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Letter

Does the BNT162b2 Vaccine Trigger Antimelanoma Differentiation-Associated Gene 5 Antibody–Positive Interstitial Lung Disease?

To the Editor:

We read the report by Kitajima et al[1] with great interest. They demonstrated 4 cases of antimelanoma differentiation-associated gene 5 (anti-MDA5)–positive interstitial lung disease (ILD) manifested following SARS-CoV-2 vaccination and suggested the possibility of the increased incidence of anti-MDA5-associated ILD (anti-MDA5-ILD) due to the vaccination. This study interested us since we also encountered a case of new-onset anti-MDA5 antibody–positive clinically amyopathic dermatomyositis (CADM) with ILD, developed 8 weeks after BNT162b2 vaccination during the SARS-CoV-2 vaccination campaign in Japan. Herein, we briefly describe the case and address several issues to advance basic and clinical research in ILD related to anti-MDA5 antibodies. Written informed consent for publication was obtained from the patient, and the study design was approved by the appropriate ethics review board; ethics approval was not required.

A 39-year-old Japanese woman with no significant medical background was referred to our hospital with a 2-month history of gradually deteriorating polyarthralgia and erythema on her fingers, and a 1-month history of face erythema, all of which developed 8 weeks after the first vaccination of BNT162b2 vaccine in early September. She received the second BNT162b2 vaccine 3 weeks after the first vaccination. Physical examination showed heliotrope rash, malar rash, V neck sign, and inverse Gottron sign without muscle weakness and shortness of breath. Elevated ferritin levels (254.9 ng/mL) and a high titer of anti-MDA5 antibody (2530 index) were detected. The PCR test for SARS-CoV-2 was negative. Chest computed tomography revealed ground-glass opacity and consolidation at the right lung field bottom region (Figure 1A). Histopathological findings on precordia erythema demonstrated interface dermatitis with vacuolization and perivascular lymphocytic infiltration in the shallow layer of the dermis. She was diagnosed with

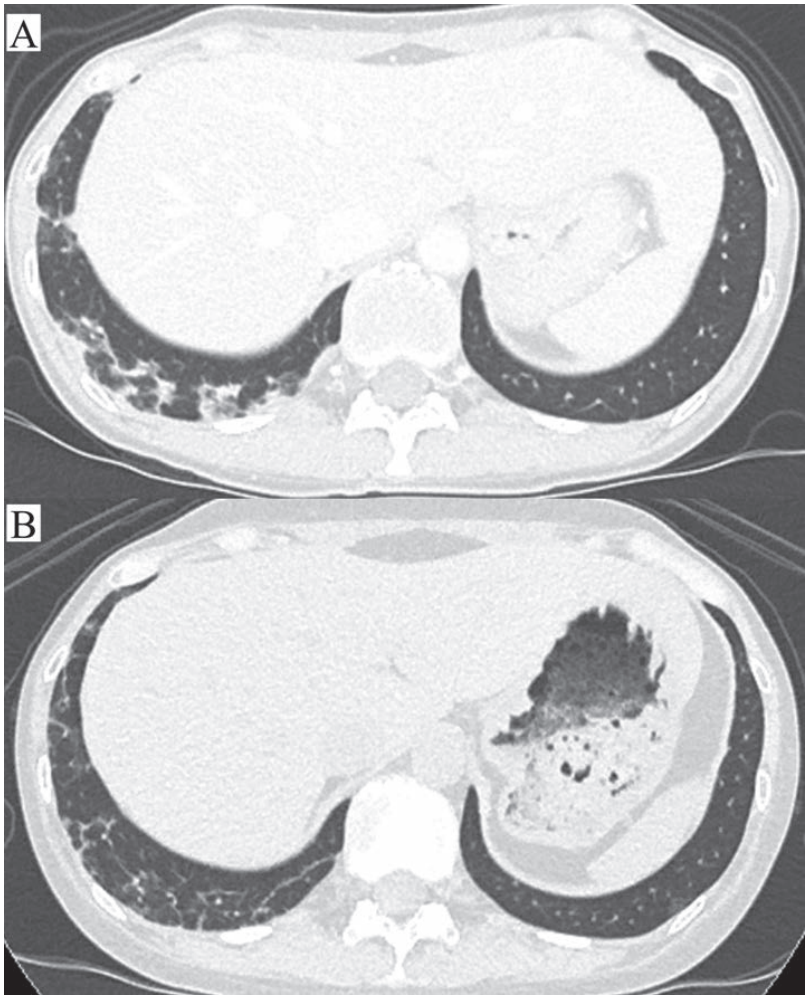

Figure 1. Chest computed tomography showing ground-glass opacity and consolidation at the right lung field bottom region (A) before treatment and (B) improved lesions after treatment.

anti-MDA5 antibody–positive CADM with ILD. High-dose glucocorticoids, tacrolimus, and intravenous cyclophosphamide dramatically improved her symptoms and ILD (Figure 1B).

Although available data on the pathogenesis of anti-MDA5-ILD remain limited, it is considered to be influenced by gene-environment interaction and associated with the upregulation of type I interferon (IFN)-stimulated genes.[2] Recognition of the BNT162b2 vaccine depends on MDA5, one of the ribonucleic acid sensors, in innate immune cells,[3] which produce multiple inflammatory mediators, including type I IFN. This results in appropriate activation of innate and adaptive immunity against SARS-CoV-2.[4] However, in genetically predisposed contexts, such as a variant of *WDFY4*,[5] MDA5 triggered by the BNT162b2 vaccine possibly induces an aberrant MDA5-mediated nuclear factor kappa B pathway, causing cell apoptosis. Excess extracellular release of MDA5 antigen amplifies expression and activation of MDA5 and increases the production of type I IFN, which create vicious cycles and then disturb immune tolerance. As a result, in individuals with certain risk HLA alleles,[2] autoantibody directed to MDA5 is postulated to be produced. We hope these possible mechanisms for anti-MDA5-ILD triggered by the vaccine would be elucidated.

On the other hand, annual positive rates of anti-MDA5 antibody and annual mean numbers of anti-MDA5-ILD were slightly higher after the SARS-CoV-2 vaccination campaign than before, but there were no statistically significant differences. This may be due to early diagnosis of the disorder, since patients are likely to seek medical examination if they present with some symptoms after being inoculated with a newly approved vaccine generated by technology different from conventional methods. Further, the 4 clusters occurred from August to October,[1] the duration of which was proposed as part of a seasonal factor attributable to disease onset.[6] Therefore, it is essential to interpret the causality of SARS-CoV-2 vaccination with caution. Further epidemiological investigation in the national population over a longer follow-up period is required to determine a direct link between SARS-CoV-2 vaccination and the development of anti-MDA5-ILD.

Predictive factors for poor prognosis in ILD associated with anti-MDA5 antibody have been vigorously explored, given the nature of rapidly progressive fatal disease course,[7] but it remains unclear whether SARS-CoV-2 vaccine-induced anti-MDA5-ILD shares a clinically similar phenotype with anti-MDA5-ILD unrelated to the vaccine, regarding demographics, symptoms, myositis subtype, and particularly, treatment responsiveness. A recent literature review reported that 6 of 7 cases (85.7%) survived,[8] but the mortality rate was 50% of 4 cases in the Kitajima et al study,[1] implying no definite conclusion about outcomes. In antineutrophil cytoplasmic antibody–associated vasculitis developed following SARS-CoV-2 vaccination, a favorable response to immunosuppressants was noted.[9] Thus, larger studies are required to reveal prognostic profiles in anti-MDA5-ILD related to SARS-CoV-2 vaccination.

More importantly, clinicians should not be discouraged from vaccination during the coronavirus disease 2019 (COVID-19) pandemic since the safety profiles of SARS-CoV-2 vaccines are confirmed in a large study including 4604 patients with rheumatic and musculoskeletal disease.[10] However, revaccination needs to be carefully judged considering the risk-benefit balance, especially in cases with a possible relationship between vaccination and developing ILD associated with anti-MDA5 antibody.

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The authors declare that they have no conflicts of interest relevant to this article.

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