INTRODUCTION

Immune-mediated thrombocytopenia (ITP) is an autoimmune condition characterized by low platelet counts and wide range of clinical manifestations from asymptomatic presentation to major bleeding manifestations. Vaccine-mediated secondary ITP is rare and is associated with influenza, measles mumps rubella (MMR), and hepatitis A and B vaccination. Most patients respond to steroids and intravenous immunoglobulin (IVIG).1 We hereby report a case of a 26-year-old woman with severe refractory ITP who presented with multiple active bleeding sites leading to a significant drop in hemoglobin post second dose of mRNA-1273 SARS-CoV-2 vaccine. She was refractory to treatment with steroids and IVIG and was eventually treated with combination of romiplostim and mycophenolate mofetil (MMF) with which her counts improved dramatically.

CASE DISCUSSION

A 25-year-old Caucasian woman with no significant past medical history except for well-controlled bronchial asthma presented to the hospital with two-day history of worsening petechiae that initially started on her face and lower extremities and eventually spread to her back, chest, abdomen, and upper extremities. She also complained of intermittent epistaxis. Vital signs on initial presentation including blood pressure, heart rate, and oxygen saturation were normal. Physical examination revealed extensive bruising over her back, chest, and extremities along with scattered petechiae all over the body. Laboratory findings on presentation included WBC of $11 \times 10^9/L$, hemoglobin (Hb) of 11 g/dl, and severe thrombocytopenia with a platelet count of $1 \times 10^9/L$. Prothrombin time (PT/INR) activated partial thromboplastin time (aPTT), fibrinogen, lactate dehydrogenase (LDH), absolute reticulocyte count, and haptoglobin levels were within normal limits. Peripheral blood smear showed profound thrombocytopenia with no evidence of schistocytes. RT-PCR testing for SARS-CoV-2 infection was negative. Autoimmune and infectious workup including antinuclear antibody (ANA), coombs testing, HIV ELISA, and serology for hepatitis B and C were negative. Ultrasound of the abdomen did not show evidence of splenomegaly or liver parenchymal changes.
Her most recent laboratory testing including Hb and platelet count from three months ago during routine primary care visit, was within normal limits. She neither reported personal or family history of bleeding disorders nor had required blood transfusions prior to this presentation. 26 days prior to this presentation, she had received her second dose of mRNA-1273 SARS-CoV-2 vaccine.

Given her clinical presentation, negative infectious and autoimmune workup, normal hemolysis and coagulation studies along with absence of other identifiable underlying etiology, she was diagnosed with ITP and was initiated on dexamethasone 40 mg daily for four days along with IVIG 1 g/kg for two days. She continued to have clinical worsening during the second and third day of hospitalization and developed multiple bleeding sites including gross hematuria, hematochezia, and subconjunctival hemorrhage. Her hemoglobin dropped from 11 g/dl on presentation to 6.4 g/dl. She was initiated on tranexamic acid for bleeding control and supportive care with platelet transfusions. Her platelet counts continued to remain low (5 × 10⁹/L) despite receiving 4 days of dexamethasone, 2 days of IVIG, and platelet transfusion support. She continued to have intermittent epistaxis; however, hematuria and rectal bleeding started improving with tranexamic acid initiation.

As there was no improvement in platelet counts with IVIG and dexamethasone, on day 7, she was initiated on MMF 1 g twice daily and romiplostim 1 mcg/kg weekly. On day 12, her platelet counts for the first time improved to 13 × 10⁹/L. Hb remained stable around 11 g/dl. She was discharged after receiving second dose of romiplostim 3 mcg/kg on day 14. During her first outpatient visit on day 21, her platelet counts improved to 140 × 10⁹/L. She went on to receive third dose of romiplostim at 3 mcg/kg. She had no evidence of active bleeding. During fourth week follow-up, platelet count recovered to 268 × 10⁹/L and MMF was tapered down to 500 mg twice daily and romiplostim to 2 mcg/kg. By fifth-week, her platelet counts continued to improve to 324 × 10⁹/L and MMF was tapered to 250 mg twice daily and romiplostim to 1 mcg/kg. She continued to have normal and stable platelet counts, and eventually, MMF and romiplostim were discontinued at her sixth-week follow-up visit. She continued follow-up in the hematology clinic for 3 months from discharge from the hospital after which she was advised to resume care with her primary care physician.

3 | DISCUSSION

ITP is an autoimmune entity characterized by autoantibodies directed against platelet antigens leading to platelet destruction and thrombocytopenia. Clinical manifestations range from asymptomatic presentation, spontaneous petechiae and purpura, mucocutaneous hemorrhage to fatal complications such as gastrointestinal bleeding or intracranial hemorrhage, which usually occur when platelet count is below 10 × 10⁹/L.²

Vaccination as an etiology for secondary ITP was previously reported with influenza, hepatitis A and B, measles, MMR, and diphtheria tetanus acellular pertussis (DTaP) vaccines. It is hypothesized that pathogenesis of ITP is mainly secondary to molecular mimicry, a phenomenon in which host antigens are recognized as antigens of immunization, provoking the development of autoantibodies. These antibody-coated platelets may undergo reticuloendothelial phagocytosis resulting in reduced platelet survival. It is also proposed that vaccine-associated autoimmunity can stem not only from antigen-mediated responses but also contributed by other constituents of vaccine such as adjuvants, preservatives, or diluents.¹,³

Lee et al. described 20 patients who developed thrombocytopenia after receiving COVID vaccination with either mRNA-1273 or Pfizer-BioNTech BNT16B2b2 mRNA SARS-CoV-2 vaccine. Sixteen of these patients did not report history of thrombocytopenia prior to their vaccination.⁴ Onset of symptoms from the date of vaccination ranged from 1 to 23 days.⁴ In the other three individually published case reports, ITP developed 12 h to 5 days post Pfizer-BioNTech BNT16B2b2 mRNA SARS-CoV-2 vaccine in patients who previously had a normal platelet count.⁵⁻⁷ Similarly, our patient had normal platelet counts prior to this presentation. ITP developed on day 26 after the second vaccine was given, which differs from previously reported cases and, so far, is the most “delayed” onset reported in the literature. It is not clear how the immunologic mimicry happens after SARS-CoV2 vaccination and what the immunologic target is. Immune responses to vaccines are highly variable between different individuals and populations, and there may be other factors implicated such as the microbiome impact on vaccine immunity.⁸ Corticosteroids, IVIG with or without platelet transfusions, have been used successfully with responses noted within 4–6 days.⁵⁻⁷ In the study by Lee et al, outcomes were reported in 16 patients, of which 13 responded to the initial treatment with IVIG, steroids, or platelet transfusion. One patient received rituximab, romiplostim, vincristine along with steroids and IVIG. Another patient developed severe thrombocytopenia and intracranial hemorrhage despite receiving corticosteroids, IVIG, and Rituximab.⁴

In our case, thrombocytopenia was refractory to initial treatment with dexamethasone and IVIG. Due to her presentation with massive and multi-site bleeding, there was concern for imminent intracranial hemorrhage in
and thrombopoietin agonists, especially among patients with refractory thrombocytopenia and bleeding complications, are warranted.

**CONFLICT OF INTEREST**
The authors report no conflict of interest.

**AUTHOR CONTRIBUTIONS**
Snigdha Nutalapati contributed to the case management and manuscript writing. Garima Gupta contributed to the case management and manuscript writing. Gerhard C. Hildebrandt contributed to the case management, manuscript writing, and final approval.

**CONSENT**
The authors confirm that the patient provided informed consent in accordance with the journal’s patient consent policy.

**DATA AVAILABILITY STATEMENT**
Data sharing is not applicable as no new data were generated.

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**How to cite this article:** Nutalapati S, Gupta G, Hildebrandt GC. Rapid response to mycophenolate mofetil in combination with romiplostim in a case of severe refractory immune thrombocytopenia post COVID-19 vaccination. *Clin Case Rep*. 2021;9:e05035. https://doi.org/10.1002/ccr3.5035