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LETTER TO THE EDITOR

Frequently Relapsing Post-COVID-19 Immune Thrombocytopenia

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Dear Sir,

Thrombocytopenia in COVID-19 patients may be caused by disseminated intravascular coagulation, sepsis, drugs, direct bone marrow suppression and viral induction of autoimmunity which can be explained by several mechanisms, including molecular mimicry, cryptic antigen expression and epitope spreading [1–3]. Recently, Bhattacharjee et al. first reported a systematic review of 45 patients diagnosed with immune thrombocytopenia (ITP) related with SARS-CoV-2 infection [1]. During the pandemic, very few cases of new onset post-COVID-19 ITP have been reported, most of them adults, without clinical bleeding signs and with adequate responses to conventional treatment [1, 4, 5]. Here, we present two additional adult cases with severe thrombocytopenia and bleeding manifestations, highlighting their relapsing evolution and the need for additional treatments.

Patient 1 is a 60-year-old woman with no past medical history except for a mild COVID-19 infection diagnosed in December 2020. On 7/1/21, she presented with scattered ecchymoses, petechiae and retinal haemorrhages in the right eye. SARS-CoV-2 PCR was negative and IgG antibodies were positive. The platelet count was 6×10^9/L with normal levels of haemoglobin, leukocytes and biochemistry panel. A bone marrow aspirate was normal. After ruling out other etiologies (Table 1), the patient was diagnosed with post-COVID-19 ITP. Methylprednisolone 1 mg/kg/day was started, with an initial response (44×10^9/L platelets). After 2 weeks of treatment, she was readmitted due to severe thrombocytopenia (6×10^9/L platelets). She was treated with 4 doses of rituximab 375 mg/m^2/week i.v. and high intravenous doses of unspecific immunoglobulins (IVIg, 1 g/kg/day i.v. for 2 days), without response. Therefore, the patient received dexamethasone (40 mg/day for 4 days), reaching a platelet complete response (116×10^9/L platelets), and was discharged home. One week later, the patient was admitted again with severe thrombocytopenia (5×10^9/L), requiring a second pulse of dexamethasone, IVIg, a fourth weekly dose of rituximab and oral thrombopoietin analogues (eltrombopag 50 mg/day), reaching a platelet count of 102×10^9/L in 6 days. On 19/2/21, she presented with a new decrease in platelet counts (2×10^9/L), spontaneous hematomas on her arms and multiple petechiae on her legs. She received again IVIg, eltrombopag was increased to 75 mg/day and a third pulse of dexamethasone was administered. A new complete response was reached (179×10^9/L platelets). Two weeks later, the number of platelets decreased to 78×10^9/L and a sixth line of treatment with mycophenolate mofetil 1 g b.i.d. was started. Since then, the patient has maintained a platelet count around 60×10^9/L with no clinical haemorrhages or apparent side effects.

Patient 2 is a 74-year-old man, living in a care home due to severe mental retardation, who was diagnosed with a mild COVID-19 infection in November 2020 (detected by PCR on 6/11/20, with positive IgG antibodies on 22/11/20 and negative PCR since 26/1//21). Two months later, in January 2021, he presented with epistaxis and melenic stools. The SARS-CoV-2 PCR was negative, but the platelet count was 6×10^9/L, refractory to platelet transfusions. Bone marrow studies were normal (Table 1). A folic acid deficiency was detected and treated without platelet improvement.

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Table 1 Complementary studies and outcomes in post-COVID-19 ITP patients.

	Patient 1	Patient 2
Immunoglobulin levels	IgG: 4900 mg/dL IgA: 273 mg/dL IgM: 22.2 mg/dL	IgG: 1120 mg/dL IgA: 232 mg/dL IgM: 91.2 mg/dL
Proteinogram	No monoclonal peak	No monoclonal peak
Antinuclear antibodies	Negative	Negative
Lupus anticoagulant antibody Antiphospholipid antibody	Negative Negative	Negative Negative
Complement levels	C3 81.3 mg/dL C4 22.2 mg/dL	C3 110 mg/dL C4 22 mg/dL
Thyroid function tests	TSH 0.478 uUI/mL T4 1.14 ng/dL	TSH 1.33 uUI/mL T4 1.55 ng/dL
Helicobacter pylori stool antigen test	Negative (×3)	Negative (×3)
Viral serologies	HBV negative HCV negative HIV-1 negative HIV-2 negative Parvovirus B19 negative	HBV negative HCV negative HIV-1 negative HIV-2 negative Parvovirus B19 negative
Viral load	CMV negative Epstein-Barr virus negative	CMV negative Epstein-Barr virus negative
Peripheral blood morphology	RS: Mild anisocytosis. WS: No alterations. PS: Thrombocytopenia with anisothrombia.	RS: Mild anisocytosis. WS: No alterations. PS: Severe thrombocytopenia.
Bone marrow aspirate	Hypercellular bone marrow. Non-central thrombocytopenia.	Normocellular bone marrow. Non-central thrombocytopenia.

TSH, thyrotropin; *T4*, thyroxine; *VHB*, hepatitis B virus; *VHC*; hepatitis B virus; *CMV*, cytomegalovirus; *RS*, red series; *WS*, white series; *PS*, platelet series

Endoscopic tests were ruled out due to the patient's baseline situation. Other causes of thrombocytopenia were excluded (Table 1) and a post-COVID-19 ITP was diagnosed. The patient received IVIg (1 g/kg/day for 2 days) achieving a quick platelet complete response. In February 2021, the patient was admitted again due to severe thrombocytopenia (6×10^9/L) and treated with intravenous IVIg and dexamethasone 40 mg/day for 4 days, and achieving a second complete platelet response. In March 2021, the patient was readmitted with severe thrombocytopenia and self-limited upper gastrointestinal bleeding. Combined treatment with IVIg and eltrombopag 50 mg/day was started, without alteration of liver function test, and a third maintained platelet complete response was observed.

Most COVID-19-associated ITP patients have been detected during COVID-19 infection [1]. In those cases, the use of corticosteroids as first-line treatment is recommended, due to the risk of thrombosis related to thrombopoietin analogues. On the contrary, thrombopoietin analogues are considered first-line in COVID-19-negative ITP patients, due to the risk of immunosuppression associated with corticosteroids [6]. Post-COVID-19 infection ITP is a rarely described type of ITP, without treatment guidelines [1, 4]. Herein, we report two adult cases observed 4 and 8 weeks after a mild COVID-19 infection. Both patients presented with bleeding manifestations as well as anti-SARS-CoV-2 IgG antibodies and negative PCR tests at the time of ITP diagnosis. In previously reported cases, standard treatment with glucocorticoids and IVig has been effective in achieving a rapidly response [5]. Similarly, our patients had initial responses, but short-lived and followed by recurrent relapses that needed additional treatment strategies. A diagrammatic presentation of treatment offered to our post-COVID-19 ITP patients has been given in Fig. 1. This atypical clinical course with bleeding signs and frequent relapses in post-COVID-19 ITP should be confirmed with further reports and points out the necessity of basic studies to ascertain the pathophysiology of post-COVID-19 ITP. Our case series show that clinicians should continue follow up of recovered COVID-19 patients so that long-term effects could be uncovered of this novel virus.

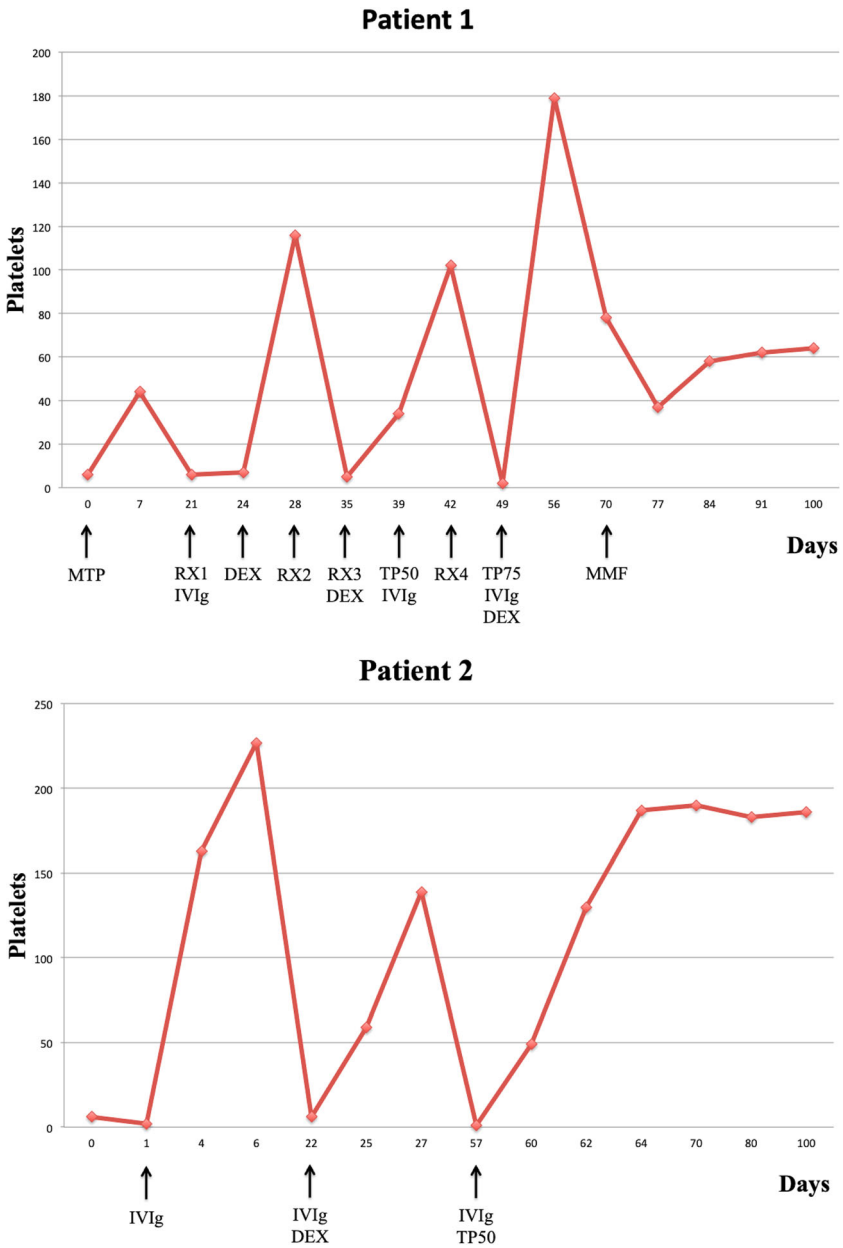

Fig. 1 Treatment offered to post-COVID-19 ITP patients. MTP, methylprednisolone (1 mg/kg/day for 7 days); RX, rituximab (375 mg/m^2/week for 4 weeks); IVIg, unspecific immunoglobulins (1 g/kg/day i.v. for 2 days); DEX, dexamethasone (40 mg/day for 4 days); TP50, eltrombopag (50 mg/day daily); TP75, eltrombopag (75 mg/day every day); MMF, mycophenolate mofetil (1 g/12 h daily)

Author Contribution The authors of the article meet the authorship criteria established by the International Committee of Medical Journal Editors.

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Declarations

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Conflict of Interest The authors declare no competing interests.

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