Pearls & Oy-sters: Multiple ischemic strokes secondary to heparin-induced thrombocytopenia

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PEARLS

- Neurologic complications of heparin-induced thrombocytopenia (HIT) are relatively rare, with ischemic stroke being the most common.
- HIT-associated strokes may be multifocal and can have arterial, venous, or cardioembolic etiologies.
- The risk for HIT-associated strokes persists 4–6 weeks after heparin use and may occur in the setting of normal platelets.

OY-STER

- Vitamin K antagonists should be used with caution in HIT until recovery of the platelet count.[6]

CASE REPORT A 57-year-old right-handed woman developed sudden onset right-sided weakness and recurrent falls while on warfarin 13 days after being diagnosed with HIT. Three weeks prior, she had an elective hysterectomy and salpingo-oophorectomy for fibroids and menorrhagia complicated by postoperative pulmonary emboli. She had been treated with unfractionated heparin for 4 days, and then began low-molecular-weight heparin for 7 days. Her initial platelet count was within normal limits at 156×10^9 g/dL. The diagnosis of HIT was based on a platelet count of 67×10^9 g/dL with a nadir of 44×10^9 g/dL, positive platelet factor antibody-4 by ELISA, and abnormal heparin-induced platelet aggregation assay. Other causes of thrombocytopenia were ruled out. As her initial treatment for HIT, she received argatroban for 8 days and was discharged from the hospital on warfarin and fondaparinux with a platelet count of 75×10^9 g/dL. Fondaparinux was stopped 4 days later given an international normalized ratio (INR) = 3 while warfarin was continued.

Her past medical history was negative for stroke but significant for tobacco use and recent onset of hypertension. On admission examination, she had cognitive deficits including difficulty with naming and math ability, dysarthria, flattening of the right nasolabial fold, and a mild right hemiparesis. She did not have any headaches. MRI showed acute left parietal and scattered bilateral supratentorial foci of infarction (figure, A and B). Magnetic resonance angiography (MRA) and CT angiography (CTA) showed diffuse narrowing of the vessels of the anterior and posterior circulation (figure, C). Transcranial Doppler revealed mildly increased velocities in the anterior circulation and bilateral posterior cerebral arteries with normal pulsatility indices consistent with mild diffuse vessel narrowing. Bilateral carotid ultrasound did not show hemodynamically significant stenosis. Transthoracic echocardiogram with microcavitation study revealed atrial shunting at rest, but no cardiac thrombus. Ultrasound of both lower extremities was negative for deep venous thrombosis. Cardiac monitoring and EKG during hospitalization did not reveal any arrhythmia. The platelet count at the time of neurologic symptoms was 186×10^9 g/dL, but INR was markedly elevated at 5.2. Warfarin was discontinued on admission and IV argatroban infusion was restarted once the INR dropped below 2 and continued for 13 days. Warfarin was reinitiated 8 days after restarting argatroban. Seven months later, the patient had recovered with the exception of mild cognitive impairment without recurrence of her symptoms. A follow-up MRA was performed and revealed resolution of the diffuse arterial stenotic lesions (figure, D).

DISCUSSION HIT is a prothrombotic disorder characterized by antibodies against heparin and platelet factor 4.[1] It may present as unexplained thrombocytopenia or thrombocytopenia complicated by thrombosis after exposure to unfractionated heparin and less commonly to low-molecular-weight heparin.[1] Thrombocytopenia could manifest either as an absolute drop in platelet count below the normal range or a relative decrease of 30%–50% from baseline counts. The magnitude of thrombocytopenia correlates with the risk for thrombotic complications, which occur in about 30%–60% of patients. Despite platelet count recovery, thrombotic risk in HIT remains high for 4–6 weeks after diagnosis.[1]

Stroke occurred in 3.1% of patients in a study of 960 patients with HIT.[2] In another retrospective study

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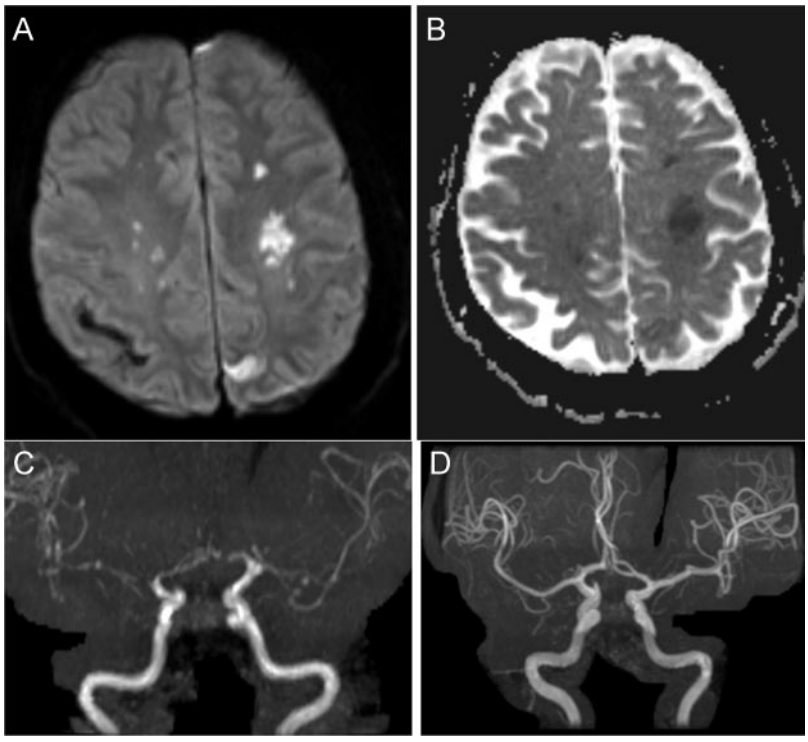
Figure Multiple bilateral strokes and diffuse vascular narrowing



(A) Foci of restricted diffusion on diffusion-weighted MRI revealing acute left parietal cortical infarct, with scattered bilateral supratentorial foci of ischemia. (B) Corresponding restricted diffusion on apparent diffusion coefficient map indicating that these infarcts are acute. (C) Magnetic resonance angiography (MRA) on presentation showing narrowing of the anterior cerebral arteries and proximal middle cerebral arteries. (D) Follow-up MRA 7 months later showing markedly improved flow in the anterior circulation.

of 120 patients with HIT, 11 patients (9.2%) presented with neurologic complications, including ischemic vascular events in 7 patients (5.8%) and cerebral venous thrombosis in 3 (2.5%).[3] Mortality was higher in patients with HIT and neurologic complications as compared to those without neurologic complications (55% vs 11%, $p < 0.01$).[3] In that study, one patient had a stroke 7 days after the initiation of treatment for HIT and 3 patients had a stroke in the setting of normal platelet counts, similar to our patient.[3]

Strokes in patients with HIT may be secondary to arterial occlusion, cerebral venous thrombosis, or cardiac emboli, and can be multifocal.[2–5] In our case, a cardioembolic etiology was unlikely in the presence of normal EKG, cardiac enzymes, and transthoracic echocardiogram. Even though cardiac shunting was present, there was no evidence of lower extremity deep venous thrombosis as a potential source for paradoxical embolism. Reversible vasoconstriction syndrome could explain the multiple strokes and the resolution of the arterial stenotic lesions on follow-up. Nonetheless, this possibility is unlikely given the coinciding HIT, the absence of headache, and the lack of precipitating factors such as the use of vasoactive medications. Vasculitis could also present similarly but is unlikely in our case given that the patient improved without steroids or other immunosuppressants. Our patient had arterial hypertension and smoking, which increased her risk for stroke in the setting of HIT by possibly causing underlying vascular injury.[3] It is unlikely, however, that hypertension and smoking solely account for the multiple acute strokes, especially in the absence of hemodynamic instability. Other usual risk factors for hypercoagulability such as abnormalities of protein C, protein S, prothrombin gene mutation, or factor V Leiden have not been correlated with HIT-associated thrombosis and were not evaluated in our patient.[1,3]

The multiple strokes and stenotic lesions detected on MRA and CTA in our case are likely due to partially thrombosed arteries secondary to HIT. Multiple arterial "white clots" consisting of platelet-rich thrombi have been previously reported in a brain autopsy of a patient with HIT-associated stroke and could potentially be the underlying mechanism of the lesions and strokes seen in our patient.[3] The improvement of these lesions on follow-up rules out a progressive vasculopathy and is not surprising given the patient's recovery from HIT. In our patient, warfarin was initiated prior to complete recovery of thrombocytopenia, which may have contributed to the observed thrombotic complications since vitamin K antagonists should not be used until the platelet count has substantially recovered.[6]

Our patient was not a candidate for tissue plasminogen activator (tPA) since she presented outside the time window. IV tPA is contraindicated in ischemic stroke if the platelet count is less than 100,000/mm^3 but its safety in patients with a higher platelet count in HIT-associated stroke is uncertain given the lack of experience in this setting. Good outcomes following thrombolytic use have been reported in other HIT thrombotic complications.[7] Cerebral arteriograms and other interventional procedures may increase the risk of arterial thrombosis if using wires with heparin-included media or if the vessels are further traumatized by catheterization.[8]

When the patient is on heparin treatment, HIT should be suspected if thrombocytopenia develops or if new thromboses including strokes occur regardless of the platelet count even after discontinuation of heparin.[3] Clinicians should also be vigilant to the occurrence of HIT associated with heparin use in patients with stroke.[9,10]

DISCLOSURE

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