



Multiple Hemorrhagic Strokes From DIC Associated With Occult Large Cell Carcinoma

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Abstract:

Background and Purpose: Multiple hemorrhagic strokes are a rare presentation of paraneoplastic disseminated intravascular coagulation (DIC). We present a case of DIC occurring in a patient with occult large cell carcinoma.

Summary of Case: A 77-year old Asian-American man presented with 1 month of vision disturbance followed by acute onset of left hemiparesis and encephalopathy. He was found to have three strokes of varying ages, and was placed on aspirin and clopidogrel. He returned 4 days later with hemorrhagic conversion of the strokes and laboratory abnormalities suggestive of DIC. Over the hospital course, he suffered recurrent ischemic strokes and intracerebral hemorrhages despite management of his coagulopathy. On autopsy, an occult large cell carcinoma was found in the hilar lymph nodes, as well as multiple intravascular thrombi.

Conclusions: Recurrent hemorrhagic strokes associated with DIC may be the initial presentation of occult malignancy. Although adenocarcinoma is classically associated with paraneoplastic DIC, this case demonstrates that large cell carcinoma may also be implicated.

Key Words: Disseminated intravascular coagulation; large cell carcinoma; ischemic stroke; intracerebral hemorrhage; paraneoplastic.

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A 77-year old Asian-American man presented with acute onset of left hemiparesis and confusion to a local emergency department. He had been involved in a motor vehicle collision 1 month previously, and his vision had been abnormal since that time. Past medical history included hypertension, hypercholesterolemia, and recent multistage oral surgery. His medications were lisinopril and simvastatin. He had a long history of tobacco use. Review of systems included easy bruising and recent unintentional weight loss. Initial laboratory studies were normal, including coagulation and hematology

profiles. Examination revealed mild left hemiparesis and right homonymous hemianopsia. Magnetic resonance imaging (MRI) of the brain showed subacute infarcts in the left posterior cerebral artery (PCA) territory, left subcortical frontoparietal region, and an acute infarct in the right operculum. Transthoracic echocardiography (EKG) and intracranial and extracranial MR angiography were normal. The patient was discharged on clopidogrel and aspirin. He returned to the emergency department 4 days later, after a generalized seizure. Head computed tomography (CT) showed hemorrhagic conversion



of the prior strokes (Figure 1). Laboratory evaluation revealed an international normalized ratio (INR) of 1.9 and an elevated D-dimer.

The patient was transferred to the Johns Hopkins Neurosciences Critical Care Unit for further evaluation. Admission laboratory studies revealed an INR of 2.5, fibrinogen less than 50 mg/dL, D-dimer 3784 mg/L, lactate dehydrogenase 350 U/L, hemoglobin 7.7 g/dL, and the presence of schistocytes on a peripheral blood smear. Von Willebrand factor (vWF)-cleaving protease activity was normal and vWF-cleaving protease inhibitor was absent. Creatinine, platelet count, cardiac enzymes, and EKG were normal. Anticardiolipin and circulating anticoagulant immunoglobulin titers were within normal limits. The laboratory studies were interpreted as consistent with disseminated intravascular coagulation (DIC). In consultation with the Hematology service, he was given vitamin K and transfused blood products to maintain fibrinogen greater than 150 mg/dL and INR less than 1.5. The initial differential diagnosis for DIC included endocarditis related to recent dental procedures, occult malignancy, and an idiosyncratic reaction to clopidogrel. A transesophageal EKG demonstrated no valvular vegetations and multiple blood cultures had no growth. CT of the chest, abdomen, and pelvis revealed a $2.1 \times 1.7 \text{ cm}^2$ left hilar lymph node. Esophagogastroduodenoscopy and colonoscopy demonstrated no mass. A positron emission tomography scan showed hypermetabolism and enlargement of multiple mediastinal and supraclavicular lymph nodes.



Fig. 1. Unenhanced head CT showing hemorrhagic infarcts in the anterior left MCA, posterior right MCA, and left PCA territories with ischemic right PCA infarct.

Despite treatment of the coagulopathy, the patient continued bleeding from multiple regions, including venopuncture sites, urethra, and upper gastrointestinal tract. Over subsequent days, his neurological function progressively declined and a second brain MRI demonstrated multiple new ischemic strokes in the right middle cerebral artery territory. In consultation with the Hematology service, the patient was placed on intravenous unfractionated heparin, titrated to a partial thromboplastin time (PTT) ratio of 1.5 to 2.0. Given declining neurological function and poor prognosis for recovery, however, the family opted to withdraw supportive measures and the patient quickly expired. Autopsy revealed multiple small thrombi within the vasculature of the brain, heart, kidneys, spleen, and lungs. Gross lymphadenopathy was present in the lung hilum and paratracheal region. On microscopic examination, a poorly differentiated large cell carcinoma was seen infiltrating these lymph nodes (Figure 2). The immunohistochemical staining pattern strongly argued in favor of a primary lung cancer; however, exhaustive sectioning of the lungs revealed no identifiable tumor. An occult salivary gland neoplasm could not be entirely excluded because limitations placed on the autopsy precluded head and neck examination.

Discussion

Remote cancer is associated with an increased risk of thrombosis and stroke through a variety of mechanisms including vascular compression and infiltration, nonbacterial thrombotic endocarditis, and antiphospholipid antibody syndrome (1–3). Based on review of the literature, this is the first reported case of DIC-related recurrent strokes associated with occult large cell carcinoma. Paraneoplastic DIC has been widely reported in the literature, most commonly in association with hematological malignancies, especially acute promyelocytic leukemia (1,2). Intraabdominal and lung adenocarcinoma is the solid

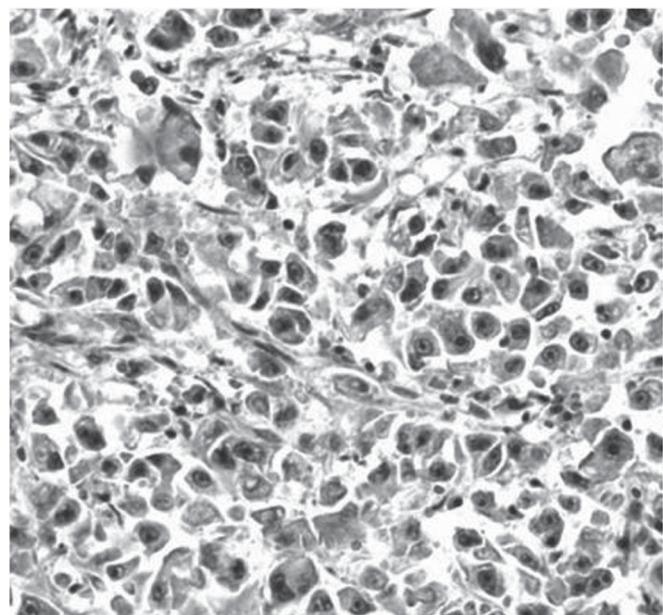


Fig. 2. 10X magnification of hilar lymph node Hematoxylin and Eosin stain showing large cell carcinoma morphology.

tumor histology most commonly associated with DIC (4). The incidence of chronic, low-grade DIC in solid tumors was reported as 6.8% in a study of 1117 patients with solid tumors referred for Oncology consultation (4). Although 5% of patients with paraneoplastic DIC experience a central nervous system hemorrhage, ischemic strokes only rarely occur in this condition (4).

DIC is a clinical syndrome characterized by excessive bleeding and thrombosis with a unique pattern of laboratory abnormalities. It is caused by microvascular deposition of fibrin leading to ischemic organ failure and intravascular shearing of erythrocytes (5). Thrombotic consumption of fibrinogen, platelets, and prothrombin also lead to hemorrhage (5). Excessive fibrinolysis yields a detectable rise in fibrin degradation products, including D-dimer. The syndrome includes episodes of thrombosis and hemorrhage in the setting of elevated PTT, fibrin degradation products, schistocytes, LDH, and D-dimer, as well as low fibrinogen and platelets.

The mechanism of paraneoplastic DIC is not fully understood, but undoubtedly differs from sepsis-related DIC, in which widespread endothelial injury is pathogenic (1,2). Tissue factor expression on cancer cells appears essential for initiating DIC (6). Tissue factor interacts with tenase and prothrombinase complexes to generate excessive circulating thrombin (7). The overproduction of thrombin leads to consumption of coagulation factors, increased fibrin production, and release of tissue plasminogen activator from endothelial cells (8). Elevation of tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6—either by the tumor itself or as a systemic immunological response to tumor cells—has also been implicated (9,10).

In this case, the other diagnostic possibility of primary concern was thrombotic thrombocytopenic purpura (TTP). Although the patient was symptomatic prior to clopidogrel exposure, the development of laboratory abnormalities within 1 week of its initiation is provocative. At least 50 cases of TTP have been associated with clopidogrel use in postmarketing analysis (11). Drug-induced TTP is caused by autoantibodies against vWF-cleaving protease (12). Impaired degradation of vWF leads to the formation of abnormally large multimers, which subsequently bind to platelets and form microthrombi (13). Patients with clopidogrel-induced TTP have demonstrated undetectable levels of vWF-cleaving protease activity

and the presence of IgG inhibitors of the protease (13). In this case, vWF-cleaving protease activity was normal and the inhibitory IgG was absent. TTP can also be distinguished from DIC by the relative normalcy of the PTT and fibrinogen and the presence of thrombocytopenia (5). Based on these criteria, the laboratory abnormalities and clinical history were highly suggestive of DIC, rather than TTP, although clopidogrel cannot be excluded as a contributory factor.

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