# Homonymous Hemianopia Caused by Occipital Lobe Infarction in Heparin-Induced Thrombocytopenia and Thrombosis Syndrome

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Abstract: A 73-year-old woman developed mental confusion and finger pain after treatment with enoxaparin following arthroplasty. A platelet count was 163,000/µL. Because digital embolism was suspected, she was emergently treated with heparin and recombinant tissue plasminogen activator (rTPA). During rTPA infusion, she reported sudden hemifield loss, so the infusion was aborted. Brain CT disclosed a non-hemorrhagic occipital infarct. Platelets had fallen to 63,000 over eight days, and antibodies against a complex of heparin and platelet factor 4 were detected. These findings led to the diagnosis of heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), an immune-mediated disorder in which venous and arterial thromboses occur. Right lower extremity deep venous thromboses were later diagnosed, and an MRI disclosed multiple cerebral infarcts of recent onset but different ages. Previous reports have documented brain arterial strokes in HITTS, mostly in the distribution of the middle cerebral artery, but clinical documentation is sparse, and there have been no imaging reports. This is the first report to document the clinical and imaging features of a HITTS stroke and the first to describe a stroke presumptively caused by a low molecular weight heparin. It emphasizes that HITTS may cause stroke even when the platelet count is normal. Diagnosis of HITTS should prompt immediate cessation of heparin treatment and substitution of a direct thrombin inhibitor or fondaparinux.

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eparin-dependent antibodies develop in 8% to 50% of patients treated with unfractionated heparin (UFH) for more than five days (1,2), and thrombocytopenia occurs in about 30% of such cases. The IgG antibodies are directed against the heparin-platelet factor 4 complex that binds to platelet FcyIIR receptor and thus induces platelet activation, thrombocytopenia, and thrombosis (3). When thrombocytopenia and heparin-dependent antibody occur together, the diagnosis of heparin-induced thrombocytopenia (HIT) is made. Among those who develop HIT, limb- or lifethreatening thromboses occur in 50-80%. The combination of heparin-dependent antibody, thrombocytopenia, and thrombosis is called heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) (3). The incidence of antibody formation, thrombocytopenia, and thrombosis appears to be at least half as likely in those treated with low molecular weight heparin (LMWH) as in those treated with UFH.

One should consider a diagnosis of HIT when the platelet count falls below 150,000/ $\mu$ L or to less than 50% below base line, even if the count remains within the normal range. One should suspect HITTS when new thrombosis occurs in a patient that is receiving or has received heparin within the previous month (3). Warkentin et al (4) described the "4 T's" system for the assessment of patients with suspected HITTS. The point system considers the degree of *Thrombocytopenia*, the *Timing* of platelet fall, presence of *Thrombosis*, and the exclusion of *oTher* causes of thrombosis. The points assigned for each of the four categories are totaled to yield a HIT pretest probability of low, intermediate, or high.

Thromboembolic complications can be venous or arterial, and they vary with different clinical settings. Venous thromboses occur more frequently in patients receiving heparin after surgical procedures, whereas arterial thromboses occur more commonly in patients receiving heparin for cardiovascular diseases. Among venous thromboses, extremity deep veins are most commonly affected, often accompanied by pulmonary embolism (5,6). Dural sinus thrombosis has also been reported, as have non-hemorrhagic

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brain infarcts. In an 11-year retrospective study of 120 patients with HIT (7), seven (5.8%) developed ischemic stroke and three developed cerebral venous thrombosis (2.5%). Another study of 960 patients with HIT disclosed 30 (3.2%) strokes (8). The ischemic strokes appear to affect primarily the middle cerebral artery territory, but clinical details are sparse, and there have been no imaging reports.

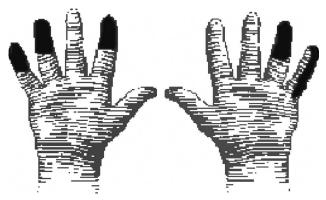
We report the clinical and imaging features of a patient that developed a homonymous hemianopia after use of enoxaparin sodium (a LMWH) following knee arthroplasty. We believe this report to be the first that documents a stroke after LMWH use and the first to show the MRI findings in HITTS stroke.

#### **CASE REPORT**

A 73 year-old woman with longstanding paroxysmal atrial fibrillation underwent a knee arthroplasty after which she was treated simultaneously with warfarin 1 mg/d and subcutaneous enoxaparin sodium 40 mg/d for deep vein thrombosis prophylaxis. When INR levels of 3.0 were reached, enoxaparin sodium was discontinued. Prior to the knee surgery, blood counts had been normal, including a platelet count of 191,000/ $\mu$ L. After the surgery, she received a blood transfusion to correct a hemoglobin level that had dropped to 7.5 g/dl.

Fourteen days after the procedure, she complained of right hand pain and family members noted that she appeared confused. Upon admission, neurologic examination showed no deficits, but the patient had blue discoloration of her fingertips in both hands. The platelet count was 163,000/ $\mu$ L and the INR was 1.61. A brain CT was negative. Doppler studies demonstrated decreased waveforms in both hands suggestive of reduced perfusion. Because of her history of paroxysmal atrial fibrillation, a presumptive diagnosis of embolic occlusion of digital arteries was made even though her electrocardiogram showed normal sinus rhythm. Accordingly, she was started on enoxaparin sodium which was changed after 48 hours to UFH at 24,000 units/24 hours, in combination with warfarin 1 mg/d. INR levels were between 1.61 and 3.26.

Three days later, an upper extremity angiogram demonstrated narrowing of the distal ulnar arteries of both hands and lack of perfusion of the distal portions of digits two, three, and five of the right hand, the ulnar aspect of digit five, and the distal aspect of digit four of the left hand (Fig. 1). She was immediately treated with intravenous recombinant tissue plasminogen activator (rTPA). Within 25 minutes of starting the infusion and instillation of only 0.5 mg rTPA, she complained of visual loss in her left hemifield. The rTPA infusion was stopped due to fear of a brain hemorrhage. But when a brain CT scan was negative, IV heparin (24,000 units/24 hours) was restarted. A follow-up brain CT scan performed 24 hours after the infusion



**FIG. 1.** Schematic illustration of the areas of ischemia in the hands as demonstrated on angiography. The solid areas indicate lack of perfusion.

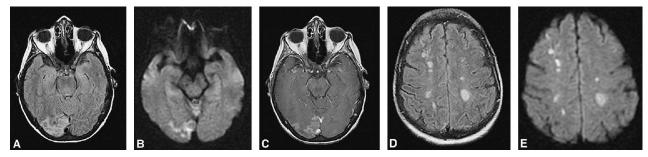
demonstrated findings consistent with ischemic infarction of the right occipital lobe. The IV heparin was continued for an additional six days (PTTs ranging from 62 to 80) as well as warfarin (INR ranging from 1.61 to 4.50). On day 20 after admission, right lower extremity deep vein thromboses of the superficial femoral, popliteal, posterior tibial and peroneal veins were diagnosed.

A work-up for thrombosis risk factors including protein C, protein S, lupus anticoagulant, factor V Leiden, and cardiolipin autoantibodies was normal. A carotid Duplex study and trans-esophageal echocardiogram did not identify an embolic source.

Repeated blood counts performed as part of routine monitoring of heparin treatment revealed a gradual drop in platelets from 163,000 to 63,000/ $\mu$ L over an eight-day period dating from the onset of heparin treatment. The wors-ening thrombocytopenia led to the diagnosis of heparin-induced thrombocytopenia (HIT). Three weeks after the original surgery, her plasma heparin antibodies were mark-edly elevated at 2.422 units (normal <0.349 units). The IV heparin was discontinued, and the patient was started on argatroban 2–3  $\mu$ g/kg/min.

Brain MRI performed three weeks after the complaint of hemifield loss demonstrated numerous focal signal abnormalities compatible with acute and sub-acute infarction. There were several areas of restricted diffusion in the right fronto-parietal white matter characteristic of acute infarction and enhancing signal abnormalities without restricted diffusion in the right occipital lobe and right inferior cerebellum characteristic of sub-acute infarction (Fig. 2). The acute infarctions were not accompanied by correlative new neurologic symptoms.

Ten months after the original visual complaint, neuro-ophthalmologic examination showed a nearly complete congruous left homonymous hemianopia (Fig. 3). The rest of the examination was normal. The hospital course of the case is outlined in Fig. 4.



**FIG. 2.** MRI performed three weeks after the onset of left hemianopia. **A**. Lower axial FLAIR image shows high signal in the right occipital region. **B**. Corresponding diffusion-weighted image does not show restricted diffusion, indicating that the occipital infarct is more than two weeks old. **C**. Corresponding T1 image with contrast shows enhancement, indicating that the occipital stroke is up to three week old. **D**. High axial FLAIR image shows high signal in frontal and parietal regions. **E**. Corresponding diffusion-weighted image shows restricted diffusion in these areas, indicating that these infarcts are less than two weeks old.

## DISCUSSION

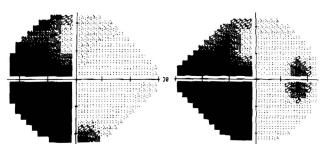
Our patient suffered multiple brain arterial ischemic strokes within weeks of being treated with LMWH. The fingertip manifestations were initially attributed to emboli linked to a history of atrial fibrillation, but the patient was in normal sinus rhythm. Ultimately, the fingertip manifestations were attributed to HITTS as they occurred in conjunction with multiple brain infarcts and venous thromboses. The offending heparin must have been enoxaparin, a LMWH which uncommonly causes thrombocytopenia and thrombosis and has not heretofore been implicated in stroke. It is conceivable than the addition of UFH to her treatment exacerbated the condition and caused additional strokes as visualized on MRI.

The literature on neurologic complications in HITT is limited. In a series of 120 UFH-treated patients diagnosed with HITTS (7), eleven (9.2%) had strokes: seven arterial ischemic events (the distribution described in only one case, a middle cerebral artery stroke), three dural venous sinus thromboses, and one transient confusional state. In that series, two of the patients had a normal platelet count at the time of stroke onset. An extensive literature review of 29 case reports of HITTS and neurologic complications found five patients with MCA ischemic strokes, three with sagittal sinus thrombosis, and one with a parietal focal seizure. The clinical manifestations of the remaining patients were not reported, nor were the imaging findings of any patients (9). There is only one reported case of stroke affecting the occipital lobe (10); it was initially misdiagnosed as thrombotic thrombocytopenic purpura. In that case, imaging was limited to CT and no visual manifestations are described.

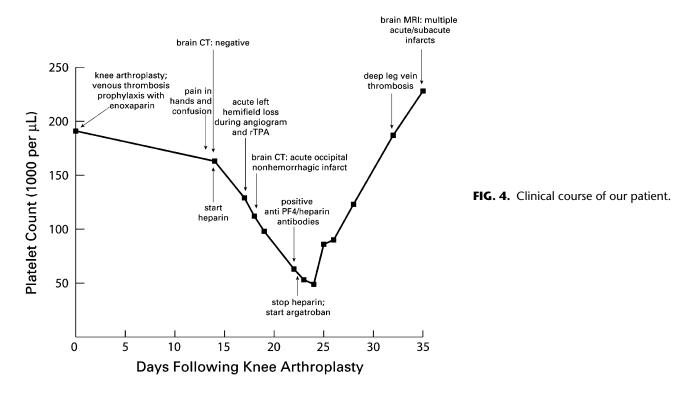
Our case is unusual in that a LMWH was the apparent inciting agent in the multiple thrombotic events. As far as we know, no stroke has been reported after use of a LMWH. A prospective study looked at the risk of developing HIT in 311 neurologic cases receiving UFH or LMWH (11,12). None of the 111 LMWH-treated patients developed HIT. Among 200 UFH-treated patients, five (2.5%) developed HIT and four of them (80%) developed HITTS. Among the four HITTS patients, there had been three deep vein thromboses, two pulmonary emboli, and three ischemic strokes. The clinical characteristics of the strokes were not specified.

Thrombosis outside the brain occurs more commonly in patients treated with UFH than in those treated with LMWH. In 665 patients that received either UFH or LMWH for deep vein thrombosis prophylaxis after hip surgery (1), HITTS occurred in 8 (2.4%) of 332 patients that received UFH and in none (0%) of 333 patients that received LMWH. Heparin-dependent antibodies occurred in 7.8% of those treated with UFH and in 2.2% of those treated with LMWH. Among the patients diagnosed with antibodies, 30% developed thrombocytopenia and 83% of them developed at least one thrombotic event, indicating that antibodies develop more often than thrombocytopenia or thrombosis. Seroconversion occurred between day 5 and 10 of heparin treatment (1). In another study, UFH had a tenfold greater likelihood than LMWH to cause production of heparin-dependent antibody (2).

The frequency of developing heparin-dependent antibodies and HITTS varies by clinical setting. Heparindependent antibodies developed in 50% of UFH-treated



**FIG. 3.** Left homonymous hemianopia 11 months after knee arthroplasty.



patients undergoing cardiac surgery but in only 14% of those undergoing orthopedic surgery. However, among patients in that study that developed antibodies, orthopedic patients were more likely to develop HITT (4.9%) than were cardiac patients (1.0%) (2).

Heparin re-treatment of patients that still have antibodies or have recently developed HITTS within a three-month to four-month interval may cause further thromboses with a median of 10.5 hours of re-exposure to heparin (13). On the other hand, if a patient had HITTS and presently has no evidence of antibodies to heparin, a single use of heparin, as for cardiopulmonary bypass surgery, may be administered safely (13).

HITTS may develop days to weeks after heparin treatment has been discontinued. Warkentin et al (14) reported a group of 12 patients who developed HITTS between 5 and 19 days after heparin treatment was withdrawn (median of 9 days). Rice et al (15) described 14 patients with delayed-onset HITTS that occurred between 9 to 40 days after heparin withdrawal (median of 14 days).

In the management of HITTS, heparin should be discontinued immediately and another anticoagulant should be started (16). Cessation of heparin alone is insufficient; serologically confirmed HITTS patients have an approximately 50% risk of developing a thrombotic event during the 30-day period following heparin stoppage (6). Warfarin is not recommended as it can worsen the thrombosis and cause venous gangrene (16). Direct thrombin inhibitors

argatroban and lepirudin have been shown in prospective studies to improve clinical outcomes in HITTS (17–19) and are therefore recommended as anticoagulants in the treatment of HITTS. Fondaparinux, a five-chain carbohydrate that has no cross-reactivity with heparin antibodies, can also be used safely in cases with HITTS.

Because limb-threatening and life-threatening thromboses can develop quickly in HITTS, it is prudent to monitor the platelet count after the third to fifth day in any patient treated with UFH. A platelet count that continues to decline after the fifth day signals the possibility of HIT and should trigger testing for heparin-dependent antibodies. Suspicion of the diagnosis of HIT or HITTS should prompt the physician to stop any UFH or LMWH treatment immediately and start an alternative anticoagulant. Because this is a prothrombotic state, stopping the heparin therapy is usually insufficient to interrupt the procoagulant process. Direct thrombin inhibitors or fondaparinux are alternative anticoagulant therapy.

The diagnosis in the presented case was understandably not considered on admission because the patient had intermediate risk for HITTS according to the point system described by Warkentin et al (4). The platelet count was still within the normal range and had been treated with a LMWH, an uncommon inciting agent in HITTS. As our patient exemplifies, HITTS may cause arterial or venous thrombosis *even when the platelet count is normal*. A 50% or greater drop in the platelet count below baseline for that patient or a new arterial or venous thrombosis after heparin treatment in any form should raise suspicion of HITTS and prompt immediate work-up and management.

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