CASE REPORT

Unusual case of venous thrombosis

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SUMMARY

A young woman developed a line-associated deep vein thrombosis (DVT), which was treated with low molecular weight heparin (dalteparin). 8 days later, the DVT had significantly extended—in spite of therapeutic heparin levels. A diagnosis of heparin-induced thrombocytopenia and thrombosis (HITT) was considered, but the platelet count had not dropped. Nevertheless, a HITT assay was carried out which came back positive, with a repeat assay confirming the result. Dalteparin was stopped and apixaban treatment started, with symptomatic recovery over the following days and weeks.

BACKGROUND

This case highlights a rare complication of heparin—heparin-induced thrombocytopenia—and its most important effect; thrombosis. It is important because it shows how an anticoagulant can actually worsen thrombosis, and how it should be considered in situations in which this occurs. This case is most unusual because it presented without the apparent key feature of thrombocytopenia. In addition, management was with a direct oral anticoagulant (DOAC), which is not specifically licenced for this indication, but is an attractive option, given its oral route and lack of cross reactivity with antiheparin antibodies.

CASE PRESENTATION

A woman aged 25 years was diagnosed with sigmoid adenocarcinoma and underwent an urgent anterior resection with loop ileostomy. The surgery was uneventful and the patient received 3 days of prophylactic dalteparin prior to discharge home. She was planned for adjuvant chemotherapy and a left arm (non-heparin bonded) peripherally inserted central catheter (PICC line) was inserted 2 months after surgery in order to help administer this therapy. One week later, she developed increasing left arm swelling and underwent a Doppler ultrasound scan which showed a line-associated deep vein thrombosis, extending from the basilic vein to the medial subclavian vein. Therapeutic low molecular weight heparin (dalteparin) was started and the PICC line removed.

Eight days later, in spite of dalteparin, she developed worsening arm symptoms and new pain and swelling of the left neck and face. She went on to have a CT scan of the neck and thorax, which showed extension of the thrombus on the left side, extending into the left internal jugular vein, and into the superior vena cava. An anti-Xa assay to check for heparin effect came back within the normal therapeutic range, and full blood count showed a normal platelet number. Consideration

was made as to whether this could still be heparin-induced thrombocytopenia and thrombosis (HITT), but with a normal platelet count, and a HITT assay was sent. The test came back positive; and a repeat assay at a different laboratory supported this result. Further tests for other prothrombotic conditions were also sent in order to exclude antiphospholipid syndrome and paroxysmal nocturnal haemoglobinuria—these tests were negative. It is also worth noting that there was no demonstrable active malignancy at this time.

INVESTIGATIONS

The baseline platelet count was 220×10^9 . On admission for progressive thrombosis, the platelet count was 240×10^9 , with the lowest count during the episode at 175×10^9 .

Other investigations were performed as follows:

- ▶ *Anti-Xa*: 1.15 IU/mL (within therapeutic range)
- ▶ *Anticardiolipin Ab screen*: 3 U/mL (0–9)
- ▶ *Anti beta2 glycoprotein-1 Ab IgG*: 2 U/mL (0–5)
- ▶ *Paroxysmal nocturnal haemoglobinuria screen*: –ve
- ▶ *HITT assay 1 (Acustar)*: 2.69 U/mL (+ve result > 1 U/mL)
- ▶ *HITT assay 2 IgG Elisa*: OD 1.468 (+ve results > 0.4) (and inhibited by >50% in the presence of excess heparin)
- ▶ *CT scan*: see [figure 1](#)

DIFFERENTIAL DIAGNOSIS

- ▶ HITT
- ▶ Subclinical antiplatelet factor 4 (PF4)/heparin antibodies
- ▶ Non-administration of medication
- ▶ Antithrombin deficiency leading to reduced effectiveness of heparin
- ▶ Aggressive thrombotic disorders, for example, antiphospholipid syndrome, paroxysmal nocturnal haemoglobinuria and active malignancy

TREATMENT

Treatment was started with apixaban at a dose of 10 mg BD, and then dropped to 5 mg BD.

OUTCOME AND FOLLOW-UP

There was dramatic symptom reduction on the next day, and the dose of apixaban was reduced to 5 mg BD after 7 days, remaining at this dose for a further 3 months. She continues to have some symptoms secondary to post-thrombotic syndrome, but repeat Doppler USS has shown partial resolution of the thrombus. Apixaban has been continued to cover completion of oral chemotherapy.

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Figure 1 CT scan performed during admission for progressive thrombosis. (A) Thrombus is seen in the left internal jugular vein (arrow), left subclavian and axillary veins and extending into the left brachiocephalic vein as far the superior vena cava. (B) Right venous system clear of thrombus.

DISCUSSION

HITT is a rare but important complication of heparin therapy, which is more common with unfractionated heparin than low molecular weight heparin, and more common in certain cohorts (eg, postcardiac surgery, malignancy and orthopaedic surgery).¹ The disorder is caused by the development of antibodies to the PF4/heparin complex, and leads to platelet activation and vascular endothelial damage.² As the name suggests, it usually causes thrombocytopenia, and is associated with thrombotic complications which may be arterial or venous. Rates of thrombosis (either new or progressive) may be as high as 50%, and require prompt recognition and management.³

The diagnosis is often challenging, with a need to carefully evaluate clinical findings against the timing of heparin administration. Immunological HITT assays in isolation tend to have a relatively poor positive predictive value, and, much like a D-dimer in the diagnosis of venous thrombosis, their real value is when coupled with a clinical diagnostic algorithm.⁴ However, their negative predictive value is excellent. The use of functional assays, such as the serotonin release assay, heparin-induced platelet aggregation or heparin-induced multiple electrode aggregometry, is available to few clinicians in a timely fashion.⁵ We believe that the timing of the worsening of the thrombosis, the two 'HITT positive' immunoassays, and a rapid response to non-heparin anticoagulation, all point towards HITT as the most likely diagnosis.

Normal platelet count HITT has been reported, although the reason for this is not clear.⁶ Variability of the fall in platelet count is recognised in the diagnostic criteria, and other coexistent reactive conditions may mask a thrombocytopenic effect. Such a condition was not present in this case, and we considered whether this may demonstrate the heterogeneity of HITT antibodies or possibly the thrombopoietic response in a young person.

Management of HITT with DOACs has been described, although it should be noted that these are not a licenced treatment for HITT.⁷ The British Society for Haematology

guidelines suggest that HITT requires therapeutic anticoagulation for at least 1 month in the absence of thrombosis, extending to 3 months for thrombotic HITT cases.⁸

Patient's perspective

I feel that had this complication been picked up sooner with the clotting, and not have been left to get much worse, I would not be left with a permanently swollen arm (4 cm larger than my right). The administration of apixaban immediately started to work and relived my symptoms, whereas the heparin did not.

Learning points

- ▶ Heparin-induced thrombocytopenia is a rare but important complication of heparin use.
- ▶ Heparin-induced thrombocytopenia and thrombosis (HITT) is a prothrombotic disorder associated with a high rate of arterial and venous thrombosis.
- ▶ HITT can present with thrombosis in the absence of thrombocytopenia; more typically, it is suspected when thrombocytopenia develops 5–10 days after heparin exposure.
- ▶ Direct oral anticoagulant medications (such as apixaban and rivaroxaban) are potentially attractive therapies for HITT, as they may be used to treat acute venous thrombosis without the need for upfront heparin, and they do not appear to show cross-reactivity for PF4/heparin antibodies.

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Competing interests None declared.

Patient consent Obtained.

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