Case Report

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Refractory Heparin-Induced Thrombocytopenia in a Liver Transplant Recipient: Intravenous Immunoglobulin Use and Perioperative Plasma Exchange

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ABSTRACT

Background : An extremely dangerous side effect of heparin that might result in a prothrombotic state is heparin-induced thrombocytopenia (HIT). In the case of HIT, prompt heparin withdrawal and non-heparin anticoagulant initiation are the recommended courses of action. Still, there may be difficulties with the treatment, especially in patients who are resistive to HIT, have contraindications to anticoagulation, or need immediate surgery. Furthermore, there are rare instances in which standard anticoagulation medication fails to provide the desired results, requiring the use of alternative therapies including intravenous immunoglobulin (IVIG) and plasma exchange (PLEX).

Case Report : Following liver transplant surgery, a 57-year-old male patient experienced mild acute cellular rejection, refractory HIT, and disseminated intravascular coagulation. Heparin was discontinued, and argatroban was started as a thromboembolism treatment; nonetheless, transplant failure resulted from hepatic artery thrombosis that happened in the context of refractory HIT. One month following the initial procedure, the patient had a second liver transplant. He had one IVIG dose prior to the operation and one during it, along with two PLEX sessions. The refractory HIT continued even after receiving extensive therapy with PLEX and IVIG. Even with catheter-directed intra-arterial thrombolysis and argatroban treatment, hepatic artery thrombosis returned in two weeks, and the transplant failed once more.

Conclusions : Refractory HIT has recently been treated with perioperative PLEX and IVIG on a few occasions. This therapy strategy was used on the first known case of a liver transplant patient with resistant HIT. Particularly in liver transplant recipients with HIT, more research is necessary to ascertain the effectiveness and safety of PLEX and IVIG therapy both before and after surgery.

KeyWords : Liver Transplantation • Plasma Exchange • Thrombocytopenia • Immunoglobulins, Intravenous • Heparin

INTRODUCTION

Background

A potentially fatal side effect of heparin medication is heparin-induced thrombocytopenia (HIT), which can result in a potentially fatal prothrombotic condition [1]. It has two categories. Within the first four days of heparin treatment, HIT type 1 is characterized by a slight and temporary decrease in platelet count that resolves on its own without medical assistance. Four to fifteen days following the first heparin exposure, HIT type 2 is typified by immune-mediated thrombocytopenia, which is brought on by antibodies against platelet factor 4 (PF4) bound to heparin. A prothrombotic condition is the paradoxical result of this [1-3]. In certain circumstances, the diagnosis can be difficult to make.Confirmatory laboratory tests including heparin-PF4 anti-bodies and serotonin release assays (SRAs) are used in conjunction with the clinical scoring system known as the 4T score to help diagnose hypothyroidism (HIT). SRA, which recognizes platelet activity as opposed to heparin-PF4 antibodies, is regarded as the functional criterion standard test for HIT diagnosis [3-5]. In order to prevent thromboembolic events, treatment for HIT necessitates the quick discontinuation of all heparin products and the use of non-heparin anticoagulants and/or strong antiplatelet medications (such cangrelor) [3]. Since they have an instantaneous start of action and a brief half-life of elimination (25 and 60 minutes, respectively), bivalirudin and argatroban are two direct thrombin inhibitors that are frequently utilized in HIT [6]. Ninety percent of patients can recover their platelets after seven days of non-heparin anticoagulation [6, 7]. Rarely, though, platelet-activating antibodies can result in “persisting/

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refractory HIT" when they last longer than seven days after heparin is stopped, even with proper HIT treatment [4]. These individuals are at a higher risk of having disseminated intravascular coagulation (DIC) due to their more severe and protracted thrombocytopenia [4,8]. Refractory heparin-induced bleeding (HIT) requires more sophisticated treatments such intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) since it is resistant to traditional anticoagulation therapy [8,9]. Anti-PF4 antibodies are moved by PLEX, whereas IVIG inhibits platelet Fcg receptors, which lowers platelet activation (decreases SRA), stabilizes platelet count, and lowers the risk of thromboembolic events [10–12].

Following significant surgeries, especially orthopedic, vascular, and cardiac procedures, HIT is more likely. The release of PF4 from intraoperatively stimulated platelets, the stimulation of endothelial cells, and the perioperative administration of heparin are probably the causes of this [8,11]. Because of this, non-urgent or elective procedures ought to wait until the platelet count has returned to normal and antibodies are no longer detectable. HIT management becomes much more difficult in patients with ongoing positive antibody assays and in situations when severe bleeding prohibits the use of therapeutic anticoagulation [4,6,11]. Researchers have recently concentrated on treating HIT in these patient groups using high-dose IVIG since it prevents HIT reaction, has no additional risk of bleeding, and has an impact that lasts longer than a week, covering the crucial early postoperative period [13].

Here, we describe our experience treating a liver transplant recipient with refractory HIT who did not respond to PLEX and IVIG and did not tolerate argatroban medication because of gastrointestinal hemorrhage. In the past, perioperative PLEX and IVIG were occasionally utilized to treat HIT that was recalcitrant. However, our patient represents the first documented instance of perioperative PLEX and IVIG treatment in the management of refractory HIT in a recipient of a liver transplant. Clinicians may find it easier to manage urgent surgery candidates with refractory HIT if they refer to this case report in conjunction with other previously documented cases.

Case Report

In December 2022, a 57-year-old man who had a medical history of complex alcoholic cirrhosis, hepatocellular cancer, and hypertension had deceased donor liver transplantation (DDLT). Acute renal damage requiring hemodialysis and atrial fibrillation with a fast ventricular response necessitating cardioversion hampered the postoperative treatment. In addition, he had a diagnosis of septic shock, which necessitated the infusion of vasopressor and broad-spectrum antibiotics. He was also extremely hypotensive.After doing a thorough clinical evaluation, the transplant team opted to proceed with an exploratory laparotomy, abdominal washout, and liver biopsy since there was no obvious source of infection. The pathology report showed focal portal venulitis, mild duct injury with marked ductular proliferation, cholestasis, and moderate portal mixed inflammation with neutrophilic infiltrate. These findings suggested mild acute cellular rejection with a rejection activ-ity index (RAI) of 3 of 9, but there were no morphological signs of anti-body-mediated rejection.

Before and after surgery, the patient was treated with subcutaneous heparin for the prevention of deep vein thrombosis (DVT). Before DDLT, the baseline platelet count was 92×103/μL (ref 150-450×103/μL), and on the eighth day following surgery, it decreased to 9×103/μL. He noticed sporadic bruising on his extremities and intermittent oozing at vascular access sites, but no petechiae. It was previously believed that thrombocytopenia was caused by a combination of factors, including splenic sequestration, bone marrow suppression from septic shock, persistent alcohol use, and negative drug reactions from immunosuppressive and antibacterial drugs. Prothrombin time 19.9 s (ref 9.6-12.4 s), activated partial thromboplastin time 78.1 s (ref 23.0-32.0 s), fibrinogen 65 mg/dL (ref 150-440 mg/dL), and D-dimer 6.9 (ref <0.50 mg/L FEU) were among the other noteworthy laboratory results.He received several blood product transfusions. The peripheral blood smear revealed rare schistocytes, spur cells, and a low platelet count without platelet clumping or big platelets. DIC and HIT were finally determined following a 4T score of 5 points and positive findings from confirmatory tests such heparin-induced platelet antibody (HIPA) and SRA. HIPA demonstrated strong positive results with an optic density (OD) of 2.76 with standard deviations of 95% and 97% utilizing 0.1 and 0.5 IU/mL of unfractionated heparin, respectively (normal value <20%). For this reason, argatroban was started and heparin was stopped as soon as HIT was detected.

Additional evaluation on day 20 following his initial transplant procedure showed that he had also acquired bilateral pulmonary embolism and DVT involving the right femoral vein. Regretfully, even after stopping heparin and starting argatroban, severe thrombocytopenia and anti-PF4 antibodies remained (platelets count was 15,000/μL on day 23 following surgery). As a result, refractory HIT was identified as his diagnosis. Liver enzyme levels and total bilirubin rose gradually in the interim.A repeat liver biopsy revealed substantial cholestasis along with a mixed population of neutrophils and lymphocytes indicating mild inflammation. The growth of portal fibrous tissue and localized bridging fibrosis were detected by Trichrome stain (stages 2-3 of 4). He received one 500 mg IV dose of methylprednisolone for liver rejection treatment, which was tapered off over the course of seven days. Nevertheless, hepatic artery thrombosis was shown by

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abdominal computed tomography angiography (CTA), which led to the transplanted liver's failure (Figure 1). An abdominal ultrasound was unable to detect hepatic arterial flow. Thirty days following the initial transplant, a multidisciplinary team assessment led to the decision to move forward with a second DDLT. Ahead of surgery, he had two PLEX sessions to lower the amount of HIPA in his blood, as his continuous refractory HIT required sophisticated therapeutic intervention. Additionally, he received one IVIG dose (1 g/kg) the day prior to the surgery as well as a second dose during it. Postoperative HIPA was initially negative on postoperative day 1 and weakly positive one week later, while postoperative SRA was negative. After he developed melena and his hemoglobin dropped to 4.2 g/dl (ref 12–16 g/dl), the argatroban was withdrawn.The patient had an esophagogastroduodenoscopy (EGD), but the results did not reveal where the bleeding was coming from. The sudden increase in total bilirubin and liver enzymes raised the possibility of recurrent hepatic artery thrombosis.

A CTA of the abdomen revealed hepatic artery stenosis along with several subcapsular hypodense arteries that were indicative of a liver infarction. As a result, he began another course of IVIG at 0.5 gr/kg/day for 4 doses and had urgent catheter-directed intra-arterial thrombolysis, although the arterial flow showed only slight improvement. The second liver transplant failure was caused by hepatic artery thrombosis, which persisted in spite of all available therapeutic measures. The patient experienced hemorrhagic shock, necessitating a large blood transfusion and up to three vasopressor doses. After his second liver transplant, he eventually suffered a cardiac attack and passed away one month later.

DISCUSSION

Hepatic vein thrombosis and other thromboembolic events have been documented in the past as an HIT consequence [14]. On the other hand, our patient represents the first documented instance of hepatic arterial thrombosis in a liver transplant recipient as a side effect of ongoing HIT. The best anticoagulant alternatives for acute hemolytic illness (HIT) are argatroban and bivalirudin, according to American Society of Hematology (ASH) guidelines [15]. The ASH guideline for argatroban use recommends dose decrease in individuals with liver impairment (bilirubin >1.5 mg/dL) as well as dose adjustment to achieve aPTT 1.5-3.0 times baseline (ref 25-32 s).However, there are currently no published guidelines for treating individuals with refractory HIT, and the only therapy options available to this patient population are IVIG and PLEX [16]. More findings in the literature have shown a tendency toward increased IVIG and/or PLEX usage in HIT over time [17], and recent studies have advised PLEX use in HIT [15]. Using PLEX and IVIG to treat refractory HIT was linked to a higher risk of infection, severe bleeding, GI hemorrhage, and inpatient mortality. This is complicated, though, by the fact that these therapies are typically applied to individuals who have more serious conditions and are not responding to traditional therapies [13, 17].It's still unclear what the best treatment plan is for PLEX. When a patient has strongly positive HIPA and/or active thrombosis during the perioperative period, as our patient did, many PLEX treatments may be required. However, PLEX may have unfavorable consequences such hemodynamic instability that could restrict its application [3]. In 1989, Frame et al. [18] reported the first study on the use of IVIG in severe HIT. Three days following high-dose IVIG treatment, the 62-year-old patient's case was described. She had severe HIT worsened by widespread venous thromboembolism, and her reaction was outstanding. Afterwards, IVIG usage in refractory HIT was documented in several publications [2,8,9], although these were isolated cases or small case series. Although the IVIG dosage varied in several studies based on the patient's characteristics and thrombosis risk, 1 g/kg per day was the most often given IVIG dose [9,12,19].In 50–70% of patients, high-dose IVIG caused a rapid increase in platelet count to >100×103/μL within 3 days; however, the platelet-inhibitory impact of IVIG was only temporary, as robust positive SRAs returned after 1 week [2,4,16,19,20]. Refractory HIT is particularly difficult to treat in patients undergoing urgent surgery because it necessitates a careful balance between thrombotic and bleeding risks. IVIG has recently been utilized for patients with HIT undergoing a variety of operations, including heart transplants [11], vascular surgery [20], left ventricular assist device (LVAD) implantation [3,22], and lung transplants [21]. A 59-year-old man needed an urgent revisionalization after developing refractory HIT due to heparin exposure during vascular surgery, as reported by Warkentin et al. in 2018 [20]. As a result, he received one IVIG dose nine hours prior to surgery and another dose during the procedure. There were no thrombotic aftereffects or recurrent thrombocytopenia following the successful procedure. A further example of HIT in a patient with end-stage lung illness who required an immediate lung transplant with intraoperative heparin usage was later reported by Mandernach et al. [21]. Lung transplantation was successfully completed without the development of recurrent HIT thanks to preoperative therapy with PLEX and IVIG. In a different trial [23], three consecutive HIT patients receiving temporary mechanical circulatory support in anticipation of an immediate heart transplant were treated with a combination of PLEX and IVIG. With this method, heparin could be used during cardiopulmonary bypass in a safer manner.

Even though the majority of previously published experiences were successful—that is, fully treated cases with refractory HIT—the majority of these studies might have been influenced by "positive-result bias," a phenomenon in which research showing favorable outcomes is more likely to be published

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than research showing unfavorable or neutral outcomes. The evaluation of the safety and effectiveness of treatments in case reports may be complicated by this publication bias [24]. There was not enough time to wait for SRA negativity prior to surgery in our patient with refractory HIT. In order to lower the risk of recurrent thrombosis, the multidisciplinary team prepared many immunomodulatory therapy.

CONCLUSIONS

Clinicians treating HIT patients having urgent surgery may find guidance from this case report and other previously published cases. There have been few prior studies [3,11,20–22] that evaluated the safety and effectiveness of IVIG and/or PLEX use in this patient population. However, as far as we are aware, we are the first to re-port the use of PLEX and perioperative IVIG in liver transplant surgery. Even though in our example the refractory HIT persisted despite extensive treatment with PLEX and IVIG, more patients may need to be included in future research to draw definitive conclusions.
Because IVIG carries a black box warning from the Food and Drug Administration (FDA) about raising the risk of thrombosis in several potential predisposing situations, like extended immobilization and the use of estrogens, cases should be chosen carefully [7,25]. However, the advantages of IVIG might surpass the dangers of thrombosis. Furthermore, a number of earlier HIT-related investigations [4,9,25] employing IVIG did not find any thrombotic events. It is unclear if the thrombosis that our patient and a few other patients had during IVIG treatment was a side effect of the drug or a result of extended refractory HIT.

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