COVID-19 presenting with immune thrombocytopenia: A case report and review of the literature

To the Editor,

Mild thrombocytopenia (platelet counts of 100-150 × 10^9/L) can be observed in novel coronavirus disease (COVID-19), however severe thrombocytopenia is rare. COVID-19-associated thrombocytopenia can be due to: the direct invasion of bone marrow, cytokine release leading to hemophagocytic lymphohistiocytosis, autoimmune destruction of platelets in peripheral blood (immune thrombocytopenia [ITP]), and increased platelet consumption as a consequence of thrombi in the microvasculature. Severe thrombocytopenia (<50 × 10^9/L) was related to poor prognosis in a recent COVID-19 cohort where thrombocytopenia was attributed to coagulopathy related consumption.

We herein report a mild disease course in a patient who had COVID-19-induced severe thrombocytopenia, along with the recently published similar cases in the literature.

A 41-year-old male was presented with petechiae and nasal bleeding. He had cough and runny nose 15 days ago, which resolved recently. He was diagnosed as ITP and referred to our center after 4 days of high-dose dexamethasone therapy, which was not effective. His medical history was otherwise unremarkable. Physical examination was normal except for petechiae and purpuric rash. Upon admission, he had isolated thrombocytopenia (9 × 10^9/L). In the differential diagnosis of isolated thrombocytopenia, the patient did not have consumption coagulopathy or thrombotic microangiopathy with no schistocytes or blasts in the peripheral blood smear. Laboratory tests including viral hepatitis panel and rheumatological markers did not reveal any cause of thrombocytopenia, and the diagnosis of ITP was made.

Since he had cough and runny nose recently, a nasopharyngeal swab was sent for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real time polymerase chain reaction, which came out to be positive. His chest computerized tomography showed bilateral ground glass opacities consistent with COVID-19 pneumonia. Favipiravir was prescribed as the antiviral agent, and his pneumonia gradually resolved in 5 days.

As ITP secondary to COVID-19 was the most likely diagnosis, intravenous immunoglobulin (IVIg) with a total dose of 2 g/kg was administered concomitantly with favipiravir in the first 2 days of admission. After the treatment, his platelet count was 54 × 10^9/L, and during 4-weeks of follow-up, platelet counts were between 50 to 100 × 10^9/L.

Recently there have been published cases of isolated severe thrombocytopenia associated with COVID-19 (Table 1). Among them, two patients (patients #1 and #2) were presented as ITP with no fever or respiratory symptoms. Additional two patients (patients #5 and #6) who were presented with ITP had prior fever and respiratory symptoms, starting 10 and 21 days before referral, respectively. Similar to our patient, these four cases were also responsive to high-dose IVIg. Thrombocytopenia was detected relatively later in the other four cases (patients #3, #4, #7, and #8). Patients #3 and #7 developed thrombocytopenia on the 5th and 12th days of admission respectively, and thrombocytopenia in both cases coincided with clinical deterioration. Patient #4 had used amoxicillin-clavulanic acid and low-molecular-weight-heparin before the detection of thrombocytopenia, which might also be related to thrombocytopenia. IVIg was not effective in these patients (#3, #4, and #7). Patients #3 and #7 died because of COVID-19 progression, whereas prednisolone and eltrombopag were administered in patient #4, which induced a good response. Another patient (patient #8) developed thrombocytopenia on 16th day of admission, which was 29 days after the initiation of respiratory symptoms. That patient had a stable disease course and was in the recovery stage. His platelet counts recovered following IVIg administration.

Thrombocytopenia has been defined as a poor prognostic factor in COVID-19, but thrombocytopenia in the disease course is not of one kind. Cytokine release or thrombi in the microvasculature may be responsible for platelet consumption in clinically deteriorated cases. Severe thrombocytopenia in the context of ITP (patients #1, #2, #5, #6, #8, and presented case) may be a different, possibly milder entity in COVID-19 than consumption thrombocytopenia (patient #3 and #7) and it can develop on different stages of the disease. Although not frequently reported to date, SARS-CoV-2 infection can be associated with secondary ITP. When COVID-19 patients are presented or complicated with ITP related severe thrombocytopenia, IVIg could be preferred first-line treatment option for a faster recovery of platelets in comparison to corticosteroids. Other treatment options including thrombopoietin mimetics can be beneficial (patient #4), although the data on COVID-19-induced ITP and its management are still very limited. We had the options to use hydroxychloroquine or favipiravir as the viral load-decreasing agent, of which we chose favipiravir, as thrombocytopenia is also among the uncommon side effects of hydroxychloroquine.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.
TABLE 1  All reported COVID-19 induced immune thrombocytopenia cases including the presented case

| Patient (reference) | Age | Sex | Presenting symptoms | COVID symptoms | Days from symptoms to referral | Viral serology and autoimmune profile | Days from admission to thrombocytopenia/COVID course | Platelet Nadir | Prior drugs | IV Ig dose/response | Further treatment | Platelets increased to (after treatment), d | Outcome |
|---------------------|-----|-----|---------------------|---------------|--------------------------------|---------------------------------------|---------------------------------------------|--------------|-------------|-------------------|----------------|---------------------------|----------|
| P#1                 | 50  | M   | Epistaxis, generalized rash | None          | Not reported                   | Negative                              | On presentation, stable COVID course       | 0            | None        | 1 g/kg: 2 doses/response | None           | 25 × 10^9/L (2), 103 × 10^9/L (14) | Discharged |
| P#2                 | 49  | F   | Bruises, gum bleed    | None          | 3                             | Negative                              | On presentation, stable COVID course       | 4 × 10^9/L   | None        | 1 g/kg: Single dose/response | None           | 52 × 10^9/L (2)         | Discharged |
| P#3                 | 96  | F   | Shortness of breath   | Shortness of breath | Not reported                   | Negative                              | 5th d, deteriorated                         | 3 × 10^9/L   | None        | 0.4 g/kg: 5 doses/not known     | None           | 16 × 10^9/L (2)         | Died      |
| P#4                 | 65  | F   | Fatigue, fever, dry cough | Fatigue, fever, dry cough | 4                             | Anti-TPO (+)                           | 4th d, complicated with subarachnoid hemorrhage | 8 × 10^9/L   | Amo-Clav, LMWH | 1 g/kg: unresponsive     | Prednisolone, TPO-RA | 139 × 10^9/L (4)        | Discharged |
| P#5                 | 59  | M   | Petechiae, skin hematoma | Cough, fever  | 10                            | GPb (+)                               | On presentation, stable COVID course       | 3 × 10^9/L   | None        | 1 g/kg: 2 doses/response     | Dexamethasone | 47 × 10^9/L (2), 51 × 10^9/L (17) | Discharged |
| P#6                 | 66  | F   | Petechiae, epistaxis  | Fever, dyspnea, cough | 21                            | GP IB IIIa (+) GPV (+)                 | On presentation, stable COVID course       | 2 × 10^9/L   | High dose dexamethasone    | 1 g/kg: dose not shared/responsive | None         | 32 × 10^9/L (22)        | Discharged |
| P#7                 | 67  | M   | Fever, cough, dyspnea  | Fever, cough, dyspnea | 9                             | Negative                              | 12th d, deteriorated, pulmonary embolism   | 3 × 10^9/L   | Unfractionated heparin    | None           | Platelet transfusion     | None      | Died      |
| P#8                 | 38  | M   | Cough, dyspnea, fever | Cough, dyspnea, fever | 13                            | Negative                              | 16th d, stable COVID course                | 2 × 10^9/L   | Interferon-α, umifenovir | 400 mg/kg: 7 doses/responsive | Dexamethasone | 60 × 10^9/L (3)         | Discharged |
| Present case        | 41  | M   | Petechiae and purpura | Cough and runny nose | 4                             | Negative                              | On presentation, stable COVID course       | 9 × 10^9/L   | High dose dexamethasone    | 1 g/kg: 2 doses/responsive | None         | 54 × 10^9/L (2)         | Discharged |

Abbreviations: anti-TPO, thyroid peroxidase antibodies; Amo-Clav, amoxicillin-clavulonic acid; COVID, coronavirus disease; GP, glycoprotein (Ib, IIBIIIa, V); IV Ig, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist.
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