

Immune thrombocytopenic purpura induced by the COVID-19 vaccine after the second dose in a 78-year-old patient: A case report

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Abstract. Coronavirus disease 2019 (COVID-19) has become a global pandemic, but treatment options remain limited. Up to now, vaccination has been the main strategy to prevent transmission and reduce disease severity. However, with follow-up observations after massive vaccination, immune thrombocytopenic purpura (ITP) induced by COVID-19 vaccines has attracted the attention of investigators. The present study reported the case of a 78-year-old elderly female who presented with 'oral bleeding for 2 days and scattered bleeding spots on the extremities for 1 day' after vaccination with the COVID-19 vaccine (Vero Cells), and blood routine analysis indicated a white blood cell count of $6.27 \times 10^9/l$, hemoglobin levels of 144 g/l and a low platelet (PLT) count of $1 \times 10^9/l$. Bone marrow cytomorphology showed thrombocytopenia, while no platelet-producing megakaryocytes were observed. The patient was diagnosed with ITP and given symptomatic and supportive treatment, such as prednisone acetate 1 mg/kg, recombinant human thrombopoietin, intravenous injection of human immunoglobulin 0.4 g/kg and prevention of bleeding. At 1 week after the treatment started, the patient's PLT count began to increase, and 9 days later, it returned to normal levels. The aim of the present study was to raise the awareness of medical staff regarding this disease and to increase the vigilance of the general public. At the same time, the present study also provided an effective method to manage this type of adverse reaction to the COVID-19 vaccine.

Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread worldwide, seriously threatening human life and health. Although SARS-CoV-2 infection may be asymptomatic, ~15% of clinically diagnosed cases have a severe course of the disease (1,2). The infection may also begin with flu-like symptoms. Indeed, nearly 2 or 3 of every 4 subjects that have positive PCR throat swab results remain without symptoms and only 10% of symptomatic patients develop dyspnea, interstitial pneumonia, acute respiratory distress syndrome and/or multiorgan dysfunction (3). Fever, headache, myalgia, fatigue, rhinorrhea, cough, mild dyspnea, sore throat and conjunctivitis are common symptoms of the disease (4,5), which are seen in other respiratory conditions as well. COVID-19 vaccines have become the most important preventive measure to control the COVID-19 pandemic. At present, there are three inactivated vaccines approved for administration in China, which are produced by Sinopharm China Biological Beijing Institute of Biological Products Co., Ltd., Wuhan Institute of Biological Products Co., Ltd. and Beijing Kexing Zhongwei Biotechnology Co., Ltd., one adenoviral vector vaccine, which is produced by Kangxino Biological Co., Ltd., and one recombinant novel coronavirus vaccine (CHO cell), which is produced by Anhui Longke Ma Biopharmaceutical Co., Ltd. With mass vaccination and subsequent follow-up, vaccine-related adverse reactions have emerged in clinical practice. In the present study, a case of immune thrombocytopenic purpura (ITP) induced by a COVID-19 vaccine (Vero Cells; Beijing Kexing Zhongwei Biotechnology Co., Ltd.) was reported.

Case report

A previously healthy 78-year-old female had received the first and second doses of the COVID-19 vaccine in early August and September 2021, respectively, 4 weeks apart. The patient was admitted to the hospital at 30 days after the second vaccination, due to 'oral bleeding for 2 days and scattered hemorrhagic spots on the limbs for 1 day'. The patient had oral bleeding

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after eating hard food at 28 days after the second vaccination. In the morning of the next day, the patient had dark red blood clots in the mouth and continuous oral bleeding with scattered hemorrhagic spots on the limbs. The patient denied any other adverse reactions after the first dose of vaccination and developed oral bleeding with scattered hemorrhagic spots on the limbs 1 month after the second dose of vaccination (Fig. 1). The patient presented at the Department of Emergency of the 940th Hospital of Joint Logistics Support Force of the Chinese People's Liberation Army (Lanzhou, China) 30 days after the second vaccination, and blood routine analysis indicated a white blood cell count (WBC) of $6.27 \times 10^9/l$ (reference interval, $4-10 \times 10^9/l$), hemoglobin (Hb) of 144 g/l (reference interval, 110-150 g/l) and a platelet (PLT) count of $1 \times 10^9/l$ (reference interval, $100-300 \times 10^9/l$). The patient did not take any medications and dietary supplements 2 months prior to hospitalization. In addition, the patient had no medical history of thrombocytopenia prior to vaccination and blood routine analysis 1 week prior to vaccination indicated a PLT count $>100 \times 10^9/l$. The patient was finally admitted to the Department of Hematology. The blood routine reexamination 2 days after hospitalization indicated the following: WBC, $8.14 \times 10^9/l$; Hb, 133 g/l; and PLT, $1 \times 10^9/l$. After admission, the patient was negative for novel coronavirus by PCR, and HIV, hepatitis C virus (HCV), HBV and *H. pylori* were also negative. At the same time, no abnormality of blood coagulation was detected and all parameters of biochemistry, immunity and autoantibody parameters were normal. Bone marrow cytology showed thrombocytopenia and no platelet-producing megakaryocytes were observed. The patient was definitely diagnosed with ITP due to significant bleeding symptoms, such as oral bleeding and scattered hemorrhagic spots on the limbs. Prednisone acetate 1 mg/kg, recombinant human thrombopoietin and intravenous human immunoglobulin (IVIG) 0.4 g/kg were given to increase platelets, and carbazochrome sodium sulfonate to reduce capillary permeability and prevent bleeding. At 1 week after the treatment was started, the patient's PLT began to increase, and 9 days later, it returned to a normal level (Fig. 2); the treatment was adjusted to oral herombopag on day 10. The patient tolerated the treatment and is currently on maintenance therapy with the oral thrombopoietin receptor agonist herombopag as an outpatient. The patient was followed up 4 months after discharge, and the PLT was still $>100 \times 10^9/l$.

Discussion

COVID-19 has become a global pandemic, but treatment options remain limited. Up to now, vaccination has been the main strategy to prevent transmission and reduce disease severity. In the initial clinical trials of vaccines, no significant adverse events other than rare allergic reactions were reported. However, with the follow-up observations after massive vaccination, ITP induced by COVID-19 vaccines has attracted the attention of investigators.

Physical examination of patients with immune thrombocytopenia revealed signs including bleeding from mucous membranes and skin. Petechiae, purpuric rashes, gingival bleeding and hemorrhagic bullae may manifest in those patients. The case of the present study suffered from gingival hemorrhage and skin rashes. The pathogenesis of ITP

involves autoantibodies produced by B cells, which target PLT membrane glycoproteins, particularly GpIIb/IIIa, and the production of anti-PLT antibodies results in T cell-mediated PLT destruction and impaired megakaryocyte function. The most common predisposing factors for ITP include environmental factors (e.g., infections, drugs and malignancies), genetic predisposition and viral infections (6-9). At the same time, there is evidence that ITP may develop after various vaccinations (10-14). There is a direct causal relationship between ITP and the measles-mumps-rubella vaccine (15). Although a causal relationship has not been established in numerous cases, ITP has been reported after multiple immunizations, including live varicella vaccine, human papilloma vaccine, *Haemophilus influenzae* vaccine, hepatitis B vaccine, poliomyelitis vaccine and diphtheria tetanus pertussis vaccine (16). It has also been reported in the literature that ITP occurred following influenza vaccination; although autoantibodies to platelets could not be detected, the diagnosis of ITP was precise (17). Alternatively, ITP may also be induced by other components of the vaccine, such as yeast proteins, adjuvants and preservatives or diluents, which have been implicated in adjuvant-induced autoimmune/inflammatory syndromes (12,16,18,19). To date, these immune mechanisms have not been fully elucidated. Certain phenomena that may explain this autoimmunity reaction include molecular mimicry, cryptic antigen expression and epitope spreading. Molecular mimicry is well explained in viruses including HIV, HCV and varicella zoster virus (VZV), as well as in *H. pylori*. However, the sequence homology between SARS-CoV-2 and platelets has yet to be identified (20). In addition, it has been reported that inactivated vaccines against COVID-19 infection may trigger immunity against platelets and may lead to recurrence of immune thrombocytopenia in these patients (21). In the present case, the patient's tests were negative for novel coronavirus by PCR, *H. pylori*, and HBV, HCV and HIV after admission. However, relevant tests for systemic lupus erythematosus, antiphospholipid syndrome, cytomegalovirus and VZV should be performed in similar cases afterwards in subsequent clinical work, as soon as the patients are admitted; positivity is less likely but it is reasonable to test.

ITP is one of the adverse events of SARS-CoV-2 vaccines and the majority of ITP patients after vaccination have exhibited good responses after treatment with steroid hormones and IVIG (13,14). In a retrospective study (22), the occurrence of ITP after mRNA COVID-19 vaccination was included in the vaccine adverse event reporting system and the results indicated that 15 cases of thrombocytopenia occurred with 18,841,309 doses of Pfizer Biotechnology COVID-19 vaccine given and 13 cases of thrombocytopenia occurred with 16,260,102 doses of Moderna COVID-19 vaccine given. Of the above 28 patients, all but one case occurred after the first vaccination. The Japanese Society of Hematology recently published a report on immune-mediated acute exacerbations of ITP after SARS-CoV-2 mRNA vaccination (23). Furthermore, the Massachusetts General Hospital ITP Center performed a prospective study of all 52 patients with ITP who received the COVID-19 vaccine on January 1, 2021 (24). The PLT counts were determined 1-7 days prior to vaccination and 3-14 days after vaccination, and the degree of thrombocytopenia and bleeding after vaccination were assessed. The results indicated that 6/52 (12%) patients had severe worsening



Figure 1. Image displaying hemorrhagic points and ecchymosis of the lower limbs of the patient.

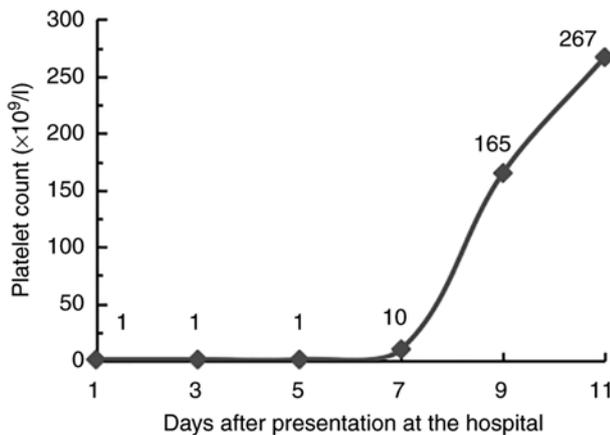


Figure 2. Changes in platelet levels prior to and after treatment.

of thrombocytopenia, accompanied by worsening of bleeding symptoms. The aggravation of thrombocytopenia usually occurred 2-5 days after vaccination and patients responded to IVIG and steroid hormones. In addition, there is increasing concern about the development of newly diagnosed ITP after SARS-CoV-2 vaccination. It has been reported that 2 patients developed severe thrombocytopenia accompanied by bleeding tendency 4 and 14 days after mRNA vaccination (22). PLT returned to normal after PLT transfusion or treatment with IVIG and steroids.

Vaccines are a major weapon against SARS-CoV-2 throughout the world. Their efficacy and safety have been

demonstrated by rigorous clinical trials, and the present report cannot question their safety in terms of possible adverse effects. However, it is still necessary to monitor PLT counts prior to and after vaccination, so as to determine the true incidence of thrombocytopenia after COVID-19 vaccination (25). The management of vaccination in patients with existing ITP is complex and still requires further study and discussion. The opinion of the Platelet Disorder Support Association Medical Advisory Committee is that in most patients, the benefits of vaccination outweigh the risk of deterioration in patients with ITP (26). Currently, for patients with ITP, it appears reasonable to obtain a baseline count prior to vaccination and then obtain additional PLT measurements after vaccination according to the patient's clinical presentation and treatment history. Active treatment according to ITP is appropriate for patients who develop severe thrombocytopenia shortly after vaccination in the absence of other possible causes. Whether a second dose of vaccine is required for patients who develop thrombocytopenia or whether a different vaccine is needed requires further investigation. In the present case, ITP occurred after vaccination with a novel coronavirus inactivated vaccine, and it has also been previously indicated that there was the development of ITP and a decrease in PLT counts in healthy subjects after mRNA vaccination (27). However, the differences between mRNA and inactivated vaccines in triggering the pathogenesis of ITP still require further study. The aim of the present study was to raise the awareness of medical staff regarding this disease and to increase the vigilance of the general public. At the same time, an effective method to manage this type of adverse reaction to COVID-19 vaccine was provided.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WL analyzed data and wrote the manuscript. FX, HT and RS collected and provided data on the treatment of the case presented, and performed cytomorphological analysis of bone marrow aspirates. TW and HB analyzed data, compiled diagnostic data and contributed to the writing of the manuscript. TW and HB read and approved the final manuscript. WL, TW and HB confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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