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Clinical Report

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Management of heparin-induced thrombocytopenia (HIT) in patients with systemic vasculitis and pulmonary haemorrhage

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Abstract
Heparin-induced thrombocytopenia (HIT) is a relatively uncommon but potentially fatal complication of the use of heparin in haemodialysis. It is associated with a risk of venous and arterial thrombosis due to the formation of a heparin-platelet factor 4 antibody. Early recognition and immediate treatment of HIT are crucial to reduce the morbidity and mortality rate. Here, we report two patients with acute kidney injury due to anti-glomerular membrane (GBM) glomerulonephritis and granulomatosis with polyangiitis respectively who developed haemoptysis and pulmonary haemorrhage complicated by HIT. We discuss the diagnostic and management challenges of such patients.

Keywords: anti-glomerular membrane (GBM) glomerulonephritis; granulomatosis with polyangiitis; heparin-induced thrombocytopenia (HIT); thrombosis

Introduction

Heparin is the most commonly prescribed anticoagulant in patients on acute or chronic haemodialysis due to its cost-effectiveness. It is used to prevent clotting of the extracorporeal circuit and for locking of the dialysis catheters. The first published report of heparin-induced thrombocytopenia (HIT) dates back to 1958 [1]. It is an immune-mediated phenomenon due to the exposure of heparin. HIT is relatively uncommon with a prevalence of 0.26% in the UK dialysis population [2]. However, it carries potentially serious complications associated with venous or arterial thrombosis and increased mortality rate [3]. Here, we describe two patients with acute kidney injury due to anti-glomerular membrane (GBM) glomerulonephritis and granulomatosis with polyangiitis respectively, who developed HIT in the presence of pulmonary haemorrhage/haemoptysis.

Case 1

An 80-year-old man was admitted to hospital for acute kidney injury secondary to anti-GBM disease with an elevated anti-GBM antibody level of 721 U/mL (normal range: 0–7) and a renal biopsy which confirmed a crescentic glomerulonephritis. He was immunosuppressed with methylprednisolone and cyclophosphamide and started on dual filter plasmapheresis (DFPP). Haemodialysis and DFPP were conducted under anticoagulation with unfractionated heparin and he was given dalteparin for deep vein thrombosis (DVT) prophylaxis. However, the fourth haemodialysis session was complicated by a clotting extracorporeal circuit with high transmembrane pressure (TMP). The platelet count was noted to decrease abruptly to 131×10^9/L (Figure 1a) and a diagnosis of HIT was made based on clinical presentation, with a '4Ts' score of 4. It was then confirmed by the detection of HIT antibody by using the enzyme-linked immunosorbent assay (ELISA) with a high optical density (OD) of 2.46 (normal range: 0–0.4). Heparin was stopped immediately, and the patient was started on IV danaparoid (heparinoid that indirectly inhibits factor Xa) with monitoring of anti-factor Xa levels.

Four days after starting danaparoid the patient developed shortness of breath with haemoptysis. The factor Xa levels were in the therapeutic range. He was transferred to the intensive care unit for further respiratory support, renal replacement therapy and plasma exchange. He was commenced on continuous veno-venous haemodiafiltration, and the danaparoid was switched to the direct thrombin inhibitor, argatroban. However, despite ongoing therapy, the patient died from respiratory and circulatory failure after 15 days of admission.

Case 2

A 71-year-old man was admitted for a 2-week history of gross haematuria with non-oliguric acute kidney injury. He was diagnosed with granulomatosis with polyangiitis

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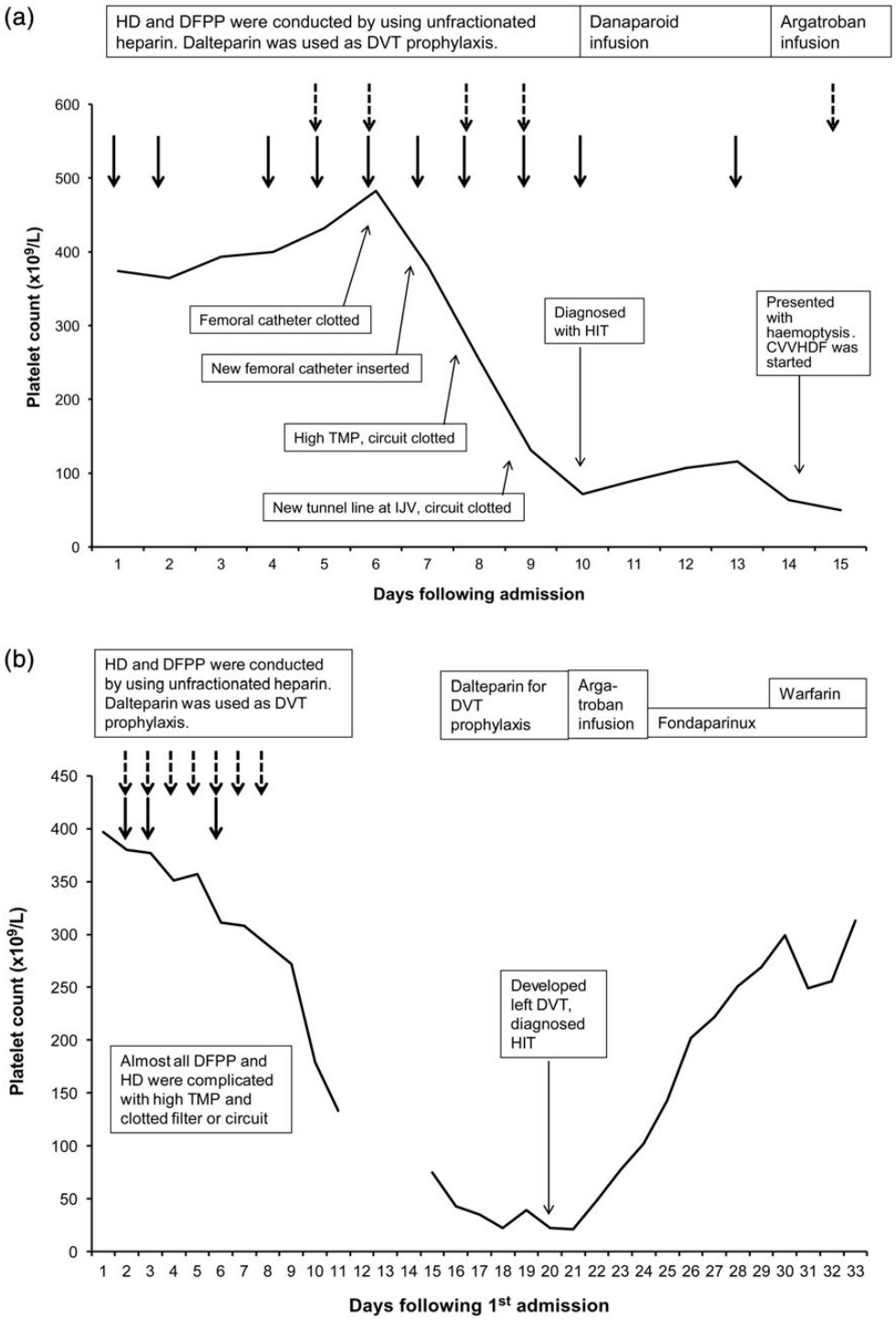

Fig. 1. Change in platelet count in Case 1 (**a**) and Case 2 (**b**). Haemodialysis (↓), dual filter plasmapheresis (DFPP) ( ).

with a positive cytoplasmic anti-neutrophil cytoplasmic autoantibody (c-ANCA) and an anti-proteinase 3 titre of 536 U/mL. He was immunosuppressed with methylprednisolone and cyclophosphamide and started on daily DFPP and intermittent haemodialysis. The anticoagulant used was unfractionated heparin; however, almost all of the plasmapheresis and haemodialysis sessions were interrupted with high TMP and clotted extracorporeal circuits. He was discharged after seven cycles of DFPP and recovered kidney function.

He was readmitted a week later for fever, cough and haemoptysis, and the chest X ray was consistent with a right lower lobe pneumonia. As the ANCA antibody remained high, he could have infection or ongoing vasculitis or both. He was commenced on antibiotics and had dalteparin for DVT prophylaxis. He improved but the platelet

count started to fall further (Figure 1b), and he developed acute left femoral vein thrombosis with a low platelet count of 22×10^9/L. The '4Ts' score was 6 and the HIT antibody was strongly positive (2.4 OD) on ELISA assay. Dalteparin was stopped, and he was commenced on an argatroban infusion. Adjustment of argatroban infusion was made based on the clinical presentation and monitoring of aPTT level. Fondaparinux (a factor Xa inhibitor) and warfarin were introduced when the platelet count normalized. The patient was discharged home once anticoagulated and remained well on warfarin.

Discussion

HIT is a clinicopathologic syndrome related to the formation of heparin-platelet factor 4 (PF4) antibodies [4, 5]. When heparin binds to PF4, a conformational change occurs leading to exposure of neo-epitopes on PF4 and production of antibodies (typically IgG). Subsequently, the heparin-PF4-antibody complexes bind to the platelet FcγIIa receptors, triggering platelet activation and consumption. It further creates a hypercoagulability state with the generation of thrombin, release of platelet microparticles, endothelial injury and activation of inflammatory cells. However, not all patients who develop HIT antibodies develop thrombocytopenia or thrombotic events. Both our patients had clotting in the extracorporeal circuits, and this could have been a manifestation of HIT.

HIT typically happens 5–14 days after initiation of heparin. However, HIT can begin rapidly in patients who have received heparin within the previous 100 days [6]. In Case 2, the HIT could be a result of dalteparin given during the second admission or previous exposure to unfractionated heparin as both are potential aetiological agents. Heparin typically causes modest thrombocytopenia with a median platelet count of $55–60 \times 10^9$/L. Invariably, the patients demonstrate a significant decline (>50%) in platelet count from the baseline [7]. Thrombocytopenia usually resolves 7–10 days after discontinuation of heparin.

The diagnosis of HIT is usually made on clinical presentation and further confirmed by laboratory testing. The '4Ts' scoring system proposed by Warkentin *et al.* [8, 9] has been recommended by the British Haemostasis and Thrombosis Task Force to assess the probability of HIT [10]. It can be calculated from four features: (i) the degree of thrombocytopenia, (ii) the timing of onset of thrombocytopenia, (iii) presence or absence of thrombosis and (iv) whether alternate causes of thrombocytopenia are likely. HIT antibodies can be detected by functional tests or commercial ELISA immunoassays. Individuals with a higher OD with ELISA (≥1.2 units) have an excellent correlation with diagnosis by the gold standard ^{14}C-serotonin release assay [11].

As soon as HIT is suspected, heparin should be discontinued and alternative anticoagulant initiated immediately to prevent thrombosis. The available options include danaparoid, and direct thrombin inhibitors (e.g. lepirudin and argatroban) [11]. The main disadvantage of danaparoid is its prolonged half-life of around 30 h in patients with renal failure. Argatroban is metabolized by the liver and does not require dose adjustment in renal diseases. Once it is discontinued, coagulation profiles normalize within 2–4 h. Argatroban appears to be well tolerated in patients with significant kidney disease and enables renal replacement therapy with little or no thrombotic or haemorrhagic complications [12].

In these two cases, the patients presented with haemoptysis, which may have been a manifestation of pulmonary haemorrhage due to anti-GBM disease or granulomatosis with polyangiitis; yet, they required systemic anticoagulation to prevent thromboembolism associated with HIT. There is also an increased risk of venous thromboembolic events in patients with ANCA-associated vasculitis [13]. In view of the bleeding risk and renal impairment, argatroban was the drug of choice in our patients because of its short half-life and no renal dose adjustment. As argatroban prolongs international normalization ratio and complicates the transition to warfarin, fondaparinux was used as a bridging therapy in Case 2. Recent guidelines recommend 4 weeks of anticoagulation in patients with isolated HIT not complicated by thrombosis, but 3 months in those with HIT and thrombosis [10]. Warfarin should be started after normalization of platelet counts because venous limb gangrene can occur when warfarin is started during acute HIT [14].

Conclusion

The combination of HIT with anti-GBM disease or granulomatosis with polyangiitis had undoubtedly posed an unmet challenge to the clinicians. Although argatroban provides alternative anticoagulation in HIT, future studies are required to define the optimal agents for this group of patients with high risk of bleeding.

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