Received: 30 November 2021 | Revised: 14 March 2022 | Accepted: 16 March 2022

DOI: 10.1002/mus.27531

MUSCLE&NERVE WILEY

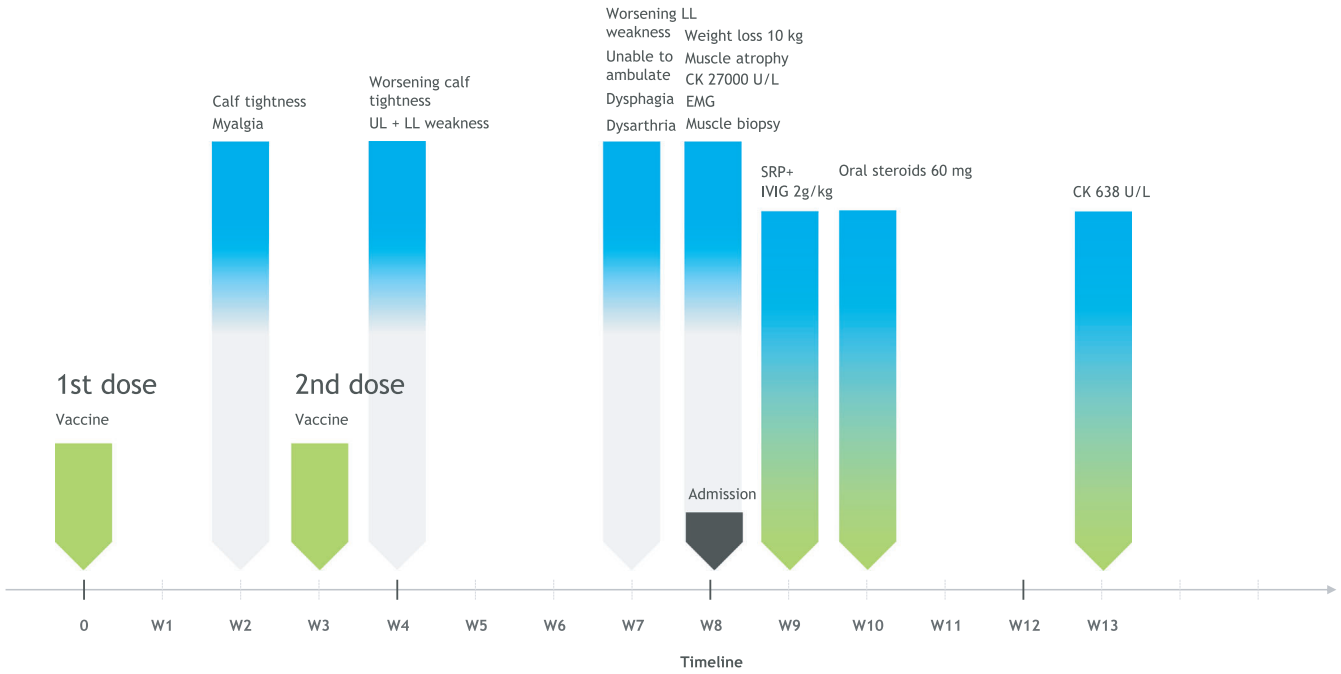
A temporal association between COVID-19 vaccination and immune-mediated necrotizing myopathy

Various neuromuscular complications of coronavirus disease 2019 (COVID-19) vaccine have been reported, including Bell's palsy and Guillain-Barré syndrome.[1] However, inflammatory myositis following COVID-19 vaccine has rarely been reported. We report a case of anti-signal recognition particle (SRP) positive immune-mediated necrotizing myopathy (IMNM) after COVID-19 vaccination.

A previously healthy 54-y-old man presented with calf muscle tightness 2 wk after the first inoculation of CoronaVac COVID-19 Vaccine (Sinovac Biotech) into his deltoid muscle (Figure 1). He received his second dose of vaccination 3 wk later. A week after the second dose, he developed bilateral proximal upper and lower limb weakness. After 3 wk, he was unable to ambulate and subsequently developed dysarthria and dysphagia. There were no sensory, urinary, or bowel symptoms. On presentation 8 wk after the first vaccination, he had lost 10 kg of weight.

On examination, there was atrophy of the quadriceps and supraspinatus muscles. He had dysarthric speech, poor palate elevation, and neck flexion weakness. Limb muscle weakness was predominantly proximal, Medical Research Council (MRC) grade 2/5 in the upper and lower limbs, while distal muscles of the upper and lower limbs were grade 4/5 and 5/5, respectively. Reflexes were reduced in the lower limbs but normal in the upper limbs. Sensory examination was normal.

His nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) tested with reverse-transcriptase polymerase chain reaction was negative. Serum creatine kinase (CK) was markedly elevated at 27,000 U/L. Nerve conduction studies were normal; needle electromyography (EMG) showed fibrillation potentials and positive sharp waves, and short duration, low amplitude motor unit potentials with early recruitment in the deltoid and iliopsoas mus-



CK, creatine kinase; EMG, electromyography; IVIG, intravenous immunoglobulin; LL, lower limb; SRP, anti-signal recognition particle antibody; UL, upper limb

FIGURE 1 Timeline of events

Abbreviations: CK, creatine kinase; COVID-19, coronavirus disease 2019; EMG, electromyography; IMNM, immune-mediated necrotizing myopathy; MRC, Medical Research Council; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SRP, signal recognition particle.

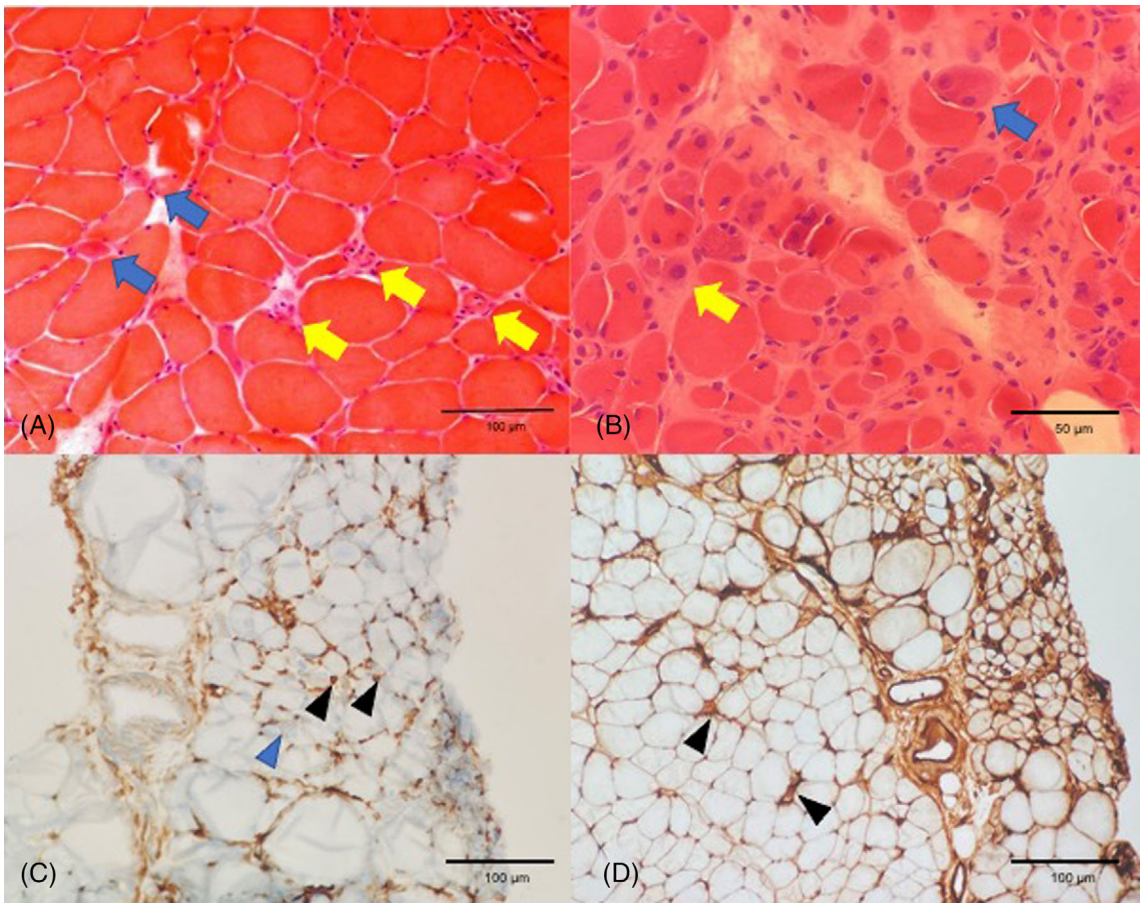


FIGURE 2 Histopathological examination of the deltoid muscle with hematoxylin and eosin (H&E) staining at low power (A) and high power (B), CD68 staining (C), and major histocompatibility complex (MHC) class 1 staining (D). A,B, H&E staining reveals scattered isolated necrotic muscle fibers (yellow arrows) and regenerating fibers (blue arrows) without marked inflammation. C, Scattered inflammatory infiltrates were predominantly $CD68^{+}$ histiocytes (black arrowheads). The atrophic fibers were accompanied by very sparse $CD3^{+}$ T-lymphocytes (blue arrowhead). D, Most of the muscle fibers exhibited sarcolemmal MHC-1 positivity, which was more intense among the atrophic and degenerated fibers (black arrowheads). Original magnification: X 10 objective (A,C,D); x 20 objective (B)

cles. Biopsy of the deltoid muscle showed scattered necrotic and regenerating muscle fibers without marked inflammation (Figure 2). Anti-SRP antibody titers were markedly elevated whereas anti-hydroxyl-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies were negative.

A diagnosis of IMNM was made, and he was treated with intravenous immunoglobulin (IVIG) 2 g/kg followed by oral prednisolone 60 mg daily. There was gradual, partial improvement with proximal upper limb power improving to MRC grade 3/5 and resolution of bulbar and neck flexion weakness. Proximal lower limbs remained at 2/5. Whole body computed tomography did not show any malignancy, and the serum CK decreased to 638 U/L 4 weeks after the IVIG.

The patient presented with myalgia and proximal muscle weakness after two doses of COVID-19 vaccination. The temporal relationship of the COVID-19 vaccination to the clinical presentation suggests an association between the two. However, the possibility of coincidental occurrence cannot be entirely excluded.

COVID-19 infection has been reported to be associated with various skeletal muscle complications, ranging from asymptomatic hyperCKemia, to myalgia, myositis, and rhabdomyolysis.[2] Several mechanisms have been hypothesized, which include direct viral invasion of the myocytes or hyperinflammation syndrome. However, evidence favors indirect muscle injury, as an autopsy case–control study showed that most patients who died of COVID-19 had myositis with little evidence of direct muscle infection.[3] COVID-19 myositis could, therefore, be due to deposition of virus-antibody complexes on myocytes or expression of muscle antigen on cell membrane induced by the virus and damage by cytokine storm.[4]

Post-vaccination inflammatory myositis could possibly develop due to the same mechanisms. The vaccine reported here is an inactivated vaccine against COVID-19 that induces the immune system to produce neutralizing antibodies to SARS-CoV-2. Anti-SARS-CoV-2 antibodies may potentially bind to human antigens due to the high antigenic similarity between the spike protein and human proteins.

There have been a few cases of inflammatory myositis post COVID-19 vaccination reported to date.[5-7] All the myositis profiles were negative, except in two cases where PM/Scl-75 or SAE1 was positive.[6] In conclusion, we think that association is not improbable considering the temporal relationship between vaccination and development of myositis. Larger population-based studies would be required to assess any causal-relationship between COVID-19 vaccination and IMNM.

ACKNOWLEDGEMENT

Not applicable.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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DOI 10.1002/mus.27531

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The difficulty of confirming pharmacovigilance signals in myasthenia gravis

We read with great interest the study of Pham Nguyen et al. on the potential of macrolides and fluoroquinolones to worsen myasthenia.[1] We were surprised by the low and insignificant odds ratios (ORs) for myasthenia worsening for fluoroquinolones and macrolides in comparison to beta lactam antibiotics. This is in contrast to a recent result from pharmacovigilance data from the World Health Organization (WHO) database VigiBase.[2] To analyze such data, reporting odds ratios (ROR) are calculated as ORs from the reporting frequencies and serve as a surrogate to quantify the risk. The recalculated RORs (with all beta lactams as a reference) from Table 1 in the previously published paper[2] were as high as 7.9 (macrolides) and 6.8 (fluoroquinolones), respectively. We can think of two mechanisms that could result in this difference:

Abbreviations: OR, odd ratio; ROR, reporting odds ratio; WHO, World Health Organization.

First, one of the strengths of the study Pham Nguyen et al.,[1] as compared to that of Trillenberg and Thern,[2] is that simultaneous prescription of the two target drugs was known and could be handled by mixed effects parametric survival regression. In the framework of VigiBase, with limited knowledge of individual cases, odd ratios would be calculated from the observed frequencies only. In this situation, a report in a subject that received both target drugs would increase the OR for both drugs to the same amount as a report of a worsening after exposure to a single drug. The survival regression, however, would distribute the increase to both drugs, resulting in lower ORs if there were many simultaneous exposures to the target drugs.

Second, apparent low ORs for the target drugs in the more recent paper[1] might be caused by selecting higher risk comparison drugs within the beta lactam group (thus increasing the denominator in the