

Transient Pseudothrombocytopenia Detected 8 Months After COVID-19 Vaccination

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ABSTRACT

Pseudothrombocytopenia is an *in vitro* phenomenon of platelet aggregation due to conformational changes and exposure of cryptic antigens on the platelet surface caused by anticoagulants, leading to the aggregation of platelets and falsely lower automated platelet counts. Although it has no clinical relevance, it can lead to unnecessary fear, diagnostic errors, or unnecessary tests and interventions when unrecognized.

Pseudothrombocytopenia was detected in a 25-year-old woman 8 months after the second dose of mRNA COVID-19 vaccine, BNT162b2. The pseudothrombocytopenia was transient and the duration was shorter than 3 months. As pseudothrombocytopenia is not detected unless blood is drawn for other objectives, it is difficult to determine its true occurrence among recipients of vaccines. This case shows that pseudothrombocytopenia may develop transiently even months after COVID-19 vaccination and should be considered when thrombocytopenia is found in recipients of the vaccine to avoid unnecessary fear, diagnostic errors, or unnecessary tests and interventions.

Case Report

The case is a 25-year-old woman taking rosuvastatin for familial hypercholesterolemia and having regular blood tests every 2 months. She received two doses of mRNA COVID-19 vaccine, BNT162b2, with a 3-week interval in March 2021. The platelet counts of the EDTA-2K-anticoagulated blood samples examined in May, July, and September did not show the aggregation of platelets and the platelet counts were $348 \times 10^9/L$, $281 \times 10^9/L$, and $302 \times 10^9/L$, respectively (TABLE 1). The EDTA-2K anticoagulated blood drawn on the occasion of an annual health check in November, 8 months after the second vaccine dose, showed platelet aggregation, and blood was drawn again in an EDTA-2K anticoagulated tube and an FC Mix tube that contained sodium fluoride,

EDTA-2Na, and sodium citrate for anticoagulation. The platelet count in the EDTA-2K anticoagulant tube was $63 \times 10^9/L$ and that in the other tube was $90 \times 10^9/L$. On microscopic peripheral blood examination, platelet aggregation was observed (FIGURE 1). The platelet count in the EDTA-2K anticoagulated tube was manually determined by counting the platelets in the sample diluted 100-fold in 1% ammonium oxalate solution with fluorescence microscopy and was $179 \times 10^9/L$. She did not have any signs or symptoms of bleeding and was diagnosed with pseudothrombocytopenia. The platelet count in the EDTA-2K anticoagulated sample drawn 3 weeks later had returned to her normal value of $306 \times 10^9/L$.

Discussion

Hematological changes are frequently complicated with COVID-19 and thrombocytopenia is detected in 5% to 41.7% of patients.^{1,2} Platelet count is lower in more severe diseases, and complex mechanisms are considered to contribute to the development of thrombocytopenia.¹ In addition to true thrombocytopenia, cases of pseudothrombocytopenia related to COVID-19 have been reported.^{3–7} Pseudothrombocytopenia is an *in vitro* phenomenon of platelet aggregation due to the conformational changes and exposure of cryptic antigens on the platelet surface caused by anticoagulants, usually EDTA, leading to the aggregation of the platelets through the immune reaction between the exposed cryptic antigens and autoantibodies and falsely lower automated platelet counts.⁸ Although pseudothrombocytopenia is observed in 0.03% to 0.27% of the general population, it is associated with some specific conditions such as autoimmune diseases, infections, pregnancy, and medications. Although it has no clinical relevance, it can lead to unnecessary fear, diagnostic errors or unnecessary tests and interventions, including platelet transfusion, when unrecognized.

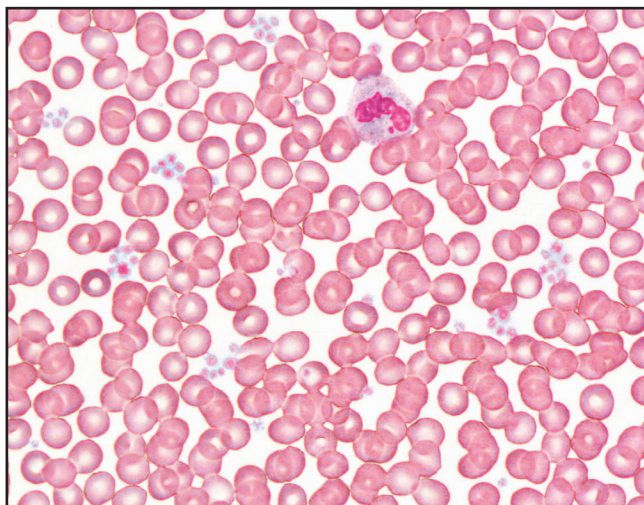
The efficacy of COVID-19 mRNA vaccines has been confirmed with acceptable safety profiles, and millions of people have been vaccinated worldwide. It is reported that they may cause a transient exacerbation of thrombocytopenia in patients with chronic immune thrombocytopenia;⁹ however, they do not appear to be associated with newly developed immune thrombocytopenia, and the overall incidence of thrombocytopenia does not appear to increase after the vaccination.¹⁰

We reported a case of pseudothrombocytopenia associated with BNT162b2 COVID-19 mRNA vaccine observed 8 months after the second dose. A case of transient pseudothrombocytopenia in a recipient of Ad26.COVS.2 adenovirus vector vaccine has been reported.¹¹

TABLE 1. Blood Cell Counts of EDTA-2K Anticoagulated Samples

Variables	May	July	Sept	Nov	Dec
White blood cells ($\times 10^9/L$)	7.1	4.7	5.0	5.0	5.1
Hemoglobin (g/dL)	11.7	11.1	11.5	12.0	11.7
Platelets ($\times 10^9/L$)	348	281	302	63	306

FIGURE 1. Peripheral blood smear of the EDTA-2K anticoagulated sample. Relatively small and loose platelet aggregates were observed in November 2021 (May-Grünwald-Giemsa, $\times 400$).



The patient was taking methotrexate for psoriatic arthritis, and pseudothrombocytopenia was diagnosed 5 days after the vaccine. However, the incidence of pseudothrombocytopenia after COVID-19 vaccination is unknown and it appears difficult to be determined because, as pseudothrombocytopenia is not associated with bleeding tendency, it is not detected unless blood is drawn for objectives other than the evaluation of bleeding tendency. Thus, many cases of pseudothrombocytopenia could have been overlooked.

In a large nationwide study of BNT162b2 vaccine in Israel, the incidence of thrombocytopenia was 56 in 884,828 recipients and not different from that of controls during 21 days of follow-up.^{12,13} However, the incidence of thrombocytopenia after this period is not known and that of pseudothrombocytopenia is all the more difficult to elucidate. In addition, as our patient developed transient pseudothrombocytopenia 8 months after vaccination, many cases of transient and/or late-onset pseudothrombocytopenia after the COVID-19 vaccination may have been unrecognized, and more cases of pseudothrombocytopenia could have been found with more frequent and prolonged follow-ups. Although anti-COVID-19 antibody levels were not measured in the present case, an observation that pseudothrombocytopenia persisted with positive IgG/IgM anti-COVID-19 antibodies 9 months after COVID-19 infection suggests that persistent high-titer anti-COVID-19 antibodies

induced by vaccination might be associated with the late-onset pseudothrombocytopenia in the present case.⁶ However, this assumption needs to be verified in the similar cases. Pseudothrombocytopenia sometimes shows alternative periods without in vitro aggregation, and the duration of pseudothrombocytopenia in the present case was shorter than 3 months.⁸ Thus, COVID-19 vaccination may lead to persisting, recurrent, or late-onset pseudothrombocytopenia.

Although it appears difficult to determine its true occurrence, the present case shows that pseudothrombocytopenia may develop transiently even months after COVID-19 vaccination and should be considered and properly evaluated when thrombocytopenia is found incidentally in recipients of the COVID-19 vaccine to avoid unnecessary fear and interventions.

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