A Pulmonary Embolism Caused by Delayed-onset Heparin-induced Thrombocytopenia in a Patient with Ischemic Stroke

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Abstract

We report a case of an acute stroke patient with pulmonary embolism (PE) caused by delayed-onset heparin-induced thrombocytopenia (HIT). She was treated with heparin to prevent neurological deterioration. However, 5 days after heparin had been given for 7 days, she developed PE. Heparin was re-started, but the platelet count decreased significantly, and a right ventricular thrombus appeared. She was finally diagnosed as having PE due to delayed-onset HIT because the HIT antibody was positive. When a patient develops thrombotic events during or after heparin therapy, the possibility of HIT should be considered.

Key words: anticoagulation, platelet count


Introduction

Heparin has been used as antithrombotic therapy in patients with progressing stroke and venous thrombosis, including pulmonary embolism (PE) and deep vein thrombosis (DVT) (1-3). On the other hand, heparin also causes serious complications, such as heparin-induced thrombocytopenia (HIT) (4). HIT rarely occurs several days after heparin therapy (delayed-onset HIT) (5). We herein report an acute stroke patient with PE caused by delayed-onset HIT.

Case Report

A 66-year-old, right-handed woman was admitted to our hospital because of sudden onset headache and vertigo. She had a history of hypertension. On day 2, she felt left leg weakness and was referred to our department. She was 154 cm tall and weighed 47.5 kg. Her temperature was 36.4°C, her blood pressure was 180/110 mmHg, and her heart rate was 110 beats/min with regular sinus rhythm. No cardiac murmurs and no carotid bruits were audible. Neurological examination revealed disturbance of consciousness, right internuclear ophthalmoplegia, left central facial palsy, left hemiparesis, and sensory disturbance. The extensor plantar response was present on the left side. The National Institute of Health stroke scale score was 7. Laboratory data showed normal blood cell counts: white blood cell count, 7.5×10^9/L; hemoglobin, 120 g/L; and platelet count, 224×10^9/L. Serum blood glucose, hemoglobin A1c, and low-density lipoprotein cholesterol levels were normal, and the prothrombin time, international normalized ratio, activated partial thromboplastin time, D-dimer, protein C and S, and antithrombin were also normal. The IgG anticardiolipin antibody titer was elevated (22 U/mL, normal <10 U/mL). Anti-nuclear antibody, anti-DNA antibody, lupus anticoagulant, and anti-β2GPI antibody were negative. Carotid ultrasound showed no abnormalities. The electrocardiogram demonstrated normal sinus rhythm. She was examined using a commercially available, echo planar system on a 1.5-T MR unit (Signa EchoSpeed Horizon; GE Medical Systems Milwaukee, WI, USA). Diffusion-weighted imaging (DWI) showed hyperintense lesions in the right cerebellum and the right side of the pons. On MR angiography (MRA), occlusions of the right vertebral artery (VA) and basilar artery (BA) were seen. Cerebral angiography revealed occlusion of
the right VA after branching of the posterior inferior cerebellar artery (PICA) and the BA in the distal portion. She was diagnosed as having an ischemic stroke due to BA occlusion, and antiplatelet therapy with aspirin was started. However, on day 3, neurological deterioration occurred, and her NIHSS score was 11. DWI showed a new hyperintense lesion in the right side of the midbrain. The antiplatelet therapy was stopped, and anticoagulation therapy with a heparin infusion (10,000 IU/day) was started to prevent stroke deterioration. On this regimen, her neurological symptoms stabilized. Since there were no abnormalities on venous ultrasonography, transesophageal echocardiography, and Holter ECG, heparin was stopped on day 7.

On day 12, she suddenly complained of dyspnea after rehabilitation therapy. Laboratory data showed an elevated D-dimer level (20 μg/mL, normal <0.5 μg/mL) and a decreased platelet count (165×10^9/L). Arterial blood gas analysis revealed hypoxia on room air (PaO₂, 51.1 mmHg; PaCO₂, 33.5 mmHg). Transthoracic echocardiography (TTE) showed a dilated right atrium and ventricle, but no intracardiac thrombus was seen. Pulmonary arteriography revealed bilateral pulmonary artery thrombi, though there was no DVT on venous ultrasonography of the lower limbs. She was diagnosed as having PE, and a continuous heparin infusion was restarted (Fig. 1).

On day 17, contrast-enhanced multi-detector row computed tomography (CE-MDCT) was performed to assess the PE. CE-MDCT showed a right ventricular thrombus (RVT) with bilateral pulmonary artery thrombi (Fig. 2-A). Although TTE showed no significant abnormality, contrast-enhanced TTE (CE-TTE) visualized the RVT (Fig. 3-A and B). Her platelet count decreased significantly to 27×10^9/L. She was tentatively diagnosed as having HIT, and the heparin was changed to argatroban infusion at 1 μg/kg per minute; the dose was adjusted until the activated partial thromboplastin time (aPTT) was 1.5 to 2 times the baseline aPTT value. The platelet count recovered rapidly and increased to 245×10^9/L on day 21. Her dyspnea also improved gradually. There was no RVT on CE-TEE on day 30 and on CE-MDCT on day 32 (Figs. 2-B, 3-C). The argatroban infusion was stopped and switched to warfarin on day 28.

Finally, since heparin antibodies were detected using the GTI-PF4 enzyme-linked immunosorbent assay (GTI Diagnostics, Waukesha, WI, USA) on day 43, she was diagnosed as having delayed-onset HIT. Although IgG anticardiolipin antibody was positive, antiphospholipid antibody syndrome was ruled out.
(APS) was not diagnosed, because other factors associated with APS were negative.

Two months later, she was transferred to a rehabilitation facility with moderate hemiparesis. At discharge, her stroke etiology was diagnosed as dissection of vertebrobasilar artery, because follow-up MRA demonstrated luminal narrowing and pearl and string of right VA and BA.

Discussion

We report a case with acute ischemic stroke who developed PE due to delayed-onset HIT. Delayed-onset HIT is diagnosed when HIT occurs after withdrawal of heparin treatment and accounts for fewer than 5% of all HIT (5).

The present case was initially treated with heparin to prevent progression in stroke. However, 5 days after heparin had been given for 7 days, she developed PE. We re-started heparin to treat PE and abrogate DVT, but PE did not improve and the platelet count decreased significantly. Therefore, she was suspected of having HIT and we replaced heparin with argatroban infusion. Following this treatment, the platelet count increased rapidly and PE and RVT disappeared. We could finally diagnose her as having PE due to delayed-onset HIT because the HIT antibody was positive and PE occurred after withdrawal of heparin. The possibility of HIT should be considered when a patient develops thrombotic events, such as PE, during or after heparin therapy.

Without any prophylaxis against venous thrombosis, the incidence of DVT in acute stroke patients with severe motor deficits is as high as 75% and that of PE is 20% (6, 7). Of several prophylactic regimens, heparin infusion is a recommended therapy (3). Therefore, heparin therapy has been occasionally used in patients with acute ischemic stroke. However, HIT occurs in about 1% of stroke patients (8).

When patients have thrombotic events with a decreased platelet count, two disorders, HIT and pseudo HIT, need to be considered. Pseudo HIT is defined as a disorder that clinically resembles HIT, but HIT antibody is negative (9). PE is one of the causes of pseudo HIT, and heparin therapy is an effective treatment for improving both the patient’s clinical status and the thrombocytopenia. On the other hand, HIT is a disorder that induces thrombocytopenia and thrombosis during and after heparin therapy, and HIT antibody is positive (10). In the present case, the platelet decrease was initially diagnosed as being caused by pseudo HIT because the mild platelet count decrease presented with PE, and the heparin infusion had already been stopped. However, re-administration of heparin resulted in a further decrease in the platelet count and RVT, and HIT antibody was positive. Therefore, the patient was diagnosed as having delayed-onset HIT. Previous study demonstrated that 40% of the HIT patients had a decrease in the platelet count before thrombosis, 26% presented with concurrent thrombocytopenia and thrombosis, and 33% developed thrombosis before an apparent fall in the platelet count (11). Thus, in order to make a precise diagnosis, HIT antibody should be measured even if heparin infusion has already been stopped and there is no accompanying decrement of platelet.

RVT with HIT has been rarely described in previous reports (12-14). One of the reasons for this may be the technical difficulty in diagnosing RVT using CT and TTE. In the present case, the RVT was initially diagnosed using CE-MDCT. Compared with single-slice CT, MDCT has the advantage of temporal resolution (11). CE-MDCT should improve the diagnostic accuracy of RVT. In the present case, the RVT was also detected using CE-TTE. TTE is a routine method of evaluating cardiac thrombus, but its small acoustic window limits its diagnostic utility. However, CE-TTE appears to have an increased sensitivity for detecting thrombus, improving the endocardial border definition (15). The combination of CE-MDCT and CE-TTE appears to be useful for detecting and evaluating intra-cardiac thrombus.

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References