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CASE REPORT

Artificial Lung / ECMO

Heparin-induced thrombocytopenia in COVID-19 patients with severe acute respiratory distress syndrome requiring extracorporeal membrane oxygenation: two case reports

Frank Bidar[1,2] · Guillaume Hékimian[1,2] · Isabelle Martin-Toutain[1,4] · Guillaume Lebreton[1,3] · Alain Combes[1,2] · Corinne Frère[1,4]

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Abstract

Veno-venous (VV) extracorporeal membrane oxygenation (ECMO) is increasingly used in Coronavirus disease-19 (COVID-19) patients with the most severe forms of acute respiratory distress syndrome (ARDS). Its use is associated with a significant hemostatic challenge, especially in COVID- 19 patients who have been demonstrated to otherwise present a COVID-19-associated coagulopathy. The systematic use of unfractionated heparin therapy to prevent circuit thrombosis is warranted during ECMO support. The clinical presentation and management of heparin-induced thrombocytopenia, which is a rare but life-threatening complication of heparin therapy, has not been described in those patients yet. We report herein two cases of laboratory-confirmed HIT in COVID-19 patients with severe ARDS admitted to our intensive care unit for VV-ECMO support and the successful use of argatroban as an alternative therapy. We also provide a brief literature review of best evidence for managing such patients. The diagnosis and management of HIT is particularly challenging in COVID-19 patients receiving ECMO support. An increased awareness is warranted in those patients who already present a procoagulant state leading to higher rates of thrombotic events which can confuse the issues. Argatroban seems to be an appropriate and safe therapeutic option in COVID-19 patients with HIT while on VV-ECMO.

Keywords COVID-19 · Extracorporeal membrane oxygenation · Heparin-induced thrombocytopenia · Argatroban

Introduction

Critically ill COVID-19 patients have been demonstrated to present a COVID-19-associated coagulopathy and an increased risk of thrombotic complications [1–5] that requires the use of therapeutic doses of anticoagulant in some cases. In patients requiring veno-venous extracorporeal membrane oxygenation (VV-ECMO) for severe ARDS [6], unfractionated heparin (UFH) is preferred for its handling. Heparin-induced thrombocytopenia (HIT) is a severe immune-mediated complication of heparin therapy resulting from the development of pathogenic antibodies that bind platelet factor 4 (PF4)-heparin complexes, leading to platelet activation, platelet consumption, and thrombin generation. Paradoxically, HIT is characterized by both a thrombocytopenia and a prothrombotic state.

The diagnosis of HIT, which is mainly based on clinical suspicion and further laboratory confirmation, appears

✉ Frank Bidar
frankbidar@gmail.com

1 Sorbonne Université, INSERM, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition, F-75013 Paris, France

2 Service de médecine Intensive-réanimation, Institut de Cardiologie, APHP Hôpital Pitié–Salpêtrière, 75013 Paris, France

3 Service de Chirurgie Thoracique Et Cardio-Vasculaire, Institut de Cardiologie, APHP Hôpital Pitié–Salpêtrière, 75013 Paris, France

4 Service D'hématologie Biologique, APHP Hôpital Pitié–Salpêtrière, 75013 Paris, France

particularly challenging in ECMO patients. Indeed, thrombocytopenia is frequently observed in those patients due to platelets consumption within the ECMO circuit and non-pathogenic anti-PF4 antibodies are found in 30 to 50% of cases when systematically searched [7, 8].

We describe herein two cases of laboratory-confirmed HIT in COVID-19 patients with severe ARDS on VV-ECMO. In accordance with the ethical standards of French legislation, only non-opposition of patient's surrogate for utilization of the deidentified data was obtained. The ICU database was registered with the national data protection authority (CNIL 1,950,673).

Case 1

A 62-year old woman with a history of arterial hypertension and asthma was referred to our ICU for COVID-19 pneumonia with persistently worsening hypoxemia requiring VV-ECMO support two days after introduction of invasive mechanical ventilation. At admission, platelet count was 237×10^9 L^{-1}, fibrinogen level was 820 mg.dL^{-1} and D-Dimer level was 15.36 µg/mL^{-1} (Table 1). No anti PF4-heparin antibodies were detected using an ELISA-based immunoassay. The computerized tomography (CT) at admission revealed a right lower lobe segmental pulmonary embolism (PE). Anticoagulation was initiated with unfractionated heparin (UFH) infused continuously targeting an antiXa activity of 0.3–0.6 IU/mL at ECMO initiation [Quadrox® membrane oxygenator with a Rotaflow pump (MAQUET Cardiopulmonary AG, Hirlingen, Germany)]. During the first 10 days, the platelet count progressively decreased from 237 to 130×10^9 L^{-1}, and the fibrinogen level simultaneously decreased from 820 mg.dL^{-1} to 590 mg.dL^{-1}. The main hypothesis was platelets and fibrinogen coating on the oxygenator, which is commonly observed in patients under ECMO therapy. However, platelet count continued to decrease to reach a nadir of 29×10^9 L^{-1} at day 16, while D-Dimer level increased from 15.36 µg/mL^{-1} to > 20 µg/mL^{-1}, and fibrin monomers transiently increased from 5 to > 150 µg/mL^{-1}. The clinical evolution allowed to rule out evolving

Table 1 Patients coagulation parameters at baseline

	Normal range	Patient 1	Patient 2
aPTT (sec)	30–36	50.1	36.1
INR	1.44	1.44	1.09
Fibrinogen (mg/dL)	< 400	820	660
D-Dimers (µg/mL)	< 0.5	15.36	> 20
Fibrin monomers(µg/mL)	< 5	5	27.55
Antithrombin (%)	80–120	121	82
Protein C (%)	80–140	142	81
Protein S (%)	60–120	134	69
VWF (%)	50–120	369	443
dRVVT normalized ratio[1]	< 1.2	1.3	1.7
APL antibodies IgG (U/mL)[2]	< 15	34	33
APL antibodies IgM (U/mL)[2]	< 15	12	32
Anticardiolipin antibodies antibodies IgG (U/mL)[3]	< 15	26	21
Anticardiolipin antibodies IgM (U/mL)[3]	< 15	6	23
Anticardiolipin antibodies IgA (U/mL)[3]	< 15	25	7
Anti-β2GP1 antibodies IgG (U/mL)[3]	< 15	< 15	< 15
Anti-β2GP1 antibodies IgM (U/mL)[4]	< 15	< 15	< 15
Anti-β2GP1 antibodies IgA (U/mL)[4]	< 15	< 15	< 15
Anti-platelet factor 4 (PF4) antibodies (optical density read at 405 nm)[5]	< 0.5	0.5	0.12
Platelet count (× 1000 cells/µL)	150–400	237	248

APL antiphospholipid, *dRVVT* diluted russel viper venom time

[1]dRVVT, screen and confirm were performed on a CS5100 analyzer using LA1 and LA2 reagent, SIEMENS (Saint-Denis, France)

[2]PHOSPO-LISA IgG/IgM, THERADIAG (Marne-la-Vallée, France); includes: anti-phosphatidyl-serin, anti-phosphatidyl-ethanolamine, anti-cardiolipin and anti- β2GP1 antibodies

[3]QUANTA Lite® ACA IgG III, INOVA (San Diego, CA, USA)

[4]Thermoscientific EliA β2Glycoprotein-1 IgG/M/A-well, Phadia (Uppsala, Sweden)

[5]ZYMUTEST™ HIA IgGAM, HYPHEN BioMed (Neuville-sur-Oise, France)

sepsis, hemorrhage, drug toxicity, disseminated intravascular coagulation (DIC), or thrombosis of the ECMO circuit. The diagnosis of HIT was therefore suspected, UFH therapy was immediately discontinued and switched to argatroban. The platelet counts rose up in a few days (Fig. 1, patient 1). The anti PF4-heparin antibodies were found to be strongly positive (optical density, 1.8; normal value < 0.5) and a heparin-induced platelet activation (HIPA) assay confirmed the diagnosis of HIT. Of note, no further thrombotic complication occurred in addition to the PE diagnosed at admission. The patient was weaned from VV-ECMO and discharged from the ICU on argatroban at day 50.

Case 2

A 38-year old man without significant medical history was admitted to our ICU for COVID-19 pneumonia complicated by severe ARDS requiring VV-ECMO support after one day of invasive mechanical ventilation. UFH was started at ECMO initiation [Quadrox® membrane oxygenator with a Rotaflow pump (MAQUET Cardiopulmonary AG, Hirrlingen, Germany)]. At admission, the platelet count was 248×10^9 L^{-1}, the fibrinogen level was 660 mg.dL^{-1} and the D-Dimer level was > 20 µg/mL^{-1} (Table 1). No anti PF4-heparin antibodies were detected at admission. Sixteen days later, the platelet count fell from 248×10^9 L^{-1} to 93×10^9 L^{-1} and the fibrinogen level from 660 mg.dL^{-1} to 450 mg.dL^{-1}. The patient was profoundly hypoxemic with a partial pressure of oxygen in arterial blood gas (PaO_2) of 53 mmHg despite VV-ECMO. The post membrane blood gas analysis to evaluate the performance of the oxygenator revealed a PO_2 of 115 mmHg (normal range > 400 mmHg), demonstrating that it was no longer functional and partially thrombosed. Despite oxygenator changing, thrombocytopenia and fibrinogen fall worsened. Five days later, the patient was once again profoundly hypoxemic with a post membrane blood PO_2 of 162 mmHg, consistently with a new membrane oxygenator thrombosis. Given such short oxygenator lifetime and thrombocytopenia, HIT was strongly suspected. UFH therapy was discontinued and switched to argatroban at Day 21. The circuit was changed for a phosphorylcholine coated and heparin-free circuit. The platelet count raised up and no further dysfunction of the oxygenator was subsequently observed (Fig. 1, patient 2). The anti-PF4 antibodies were strongly positive (optical density of 1.6) and the diagnosis of HIT was confirmed by HIPA. The thoracic CT performed after oxygenator change did not reveal any sign of PE. The patient was weaned from VV-ECMO and discharged from the ICU on argatroban at day 53.

Discussion

Thrombocytopenia is one of the most common complication in patients receiving ECMO therapy, severe thrombocytopenia (< 50 G × 10^9 L^{-1}) occurring in more than 20% of cases [9]. In most cases, thrombocytopenia is related to shear stress leading to platelets adhesion to the protein-coated monolayer of the ECMO circuit biosurface, which makes anticoagulation mandatory during ECMO support to prevent clotting of the circuit [10]. Thrombocytopenia is explained by this consumption in some cases, but other causes such as sepsis, bleeding, drug-induced thrombocytopenia or DIC are common in critically ill patients. Among these etiologies, HIT diagnosis is particularly challenging since usual scoring system 4 T-score have been reported to present a lower performance in ECMO patients [11] and anti-PF4-heparin antibodies are found in almost 50% of patients [7]. Most of these antibodies are non-pathogenic and do not affect the clinical course of patients. In that respect, increasing the value of the optical density threshold to 1.0 could enhance their specificity up to 89% [12].

HIT may have very heterogeneous clinical manifestations varying from asymptomatic forms to life-threatening thrombosis [13]. Our two cases illustrated this heterogeneity: one patient had previously known COVID-19 induced PE and isolated thrombocytopenia while the second had a thrombocytopenia associated with repeated oxygenator thrombosis. The latter requires, in addition to discontinuation of heparin therapy which is the cornerstone of HIT management, the change of the circuit for a heparin-free one. Anticoagulation must then be ensured by another medication. Concerning our two patients, we opted for argatroban infused continuously at a dose of 0.25 µg/Kg/min and then monitored according to aPTT ratio. This choice was safe since no bleeding complication occurred.

From March 2020 to April 2020, among all COVID-19 patients with severe ARDS admitted in our ICU, which serves as an ECMO referral center for the Greater Paris, and who were implanted with VV-ECMO support, 2 out of 46 (4.3%) had HIT diagnosis confirmation, while HIT prevalence is estimated to be inferior to 0.5% in this population [14, 15]. This raises the question of an association between COVID-19 and HIT. Indeed, COVID-19 could induce dysregulated immunologic response as suggested by abnormal elevation of antiphospholipid antibodies in these patients [16]. Moreover, platelet activation induced by both ECMO [17] and COVID- 19 [18] could result in a significant increase of PF4 plasma levels potentially contributing to the development of HIT. Lastly, this phenomenon could be enhanced by the higher dose of UFH requested [19] to obtain a therapeutic anticoagulation in

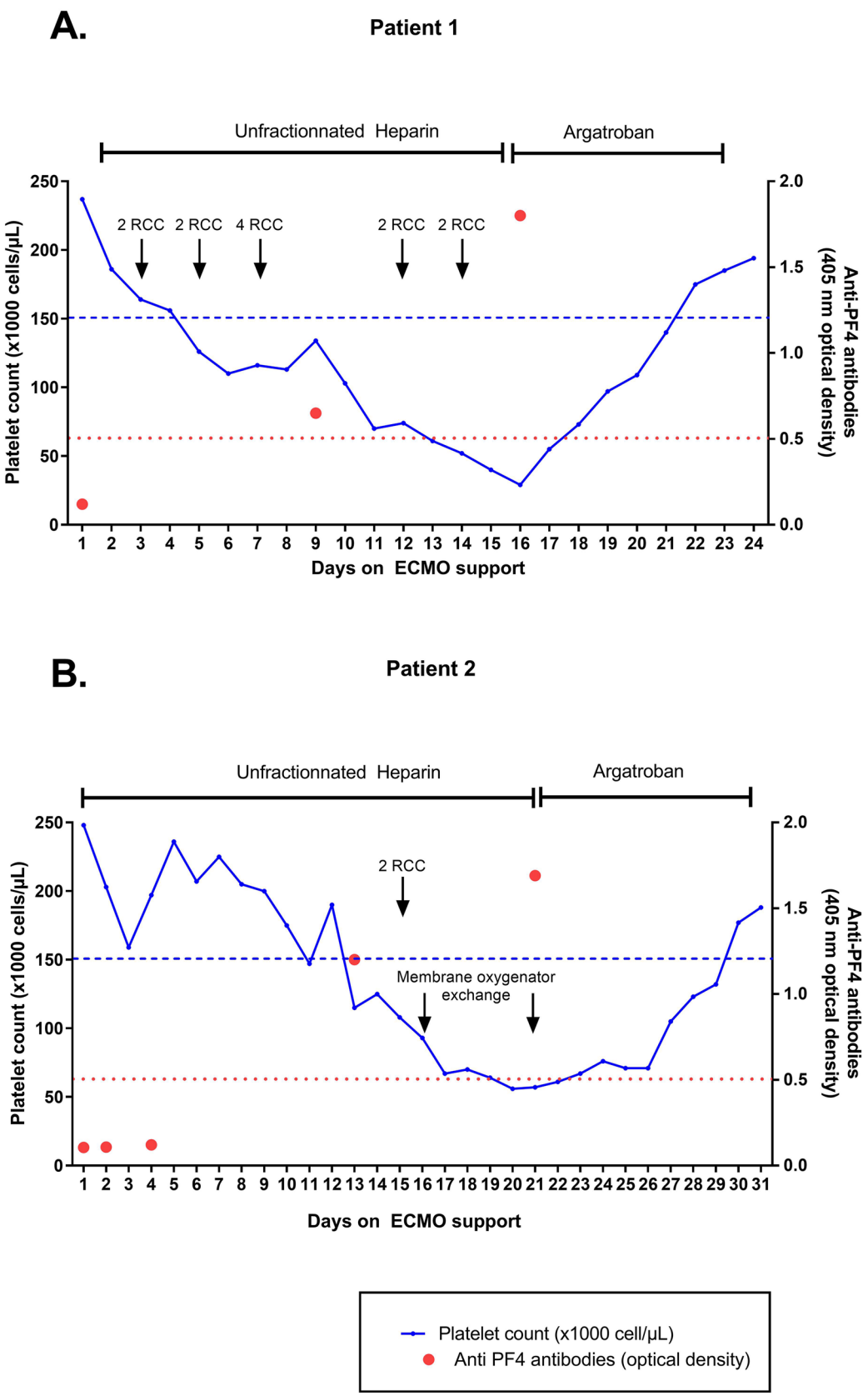

Fig. 1 Kinetics of Platelet count and Anti-platelet Factor 4 (PF4)-heparin antibodies. **a** Patient 1; **b** Patient 2. *RCC* red blood cells concentrates

COVID-19 patients in whom COVID-19-associated coagulopathy is responsible for increased incidence of venous thromboembolic events. In line with this hypothesis, a recent retrospective study reported a cumulative incidence of detectable HIT antibodies of 12% at 25 days in 88 severe COVID-19 patients who received at least 5 days of UFH [20]. In COVID-19 patients treated with VV-ECMO, a systematic HIT antibody testing might therefore help to avoid preventable platelet diminishment.

In conclusion, physicians should increase their awareness of HIT in COVID-19 patients receiving ECMO support who may present other coagulation abnormalities and higher rates of thrombotic events which may confuse the issues.

Author contributions Role and contribution of the authors: FB and CF collected the data and wrote the manuscript. GH, IMT, GL and AC wrote the manuscript.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest related to the submitted work to disclose.

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