Case Report

Indian Journal of Emergency Medicine
Volume 7 Number 1, January – March 2021
DOI: http://dx.doi.org/10.21088/ijem.2395.311X.7121.8

Decreased Platelet Count Due to Heparin in Covid-19

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Received on 29.01.2021, **Accepted on** 31.03.2021.

How to cite this article:

Ashar Khan, Kishalay Datta, Siddharth Verma, et al / Decreased Platelet Count Due to Heparin in Covid-19. Indian J Emerg Med. 2021;7(1):43–45.

Abstract

COVID-19 (coronavirus disease-2019) infection may be a extremely prothrombotic state, ensuing from a dysregulation of the coagulation cascade. Therefore, thromboprophylaxis is powerfully suggested in these patients, with some consultants even advocating for therapeutic dosing to forestall thromboembolic events. Heparin-induced blood disorder (HIT) may be a well-known complication of heparin therapy. during this article, we tend to report a case of HIT in a patient with COVID-19. A 52-year-old male with history of one week of dry cough and loose stools. He had a positive COVID-19 reverse-transcriptase–polymerase chain reaction. On admission, the platelet count and liver function test were within normal limits. Throughout his hospitalization, he developed a right femoral deep venous thrombosis and was started on therapeutic anticoagulations. Due to worsening respiratory failure, he was intubated and mechanically ventilated. Between days eight and nine of hospitalization, platelet count decreased from 294000 to 89000 cells/μL. He had a high pretest likelihood for HIT with a 4T score of 6 and a positive anti-PF4/heparin antibody. Heparin drip was interrupted and was switched to Argatroban. The serotinin assay eventually came back positive, that confirmed the diagnosis of HIT.

Keywords: Covid-19; Heparin; Thrombocytopenia.

Introduction

An outbreak of novel coronavirus (2019-nCoV) that began in Wuhan, China, is now a serious public health concern worldwide. After the primary reported case within the state of Washington, the amount of cases within the United States has rapidly increased to over 2,000,000 with more than 100,000 deaths.[1] In addition to the typical presentation of respiratory symptoms, hematologic complications have been a significant concern in these patients. Thrombocytopenia has been reported in up to 55% of patients with COVID-19.[2] A meta-analysis of 9 studies has shown that platelet counts were significantly lower in those with more severe COVID-19 infection, and thrombocytopenia predicts mortality.[2] Heparin-induced thrombocytopenia (HIT) is a differential for thrombocytopenia, especially within the intensive care setting. In one review, the authors suggested that clinicians routinely evaluate all COVID-19 patients on heparin for indices of HIT by per-forming the 4T score.[3] We report a case of HIT in a patient with critical COVID-19 infection.

Case Presentation

A 52-year-old male without comorbidities presented with 1 week of dry cough, myalgias, and loose stools. On examination, he was afebrile but appeared to be in distress, saturating at 87% on room air. Chest X-ray showed bilateral interstitial opacities. Initial laboratory tests revealed an elevated C-reactive protein of 25.13 mg/dL and a high interleukin-6 level of 63 pg/mL. Fibrinogen and D-dimer were also elevated to 698 mg/dL and 1.53 fibrinogen equivalent units, respectively. The platelet count and liver function test were normal. His COVID-19 by nasopharyngeal RTPCR was positive. Low-molecular-weight heparin was started for thromboprophylaxis. On day 2 of admission, he developed progressive worsening of dyspnea and was transferred to the intensive care unit (ICU).On day 6, his right lower extremity was noted to be swollen. Ultrasound duplex revealed a non-occlusive thrombus within the right common femoral vein. He was started on therapeutic anticoagulation for deep vein thrombosis (DVT) with enoxaparin, which was switched to unfractionated heparin later, due to worsening renal function. On day 7 of hospitalization, due to worsening respiratory failure, he was intubated and mechanically ventilated. Between days 8 and 9 of hospitalization, platelet count dropped from 294 000 to 89 000 cells/μL. He had a high pre-test probability for HIT with a 4T score of 6. HIT antibody testing (anti-PF4/heparin antibody, by enzyme-linked immunosorbent assay) was sent, which returned positive with an optical density (OD) of 1.321 units. Heparin drip was stopped and was changed to Argatroban. Unfortunately, he died a 2 days later, following a cardiac arrest. Serotonin release assay (SRA) eventually returned positive, with 48% serotonin release at low UFH dose (0.1 IU/mL) with a reduction to 0% release at high UFH dose (100 IU/mL). This confirmed the diagnosis of HIT.

Discussion

HIT is an immune-mediated condition, characterized by decreased platelet count, typically within 5 to 10 days of exposure to heparin, resulting in hypercoagulability and presence of platelet-activating IgG antibodies.[4-6] These antibodies target complexes of PF4 and heparin.[6] The IgG-PF4-heparin immune complexes cross-link Fcy (γ) receptors on platelets and monocytes and activate them. Activation of monocytes and platelets increases thrombin generation, resulting in thromboembolic complications.[4] HIT affects 1 in 5000 hospitalized patients and paradoxically leads to a prothrombotic state and typically doesn't induce bleeding.[4] Thromboembolic phenomena are seen in half the patients with confirmed HIT.[4] The deathrate is around 5% and 10%.[6] In our patient with HIT, the diagnosis of venous thromboembolism preceded thrombocytopenia, which isn't uncommon.[7] American Society of Hematology guidelines recommends the utilization of 4T score to estimate the pretest probability of HIT.[6] In those with intermediate or high pretest probability, testing for the presence of HIT antibodies should be done, by using immunoassays or platelet activation assays.[4,5] The initiative within the management of highly suspected or confirmed HIT is to stop heparin (including heparin flushes), and to initiate a non-heparin anticoagulant, to prevent thrombotic events, in the setting of ongoing massive thrombin generation.[4]Available options for anticoagulation include argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant.[6] Argatroban is a reversible inhibitor of thrombin[5] with a short half-life and is not renally cleared. It is commonly utilized in for HIT.[4] In 2 multicenter trials of patients with HIT, argatroban resulted in reduced composite endpoint of death, amputation, and thrombosis, in comparison with historic controls.[5] a serious concern with argatroban is potential under-anticoagulation in patients with elevated partial thromboplastin time, secondary to additional coagulopathies (hepatic dysfunction, prior anticoagulation with warfarin, consumptive coagulopathy, and more recently, COVID-19). [4] Partial thromboplastin time confounding can also occur within the presence of a nonspecific inhibitor (such as lupus anticoagulant).[8] this is able to increase the danger of thrombosis and limb loss. Data supporting the efficacy of argatroban is restricted to patients with suspected or confirmed HIT.[8,9] A major problem of HIT is its overdiagnosis. Only approx. 50% of EIA+ sera have platelet-activating properties and, therefore, do not have true HIT.[10] Antiphospholipid syndrome has been reported in COVID-19 patients,[11] and these patients often test false positive with HIT serology.[9] within the ICU setting, HIT explains about 1 out of 100 cases of thrombocytopenia.[8] Critically ill patients produce other plausible non-HIT mechanisms to elucidate their thrombocytopenia, including septicemia, consumptive coagulopathy in non-HIT-related pulmonary embolism, or catastrophic antiphos-pholipid syndrome.[8] Many laboratories report EIA results qualitatively as positive or

negative.[10] Interpretation of this immunoassay is improved with quantitative reporting in the sort of OD levels.[1,10,12] Higher OD levels correspond to a better likelihood of true HIT.[10] Weak-positive EIA (OD 0.4 to 1 unit) points strongly against the diagnosis of HIT (≤5% have a strong-positive SRA). Patients with EIA OD ≥2 have a ~90% chance of strong-positive SRA.[10,12] Accuracy of diagnosing HIT is significantly improved by combining an immunoassay with functional tests, such as platelet activation assays (eg, SRA).[4] A negative functional assay essentially rules out HIT.[4] Often, SRA may be a "send-out test" and results are unavailable to help with initial deciding.[13] Liu et al.[14] suggested that anti-heparin-PF4 antibodies are induced in critical COVID-19 patients, leading to HIT. However, OD analysis and SRA weren't performed in these patients thanks to limited resources. A misdiagnosis of HIT could potentially lead to exposure to alternate anticoagulants with risks of major haemorrhage, non-availability of reversal agents, a potential increase in thrombosis from discontinuation of heparin, and increased medical expenditure in comparison with heparin.[13]

Conclusion

COVID-19 infection is a highly prothrombotic state, resulting from the coagulation cascade dysregulation. COVID-19 and HIT are both prothrombotic which can lead to thrombocytopenia. Both entities may be complicated by DIC. Given a considerable overlap, there is potential for devastating consequences, if a diagnosis of HIT is missed. As most patients with COVID-19 receive prophylactic heparin, and those with severe disease are likely to develop venous thromboembolism and thrombocytopenia, unrelated to HIT, there could be an even greater potential for overdiagnosis of HIT.

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