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Persisting autoimmune heparin-induced thrombocytopenia after elective abdominal aortic aneurysm repair: a case report

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Abstract
Persisting heparin-induced thrombocytopenia (HIT) is characterized by ongoing thrombocytopenia more than 7 days after stopping heparin. It is part of cases referred to as autoimmune HIT (aHIT). In contrast to typical HIT cases, aHIT involves heparin-independent platelet activation mechanism highlighted by a strongly positive functional assay done without heparin. We report the first case of persisting HIT after an elective abdominal aortic aneurysm repair presenting with arterial and venous thrombosis, and describe the potential role of intravenous immunoglobulin in such patients.

Keywords Case report · Heparin · Thrombocytopenia · Thrombosis · Immunoglobulin

Highlights

- Ongoing thrombocytopenia more than 7 days after stopping heparin and new thrombosis despite receiving treatment characterize persisting HIT.
- Autoimmune HIT is characterized by a strongly positive functional assay done without heparin.
- Intravenous immunoglobulin for treatment of autoimmune HIT results in improvement of thrombocytopenia and the most used dosing schedule is 1 g/kg daily for 2 doses.
- Intravenous immunoglobulin should be considered as an emerging therapy for autoimmune HIT.

Introduction

Heparin-induced thrombocytopenia (HIT) is an immunologic condition characterised by the association of venous and arterial thrombosis with thrombocytopenia classically in the context of heparin exposure [1]. HIT usually starts 5–10 days after initiation of heparin, in many cases after major surgery [2, 3].

The pathogenesis of HIT is complex and not completely understood. HIT is induced by pathologic IgG class antibodies recognizing macromolecular complexes formed by the cationic platelet factor 4 (PF4) and the polyanionic heparin. The immune complexes then activate platelets, endothelial cells and monocytes by binding to their Fcγ specific receptors. The subsequent increase in thrombin generation explains the thrombotic processes seen in this pathology [4].

Over the past decade, it has been recognized that cases of particularly severe HIT involve a heparin-independent platelet activation mechanism in which other polyanions, such as glycosaminoglycans released from cartilage after knee surgery [5], may trigger the immune response. Moreover, immune complex formation characterized by a high-binding-force antibody, which binds two PF4 molecules without involving a polyanion, has been described in patients with

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spontaneous HIT [6]. These cases of HIT with heparin-independent platelet activation are referred to as autoimmune HIT (aHIT) which includes clinical entities such as spontaneous HIT, delayed-onset HIT and persisting HIT [7].

We describe here a case of persisting HIT after an elective abdominal aortic aneurysm repair and the potential role of intravenous immunoglobulin (IVIG) in such patients.

Case

A 68-year-old man was admitted for an elective abdominal aortic aneurysm repair with a Dacron tube graft. He had a prior history of coronary and peripheral artery disease, stage 3b chronic kidney disease and hypertension. The patient underwent surgery without any relevant early complications and received 7000 units of intravenous heparin during the procedure. He was started on thromboprophylaxis with unfractionated heparin 5000 units every 8 h subcutaneously on postoperative day (POD) 1. The dose was subsequently adjusted to 5000 units twice daily on POD 3. His platelet count on the day of surgery was 148,000/µL and remained stable until a sudden drop to 81,000/µL on POD 9 (Fig. 1). On the same day, the patient suffered an ischemic right middle cerebral artery stroke and underwent mechanical thrombectomy. The diagnosis of HIT was suspected given a 4Ts score of eight points. Heparin was stopped after the procedure and argatroban was started on POD 10. Polyspecific anti-PF4 immunoassay (GTI Polyspecific) was positive with an optical density of 2.132 and the functional assay (ATP release lumi-aggregometry) was positive. 5 days after the last dose of heparin (POD 14), the patient developed an acute main, right and left portal vein thrombosis, despite having an aPTT that was consistently therapeutic while on argatroban. Considering the persisting thrombocytopenia (the platelet count was still only 29,000/µL without evidence of disseminated intravascular coagulation) and the new thrombosis while on treatment, a heparin-independent persistent HIT was suspected and IVIG (Gamunex®) 0.5 g/kg on POD 14 and 1 g/kg on POD 15 was administered. On POD 16, repeat HIT immunoassay revealed an optical density of 2.677 and the functional test remained positive. This functional test was done without adding heparin, confirming the heparin-independent activating nature of this antibody. Because the platelet count remained low between 50,000 and 80,000/µL, IVIG 1 g/kg/day was again given on POD 21 (Gamunex®) and 22 (IGIVnex®). The platelet count then slowly increased to 113,000/µL on POD 37 when warfarin was started. On POD 45, while being on argatroban awaiting a therapeutic INR on warfarin, a computed tomography angiography has been done in the context of a non-palpable right pedal pulse and a 10-day history of right

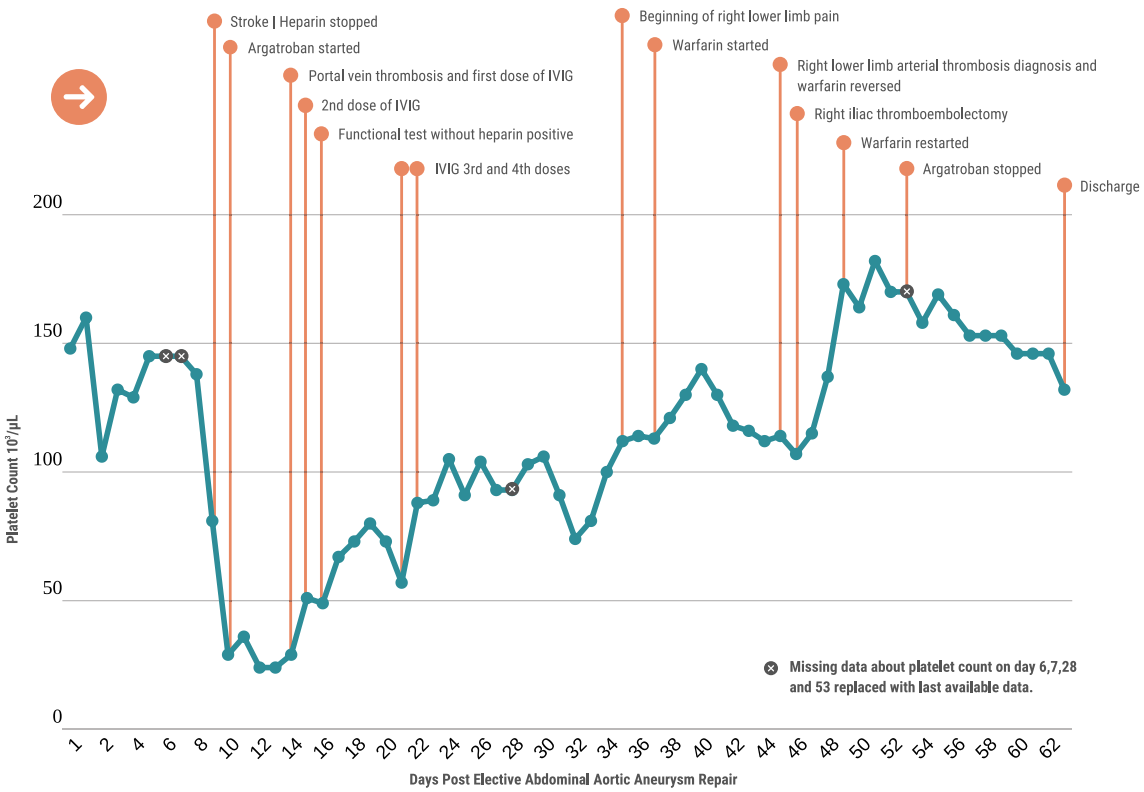

Fig. 1 Platelet count, thrombotic events and treatment in a patient with persistent HIT after surgical abdominal aortic aneurysm repair

great toe pain. It revealed a new severe stenosis of the right proximal external iliac artery and occlusion of the anterior tibial artery. A diagnosis of right forefoot ischemia secondary to iliac artery near-occlusion and distal embolization was made (which probably occurred around POD 35). Warfarin was then stopped and reversed with vitamin K. The next day (POD 46), the patient underwent a right iliac thromboembolectomy, retrieving a piece of 3.7 × 0.7 × 0.7 cm tan to red-brown organizing thrombus (Fig. 2). No heparin was used during the procedure. The platelet count then increased to 173,000/µL on POD 49 and warfarin was resumed at 5 mg daily. Argatroban was stopped on POD 53 after a total duration of 43 days. The patient was discharged on POD 63 with a platelet count of 132,000/µL.

Discussion

HIT is a recognized complication in patients undergoing major surgery, especially in those receiving unfractionated heparin (UFH) [8]. The incidence of HIT after vascular surgery is approximately 0.3% [9]. Most patients with HIT manifest initially with a 50% drop in platelet count [10]. Thrombocytopenia resolves in 50% of the cases after 4 days of treatment and in 90% after one week [11, 12].

Autoimmune HIT was first described in 2001 in case series of 12 patients with an atypical clinical picture of worsening of newly diagnosed HIT after stopping heparin (delayed-onset HIT) [13]. Cases of aHIT caused by heparin flushes [14], fondaparinux [15] and even spontaneous HIT [16] without any identified polyanion have been described and share the same characteristic of being more severe (refractory lower platelet count and thrombosis process) [17]. Ongoing thrombocytopenia more than 7 days after stopping heparin and new thrombosis despite receiving treatment characterize persisting HIT [17].

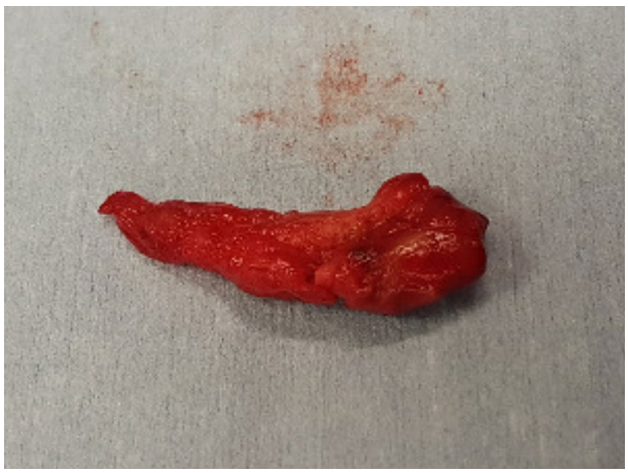

Fig. 2 Right iliac clot

The diagnosis of persisting HIT is based on clinical assessment with the 4Ts score [18] associated with a strongly positive immunoassay [19, 20]. It is confirmed by a positive functional assay performed without adding heparin to show heparin-independent platelet activation [21]. The serotonin release assay is considered the gold standard for diagnosing HIT [22]. In our case, we used an ATP-release lumi-aggregometry test, which has been reported to have the same accuracy as the serotonin release assay [23].

Treatment of HIT with IVIG was first described in 1989 [24], but IVIG as a treatment option has received little attention until the recognition of aHIT. The rationale for IVIG use is that IgG blocks FcγIIa receptors on platelets and inhibits their activation by HIT antibodies. A recent article reported 36 cases who have been treated for aHIT with IVIG and showed a rapid favorable platelet response. The most commonly used dosing schedule of IVIG is 1 g/kg daily for two doses [25]. After IVIG administration, thrombocytopenia seems to improve significantly within 1 week [26, 27]. Our patient received a lower than described first dose and the platelet response was mild. His second treatment course included a higher dose, but the platelet response was slower than expected. He received Gamunex® for the first three doses and IGIVnex® for the last one. It is uncertain if the slow response was related to variability in inhibitory effect of different IVIG products [28, 29].

There are concerns about potential thrombotic side effects of IVIG, but their benefits in aHIT most likely outweigh the risks. The pathology report of the thrombus on POD 46 revealed organization, which is compatible with a non-fresh clot. Our patient has begun to develop right lower limb ischemic symptoms around 13 days after he had received the last dose of IVIG. However, the association between IVIG use and arterial thrombosis in our case remains uncertain, because it usually manifests within hours to days after IVIG use[30] and arterial thrombotic complications post-IVIG have not been confirmed in HIT patients in previous case reports [29].

Three cases of aHIT have been described in vascular surgery patients. One case was associated with a cardiopulmonary bypass for a type A aortic dissection repair [29]. Two other cases reported delayed-HIT after thoracic aorta vascular surgery, but without confirming the heparin-independent platelet activation process [31]. All three cases were treated with different IVIG doses and resulted in variable thrombocytopenia improvement. Our case is the first to describe the development of aHIT after an elective vascular surgery. It illustrates the often-observed severity of persisting HIT with development of arterial and venous thrombosis despite treatment with direct thrombin inhibitors. By describing a slow but positive response to

repeated courses of IVIG, this case of confirmed severe persisting HIT supports the use of IVIG as emerging therapy for aHIT.

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Conflict of interest All authors declare that they have no conflict of interest.

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