**Case Study**

**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 × 10⁹/L, 281 × 10⁹/L, and 302 × 10⁹/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 × 10⁹/L and that in the other tube was 90 × 10⁹/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 × 10⁹/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 × 10⁹/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 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.COV2.S adenovirus vector vaccine has been reported. 11

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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. However, the incidence of thrombocytopenia after this period is not known and it appears difficult to determine its true occurrence.

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.

REFERENCES

1. Zhang Y, Zeng X, Jiao Y, et al. Mechanisms involved in the development of thrombocytopenia in patients with COVID-19. Thromb Res. 2020;193:110–115.
2. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 2020;506:145–148.
3. Kuhlman P, Nasim J, Goodman M. Pan-pseudothrombocytopenia in COVID-19: a harbinger for lethal arterial thrombosis? Fed Pract. 2020;37:354–358.
4. Van Dijk R, Lauw MN, Swinkels M, Russcher H, Jansen AJG. COVID-19-associated pseudothrombocytopenia. EJHaem. 2021;2:475–477.
5. Li H, Wang B, Ning L, Luo Y, Xiang S. Transient appearance of EDTA dependent pseudothrombocytopenia in a patient with 2019 novel coronavirus pneumonia. Platelets. 2020;31:825–826.
6. Bereczki D, Nagy B, Kerényi A, et al. EDTA-induced pseudothrombocytopenia up to 9 months after initial COVID-19 infection associated with persistent anti-SARS-CoV-2 IgM/IgG seropositivity. Lab Med. 2021; Aug 20 [online ahead of print].
7. Can F, Gökräfte D, Güney T, Akunç S, Dilek İ. Massive platelet clumping on peripheral blood smear and pseudothrombocytopenia in a patient with COVID-19. Balkan Med J. 2021;38:194.
8. Lardinois B, Favresse J, Chatelain B, Lippi G, Mullier F. Pseudothrombocytopenia: a review on causes, occurrence and clinical implications. J Clin Med. 2021;10:594.
9. Kuter DJ. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. Br J Haematol. 2021;195:365–370.
10. Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2021;39:3329–3332.
11. Kemper M, Berssenbrügge C, Lenz G, Mesters RM. Vaccine-induced pseudothrombocytopenia after Ad26.COV2.S vaccination. Ann Hematol. 2021; Aug 10:1–2 [online ahead of print].
12. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med. 2021;385:1078–1090.
13. Dagan N, Barda N, Balicer RD. Adverse effects after BNT162b2 vaccine and SARS-CoV-2 infection, according to age and sex. N Engl J Med. 2021;385:2299.

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

| Variables                  | May  | July | Sept | Nov  | Dec  |
|----------------------------|------|------|------|------|------|
| White blood cells (×10³/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 (×10³/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, ×400).