Outcomes and management of immune thrombocytopenia secondary to COVID-19: Cleveland clinic experience

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Abstract

Background: Immune thrombocytopenia (ITP) is an acquired disease characterized by thrombocytopenia secondary to autoantibodies against platelets. Here, we report the clinical characteristics of coronavirus disease 2019 (COVID-19)-induced ITP cases.

Study Design and Methods: We retrospectively reviewed 3255 COVID-19 patients. COVID-19-induced ITP was diagnosed after excluding possible common causes. Bleeding severity was assessed based on the modified World Health Organization (WHO) bleeding severity score.

Results: We identified 11 (0.34%) patients with COVID-19-induced ITP. Of all patients, 63.6% were males and the median age was 63 years. The median time from COVID-19 diagnosis to the onset of ITP was 10 days. Bleeding observed in 63.6% of the patients. Clinically significant bleeding (WHO Grade 3) occurred in single patient who required blood transfusion. Standard treatment with glucocorticoids and intravenous immunoglobulin (IVIG) was effective in achieving excellent response in most cases. Of all patients, complete response and response to treatment were achieved in 45.5% and 27.3% patients, respectively. The median time to ITP recovery was 4 days. Eltrombopag was used in three patients who relapsed. Four patients required mechanical ventilation, and none of them survived secondary to hypoxic respiratory failure.

Conclusion: ITP secondary to COVID-19 usually presents after the first week of symptoms beginning. Most of our patients had WHO Grade 1–2 bleeding scores. Standard treatment with glucocorticoids and IVIG is effective in achieving an excellent response. The safety of eltrombopag is not very well established in COVID-19 patients, and additional studies are needed for a better safety profile.

Keywords
immune thrombocytopenia, intravenous immunoglobulin
1 | INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired disease characterized by thrombocytopenia secondary to autoantibodies against platelet antigens. Secondary ITP is common after viral infections and accounts for 18%–20% of all adult ITP cases. The exact mechanism of secondary ITP is not very well understood; antibodies against virus glycoprotein may cross-react with platelet surface antigens causing platelet destruction. Clinically patients with ITP may be asymptomatic or can present with severe bleeding. ITP is a diagnosis of exclusion; it can be diagnosed after excluding all possible causes of thrombocytopenia.

Thrombocytopenia has been reported in patients diagnosed with coronavirus disease 2019 (COVID-19). Increased platelet destruction and decreased platelet production might be contributing to thrombocytopenia among COVID-19 patients. Case reports and case series of ITP induced by COVID-19 have been reported in the literature, and multiple treatment protocols have been suggested. Here, we report the clinical manifestations, mortality rate, and management of all COVID-19 patients admitted to the hospital and diagnosed with secondary ITP.

2 | MATERIALS AND METHODS

We retrospectively reviewed all patients diagnosed with COVID-19 via reverse transcriptase–polymerase chain reaction (RT-PCR) and ITP admitted to Cleveland Clinic Foundation Hospitals between March 2020 and November 2020. ITP was diagnosed based on the International Working Group definition after excluding all other possible causes including thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), sepsis-induced thrombocytopenia, and heparin-induced thrombocytopenia (HIT). Thrombocytopenia secondary to other autoimmune disorders or other infections was excluded based on the timing of the presentation with COVID-19 infection. None of our patients had human immunodeficiency virus or hepatitis virus screening. HIT was excluded based on the 4T score; negative platelet factor 4 antibodies were required to exclude HIT in patients with intermediate and high probabilities 4T scores. Qualitative flow cytometry assay (sensitivity of 53% and specificity of >90%) was used to test for direct immunoglobulins M and G (IgM and IgG) against platelets in two patients. Patients with a previous diagnosis of thrombocytopenia, hematological malignancies, or chronic ITP were excluded. COVID-19-induced ITP was diagnosed based on a new-onset thrombocytopenia in the setting of positive COVID-19 RT-PCR, acute thrombocytopenia, and the absence of identifiable clear cause. Complete response (CR) was defined based on platelet count >100 × 10⁹/L. Response to treatment was defined based on a platelet count of >30 × 10⁹/L and doubling of the baseline value. Bleeding severity was assessed based on the modified World Health Organization (WHO) bleeding severity score (1–4).

3 | RESULTS

We manually reviewed the electronic medical records of 3255 COVID-19 inpatients and identified 11 (0.34%) with COVID-19-induced ITP diagnosis based on hematologist evaluation at the time of admission. Of all patients, seven (63.6%) were men, and the median (range) age was 63 (26–95) years. The median (range) time from COVID-19 diagnosis to the onset of ITP was 10 (0–125) days. On presentation, six (54.5%) patients had a cough, and only three (27.3%) patients had a fever. Only one patient was pregnant (Patient #4), and two patients had a history of autoimmune diseases (Patient #7 and #10). Among all patients, four (36.4%) patients required mechanical ventilation, and none of them survived secondary to hypoxic respiratory failure. None of our patients developed venous thromboembolism. Of all patients, only five (45%) received remdesivir, and none received convalescent plasma or required extracorporeal membrane oxygenation (ECMO). The median (range) follow-up time was 38 (9–198) days. Table 1 summarizes the clinical characteristics and treatment lines of all patients.

The median (range) lowest platelet count was 3 (0–59) × 10⁹/L. Only one patient (Patient #9) had clinically significant bleeding (WHO Grade 3) with a hemorrhagic ovarian cyst and required two units of blood transfusion. Petechiae, mucosal bleeding, gastrointestinal bleeding, and epistaxis were observed in five (45.5%), four (36.4%), two (18.2%), and one (9.1%) patients, respectively. None of the patients who developed bleeding were receiving therapeutic anticoagulation at the time of bleeding. Regarding the treatment lines used, all patients except one were treated with corticosteroids. Dexamethasone 40 mg daily for 4 days was used in six (54.5%) patients. In two patients, a lower dose of dexamethasone (6 mg daily) was used; both patients did not achieve a response. Two patients (Patient #5 and #10) were treated with methylprednisolone 125 and 250 mg daily, and both achieved CR. Intravenous immunoglobulin (IVIG) was used in five patients with corticosteroid therapy. IVIG was used alone in one patient only (Patient #6). Of all patients, CR and response to treatment were achieved in five (45.5%) and three (27.3%) patients, respectively. Only one patient (Patient #11) relapsed after CR. The median (range) time to ITP recovery was 4 (2–7) days.
| #  | Sex | Age (years) | Race       | Past medical history | COVID-19 symptoms             | Time from COVID-19 diagnosis to ITP (days) | Lowest platelet count (× 10^9/L) | Bleeding type (WHO Grade) | ITP treatment                                                                 | ITP outcome | Time to ITP recovery (days) | COVID-19 outcome | Total follow-up (days) |
|----|-----|------------|------------|--------------------|-------------------------------|------------------------------------------|-------------------------------------|----------------------------|----------------------------|--------------------------|---------------------|----------------------|----------------------|---------------------|
| 1  | Male| 89         | White      | Hypertension, atrial fibrillation, diabetes, CKD | Fever, cough, SOB, GI symptoms | 12                          | 2                                  | No bleeding                  | Dexamethasone 40 mg (D1–D4), IVIG (D1–D2) | Response     | 4                   | Deceased           | 23                  |
| 2  | Male| 58         | African American | Hypertension, atrial fibrillation, diabetes, CKD | SOB                           | 5                          | 59                                 | No bleeding                  | Dexamethasone 40 mg (D1–D4) | Complete response | 6                   | Recovery            | 31                  |
| 3  | Male| 53         | White      | Prostate cancer | Cough and SOB               | 19                          | 2                                  | Mucosal bleeding (Grade 1)    | Dexamethasone 40 mg (D1–D4), Eltrombopag (D5–D30) | Response     | 3                   | Recovery            | 172                 |
| 4  | Female| 26      | White      | Pregnancy (third trimester), hypertension | No symptoms                   | 125                         | 0                                  | Petechiae, mucosal bleeding (Grade 1) | Dexamethasone 40 mg (D1–D4), IVIG (D1–D3) | Complete response | 3                   | Recovery            | 198                 |
| 5  | Male| 65         | African American | Hypertension, lung cancer, CKD | Cough and GI symptoms         | 7                          | 3                                  | No bleeding                  | Methylprednisolone 125 mg (D1–D2), IVIG (D1–D2) | Complete response | 5                   | Recovery            | 119                 |
| 6  | Male| 95         | White      | Hypertension, atrial fibrillation | Fever, cough, SOB            | 10                          | 5                                  | Petechiae (Grade 1)           | IVIG (D1–D3)                | Response     | 7                   | Deceased           | 17                  |
| 7  | Female| 70     | African American | SLE and CKD | No symptoms                  | 4                          | 10                                 | Petechiae and rectal bleeding (Grade 2) | Dexamethasone 6 mg (D1–D6), methylprednisolone 1000 mg (D7), Eltrombopag (D7) | No response   | _                   | Deceased           | 9                   |
| 8  | Male| 68         | White      | No medical disease | Fever, cough, SOB            | 31                          | 13                                 | Rectal bleeding (Grade 2)     | Dexamethasone 6 mg (D1–D10) | No response   | _                   | Deceased           | 39                  |
| 9  | Female| 35      | White      | Hypertension, lung cancer, CKD | GI symptoms                   | At time of diagnosis          | 3                                  | Petechiae, mucosal bleeding, hemorrhagic ovarian cyst (Grade 3) | Dexamethasone 40 mg (D1–D4) | Complete response | 2                   | Recovery            | 25                  |
| 10 | Female| 60      | African American | Hypertension, diabetes, vitiligo | Cough and SOB                | At time of diagnosis          | 53                                 | No bleeding                  | Methylprednisolone 250 mg (D1–D5) and IVIG (D1–D5) | Complete response | 4                   | Recovery            | 38                  |
| 11 | Male| 63         | White      | Hypertension | No symptoms                  | 30                          | 2                                  | Petechiae, mucosal bleeding, epistaxis (Grade 1) | Dexamethasone 40 mg (D1–D4), IVIG (D1–D2), Eltrombopag (D5–D28) | Complete response then relapse | 6                   | Recovery            | 61                  |

Abbreviations: CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; GI, gastrointestinal; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; SLE, systemic lupus erythematosus; SOB, shortness of breath.
Eltrombopag was used in three (27.3%) patients; it was used in Patient #3 to achieve CR and Patient #11 after relapse. Both patients who did not respond to treatment died, and lack of follow-up limited treatment response evaluation.

4 | DISCUSSION

In our multicenter retrospective study, the incidence rate of ITP secondary to COVID-19 was 0.34%. Most of the cases occurred after the first week of COVID-19 diagnosis or symptoms initiation. Bleeding was observed in 63.6% of the patients. Clinically significant bleeding (WHO Grade 3 or higher) was rare in our cohort. The overall outcome was excellent, and none of the deaths were related to bleeding or ITP. The response rate to standard ITP treatment with corticosteroids and IVIG was 72.8%. The exact mechanism of thrombocytopenia in our patients might be immune-related because other causes of thrombocytopenia including DIC, TTP, and sepsis-induced thrombocytopenia have been excluded. Also, two patients in our cohort were found to have IgM against platelet surface antigens, which may support the immune-mediated mechanism; however, complete immunological panels were not performed for all patients. Our findings are supported by previously reported ITP cases secondary to viral infections. In the study published by Mahevas and colleagues, the same immune-mediated mechanism was suggested to induce ITP in COVID-19 patients after excluding other possible causes. ITP incidence has been estimated to be from 1.6 to 3.9/100,000 person-years in adults. Compared to COVID-19 infection, few case reports of ITP secondary to influenza virus infection were reported and ITP induced by influenza virus infection is infrequent.

Studies have shown that severe COVID-19 patients produce a large number of antibodies after the first week of the disease. This theory can explain the cytokine storm that may complicate the course of the disease. Some patients in our cohort presented with ITP at the same time of COVID-19 diagnosis; however, those patients presented after at least 1 week of symptoms initiation, and COVID-19 diagnosis was delayed until presentation. Three of our patients presented with ITP after 1 month of COVID-19 diagnosis, and this time delay might be explained by a germinal center response with persistent antibodies secretion. One of the patients included in our cohort presented with ITP after 125 days of the initial COVID-19 diagnosis, but the patient’s COVID-19 RT-PCR was positive at the time of ITP diagnosis.

Clinically, patients with ITP may be asymptomatic or can present with bleeding. In a recently published case report, a COVID-19 patient developed thrombocytopenia, petechiae, and epistaxis on day 4 after admission secondary to ITP. In another case series, eight out of 14 (57.1%) COVID-19-induced ITP patients developed bleeding, and only one patient had an intracerebral hemorrhage. In a recent meta-analysis, 45 bleeding events were observed among 45 patients diagnosed with ITP secondary to COVID-19. Cutaneous bleeding and ICH were observed in 22 and four patients, respectively. In our case series, cutaneous bleeding was the most common form of bleeding and only one WHO Grade 3 bleeding event was observed.

ITP treatment consists of systemic steroids and IVIG as the first line. Second-line treatment options may include thrombopoietin receptor agonists (TPRAs). More than 70% of patients respond to conventional therapy. Recent guidelines recommended steroids as a first-line therapy for COVID-19-induced ITP. IVIG is recommended to be used when immediate platelet count elevation is needed. In the meta-analysis published by Bhattachajree and colleagues, IVIG, steroids, and TPRAs were used in 32 (71.1%), 24 (53.3%), and 9 (20%) patients, respectively. CR and response were achieved in 67% and 18% of the patients, and only one patient had relapsed after response. Compared to our case series, CR and response to treatment were achieved in 45.5% and 27.3% of the cases. Relapse after response was detected in one case only.

Our case series has several limitations. First, the study is retrospective in nature. Second, the causal relation between COVID-19 infection and ITP was not clear in three patients who presented with delayed ITP after 30 days of COVID-19 diagnosis, although all other possible causes were excluded. Third, other viral infections were not excluded in most patients because most patients presented before the influenza season in the United States and influenza testing was not done at that time. Also, hepatitis C virus and human immunodeficiency virus infections were not excluded in our study. Fourth, complete exclusion of other possible secondary causes of ITP was not possible and COVID-19 infection was the most likely cause in our study.

In summary, our case series highlights the fact that ITP secondary to COVID-19 can present after the first week of symptoms and even delayed in some cases. Most of our patients had Grade 1–2 bleeding based on the modified WHO bleeding score. Standard treatment with glucocorticoids and IVIG is effective in achieving an excellent response in most cases. The safety of TPRAs is not very well established in COVID-19 patients given the risk of hypercoagulability, and additional studies are needed for a better safety profile.

CONSENT

Cleveland Clinic Committee on Human Research approved the study. Informed consent was obtained.
AUTHORS’ CONTRIBUTIONS
TK, TNG, KM, DA, HD, and AD contributed to the conception and design of study. TK, TNG, KM, and DA screened all medical records, collected the data, and interpreted the data. TK wrote the first draft of the report. All authors contributed to article revision and approved the submitted version.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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