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Quick drop of platelet counts in children with chronic immune thrombocytopenia after COVID-19 mRNA vaccination: case reports

Giuseppe Lassandro, Francesco Carriero, Valentina Palladino, Giovanni Carlo Del Vecchio, Paola Giordano

Department Interdisciplinary of Medicine, Pediatric Unit "B. Trambusti", University of Bari "Aldo Moro", Bari, Italy

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Corresponding author:
Giuseppe Lassandro, MD, PhD
Department Interdisciplinary of Medicine, Pediatric Unit "B. Trambusti", University of Bari "Aldo Moro", Via Amendola 207, 70126 Bari, Italy
Tel: +39-0805592950, Fax: +39-0805592287
E-mail: giuseppelassandro@live.com

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Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia. Many viruses and some vaccines have been identified as triggering the autoimmune process, including parvovirus, human immunodeficiency virus, Epstein-Barr virus, rubella, and measles. However, ITP in association with coronavirus disease 2019 (COVID-19) vaccination has not been reported so far. We describe the cases of two young girls affected by ITP presenting a quick reduction of platelet count after receiving Pfizer-BioNTech COVID-19 vaccine.

Keywords: Immune thrombocytopenia, COVID-19, Child, Case report

Introduction

Immune thrombocytopenia (ITP) is an acquired immuno-mediated disorder characterized by thrombocytopenia, i.e., a peripheral blood platelet counts less than 100×10^9/L, with an increased risk of bleeding [1]. Overall, 80% of ITP is considered primary, favored by a rupture of the immune tolerance leading to an autoimmune process involving both innate and adaptive immune responses. Secondary causes of ITP can include infection, immunodeficiency, autoimmune diseases, and vaccination [2,3]. A novel coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), has affected over 21 million people worldwide since its inception. The outbreak of COVID-19 infection began in Wuhan, Hubei, China, in December 2019, and then spread rapidly to other provinces of China and around the world. On January 30, 2020, the World Health Organization declared the outbreak of a Public Health Emergency of International Concern and, on March 11, 2020, a pandemic [4]. Children with ITP might be more susceptible to infectious diseases than others in general and the presence of an association between ITP and COVID-19 infection has not been well known [5]. In order to face the SARS-CoV-2 emergency, Food and Drug Administration issued an Emergency Use Authorization for the Pfizer-BioNTech COVID-19 vaccine on December 11, 2020 in individuals 16 years of age and older, as a two-dose series administered 21 days apart [6]. This vaccine consists in lipid-nanoparticle encapsulated mRNA platform that encodes the SARS-CoV-2 viral spike (S) glycoprotein. Several cases of ITP have been reported to the Vaccine Adverse Event Reporting System (VAERS) after receiving the Pfizer-BioNTech COVID-19 vaccine. In particular, cases of de novo ITP have been reported after SARS-

CoV-2 vaccination, although its effect on preexisting ITP has not been well characterized [7,8].

Herein we report two cases of the rapid drop in platelet count following the Pfizer/BioNTech mRNA SARS-CoV-2 vaccine in two 16-year-old females affected by chronic ITP.

Case Report

Case 1

A 16-year-old female with a medical history of ITP presented to the hospital with diffuse petechiae and easy bruising a few days after receiving the first dose of Pfizer-BioNTech mRNA vaccine. She was diagnosed with ITP at the age of 4 years during investigations for episodes of post-traumatic colporrhagia. The patient received therapy with cycles of intravenous human immunoglobulin and methylprednisolone at high doses (15–30 mg/kg) for the first year. For the persistence of thrombocytopenia at the age of 5 and 9 years, it was necessary to initiate immunosuppressive therapy with rituximab anti-CD20 at a dose of 375 mg/m^2. At the age of 12 years, for unstable platelet count, therapy with mycophenolate mofetil was started until the age of 15 years. One month before the vaccination, the patient had a stable platelet count of 50×10^9/L and was in therapy with thrombopoietin receptor agonist eltrombopag (75 mg/day) [9].

The SARS-CoV-2 vaccine was administered on April 21, 2021, and after 4 days she experienced severe epistaxis, bruising of the limbs, and diffuse purpura. Therefore, she presented to an emergency department and laboratory findings revealed a platelet count of 14×10^9/L. She was hospitalized at the operating unit of Pediatrics "B. Trambusti" of the Giovanni XXIII Hospital in Bari for 4 days and received two doses of intravenous immunoglobulin (800 mg/kg). On day 9, post-vaccination, petechiae and mucocutaneous bleeding decreased and the platelet count rose to 117×10^9/L (Fig. 1).

The patient provided written informed consent for publication of the research details.

Case 2

A 16-year-old female with chronic ITP received a second dose of the Pfizer-BioNTech mRNA vaccine. Diagnosis of ITP was made at the age of 8 years old and she has been treated with intravenous immunoglobulin for platelet counts below 20×10^9/L, about 3 times a year. Two months prior to receiving the vaccine, she has a normal platelet count of 168×10^9/L.

The patient received the second dose of SARS-CoV2-vaccine on May 12, 2021, 4 days prior to presentation. The day after receiving her vaccination, the patient awoke with mild headache and pain at the injection site of the vaccine. On day 3, post-vaccination, she experienced widespread petechiae, especially on lower extremities, which were observed during the exam in the emergency department. Laboratory tests revealed severe thrombocytopenia with a platelet count of 8×10^9/L. Therefore, the patient was admitted to the operative unit of Pediatrics "B. Trambusti" of the Giovanni XXIII Hospital in Bari and received two doses of intravenous immunoglobulin (800 mg/kg). On day 7, post-vaccination, petechiae decreased, and the patient was discharged with a platelet count of 140×10^9/L (Fig. 1).

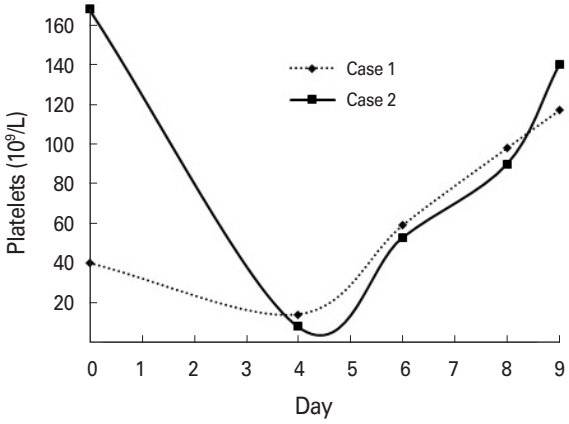

Fig. 1. Platelet count prior and after severe acute respiratory syndrome coronavirus vaccine in our two cases.

The patient provided written informed consent for publication of the research details.

Discussion

We report two cases of rapid drop in platelet count in teenagers affected by chronic ITP that could likely be the side effect of COVID-19 mRNA vaccination.

ITP is a hematological autoimmune disorder characterized by low platelet count of less than 100×10^9/L. Due to low levels of platelets, ITP is associated with bruising and bleeding. Recent evidence suggests that low platelet counts in ITP are the result of multiple factors, including impaired thrombopoiesis and variations in immune response leading to platelet destruction during pathological conditions. Moreover, the pathogenesis of ITP also consists of an alteration of B-cell function and B-cell hyperreactivity that could explain the relapse also after splenectomy in these patients [10]. ITP is often a retrospective diagnosis based on exclusion of other pos-

sible causes of thrombocytopenia and assessment of the response to treatment. It can be distinguished, in terms of duration, into newly diagnosed, persistent and chronic ITP when ITP lasting for more than 12 months [11].

In most cases, ITP is primary, but some patient with acute ITP symptoms may usually have a history of preceding infection a few days before the onset of symptoms. Common infections include Epstein-Barr virus, varicella zoster virus, rubella, and influenza virus. There is also an increased risk of ITP after the administration of vaccines like influenza, measles-mumps-rubella, hepatitis B, human papillomavirus, varicella, and diphtheria-tetanus-pertussis vaccines in children and adolescents. The pathogenesis of vaccine-related thrombocytopenia is not completely clear. During the COVID-19 pandemic, it has become widely recognized that the SARS-CoV-2 virus has the capability of generating an extraordinary immune response with devastating multi-systemic consequences. There is an uncertain relationship between SARS-CoV-2 vaccination and secondary ITP but there are several possible mechanisms by which this might occur. Mechanisms involve inhibition of platelet synthesis due to direct infection of the bone marrow cells or platelets by the virus and dysfunctional marrow microenvironment. Viral induction of autoimmunity can be explained by various phenomena, including molecular mimicry, cryptic antigen expression, and epitope spreading [12].

In a recent commentary, 20 cases of secondary ITP were reported after vaccination with both Pfizer and Moderna SARS-CoV-2 vaccines, 17 of which had no history of thrombocytopenia. Exacerbations of preexisting ITP have been suspected, but not confirmed [8].

The thrombocytopenia exacerbation in patients with chronic ITP may have been induced by increase of macrophage-mediated clearance or impaired platelet production in the context of a systemic inflammatory response to vaccination [13]. This is compatible with patients in whom severe thrombocytopenia was first noted 1–3 days post-vaccination [14]. The timeline of events that we describe in our case reports, suggests an exacerbation of our patient's chronic thrombocytopenia related to the administration of the COVID-19 mRNA vaccine. In addition, whereas cases of *de novo* ITP primarily occurred with a first vaccine dose [8], case 2 demonstrates how the exacerbation of preexisting ITP can sequentially increase in severity with each of the two doses.

The effect of SARS-CoV-2 vaccination on patients with preexisting autoimmune hematological conditions is poorly understood, but it is of considerable public health interest in order to maintain a good quality of life for patients with chronic diseases [15].

These clinical cases demonstrate that patients with underlying conditions, such as ITP, should be monitored for any suspicious symptoms after vaccination. However, these conditions should not be a reason to avoid vaccination. In these cases, in fact, it is important to report any VAERS to deepen the knowledge on possible side effects and on mitigating potential risks.

ORCID

Giuseppe Lassandro *https://orcid.org/0000-0001-7858-1632*
Francesco Carriero *https://orcid.org/0000-0002-4678-8855*
Valentina Palladino *https://orcid.org/0000-0002-3976-6463*
Giovanni Carlo Del Vecchio *https://orcid.org/0000-0001-5462-0027*
Paola Giordano *https://orcid.org/0000-0002-7762-3500*

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