African Journal of Nephrology
Official publication of the African Association of Nephrology
Volume 28, No 1, 2025, 86-89

CASE REPORT

Heparin-induced cardiopulmonary arrest in a patient with heparin-induced thrombocytopenia: a rare severe anaphylactoid reaction

Hekkie Breytenbach[1*], Sashen Mohan[1*], Jason Ensor[2,3], Nkululo Gigi[3], Jessica Opie[4], Leriska Haupt[5], Jonny Peter[6], Noel Walton[3], Robert Freercks[2,3]

[1]Department of Internal Medicine, Livingstone Tertiary Hospital, Gqeberha, South Africa; [2]Department of Medicine, Nelson Mandela University, Gqeberha, South Africa; [3]Division of Nephrology, Livingstone Tertiary Hospital, Gqeberha, South Africa; [4]Division of Haematology, University of Cape Town and National Health Laboratory Service, Groote Schuur Hospital, Cape Town, South Africa; [5]Department of Haematology and Cell Biology, University of the Free State and National Health Laboratory Service, Bloemfontein, South Africa; [6]Division of Allergy and Clinical Immunology, Groote Schuur Hospital and University of Cape Town and Allergy and Immunology Unit, University of Cape Town Lung Institute, Cape Town, South Africa.

[*]Contributed equally

ABSTRACT

Heparin-induced thrombocytopenia (HIT) is a serious complication arising from heparin therapy, with features of thrombocytopenia and increased risk for thromboembolism. This report details cardiopulmonary arrest as an uncommon association of HIT in a 49-year-old female on chronic haemodialysis. Anaphylactoid reactions are reported in 1–4% of HIT cases and occur via non-IgE mediated mechanisms. This case also highlights the complexity of HIT diagnosis, with an initially negative platelet aggregation test later found to be positive at a reference laboratory. The patient was treated successfully with fondaparinux and warfarin, leading to a full recovery. We highlight the need for vigilance in recognizing HIT in dialysis patients and discuss some of the pitfalls relating to heparin-induced platelet aggregation testing.

Keywords: heparin-induced thrombocytopenia; cardiac arrest; dialysis; anaphylactoid reaction.

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a rare, but serious, complication of heparin therapy. Type II HIT typically presents 5 to 10 days after heparin initiation with thrombocytopenia and is often associated with arterial or venous thrombosis. In this article it will be referred to as HIT. Anaphylactoid reactions are rare, occurring in <5% of HIT cases [1-4]. Type I HIT is a benign, transient and mild reduction in platelet count that resolves spontaneously due to direct platelet activation by heparin and will not be discussed further [5].

The presentation of HIT in the haemodialysis (HD) population is variable but can include clotting of the dialysis circuit or catheter, acute dyspnoea, and cardiopulmonary arrest [5]. Many of these complications are common in dialysis patients and vigilance is required to consider HIT in such cases.

We present a case of a 49-year-old female on chronic HD who presented with cardiopulmonary arrest related to HIT.

CASE REPORT

A 49-year-old female with kidney failure secondary to chronic glomerulonephritis experienced cardiopulmonary arrest shortly after initiation of her HD session. Chronic medications were: amlodipine, furosemide, carvedilol, doxazosin, iron sucrose, epoetin beta, abacavir, lamivu-

Received 17 February 2025; accepted 23 June 2025; published 16 July 2025.
Correspondence: Hekkie Breytenbach, hekkiebreytenbach@gmail.com.

DOI: https://doi.org/10.21804/28-1-7064.

dine, dolutegravir, isoniazid and pyridoxine. She was not receiving an ACE-inhibitor due to a previous episode of angioedema (lower lip swelling), which resolved on stopping it. She had HIV infection, currently with an undetectable viral load, and had been receiving chronic HD with unfractionated heparin (UFH) for 10 months using steam-sterilised polysulfone dialysers. Approximately 5–10 minutes following initiation of dialysis and administration of UFH, she reported feeling hot and then suffered a cardiopulmonary arrest. One cycle of cardiopulmonary resuscitation (CPR) was performed and return of spontaneous circulation was achieved. She recovered completely and completed the dialysis session without further complications or additional heparin administration.

The dialysate potassium concentration was 2.0 mmol/L, pump speed 300 mL/min and the target ultrafiltration was 3.0 L for the day, in keeping with her usual HD script. There had been no recent episodes of hypotension. No air was observed in the dialysis line and the electrocardiogram revealed sinus rhythm with normal corrected QT. Her venous blood gas potassium was 5.5 mmol/L post arrest. The dialyser composition was polysulfone and steam-sterilised, therefore ethylene oxide and cellulose reactions were not considered. Echocardiogram showed no evidence of pulmonary hypertension nor regional wall motion abnormalities. Chest radiograph showed right lower lobe consolidation. Laboratory investigations revealed thrombocytopenia and elevated inflammatory markers (Table 1 and Figure 1). The 4T score [6] was seven, losing one point for possible other causes of thrombocytopenia, which indicated a high pre-test probability for HIT, so laboratory testing for HIT was requested. The presumptive diagnosis was community acquired pneumonia, although pulmonary embolism was also considered. She was admitted for intravenous antibiotics and further evaluation.

Table 1. Summary of laboratory investigations on date of cardiopulmonary arrest.

Result	Value	Reference range
White cell count, $\times 10^9$/L	8.52	3.90–12.60
Haemoglobin, g/dL	7.5	12.0–15.0
Platelet count, $\times 10^9$/L	26	186–454
C-reactive protein, mg/L	201	<10
Procalcitonin, µg/L	4.86	<0.1
Cardiac troponin I, ng/L	44	Rule-in value >500
Sodium, mmol/L	140	136–145
Potassium, mmol/L	5.2	3.5–5.1
Urea, mmol/L	16.0	2.1–7.1
Creatinine, µmol/L	719	49–90
Alanine transaminase, U/L	40	7–35
Alkaline phosphatase, U/L	134	42–98
INR, ratio	1.39	
D-dimer, mg/L	8.05	0–0.25

Sputum was negative for tuberculosis, and inflammatory markers trended downward. Contrast-enhanced computed tomography (CT) revealed right middle and lower lobe consolidation.

Three days later, the patient experienced a second episode of cardiopulmonary arrest shortly after initiation of a subsequent dialysis session and within a few minutes of UFH administration. CPR was performed and return of spontaneous circulation was achieved. The patient recovered fully and was able to complete the dialysis session. A consultant review of the initial CT scan reported filling defects involving the left posterior basal segmental pulmonary arteries in keeping with pulmonary embolism. Notably, on both occasions, there were no signs of urticaria/angioedema and no bronchospasm, and the mast cell tryptase test conducted within 1 hour was normal. The anti-platelet factor 4 (PF4) IgG antibody was positive, but initial heparin-induced platelet aggregation (HIPA) tests were negative. However, due to the temporal association with heparin administration and the high clinical index of suspicion, repeat HIPA testing was requested at an academic reference laboratory, which was positive.

No further heparin was administered and fondaparinux anticoagulation therapy was started and followed later by warfarin for a period of 6 months. Dialysis was continued with the same dialyser, therefore a dialyser reaction was very unlikely. The patient remained well one year later with no further cardiopulmonary complications.

DISCUSSION

HIT is caused by heparin-induced antibodies against PF4–heparin complexes, leading to platelet and monocyte activation, thrombin generation, and thrombosis [7]. The mechanism responsible for anaphylactoid reactions remains uncertain and is likely multifactorial in many patients. Importantly, there is no evidence for IgE-mediated mast cell degranulation, rather there is platelet activation by anti-PF4 IgG leading to C3a, C4a, and C5a generation. This is associated with other markers of systemic inflammation such as fever and chills, which frequently occur [2], and kallikrein system activation with overproduction of bradykinin, which is regarded as the most the likely mechanism responsible for the spectrum of clinical features [3].

Patients undergoing dialysis are frequently exposed to heparin. The risk of HIT is 5–10 times higher using UFH compared to low-molecular weight heparin [8,9]. HIT is more frequent in females and patients undergoing cardiopulmonary bypass [10]. HIV infection may also increase the incidence of HIT [11]. HIT typically occurs 5–10 days after UFH or LMWH initiation but can occur at any time

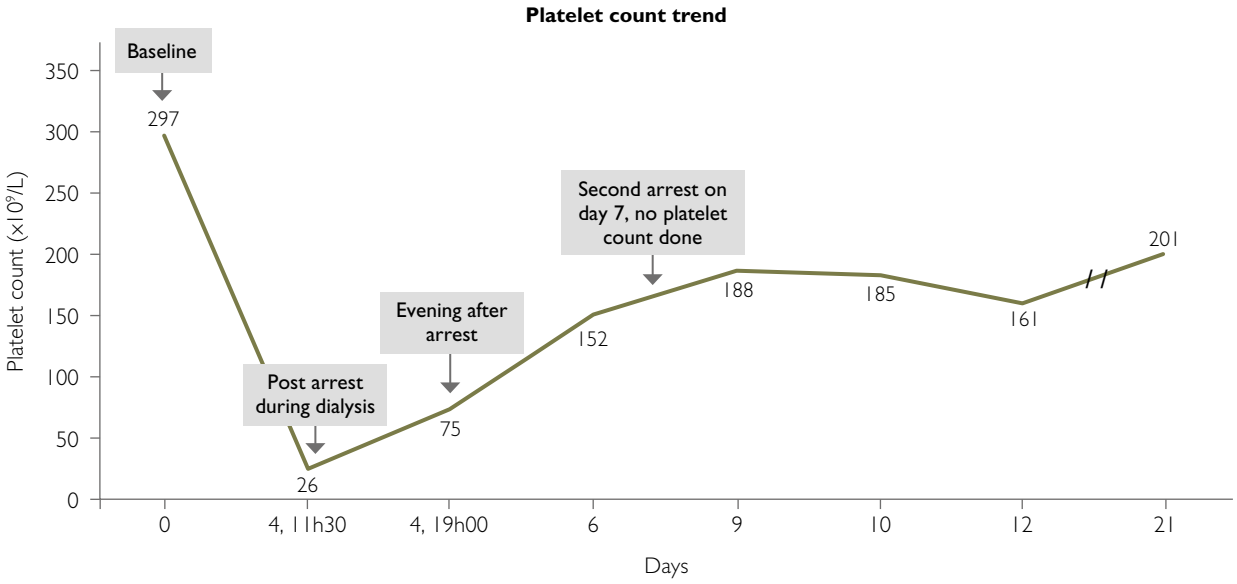

Figure 1. Trend of platelet counts showing abrupt decline in platelet count on day 4, with slow normalisation after stopping heparin therapy. A baseline value was available 4 days prior to the initial arrest. Unfortunately, no platelet count was done at the time of the second cardiac arrest.

afterwards [12,13]. Similar to our case, Throll et al. have reported a case of an anaphylactoid reaction to heparin after 2 years of dialysis, with resolution of thrombocytopenia and thrombotic events after change to danaparoid sodium [14]. Anaphylactoid reactions to heparin usually present with clinical features such as fever, chills, vomiting and hypertension [3]. However, hypotension, including cardiopulmonary arrest, has also been reported [1-4].

Heparin-induced antibodies against PF4–heparin complexes are prevalent in patients on HD. Studies have found a prevalence of these antibodies of up to 47%, with peak prevalence in the first 6 months on HD [15]. Despite this, few seem to develop clinical HIT [12,16]. Because of this, it is important to evaluate the pre-test probability using a clinical scoring system such as the 4T score (scored on thrombocytopenia, timing of platelet count fall, the presence of thrombosis and whether other causes of thrombocytopenia are present – maximum score of 8) to reduce unnecessary and misleading testing [6]. Antibody testing for PF4–heparin complexes thus has good sensitivity but should be followed by a confirmatory functional assay if available [5,13].

The functional testing for HIT includes ^{14}C-serotonin release assays, which is considered the gold standard (no longer available in Africa), and HIPA, a functional assay, which measures the ability of patient plasma to cause platelet activation and aggregation in the presence of heparin as an agonist [17]. In our patient, the initial HIPA was negative. In view of the high 4T score, repeat HIPA testing was conducted at an academic centre with four different platelet donors. However, only one donor's platelets showed reactivity with our patient's serum, with maximum platelet aggregation at therapeutic heparin concentrations, thereby confirming HIT. Sensitivities of HIPA testing have been reported to be 69%, but with high specificity, due to differing reactivity of donor platelets [18]. This highlights the considerable variability in HIPA and ^{14}C-serotonin release assay testing, since not all donor platelets react similarly, limiting negative predictive value [17].

Treatment of HIT includes stopping heparin administration as soon as HIT is suspected, with initiation of non-heparin anticoagulation to prevent HIT-associated thrombosis. Warfarin is best deferred until the platelet count has recovered, and platelet transfusions avoided unless bleeding occurs or the bleeding risk is very high. The duration of anticoagulation remains uncertain. Therapeutic options for anticoagulation are numerous and patient-specific, as reviewed elsewhere [10,12].

In summary, we have presented a rare case of cardiopulmonary arrest attributable to HIT in a chronic dialysis patient. This case and the variable nature of the clinical presentation of HIT serve as a reminder to the medical community to be vigilant as to the possible diagnosis. Furthermore, the lack of laboratory standardisation in HIPA testing and inconsistent donor platelet reactivity highlights the need for a nuanced approach when interpreting testing in such patients.

Acknowledgement

The authors gratefully acknowledge the Kidneys, Infectious Diseases and Critical Care NPC (KICC NPC) for the provision of publication funding.

Conflict of interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. Chest. 2005; 127:1857-1861.
2. Singla A, Amini MR, Alpert MA, Gornik HL. Fatal anaphylactoid reaction associated with heparin-induced thrombocytopenia. Vasc Med. 2013;18:136-138.
3. Warkentin TE, Greinacher A. Heparin-induced anaphylactic and anaphylactoid reactions: two distinct but overlapping syndromes. Expert Opin Drug Saf. 2009; 8(2):129-144.
4. Jayarangaiah A, Epperla N. Early recognition is the key to success: pulseless electrical activity (PEA) as a manifestation of heparin-induced anaphylactoid reaction. BMJ Case Rep. 2015; bcr2015210828. DOI:10.1136/bcr-2015-210828.
5. Dutt T, Schulz M. Heparin-induced thrombocytopaenia (HIT) – an overview: what does the nephrologist need to know and do? Clin Kidney J. 2013; 6:563-567.
6. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost. 2006; 4:759-765.
7. McKenzie SE, Sachais BS. Advances in the pathophysiology and treatment of heparin-induced thrombocytopenia. Curr Opin Hematol. 2014; 21:380-387.
8. Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2017; CD007557. DOI:10.1002/14651858.CD007557.pub3.
9. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005; 106:2710-2715.
10. Hogan M, Berger JS. Heparin-induced thrombocytopenia (HIT): review of incidence, diagnosis, and management. Vasc Med. 2020; 25:160-173.
11. Thompson GR, Lawrence VA, Crawford GE. HIV infection increases the risk of heparin-induced thrombocytopenia. Clin Infect Dis. 2007; 45:1393-1396.
12. Chang JJY, Parikh CR. When heparin causes thrombosis: significance, recognition, and management of heparin-induced thrombocytopenia in dialysis patients. Semin Dial. 2006; 19:297-304.
13. Hamadi R, Sakr F, Aridi H, Alameddine Z, Dimachkie R, Assaad M, et al. Heparin-induced thrombocytopenia in chronic hemodialysis patients. Clin Appl Thromb Hemost. 2023; 29. DOI:10.1177/10760296231177993.
14. Tholl U, Greinacher A, Overdick K, Anlauf M. Life-threatening anaphylactic reaction following parathyroidectomy in a dialysis patient with heparin-induced thrombocytopenia. Nephrol Dial Transplant. 1997; 12:2750-2755.
15. Maharaj S, Chang S, Seegobin K, Morales J, Aysola A, Rana F, et al. Temporality of heparin-induced antibodies: a retrospective study in outpatients undergoing hemodialysis on unfractionated heparin. Exp Hematol Oncol. 2018; 7:23. DOI:10.1186/s40164-018-0115-8.
16. Palomo I, Pereira J, Alarcón M, Díaz G, Hidalgo P, Pizarro I, et al. Prevalence of heparin-induced antibodies in patients with chronic renal failure undergoing hemodialysis. J Clin Lab Anal. 2005; 19:189-195.
17. Eekels JJM, Althaus K, Bakchoul T, Kroll H, Kiefel V, Nazy I, et al. An international external quality assessment for laboratory diagnosis of heparin-induced thrombocytopenia. J Thromb Haemost. 2019; 17:525-531.
18. Brodard J, Alberio L, Angelillo-Scherrer A, Nagler M. Accuracy of heparin-induced platelet aggregation test for the diagnosis of heparin-induced thrombocytopenia. Thromb Res. 2020; 185:27-30.