CLINICAL VIGNETTE

Heparin-Induced Thrombocytopenia and the New Oral Anticoagulants

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Introduction

Heparin-induced thrombocytopenia (HIT) is a common cause of thrombocytopenia and thrombosis encountered in both surgical and medical services. In this clinical vignette, we describe a common presentation of this clinical entity as well as alternative methods of anticoagulation.

Clinical Case

An 83-year-old female was admitted with chest pain and shortness of breath. She had a medical history significant for diabetes mellitus, hypertension, and hyperlipidemia. On initial evaluation by the cardiologist, she was noted to have elevated troponin I levels, and given her presenting symptoms, this was concerning for a non-ST elevation myocardial infarction. Further laboratory evaluation revealed a platelet level of 92,000 per µL with normal white blood cell count and hemoglobin levels. A comprehensive metabolic panel showed normal kidney and liver function with normal prothrombin and activated partial thromboplastin times. Patient was initiated on medical treatment for acute coronary syndrome including enoxaparin.

A hematology consultation was requested given patient's isolated thrombocytopenia. Review of her medical records revealed that patient had had a previous admission with similar presenting symptoms a year prior. At that time, she had also received medical treatment including enoxaparin. Further diagnostic tests revealed normal viral hepatitis and HIV serologies. An abdominal ultrasound showed no abnormalities of liver and spleen. Subsequent diagnostic testing for her thrombocytopenia was consistent with a positive HIT antibody with an absorbance of 1.804 OD. At this time, therapy was initiated with argatroban drip and patient proceeded to have a diagnostic left heart catheterization. This showed evidence of apical hypertrophic cardiomyopathy and a coronary-cameral fistula to left ventricle with non-obstructive coronary artery disease. Patient was discharged home to complete a three-month course of anticoagulation with dabigatran at a reduced dose of 110 mg twice daily. At her outpatient Hematology follow up, platelet level had increased to 144,000 per µL without any thrombotic or bleeding complications.

Discussion

Immune-mediated heparin-induced thrombocytopenia is commonly encountered in routine clinical practice. Despite associated low platelet counts, it is not associated with bleeding but rather represents a prothrombotic state. It occurs in about 1 in 5000 hospitalized patients, depending on patient populations.[1] Early recognition is vital given that patients are susceptible to development of both arterial and venous thrombotic events with significant clinical complications. Scoring systems have been developed that are useful in estimating the probability of HIT, although the diagnosis remains a clinical one supported by confirmatory laboratory testing. The therapeutic management of HIT involves the cessation of all heparin products, and the immediate institution of non-heparin based anticoagulant therapy to prevent or treat thrombotic events.

The only approved drug for the treatment of HIT in the United States is the direct thrombin inhibitor argatroban. This agent is commonly used in the inpatient setting, and it is efficacious in the treatment of HIT. In this setting, argatroban has been shown to reduce incidence of thrombosis and death due to thrombosis.[1] An alternative anticoagulant used off label in the treatment of HIT is fondaparinux.[2] After this initial period of parenteral anticoagulation and once platelet levels have improved, patients are transitioned to an oral anticoagulant.[3] Traditionally the agent of choice has been the vitamin K antagonist warfarin. Anticoagulation is continued for a predefined period of time based on presence or absence of associated thrombotic events.

New oral anticoagulants (NOACs) are now well-established in routine clinical practice. Clinical studies have demonstrated similar efficacy and safety to warfarin in the treatment of venous thromboembolism. The two types of NOACs currently available have a different mechanism of action, which becomes clinically relevant in the treatment of HIT. Oral factor Xa active site inhibitors include rivaroxaban and apixaban. Dabigatran etexilate on the other hand is an oral prodrug that is converted to dabigatran, which functions as a direct thrombin inhibitor.[4,5] There are limited data on the off label use of NOACs in the management of HIT, although case

reports are available suggesting the feasibility of this treatment strategy.

The pathogenesis of HIT involves the formation of IgG antibodies that recognize the positively charged Platelet factor 4 (PF4) chemokine within the PF4-heparin complex. This immune complex cross-links with receptors on the surface of platelets and monocytes, leading to their respective activation. This, in turn, results in increased generation of thrombin and clinical sequelae associated with HIT.[1] In vitro studies based on the understanding of HIT pathogenesis are supporting of NOACs as a viable option for the treatment of HIT. One particular study showed that rivaroxaban did not cross-react with HIT antibodies in a series of platelet function assays.[6] Other studies have also confirmed the non-cross-reactivity of oral factor Xa inhibitors as they are in essence structurally unrelated to heparin. On review of the pertinent medical literature, multiple case reports describe the successful and safe use of either rivaroxaban or dabigatran for patients with HIT and associated thrombosis.[7,8] Further support comes from the Canadian Rivaroxaban for HIT study presented in abstract format at the American Society of Hematology meeting December 2015.[9] In this multicenter, single-arm, prospective study, HIT positivity was defined as a 4Ts score of ≥ 4 plus serotonin release assay $\geq 50\%$. Out of a total of 12 HIT positive patients, only one had a possible symptomatic recurrent venous thromboembolism and 11 patients achieved platelet recovery with mean time to recovery of 9 days.

Conclusion

Heparin-induced thrombocytopenia is a serious prothrombotic hematologic condition that warrants early recognition in order to prevent potential life-threatening complications. Empiric treatment with a non-heparin anticoagulant should be initiated based on a clinical diagnosis that can be confirmed with laboratory testing. Simultaneously, cessation of all heparin and heparin-like products should be instituted. Traditional treatment has been with parenteral agents with transition to warfarin. The approval of the new oral anticoagulants represents a milestone in the prevention and treatment of arterial and venous thrombosis in medical and surgical patients. It remains to be determined whether their efficacy and safety can be extrapolated to this subset population of patients. Available data from in vitro studies and case reports appear to provide proof-of-principle support for the use of NOACs in patients with HIT. In carefully selected patients, NOACs can be a viable option since is it unlikely that large randomized controlled trials will be performed in this patient population.

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