Rapid response to mycophenolate mofetil in combination with romiplostim in a case of severe refractory immune thrombocytopenia post COVID-19 vaccination

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Abstract

Vaccine mediated immune mediated thrombocytopenia (ITP) is an exceedingly rare. We present a 25-year-old female who developed severe refractory ITP with multiple active bleeding sites post second dose of COVID vaccination. She was treated with a combination of Romiplostim and Mycophenolate mofetil that resulted in rapid platelet count recovery.

TITLE PAGE

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Key Words: Immune thrombocytopenia, SARS -CoV2 vaccination, Romiplostim, Mycophenolate mofetil

Key Clinical Message: Though it could not entirely be determined if ITP post COVID vaccination is truly causative or mere coincidence, it should be reported and considered as a differential in all patients who present with thrombocytopenia post COVID vaccination.

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Snigdha Nutalapati contributed to the case management and manuscript writing.

Gerhard C. Hildebrandt contributed to the case management, manuscript writing and final approval.

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predisposed patients. It is advisable to warn patients with CAD or other immune cytopenias and monitor the occurrence of these phenomena when they receive the vaccine. It would be useful to explore possible immunosuppressive therapy regimens to control flares, as well as to estimate the impact of these drugs on the vaccine serological response.

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Data availability: Other laboratory or clinical data is available from the corresponding author on reasonable request.

Author contributions:

M.J.G is the consultant hematologist responsible for the patient, P.L.L and M.J.G did the bibliographic research, wrote the clinical case and its discussion. V.K.K, T.N.MC, J.M.A and V.C.A provided technical guidance and advice. J.C.C, A.M.B and N.T.C were involved in critical revision of the report. L.J.FJ and G.G.V helped with the literature review and provided overall

Introduction:

Immune mediated thrombocytopenia (ITP) is a 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), hepatitis A and B vaccination. Most patients respond with steroids and intravenous immunoglobulin.[1] We hereby report a case of a 26-year-old female with severe refractory ITP who presented with multiple active bleeding sites leading to a significant drop in hemoglobin post second dose of COVID vaccination. She was refractory to treatment with steroids and intravenous immunoglobulin(IVIG) and was eventually treated with combination of romiplostim and mycophenolate mofetil with which her counts improved dramatically.

Case discussion:

A 25-year-old Caucasian female with no significant past medical history except for well controlled bronchial asthma presented to us with two-day history of worsening petechiae that initially started on her face and lower extremities and eventually spread to 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 include WBC of $11x10^9$/L, hemoglobin (Hb) of 11g/dl and severe thrombocytopenia with a platelet count of $1x10^9$/L. Prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), fibrinogen, Lactate dehydrogenase (LDH), absolute reticulocyte count and haptoglobin levels resulted normal. 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) screening, 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 hematological labs including Hb, platelet count from three months ago during routine primary care visit were within normal limits. She neither reported personal or family history of bleeding disorders nor required blood transfusions prior to this presentation. 26 days prior to this presentation she had received her second dose of Moderna mRNA vaccination.

Given her clinical presentation, negative infectious and autoimmune workup, normal hemolysis and coagulation studies along with absence of other identifiable underlying etiology, she was presumed to be having immune mediated thrombocytopenic purpura (ITP) and was initiated on dexamethasone 40mg daily for four days along with intravenous immunoglobulin (IVIG) 1g/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, subconjunctival hemorrhage. Her hemoglobin dropped from 11g/dl on presentation to 6.4g/dl. She was initiated on tranexamic acid for bleeding control and supportive care with platelet transfusions. Her platelet counts continued to remain low ($5x10^9$/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 mycophenolate mofetil (MMF) 1 gram twice daily and Romiplostim 1 mcg/kg weekly. On day 12 her platelet counts for the first time improved to $13x10^9$/L. Hb remained stable around 11g/dl. She was discharged after receiving second dose of Romiplostim 3mcg/kg on day 14. During her first outpatient visit on day 21 her platelet counts improved to $140x10^9$/L. She went on to receive third dose of Romiplostim at 3mcg/kg. She continued to have no active sites of bleeding. During fourth week follow up, platelet count recovered to $268x10^9$/L and MMF was tapered down to 500mg twice daily and Romiplostim to 2mcg/kg. By fifth week, her platelet counts continued to improve to $324x10^9$/L and MMF was tapered to 250mg twice daily and Romiplostim to 1mcg/kg. She continued to have normal and stable platelet counts and eventually MMF and Romiplostim were discontinued.

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 $10x10^9$/L.[2]

Vaccination as an etiology for secondary ITP was previously reported with influenza, hepatitis A and B, measles, mumps and rubella (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 antigens of host 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 form antigen mediated responses but also contributed by 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 Moderna or Pfizer vaccine. Sixteen of these patients did not report history of thrombocytopenia prior to their vaccination. Onset of symptoms from the date of vaccination ranged from 1-23 days. Similarly, our patient had normal platelet counts prior to this presentation however ITP developed on day 26 after the second vaccine was given which differs from cases reported by Lee et al. [4] It is not clear how the immunologic mimicry happens after SARS-CoV2 vaccination, nor what the immunologic target is. Immune response 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.[5] Most common treatments received in these patients were corticosteroids, IVIG along with platelet transfusions. Outcomes were reported in 16 patients of which 13 responded to initial treatment with IVIG, steroids or platelet transfusion, one patient received Rituximab, thrombopoietin receptor agonist, vincristine along with steroids and IVIG and one patient developed severe thrombocytopenia and intracranial hemorrhage despite receiving corticosteroids, IVIG and Rituximab. 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 this young and otherwise healthy female, and a rapid response to treatment of her refractory ITP seemed critical. Commonly used options for refractory ITP, such as rituximab, single agent thrombopoietin stimulating agent (TSA), spleen tyrosine kinase inhibitor fostamatinib seemed either to be too delayed or insufficient in their response rates for this case. Splenectomy was prohibited due to bleeding risk and would increase lifelong susceptibility to encapsulated bacteria. [6]

Promising activity for MMF in the treatment of de novo and refractory ITP has emerged over the recent years, and after careful consideration and in detail discussion with the patient and her family, we decided to combine MMF with the TSA Romiplostim. The combination of immunosuppressants with IVIG and TSA has been reported in a small series to be efficacious and safe.[7,8] The response to this combination was rapid and vigorous.

As COVID 19 pandemic persists concerns for vaccine related side effects remain both among care givers and general population. As of June 26,2021 around 46.4% of United states population received full vaccination

against COVID 19 and the risk of serious adverse events remains extremely low. Like primary ITP, vaccine related ITP can have a broad spectrum of presentation ranging from mild bleeding and petechiae to fatal bleeding manifestations. When patients present with ITP, a thorough vaccination history is needed. ITP after COVID 19 vaccination is rare and the potential association is often overlooked and missed. With neither of the clinical trials studying Moderna or Pfizer vaccination had documented cases of thrombocytopenia,[9]it is worthwhile to note that possibility of reported thrombocytopenia post vaccination could be merely a coincidence rather than causative factor. Nevertheless, we are probably just now only at the beginning of our understanding of the plethora and complexity of side effects and immunological impact of the SARS-CoV 2 directed vaccination and the virus itself. Continued vigilance and reporting of the possible side effects with vaccinations is needed, and we believe this should not preclude individuals from getting vaccinated given rarity of these events and the proven effectiveness of vaccine in mitigating this horrendous pandemic.

Further studies on the aggressive management with combination regimens including immunosuppressants and thrombopoietin agonist, especially among patient's refractory thrombocytopenia and bleeding complications is warranted.

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