TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Case Series

Management of Immune Thrombocytopenic Patient Associated With COVID-19 Viral Infection: A Case Series

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ABSTRACT

Severe thrombocytopenia is a cause of morbidity and mortality for patients with COVID-19 infection. The common causes of thrombocytopenia in these patients are sepsis, drug-related, disseminated intravascular coagulation (DIC), heparin-associated thrombocytopenia (HIT), and microangiopathic hemolytic anemia (MAHA). Recently, cases of COVID-19 infection-associated immune thrombocytopenic purpura (ITP) have been reported in the literature. Herein, we presented our case series of 10 patients related to COVID-19.

Turk J Int Med 2022;4(2):87-93
DOI: 10.46310/tjim.1009709

Keywords: *COVID-19, hematology, pandemic, thrombocytopenia.*

Introduction

The coronavirus disease emerged in December 2019 in Wuhan city of China. SARS-CoV-2 is a new type of RNA virus, affected more than 21 million people worldwide. The newly discovered coronavirus is a β-coronavirus with crown-enveloped virus particles.[1] The most common symptoms seen in COVID-19 infection are dry cough, fever, fatigue, joint pain and shortness of breath. Uncommon symptoms include diarrhea, headache, palpitations and chest pain. Hematological changes such as lymphopenia and thrombocytopenia are frequently observed in patients with COVID-19.[2] In a study involving 1099 patients, it was shown that 82.1% of the patients had lymphopenia, 36.2% had thrombocytopenia and 33.7% had leukopenia.[3] The platelet count is between 150-450,000 10^3/uL, below 100,000 10^3/uL is called thrombocytopenia. A comprehensive approach is required to diagnose COVID-19 infection-associated associated with COVID-19 infection after excluding several concomitant factors that may cause thrombocytopenia.[3] There are several hypotheses for the mechanism of thrombocytopenia in COVID-19. The first is that the virus infects bone marrow cells, leading to abnormal hematopoiesis. SARS-CoV-2 and HCoV-229E enter bone marrow

Received: October 14, 2021; Accepted: December 19, 2021; Published Online: January 29, 2022

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cells and platelets via CD13 receptors and induce bone marrow growth inhibition and apoptosis, leading to abnormal hematopoiesis and thrombocytopenia.[4] The second is secondary hemophagocytic lymphohistiocytosis (HLH) and results from excessive proliferation and activation of the mononuclear macrophage system, in which inflammatory cytokines are released and large numbers of blood cells are engulfed. HLH has a rapid response with high mortality and causes cytopenia.[5] Another mechanism is the COVID-19 virus causes increased levels of autoantibodies and immune complexes, which can cause specific destruction of platelets by immune cells. One study reported that immune-mediated thrombocytopenia phenomenon is common in HIV-1 infected patients.[6] After excluding all causes of thrombocytopenia, ITP should be considered in the patient. Primary ITP is an acquired autoimmune disorder characterized by isolated thrombocytopenia caused by increased platelet destruction and impaired platelet production.[7] There is no definitive diagnostic test for ITP; therefore, primary ITP remains a diagnosis of exclusion after ruling out any underlying and/or initiating causes of the thrombocytopenia.[8] ITP is classified based on duration into newly diagnosed, persistent (3-<12 months), and chronic (≥12 months). Since the beginning of the pandemic, we have started to see case articles in the literature. According to the 2019 guideline of the American hematology community, a platelet count of less than 30,000 10^3/uL supports the diagnosis of ITP.[9] They recommend corticosteroids as first-line therapy for adult-onset ITP. 2020 recommendations of the UK hematology community: The standard first-line therapy for the treatment of acute ITP diagnosed for the first time or relapsed is prednisolone given at a dose of 1 mg/kg (maximum 80 mg) for 2 weeks and then stopped.[7] There is little data to show whether corticosteroids pose a higher risk of worsening symptoms after being infected with the COVID-19 virus. However, the first treatment option under WHO's guidance is alternative treatments rather than corticosteroids. The use of thrombopoietin receptor agonists (TPO-RAs) may be the preferred option first. Since the onset of the effect of TPO-RAs may take 7-14 days and in cases where urgent platelet elevation is required, intravenous immunoglobulin, CD20 inhibitor Rituximab, and thrombocyte suspensions in the presence of hemorrhage are recommended. Although patients with chronic ITP are not included in the high-risk group for COVID-19 infection, it recommends that patients with splenectomy be up-to-date with encapsulated bacteria vaccines.[9]

Material and Methods

Among the patients with thrombocytopenia (<30,000 10^3/uL) who were positive for the COVID-19 PCR test (polymerase chain reaction) from the declaration of the COVID-19 Pandemic (March 2020) to the present (August 2021), those with ITP diagnosis were included in the study. Viral markers (EBV, CMV, hepatitis, HIV etc.), tumor markers (CEA, CA-19.9, AFP, PSA etc.), autoimmune antibodies (ANA, anti-dsDNA, antiphospholipid, c3, c4 etc.) involved in the etiology of thrombocytopenia were sent from all patients. Peripheral blood smears were evaluated by internal medicine specialists and reported. Patients with positive tests other than PCR positivity were excluded from the study. Trauma history, pregnancy status, cancer patients, patients under 18 years of age, patients receiving anticoagulant, antiaggregant therapy, and chronic ITP patients were excluded from the study. Patients who developed thrombocytopenia after hospitalization were not included in the study, and these patients were excluded from the study because it was thought that drug-related thrombocytopenia could develop in the foreground. Patients whose chest tomography was compatible with COVID-19 viral pneumonia and whose PCR test was negative were excluded from the study. A total of 10 patients who met the criteria were reached. Our study involving human participation is in line with the 1964 Declaration of Helsinki and its subsequent amendments. The study is a case series and retrospective. According to the 2017 TUBA-clinical research phase studies and ethics committees workshop report, ethics committee approval is not required for case series included in retrospective studies. Patients who responded to the treatment were followed up in the internal medicine outpatient clinic for 12 months.

Table 1. The characteristics of the patients.

Patient	Age	Gender	Symptoms	Time/day elapsed	Initial platelet count (10^3/uL)	Comorbid disease	Treatment	Last platelet count (10^3/uL)	Prognosis	Treatment response day
1	79	Female	Asymptomatic	9	1,000	Diabetes, hypertension	Methyl-prednisolone	54,000	Exitus	-
2	84	Male	Melena	14	17,000	Dementia	Methyl-prednisolone	86,000	Exitus	-
3	68	Female	Petechia	8	4,000	Diabetes	Prednisolone	239,000	Complete response	4
4	39	Female	Petechia	24	22,000	No	Prednisolone	312,000	Complete response	5
5	55	Male	Hematuria	10	29,000	Hypothyroidism	Prednisolone	156,000	Complete response	6
6	71	Male	Hemoptysis	6	8,000	Hypertension, LVH	Methyl-prednisolone	27,000	Exitus	-
7	65	Female	Asymptomatic	20	33,000	Diabetes, hypothyroidism	Prednisolone	362,000	Complete response	3
8	33	Female	Asymptomatic	15	19,000	Vertigo	Prednisolone	263,000	Complete response	10
9	63	Male	Petechia	6	36,000	Hypertension	Prednisolone	190,000	Complete response	3
10	44	Female	Petechia	7	11,000	Diabetes, hypertension	Prednisolone	274,000	Complete response	5

Results

A total of 10 patients who met the criteria were reached among the patients who applied to our hospital since the beginning of the pandemic *(Table 1)*. 60% of the patients were female and 40% were male. The mean age of the patients was 60.1. The mean time from the onset of symptoms to the day when thrombocytopenia was detected was 11.9 days. 30% of the patients died while being followed up in intensive care units for COVID-19. Complete response was obtained from 70% of the patients. Hemorrhage was observed in 60% of the patients' physical examination findings. Among these, petechiae with 40% were the most common, followed by asymptomatic 30%, melena 10%, hemoptysis 10%, and hematuria 10%. In 2 patients (20%) with complete response, the diagnosis was made at the time of admission to the internal medicine outpatient clinic after the end of the COVID-19 treatment. The COVID-19 treatment process of these 2 patients did not require hospitalization, there was no lung involvement, and they survived the disease with a mild course. Other patients (80%) had hospitalization. While 3 patients were followed up in 30% COVID-19 intensive care units, 5 50% patients were diagnosed with COVID-19 during hospitalization. Corticosteroid treatment doses were adjusted during discharge for patients who were cured for ITP, and internal diseases polyclinic control was recommended 7 days after discharge. After 7 days, they came to the internal diseases outpatient clinic controls, they were followed up for about 12 months and no recurrence was observed. Organomegaly was not observed in any of the patients (100%). Other patients (80%) had hospitalization. One patient (10%) with melena developed a need for erythrocyte suspension, other patients did not have life-threatening hemorrhage. Three patients with exitus COVID-19 were followed up in the intensive care unit, and their platelet counts (mean 8,600 10^3/uL) were found to be very low. Since the final platelet counts of the patients with exitus did not exceed 100,000 10^3/uL, response evaluation could not be performed. Initially, no platelet clumps or giant platelets were seen in the peripheral blood smears of the patients. No schistocyte with signs of hemolysis was observed, and no atypical cells were observed *(Figure 1)*. All peripheral blood smears were examined and reported by internal medicine specialists. Daily hemogram and peripheral blood smears were followed up from the patients who were hospitalized in the COVID-19 service and intensive care units and were evaluated and

followed up daily by internal medicine specialists.

IVIG was not given to any of the patients. Out of 3 patients (30%) who died, 2 patients (20%) died due to complications related to acute renal failure, and 1 patient (10%) died due to multiorgan failure. The initial platelet counts of patients with exitus at hospital admission were observed to be very low, with an average of 8,600 10^3/uL. Cure was achieved in 7 patients (70%). The platelet count detected at the baseline was the lowest 1,000 10^3/uL, the highest 36,000 10^3/uL, and the mean 18,000 10^3/uL.

The mean platelet counts after treatment were 19,500 10^3/uL. The most common comorbid diseases were hypertension with 30%, diabetes mellitus 23%, hypothyroidism 15%, dementia 7.5%, vertigo 7.5%, cerebrovascular disease 7.5%. 30% of the patients were vaccinated. The mean time passed after vaccination was 2 months, and the rate of unvaccinated patients was 70%. However, it was observed that all unvaccinated patients were diagnosed before the vaccination program was started. It was observed that 5 patients (50%) were given prednisolone, 3 patients (30%) methylprednisolone and 2 (20%) dexamethasone treatments. No elevation was observed in hemolysis markers (LDH, indirect bilirubin, reticulocyte count etc.) and coagulation markers (INR, prothrombin time, D-dimer etc.) of the patients. Since hemorrhage was observed in 70% of the patients, platelet suspension replacement was performed. When the first and last platelet counts were compared, it was observed that the platelet counts of all patients (100%) increased, and no recurrence was observed in the follow-ups *(Table 2)*.

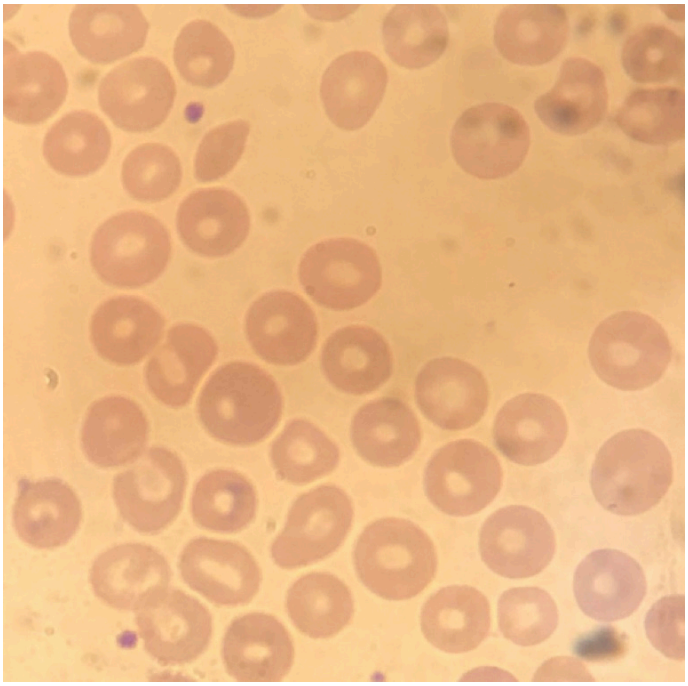

Figure 1. Peripheral smear image of a patient followed for ITP.

Discussion

ITP is a risky condition in the presence of hemorrhage because of its high mortality. In the course of COVID-19 infection, autoimmune diseases such as antiphospholipid syndrome and Guillain-Barré, hematologically COVID-19-related thrombocytopenias, autoimmune hemolytic anemia and immune thrombocytopenias have been described.[10] Our patients were included in the study after excluding other viral agents associated with secondary ITP, drug-related, autoimmune diseases and malignant diseases. Viral infections were excluded because the viral markers sent to the patients were negative. It is thought that viruses cause a decrease in platelet production by infecting megakaryocytes in the bone marrow in the mechanism of thrombocytopenia. This results in apoptosis of megakaryocytes, decreased maturation of megakaryocytes, or decreased expression of the thrombopoietin receptor. Besides, viruses can infect hematopoietic stem cells and cause a reduction of progenitor cells and the induction of growth-deficient megakaryocyte colony forming units due to unregulated production of cytokines by infected cells in the bone marrow. Another suggestion is platelet destruction, where viruses interact directly with platelets or recognize immune complexes of IgGs and viral antigens.[11] Absence of anemia, absence of signs of hemolysis, absence of schistocyte in peripheral blood smear, only low platelet count enabled us to avoid both micro and macroangiopathic hemolytic anemia in the diagnosis. Absence of alarm symptoms (weight loss, night sweats etc.), no mass or organomegaly detected on imaging, and negative tumor markers have led us to stay away from malignant diseases. In

Table 2. Patients' findings.

Prognosis	70% recovery, 30% died
Physical examination signs	40% petechia, 30% asymptomatic, 10% melena, 10% hemoptysis, 10% hematuria
Peripheral blood smear findings	In all of the patients, 100% thrombocyte clusters, schistocytes, and atypical cells were not observed
Comorbid disease	30% hypertension, 23% diabetes mellitus, 1.5% hypothyroidism, 7.5% dementia, 7.5% vertigo, 7.5% cerebrovascular disease
Vaccination rate	30%
Treatments	50% prednisolone, 30% methylprednisolone, 20% dexamethasone

drug-related thrombocytopenia, an increase in thrombocyte count following discontinuation of the drug causes the diagnosis to go away from ITP. Low molecular weight heparin used in thromboembolism prophylaxis, a common complication of COVID-19, causes HIT. Also, some antibiotics used to prevent the development of secondary bacterial infection (ceftriaxone, linezolid, vancomycin etc.) cause drug-related thrombocytopenia. Since there is an autoimmune mechanism in ITP, elevation is not an expected situation. Thrombocytopenia, leukopenia, and hemolytic anemia may develop in cases of hypersplenism such as liver cirrhosis, infiltrative diseases (Gaucher, lymphocytic histiocytosis, infectious mononucleosis etc.), and malignant diseases (leukemia, lymphoma, malignant tumor metastasis etc.). The fact that our patients had a low hematologic series and the absence of hepatosplenomegaly enabled us to avoid the diagnosis of hypersplenism. Peripheral blood smear examination was sufficient to differentiate pseudothrombocytopenia. In summary, after anamnesis, physical examination, and laboratory examinations, no other cause could be found to explain ITP, it was decided that autoimmune thrombocytopenic purpura was present, and steroid treatment was started and followed up. Response to steroids helped support the diagnosis, except in patients with other complications. In order to be called a complete response in the treatment of ITP, the platelet count should double since the start of the treatment or the platelet count should be above 100,000 and the clinical findings should improve.2 According to the American Society of Hematology Association, in the treatment of persistent ITP or chronic ITP, splenectomy, IVIG treatment including rituximab or thrombopoietin receptor antagonist is not recommended.9 On the other hand, we mentioned that the British hematology community recommends IVIG and thrombopoietin receptor antibody (eltrombopag) instead of corticosteroids. Since eltrombopag will take effect in 7-14 days, it should not be preferred in case of emergency bleeding. IVIG treatment, on the other hand, is expensive and has side effects such as fever, arrhythmia, kidney failure, and thrombosis. Since D-dimer elevation and a predisposition to thrombosis are in question in COVID-19 patients, IVIG was not given in the treatment. High-dose corticosteroid therapy was administered to 3 patients in the intensive care unit because they were in the MAS (macrophage activation syndrome). Anti-D treatment, on the other hand, was not preferred in high-risk patients since the response started on the 5th day.

There are various opinions about whether bone marrow aspiration should be performed in patients with ITP. The American Society of Hematology recommended bone marrow aspiration only if there is persistent thrombocytopenia and there is no response to treatment.[12] Since there was no patient among our cases who could not respond to steroid treatment, there was no need for bone marrow aspiration. Recurrence has been shown in patients with ANA positivity or in ITP cases accompanying the course of other autoimmune diseases.[13] The reason for the absence of recurrence in our cases may be considered to be negative autoimmune antibodies.

Conclusions

As clinicians, in suspected cases, secondary causes should be ruled out quickly, ITP diagnosis should be made and steroid treatment should be started. Mostly, cases respond to steroid treatment, but there are options such as IVIG, immunosuppressants, splenectomy in cases that do not respond. In the literature, patients who need advanced treatment in cases of COVID-19-related ITP have been stated. In our study, we think that we contributed to the literature because there was no need for further treatment.

Conflict of interest

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Study Conception, Data Collection and/or Processing, Materials, Literature Review, Manuscript Preparation held by DI.

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