CASE REPORT

Lower limb gangrene postcardiac surgery

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SUMMARY

A 67-year-old gentleman presented with a 1-day history of left foot pain. He had recently been discharged following a coronary artery bypass graft; during the admission, he had received an intravenous heparin infusion. Examination revealed black–purple discolouration of the first and second digits of the left foot with pitting oedema to the level of the knee. The posterior tibial and dorsalis pedis pulses were both shown to be patent. A new thrombocytopenia was noted. Ultrasound imaging revealed multiple deep vein thrombosis. The history of recent heparin exposure coupled with venous gangrene secondary to deep vein thrombosis was consistent with heparin-induced thrombocytopenia. He was treated acutely with intravenous danaparoid and later with warfarin. There was complete resolution of the venous gangrene at 1 month follow-up.

BACKGROUND

Heparin-induced thrombocytopenia (HIT) is an uncommon yet important cause of lower limb gangrene. Prompt recognition is important, as early cessation of heparin exposure minimises morbidity. However, poor understanding of the condition's presentation has now led to a threat of overdiagnosis.¹ This article presents a typical case of lower limb gangrene caused by venous thrombosis secondary to HIT, with the hope that it will aid physicians when considering this diagnosis.

CASE PRESENTATION

A 67-year-old gentleman was admitted with a 1-day history of pain and associated dark discolouration of his left foot. He had undergone a two-vessel coronary artery bypass graft 10 days previously, prior to which he had received an intravenous heparin infusion for 72 h. His recovery postprocedure had been unremarkable and he was discharged 7 days ago. His medical history includes type 2 diabetes mellitus, ischaemic heart disease, hypercholesterolaemia and hypertension.

Upon examination, there was a blue–black discolouration involving the toes of the left foot with the first and second toes more markedly affected. Blisters were evident over the dorsal aspect of the first toe (figure 1). There was pitting oedema up to the level of the left knee. Neurological examination of the lower limbs was unremarkable. Neither the posterior tibial nor dorsalis pedis pulses were palpable. The foot was warm to touch with a capillary refill time of 3 s. Examination of the right lower limb was normal. Chest was clear to auscultation. He was afebrile with normal observations with an oxygen saturation of 99% in room air.

INVESTIGATIONS

A platelet count of $39 \times 10^9/l$ was noted on his admission blood tests. All other haematological, biochemical and coagulation tests were normal. His platelet count had been $151 \times 10^9/l$ on discharge 7 days previously. Both posterior tibial and dorsalis pedis pulses of the left foot were detected with hand-held doppler, with ankle–brachial pulse indices within normal limits. Duplex ultrasound found multiple deep vein thromboses within the left calf veins.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the clinical signs was venous or arterial gangrene. Gangrene resulting from venous pathology is less common than that

Figure 1 (A) Dorsal aspect of left foot, (B) medial aspect of left foot and (C) Plantar aspect of left foot.

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from arterial pathology. Venous pathology is suggested by early onset cyanosis, conserved skin temperature, oedema and patent peripheral arteries.² Extensive oedema can cause difficulty palpating the peripheral pulses difficult, which can lead to the false conclusion that they are absent and thus a misdiagnosis of arterial gangrene. A bed-side doppler to calculate the ankle-brachial pulse indices of the peripheral arteries is necessary to ensure their patency and exclude arterial thrombosis.

Recent cardiothoracic surgery, with its associated increased risk of both arterial and venous thromboses, may account for this presentation.³ However, the added history of recent heparin exposure, coupled with the pattern of the fall in the platelet count, suggests an alternate diagnosis of HIT. While characterised by thrombocytopenia, HIT in actuality leads to a prothrombotic state. As in this case, patients typically present with a secondary fall in the platelet count, 5–14 days following heparin exposure. While there is often a drop of >50%, the total platelet count rarely reaches a nadir less than $20 \times 10^9/l$.¹ It is important to note this pattern as there is often overdiagnosis in this setting. A persistently low platelet count following a cardiac surgery would likely be due to an alternative cause.⁴

Many of the clinical features seen in HIT may be expected following a cardiac surgery. For example, the presence of cyanotic peripheries is often seen and may be secondary to hypotension, underlying peripheral vascular disease or the effect of anaesthesia rather than thrombocytopenia.⁵ Therefore, in this patient, it was the combination of the delayed onset of the platelet drop with a nadir $>20 \times 10^9/l$, coupled with the lower limb thrombosis, lack of evidence of haemorrhage and the timescale of the recent heparin exposure which made HIT a likely cause. Once the diagnosis of HIT was suspected, an ELISA test was carried out.

TREATMENT

The patient was initially started on an unfractionated heparin infusion on the suspicion of thrombosis postsurgery and remained on this for 8 h. Once HIT was clinically suspected, heparin was stopped and replaced with an infusion of the alternative anticoagulant danaparoid. This was done before the result of the ELISA was back owing to high clinical suspicion. The platelet count was monitored daily, which began to recover, reaching $165 \times 10^9/l$ after 48 h. The patient was then loaded onto warfarin for long-term anticoagulation. To avoid the complications associated with warfarin therapy in HIT large loading doses (>5 mg) were avoided. Danaparoid was continued alongside warfarin until a target INR of 2–3 was reached. The patient received danaparoid for a total of 7 days.

OUTCOME AND FOLLOW-UP

The gangrene improved after starting the danaparoid infusion and the platelet count remained stable at greater than $150 \times 10^9/l$. He remained an inpatient while being slow-loaded onto warfarin, and was discharged 9 days after admission. At follow-up 1 month later, there was no evidence of gangrene and he was discharged from our care. The patient is to remain anticoagulated for a total of 4 months, a duration recommended by *British Journal of Haematology* guidelines. There is an ongoing debate around the risk of recurrence of HIT with future heparin exposure. Although thought to be rare, recommendations are to use an alternative to heparin when a period of anticoagulation is required.⁶

DISCUSSION

Venous gangrene can be precipitated by a number of conditions, including (most commonly) malignancy, hypercoagulable syndromes, surgery, trauma and the May-Thurner syndrome (caused

by the compression of the left common iliac vein by the overlying right common iliac artery).⁷ However, in this case, it was secondary to deep vein thrombosis owing to an underlying HIT.

HIT is caused by antibodies against multimolecular complexes of heparin and platelet factor-4 (PF4). This immune complex binds to circulating platelets, induces platelet activation and leads to aggregation and thrombin generation. This causes a prothrombotic state.⁸ Although most cases of HIT are linked to the use of low molecular weight heparin owing to its widespread use, the relative risk associated with the use of unfractionated heparin is greater.⁹ Further studies have shown that HIT is rare in those aged under 40 years, is more common in females, is more common in surgical rather than medical patients and that the risk increases with duration of treatment (with treatment >6 days being considered high risk). Medication dose does not appear to be a contributing factor.¹⁰

It is still often difficult to confidently make the diagnosis of HIT owing to the prevalence of thrombocytopenia in the hospital setting. Common causes include infection, medications other than heparin, disseminated intravascular coagulopathy (DIC), haemodilution and the presence of intravascular devices.¹¹ These causes are especially common in patients with critical illness and those recovering from surgery with cardiopulmonary bypass, contributing to particularly frequent overdiagnosis in these cases.¹² One recent observational study showed that although 63 of 1722 patients undergoing cardiac surgery were suspected of having HIT because of subsequent thrombocytopenia, only 24 of these were later confirmed by laboratory tests.¹³ The 4T score has been advocated as a useful scoring tool to quantify the risk of HIT. It calculates a score based on the level of thrombocytopenia, the timing of the fall in platelets, the presence of any new thrombosis and the likelihood of any alternative diagnoses.¹⁴ Although its limitations in terms of sensitivity and specificity have been documented, it is still the most commonly used method for risk stratification.¹⁵

There are laboratory tests which are used in the diagnosis of HIT. One such test is the ELISA to detect circulating anti-PF4/heparin antibodies. Despite having a sensitivity approaching 100%, its use is limited by its relatively poor specificity. One study showed approximately half the number of patients undergoing cardiac surgery shows positive for anti-PF4/heparin antibodies, while the actual incidence of HIT in this group is only 2–3%.¹⁶ Because of this, HIT currently remains a clinical diagnosis. The ELISA does, however, have a high negative predictive value which is useful in ruling out HIT. Functional assays such as the C-serotonin release assay and the heparin-induced platelet activation assay have been developed to detect antibodies specific for inducing platelet activation and which have a sensitivity >95% and specificity >99%.¹⁷ However, these tests are not routinely available in the majority of secondary centres.⁶

The specificity of the ELISA may be improved when taking into account the magnitude of the positive optical density; this has been shown in one recent study to aid in the diagnosis of HIT.¹⁸ Taking this into account, a suggested algorithm for diagnosing HIT is presented in figure 2.

It is important to differentiate between HIT and alternative causes of venous gangrene as their treatments vary considerably. Venous thrombosis is treated with heparin and warfarin, both of which are avoided in the treatment of HIT-induced venous gangrene. Warfarin can increase the risk of microvascular thrombosis in HIT and its introduction should be delayed until there has been a resolution of the thrombocytopenia.^{19,20} This is why the use of alternative anticoagulants such as dabigatran is necessary. It is, however, important not to begin these treatments

Figure 2 Our suggested approach to the management of suspected cases of heparin-induced thrombocytopenia.

without a high index of suspicion for HIT. They require frequent monitoring and specialist laboratory tests, lead to increased expenditure owing to prolonged hospital stay and are associated with an increased risk of haemorrhage.²¹

Danaparoid, an antithrombin-dependent inhibitor of activated factor X, has been recommended as first-line treatment ever since a 42-patient randomised controlled trial demonstrated its superiority over the previously used dextran.²² Other options include the thrombin-specific inhibitors lepirudin and argatroban. Fondaparinux is also considered an acceptable treatment choice, though it is not licensed for this use.⁶

There has been a reluctance to use platelet therapy in HIT patients owing to the fact that the condition primarily causes a pro-thrombotic state, and because of a previously documented risk that platelet transfusion precipitates thrombosis. However, there is limited evidence to demonstrate this and so, though it is not used prophylactically, platelets may still be used in the rare cases of HIT leading to evidence of haemorrhage, or where the diagnosis is in doubt.²³

Competing interests None.

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Learning points

- ▶ Venous gangrene secondary to any cause is rare, but should still be considered in the case of ischaemic peripheries.
- ▶ Diagnosing heparin-induced thrombocytopenia requires careful consideration of the history, clinical features and use of investigations.
- ▶ Prompt recognition and treatment can avoid morbidity.
- ▶ Heparin-induced thrombocytopenia is currently overdiagnosed which may be owing to a lack of understanding over its presentation.

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