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Heparin-Induced Thrombocytopenia in a Glioblastoma Multiforme Patient With Inferior Vena Cava Filter Placement for Deep Venous Thrombosis

—Case Report—

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Abstract

A 58-year-old woman presented with right supplementary motor area glioblastoma multiforme and deep venous thrombosis in her legs. The tumor was resected after temporary inferior vena cava filter placement, considering that increased thrombosis during and after the operation would cause fatal pulmonary embolism. After anticoagulation with unfractionated heparin, thrombocytopenia was aggravated, and computed tomography showed filter catheter-related thrombosis in the inferior vena cava. The diagnosis was heparin-induced thrombocytopenia, and argatroban and urokinase were administered. Thrombolysis with urokinase was completed and the temporary inferior vena cava filter catheter was removed without complication. The present case illustrates the possibility of heparin-induced thrombocytopenia associated with catheter-related thrombosis in neurosurgery.

Key words: heparin-induced thrombocytopenia, filter catheter-related thrombosis, glioblastoma multiforme, inferior vena cava filter, deep venous thrombosis

Introduction

Patients with glioma suffer very high incidences of symptomatic deep venous thrombosis (DVT) and pulmonary embolism (PE), particularly within 2 months after neurosurgical procedures.[16] DVT can induce serious clinical outcomes, so adequate treatments, such as anticoagulation with heparin, should be performed without delay. However, resection is an option to treat rapidly progressive brain tumors complicated with preoperative DVT, after the placement of a temporary inferior vena cava (IVC) filter, which would prevent fatal pulmonary embolism caused by increased thrombosis during and after the operation.

Heparin-induced thrombocytopenia (HIT) is a life-threatening disorder that is often associated with thrombosis. HIT is usually caused by antibodies against complexes of platelet factor 4 (PF4) and heparin. The incidence of HIT type II in patients with subarachnoid hemorrhage at a single center was 15%, but only six other neurosurgical patients with HIT have been described.[2–4,7,12,14]

We describe a case of HIT with filter catheter-related IVC thrombosis, in a patient with brain tumor receiving doses of unfractionated heparin 10000 units per day after placement of an IVC filter catheter for DVT, which exposes the risks of DVT as a perioperative complication.

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Case Report

A 58-year-old woman was admitted with a history of progressive weakness of the left upper and lower extremities over 2 weeks. Physical examination revealed severe left hemiparesis (Medical Research Council [MRC] scale; upper 0, lower 1). Magnetic resonance imaging with contrast medium showed a ring-enhanced mass in the right supplementary motor area (Fig. 1A). The platelet count was 304000/mm^3 and the D-dimer level was 6.2 mg per ml. Computed tomography (CT) with contrast medium showed small thrombi in the bilateral lower legs, and double IVC with confluence superior to the renal veins (Fig. 1B, C).

On hospital day 2, the patient underwent subtotal resec-

Fig. 1 A: Sagittal T_1-weighted magnetic resonance image with contrast medium of the head showing a ring-enhanced mass in the right supplementary motor area. B, C: Computed tomography scans with contrast medium of the lower leg (B) showing thrombus (*arrowhead*), and of the abdomen (C) showing double inferior vena cava (*arrows*).

Table 1 Course of the present case

Day	CT	IVC filter	Platelets (/mm^3)	D-dimer (m/ml)	Heparin (units/day)	Argatroban (mg/day)	Urokinase (units/day)
−1	bil distal DVT	−	304000	6.2	0	0	0
operation	−	placed	−	−	0	0	0
1	−	+	231000	9.9	0	0	0
2	−	+	−	−	10000	0	0
3	−	+	−	−	10000	0	0
4	−	+	−	−	10000	0	0
5	−	+	−	−	10000	0	0
6	−	+	156000	11.8	10000	0	0
7	−	+	−	−	10000	0	0
8	−	+	58000	−	0	0	0
9	−	+	−	−	0	0	0
10	thrombus in IVC	+	32000	−	0	30	0
11	−	+	24000	−	0	30	0
12	−	+	45000	−	0	30	0
13	−	+	48000	19.8	0	30	0
14	unchanged	+	46000	−	0	30	60000
15	−	+	48000	−	0	30	60000
16	−	+	57000	−	0	60	120000
17	−	+	59000	32.8	0	60	120000
18	−	+	59000	−	0	60	180000
19	−	+	77000	−	0	60	180000
20	unchanged	+	95000	23.9	0	60	960000
21	−	+	−	−	0	60	960000
22	−	+	99000	−	0	60	240000
23	no thrombus	removed	126000	−	0	60	240000

bil: bilateral, CT: computed tomography, DVT: deep venous thrombosis, IVC: inferior vena cava.

tion of the glioblastoma after placement of a temporary IVC filter catheter (Neuhaus Protect^{TM}; Toray Industries, Inc., Tokyo) immediately caudal to the hepatic veins, above the confluence of the double IVC. On postoperative day 2, anticoagulation with unfractionated heparin 10000 units per day and warfarin was initiated (Table 1). On postoperative day 8, laboratory data showed marked elevation of aspartate transaminase and alanine transaminase, and decreased platelet count to 58000/mm^3 (Table 1). Anticoagulation with heparin was discontinued for fear that heparin might contribute to liver dysfunction. On postoperative day 10, thrombocytopenia was aggravated (32000/mm^3) and CT with contrast medium showed catheter-related thrombosis, which measured 17 mm in maximum diameter and 280 mm in length, and was located immediately distal to the IVC filter (Fig. 2A). A high score on a clinical scoring system for estimating the pretest probability of HIT indicated a clinical profile compatible with HIT.[19]

Her condition was diagnosed as HIT, and continuous administration of argatroban was initiated (Table 1). The administration of warfarin was discontinued. On postoperative day 14, the catheter-related thrombosis had not diminished in size, so continuous administration of 60000 units of urokinase per day through the sheath line of the IVC filter catheter was initiated (Table 1). Heparin-dependent antibodies were detected on postoperative day 16. Although the dose of urokinase was increased gradually (120000 units per day for 2 days, 180000 units per day for 2 days), catheter-related thrombosis did not diminish in size on postoperative day 20 (Table 1). A 2-day course of 960000 units of urokinase and then 240000 units of urokinase daily were administered (Table 1). On postoperative day 23, thrombolysis was completed and the IVC filter catheter was removed without complication (Fig. 2B). Fortunately, the patient suffered no hemorrhagic complication during the treatment for HIT. After that, the patient underwent conventional radiation treatment and chemotherapy with temozolomide, and her hemiparesis improved (MRC scale; upper 4, lower 3). The administration of warfarin has been continued and DVT has not been observed for 3 months.

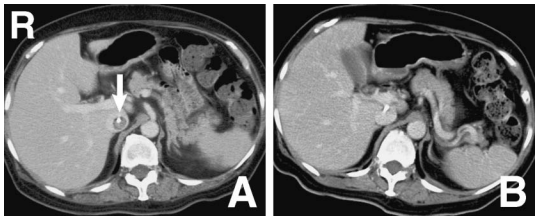

Fig. 2 Computed tomography scans with contrast medium of the abdomen before treatment with urokinase (A) showing catheter-related thrombosis (*arrow*) of the inferior vena cava, and after treatment (B) showing thrombolysis.

Discussion

The 2-year cumulative incidence of symptomatic DVT and

PE in patients with malignant glioma is 7.5%, with a rate of 16.1 events per 100 person-years during the first 6 months.[16] The diagnosis was established within 61 days of major neurosurgery in 55% of cases and 15.7% of these cases were diagnosed spontaneously.[16] The present patient developed distal DVT spontaneously before the operation.

Routine use of an IVC filter in addition to anticoagulants is not recommended in patients with DVT or PE.[9] However, if anticoagulant therapy is not possible because of the risk of bleeding, placement of an IVC filter is recommended in patients with acute proximal DVT or acute PE.[9] Our patient had only distal DVT, so placement of an IVC filter was not recommended. If the patient's symptoms had been stable, we could have performed resection of the brain tumor after anticoagulation therapy. However, the patient had progressive severe hemiparesis, which suggested that delayed treatment of the brain lesion would cause permanent hemiparesis. Furthermore, permanent hemiparesis might cause new DVT in the future. Therefore, we thought that the brain lesion should be resected first. However, major surgery like brain tumor resection is a clear risk factor for DVT. The patient already had DVT and anticoagulation therapy should be discontinued for some time during and after the operation because of the risk of bleeding, suggesting that DVT might progress during and after the operation. Therefore, we performed brain lesion resection after the placement of a temporary IVC filter to prevent fatal PE after the operation.

The reported prevalence of double IVC is about 0.2–2.2%.[5,13,18] Two methods of placement of IVC filter for double IVC have been reported: Two IVC filters are placed caudally to the renal vein inflow in each IVC[15]; and one IVC filter is placed in the suprarenal portion of the IVC, after the confluence of the two IVCs.[17] Although an IVC filter is usually placed in the infrarenal portion of the IVC to prevent obstruction of the renal veins by the filter, IVC filters placed above the renal vein also provide protection from PE with minimal risk of occlusion.[6] In the present case, we chose the latter method.

HIT is a life-threatening disorder caused by antibodies against complexes of PF4 and heparin, and develops 5 to 10 days after exposure to heparin.[1] Patients present with a low platelet count or a relative decrease of 50% or more from baseline. Thrombotic complications develop in approximately 20–50% of patients.[1] The present case conformed to all these characteristics. Venous thromboembolism is infrequently associated with HIT ($<1\%$) in low molecular weight heparin-treated patients, yet often (12.8%) in unfractionated heparin-treated patients.[11] Early antithrombotic prophylaxis with low molecular weight heparin is safe and efficacious without HIT in neurosurgical patients.[10] However, treatment with low molecular weight heparin for DVT or PE has not been approved by the authorities in Japan.

Stopping heparin therapy does not prevent further thrombosis in patients with HIT, necessitating inhibition of thrombin or generation by rapidly acting non-heparin anticoagulant like argatroban.[20] The combined outcomes of death, amputation, and thrombosis is significantly lower among patients receiving argatroban than controls.[1] In the present case, HIT was complicated with catheter-related IVC thrombosis. Although we treated HIT with argatroban, the treatment for postoperative catheter-related IVC thrombosis remains controversial. Catheter-related thrombosis may result in vascular occlusion but also in infection, so thrombolysis and removal of the catheter should be completed as soon as possible. After considering the risks associated with thrombolysis including intracranial hemorrhage, we administered only argatroban on postoperative day 10. On postoperative day 13, the catheter-related thrombosis had not decreased, so we started the administration of 60000 units of urokinase through the sheath line of the IVC filter catheter for thrombolysis. We administered a 2-day course of 960000 units of urokinase daily starting on postoperative day 20, and thrombolysis and removal of IVC filter catheter were completed without complication. The administration of urokinase eventually led to the best result in the present case. However, the present treatment is not recommended after brain surgery, because urokinase treatment might cause intracranial hemorrhage. In another case of HIT with IVC filter catheter-related thrombosis, placement of a second IVC filter proximally and mechanical fragmentation of the thrombus by pigtail-catheter rotation prevented the development of PE.[8] Another option for the treatment of IVC catheter-related thrombosis is probably surgical removal, which is more invasive for large thrombosis.

In the present case, thrombolysis therapy using urokinase for removal of the IVC filter was performed. However, the best method for such a case is probably as follows. A second IVC filter is placed proximally via the jugular vein for inhibition of PE. Another catheter is inserted via the femoral vein on the same side as the IVC filter, and thrombus is fragmentized mechanically or aspirated by the catheter. Thrombi caught by the first IVC filter are aspirated. The first IVC filter is removed, and then the second IVC filter is removed.

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