A rare occurrence of anti-glomerular basement membrane glomerulonephritis complicated by heparin-induced thrombocytopenia

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ABSTRACT

Introduction: Anti-glomerular basement membrane (GBM) disease is a rare condition that often presents as severe glomerulonephritis and pulmonary hemorrhage. Heparin-induced thrombocytopenia (HIT) is a well-known but uncommon complication of heparin exposure that is characterized by autoantibodies against platelet factor 4 (PF4)/heparin complexes. Although these conditions are well described in the literature, the coexistence of HIT and anti-GBM glomerulonephritis is extremely rare. Case Report: We present a case of a 59-year-old gentleman with newly diagnosed anti-GBM glomerulonephritis who was treated with plasmapheresis and subsequently developed HIT with a delayed manifestation. Conclusion: This case demonstrates an interesting example of poly-autoimmunity and highlights the importance of platelet monitoring in patients with heparin exposure undergoing plasmapheresis.

Keywords: Glomerulonephritis, Heparin-induced thrombocytopenia

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INTRODUCTION

Anti-GBM disease is a rare autoimmune disorder where autoantibodies are produced against alpha-3 chains of type IV collagen, which is present in the GBM and alveolar basement membrane [1]. The condition carries a poor prognosis, with up to 90% of patients presenting with rapidly progressive glomerulonephritis (GN) and more than half with concurrent pulmonary hemorrhage [1]. Anti-GBM GN is often treated with high dose immunosuppression accompanied by plasmapheresis. However, plasmapheresis has a high clotting tendency and anticoagulants, such as heparin, are often required to maintain blood circulation.

Heparin-induced thrombocytopenia is an autoimmune condition which is characterized by thrombocytopenia secondary to heparin administration. Plasmapheresis has been suggested as a treatment strategy for HIT to reduce antibody burden, which has been trialed with varying degrees of success. In patients exposed to heparin, plasmapheresis can potentially delay the diagnosis of HIT by removing anti-PF4/heparin immunoglobulin G (IgG) and thereby slowing down the decline in platelet count [2, 3]. We present a case of a 59-year-old man who presented with anti-GBM GN and was treated with plasmapheresis who later developed delayed-onset HIT. We hope to add to the literature a rare example of poly-autoimmunity and highlight the importance of monitoring platelet count in patients treated with plasmapheresis and using heparin as anticoagulant.

CASE REPORT

A 59-year-old man was admitted with a 2-week history of general fatigue, anorexia, and rapid deterioration in
his renal function. There was no history of hematuria, hemoptysis or rash. His past medical history was significant for gout, depression, and gastroesophageal reflux disease. His medications included esomeprazole and mirtazapine. He denied taking nonsteroidal anti-inflammatory drugs and nonprescription medications. He had no history of renal dysfunction and his last renal function 12 months ago was normal. He had no history of heparin exposure previously.

Physical examination at the time of admission showed that his blood pressure was 159/89 mmHg and he was afebrile. His oxygen saturation was 93% on ambient air but there was evidence of fluid overload with an elevated jugular venous pressure, reduced breath sounds at the lung bases and peripheral pitting edema in the lower extremities. His heart sounds were normal. There was no rash or petechiae.

Initial laboratory evaluation showed: hemoglobin 112 (RR 130–180 g/L), platelet count 499 (RR 150–450 × 10^9/L), sodium 132 mmol/L (RR 135–145 mmol/L), potassium 4.9 mmol/L (RR 3.5–5.2 mmol/L), bicarbonate 25 mmol/L (RR 22–32 mmol/L), chloride 90 mmol/L (95–110 mmol/L), urea 21.1 mmol/L, creatinine 563 µmol/L (60–110 µmol/L), corrected calcium 2.30 mmol/L (2.10–2.60 mmol/L), phosphate 1.78 mmol/L (0.75–1.10 mmol/L), albumin 21 mg/L (RR 34–54 mg/L), and C-reactive protein 318 mg/L (RR <5 mg/L). His urine protein-creatinine ratio was 217 mg/mmol (RR 0.75–1.10 mmol/L), and urine microscopy showed more than 1000 erythrocytes × 10^6/mm^3, no casts or crystals. His anti-glomerular basement membrane antibodies were markedly elevated at 6.6 (RR < 1.0). A further screening for other causes of acute renal failure revealed the following: kappa/lambda free light chain ratio 1.95 (RR 0.37–3.10), anti-nuclear antibodies (ANA) negative, extractable nuclear antigens (ENA) negative, anti-neutrophil cytoplasmic antibodies (ANCA) negative, complement C3 1.90 (RR 0.79–1.77), and complement C4 0.41 (RR 0.16–0.38). Hepatitis B surface antigen, hepatitis C antibodies, and HIV serology were negative. He started on trimethoprim-sulfamethoxazole at 800/160 mg three times weekly daily for prophylaxis against pneumocystis jirovecii pneumonia. His platelet count on admission to intensive care was 475 × 10^9/L. He continued to receive alternate-day plasmapheresis with 5000 units of heparin each session for eight sessions in total. During this time, he continued to have intermittent HD three times a week with 500 units of heparin per hour for line patency. His platelet count gradually declined since commencing heparin but this was not evident until day 15 admission when his platelet count was below normal limit at 99 × 10^9/L. Platelet count continued to drop until it reached a nadir of 37 × 10^9/L on day 19 admission (Figure 1). Cyclophosphamide and trimethoprim-sulfamethoxazole were ceased due to potential myelosuppression. Enoxaparin and heparin were suspended. Presence of anti-PF4/heparin antibody complexes were subsequently detected, confirming clinical suspicion of HIT. He was immediately commenced on therapeutic anticoagulation with fondaparinux. Although the diagnosis was made more than two weeks after heparin exposure, the patient did not develop any thrombotic complications. His platelet count gradually improved after cessation of all heparin. Trimethoprim-sulfamethoxazole and cyclophosphamide were subsequently recommenced with no effect on platelet count. Our patient was discharged after a 29-day admission with a platelet count of 226 × 10^9/L and continued to have maintenance hemodialysis with fondaparinux.

**DISCUSSION**

Anti-GBM glomerulonephritis with crescentic formation can rapidly progress and therefore requires timely management. Early diagnosis is essential and long-term prognosis is dependent on renal function at presentation and percentage of crescentic glomeruli on renal biopsy [4, 5]. Plasmapheresis is generally performed as soon as possible following the diagnosis of HIT and is recommended until platelet count increases to at least 100 × 10^9/L. In our case, he was commenced on plasmapheresis the same day and an elevated anti-GBM titer. He was admitted to the intensive care unit on day 2 of admission. He was commenced on plasmapheresis the same day and required systemic heparinization due to recurrent circuit clotting. Despite commencing high dose corticosteroids, cyclophosphamide, and plasmapheresis, he subsequently became anuric with no evidence of renal recovery and required initiation of hemodialysis (HD). He was also started on trimethoprim/sulfamethoxazole at 800/160 mg three times weekly daily for prophylaxis against pneumocystis jirovecii pneumonia. His platelet count on admission to intensive care was 475 × 10^9/L. He continued to receive alternate-day plasmapheresis with 5000 units of heparin each session for eight sessions in total. During this time, he continued to have intermittent HD three times a week with 500 units of heparin per hour for line patency. His platelet count gradually declined since commencing heparin but this was not evident until day 15 admission when his platelet count was below normal limit at 99 × 10^9/L. Platelet count continued to drop until it reached a nadir of 37 × 10^9/L on day 19 admission (Figure 1). Cyclophosphamide and trimethoprim-sulfamethoxazole were ceased due to potential myelosuppression. Enoxaparin and heparin were suspended. Presence of anti-PF4/heparin antibody complexes were subsequently detected, confirming clinical suspicion of HIT. He was immediately commenced on therapeutic anticoagulation with fondaparinux. Although the diagnosis was made more than two weeks after heparin exposure, the patient did not develop any thrombotic complications. His platelet count gradually improved after cessation of all heparin. Trimethoprim-sulfamethoxazole and cyclophosphamide were subsequently recommenced with no effect on platelet count. Our patient was discharged after a 29-day admission with a platelet count of 226 × 10^9/L and continued to have maintenance hemodialysis with fondaparinux.
recommended for treatment of anti-GBM disease, in combination with high dose immunosuppression [1]. Plasmapheresis is an extracorporeal therapy which involves removal, filtration, and return of blood plasma from blood circulation [1]. However, the treatment is prothrombotic due to removal of blood from the body and being exposed to the extracorporeal circuit. This activates the coagulation cascade and also leads to platelet activation. As a result, anticoagulation is often used to maintain blood flow and allow effective treatment [6].

Heparin-induced thrombocytopenia is an autoimmune condition secondary to autoantibodies against PF4/heparin complexes, which occurs in up to 2.6% of patients on unfractionated heparin and 0.2% in patients receiving low molecular weight heparin [7, 8]. PF4 is a protein produced by activated platelets and has a high affinity to heparin. There are two different types of HIT. Type I is associated with a transient platelet drop in the first two days of heparin exposure and is not clinically significant. On the other hand, type II HIT is characterized by thrombocytopenia (platelet count <150 × 10^9/L), presence of thrombosis or skin necrosis in response to intravenous heparin administration, more than 50% fall in platelet count from baseline and nadir usually more than 20 × 10^9. Type II HIT typically begins 5–10 days after heparin exposure [7]. Management of HIT includes immediate cessation of all heparin and aims to minimize thrombotic risk by using alternate anticoagulation agents, such as argatroban, danaparoid, and fondaparinux [7]. In our case, the development of thrombocytopenia was not evident until day 15 after heparin exposure. We hypothesize that this is due to clearance of autoantibodies by ongoing plasma exchange. Although there were no thrombotic complications in our case, a delay in diagnosis can significantly increase risk of complications due to delay in therapeutic anticoagulation. On the other hand, the gradual decline in platelets suggested that plasmapheresis could potentially, at least in part, remove anti-PF4/heparin complexes that are implicated in the pathogenesis of HIT. This is in keeping with some evidence in the literature suggesting plasmapheresis as an alternate treatment in refractory cases [2, 3, 9, 10].

Association of anti-GBM disease and HIT had been described in the literature. However, anti-GBM disease is a rare condition that is estimated to occur in less than one case per million people [1]. As HIT is an uncommon complication of heparin exposure, the combination of anti-GBM and HIT in the same individual is exceptionally rare. This case report presents an unusual and interesting example of poly-autoimmunity.

**CONCLUSION**

This case demonstrates a rare occurrence of anti-GBM disease complicated by HIT. Clinicians need to be aware of this serious complication and potential delay in diagnosis in patients with heparin exposure treated with plasmapheresis, which can lead to life-threatening thrombotic complications.

**REFERENCES**

1. McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease. Clin J Am Soc Nephrol 2017;12(7):1162–72.
2. Welsby LJ, Um J, Milano CA, Ortel TL, Arepally G. Plasmapheresis and heparin reexposure as a management strategy for cardiac surgical patients with heparin-induced thrombocytopenia. Anesth Analg 2010;110(1):30–5.
3. Warkentin TE, Sheppard JA, Chu FV, Kapoor A, Crowther MA, Gangji A. Plasma exchange to remove HIT antibodies: Dissociation between enzyme-immunoassay and platelet activation test reactivities. Blood 2015;125(1):195–8.
4. Levy JB, Turner AN, Rees AJ, Pusey CD. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med 2001;134(11):1033–42.
5. Hirayama K, Yamagata K, Kobayashi M, Koyama A. Anti-glomerular basement membrane antibody disease in Japan: Part of the nationwide rapidly progressive glomerulonephritis survey in Japan. Clin Exp Nephrol 2008;12(5):339–47.
6. Jagdish K, Jacob S, Varughese S, et al. Effect of double filtration plasmapheresis on various plasma components and patient safety: A prospective observational cohort study. Indian J Nephrol 2017;27(5):377–83.
7. Ahmed I, Majeed A, Powell R. Heparin induced thrombocytopenia: Diagnosis and management update. Postgrad Med J 2007;83(983):575–82.
8. 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(8):2710–5.
9. Robinson JA, Lewis BE. Plasmapheresis in the management of heparin-induced thrombocytopenia. Semin Hematol 1999;36(1 Suppl 1):29–32.
10. Voeller RK, Melby SJ, Grizzell BE, Moazzami N. Novel use of plasmapheresis in a patient with heparin-induced thrombocytopenia requiring urgent insertion of a left ventricular assist device under cardiopulmonary bypass. J Thorac Cardiovasc Surg 2010;140(3):e56–8.

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**Author Contributions**

Rebecca Xu – Conception of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published. Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Minh Huan Dang – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Authors declare no conflict of interest.

**Data Availability**
All relevant data are within the paper and its Supporting Information files.

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