients with other conditions [15]. Clinical staging and pathology of the neoplasm or the hematological abnormality are the main determinants for influencing treatment modalities. Prognosis is primarily determined by the underlying malady and the residual neurological status. JAK2 mutation does not exist in all PV patients. Its role in hematological area is still obscure. Routine work-up JAK2, in terms of preventing stroke in PV patients, is crucial because it can greatly alter prognosis. Thus first-line clinician should be alert and prompt use of anticoagulant might serve as a thumb of rule in treatment guideline.

REFERENCES
JAK2 基因突變與腦梗塞的不尋常關係：
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我們報導一位 71 歲女性，她之前有真性紅血球增多症。這次住院的原因是因為反覆中風，縱使在用完抗血小板劑及放血治療後仍然無效。腦部檢查發現他有右側頸動脈狹窄的問題。在我們把抗血小板換成抗凝血劑之後她的中風情況大有改善。在這篇文章裡面我們討論了血液黏稠（JAK2 基因突變）及中風本身的關係，其中的生理病理均有論述。