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Clinicopathological Characteristics of Inflammatory Myositis Induced by COVID-19 Vaccine (Pfizer-BioNTech BNT162b2): A Case Report

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ABSTRACT

As more individuals were coronavirus disease 2019 (COVID-19) vaccinated, unexpected side effects appeared. Herein, we present the case of a 30-year-old male patient with myopathy in both extremities after the second dose of the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine. Symptoms, swelling and pain, started from the proximal upper and lower extremities and extended to the distal parts. Although he underwent massive hydration, the muscle enzyme level continuously increased. He complained of dysphagia and dysarthria. Microscopically, muscle biopsy showed multifocal or scattered macrophage infiltration and degenerated myofibers. In contrast to general myopathy including inflammatory myositis and rhabdomyolysis, vaccine-induced inflammatory myositis shows a prolonged increase in muscle enzyme levels and multifocal macrophage infiltration with necrosis of the muscle fibers. Symptoms improved with glucocorticoid and immunosuppressive treatment. If vaccinated individuals experience severe and continuous muscle pain and swelling, clinicians should consider vaccine-induced inflammatory myositis, measure the muscle enzyme levels, and perform muscle biopsy for a definite diagnosis.

Keywords: Coronavirus; Vaccination; Myopathy; Rhabdomyolysis; Inflammatory Myositis

INTRODUCTION

The coronavirus disease 2019 (COVID-19) epidemic has caused public health emergencies worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, is an enveloped, positive-sense, single-stranded RNA virus with spike glycoprotein. The spike protein has been shown to interact by binding with cellular receptors, which allows the entry of the virus into host cells. The study of this mechanism contributed to the development of vaccines to control COVID-19.[1] The mRNA-based vaccine demonstrated safety and efficacy in a clinical trial (NCT04368728), and in December 2020, the US Food and Drug Administration issued an Emergency Use Authorization for the Pfizer-BioNTech (BNT162b2) vaccine.[2,3]

Author Contributions

Conceptualization: Kim JH,[1] Woo CG. Data curation: Kim JH1, Woo CG. Formal analysis: Woo CG. Funding acquisition: Woo CG. Investigation: Kim JH,[1] Kim JH.[2] Methodology: Kim JH,[1] Kim JH.[2] Software: Kim JH,[1] Kim JH.[2] Validation: Kim JH,[1] Woo CG. Visualization: Kim JH,[1] Woo CG. Writing - original draft: Kim JH,[1] Woo CG. Writing - review & editing: Kim JH,[1] Kim JH,[2] Woo CG.

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Inevitably, various side effects were encountered following COVID-19 vaccination.[4] We encountered a case of rhabdomyopathy after vaccination. To the best of our knowledge, little is known about the clinicopathological characteristics of COVID-19 vaccine-induced rhabdomyopathy. Here, we present the first case in South Korea of rhabdomyopathy in a young man after receiving the second dose of the Pfizer-BioNTech (BNT162b2) vaccine.

CASE DESCRIPTION

Herein, we present the case of a 30-year-old man with progressively worsening muscle swelling and pain in both extremities after the second dose of the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine.

He presented to the emergency room (ER) of our tertiary hospital for intermittent fever (> 38^{0}C), skin rash, and polymyalgia 6 days after receiving the second dose of the BNT162b2 vaccine. The initial serum level of aspartate aminotransferase (AST) was 45 IU/L, alanine aminotransferase (ALT) was 37 IU/L, creatinine phosphokinase (CPK) was 842 U/L (normal range 58–348 U/L), and creatinine kinase-myocardial band (CK-MB) was 6.1 U/L (normal range 0–4.9 U/L). Complete blood count profiles and acute-phase reactant were within the normal range. The urinalysis results were unremarkable. Since no specific findings were observed in the work-up, he returned home after receiving propacetamol.

After 13 days, the patient revisited the ER for worsening symptoms. He had an erythematous purpuric skin rash with an itching sensation on his face, knuckles of both hands, and trunk (**Fig. 1**). He complained of pain, tenderness, swelling, and a heating sensation in the proximal upper and lower extremities. The patient denied any previous medical history, current allopathic or herbal medication, excessive exercise, trauma, and alcohol consumption. He had no family history of autoimmune or musculoskeletal diseases. His vital signs were unremarkable. Muscle power and neurological signs were normal during the initial physical examination. Laboratory results included CPK, 4778 U/L; CK-MB, 43.78 U/L; lactate dehydrogenase, 1120 U/L; AST, 275 IU/L; ALT, 210 IU/L; and myoglobin, 442.8 ng/ml. Blood urea nitrogen, creatinine, erythrocyte sedimentation rate (ESR), and hs C-reactive protein (CRP) were within the normal range.

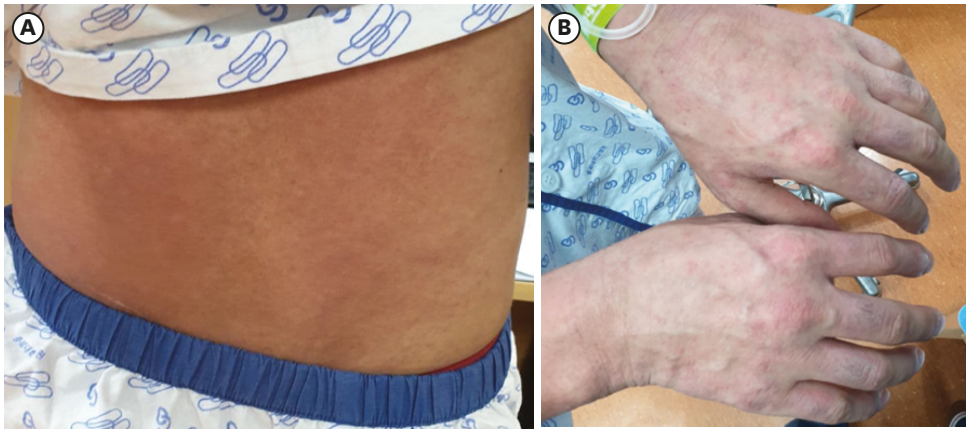

Fig. 1. Erythematous purpuric plaques on the trunk (**A**) and both hands (**B**).

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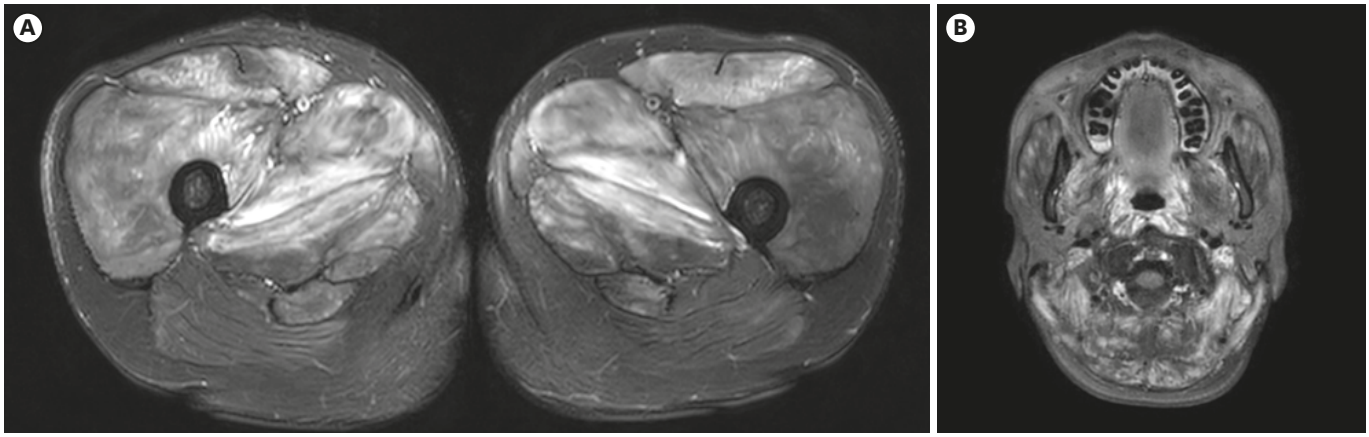

Fig. 2. Diffuse muscular enhancement on the adductor, quadriceps femoris, and hamstring muscles of both thighs (**A**) and the entire head and neck muscles (**B**) on enhanced magnetic resonance imaging.

Anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, anti-cyclic citrullinated peptide, and anti-Jo-1were not detected. The patient did not have darkened urine. There were no specific findings on chest radiography, abdominal computerized tomography, echocardiography, or transthoracic echocardiogram. The SARS-CoV-2 reverse transcription polymerase chain reaction result was also negative. Contrast-enhanced magnetic resonance imaging (MRI) showed signal changes in the adductor, quadriceps femoris, and hamstring muscles (**Fig. 2A**). Under the diagnosis of rhabdomyolysis, the patient underwent massive hydration with normal saline for 7 days. However, the muscle enzyme level continuously increased, and he complained of progressive myalgia and muscle weakness. In addition, the patient complained of dysphagia and dysarthria, and MRI showed diffuse enhancement in the entire head and neck muscles (**Fig. 2B**). Erythematous skin lesions extended to the upper and lower extremities and whole trunk, accompanied by exfoliative scaling despite topical corticosteroid treatment. For re-evaluation of other muscular diseases, a muscle biopsy of the right thigh was performed.

Microscopically, the specimen showed multifocal infiltration of large polygonal-shaped macrophages with amphophilic cytoplasm in the perimysium, epimysium, and endomysium, intermingled with a few lymphocytes on hematoxylin and eosin staining (**Fig. 3A**). Macrophage infiltration was confirmed by immunohistochemistry, with the macrophages expressing CD68 (**Fig. 3B**); the macrophages were periodic acid-Schiff (PAS)-negative. The muscle fibers infiltrated by macrophages were degenerated or necrotic and well-delineated by Masson's trichrome staining (**Fig. 3C**). Fibers remote from the infiltrate were intact. Perivascular lymphocytic aggregation was also observed, and these lymphocytes were mostly CD3-positive T-cells. We performed other special stains including modified Gomori trichrome, PAS, and toluidine blue stains, in which there were no specific findings.

After the diagnosis of vaccine-related myositis, glucocorticoid treatment was initiated. Azathioprine (100 mg) of, an immunosuppressive agent, was administrated daily. Due to neutropenia, azathioprine was changed to tacrolimus, 2 mg/day. The glucocorticoid dose was tapered as muscle enzyme levels decreased and clinical symptoms gradually improved (**Supplementary Fig. 1**). The patient was discharged and will be followed up in an outpatient clinic and his medication will be adjusted accordingly

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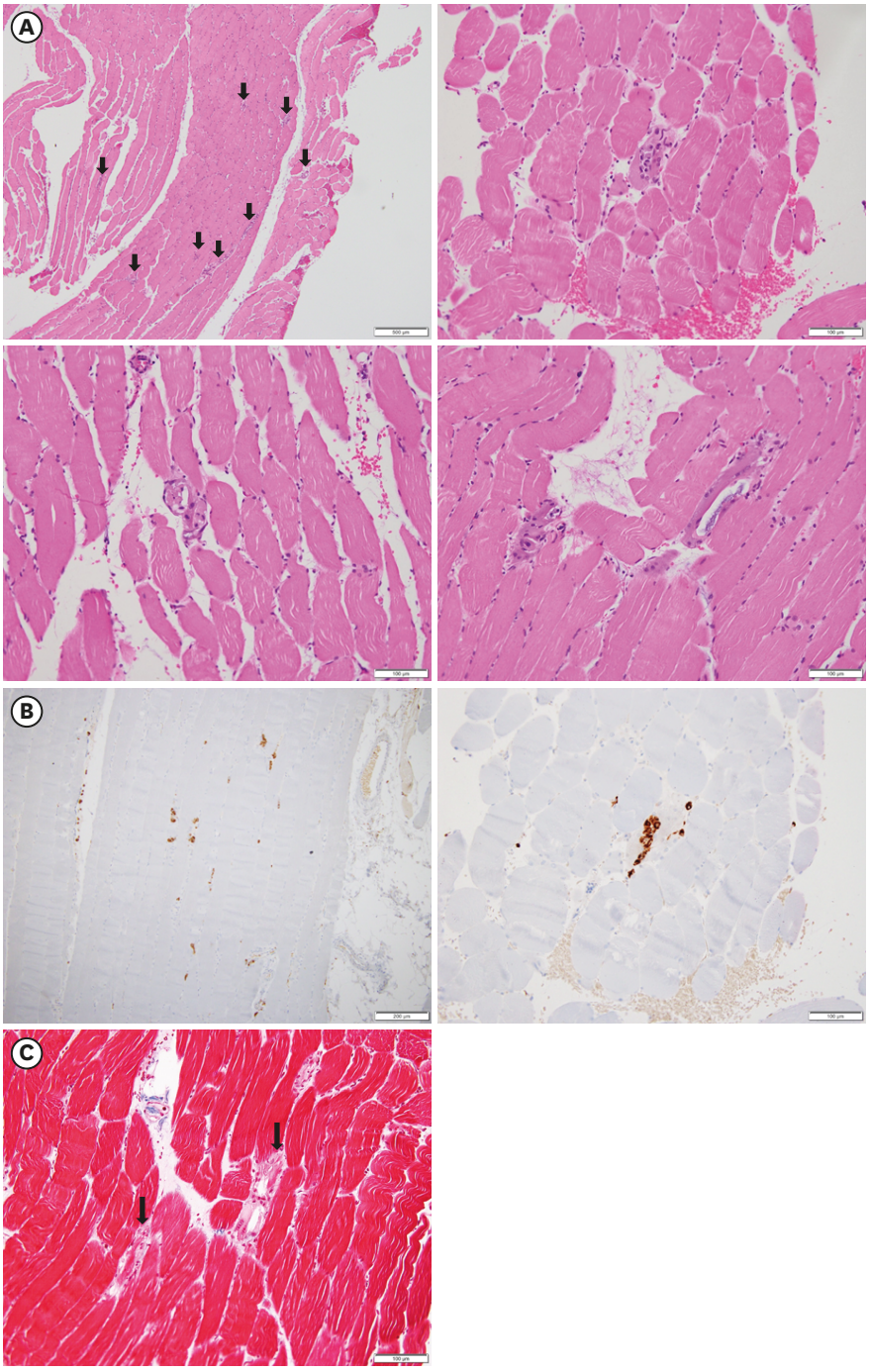

Fig. 3. Histopathology of muscle biopsy in the thigh. Multifocal infiltrates (arrows) of large polygonal-shaped macrophages having amphophilic cytoplasm in the endomysium, intermingled with a few lymphocytes on hematoxylin and eosin staining (**A**). Multifocal and scattered macrophages infiltration in the perimysium, epimysium, and endomysium, confirmed by immunohistochemistry for CD68 (**B**). The degenerated or necrotic muscle fibers (arrows) demonstrated with Masson's trichrome staining (**C**).

Ethics statement

This study was approved by the Institutional Review Board and the requirement for informed consent was waived (CBNUH IRB, Cheongju, No. 2022-01-022).

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DISCUSSION

COVID-19 vaccine (BNT162b2)-induced inflammatory myositis was pathologically diagnosed as inflammatory myositis by macrophages, reminiscent of macrophagic myofasciitis (MMF) and inflammatory myopathy with abundant macrophages (IMAM).[5,6] In the present case, the myositis was histologically different from MMF, in which macrophage infiltration was massive, and the macrophages had a basophilic cytoplasm, which was PAS-positive.[7] MMF is immune-mediated, characterized by post-vaccination and immunologically active lesions at the site of inoculation. Aluminum oxyhydroxide is the most used adjuvant in human vaccines. Although it can enhance an adaptive immune response to a co-antigen, it may cause MMF. However, BNT162b2 did not compose aluminum oxyhydroxide as an adjuvant. The affected thigh muscles (adductor, quadriceps femoris, and hamstring muscles) are not affected by the injection site (deltoid). IMAM, a variant of dermatomyositis, is characterized by infiltration of numerous macrophages in muscle and connective tissue. The intensity of macrophage infiltration in IMAM showed remarkable accumulation and diffuse infiltration of macrophages, while the main histological features in the present case included multifocal and/or scattered macrophage infiltration and degenerated myofibers.

Other differential diagnosis to be considered includes drug-induced myopathy, which is classified into direct myotoxicity and immunologically induced inflammatory myopathy. Acute direct myotoxicity showed muscle fiber necrosis without infiltrates of inflammatory cells, while chronic form demonstrated no myopathic changes on light microscopy. Immunologically induced inflammatory myopathy demonstrated infiltrates of lymphocytes, not macrophages. The patient clinically showed unique characteristics. Clinical symptoms similar to those of inflammatory myositis, such as dermatomyositis and polymyositis, were observed. 1) It started from the proximal parts of the upper and lower extremities and extended to the distal parts. Initially, there were swelling, pain, tenderness, erythema, and heating sensation in the extremities, accompanied by progressive muscle weakness. 2) There was no increase in inflammatory markers such as CRP and ESR; however, ferritin (normal range 21.81–274 ng/mL), an inflammatory marker, increased to 2,465 ng/mL. 3) Clinical course of the disease improved with glucocorticoid and immunosuppressive treatment. Glucocorticoids are the first-line treatment for inflammatory myositis. Azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, rituximab, and calcineurin inhibitor (cyclosporine, tacrolimus) can be considered as immune-modulating agents for steroid sparing purposes.[8] Since there is no standard treatment for vaccine-related inflammatory myositis, we managed it according to the treatment protocol for inflammatory myositis.

The mechanism of inflammatory myositis after vaccination in the present case is unclear; however, viral cell invasion and cytokine-mediated direct muscle cell damage have been implicated.[9] In Middle East respiratory syndrome (MERS-CoV) cases, viral particles were found in the skeletal muscle invading macrophages.[10] Like MERS-CoV, SARS-CoV-2 uses the angiotensin-converting enzyme II receptors, which is a highly suggested route for SARS-CoV-2 invasion. Rhabdomyolysis can present with COVID-19 and develop secondary to COVID-19.[10,11] In a previous report, rhabdomyolysis in patients with SARS-CoV-2 infection was well described.[12] The mRNA vaccine (BNT162b2) encodes a mutated form of the full-length spike protein of SARS-CoV-2, which is encapsulated in lipid nanoparticles.[13] The viral protein translated from an mRNA vaccine may use the same route. Therefore, vaccination can be followed by inflammatory myositis. In addition, COVID-19 alters the immune system and leads to type 3 hypersensitivity with immune complex deposition.[14] COVID-19

vaccination can be associated with immune-mediated diseases, which develop through the same mechanism that causes COVID-19 related inflammatory myositis. Multifocal inflammatory myositis induced by COVID-19 vaccination is rare and unfamiliar to clinicians and pathologists. To the best of our knowledge, a few cases have been reported worldwide, and this was the first case in South Korea.[15-18] This suggests that inflammatory myositis after COVID-19 vaccination is temporally, clinically, and histologically heterogeneous. Herein, muscle biopsy enabled accurate diagnosis.

As more individuals were COVID-19 vaccinated, unexpected side effects appeared, making it challenging to prevent the COVID-19.[19-22] The most common systemic adverse effects were fever, fatigue, headache, and myalgia. Younger individuals reported more local or systemic adverse effects than older individuals. The second dose produced a similar profile of systemic adverse effects seen after the first dose but to a greater extent.[2] If vaccinated individuals experience severe and continuous muscle pain and increased muscle enzymes, clinicians should consider vaccine-induced inflammatory myositis, measure the muscle enzyme levels, and perform muscle biopsy for a definite diagnosis. In contrast to general rhabdomyolysis, vaccine-induced inflammatory myositis shows a prolonged increase in muscle enzyme levels and multifocal macrophage infiltration with necrosis of the muscle fibers.

Given that inflammatory myositis showed a temporal relationship to vaccination, this unique case provides an example of a serious adverse event following COVID-19 mRNA vaccination. It is not understood whether this case is related to the vaccine type or a specific vaccine component. Comprehensive clinical and pathological evaluations of additional cases are needed to clarify the relationship between COVID-19 vaccination and inflammatory myositis.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Variations of laboratory results during hospitalization.

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