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Subcortical Hemorrhage in Disseminated Intravascular Coagulation Associated with Sepsis

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Summary: Cranial CT features of two patients with intracerebral hemorrhages in the setting of sepsis and disseminated intravascular coagulation are reported. Multiple predominantly subcortical hemorrhages were seen. This pattern of cerebral hemorrhage should raise suspicion of disseminated intravascular coagulation as an underlying cause.

Index terms: Cerebral hemorrhage; Blood, coagulation; Nervous system, infection; Brain, computed tomography

Disseminated intravascular coagulation is a common complication of severe sepsis. The transition to multiorgan failure suggests a poor prognosis (1). Intracerebral hemorrhage associated with disseminated intravascular coagulation has been recognized in autopsy studies (2–5). Radiologic findings of subdural hematoma, subarachnoid and massive lobar hemorrhages, and hemorrhagic infarcts (often in association with venous sinus thrombosis), have been occasionally described (6–9).

We report two patients with disseminated intravascular coagulation and multiple intracerebral hemorrhages.

Case Histories

Patient 1

A 74-year-old man presented with fever and dyspnea. He had a history of a total colectomy for ulcerative colitis, recurrent small-bowel obstruction, and subsequent short bowel syndrome as a result of bowel ischemia and surgical resection. On admission he was oriented, but dehydrated, and tachypneic with a blood pressure of 90/50. Laboratory examination showed a metabolic acidosis, with a creatinine level of 7.1 mg/dL, platelet count of 20×10^9/L, activated partial thromboplastin time of 46.8 seconds (26 to 41 seconds), prothrombin time of 15.3 seconds, (10.9 to12.8 seconds), fibrinogen of 205 mg/dL (195 to 365), and fibrinogen split products of more than 40 mcg/mL (normal less than 10 mcg/mL). Blood cultures grew *Klebsiella oxytoca*. The patient required intubation and ventilation and was aggressively treated with fluid resuscitation, colloids, fresh frozen plasma, and intravenous antibiotics (imipenem and aztreonam). Over the subsequent days oxygen delivery was transiently poor from adult respiratory distress syndrome, and hemodialysis for acute renal failure was required. Blood pressure remained labile with periods of hypotension to a systolic blood pressure of 70 mmHg responding to increasing doses of inotropes. Cranial computed tomography (CT) 12 days after admission revealed petechial subcortical hemorrhages (Fig 1). After discontinuation of sedation (midazolam) 1 week later, the patient remained unresponsive to pain with otherwise intact brain stem reflexes and ability to trigger the ventilator. The patient died 12 days after admission after withdrawal of support, and permission for autopsy was not granted.

Patient 2

A 62-year-old man was transferred from another hospital with acute renal failure secondary to sepsis and myoglobinuria after a failed femoral-popliteal graft. On admission the patient was drowsy, with a temperature of 37.8°C and blood pressure of 136/50 mmHg. His right leg was ischemic from the upper thigh down and was cool and mottled in appearance with infected surgical wounds. A hemipelvectomy was performed. The patient required large volumes of intravenous fluid replacement, but his blood pressure was well maintained with only a small amount of inotropic support. Investigations included a prothrombin time of 13.8 seconds (10.9 to 12.8 seconds), activated partial thromboplastin time 64.5 seconds (26 to 41 seconds), and platelets 36×10^9/L. Renal function was slow to improve; hemodialysis was required on days 5 and 7, with blood pressure well maintained and 2000 and 3500 U of heparin being given with each dialysis. His level of consciousness did not improve, and neurologic examination revealed withdrawal to painful stimuli and bilateral Babinski responses. A cranial CT scan showed multiple intracerebral hemorrhages in the deep white matter (Fig 2). The patient died 15 days after admission, after withdrawal

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of support. Autopsy revealed multiple areas of infarction in the spleen, liver, and kidneys. The heart showed evidence of uremic pericarditis with no evidence of cardiac dilatation, hypertrophy, endocarditis, or myocardial infarction. Multiple petechial and small hemorrhages were found in the cerebral subcortical white matter, some of which were partially confluent up to 2.5 × 1.0 cm. Petechiae were also present in the right superior cerebellar peduncle. The cerebral venous sinuses were all patent. Microscopic examination of the brain revealed hemorrhages with no evidence of septic emboli, occluded vessels, or mycotic aneurysms.

Discussion

The central nervous system manifestations of sepsis have been predominantly described under the umbrella term *septic encephalopathy* (10, 11). Failure to awaken after fulminant sepsis and intravascular coagulation is ill-understood, but recent evidence suggests that severe hypotension significantly contributes to the development of what used to be called septic encephalopathy (11). In this clinical setting anoxic-ischemic insult to the brain is the probable main instigator. CT scans in patients who failed to awaken after septic shock have been invariably normal (10, 11). Therefore it would seem, particularly in our first patient, that the petechial hemorrhages could not entirely account for the persistent vegetative state, and hypotension may have played an additional role.

The pathophysiology of disseminated intravascular coagulation relates primarily to generation of thrombin through activation of the coagulation pathway. This may occur through intrinsic pathway activation in sepsis or extrinsic pathway activation in trauma and neoplasia. Widespread thrombin generation and clotting results in coagulopathies from depletion of coagulation factors and platelets and secondary fibrinolysis with resultant hemorrhage (12). Neuropathologic changes include areas of infarction and hemorrhage in multiple vascular territories, scattered throughout cortical, subcortical, and deep white matter areas. Thrombi involve mainly the me-

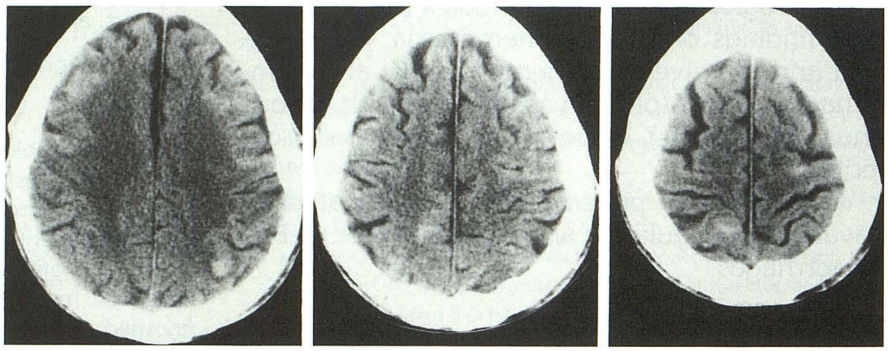

Fig. 1. Patient 1. Multiple discrete hemorrhages in the peripheral white matter bilaterally. These are primary, that is, not associated with cortical infarction.

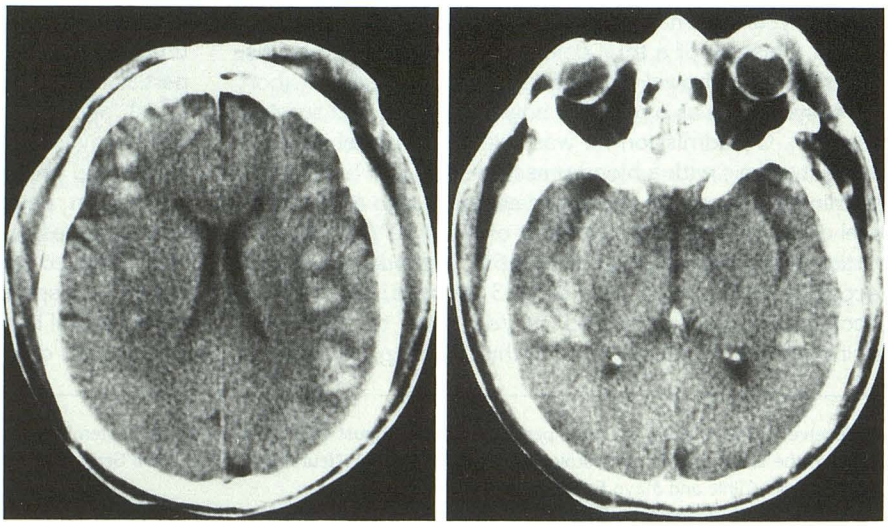

Fig. 2. Patient 2. Two sections from a head CT without contrast demonstrate multiple discrete hemorrhages of various sizes. These are located primarily in the peripheral hemispheric white matter bilaterally. These hemorrhages seem to be primary; that is, there is no evidence that these are secondary hemorrhages into areas of cortical infarction.

dium and small penetrating arteries in the gray and white matter. Similar changes are commonly found in the lungs, kidneys, spleen, and liver (3, 4, 13). Venous occlusion also may play a role, and in a series by Buonanno et al (6) two-thirds of their patients showed involvement of large draining veins.

Patient 1 had significant periods of hypotension. However, the predominantly subcortical distribution of these areas of hemorrhage or hemorrhagic infarction is not typical of that seen in border zone or watershed infarction. Patient 2 had multiple areas of infarction in other organs, but no evidence of a cardiac source for emboli could be found. In addition, a careful search of the postmortem brain specimen did not reveal septic emboli, arteritis, or mycotic aneurysms. The distribution and subcortical location of these hemorrhages on cranial CT scan (and at postmortem in case 2) would be in keeping with previous reports of pathologic findings in patients with disseminated intravascular coagulation (3, 4).

Multiple intracranial hemorrhages are uncommon in critically ill patients but have been reported with thrombocytopenia (14), thrombolytic agent use (15), fulminant toxoplasmosis (16), or aspergillosis (17) in immunocompromised patients, or with venous sinus thrombosis in patients with any severe coagulopathy (6). Our CT scan findings in these two patients with fulminant sepsis suggest that, in occasional patients, subcortical intracerebral hemorrhages can be responsible for or contribute to stupor or coma. The incidence of intracerebral hemorrhage in an intensive care population with disseminated intravascular coagulation is not known. In many patients with life-threatening sepsis and progressively failing organs, transport to the CT or magnetic resonance suite is often deferred until gas exchange and circulation is stabilized. If neuroimaging is performed in this setting, recognition of the unusual pattern of intracerebral hemorrhages assumes considerable importance for raising the suspicion of the diagnosis of disseminated intravascular coagulation and should allow aggressive treatment with fresh frozen plasma and platelets.

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