Letters to the Editors

Macrophage activation syndrome after BNT162b2 mRNA vaccination successfully treated with corticosteroids

Sirs,

Two messenger RNA-based vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), and two adenoviral vector vaccines (ChAdOx1 nCov-19 (AstraZeneca) and Ad26.COV2.S (Johnson & Johnson/Janssen) have been approved in many countries worldwide. However, these vaccines were rapidly approved in short periods due to the societal need to control the pandemic. Therefore, clinicians need to be very careful about the unexpected adverse effects. Here, we report the first case of macrophage activation syndrome (MAS) with thrombocytopenia after BNT162b2 vaccination, successfully treated by corticosteroid.

A previously healthy 51-year-old woman developed high fever, headache, and atypical genital bleeding on the following day after second shot of BNT162b2 vaccine. She presented to the hospital 5 days after the vaccination without history of contact with COVID-19 patients. On admission, laboratory tests revealed thrombocytopenia (7.3×10^4 /μL), elevated fibrin degradation products (86.5 μg/mL), D-dimer (39.28 μg/mL), lactate dehydrogenase (LDH) (812 U/L), and ferritin (7644 ng/mL) levels. No thrombosis, infarction, hemorrhage or abnormal opacity of lung field was observed with image analysis. A SARS-CoV-2 polymerase chain reaction, blood cultures, antinuclear antibody, rheumatoid factor, and cardiolipin antibodies were all negative. Argatroban and intravenous immunoglobulin were initiated considering the possibility of thrombotic thrombocytopenia which has been reported after the ChAdOx1 nCov-19 vaccine (1). Consequently, the anti-platelet factor 4 antibody was negative. However, her general condition and her laboratory test results such as LDH, ferritin, and transaminase levels deteriorated. Therefore, we initiated steroid pulse therapy (methylprednisolone 1g daily for 3 days) followed by oral prednisolone for the diagnosis of MAS triggered by SARS-CoV-2 vaccination. After the corticosteroid treatment, her symptoms and laboratory data improved dramatically without relapse. MAS-related cytokines, such as granulocyte-macrophage colony-stimulating factor, interleukin (IL)-6, IL-18, and interferon-gamma (IFN-γ) showed high serum concentrations on the day of admission; The IL-18 titre was particularly high. The levels of these cytokines had decreased by the day of discharge (hospital day 14) (Table I). We also confirmed that no pathological variants of genes associated with hereditary autoinflammatory diseases were detected. The schema of the clinical course and the methods for performing the cytokine multiplex arrays and genetic analysis are shown in the online Supplementary file. Severe COVID-19 is often associated with hypercytokinaemia (2) and the lung pathology in severe COVID-19 cases shows marked microvascular thrombosis and haemorrhage with severe inflammation that shares features with MAS (3). In patients with severe COVID-19, serum IL-18 and IL-6 levels tend to be significantly higher than those in patients with influenza virus infection (4), and these cytokines play pivotal roles in the development of MAS (5). In addition, IL-18 is reported to be a prognostic biomarker of severe COVID-19 and is correlated with haematologic/coagulation parameters (6). Aberrant IL-18 production by activated macrophages induces inadequate IFN-γ production, resulting in further activation of T helper 1 and natural killer cells, and M1 macrophages (7). In our case, the marked elevation of IL-18 in the patient's serum might reflect the macrophage activation induced by the SARS-CoV-2 spike protein produced by mRNA vaccination, and it also seemed to mimic the biopathology of severe COVID-19. Elevated levels of IL-18 and a hyperactive coagulation system leading to elevated D-dimer and ferritin levels are detected in patients with COVID-19 and MAS (8). Corticosteroids are currently the only confirmed therapeutic agents for improving the survival of COVID-19 patients. They were also effective at treating this case of MAS.

There is no known association between SARS-CoV-2 mRNA vaccines and MAS; however, our case suggests that MAS should be taken into consideration in patients who have a severe inflammatory reaction and disseminated intravascular coagulation after receiving SARS-CoV-2 mRNA vaccines.

Table I. The results of the cytokine multiplex array: Our patient's data and those of 98 healthy individuals.

	Case patient on the day of admission	Case patient on the day of discharge	Healthy individuals (95% CI)
GM-CSF (pg/mL)	194.6	Undetectable	41.2–64.4
IL-1β (pg/mL)	42.0	2.9	24.6–45.2
IL-6 (pg/mL)	7.9	0.8	1.0–1.8
IL-18 (pg/mL)	7,867.6	2,230.5	20.4–28.1
IFN-γ (pg/mL)	111.9	Undetectable	18.6–32.0

The 95% confidence interval (CI) of the serum cytokine levels of healthy individuals (n=98) are shown for comparison purposes.
GM-CSF: granulocyte-macrophage colony-stimulating factor; IL: interleukin; IFN-γ: interferon-gamma.

N. Ashizawa[1,2], *MD, PhD*
T. Takazono[2,3], *MD, PhD*
M. Umeda[4], *MD, PhD*
K. Yamamoto[2], *MD, PhD*
A. Kawakami[4], *MD, PhD*
H. Mukae[2,5], *MD, PhD*

[1]Infection Control and Education Center, [2]Department of Respiratory Medicine, Nagasaki University Hospital, Nagasaki, Japan; [3]Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [4]Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, [5]Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Please address correspondence to:
Takahiro Takazono,
Department of Infectious Diseases,
Nagasaki University Graduate
School of Biomedical Sciences,
1-7-1 Sakamoto,
Nagasaki 852-8501, Japan.
E-mail: takahiro-takazono@nagasaki-u.ac.jp

Competing interests: none declared.

References

1. Greinacher A, Thiele T, Warkentin TE *et al.*: Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021; 384: 2092-101.
2. Otsuka R, Seino KI: Macrophage activation syndrome and COVID-19. *Inflamm Regen* 2020; 40: 19.
3. McGonagle D, O'Donnell JS, Sharif K *et al.*: Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol* 2020; 2: e437-45.
4. Karaba AH, Zhou W, Hsieh LL *et al.*: Differential cytokine signatures of SARS-CoV-2 and influenza infection highlight key differences in pathobiology. *Clin Infect Dis* 2021 May 20 [Online ahead of print].
5. Schulert GS, Grom AA: Macrophage activation syndrome and cytokine-directed therapies. *Best Pract Res Clin Rheumatol* 2014; 28: 277-92.
6. Satiş H, Özger HS, Aysert Yildiz P *et al.*: Prognostic value of interleukin-18 and its association with other inflammatory markers and disease severity in COVID-19. *Cytokine* 2021; 137: 155302.
7. Migliorini P, Italiani P, Pratesi F *et al.*: The IL-1 family cytokines and receptors in autoimmune diseases. *Autoimmun Rev* 2020; 19: 102617.
8. Morris G, Bortolasci CC, Puri BK *et al.*: The cytokine storms of COVID-19, H1N1 influenza, CRS and MAS compared. Can one sized treatment fit all? *Cytokine* 2021; 144: 155593.