Case Report

Severe immune thrombocytopenia in a critically ill COVID-19 patient

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\textbf{A B S T R A C T}

The novel coronavirus SARS-CoV-2 can cause a severe and even fatal respiratory illness named COVID-19. Apart from respiratory failure, COVID-19 may be associated with various autoimmune complications. We present a case of a critically ill patient with COVID-19 who developed severe immune thrombocytopenia that was successfully treated with a concomitant use of corticosteroids and intravenous immunoglobulins.

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\section*{Introduction}

Coronavirus disease (COVID-19) follows a mild course in about 80 \% of cases, but some patients develop severe pneumonia and other non-pulmonary life-threatening complications (Wu and McGoogan 2020). Among the latter, thrombotic events, hyper-inflammatory syndrome and autoimmune diseases have been described as important features of severe disease (Galeotti and Bayry 2020; Levi et al. 2020). Immune thrombocytopenia (ITP) is an autoantibody and T-cell-mediated autoimmune disorder characterized by isolated thrombocytopenia, which can be triggered by infection (Cines et al. 2009). First line treatment of severe ITP includes platelet transfusions, corticosteroids and intravenous immunoglobulins (IVIG) (Provan et al. 2019). Very few cases of COVID-19-associated ITP have been reported so far, especially in critically ill patients. Moreover, treatment of severe COVID-19-associated ITP in critically ill patients may be particularly challenging. Besides known side effects, corticosteroids may have detrimental effects on immune function and viral clearance and effects of both corticosteroids and IVIG on COVID-19 outcome are currently unknown (Russell et al. 2020). On the other hand, concomitant treatment with corticosteroids and IVIG may be associated with rapid treatment response in ITP (Neunert et al. 2011). We present a case of a critically ill COVID-19 patient with severe ITP, which was successfully treated with a concomitant use of corticosteroids and IVIG.

\section*{Case report}

A 48-year-old man with type 2 diabetes, obesity (BMI 43.4 kg/m$^2$) and obstructive sleep apnea presented to the emergency department on 29th March 2020 with a 3-day history of progressive dyspnea, cough, fever with the highest temperature of 38.5 °C, headache and muscle soreness. His only regular medication was metformin. On examination, he had a respiratory rate of 42 breaths per minute and oxygen saturation of 60\% while receiving high flow oxygen (15 L/min) via a non-rebreather mask. Other vitals revealed a body temperature of 37.5 °C, pulse 125 beats per minute and blood pressure 163/60 mmHg. The patient was promptly transferred to the intensive care unit (ICU), sedated, intubated, and mechanically ventilated. A chest X-ray showed diffuse bilateral consolidations and a reverse transcription polymerase chain reaction (RT-PCR) test of a nasopharyngeal swab was positive for SARS-CoV-2. Co-infection with other respiratory viruses, including influenza, was excluded by multiplex nasopharyngeal RT-PCR test. Blood tests on admission showed a white blood cell count of 16,700/mm$^3$, C-reactive protein of 293 mg/L, procalcitonin of 2.31 µg/L, a creatinine of 188 µmol/L, a fibrinogen of 9.4 g/L and a D-dimer of 1,675 µg/L. The platelet count and hemoglobin level were normal (347,000/mm$^3$ and 13.7 g/dL, respectively).
accordance with interim local guidelines, experimental antiviral therapy with lopinavir/ritonavir 400 mg/100 mg BID and hydroxychloroquine sulphate 400 mg BID (on the first day, followed by 200 mg BID) via nasogastric tube was initiated. The patient also received piperacillin/tazobactam 4 g/0.5 g QID intravenously, sedation with fentanyl and midazolam, low-dose noradrenaline, pantoprazole and thromboprophylaxis with nadroparin 5,600 IU daily. Hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV) serologic tests were negative.

On the 9th day after admission, macroscopic hematuria developed after a non-traumatic re-insertion of a urinary catheter. Concurrently, minor bleeding from oral mucosa and blood clots in gastric residual volume were observed. Upper gastrointestinal tract endoscopy showed non-bleeding ulcers at the tip of the nasogastric tube, for which no intervention was needed. Complete blood count revealed an isolated thrombocytopenia with a platelet count of 96,000/mm³, with a further decline to 2,000/mm³ on the 12th day. At that time petechial bleeding appeared on the torso. Due to severe thrombocytopenia, low molecular weight heparin (LMWH) and antiviral therapies were discontinued. Other blood tests showed normal coagulation times and moderately elevated fibrinogen, D-dimer, and ferritin levels (4.8 g/L, 2,244 μg/L, and 766 μg/L, respectively). The percentage of schistocytes in peripheral blood, haptoglobin and bilirubin were normal. Direct Coombs test was positive for IgG, indirect Coombs test was negative. Heparin-induced thrombocytopenia (HIT) antibodies were negative. Quantitative cytomegalovirus PCR test was negative and quantitative Epstein-Barr virus PCR test from plasma detected less than 2.88 log₁₀ copies/ml. Renal and liver function were improving. Due to the bleeding, the patient received a transfusion of one unit (325 ml) of pooled platelet concentrate with a one-hour post transfusion platelet increment of 5,000/mm³ (from 4,000/mm³ to 9,000/mm³). Based on these findings, a diagnosis of COVID-19-associated ITP was suspected. The patient was started on IVIG for a total of 1 g per kilogram of adjusted body weight (100 g), divided into two daily doses (50 g/day) concomitantly with intravenous dexamethasone 40 mg daily. The platelet count rose to 185,000/mm³ on the third day of treatment; therefore, corticosteroids were discontinued after three daily doses. According to an inpatient anticoagulation management service consultation, thromboprophylaxis was restarted with a continuous infusion of unfractionated heparin due to a higher risk of bleeding and moderate renal failure. After renal function recovery, the therapy was changed to higher dose prophylactic LMWH (dalteparin 7,500 IU q12 h) and no bleeding or other adverse events were noted for the rest of the treatment. At the end of the corticosteroid therapy, improvement in oxygenation was noticed and a consecutive chest X-ray showed regression of pulmonary consolidations. The patient was successfully weaned from ventilator support and extubated after 32 days of mechanical ventilation. No neurologic complications were noted. The patient was transferred to another hospital for further rehabilitation and was discharged on 22nd May 2020. The platelet count remained normal during the rest of the hospitalization and on follow-up laboratory tests in the next two months.

Discussion

Persistent thrombocytopenia in critically ill patients is associated with increased mortality, so identification of the underlying cause and early targeted treatment is crucial (Brogley et al. 2007). In our patient, the diagnosis of COVID-19-associated ITP is supported by an isolated thrombocytopenia, the chronological sequence of events, a low post-transfusion platelet increment, the exclusion of other causes and a good response to first line treatment. The SARS-CoV-2 has many immunogenic peptides with homology to human proteins that have an important role in the adaptive immune system (Lyons-Weiler 2020). That could explain the association between severe disease presentations of COVID-19 and the reported autoimmune complications (Lazarian et al. 2020).

At the time of writing of this report, only two cases of COVID-19-associated ITP have been described in critically ill patients (Bomhof et al. 2020; Lévesque et al. 2020). One patient died due to intracerebral bleeding before corticosteroid and IVIG was initiated. In another case, the application of IVIG followed by high dose dexamethasone did not result in improvement of platelet count; therefore, second-line therapy and extensive transfusion support was needed to achieve an adequate platelet count and stop the bleeding. In our case, treatment with high dose dexamethasone and IVIG was started concomitantly as soon as other probable causes of thrombocytopenia were excluded. This led to a rapid increase in platelets and prevented further bleeding. Importantly, extensive transfusion of blood components was avoided as well as transfusion related complications. Furthermore, although the follow-up period is short, there is no relapse of thrombocytopenia.

According to recently published guidelines from a working group of German, Austrian and Swiss experts, for emergency treatment of ITP complicated by severe bleeding, IVIG should be administered in addition to corticosteroids to increase platelet count rapidly (Matzdorf et al. 2018). As randomized trials on this topic are lacking, this recommendation is supported by small observational studies; therefore, we believe that our case adds to the body of evidence that this approach may be beneficial in critically ill patients.

Finally, of interest is the fact that we observed an improvement in oxygenation following dexamethasone and IVIG treatment. This effect should be interpreted with caution, as the improvement also could be attributed to supportive treatment or to a natural course of the disease. It should be stressed that dexamethasone was initiated late in the COVID-19 course (15th day of illness), by which time the inflammatory phase was in resolution, according to decrement of inflammatory markers. In COVID-19, the use of corticosteroids is controversial until more evidence is available (Russell et al. 2020). However, recently published preliminary results of the RECOVERY trial point to a beneficial effect of dexamethasone regarding 28-day mortality, especially in patients who require oxygen supplementation and mechanical ventilation (Horby et al. 2020). Regarding IVIG, there have been limited reports of its use in COVID-19 with inconsistent results. (Xie et al. 2020; Zhang et al. 2020). On the basis of our experience with one patient, we are not able to provide sufficient evidence that this therapy was of benefit regarding the pneumonia.

Conclusion

ITP is a seemingly rare but important complication that can lead to disability and higher mortality in COVID-19 patients. Early recognition, diagnosis and treatment are essential to prevent severe consequences. In our case, concomitant treatment with corticosteroids and IVIG resulted in rapid increase in the thrombocytes level, cessation of bleeding and improved oxygenation without therapy related side effects.

Conflict of interest

There are no competing interests to declare among the authors of this work.
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Ethical approval

Ethical approval was not needed as this is a case report; an informed signed consent for publication was obtained from the patient.

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References

Bomhof G, Mutsaers PGJ, Leebeek FWG, te Boekhorst P, Hofland J, Croles FN, et al. COVID-19-associated immune thrombocytopenia. Br J Haematol Br J Haematol 2020;190(2):e61–4.

Brogly N, Devos P, Boussekey N, Georges H, Chiche A, Leroy O. Impact of thrombocytopenia on outcome of patients admitted to ICU for severe community-acquired pneumonia. J Infect 2007;55(2):136–40.

Cines DB, Bussel JB, Liebman HA, Luning Prak E. The ITP syndrome: Pathogenic and clinical diversity. Blood 2009;113(26):6511–21.

Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol 2020;[June]1–2, doi:http://dx.doi.org/10.1038/s41584-020-0448-7 Online ahead of print.

Horby P, Lim WS, Emberson J, Matham M, Bell J, Linsell L, et al. Dexmethylone in Hospitalized Patients with COVID-19: Preliminary Report. N Engl J Med 2020;[July], doi:http://dx.doi.org/10.1056/NEJMoa2021436 Online ahead of print.

Lazarian G, Quinquevel A, Bellal M, Siavellis J, Jacqy C, Re D, et al. Autoimmune hemolytic anemia associated with Covid-19 infection. Br J Haematol 2020;190 (July [1])29–31, doi:http://dx.doi.org/10.1111/bjh.16794 Epub 2020 May 27.

Lèvesque V, Milaure E, Corsilli D, Boix-Massé R, Carrier F-M-M. Severe immune thrombocytopenic purpura in critical COVID-19. Int J Hematol 2020;(July):1–5, doi:http://dx.doi.org/10.1007/s12185-020-02931-9.

Lev I, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 2020;7(6):e438–40.

Lyons-Weiler J. Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity. J Transl Autoimmun 2020;3:100051.

Matzdorf A, Meyer O, Ostermann H, Kiefel V, Eberli W, Kühne T, et al. Immune Thrombocytopenia - Current Diagnostics and Therapy: Recommendations of a Joint Working Group of DGHÖ, OGHÖ, SGH, GPOH, and DCTI. Oncol Res Treat 2018;41(suppl5):1–30.

Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Crowther MA, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117(16):4190–207, doi:http://dx.doi.org/10.1182/blood-2010-08-302984.

Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv 2019;3:3780–817, doi:http://dx.doi.org/10.1182/bloodadvances.2019000812.

Russell CD, Millar JE, Bailie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395(February)473–5, doi:http://dx.doi.org/10.1016/S0140-6736(20)30317-2 Epub 2020 Feb 7.

Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–42.

Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect 2020;[April], doi:http://dx.doi.org/10.1016/j.jinf.2020.03.044 S0163-4453(20)30172-3 Online ahead of print.

Zhang J, Yang Y, Yang N, Ma Y, Zhou Q, et al. Effectiveness of intravenous immunoglobulin for children with severe COVID-19: a rapid review. Ann Transl Med. 2020;8(May [10]):625, doi:http://dx.doi.org/10.21037/atm-20-3305.