CASE REPORT

Severe immune thrombocytopenic purpura in critical COVID-19

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Abstract

COVID-19 is a new disease with many undescribed clinical manifestations. We report herein a case of severe immune thrombocytopenic purpura (ITP) in a critical COVID-19 patient. A patient presented a severe episode of immune thrombocytopenia ($< 10 \times 10^9$/L) 20 days after admission for a critical COVID-19. This thrombocytopenia was associated with a life-threatening bleeding. Response to first-line therapies was delayed as it took up to 13 days after initiation of intravenous immunoglobulin and high-dose dexamethasone to observe an increase in platelet count. COVID-19 may be associated with late presenting severe ITP. Such ITP may also be relatively resistant to first-line agents. Hematological manifestations of COVID-19, such as the ones associated with life-threatening bleeding, must be recognized.

Keywords COVID-19 · Thrombocytopenia · Bleeding · Immunoglobulin · Corticosteroids

Introduction

Many different clinical manifestations of COVID-19 has been described, the most common being a respiratory disease [1]. Hematologic abnormalities are amongst them and thrombocytopenia seems to occur in up to one third of patients [1].

SARS-CoV-1 associated thrombocytopenias were most of the time mild and recovered during the hospital stay [2]. These thrombocytopenias were likely multifactorial. Proposed etiologies in the Severe Acute Respiratory Syndrome (SARS), caused by SARS-CoV-1, included decreased bone marrow production, diffuse endothelial consumption and autoantibodies produced by the immune viral response [2].

Immune thrombocytopenic purpura (ITP) is caused by the production of platelet autoantibodies. ITP may occur after several viral infections, including human immunodeficiency virus (HIV), hepatitis C virus (HCV), cytomegalovirus, herpes simplex virus, zika virus and others [3]. ITP episodes can vary from being mild to life-threatening. They often require treatment of the underlying infection with appropriate antiviral therapy, when available, in addition to ITP therapies such as intravenous immunoglobulin and glucocorticoids [4].

COVID-19 associated ITP has been recently reported early in the disease course [5, 6]. We present herein a case of very severe COVID-19 associated ITP that occurred later in the disease course than previously published cases. We obtained consent from the decision surrogate maker to publish this case.

Case report

A 53-year-old man with well-controlled hypertension, dyslipidemia, type 2 diabetes and a body mass index of 24 presented with a 3-day history of dyspnea, dry cough and fever. His usual medication included Metformin, Rosuvastatin, Irbesartan, Amlodipine and Hydrochlorothiazide. His initial laboratory tests showed a hemoglobin concentration of 117 g/L (normal range 130–170), a white blood cell count of 10.2×10^9/L (4.0–10.0), a lymphopenia of 0.1×10^9/L

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(1.0–4.0), a platelet count of 244×10^9/L (130–400), a creatinine of 222 µmol/L (53–112), normal coagulation times and mildly elevated liver enzymes [AST 59 U/L (13–39), ALT 30 U/L (10–39)]. An endotracheal RT-PCR test was positive for SARS-CoV-2.

He quickly developed severe acute respiratory distress syndrome (ARDS), requiring endotracheal intubation. He was mechanically ventilated with lung protective ventilation and prone positioning and was sedated with propofol, fentanyl and cisatracurium infusions. He received ceftriaxone, azithromycin and a thromboprophylaxis with unfractionated heparin. His disease was complicated by acute kidney injury (creatinine rising up to 689 µmol/L) that required renal replacement therapy and by a methicillin-sensitive staphylococcus aureus ventilator-associated pneumonia treated with a 2-day course of empirical piperacillin–tazobactam and 6 days of cefazolin. On the 20th day, the patient was spontaneously breathing on pressure support ventilation with an inspired concentration of oxygen of 35%. Since he developed ICU-acquired neuromyopathy, a tracheotomy was performed to facilitate weaning of mechanical ventilation. During the procedure, abnormal bleeding from the tracheotomy site and the left main stem bronchus was noticed. We observed afterwards that the platelet count had dramatically fallen from 311×10^9/L the day before to 23×10^9/L with stable other blood cell counts (Table 1). The patient did not have any skin purpura. However, a head CT scan performed later on hospitalization day 39 showed a small spontaneous intraventricular hemorrhage deemed related to thrombocytopenia.

This severe thrombocytopenia prompted discontinuation of heparin and a change in antibiotics. The patient had normal coagulation times and fibrinogen level and did not present any laboratory signs of hemolysis or microangiopathy. The blood smear was normal other than thrombocytopenia and did not show any schistocyte. An anti-PF4 assay was weakly positive (0.72 optical density) but a serotonin release assay came back negative. The ferritin and triglycerides concentrations were mildly elevated. An abdominal computed tomography (CT) scan did not show any hepatomegaly, splenomegaly or lymphadenopathy. Complement dosage was normal and an ADAMTS-13 assay came back negative. Serologies for HIV, HBV and HCV were negative. A bone marrow biopsy or aspiration was deemed uninformative in this context. Our working diagnosis was thus COVID-19 associated ITP.

We administered intravenous immune globulin (IVIG) at a dose of 1 g per kilogram of body weight daily on ITP days 1 and 2 and a daily dose of 40 mg of intravenous dexamethasone on days 3–6. We also administered several platelet and red blood cell transfusions as well as intravenous tranexamic acid. Due to bleeding and clotting causing complete atelectasis of his left lung and thus severe hypoxemia, he required several daily endobronchial clot removal procedures. The bleeding finally stopped with the aforementioned high platelet transfusion support, although we did not observe any improvement in the platelet count at ITP day 5. In spite of 4 days of optimal first-line therapy, the patient still presented profound thrombocytopenia requiring continuous platelet transfusion support (Table 1). We then decided to proceed with second-line agents and administered romiplostim daily from ITP day 5–14 and a dose of vincristine on ITP day 9. We also administered pulse doses of 500 milligrams of intravenous methylprednisolone daily from ITP days 10–13 (Table 1). We did not consider splenectomy as an appropriate treatment at this stage of the disease. The platelet count started to increase on ITP day 11 and progressively reached 178×10^9/L, 14 days after first dose of IVIG (Table 1).

Discussion

We believe that severe late ITP associated with COVID-19 was the most likely diagnosis to explain the observed isolated fulminant drop in platelet count that caused significant bleeding in this patient. There was no evidence of thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, heparin-induced thrombocytopenia, hemophagocytic lymphohistiocytosis or any lymphoproliferative disorder. The observed thrombocytopenia was relatively resistant to first-line therapies and additional therapies such as romiplostim, an erythropoietin (TPO) receptor agonist, and low-dose vincristine were administered. Thrombocytopenia finally started to improve after 10 days of treatments. Although the patient presented life-threatening bleeding, he improved and survived this episode.

The patient had received several days of penicillin-based treatment and cephalosporins. However, we do not believe that his thrombocytopenia was an adverse effect of the antibiotic treatments due to the rapidity and the severity of the platelet fall. Rare cases of antibiotic associated ITP have been described, but the thrombocytopenia seemed to recover quickly after the agent had been stopped [7]. Besides, cefazolin was not specifically one of them.

Different hematologic abnormalities have been observed in COVID-19 patients. Most of them have resulted in a hypercoagulable state causing thrombotic complications [8]. Nevertheless, mild thrombocytopenia has been observed in up to one third of patients with COVID-19 [1]. A recent study described characteristics of patients presenting with delayed (14 days after symptom onset) SARS-CoV-2 associated thrombocytopenia [9]. Although observed thrombocytopenias were associated with a longer hospital stay and a higher mortality, they were mild and transient (lasting less than 7 days) and not associated with bleeding [9]. These thrombocytopenias were likely multifactorial and etiologies

Table 1 Timeline of laboratory values and treatments

Hospi-talization day[a]	ITP day[a]	Hb (g/L)	Plt count (×10⁹/L)	WBC (×10⁹/L)	Lym-phocytes (×10⁹/L)	Cre-atinine (µmol/L)	INR	aPTT (s)	Fibrino-gen (g/L)	D-dimers (µg/L)	Max FiO₂ (%)	Started treatments (excluding transfusions)
1		117	244	10.2	0.1	222	1.0	25	5.6	–	70	–
19		76	311	11.9	–		1.0	28	8.9	–	35	–
20	1	77	23	13.2	–	384	1.1	29	6.7	–	100[b]	IVIG × 2 days + high-dose dexametha-sone × 4 days (days 3–6)
24	5	71	<10	19.3	–	132	0.9	23	6.8	–	60	Romiplostim × 10 days
28	9	98	12	34.3	–	90	0.9	24	6.7	–	40	Vincristine (1 dose)
29	10	99	19	34.1	–	80	1.1	26	6.7	–	35	Very high dose of methylpredniso-lone × 4 days
30	11	100	38	18.1	–	93	1.0	26	5.1	–	35	–
33	14	93	178	17	1.56	66	1.1	27	4.2	29710	30	–

Normal values: hemoglobin—130–170 g/L, platelets—130–400 × 10⁹/L, white blood cells count—4.0–10.0 × 10⁹/L, lymphocytes count—1.0–4.0 × 10⁹/L, creatinine—53–112 µmol/L, INR—0.8–1.1, aPTT—22–31 s, fibrinogen—2–4.5 g/L, D-dimers—<600 µg/L (<500 µg/L to rule out thromboembolic diseases in outpatients)

ITP immune thrombocytopenic purpura, *Hb* hemoglobin, *Plt* platelet, *WBC* white blood cells, *INR* international normalized ratio, *aPTT* activated thromboplastin time, *IVIG* intravenous immune globulin

[a]"Hospitalization day" refers to number of days since hospital admission and "ITP day" refer to number of days since ITP diagnosis. The patient had COVID-19 related symptoms for 3 days before he was hospitalized

[b]FiO₂ increased from 35 to 100% this day because of endobronchial hemorrhage

such as decreased bone marrow production and immune destruction were proposed. Most of them were probably not ITP. Such mild thrombocytopenia has also been described in ARDS of pulmonary and extra-pulmonary etiologies and has also been associated with higher mortality [10].

Very few reported cases of hematological manifestations of COVID-19, such as our case, led to severe bleeding complications. Although four cases of COVID-19 ITP have already been reported, most of them occurred early after COVID-19 disease onset and responded well to first-line agents [5, 6]. One of the recently published cases presented a similar thrombocytopenia timeline to our case [6]. This patient presented a severe thrombocytopenia at day 12 of hospitalization while under anticoagulants for a pulmonary embolism for 48 h. He presented an important hemorrhagic episode, only received platelet transfusions to treat thrombocytopenia and died within 24 h, precluding any further observation [6]. Although our case shares with this case the late presentation characteristic, ours is the only one that presented itself with life-threatening bleeding and intracerebral hemorrhage solely due to such a late occurring severe thrombocytopenia. Furthermore, it is the first case of COVID-19 associated ITP showing relative resistance to first-line ITP agents, as all other reported cases presented platelet count improvement within few days after IVIG administration [5, 6]. Although we administered therapies that have been previously used to increase platelet production in refractory cases that are at high risk of bleeding, we believed we observed a late response to first-line agents, since second-line agents did not have time to show any significant clinical effect [4, 11].

ITP is not commonly associated with severe bleeding, as only 10% of adult patients with ITP presented any severe non-intracranial hemorrhage and 2% an intracerebral hemorrhage in a recent review [12]. Amongst reported COVID-19 associated ITP cases, including ours, bleeding is frequently reported [5, 6]. This observation may be either related to specific pathophysiological characteristics of the disease or to a reporting bias but needs further attention. We also observed a relative time lag in the clinical response to ITP first-line agents in our case. This relative lag may be caused by the underlying disease severity and its associated high antibody load but may also be related to the ongoing bleeding that may have contributed to platelet consumption and loss of the administered IVIG. Although it is not unusual for ITP to start to improve after 7–10 days of treatment, such a late response is not common [4].

As in many cases of ITP, there is no absolute proof that a specific etiology is the true causal factor for the immune reaction. However, several viral infections have been associated with ITP in the past [3]. In COVID-19, disruption of the immune response is thought to play an important role in the disease, although the pathophysiology is yet to be better understood [13]. A better understanding of such

immune pathway will be essential to define best therapeutic approaches to ITP, either associated or not with COVID-19, in the context of the pandemic [13].

Conclusion

Our case of ITP presented itself late after the COVID-related classical clinical manifestations began, was not associated with any skin manifestations of ITP, presented severe hemorrhages and was relatively resistant to first-line agents. To our knowledge, our case is the first severe ITP occurring late in the disease process of COVID-19, associated with severe bleeding and relatively resistant to IVIG treatment. This case suggests that hematologic complications may occur in COVID-19 and cause life-threatening bleeding complications. Such manifestations must be included in the clinical evaluation of patients infected by SARS-CoV-2.

Compliance with ethical standards

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