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Case Report

Spontaneous Heparin-Induced Thrombocytopenia, Secondary to Dengue Infection

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Abstract: Heparin-induced thrombocytopenia (HIT) is characterized clinically by thrombocytopenia, hypercoagulability, and increased risk of thrombosis, and serologically by the presence of antibodies against platelet factor 4 (PF4). We present a 27-year-old male with persistent holocranial headache and depersonalization, initially attributed to thrombocytopenia following a positive Dengue virus serology. Despite no initial evidence of ischemia on imaging, subsequent findings included extensive venous thrombosis in the right lower limb, contraindicating immediate anticoagulation. The patient later developed a left lacunar ischemic stroke with hemorrhagic transformation and bilateral pulmonary thromboembolism. Examination findings revealed right hemibody weakness and dysplastic megakaryocytes on bone marrow aspirate. This case highlights the diagnostic challenges and clinical complexities in managing thrombotic events associated with thrombocytopenia and viral infections.

Keywords: Thrombocytopenia, dengue, spontaneous.

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is characterized clinically by thrombocytopenia, hypercoagulability, and increased risk of thrombosis, and serologically by the presence of antibodies against platelet-activating factor 4 (PF4) [1]. It is generally associated with the appearance of antibodies due to immune exposure to heparin, hence its name "heparin-induced."[2]. However, it has been observed that other medications that are not heparin can trigger "HIT." In 2008, what we currently know as "spontaneous HIT syndrome" was reported for the first time, which is HIT triggered by mechanisms other than heparin, and two subtypes are recognized: surgical, frequently post-total knee arthroplasty, and medical, usually post-infectious [3]. This is how we understand spontaneous HIT, which presents heparin-independent platelet-activating anti-PF4 antibodies, although the precise relationships between the targets of the PF4 epitope and clinical syndromes have not yet been fully determined. Treatment of spontaneous HIT syndrome includes anticoagulation without heparin, among which direct oral Xa inhibitors are preferred, and high-dose immunoglobulin [4].

CASE PRESENTATION

A 27-year-old male with no significant medical history. His current illness began three weeks prior to admission with a holocranial headache rated 4/10 on the ENA scale. He consulted an external neurologist due to the headache and feelings of depersonalization, leading to the request for imaging studies. A cranial CT scan and MRI were performed, showing no evidence of ischemia. However, due to the persistent headache, additional tests were conducted, revealing thrombocytopenia. Consequently, he was evaluated externally by the hematology service. During a directed interrogation, the patient reported pain in the popliteal region of the right lower limb, leading to a visit with a vascular specialist who performed a Doppler study identifying extensive venous thrombosis. However, due to the thrombocytopenia levels,

immediate anticoagulation was contraindicated. The patient continued to experience headaches, and in the days prior, developed weakness in the right pelvic limb with preserved sensitivity. This prompted another imaging study at the time of his emergency evaluation, revealing a left lacunar ischemic stroke with evidence of bleeding. For this reason, the treating physician referred him to the emergency department. The patient denies precordial pain, dyspnea, or any other symptoms.

Symmetrical, well-nourished limbs with weakness in the right hemibody, Daniels scale 4/5. Neurological Examination: The patient is conscious, alert, and oriented to time, person, place, and situation. Cranial Nerves: I: not assessed, II: visual field without alterations, III, IV, VI: ocular movements preserved in all directions, photomotor reflex decreased and consensual reflex preserved. V: sensation preserved in all three branches, muscle tone, and strength of mastication muscles preserved. VII: static and facial mimicry symmetrical. VIII: hearing preserved, no nystagmus. IX and X: gag reflex present, uvula central. XI: adequate tone and strength of sternocleidomastoids and trapezius muscles. XII: tongue movements preserved in all directions. Muscle strength 5/5 in the left hemibody, 4/5 in the right upper limb, right pelvic limb not assessable due to the current condition. Meningeal signs absent. No dysmetria or dysdiadochokinesia. Gait not assessable.

Laboratory and imaging studies were performed, revealing thrombocytopenia with 54,000 platelets. Venous Doppler ultrasound reported deep vein thrombosis of the right common femoral vein with distal extension. Superficial venous system patent. Chest CT angiography showed bilateral pulmonary thromboembolism; lobar, segmental, and subsegmental arteries of the lower left lobe with filling defects, a posterobasal infarction area, and filling defects in the right lobar and segmental arteries.

The patient had a history of dengue days prior and had a positive serological test, which was repeated with the following result: PCR (quantitative) Dengue Virus 380 copies/ml. Anti-Platelet Factor 4 antibodies were requested and reported positive. A bone marrow aspirate was performed with the following result: Cellular content 70%, normal for age, heterogeneous. Megakaryocytes up to 20 per field, 50% dwarf and dysplastic. Differential count: segmented cells 28%, bands 10%, lymphocytes 8%, monocytes 1%, eosinophils 2%, myeloblasts 1%, metamyelocytes 1%, myelocytes 14%, plasma cells 4%, promyelocytes 3%, normoblasts 28%.

DISCUSSION

Heparin-induced thrombocytopenia (HIT) is a prothrombotic reaction caused by the transient production of platelet-activating IgG antibodies that recognize multimolecular complexes of platelet factor 4 (PF4) (cationic) bound to heparin (polyanionic) [5]. However, these characteristics of "heparin-independent" platelet activation are not exclusive to spontaneous HIT syndrome, but are also found in delayed-onset HIT, persistent HIT, HIT associated with fondaparinux, and HIT induced by exposure to heparin "flushes."[6].

Several systems are activated by negative charges, including the innate immune system, complement system, and the intrinsic coagulation system, among others [7-9]. However, the adaptive immune system recognizes structures rather than charges, requiring "adapter molecules" to translate the charge into structure. The chemokine PF4 (CXCL4) is composed of four monomers that expose a ring of positive charges formed by lysines. Each monomer contains antiparallel β-sheets of three chains folded into an N-terminal aperiodic domain and a C-terminal amphipathic α-helix [10]. A certain energy threshold is required to force PF4 to adopt a conformational change. Short polyanions bind to a single PF4 tetramer, while longer ones bind to two PF4 tetramers [11]. In autoimmune HIT, this phenomenon can be explained by antigens other than heparin, such as hypersulfated chondroitin sulfate, DNA and RNA, and bacterial wall components, which can present the other HIT subtypes (delayed-onset HIT, persistent HIT, and fondaparinux-associated HIT) [12-14].

Patients generally present with thrombocytopenia and thrombosis. However, the onset of thrombosis is often the event that prompts blood tests revealing thrombocytopenia, as thrombocytopenia is usually silent. Frequently, suspicion of thrombosis leads to heparin administration, resulting in an abrupt and unexpected drop in platelet count. Patients with extremely low platelet counts (< 20 × 10^9/L) are at higher risk of bleeding. The most common bleeding sites include intracranial and adrenal, with adrenal bleeding usually associated with primary thrombosis (i.e., hemorrhagic infarction).

Patients with spontaneous HIT syndrome resemble those with classic HIT both clinically (thrombocytopenia and thrombosis) and serologically (positive PF4 results), despite no prior heparin exposure. Most reported patients with spontaneous HIT had undergone prior orthopedic surgery (usually knee replacement surgery), suggesting different possible antigens (e.g., release of glycosaminoglycans or RNA from knee cartilage due to tourniquet-related cell damage) [15]. Previous infections were another associated cause, suggesting that exposure to microorganisms could trigger an immune response similar to HIT. It has also been associated with COVID-19 vaccinations, particularly the AstraZeneca vaccine [16,17].

Although discontinuing heparin is the main treatment principle, in the case of spontaneous HIT syndrome, there is no prior heparin exposure, so it would not be the underlying pathophysiology. Nevertheless, administering heparin could have adverse consequences by recruiting coexisting heparin-dependent HIT antibodies, generating classic HIT. These patients require intensive therapeutic dose anticoagulation with an alternative anticoagulant to heparin until thrombocytopenia resolves and, in some cases, for a longer period if associated thrombosis is present.

The most commonly used alternative anticoagulants are argatroban, bivalirudin, danaparoid, and fondaparinux, as well as direct oral anticoagulants (DOACs) [18]. The use of high-dose intravenous immunoglobulin (IVIG) is another therapeutic alternative, described over 25 years ago. In vitro studies demonstrate that the Fc domain of IgG dose-dependently inhibits platelet activation by HIT antibodies. Recently, abrupt recovery of platelet count after high-dose IVIG treatment has been described. The dose is 1 g/kg administered twice a day for two consecutive days.

CONCLUSION

HIT is a hypercoagulable state that is often devastating and paradoxically produces thrombotic complications even when heparin is no longer administered, or as in the case of this patient, despite never having received heparin previously. It is important to remember that HIT is not solely caused by prior exposure to heparin; it has also been associated with other causes such as vaccines, infections, or orthopedic surgeries, particularly knee surgeries. High diagnostic suspicion is required, and we should always consider it in cases of sudden platelet drop associated with thrombosis, to request the necessary studies for diagnosis and provide appropriate treatment. High therapeutic doses of anticoagulation should always be given, using alternative anticoagulants to heparin, such as fondaparinux or direct oral anticoagulants. IVIG is an interesting tool for managing HIT because it quickly interferes with the pathogenesis of the disease.

Conflict of interest

The authors declare that there are no conflicts of interest at the time of publication of this article.

REFERENCES

1. Warkentin, T. E., & Greinacher, A. (2021). Spontaneous HIT syndrome: knee replacement, infection, and parallels with vaccine-induced immune thrombotic thrombocytopenia. *Thrombosis Research*, *204*, 40-51.
2. Ahmed, I., Majeed, A., & Powell, R. (2007). Heparin induced thrombocytopenia: diagnosis and management update. *Postgraduate medical journal*, *83*(983), 575-582.
3. Warkentin, T. E., Makris, M., Jay, R. M., & Kelton, J. G. (2008). A spontaneous prothrombotic disorder resembling heparin-induced thrombocytopenia. *The American journal of medicine*, *121*(7), 632-636.
4. Gabarin, N., Arnold, D. M., Nazy, I., & Warkentin, T. E. (2022, April). Treatment of vaccine-induced immune thrombotic thrombocytopenia (VITT). In *Seminars in hematology* (Vol. 59, No. 2, pp. 89-96). WB Saunders.
5. Bakchoul, T., & Greinacher, A. (2012). Recent advances in the diagnosis and treatment of heparin-induced thrombocytopenia. *Therapeutic advances in hematology*, *3*(4), 237-251.
6. Warkentin, T. E. (2023). Autoimmune heparin-induced thrombocytopenia. *Journal of Clinical Medicine*, *12*(21), 6921.
7. Oikonomopoulou, K., Ricklin, D., Ward, P. A., & Lambris, J. D. (2012, January). Interactions between coagulation and complement—their role in inflammation. In *Seminars in immunopathology* (Vol. 34, pp. 151-165). Springer-Verlag.
8. Warkentin, T. E., & Greinacher, A. (2009). Heparin-induced anaphylactic and anaphylactoid reactions: two distinct but overlapping syndromes. *Expert opinion on drug safety*, *8*(2), 129-144.
9. Nicodemus, C. F., & Berek, J. S. (2010). TLR3 agonists as immunotherapeutic agents. *Immunotherapy*, *2*(2), 137-140.
10. Zhang, X., Chen, L., Bancroft, D. P., Lai, C. K., & Maione, T. E. (1994). Crystal structure of recombinant human platelet factor 4. *Biochemistry*, *33*(27), 8361-8366.
11. Kreimann, M., Brandt, S., Krauel, K., Block, S., Helm, C. A., Weitschies, W., ... & Delcea, M. (2014). Binding of anti–platelet factor 4/heparin antibodies depends on the thermodynamics of conformational changes in platelet factor 4. *Blood, The Journal of the American Society of Hematology*, *124*(15), 2442-2449.
12. Jaax, M. E., Krauel, K., Marschall, T., Brandt, S., Gansler, J., Fürll, B., ... & Greinacher, A. (2013). Complex formation with nucleic acids and aptamers alters the antigenic properties of platelet factor 4. *Blood, The Journal of the American Society of Hematology*, *122*(2), 272-281.
13. Brandt, S., Krauel, K., Jaax, M., Renné, T., Helm, C. A., Hammerschmidt, S., ... & Greinacher, A. (2015). Polyphosphates form antigenic complexes with platelet factor 4 (PF4) and enhance PF4-binding to bacteria. *Thrombosis and haemostasis*, *114*(12), 1189-1198.
14. Cines, D. B., Yarovoi, S. V., Zaitsev, S. V., Lebedeva, T., Rauova, L., Poncz, M., ... & Conway, E. M. (2016). Polyphosphate/platelet factor 4 complexes can mediate heparin-independent platelet activation in heparin-induced thrombocytopenia. *Blood advances*, *1*(1), 62-74.

15. Poudel, D. R., Ghimire, S., Dhital, R., Forman, D. A., & Warkentin, T. E. (2017). Spontaneous HIT syndrome post-knee replacement surgery with delayed recovery of thrombocytopenia: a case report and literature review. *Platelets*, *28*(6), 614-620.
16. Franchini, M., Liumbruno, G. M., & Pezzo, M. (2021). COVID-19 Vaccine-associated Immune Thrombosis and Thrombocytopenia (VITT): diagnostic and therapeutic recommendations for a new syndrome. *European Journal of Haematology*, *107*(2), 173-180.
17. Favaloro, E. J., & Pasalic, L. (2023). Heparin-induced thrombotic thrombocytopenia (HITT) and vaccine-induced immune thrombotic thrombocytopenia (VITT): similar but different. In *Hemostasis and Thrombosis: Methods and Protocols* (pp. 405-415). New York, NY: Springer US.
18. Kelton, J. G., Arnold, D. M., & Bates, S. M. (2013). Nonheparin anticoagulants for heparin-induced thrombocytopenia. *New England Journal of Medicine*, *368*(8), 737-744.