Successful Treatment of Delayed Localized Necrotizing Inflammatory Myositis After Severe Acute Respiratory Syndrome Coronavirus 2 mRNA-1273 Vaccine: A Case Report

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Reported adverse reactions to the mRNA-1273 vaccine (Spikevax, Moderna Inc) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) range from mild, local delayed cutaneous reactions to rarer, more serious reactions such as myocardiitis. Here, we describe the presentation and successful treatment of delayed, localized necrotizing inflammatory myositis following a third dose of the mRNA-1273 SARS-CoV-2 vaccine. To our knowledge, this is the first report of biopsy-confirmed, delayed inflammatory myositis after administration of an mRNA-1273 SARS-CoV-2 vaccine booster.

Keywords. COVID-19; myositis; mRNA vaccine; SARS-CoV-2.

More than 95 million Americans have received a booster (third or subsequent) dose of a coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccine since boosters were initially authorized in September 2021 [1]. Adverse reactions to COVID-19 mRNA vaccines are not uncommon, although most are mild local reactions, such as pain, tenderness, or redness at the injection site, or brief, self-limited systemic symptoms [2]. A minority of vaccine recipients develop mild, delayed, large local cutaneous reactions, and a much smaller number develop severe reactions including myocardiitis and pericarditis [3–6]. A few cases of myositis have also been reported following first or second doses of both types of currently licensed COVID-19 mRNA vaccines, largely with the BNT162b2 (Pfizer/BioNTech) vaccine [7–12]. We present a novel case of delayed, localized necrotizing inflammatory myositis following a third dose of the mRNA-1273 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine.

CASE REPORT

A 64-year-old man with coronary artery disease and diabetes presented to our hospital with 2.5 weeks of left upper arm pain and swelling accompanied by fevers and fatigue that developed 1 week after a third (booster, 50 µg) dose of the mRNA-1273 vaccine.

The patient had no prior history of adverse medication or vaccine reactions, nor of SARS-CoV-2 infection. He had received the primary series of 2 doses of the mRNA-1273 vaccine 7 and 8 months before, both in the left upper arm. Each dose induced 1 day of subjective fever and mild arm soreness, neither requiring medical attention. His third dose was administered in the same arm without known breach of sterile technique. The following day he experienced mild, self-resolving subjective fever and soreness. Six days later, intermittent low-grade fevers, fatigue, and severe left upper arm pain developed, with swelling extending to his hand and redness overlying the injection site. His symptoms prompted 2 emergency department visits and a primary care evaluation. An ultrasound was negative for deep vein thrombosis (DVT), and computed tomographic scan showed superficial soft tissue edema without fluid collection. He was initially managed conservatively, then prescribed oral cephalexin (500 mg 4 times daily) for 1 week, but symptoms progressed.

The patient presented to our hospital 2.5 weeks after symptom onset. He had fever (38.7°C) and left arm swelling with tenderness, woody induration of the left deltoid and triceps with overlying erythema (Figure 1). Shoulder and elbow range of motion were limited by muscular pain and swelling. Erythrocyte sedimentation rate was 127 mm/hour (reference, 0–13 mm/hour), and C-reactive protein level was 250.8 mg/L (reference, <8.0 mg/L). Table 1 shows additional laboratory results. He had macrocytic anemia and acute kidney injury but no myoglobinuria. Blood cultures and SARS-CoV-2 polymerase chain reaction were negative. Troponin level was 30 ng/L (reference, 0–14 ng/L), but serum creatine kinase (CK) was not elevated and electrocardiography showed no evidence of active
ischemia or myocarditis. SARS-CoV-2 spike antibody titer was >25,000 units/mL. Extensive testing for rheumatologic and myositis-associated autoantibodies was negative. Magnetic resonance imaging (MRI) showed extensive left deltoid, triceps, and brachioradialis myositis without abscess or osteomyelitis (Figure 2). Pathologic examination of tissue obtained via surgical muscle biopsy revealed necrotizing inflammatory myopathy (Figure 3A–C), with negative microbiologic stains, negative tissue cultures, and negative in situ hybridization for SARS-CoV-2 spike mRNA (Figure 3D).

The patient initially received intravenous vancomycin and piperacillin-tazobactam without improvement. Antibiotics were stopped when blood and tissue cultures returned negative. Oral prednisone (40 mg/day) was initiated with near-immediate relief. Pain and fevers largely resolved within 2 days, accompanied by objectively diminished swelling and tenderness and improved range of motion. Inflammatory markers and renal function improved, but anemia persisted.

Subsequent bone marrow biopsies revealed findings consistent with myelodysplastic syndrome (MDS) with multilineage dysplasia, with evidence of mutation in U2AF1 on genetic testing. Two months after discharge, the patient developed fevers, right peroneal vein DVT, overlying superficial bullae consistent with Sweet syndrome (neutrophilic dermatosis) on skin biopsy, and adjacent right lower leg myositis noted on MRI. Genetic testing for VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome was negative. He received prednisone and apixaban with symptomatic improvement.

**Table 1. Results of Selected Studies**

| Laboratory Investigation                  | Reference Range | Initial Value During Hospitalization | Maximum Value During Hospitalization | Value 1 mo After Discharge |
|-------------------------------------------|-----------------|-------------------------------------|-------------------------------------|---------------------------|
| SARS-CoV-2 spike Ab, U/mL                 | <0.80           | >25,000                             |                                     | >25,000                   |
| Inflammatory markers                      |                 |                                     |                                     |                           |
| Sedimentation rate, mm/h                  | 0–13            | 127                                 | ...                                 | 31                        |
| C-reactive protein, mg/L                  | <8.0            | 187.9                               | 250.8                               | 1.4                       |
| D-dimer, ng/mL                            | <500            | 1499                                | ...                                 | 1969                      |
| Ferritin, µg/L                            | 20–300          | 1279                                | ...                                 | 542                       |
| Metabolic labs                            |                 |                                     |                                     |                           |
| Creatine kinase, U/L                      | 60–400          | 161                                 | ...                                 | ...                       |
| Troponin, ng/L                            | 0–14            | 30                                  | ...                                 | ...                       |
| Creatinine, mg/dL                         | 0.60–1.50       | 1.13                                | 2.13                                | 1.69                      |
| BUN, mg/dL                                | 8–25            | 23                                  | 48                                  | 27                        |
| Hematologic labs                          |                 |                                     |                                     |                           |
| Hemoglobin, g/dL                          | 13.5–17.5       | 8.4                                 | 9.2                                 | 7.7                       |
| MCV, fl                                   | 80.0–100.0      | 109.4                               | ...                                 | 108.0                     |
| LDH, U/L                                  | 110–210         | 169                                 | ...                                 | 236                       |
| Haptoglobin, mg/dL                        | 30–200          | 367                                 | ...                                 | 47                        |
| Reticulocytes, %                          | 0.5–2.5         | 1.6                                 | ...                                 | 2.4                       |
| Rheumatologic labs                        |                 |                                     |                                     |                           |
| ANA                                        | ...             | 1:40 speckled (negative)            | ...                                 | ...                       |
| ANCA                                       | ...             | Negative                            | ...                                 | ...                       |
| Autoantibodies: anti-HMG-CoA reductase, ... | ...             | Negative                            | ...                                 | ...                       |

Abbreviations: Ab, antibody; ANCA, anti-neutrophil cytoplasmic antibody; ANA, antinuclear antibody; BUN, blood urea nitrogen; EJ, glycyl-tRNA synthetase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; Jo-1, histidyl-tRNA synthetase; La, Sjögren’s-syndrome-related antigen B; LDH, lactate dehydrogenase; OJ, isoleucyl-tRNA synthetase; MCV, mean corpuscular volume; MDAs, melanoma differentiation-associated gene 5; NXP-2, nuclear matrix protein; PL-7, threonyl-tRNA synthetase; PL-12, alanyl-tRNA synthetase; PM, polymyositis; RNP, ribonucleoprotein; Ro, Sjögren’s-syndrome-related antigen A; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Scl, scleroderma; SRP, signal recognition particle; TIF, transcription intermediary factor.
DISCUSSION

Here we describe a novel presentation and successful treatment of biopsy-confirmed, delayed, localized myositis requiring hospitalization after a third (ie, booster, 50 µg) dose of the mRNA-1273 vaccine. Microbiologic testing, serologic investigations, and a trial of broad-spectrum antibiotics failed to identify non-vaccine-related etiologies. During the patient’s presentation, he was found to have significant anemia that persisted after myositis resolution, and subsequent bone marrow biopsies showed pathologic and genetic features consistent with previously undiagnosed MDS. Two months after his initial, vaccine-associated hospitalization, the patient re-presented with fevers and right lower extremity DVT, biopsy-confirmed Sweet syndrome, and MRI evidence of myositis in the contiguous musculature. The clinical, pathologic, and radiographic differences between these 2 episodes suggest that his second presentation was attributable to underlying MDS. We know of no existing evidence that MDS increases adverse event risk after mRNA vaccination, although a potential contribution cannot be excluded.

Adverse delayed cutaneous reactions to the initial series of the mRNA-1273 vaccine have been previously studied. In the phase 3 clinical trial of the vaccine, delayed injection-site reactions (defined as onset on or after day 8) occurred in 0.8% of participants after the first dose and in 0.2% of participants after the second dose [2]. Subsequent case series have further characterized these delayed large local cutaneous reactions to the initial mRNA-1273 vaccine dose [3, 4], with median onset after 1 week, similar to our patient. Symptoms after the initial dose typically resolved in 5–6 days, usually treated with ice and antihistamines, and patients were able to tolerate the second dose. Skin biopsy in 1 patient showed superficial perivascular and perifollicular lymphocytic infiltrates with rare eosinophils and scattered mast cells, suggestive of T-cell-mediated hypersensitivity [3]. A separate case series followed patients who had experienced delayed, large, local cutaneous reactions during their initial vaccine series, as they subsequently received booster doses of a COVID-19 mRNA vaccine [6]. Only 4 of the 12 patients developed local cutaneous reactions, which were generally mild, early in onset, and self-resolved at a median duration of 4.5 days without requiring steroid treatment.

Both mild cutaneous reactions, as well as more severe local reactions like our patient’s, can be easily misdiagnosed as infectious cellulitis. However, the risk of infection after intramuscular vaccination injections performed with sterile technique is very low [13]. Prior literature has reported on extensive limb swelling and myositis associated with a wide variety of vaccines, including both live attenuated and inactivated vaccines. Some of these effects have been attributed to adjuvants, such as alum, that are not present in the mRNA-1273 vaccine [14–16]. There have been sporadic case reports describing inflammatory myositis (mainly dermatomyositis and very rarely macrophagic myofasciitis) following certain vaccines, including for hepatitis B virus [17, 18]. One case report described postvaccination inflammatory myositis within 2 days after the first dose (2 patients) or second dose (1 patient) of the ChAdOx1 COVID-19 vaccine, 1 of whom had a muscle biopsy showing features of small- and medium-vessel vasculitis [19].
Several cases of myositis after first or second doses of SARS-CoV-2 mRNA vaccination have been reported [7–12]. In these cases, 4 patients’ reactions were ascribed to the first or second doses of the BNT162b2 vaccine, of which 1 was biopsy-proven. One patient’s reaction was attributed to the first dose of the mRNA-1273 vaccine, and 2 patients’ reactions were ascribed to the second dose of an unspecified mRNA vaccine. In the case we report here, the myositis occurred with the third (reduced) booster dose of the mRNA-1273 vaccine dose, after the initial 2-dose series had been well tolerated.

In prior reports, the latency of onset, clinical features, and severity of myositis after mRNA COVID-19 vaccination have varied substantially, suggesting potentially divergent underlying mechanisms (Table 2) [7–12]. Some patients, like our

Table 2. Summary of Case Reports Describing Myositis Following SARS-CoV-2 mRNA Vaccination

| Vaccine Type | Dose | Time to Myositis Onset After Dose, d | Location of Myositis | Peak Reported CK Level, U/L | Myositis-Specific Autoantibody | Treatments Used | Response to Treatment |
|--------------|------|-----------------------------------|---------------------|---------------------------|-------------------------------|----------------|----------------------|
| mRNA-1273a  | Third 7 | Arm, unilateral (injection site) | 161 (not elevated) | Negative | Prednisone | Symptoms resolved after 2 d |
| mRNA-1273[9] | First 5 | Bilateral proximal lower extremities | 17 959 | Negative | Methylprednisolone | Symptomatic improvement within days, complete resolution after 4 wk |
| BNT162b2[10] | First | 1 Lower back | 22 000 | Negative | Conservative management | Symptomatic improvement after 5 d |
| BNT162b2[11] | First 2 | Bilateral proximal lower extremities | 11 330 | Positive: anti-Mi-2a, anti-Ro-52 | Methylprednisolone, prednisolone, IVIG, cyclophosphamide, mycophenolate | Did not improve with 1 wk on steroids, myopathy resolved 5 mo after IVIG and cyclophosphamide, rash resolved later on mycophenolate and steroid taper |
| BNT162b2[11] | Second 1 | Bilateral shoulders, hips | 10 222 | Positive: antifibrillarin | Methylprednisolone, prednisolone, IVIG | Did not improve with 6 d on steroids, improved after IVIG and steroid taper (duration not specified) |
| BNT162b2[12] | Second 6 | Neck, bilateral proximal upper and lower extremities | 4778 | Negative | Glucocorticoids, azathioprine, tacrolimus | Symptoms gradually improved after steroids and azathioprine (changed to tacrolimus due to neutropenia) (duration not specified) |
| Unspecified[8] | First 28 | Arm, contralateral (not injection site) | 236 | No testing described | Methylprednisolone, prednisolone | Symptoms improved after treatment (duration not specified) |
| Unspecified[7] | Second 8 | Arm, unilateral (injection site) | Elevated (no value specified) | No testing described | Conservative management | Symptoms resolved over the course of 6 wk |

Abbreviations: CK, creatinine kinase; IVIG, intravenous immunoglobulin; mRNA, messenger RNA.

[8] The patient described in this case report.
case, developed localized myositis at the injection site or had similar latency of onset approximately 1 week following the vaccine, while some developed myositis at distant sites or developed symptoms 1 day following the vaccine. For the previously reported cases, all patients reportedly had elevated CK, unlike our patient. One patient developed myositis at the injection site 8 days after second dose of an unspecified COVID-19 mRNA vaccine with increased CK that was managed conservatively [7]. Another patient developed myositis in the arm (not at the injection site) 4 weeks later with mildly elevated CK treated with glucocorticoids [8]. One patient case occurred 5 days following first dose of the mRNA-1273 vaccine with lower leg myositis (distant from injection site) with markedly elevated CK and aminotransferases, though only mildly elevated creatinine [9]. Symptoms were treated with intravenous methylprednisolone followed by oral tapering. Several cases of myositis following the BNT162b2 vaccine have been described [10–12]. One patient developed lower back pain (distant from injection site) 1 day after the first dose of the BNT162b2 vaccine with elevated CK, transaminitis, and hematuria [10]. The patient had negative testing for myositis-associated autoantibodies and was treated conservatively for rhabdomyolysis without steroids. A case series described 2 patients with dermatomyositis and inflammatory myositis, respectively (neither of which were localized to the injection site) following the BNT162b2 vaccine [11]. One patient developed rash and proximal myopathy 2 days following the BNT162b2 vaccine with elevated CK and had positive anti–Mi-2a and anti–Ro-62 antibodies [11]. The other developed diffuse proximal myopathy 1 day following second dose of BNT162b2 vaccine with elevated CK, acute kidney injury, and positive anti-fibrillarin antibody. Both patients were treated with intravenous methylprednisolone followed by oral tapering and intravenous immunoglobulin therapy. Last, 1 patient developed diffuse myositis (not localized to the injection site) 6 days after the second dose of the BNT162b2 vaccine with rash and elevated CK with unremarkable urinalysis [12]. The patient was treated with glucocorticoids and azathioprine transitioned to tacrolimus. Interestingly, the biopsy showed massive macrophage infiltration, whereas our patient’s biopsy showed only occasional myophagocytosis [12]. Notably, our report is unique in documenting absence of residual (ie, vaccine-derived) SARS-CoV-2 spike mRNA on biopsy.

The mechanisms of myositis following COVID-19 mRNA vaccination are unclear and warrant additional study. Our patient’s presentation and findings on muscle biopsy, including the degree of inflammation and necrosis, are not consistent with the simple delayed T-cell–mediated hypersensitivity reaction observed in more benign cutaneous reactions [3]. Another possible etiology could be antigenic similarity between human proteins and SARS-CoV-2 spike protein, which could lead to anti-SARS-CoV-2 antibodies with cross-specificity against human antigens. Critically ill patients with COVID-19 can develop a postinfectious immune-mediated myopathy, with some displaying a perifascicular expression of major histocompatibility complex antigens as in dermatomyositis [20]. Case reports of rhabdomyolysis presenting secondary to COVID-19 have also been described [21–23]. COVID-19 mRNA vaccines are associated with far fewer systemic immune-mediated adverse events than COVID-19 itself, although these vaccines have been linked to self-limited myocarditis and pericarditis in a small minority of patients [5, 19]. In our patient, the level of anti-SARS-CoV-2 spike antibody was extremely high (>25 000 units/mL) and there was evidence of significant inflammatory infiltrate and complement activation in the muscle biopsy (though the pattern was not strongly consistent with dermatomyositis). However, testing for autoantibodies against antigens classically associated with myositis was negative in our patient. It is also notable that his myositis affected only muscles at the injection site, suggesting a reaction driven by localized constituents or effects of the vaccine.

In conclusion, serious adverse reactions to SARS-CoV-2 mRNA vaccines—including myositis—are rare but can occur even after a third vaccine dose. Importantly, our patient’s reaction proved exquisitely steroid-responsive. We hope this report provides additional insight and guidance to clinicians regarding diagnosis and management of adverse vaccine reactions. Clinical awareness of this rare presentation is important, but we urge that it not dissuade clinicians and patients from pursuing the extraordinary clinical and public health benefits of vaccination against SARS-CoV-2.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest.

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