Cardiovascular Innovations and Applications

Vol. 7 (2023) 19
ISSN 2009-8618
DOI 10.15212/CVIA.2023.0007

CASE STUDY/REPORT

Spontaneous Heparin-Induced Thrombocytopenia Presenting as Concomitant Bilateral Cerebrovascular Infarction and Acute Coronary Syndrome

Jong Kun Park, MD[1], Ilan Vavilin, MD[2], Jacob Zaemes, MD[2], Araba Ofosu-Somuah, MD[3], Raghav Gattani, MD[3], Camila Sahebi, MD[4] and Alexander G. Truesdell, MD[3]

[1]*The University of Texas Health Science Center at Houston, Houston, TX, USA*
[2]*MedStar Georgetown University Hospital, Washington D.C., USA*
[3]*Inova Heart and Vascular Institute, Falls Church, VA, USA*
[4]*Inova Fairfax Hospital Department of Hematology and Oncology, Falls Church, VA, USA*

Received: 19 November 2022; Revised: 19 December 2022; Accepted: 17 January 2023

Abstract

Background: Spontaneous heparin-induced thrombocytopenia is a pro-thrombotic syndrome in which anti-heparin antibodies develop without heparin exposure.
Case presentation: A 78-year-old man who underwent a successful lumbar laminectomy presented to the hospital 5 days after discharge for stroke-like symptoms and was found to have acute infarcts of the bilateral frontal lobes. The patient was found to be severely thrombocytopenic and was incidentally found to have an inferior wall myocardial infarction. Further investigation led to the diagnosis of bilateral lower extremity deep vein thromboses. His overall clinical presentation prompted a detailed hematologic workup that indicated positivity for heparin-induced thrombocytopenia despite no previous exposure to heparin products.
Conclusions: This case illustrates a patient with no prior lifetime heparin exposure who underwent laminectomy with subsequent development of acute infarcts of the bilateral frontal lobes, an inferior wall myocardial infarction, and bilateral lower extremity deep vein thromboses, with concern for sequelae of spontaneous heparin-induced thrombocytopenia.

Keywords: Acute coronary syndrome; deep vein thrombosis; myocardial infarction; cerebrovascular infarction; spontaneous heparin-induced thrombocytopenia

Correspondence: **Jong Kun Park, MD**, Department of Internal Medicine, The University of Texas Health Science Center at Houston, 6431 Fannin MSB 1.134, Houston, TX, 77030, USA, Phone: 352-222-7891,
E-mail: jongkun.park@uth.tmc.edu

Introduction

Heparin-induced thrombocytopenia (HIT) is a prothrombotic disorder in which IgG-mediated platelet activation leads to thrombosis and thrombocytopenia, whose presentation may include arterial

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or venous thrombosis [1, 2]. Evaluation of HIT requires a quantitative enzyme immunoassay measuring the antibodies that bind PF4-heparin complexes [3], but confirmatory testing with functional assays, such as serotonin release assays, is typically recommended. Recently, patients have been found to develop HIT, including the formation of HIT antibodies, without any known exposure to heparin products [4]. Spontaneous HIT syndrome has been identified predominantly in post-orthopedic procedures [5, 6] but has also been described in post-infectious scenarios [4].

Case Report

A 78-year-old man who initially presented for laminectomy with posterior lumbar decompression of L2-S1 was readmitted to the hospital 5 days after discharge with worse right than left lower extremity weakness, vertigo, and slurred speech, thus prompting concern for a cerebrovascular accident (CVA). The patient had a history of essential hypertension, insulin-dependent diabetes mellitus, and mild aortic stenosis. Head computed tomography (CT) without contrast showed no visible acute intracranial abnormality, and spinal CT without contrast showed soft tissue and possible fluid density within the previous surgical bed dorsal to the spinal canal. Follow-up brain magnetic resonance imaging (MRI) without contrast was performed to further evaluate neurologic deficits and showed remarkable findings of three small acute infarcts involving the left frontal lobe, and a single punctate acute infarct involving the right frontal lobe with underlying atrophy and chronic ischemic disease. The infarcts were deemed to be small and not to require acute stroke intervention at the initial time of presentation. Although the patient was not experiencing chest pain or shortness of breath at admission, he was incidentally noted to have ST elevations in the inferior leads suggestive of inferior ST-elevation myocardial infarction (MI) on his initial admission electrocardiogram (ECG). The initial differential diagnoses for the ECG included spontaneous MI secondary to coronary embolism, spontaneous MI secondary to direct thrombus formation from plaque rupture, and spontaneous MI secondary to vasospasm. A 12-lead ECG indicated sinus bradycardia with heart rate of 56 beats per minute with atrioventricular dissociation, thus prompting concern for third degree heart block and ST-elevations in leads II, III, and aVF with reciprocal ST-depressions in leads V2 and V3 (Figure 1). Troponin I peaked at 34 ng/mL. A transthoracic echocardiogram demonstrated a left ventricular ejection fraction of 55–60%, and mild basal and sigmoid septal hypertrophy with no wall motion abnormalities. His platelet count had decreased from 343,000/μL to 12,000/μL five days after laminectomy and surgical lumbar decompression. Upon evaluation of the ECG suggesting ST-elevation MI, the interventional cardiology department was consulted for left heart catheterization. However, in the setting of severe thrombocytopenia, likely acute CVA, recent spinal surgery, and the absence of hemodynamic instability, intervention was deferred, because the risk of bleeding was deemed too high. He was empirically initiated on high-dose statin therapy and medically managed in the cardiac step-down unit.

In the setting of lower extremity edema on admission physical examination, the patient also underwent bilateral lower extremity venous doppler imaging, which revealed bilateral lower extremity deep vein thrombosis (DVT). Owing to the patient's thrombocytopenia with evidence of DVT, stroke, and MI, we requested a heparin induced platelet antibody and serotonin release assay for low molecular weight heparin and unfractionated heparin (UFH), which yielded positive results for heparin induced platelet antibody, and a UFH serotonin release assay with indeterminate low molecular weight heparin serotonin release assay. The differential diagnosis before the HIT workup included immune-thrombocytopenic purpura, for which the patient was initiated on 1 mg/kg of prednisone. Because the patient was not anticoagulated, owing to recent spinal surgery with neurosurgical concerns regarding spinal bleeding, an IVC filter was inserted to decrease the risk of pulmonary embolism from his bilateral DVTs. Heparin products were avoided during his hospitalization, and the patient was initiated on bivalirudin for therapeutic anticoagulation after his platelet count exceeded 50,000/μL. At the time of discharge, he was switched to apixaban and continued prednisone for empiric therapy.

Thorough chart review indicated no exposure to heparin during the intraoperative and post-operative periods. Further evaluation with abdominal/pelvic

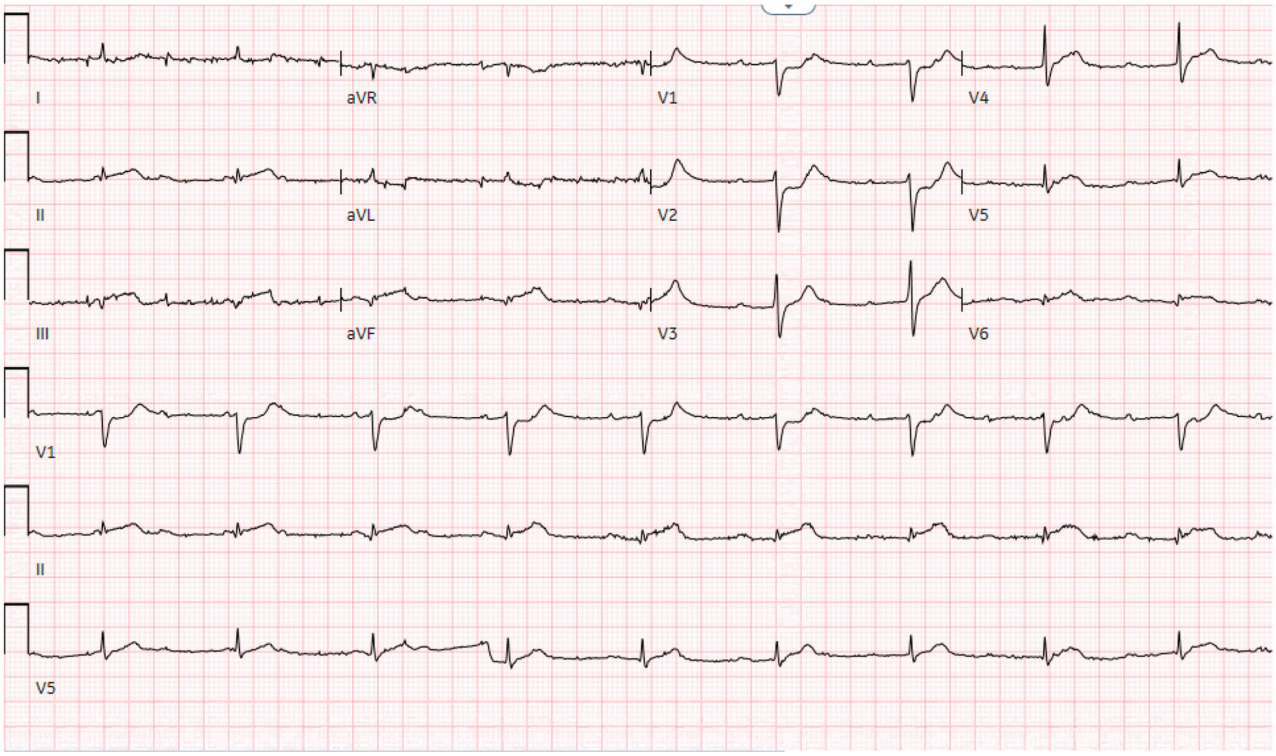

Figure 1 Admission Electrocardiogram.
Sinus bradycardia with atrioventricular dissociation and ST elevations in leads II, III, and aVF with reciprocal ST-depressions in leads V2 and V3.

CT was performed to rule out occult malignant etiologies of hypercoagulability, and none were detected. Bone marrow aspirate indicated hypercellular trilineage hematopoietic bone marrow with progressive maturation and increased megakaryocytes favoring a reactive process indicative of increased cellular production (Figure 2).

After the platelet count reached 50,000/μL, and the risk of hemorrhagic conversion of CVA was determined to be small, a left heart catheterization was performed, which showed mild non-obstructive coronary artery disease (Video 1). Follow-up cardiac MRI demonstrated sequelae of transmural, nonviable myocardium involving the inferior wall extending from the apex to the base, with involvement of the inferolateral and inferoseptal walls at the level of the left ventricular base, and a calculated left ventricular ejection fraction of 49% (Video 2). The territory of nonviable myocardium found on the cardiac MRI was consistent with the patient's initial clinical presentation of inferior STEMI, which was thought to be in the setting of a thrombus in the right coronary artery that had probably resolved by the time of the left heart catheterization.

On day nine of hospitalization, he had an episode of ventricular tachycardia, which was unresponsive to amiodarone. He subsequently required defibrillation with transient pulseless electrical activity arrest and achieved return of spontaneous circulation after 2 minutes of cardiopulmonary resuscitation. He was initiated on a lidocaine drip and had no further episodes of ventricular tachycardia. Before discharge, he underwent successful implantation of a dual-chamber implantable cardioverter defibrillator and was continued on amiodarone.

Discussion

Heparin-induced thrombocytopenia is clinically characterized by thrombocytopenia and hypercoagulability due to platelet-activating anti-platelet 4 heparin antibodies. Although the pattern of thrombosis in HIT typically occurs on the venous side, arterial thromboembolic complications have been documented [2], and cases of coronary thrombosis have been reported in association with HIT. These instances have presented as acute coronary syndrome and at times have led to life-threatening

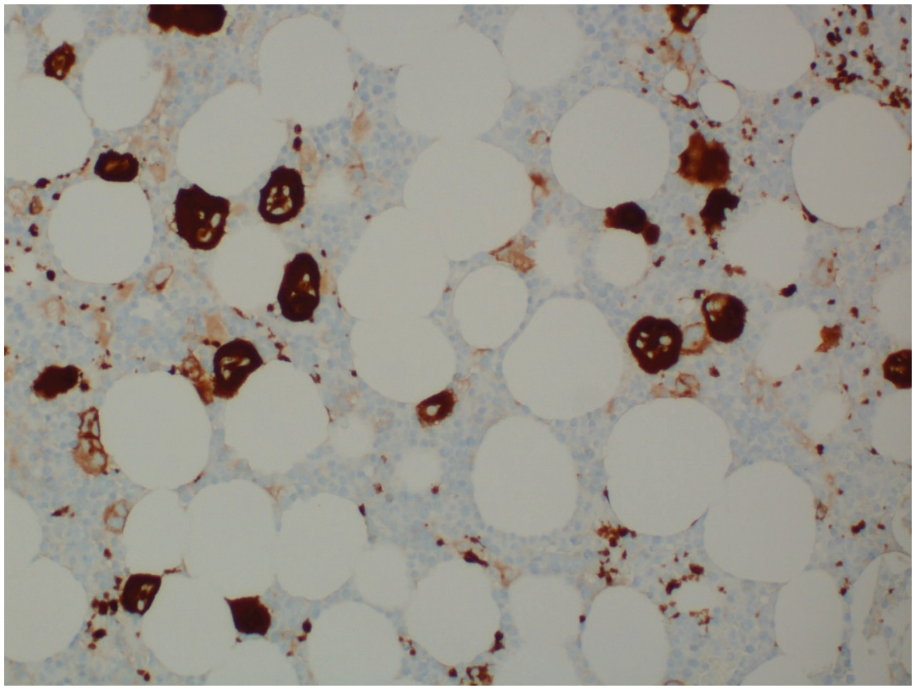

Figure 2 Pathology Slide from Bone Marrow Aspirate: Immunohistochemical Stain at 20x Magnification. Hypercellular trilineage hematopoietic bone marrow with progressive maturation and increased megakaryocytes.

emergencies. In addition, growing evidence of a heparin-induced thrombocytopenia mimicking disorder is being reported. This disorder has a clinically similar presentation to that of heparin-induced thrombocytopenia, despite a lack of any preceding exposure to heparin; therefore, it has been termed spontaneous heparin-induced thrombocytopenia syndrome. Two primary subtypes of spontaneous HIT syndrome have been described: (a) post-surgical (primarily orthopedic interventions) and (b) medical (typically post-infectious). Although our case is in the former category of post-orthopedic surgical intervention with no likely infectious etiology, the SARS-CoV-2 pandemic might result in an increase in unexplained cases of pro-thrombotic states in the future, which may require additional evaluation to rule out etiologies such as spontaneous HIT syndrome (our patient tested negative for COVID-19 on initial presentation).

Why spontaneous HIT syndrome is associated with orthopedic surgeries remains unclear, but in orthopedic knee replacements, polyanionic glycosaminoglycans from the joint have been hypothesized to be released into the systemic circulation, and a tourniquet release might even deliver a bolus to the body [7]. Polyanionic glycosaminoglycans may mimic UFH in molecular structure, bind platelet factor 4, and stimulate the antibody response, thus leading to the cascade of intravascular platelet activation, aggregation, and thrombosis seen in heparin-induced thrombocytopenia.

Although a case of spontaneous thrombosis in a previously untreated native coronary artery in the setting of HIT has been reported [8], this thrombosis has been documented primarily in the settings of previous coronary intervention, stenting, or coronary bypass graft [9, 10]. These reports suggest that early recognition and treatment of coronary thrombosis in patients with suspicion for HIT should be considered in both untreated and treated coronary vasculature.

We hypothesize that spontaneous HIT triggered the formation of microthrombi in both the arterial and venous circulations, and caused the manifestations of the CVA, DVT, and MI. Another possibility might have been thrombotic events from a patent foramen ovale; however, negative agitated saline contrast echocardiography did not suggest this mechanism of action.

Three months after discharge, the patient remained asymptomatic from a cardiovascular standpoint, and his platelet count ranged from 208,000 to 269,000/μL, with no further hypercoagulable sequelae.

Conclusion

In summary, we report a case of acute coronary syndrome in a patient with presumed spontaneous HIT syndrome post-laminectomy. The onset of hypercoagulable clinical findings shortly after this patient's spinal surgical intervention indicated that clinical vigilance is needed in the evaluation of post-thrombotic processes. A patient presenting with a hypercoagulable state in the postoperative setting without heparin exposure may have spontaneous HIT syndrome, manifested through various clinical mechanisms including acute coronary syndrome by means of microvascular obstruction. To date, only a few cases of spontaneous HIT syndrome have been reported, and the recommended treatments are mainly direct oral anticoagulants, direct thrombin inhibitors, or warfarin.

Abbreviations

CT computed tomography
DVT deep vein thrombosis
ECG electrocardiogram
HIT heparin-induced thrombocytopenia
MI myocardial infarction
UFH unfractionated heparin

Statement of Authorship

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Jong Kun Park collected the data, reviewed the literature, and drafted the manuscript. Araba Ofosu-Somuah contributed to data interpretation and organization. Ilan Vavilin, Jacob Zaemes, Raghav Gattani, Camila Sahebi, and Alexander Truesdell revised the manuscript.

Conflicts of Interests

The authors have no financial or personal conflicts of interests to declare.

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Supplementary Material: Supplementary videos for this paper are available at the following link. https://cvia-journal.org/supplementary-figures-2/.