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COVID-19-Associated Immune Thrombocytopenic Purpura in a Hemodialysis Patient

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Background: Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection has been a global threat since the end of 2019. Although the main clinical manifestation of coronavirus disease 2019 (COVID-19) is respiratory, its range of clinical manifestation is extensive and may include various systems, including hematological disorders, such as lymphopenia, thrombotic events, thrombocytopenia and immune thrombocytopenic purpura (ITP). The present case was the first one that aimed to raise awareness of ITP induced by COVID-19 in patients undergoing maintenance hemodialysis.

Case Presentation: This is the case of a 75-year-old Asian woman who was diagnosed COVID-19 positive 15 days before attending our Emergency Department on January 19th, 2023, with a three-day history of severe bleeding symptoms, including gastrointestinal, mucosal bleeding, epistaxis, and the platelet count of 5×10^9/L. She suffered from end-stage kidney disease due to autosomal dominant polycystic kidney disease and has received thrice-weekly maintenance hemodialysis (MHD) since 2012. Platelet count recovery was observed after 45 days of combined treatment with corticosteroids, intravenous immunoglobulin, thrombopoietin receptor agonists, and rituximab. The count of platelets rose to 180×10^9/L after four dosages of Rituximab.

Conclusion: In brief, SARS-CoV-2 infection might trigger the onset of ITP. To our knowledge, this is the first case with severe and refractory ITP secondary to COVID-19 in MHD patients and no guidelines were able to be referred on the therapy. Nephrologists must be concerned with clinical characteristics, diagnostic flowcharts, and therapy for SARS-CoV-2-induced ITP.

Keywords: COVID-19, SARS-CoV-2, immune thrombocytopenic purpura, bleeding, platelet

Introduction

Thrombocytopenia is a risk factor for increased morbidity and mortality in patients with the new severe SARS-CoV-2 infection (COVID-19 infection) since the end of 2019.[1] Thrombocytopenia in COVID-19 patients may be caused by viral infections, sepsis, disseminated intravascular coagulation (DIC), or drugs.[2] Recently, several cases reported that (ITP) may be associated with COVID-19 infection and the mechanism may include changes in the bone marrow environment, changes in megakaryocytic differentiation, and maturation resulting from infection.[3,4] Additionally, the correlation mechanism between SARS-CoV-2 and ITP may involve multiple pathways, including direct viral infection of megakaryocytes, which impairs platelet production, and immune-mediated mechanisms where autoantibodies target platelets, leading to their destruction.[1] SARS-CoV-2 infection can also result in an inflammatory environment, with elevated cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) contributing to both platelet destruction and inhibition of megakaryocyte maturation.[5]

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Although the emergence of ITP in patients with COVID-19 is not a novel subject, we firstly present a patient undergoing maintenance hemodialysis (MHD) with COVID-19 infection, with a nadir platelet count of 1×10^9/L and complete response to corticosteroids, intravenous immunoglobulin (IVIG), thrombopoietin receptor agonists (TPO-RAs) and rituximab. Hemodialysis patients are already immunocompromised, which further complicates the management of ITP, as they are at increased risk for both bleeding and thrombotic events. This immune dysregulation, coupled with the inflammatory response to COVID-19, creates unique challenges for ITP management in this population.

Case Description

A 75-year-old Asian woman, who was diagnosed with SARS-CoV-2 positive 15 days before, was admitted to our Emergency Department on January 19th, 2023, with a three-day history of severe bleeding symptoms, including gastrointestinal, mucosal bleeding, and epistaxis. Written informed consent was obtained from the patient, and the study was approved by the institutional review board. She suffered from end-stage kidney disease (ESRD) due to autosomal dominant polycystic kidney disease (ADPKD) and has received thrice-weekly MHD since 2012. The patient had been on long-term hemodialysis and was regularly taking valsartan to control blood pressure. The patient was diagnosed with a femoral neck fracture due to a fall on November 18th, 2021, and the arteriovenous fistula thrombosis occurred on December 5th, 2021. A central venous catheter was placed for subsequent hemodialysis, and the arteriovenous fistula was abandoned. The patient underwent cerebral imaging, which revealed no abnormalities. One week before admission, she received thrombolytic therapy with urokinase for central venous catheter dysfunction, but this was not the first time she had used urokinase. Laboratory evaluation revealed a white blood cell (WBC) of 3×10^9/L, lymphocyte% 10.8%, hemoglobin (Hb) level of 36 g/L, and platelet count of 3×10^9/L. And the RT-PCR test for COVID-19 was negative. Chest radiography revealed no pathological findings. She was treated with a transfusion of red blood cells, platelet units, intravenous immunoglobulin, human recombinant thrombopoietin (rhTPO), and TPO-RAs for several days, but there was no response to the platelet, then she was transferred to our department on February 10th, 2023.

On physical examination, she was pale and afebrile and showed no difficulty breathing in room air with a peripheral oxygen saturation of 95%. Examination of the skin and mucosa showed extensive ecchymosis, especially on both upper extremities. Laboratory evaluation revealed a severe thrombocytopenia of 2×10^9/L, hemoglobin value of Hb 81 g/L, and reticulocytosis of 9.02%, WBC count of 2.8×10^9/L, and a CRP of 9.14 mg/L. Coagulation tests showed D-Dimer was elevated to 2.43 μg/mL and fibrinogen levels were normal. Biochemical tests also showed the following were abnormal: lactate dehydrogenase (LDH) 280 U/L, total bilirubin 35.6 umol/L, direct bilirubin 9.5 umol/L and creatinine 254 umol/L (Table 1). The viral hepatitis panel and rheumatological markers did not reveal any causes of thrombocytopenia. The fecal occult blood test still showed a weak positive. The direct and indirect Coombs tests were both negative. On a peripheral blood smear, there were no schistocytes visible and the platelet count was scarce. ADAMTS 13 activity was 19.1% (68–131). However, platelet autoantibodies and ADAMTS 13 antibodies were negative. Due to the long-term exposure of low molecular weight heparin and unfractionated heparin in hemodialysis sessions before the bleeding symptoms, the heparin-induced thrombocytopenia (HIT) was screened. Anti-platelet factor 4 (PF-4)/heparin antibodies or functional assays were negative. Bone marrow biopsy was performed after the platelet count rose and showed active thrombopoiesis. All relevant medications (valsartan, urokinase, erythropoietin, calcitriol) were checked to rule out drug-induced thrombocytopenia.

Since severe thrombocytopenia carried a high risk of fatal bleeding in hemodialysis, although the exact mechanism of thrombocytopenia remained unclear, we speculated it might be immune-related because other causes of thrombocytopenia including DIC, thrombotic thrombocytopenic purpura with no hemolytic anemia, HIT and sepsis-induced thrombocytopenia had been excluded. So the patient was treated with a low dose of methylprednisolone (40 mg daily), IVIG (20 g daily for 5 days), and platelet transfusion (1 unit daily for 5 days) on February 10th, along with other protection strategies, such as PPI, albumin, erythropoietin, folic acid, and VitB12 supplement (Table 2). We stopped the transfusion of platelet units because of no bleeding events and the stable hemoglobin level. Nafamostat mesylate 20mg/h was chosen as the anticoagulant to prevent additional consumption of the platelet during hemodialysis. However, no response of platelet count was observed. By the 8th day after admission to our department, her platelet count was still only 5×10^9/L, and her Hb level rose to 96 g/L. Since February 22nd, the dexamethasone (20 mg daily for 3 days) and the second-line

Table 1 Laboratory Changes During This Case

Laboratory Data	Normal Range	Day1	Day23	Day53	Day61	Day65	Day69
WBC	3.5–9.5×10^9/L	3	2.8	3.8	10.3	9	6.4
Neutrophils	40–75%	73.7	63.8	70	86.8	88.2	86
Lymphocytes	20–50%	10.8	17.4	17	18.6	16.8	18.7
RBC	3.8–5.1×10^{12}/L	1.26	2.55	3.3	3.38	3.34	3.59
Hemoglobin	115–150g/L	36	81	104	100	97	102
Platelet	125–350×10^9/L	3	2	57	180	221	304
CRP	0–10mg/L	13.14	9.14	22.42	51.19	62.41	40
Total bilirubin	3.4–17.1μmol/L	18.4	35.6	16.2	21	18.6	17.2
Direct bilirubin	0–3.4μmol/L	0	9.5	3.3	4.2	5	5.4
AST	7–40U/L	6	2	9	9	4	2
ALT	13–36U/L	13	19	11	11	9	14
LDH	120–250U/L	290	280	203	211	184	180
BUN	2.6–8.8mmol/L	32.3	6.6	23.8	21.6	16.3	20.8
Serum creatinine	41–81μmol/L	646	254	363	372	386	378
Fibrinogen	2–4.5g/L	3.08	2.09	3.55	2.89	1.04	2.89
D-dimers	0–1.0μg/mL	3.7	3.42	2.39	1.9	4.83	1.9
FDP	<5.0mg/L	12	8.6	8.8	6.2	14.3	6.2
PCT	<0.5ng/mL	-	0.433	0.584	-	1.36	1.18
IL-6	<7pg/mL	-	59.25	55.4	-	400.5	101.6

Abbreviations: WBC, white blood cells; RBC, red blood cells; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; FDP, fibrin degradation product; PCT, procalcitonin.

Table 2 Medication History and Treatment Strategies

Medication/Treatment	Indication	Outcome
Valsartan	Hypertension control	Stable blood pressure
Urokinase	Thrombolytic therapy (AVF)	No adverse effects; used multiple times
Methylprednisolone	Initial ITP treatment	No significant improvement in platelet count
IVIG	Second-line therapy for ITP	No response after 5 days of treatment
Platelet transfusions	Bleeding symptoms	No sustained improvement in platelet count
Eltrombopag	TPO-RA, second-line therapy	Platelet count started to rise
Rituximab	Refractory ITP treatment	Significant increase in platelets after 4 doses

treatment of eltrombopag (50 mg daily for 28 days), rhTPO (15000U for 30 days), and Rituximab (100 mg once weekly for 4 doses) were used for treatment. The count of platelets rose to 180×10^9/L after four dosages of Rituximab until March 20th and reached 304×10^9/L on March 28th (Figure 1). The patient was discharged after her platelet count normalized, and she exhibited no signs of bleeding. She continues to visit our dialysis center three times a week, where her platelet count is regularly monitored as part of her follow-up care. The excellent prognosis after immunosuppressive therapy was observed until 1.5 months later upon admission to our department, which confirmed the immune mechanism mediated thrombocytopenia.

Discussion

To our knowledge, this is the first case with severe and refractory ITP secondary to COVID-19 in MHD patients and no guidelines were able to be referred on the therapy. ITP is an immune-mediated acquired hemorrhagic disorder with a low platelet count characterized by increased peripheral platelet destruction and insufficient platelet production.[6] ITP incidence has been estimated to be from 1.6–3.9/100,000 person-years in adults,[1] and the incidence of ITP in COVID-19 patients is estimated to be rarer. While most cases are mild, severe thrombocytopenia can occur in 10–20% of cases, with a higher risk of mortality in patients with comorbidities, such as ESRD or those undergoing hemodialysis.[7] Thrombocytopenia in COVID-19 can be attributed to various mechanisms, including direct viral infection of bone

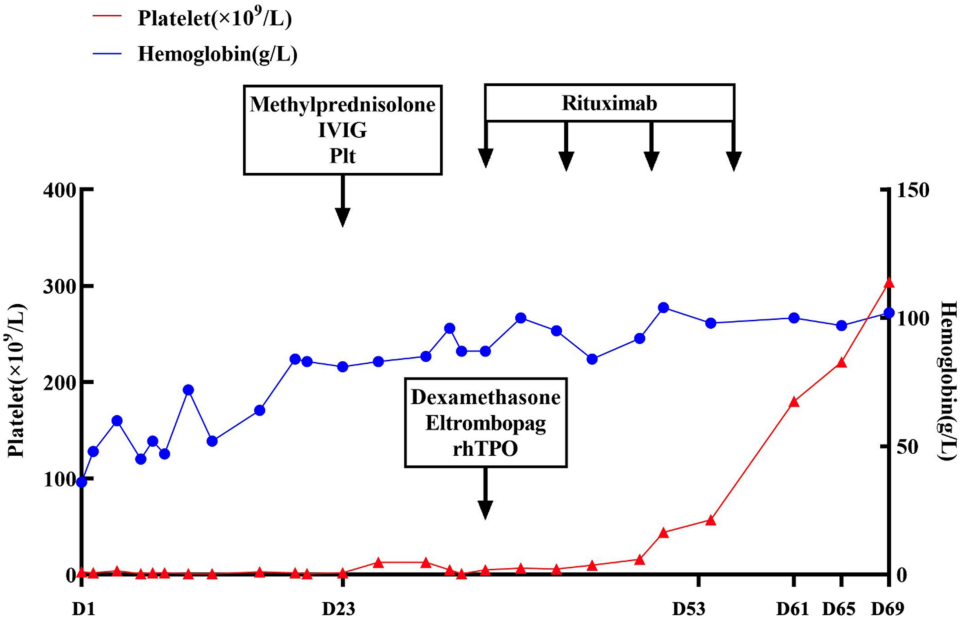

Figure 1 The trends of the patient's platelet and hemoglobin count.

marrow megakaryocytes, the cells responsible for platelet production. The inflammatory milieu, characterized by elevated levels of cytokines such as IL-6 and TNF-α can contribute to platelet destruction and impaired megakaryocyte function.[8] For most patients, the mechanism is mediated by the antiplatelet antibodies secreted by plasma cells linked to the platelet surface glycoproteins GPIb/IX and GPIIb/IIIa, leading to the clearance of platelets. Moreover, antibodies linked to megakaryocytes can inhibit their maturation and can trigger their destruction. However, up to 30–40% of ITP patients show negative antibodies. So in most cases, it is an exclusive diagnosis based on clinical judgment and independent of antibody status. The proposed causes include viral infections, changes in the bone marrow environment, changes in megakaryocytic differentiation and maturation, abnormal T cells, imbalance in cytokine secretion, and immune dysregulation.[9]

Thorough evaluation is crucial to differentiate COVID-19-induced ITP from idiopathic ITP. This may involve ruling out other causes of thrombocytopenia, such as drug-induced, sepsis-associated, or DIC-related thrombocytopenia. ITP has emerged as a complication after COVID-19 vaccination and infection. The incidence of ITP secondary to COVID-19 infection is more common among males (54.8%) and it is more prevalent among the elderly with a median age of 63 years.[2] COVID-19-induced ITP occurred within 2–3 weeks with an estimated mean 18.1±21 days after SARS-CoV-2 infection and in most cases presented with asymptomatic mild and moderate thrombocytopenia. Severe and persistent thrombocytopenia, like in our case, was seldom reported. The possible thrombocytopenia pathogenic mechanisms such as molecular mimicry, cryptic antigen expression, or epitope spreading depend on the phase of COVID-19.[10]

Usually, the first-line therapy for ITP treatment aims to get a rapid response and increase the platelet count, especially for those patients with active bleeding. Corticosteroids remain the initial treatment and prednisone (0.5–2.0 mg/kg per day) or dexamethasone (40 mg per day for 4 days) are preferred, which can reduce the inflammation and autoimmunity. IVIG is another first-line treatment option for patients at risk of serious bleeding since it can provide passive immunity and modulate the immune system by neutralizing autoantibodies and inhibiting complement deposition. IVIG should be administrated at a dose of 400 mg/Kg/day for 5 days or 1 g/kg for 1–3 days, which could be combined with or without corticosteroids. Rituximab was used for ITP for the first time in 2001. The rationale for its use in refractory cases by explaining its mechanism of depleting CD20-positive B cells, which are implicated in the pathogenesis of autoantibody-mediated conditions like ITP.[11] The dosage of rituximab of 375 mg/m^2 and lower 100 mg were both reported in several studies.[12] TPO-RAs, whose effectiveness in stimulating platelet production in the bone marrow is highlighted, are particularly pertinent in cases where thrombocytopenia persists despite control of the

underlying disease process. Leading to a sustained increase in platelet count 1–2 weeks after treatment. However, it also increases the risk of venous thromboembolism and hepatotoxicity, recommendations suggest using TPO-RAs as a second-line treatment.[13] RhTPO is also used in China and has shown efficiency in ITP. Moreover, hemodialysis patients are at increased risk of infections and complications due to their immunocompromised status. Monitoring for complications, including infection and coagulation function disorders like hemorrhage, is crucial in this population.[7]

The management of COVID-19-associated ITP in hemodialysis patients presents unique challenges. These patients are more vulnerable to infections and have an increased thrombotic risk due to both the nature of ESRD and the treatments used for ITP, such as corticosteroids and TPO receptor agonists. The uniqueness of this case lies in the difficulty of managing refractory ITP in a patient with ESRD on long-term hemodialysis, in the context of SARS-CoV-2 infection, without the usual COVID-19 respiratory complications. The absence of established guidelines for treating ITP in this specific population adds to the complexity.

This case report has several limitations. First, although drug-induced thrombocytopenia was considered and evaluated, we cannot completely exclude the possibility of unreported medications or supplements contributing to thrombocytopenia. Second, the patient's comorbid conditions, apart from ADPKD and ESRD, were not thoroughly investigated due to the urgency of her presentation, which could have influenced the clinical outcome. Third, given the rarity of COVID-19-induced ITP in MHD patients, the generalizability of this case may be limited. Further studies and case reports are necessary to better understand the pathophysiological mechanisms and optimal treatment strategies for ITP in this specific population. Finally, the absence of established guidelines for the management of COVID-19-associated ITP in MHD patients limited our ability to follow standardized treatment protocols, resulting in a reliance on clinical judgment and available therapeutic options.

In brief, SARS-CoV-2 infection might trigger the onset of ITP. Thrombocytopenia in the context of COVID-19 presents unique challenges, especially in vulnerable populations like hemodialysis patients. The development of ITP following COVID-19, although rare, should be considered in cases of persistent thrombocytopenia. Timely diagnosis, appropriate immunosuppressive therapy, and close monitoring are essential for achieving optimal outcomes in these patients. Further research is needed to elucidate the pathophysiological mechanisms underlying COVID-19-associated thrombocytopenia and its potential role in triggering immune-mediated disorders like ITP. The SARS-CoV-2 Omicron variant is still prevalent in hemodialysis populations with poor prognosis worldwide. Nephrologists must be concerned with clinical characteristics, diagnostic flowcharts, and therapy for SARS-CoV-2-induced ITP.

Abbreviations

WBC, white blood cells; RBC, red blood cells; Ne, neutrophils; Ly, lymphocytes; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; FDP, fibrin degradation product; PCT, procalcitonin; ITP, immune thrombocytopenia; MHD, maintenance hemodialysis; IVIG, intravenous immunoglobulin; TPO-RAs, thrombopoietin receptor agonists; ESRD, end-stage kidney disease; HIT, heparin-induced thrombocytopenia; ADPKD, autosomal dominant polycystic kidney disease, DIC, disseminated intravascular coagulation.

Data Sharing Statement

All data collected from the patient were obtained from Changzheng Hospital and were available in this paper.

Ethics Statement

The patient received all information regarding this case report. Written informed consent for publication in Journal of Blood Medicine was obtained from the patient.

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Disclosure

The authors declare that they have no competing interests.

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