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LETTER TO THE EDITOR

Vincristine therapy for severe and refractory immune thrombocytopenia following COVID-19 vaccination

Kei Saito[1,2] · Satoshi Ichikawa[2] · Shunsuke Hatta[1,2] · Yuna Katsuoka[1] · Hideo Harigae[2] · Tohru Izumi[1]

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Dear Editor,

Among various medical conditions associated with COVID-19 vaccination, thrombocytopenia is a rare but important hematologic condition, which can be associated with severe hemorrhagic or thromboembolic complications [1, 2].

A 66-year-old woman presented with malaise, lymphadenopathy, oral bleeding, and purpura 2 days after receiving the first dose of the BNT162b2 vaccine (Pfizer-BioNTech). The patient had no medical history of thrombocytopenia. A blood test performed 2 years ago revealed a normal platelet count. The patient was febrile and generally ill with bleeding symptoms such as purpura and hematuria. Multiple soft and non-tender enlarged lymph nodes were observed in the bilateral neck and axilla. Blood tests showed severe thrombocytopenia ($< 1 \times 10^9$/L) with undetectable levels of immature platelet fraction (IPF) and mild normocytic anemia (hemoglobin, 11.6 g/dL). Although the white blood cell count (5.7×10^9/L) was normal, the lymphocyte count was slightly decreased (12.9%; 75.4% neutrophils and 7.5% monocytes). Coagulation tests showed normal results except for a slight increase of fibrin degradation product level. Serum anti-platelet factor 4 (PF4) antibodies were not detected. Biochemical analysis showed mildly elevated levels of lactate dehydrogenase (390 U/L) and inflammatory markers (C-reactive protein [2.6 mg/dL] and ferritin [182 ng/mL]). The levels of soluble interleukin-2 receptor (sIL-2R, 3283 U/mL) and platelet-associated IgG (PAIgG, 6280 ng/10^7 cells) were highly elevated. Computed tomography (CT) showed right pulmonary basilar consolidation, mild hepatosplenomegaly, and systemic lymphadenopathy, without brain infarctions or hemorrhages. The PCR test for SARS-CoV-2 using nasopharyngeal swabs showed negative results.

Platelet transfusion did not ameliorate the thrombocytopenia. Bone marrow examination revealed hypercellular marrow with markedly increased megakaryocytes, suggesting immune thrombocytopenia (ITP). Neither prednisolone (1 mg/kg/day) and intravenous immunoglobulin (IVIG) treatment nor subsequent treatment with pulsed methylprednisolone (500 mg/day; 3 days), romiplostim, and danazol improved her platelet count (Fig. 1). Blood samples collected on the fifth day of admission showed anti-platelet glycoprotein IIb/IIIa antibodies, which confirm a diagnosis of ITP. Slow vincristine infusion (0.04 mg/kg; 8 h) on the seventh day slightly increased her platelet count with marked elevation of IPF. Thereafter, her platelet count, and the associated symptoms gradually improved. On the 13th day, CT showed resolution of the lung consolidation, lymphadenopathy, and splenomegaly. On the 22nd day, she was discharged without any sequelae.

Thrombocytopenia after COVID-19 vaccination accompanied by thrombosis is usually reported as thrombosis with thrombocytopenia syndrome or vaccine-induced immune thrombotic thrombocytopenia [3], which is associated with anti-PF4 antibodies and usually develops after inoculation with adenoviral vector-based vaccines. Further, ITP after COVID-19 vaccination usually presents with severe thrombocytopenia and hemorrhagic symptoms [1, 4–7]. The present case was considered vaccine-associated ITP, established by the presence of serum anti-glycoprotein IIb/IIIa antibody, one of the platelet autoantibodies [8]. These were speculated to be present before vaccination, suggesting the existence of subclinical ITP prior to vaccination. Thus, COVID-19 vaccination may aggravate thrombocytopenia in patients with unrecognized subclinical ITP.

Although most cases of COVID-19 vaccine-related ITP were responsive to initial treatment with steroids and/or IVIG [1, 4–7], some patients died of intracranial hemorrhage according to reports from the Vaccine Adverse Event

✉ Satoshi Ichikawa
satoshi.ichikawa.b4@tohoku.ac.jp

[1] Department of Hematology, National Hospital Organization Sendai Medical Center, Sendai, Japan

[2] Department of Hematology, Tohoku University Hospital, Sendai, Japan

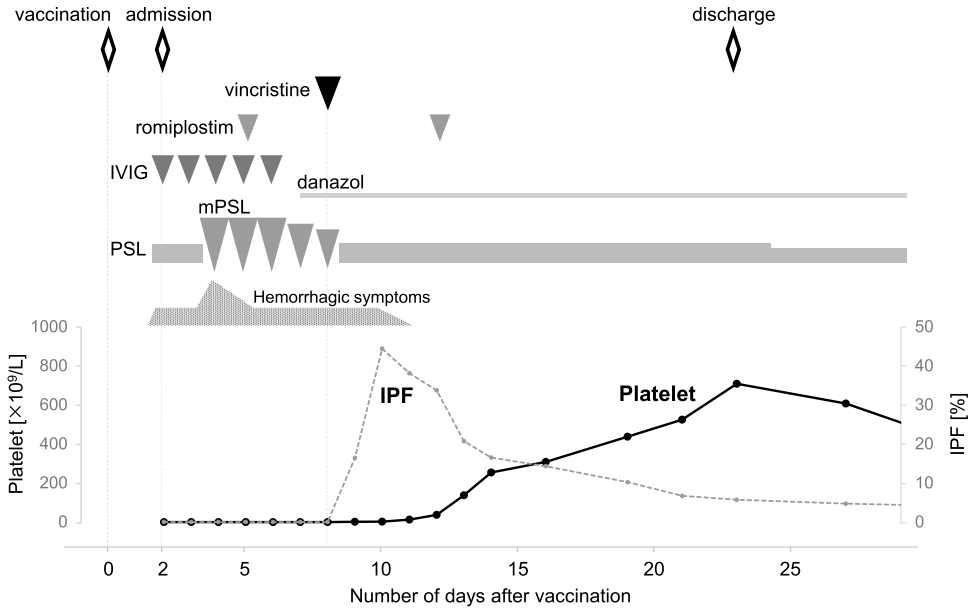

Fig. 1 Clinical course of the patient. The vertical axes represent the patient's platelet count (left) and IPF (right) across time. Abbreviations: IPF, immature platelet fraction; IVIG, intravenous immunoglobulin; mPSL, methylprednisolone; PSL, prednisolone

Reporting System [9]. Although the present case showed a very high risk of life-threatening hemorrhage, vincristine yielded a rapid response. It is reported that a slow infusion of vincristine can inhibit macrophage function and platelet phagocytosis in ITP [10]. We selected vincristine treatment based on the following reasons: (i) the increased PAIgG levels imply the existence of well-opsonized platelets, resulting in efficient vincristine uptake by the macrophages through phagocytosis, and (ii) the elevated sIL-2R levels indicated macrophage activation-associated hypercytokinemia, which may present with systemic lymphadenopathy and hepatosplenomegaly. It might be that mRNA COVID-19 vaccines stimulate macrophage activity, which in turn might be especially sensitive to vincristine.

In summary, we describe a case of severe and refractory ITP associated with COVID-19 vaccination, which ameliorated rapidly after vincristine treatment. COVID-19 vaccination could cause the sudden development of severe ITP even in previously healthy patients, in whom platelet autoantibody could be present. Although further studies are required to establish a standard therapy for COVID-19 vaccine-associated ITP, vincristine could be considered a treatment option for refractory ITP, especially in patients with clinical findings suggestive of hypercytokinemia and macrophage activation.

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Author contribution K.S. designed the research, analyzed and interpreted the data, and wrote the paper. S.I. analyzed and interpreted the data, and wrote and organized the paper. S.H. and Y.K. analyzed and interpreted the data. H.H. and T.I. analyzed and interpreted the data and supervised the paper. All authors approved the final manuscript.

Declarations

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 and its later amendments.

Informed consent Informed consent was obtained from the patient for being included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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