Disseminated Intravascular Coagulation in a Patient Undergoing Removal of Metastatic Brain Tumor

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INTRODUCTION

Disseminated intravascular coagulation (DIC) is a hemorrhagic disorder that can occur as a complication in a variety of diseases and is characterized by laboratory evidence of consumptive coagulopathy and proteolytic degradation products. Varying degrees of DIC have been widely recognized as potential complication of head injury. However, brain tumors are rarely responsible for hemostatic disorders. Although a hypercoagulable state exists in virtually all patients with malignancy, the incidence of overt DIC is considerably low. The mortality associated with DIC accompanying brain tumor operation is very high. The authors present a patient who developed DIC immediately after operation for metastatic brain tumor. This patient was successfully treated owing to early recognition of the condition and immediate treatment with transfusion. Neurosurgeons should be alert that hypercoagulable state is common in cancer patients and consumptive coagulopathy can occur after resection of metastatic brain tumor.

CASE REPORT

A 68-year-old woman was admitted with complaints of impairment in recent memory and gait disturbance. She underwent low anterior resection of the rectum for adenocarcinoma and received five courses of chemotherapy using leucovorin and 5-FU (Mayo Clinic regimen) and 5,500 cGy of radiotherapy 2 years ago. She underwent right upper lobectomy of the lung for metastatic adenocarcinoma 4 months ago. Neurological examination revealed left homonymous hemianopia and mild right hemiparesis. Cranial computerized tomography (CT) scan revealed an isodense spherical mass in the left parietooccipital area, with heterogeneous enhancement. Edema was observed around the tumoral mass, and the lateral ventricle appeared compressed (Fig. 1A). Cranial magnetic resonance imaging revealed a mass measuring 35×33×38 mm that showed iso-signal intensity on T1 and T2-weighted images; moreover, it revealed strong heterogeneous contrast enhancement following the administration of the contrast agent. Thoracic and abdominal CT revealed no tumor recurrence.

Four days before surgery, laboratory evaluation revealed a normal activated partial thromboplastin time (aPTT) of 24.5 seconds (normal range, 23-35 seconds), prothrombin time (PT) of 106.2% (70-120%), international normalization ratio (INR) 0.97 (0.9-1.25), and a platelet count of 173,000/µL (150,000-450,000/µL). The patient did not receive medication that may impair hemostasis or platelet function. In August 2007, surgical removal of the mass via a left parietooccipital approach was performed in the prone position. The tumor was completely excised. The
intraoperative course was uneventful and bleeding was not excessive; therefore, we did not perform transfusion. However, after closure of the scalp incision, increased bleeding from the suture line was noted. A considerable volume of unclotted blood was continuously aspirated through Hemovac drainage catheter. The dressing was saturated with blood. A CT scan was obtained immediately after operation. The scan revealed an acute epidural hemorrhage with a density lower than that of usual hematoma and multiple air densities under the bone flap. Contrast-enhanced CT revealed that the contrast medium leaked into the epidural space immediately following the administration of the contrast agent. The catheter is noted (white arrows) within epidural space.

The dressing was saturated with blood. A CT scan was obtained immediately after operation. The scan revealed an acute epidural hemorrhage with a density lower than that of usual hematoma and multiple air densities under the bone flap. Contrast-enhanced CT revealed that the contrast medium leaked into the epidural space immediately (Fig. 1B). Immediate re-exploration and evacuation of hemorrhage were performed. As soon as the bone flap was removed, excessive blood loss from the epidural space occurred without clotting. Profuse oozing was observed from all exposed tissues, including the skin, galea, subgaleal space, inner table, and dura mater, and could not be controlled. Bleeding was particularly more severe from the catheter site. Bipolar coagulation was not successful in reducing bleeding loss, and massive diffuse bleeding persisted. Therefore, we performed blood transfusion and placed gauze on the wound and applied direct continuous pressure with our hands over all the exposed tissues. At this stage, investigations revealed that the aPTT was 45 seconds; PT, 39.7%; platelet count, 78,000/µL; fibrinogen concentration, 95.3 mg/dL (200-400 mg/dL); concentration of fibrin degradation products (FDP), 25 µg/mL (0-5 µg/mL); INR, 1.75; D-dimer concentration, 2.4 µg/mL (0-0.5 µg/mL); hemoglobin, 8.8 g/dL (12-16 g/dL); and hematocrit value, 26.5% (36-48%). The diagnosis of DIC was clearly established, and the patient received 6 units of packed red blood cell (RBC), 12 units of fresh-frozen plasma (FFP), 8 units of platelet concentrate, and 1 unit of platelet pheresis. Oozing began to slow down with less amount of blood four hours after the initiation of transfusion, and at the same time, clotted blood was observed. Investigations revealed that the aPTT was 29.8 seconds; PT, 65.9%; INR, 1.25; platelet concentration, 98,000/µL; hemoglobin, 10.2 g/dL; and hematocrit value, 30.5%. Bleeding was controlled five hours later, and we could finish the operation. Postoperatively, the patient was transferred to the intensive care unit where she received a further 2 units of packed RBC and 4 units of FFP. At 5 hours postoperation, she continued to improve, and her hematologic and coagulation parameters had stabilized. A CT scan revealed a small intraparenchymal hemorrhage, with surrounding edema and epidural hematoma in the left parietal area (Fig. 2). The patient was stable, without left homonymous hemianopia, and remained free of clinical or laboratory signs of DIC at repeated follow-up visits over the next month. The final histological diagnosis was a metastatic adenocarcinoma.

DISCUSSION

The most common causes of DIC are the release of thromboplastic substances or tissue factors into the circulation and the promotion of platelet aggregation. Brain tissue appears to be rich in thromboplastin, which increases after head trauma, or in brain tumor patients, and is thought to trigger the extrinsic pathway8. Tissue factors can be released in high concentrations after extensive trauma, surgery, and
burns. Necrotic and tumorous tissues also produce tissue factors that have a similar effect, recently shown to play the central role in initiating the coagulation cascade in any body tissue\textsuperscript{12}. Brecknell et al.\textsuperscript{2} reported that a 70-year-old woman developed DIC during intra-operative manipulation of a malignant meningioma that could be controlled only after complete resection of the tumor. The tumor was demonstrated to express tissue factors, an important causative factor in other tumors accompanied with DIC. The surgical trauma by itself is important in promoting the DIC, but the phenomenon is usually self-limiting and only occasionally requires blood component therapy. It may result from endothelial cell injury, leading to activation of the intrinsic pathway, and/or from direct injury to red cells and thrombocytes with release of activating factors\textsuperscript{1}. The question was why this patient underwent to DIC immediate after operation. Malignancy is a well recognized cause of a prothrombotic state, with DIC occurring in up to 7\% of solid organ tumours\textsuperscript{10}. It is most frequently associated with adenocarcinomas such as pancreatic, breast and prostate cancer\textsuperscript{10}. However, the etiology of the activation of coagulability in malignancy is multifactorial and poorly understood. In our case, there were metastases in brain and lung. The surgery itself as a severe trauma or the release of procoagulant molecules from the metastatic tumor cells or a hypoxic situation during surgery may have caused the occurrence of DIC in this particular patient.

The clinical expression varies and maybe manifested by laboratory abnormality alone or in combination with hemorrhagic and thrombotic complications\textsuperscript{5}. Since DIC occurs in association with different systemic malignancies, different clinical manifestations of abnormal hemostasis may be associated with different brain tumor types and grades of malignancy\textsuperscript{5}. Extensive skin and mucous membrane bleeding from surgical incision or catheter sites are the most likely clinical presentations. Patients with metastatic malignancy, in particular, appear to have a higher risk of asymptomatic DIC that becomes clinically evident after surgery. The laboratory criteria for DIC diagnosis were thrombocytopenia, decreased fibrinogen, prolonged prothrombin, and thrombin times, and presence of FDP. Since the presence of only three abnormal parameters is considered sufficient for the diagnosis of DIC\textsuperscript{7}, this patient clearly had the required diagnostic signs. Intraoperative or postoperative DIC is a very serious condition since among the five patients previously described in the English literature, most died in the early postoperative phase and only few of them survived despite neurological deficit\textsuperscript{1,2,6,8,9} (Table 1). This case was clinically characterized by profuse uncontrollable hemorrhage from the surgical wound. Acute disturbances of blood coagulation during surgery require rapid specific action in order to avoid a life-threatening situation. Direct pressure is one of the most effective methods to control bleeding during operation. Fortunately, bleeding was controlled and the patient recovered without any specific postoperative complication.

The removal of the original pathogenic factor is important as the first step of treatment. At the same time, anticoagulant treatment has been suggested as primary therapy. FFP and platelets are recommended against bleeding. Heparin, the drug of choice against the thrombotic phase, can keep asymptomatic DIC from exacerbation postsurgically\textsuperscript{11}. However, it still remains controversial in the treatment of bleeding. Today, the advancements in surgical technique and therapy with blood components have reduced the likelihood of bleeding complications. Hartmann et al.\textsuperscript{4} reported two pediatric cases in which application of recombinant activated factor VII could control otherwise untreated hemorrhage during glioblastoma multiforme surgery. This case was clinically characterized by profuse

| Authors, year | Age/sex | Preoperative LAB data | Site of brain tumor | Histology | Occurrence of DIC | Outcome |
|---------------|---------|-----------------------|---------------------|-----------|-------------------|---------|
| Matjasko MU et al., 1977\textsuperscript{3} | 23 yr/F | Normal | Third ventricle | Oligodendroglioma | Intraoperatively | Death |
| Portugal JR et al., 1984\textsuperscript{4} | 63 yr/F | N/A | Posterior fossa | Melanotic meningioma | 15 hr after Op. | Death |
| Huang PS et al., 1990\textsuperscript{4} | 6 m/F | N/A | Fourth ventricle (SMV) | Central neuroblastoma | Immediately after Op. | Death |
| Berger MM et al., 1995\textsuperscript{5} | 54 yr/F | Normal | Left P-O region | Grade II astrocytoma | Intraoperatively | TNW |
| Brecknell JE et al., 2000\textsuperscript{5} | 70 yr/F | Neutrophilia | Right F convexity | Malignant meningioma | Intraoperatively | Persistent hemiplegia |
| Present case, 2008 | 68 yr/F | Normal | Left PO region | Metastatic adenocarcinoma | Immediately after Op. | No complication |

F : female, M : male, LAB : laboratory, N/A : non-available, P-O : parieto-occipital, F : frontal, DIC : disseminated intravascular coagulation, Op : operation, TNW : transient neurological worsening, SMV : superior medullary

Table 1. Literature review of cases of disseminated intravascular coagulation complicating brain tumor surgery

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uncontrollable hemorrhage from the surgical wound.

CONCLUSION

Although the incidence of DIC during or after resection of metastatic brain tumor in cancer patient with probable hypercoagulable state is low, it is associated with a high mortality rate. We suggest that early recognition of the condition and immediate treatment with transfusion, without waiting for the laboratory conclusions of the initial blood probe, can help achieve survival and avoid a fatal outcome.

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