Suspected Heparin-Induced Thrombocytopenia in a COVID-19 Patient on Extracorporeal Membrane Oxygenation Support: A Case Report.

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Case report

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) support can be life-saving in critically ill COVID-19 patients. However, there are many complications associated with this procedure, including Heparin-induced thrombocytopenia (HIT.) Despite its rarity in ECMO cases, HIT can lead to devastating consequences and is difficult to manage.

Case presentation: In this report, we present a case of a COVID-19 patient on ECMO support who was diagnosed with HIT and required intensive treatment. Initially, the patient showed no remarkable sign of thrombosis and HIT was only suspected due to newly-developed thrombocytopenia and oxygenator dysfunction. Regarding his treatment, since there was no recommended replacement to heparin available to us at the time of diagnosis, we decided to use Rivaroxaban temporarily. No adverse events were recorded during that period. The patient was able to make a full recovery.

Conclusion: HIT may jeopardize patient's care during ECMO. As COVID-19 may bring about a surge in the number of patients requiring ECMO support, we need consented guidance to optimize treatment in this specific situation.

Background

Coronavirus disease 2019 (COVID-19), the disease caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is an ongoing medical problem worldwide [1]. Patients may have different severity levels, ranging from mild dyspnea or coughing to multiorgan failure [1]. For those with life-threatening complications, intensive interventions may be requisite. Extracorporeal membrane oxygenation (ECMO) is a potentially life-saving procedure, in which the patient's blood is circulated through an oxygenator to provide oxygen to vital organs [2]. In ECMO, the tubing system is usually coated with heparin to reduce to risk of thrombosis due to widespread coagulation activation throughout the set [2]. However, this practice gives rise to an increased risk of Heparin-induced thrombocytopenia (HIT), a condition in which platelets are incessantly activated by anti-PF4/Heparin antibodies, leading to catastrophic thrombotic events [2]. In this report, we describe a case of a COVID-19 patient on ECMO with suspected HIT who was particularly difficult to manage due to our lack of resources.

Case Report

A 43-year-old Caucasian male patient was admitted to the Hospital for Tropical Diseases in Ho Chi Minh City due to fatigue, mild fever, dry coughing and shortness of breath. He was diagnosed with SARS-CoV2 infection after his positive PCR result and was transferred to the isolation room. He was also given subcutaneous Enoxaparin for venous thrombosis prophylaxis as part of COVID-19 treatment. His condition quickly worsened and he required intubation and mechanical ventilation 2 weeks after admission, and veno-venous extracorporeal membrane oxygenation (ECMO) using ROTAFLOW pump (Maquet, Germany) and PLS-i oxygenator (Maquet, Germany), together with continuous renal

replacement therapy (CRRT) 1 day later. Unfractionated heparin (UFH) was given as a bolus dose of 8000 units, then 1200–1700 units/hour to maintain an activated partial thromboplastin time (aPTT) of 60–80 seconds. After the start of ECMO, he was routinely monitored by complete blood count (CBC) every 12 hours, which revealed a drop is his platelet count to 44 × 10e9/l one day after ECMO start, necessitating platelet transfusion. For the next few days, his platelet count continued to fluctuate (Fig. 1.) Furthermore, the patient required 2 oxygenator exchanges within 4 days due to increased transmembrane pressure. After the second exchange, several tests were performed to clarify his hypercoagulable status, including Anti-β2-glycoprotein, Anti-Cardiolipin, Anti-PF4/Heparin antibodies, Plasminogen, Plasminogen activator inhibitor-1 (PAI-1), α2-antiplasmin quantification assays. All the assays were within normal ranges or negative, except for the Anti-PF4/Heparin antibody test (HemosIL® HIT-Ab, Instrumentation Laboratory, Bedford, MA,) which showed a high antibody titer of 2.9 U/ml (normal range 0.0–1.0 U/ml). A repeated Anti-PF4/Heparin antibody test was done 24 hours later and showed an even higher titer of 4.0 U/ml. On the same day, thrombi were detected in the patient's inferior vena cava, causing partial occlusion in the outflow cannula. As a result, HIT was suspected and UFH was stopped. However, we did not have access to other intravenous anticoagulants and the non-heparin coated disposables for ECMO at that moment. Therefore, we decided to start Rivaroxaban given through the patient's nasogastric tube at 15 mg twice daily and continued using the current ECMO set. An Anti-Xa based assay (HemosIL Liquid anti Xa, Instrumentation Laboratory, Bedford, MA) was also performed 4 times per day to monitor the trough and peak Rivaroxaban levels (Fig. 2). Anti PF4-Heparin was undetectable 48 hours after the start of Rivaroxaban. Platelet count also bounced back after 4 days of Rivaroxaban use. Moreover, no thrombotic event, including unexpected oxygenator exchange (besides fortnightly replacements recommended by the manufacturer,) was recorded during Rivaroxaban administration After 10 days, we managed to get Argatroban and switched to such anticoagulant. The patient required ECMO support with Argatroban infusion for 42 more days. He was able to wean off ECMO and other mechanical supports and made a full recovery. He was discharged on oral Rivaroxaban for venous thrombosis prophylaxis, after more than 3 months of hospitalization.

Discussion And Conclusions

Current reports have highlighted the hypercoagulable state of COVID-19 patients and its implication in the patients' prognosis [1]. Consequently, the International Society on Thrombosis and Hemostasis (ISTH) have issued guidelines that recommend prophylactic Low-molecular-weight Heparin for almost all COVID-19 patients [3]. However, this routine use of heparin may precipitate an increased risk of HIT, a potentially catastrophic thrombotic event, especially in critically ill patients. In patients on ECMO support, the incidence of HIT is reported to be 0.36% [2]. In critically ill COVID-19 patients, only a few cases have been described, with devastating consequences [4]. To evaluate the probability of HIT, physicians normally use a clinical assessment tool, such as the 4Ts Scoring system [2]. Our patient had a 4Ts score of 5, suggesting an intermediate probability of HIT [5]. Nevertheless, the 4Ts score may be of little value in COVID-19, since there are many factors affecting its credibility. For example, in COVID-19, thrombocytopenia is a common finding and is linked to a plethora of etiologies [6]. Furthermore,

thrombosis may prove difficult to detect, partly due to the isolation requirements. Indeed, only 1 in the first 3 reported COVID-19 patients with HIT had typical clinical manifestations [4]. In our patient, a sudden drop in platelet count were the signs of HIT, and thrombi were only detected a few days later. Actually, several reports have shown that thrombocytopenia and associated oxygenator dysfunction should prompt the suspicion of HIT in patients on ECMO support [7, 8]. To make a definitive diagnosis of HIT, an immunologic assay and a functional assay are required [9]. However, functional assays like the Serotonin-releasing assay are time-consuming, difficult to perform and, as we encountered in our case, are not always available [9]. Immunologic tests are generally very sensitive and easy to perform, but not very specific [9]. Our patient had 2 separate positive results for anti-PF4/Heparin antibodies and matching clinical manifestations, thus his HIT diagnosis is highly likely, although without results from a functional test.

While establishing the diagnosis of HIT in this patient was difficult, managing his condition was even more challenging. Firstly, it is recommended that when HIT is suspected, heparinoids should be stopped immediately and switching to another type of anticoagulants is warranted [2]. In ECMO, the preferred alternatives are intravenous anticoagulants such as Bivalirudin, Danaparoid, Argatroban and Fondaparinux [6, 10]. Unfortunately, none of the mentioned drugs was available to us at the time of HIT diagnosis. Consequently, we decided to start oral Rivaroxaban, a factor Xa direct inhibitor. Although there have been reports regarding the efficacy and safety of Rivaroxaban in patients with HIT [2], there is very little data about its use in the ECMO setting. From our experience, Rivaroxaban was seemingly effective and safe, as we observed no thrombotic or bleeding events during our obligatory use of such drug. Nevertheless, there was much fluctuation in Rivaroxaban peak and trough levels in our case. Whether this phenomenon has any clinical significance is still unknown. Another aspect of HIT management is whether to change the ECMO circuit or not. There are currently commercially available non-heparin coated tubing sets intent to use in HIT cases [8]. Nevertheless, many reports have showed that changing the ECMO circuit has no impact on the patients' survival, since heparin in the tubing set cannot diffuse into the patients' blood [10]. In our case, we did not, and admittedly could not, change the ECMO circuit, as there was no available alternative. However, we encountered no complication with continuous use of the heparin-coated tubing set.

The patient presented in this report is arguably the most complex COVID-19 case treated in Vietnam up to this date. His treatment was complicated by many affecting factors, most notably HIT. In general, management of HIT in patients on ECMO support is still difficult, as there is a lack of well-designed trials to clarify the importance of various practices in this setting. Our case highlights the need for consented guidelines in this specific situation, especially when COVID-19 is causing more and more patients to require life-saving ECMO support.

Declarations

Consent

The patient gave written consent for the publication of this article.

Conflicts of interests

The authors declare that they have no conflict of interest.

Author contributions

TH Nguyen and XT Phan wrote the manuscript. All authors participated in the patient's management. All authors reviewed and approved the final version of the manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Abbreviations

aPTT: activated partial thromboplastin time

CBC: Complete blood count

COVID-19: Coronavirus disease 2019

CRRT: Continuous renal replacement therapy

ECMO: Extracorporeal membrane oxygenation

HIT: Heparin-induced thrombocytopenia

ISTH: International Society on Thrombosis and Hemostasis

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

UFH: Unfractionated heparin

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Figures

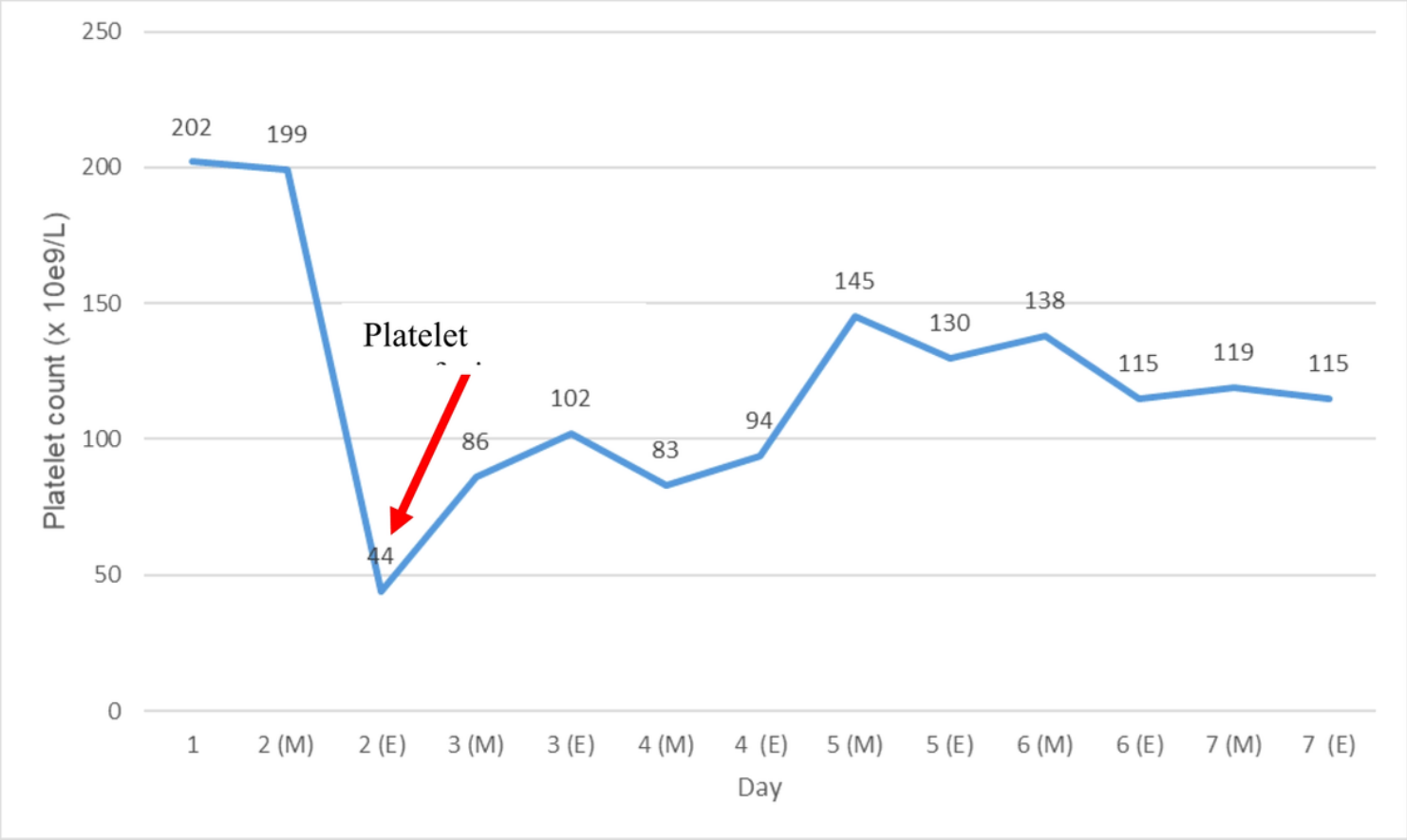

Figure 1

Platelet counts from the start of ECMO (Day 1) to HIT diagnosis (Day 7) (M: Morning, E: Evening)

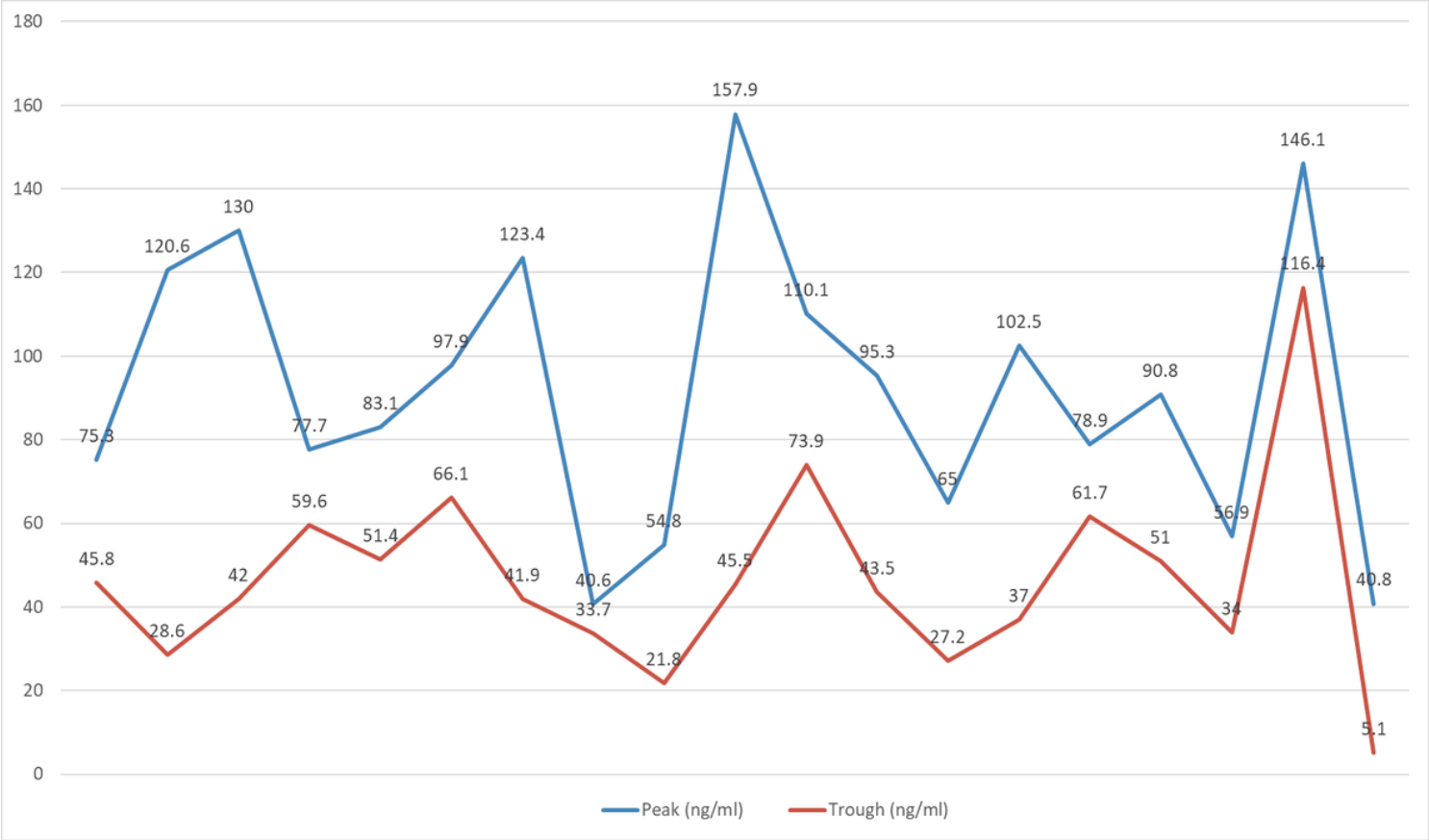

Figure 2

Peak and trough levels of Rivaroxaban.