The Journal of Rheumatology 2022;xx:xxxx
doi:10.3899/jrheum.220777
First Release October 1 2022

Dr. Kitajima et al reply

To the Editor:

We thank Mutoh et al[1] for their interest in our study on antimelanoma differentiation-associated gene 5 antibody–positive interstitial lung disease (anti-MDA5-ILD) after vaccination with coronavirus disease 2019 (COVID-19) mRNA vaccines[2] and for sharing their clinical experience.

Mutoh et al[1] reported a case of anti-MDA5-ILD that developed 8 weeks after COVID-19 mRNA vaccination in Japan. This case is similar to the cases that we have encountered. A recent literature review also reported 7 cases of anti-MDA5-ILD after COVID-19 vaccination.[3] Collectively, these cases provide evidence of an association between vaccination with COVID-19 mRNA vaccines and anti-MDA5-ILD, and suggest the possibility of COVID-19 mRNA-vaccine-induced anti-MDA5-ILD. However, these cases do not explain the relationship between vaccination with COVID-19 mRNA vaccines and anti-MDA5-ILD. In our single-center retrospective analysis, we did not find a statistically significant difference in the annual number of cases of anti-MDA5-ILD before and after the COVID-19 vaccination campaign in Japan.[2] We agree with Mutoh et al[1] that further large epidemiological population-based studies are needed to clarify the relationship between anti-MDA5-ILD and vaccination with COVID-19 mRNA vaccines.

Mutoh et al[1] pointed out the possibility that COVID-19 vaccination could lead to early diagnosis of anti-MDA5-ILD, as patients are likely to seek medical attention if they develop symptoms shortly after being inoculated with a new vaccine. However, the cases in our study were not diagnosed early. All 4 cases of anti-MDA5-ILD in our study had multiple poor prognostic indicators on admission (hypoxia, hyperferritinemia, computed tomography findings, and high lactate dehydrogenase levels), suggesting advanced disease.[4] We are concerned about the delay in the diagnosis of cases of anti-MDA5-ILD during the COVID-19 pandemic. Anti-MDA5-ILD is often regarded as a form of pneumonia, similar to COVID-19, rather than as a connective tissue disease complicated by ILD and a dermatomyositis (DM)-specific rash.[5] Therefore, it is important to rule out anti-MDA5-ILD in patients with COVID-19–like lung disease. Delayed diagnosis of anti-MDA5-ILD may further delay the initiation of aggressive immunosuppressive therapy needed to control anti-MDA5-ILD and may worsen the prognosis.[4] In particular, the widespread use of telemedicine during the COVID-19 pandemic may lead to a lack of a full physical examination, and the DM-specific rash, which is necessary for the diagnosis of anti-MDA5-ILD, may be missed. In addition, patients with suspected COVID-19 are often examined by general physicians, and not by rheumatologists or respiratory physicians. Therefore, physicians should consider anti-MDA5-ILD in the differential diagnosis of patients with COVID-19–like lung disease.

COVID-19 vaccination has changed the course of the pandemic and has saved tens of millions of lives globally.[6] In addition, third or fourth vaccinations have been approved because of the emergence of new Omicron subvariants and the reduced protection provided by 2 doses of COVID-19 vaccines.[7] Without an ongoing large-scale vaccination campaign, the healthcare system could become overwhelmed. Therefore, COVID-19 vaccination campaigns should continue. In clinical practice, it is difficult to determine the risk of developing anti-MDA5-ILD based on the associated genetic factors.[8] Therefore, in patients with pneumonia and a rash after COVID-19 vaccination, anti-MDA5-ILD should always be considered in the differential diagnosis.

In order to improve our understanding of anti-MDA5-ILD after COVID-19 vaccination, further case reports are required, and further studies are needed to clarify the pathogenesis of anti-MDA5-ILD after COVID-19 vaccination and its association with the type of vaccine.

Takamasa Kitajima[1], MD
Atsushi Funauchi[1], MD
Toshiki Nakajima[2], MD, PhD
Satoshi Marumo[1], MD, PhD
Yoshitaka Imura[2], MD, PhD
Motonari Fukui[1], MD, PhD
[1]Respiratory Disease Center, Kitano Hospital, Tazuke Kofukai Medical Research Institute;
[2]Department of Clinical Immunology and Rheumatology, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan.

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

Address correspondence to Dr. T. Kitajima, Respiratory Disease Center, Tazuke Kofukai Medical Research Institute, Kitano Hospital, 2-4-20 Ohgimachi, Kita-ku, Osaka 530-8480, Japan. Email: m-kitajima@kitano-hp.or.jp.

REFERENCES

1. Mutoh T, Takahashi M, Nagai T, Kudo M. Does the BNT162b2 vaccine trigger anti-melanoma differentiation-associated gene 5 antibody–positive interstitial lung disease? J Rheumatol 2022;xxxxxxxxx.
2. Kitajima T, Funauchi A, Nakajima T, Marumo S, Imura Y, Fukui M. Anti-melanoma differentiation-associated gene 5 antibody-positive interstitial lung disease after vaccination with COVID-19 mRNA vaccine. J Rheumatol 2022 Jun 15 (Epub ahead of print).
3. Gonzalez D, Gupta L, Murthy V, et al. Anti-MDA5 dermatomyositis after COVID-19 vaccination: a case-based review Rheumatol Int 2022:42:1629-41.
4. Wu W, Guo L, Fu Y, et al. Interstitial lung disease in anti-MDA5 positive dermatomyositis. Clin Rev Allergy Immunol 2021; 60:293-304.
5. Giannini M, Ohana M, Nespola B, Zanframundo G, Geny B, Meyer A. Similarities between COVID-19 and anti-MDA5 syndrome: what can we learn for better care? Eur Respir J 2020;56:2001618.
6. Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani

AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. Lancet Infect Dis 2022 Jun 23 (Epub ahead of print).
7. Magen O, Waxman JG, Makov-Assif M, et al. Fourth dose of BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med 2022;386:1603-14.
8. Kochi Y, Kamatani Y, Kondo Y, et al. Splicing variant of WDFY4 augments MDA5 signalling and the risk of clinically amyopathic dermatomyositis. Ann Rheum Dis 2018;77:602-11.