Cerebral Infarction Associated with Heparin-Induced Thrombocytopenia in a Patient with Encephalitis

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Abstract

We report a patient who had cerebral infarction associated with heparin-induced thrombocytopenia (HIT) during treatment of aseptic encephalitis. In patients with intracranial inflammation, such as ours, the possibility of HIT has to be considered when heparin is used, since inflammatory cerebral lesions often cause vascular damage, which is an aggravating factor for HIT-associated thrombosis.

Key words: cerebral infarction, encephalitis, heparin-induced thrombocytopenia


Heparin-induced thrombocytopenia (HIT) is a life-threatening thrombotic disorder caused by antibodies (HIT-Ab) against a complex of heparin and platelet factor 4 (1). Thrombotic complications include cerebral infarction and peripheral deep venous thrombosis (DVT), often occurring 5-15 days after the start of heparin (2). Encephalitis occasionally involves cerebral arteries, leading to cerebral infarction (2). However, whether heparin use triggers cerebral infarction is unknown. We report an encephalitis patient with HIT-associated cerebral infarction.

Case Report

A 73-year-old man was admitted to a local hospital because of headache, drowsiness, and mild left hemiparesis including the facial muscles, without apparent sensory disturbance. Abnormal MRI findings (Fig. 1A, B) initially suggested cerebral infarction, and he was given heparin (10,000 IU/day) for 2 days. He had no risk factors for cerebral infarction, including hypertension, hyperlipidemia, diabetes mellitus, hereditary coagulation disorders (Protein C, Protein S, AT III deficiencies), and cardiac diseases; there was no evidence of cerebral infarction on cerebral angiography (Fig. 1C). The next day, pleocytosis (187/mm 3, 58% lymphocytes), elevated protein (159 mg/dL), and normal glucose in the CSF suggested the diagnosis of encephalitis. Heparin was stopped. The patient was transferred to our hospital on day 4. He had almost normal blood chemistry and cell counts, including a normal platelet count (192×10 3/μL). Anticoagulation testing revealed slightly elevated levels of D-dimer (6.8 μg/mL [normal <1.0 μg/mL]) and FDP (11.6 μg/mL [normal <10 μg/mL]), but normal PT and APTT levels. On CSF testing, Herpes simplex and Varicella zoster DNA were negative. Serum antibody titers excluded infection with various bacteria, fungi, and viruses. No organisms (including Mycobacterium tuberculosis) were cultured from the CSF. Serum auto-antibodies against the nucleus, ds-DNA, cardiolipin, galactose, RNP, Sm, SSA, SSB, and neutrophil cytoplasm were negative. These findings suggested that the patient had aseptic encephalitis. On day 8, total parenteral nutrition was started, and heparin was flushed (100 IU) once daily to maintain central catheter patency. The patient gradually recovered consciousness so that he was able to eat meals by himself, and the CSF abnormalities improved (37 cells/mm 3 and 124 mg protein/dL) on day 21. On day 23, he suddenly became semicomatose and developed right hemiplegia with total aphasia. A brain diffusion-weighted image (DWI) showed high intensity in the left basal ganglia and corona radiata (Fig. 1D, E). On MRA, the main trunk of the left middle cerebral artery was occluded (Fig. 1F). Electrocardiography (ECG) including bedside ECG monitoring showed normal sinus rhythm during the entire disease

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Received for publication July 8, 2008; Accepted for publication September 16, 2008

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Figure 1. Radiological findings before (A-C) and after (D-F) cerebral infarction associated with HIT. (A, B) FLAIR images (TE/TR=124/9000, 1.5-T whole-body magnetic resonance system, Magnetom Sonata A.G., Siemens, Erlangen, Germany) obtained 9 days after disease onset (day 9) show hyperintense lesions in the right hippocampus, temporal lobe, and corona radiata. (C) Cerebral angiography done 3 days after disease onset shows no stenosis or occlusion in bilateral internal carotid arteries. (D) DWI (TR/TE=180/96, b=1,000 s/mm^2, matrix 128×128, field of view 230 mm) on day 23 shows a hyperintense lesion in the left corona radiata. (E) A FLAIR image on day 23 shows a hyperintense lesion in the corona radiata bilaterally. (F) Brain MRA on day 23 shows occlusion of the main trunk of the left middle cerebral artery.

course; transthoracic and transesophageal echocardiography revealed no cardiac thrombus, patent foramen ovale, or complicated aortic arch lesions. The platelet count remained normal (211×10^3/μL). On day 24, intravenous continuous heparin injection (8,000 IU/day) was resumed. On day 30, the platelet count decreased to 9.9×10^3/μL, with an extremely high D-dimer level (42.4 μg/mL) (Fig. 2). Venous ultrasonography showed DVT in the right popliteal vein on day 32. Since these findings suggested the possibility of HIT, we stopped heparin and started argatroban on day 34. HIT-Ab was subsequently found to be positive in the blood sample obtained at the onset of cerebral infarction (OD_{405}=0.652, normal <0.4, enzyme-linked immunosorbent assay GTI-PF4, Genetic Testing Institute, Waukesha WI, USA). According to a previous report, the clinical probability score at the onset of stroke was 4 points, indicating an intermediate probability
Figure 2. Time course of the platelet count and the D-dimer level with heparin use.

Discussion

We report a patient with encephalitis and HIT, the combination of which has not been previously described. Even though encephalitis can cause cerebral infarction or inflammatory lesions with similar neurological deficits, the symptoms our patient which developed on day 23 were likely due to HIT-associated cerebral infarction for several reasons. First, HIT-Ab was positive with severe thrombosis and decreased platelets, and these findings were resolved by discontinuation of heparin and administration of argatroban. Second, the improved CSF findings and clinical recovery at the onset of cerebral infarction seemed to rule out aggravation of encephalitis. Furthermore, while inflammatory-associated cerebral infarction often occurs in the territories of small arteries, our patient had a new lesion in the main trunk of the left middle cerebral artery, with a high intensity DWI lesion matching the vascular territory. Development of cerebral infarction 7 days before thrombocytopenia in our patient also does not rule out HIT, since recent studies demonstrated that thrombocytopenia is often absent at the onset of thromboembolic complications and, sometimes, may be absent during the entire disease course (4). We cannot exclude the possibility that the HIT-associated cerebral infarction occurred independently of the encephalitis; however, the lack of other causes of vascular damage suggests that encephalitis may trigger or predispose to HIT-associated infarction.

The pathophysiological mechanism by which encephalitis causes HIT-associated cerebral infarction remains unknown. However, in encephalitis, vascular damage in cerebral arteries involves leukocyte infiltration into arterial walls (5). These activated leukocytes release chemokines, such as CCL17 and CCL22, which may subsequently activate platelets, thereby releasing platelet factor 4 to form a complex with HIT-Ab and heparin (6). Thus, inflammation-mediated vascular damage in encephalitis may trigger thrombosis and subsequent HIT-associated cerebral infarction (6).

Some issues and limitations related to the present case report need to be considered. First, the dose of heparin that triggered HIT was low. A therapeutic dose (10,000 IU/day) was administered for two days, and heparin flushes (100 IU/day) were given for 15 days. It is true that HIT due to heparin flushes is rare (7), but several reports suggested a risk of HIT after exposures to small quantities of heparin from catheter flushes (8). The initial therapeutic dose may have triggered immune sensitization, and the daily small amount for heparin flush may have resulted in cerebral infarction. Second, HIT-Ab was measured by enzyme-immunoassays (EIAs) in the present case. EIAs have limited sensitivity and specificity compared to the serotonin release assay (SRA) that is considered the “gold standard” for the diagnosis of HIT (9). However, SRA is available in only a few laboratories in Japan. Although the laboratory findings (positive HIT-Ab by EIAs) did not demonstrate definite HIT in our patient, these findings in combination with a clinical score suggest the diagnosis of HIT (3). Third, the possibility of DIC and other drug-induced thrombocytopenia cannot be completely excluded. However, the low DIC score and successful treatment with argatroban, in addition to the continuation of the drugs for encephalitis, suggest that the possibil-
ity of DIC and other drug-induced thrombocytopenia was low.

Heparin is widely used as anticoagulation therapy to prevent worsening or recurrence of ischemic stroke, and it is often used as continuous infusion therapy for cardioembolic stroke. HIT sometimes causes recurrence of cerebral infarction and worsens neurological complications (10, 11). Recent reports have advocated the use of heparin to prevent DVTs in patients with a consciousness disturbance, since they have decreased spontaneous limb movements (12). However, HIT may develop with heparin therapy, especially in patients with intracranial inflammation.

Acknowledgement

The authors thank Drs. M. Matsumoto and Y. Fujimura (Departments of Blood Transfusion Medicine, Nara Medical University) for their helpful comments. We also thank Drs. T. Matsuo (Hyogo Prefectural Awaji Hospital), S. Suzuki, and K. Wanaka (Japan Clearinghouse for Heparin-induced Thrombocytopenia) for the measurement of HIT antibodies.

References


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