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Correspondence

Letter to the Editor: Propacetamol-Induced Rhabdomyolysis or COVID-Vaccine-Related Inflammatory Myopathy?

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▸ See the article "Clinicopathological Characteristics of Inflammatory Myositis Induced by COVID-19 Vaccine (Pfizer-BioNTech BNT162b2): A Case Report" in volume 37, number 11, e91.

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Dear Editor,

We read with interest the article by Kim et al.[1] about a 30-years-old male who developed fever, skin rash, and polymyalgia with mildly elevated muscle enzymes 6 days after the second dose of BNT162b2 (Biontech Pfizer vaccine (BPV)). Despite taking propacetamol, the symptoms worsened and he also developed facial itching, knuckles of hands and trunk, pain, tenderness, swelling, and warmth of the limb muscles, dysphagia, dysarthria, and rhabdomyolysis.[1] Muscle biopsy revealed an inflammatory myopathy. He partially recovered on steroids and tacrolimus.[1] The study is attractive but raises concerns that should be discussed.

We disagree with the interpretation of rhabdomyolysis as a consequence of immune myositis.[1] The patient received propacetamol at his first presentation to the emergency ward.[1] Propacetamol is known to increase muscle enzymes.[2] There are also reports of liver toxicity of the compound.[3] We should be told how often and at what dosage the patient took propacetamol at home. It is also desirable to know if he was taking any medications other than propacetamol between the first and second presentation that could have triggered rhabdomyolysis.

The course and the maximum serum values of creatine-kinase and myoglobin are not mentioned. There is no determination of myoglobin in the urine to assess whether myoglobinuria was present or not.

A detailed family history was not provided. Because rhabdomyolysis is a common occurrence in hereditary myopathies, we should be told if any of the first-degree relatives had muscle disease or had ever experienced an episode of rhabdomyolysis or malignant hyperthermia.

There is no explanation for the symptoms dysphagia, and dysarthria. It should be discussed whether these symptoms were due to smooth muscle cell involvement, neuropathy secondary to myocyte injury, or a cerebral lesion. It is also conceivable that dysphagia and dysarthria were due to swelling of adjacent striated muscles.

There is also a lack of medication history. We should be told which medications the index patient was regularly taking prior to vaccination.

Did muscle biopsy show muscle cell necrosis, a typical feature of rhabdomyolysis? Is it conceivable that the morphological abnormalities described in muscle biopsy represent drug-induced rhabdomyolysis? Toxin-induced rhabdomyolysis can be accompanied by an inflammatory response, as has been previously reported.[4]

Since the index patient presented with dermatological abnormalities, it should be discussed whether he had dermatomyositis rather than myositis. A skin biopsy could be helpful in this regard.

Since the CK-MB was also elevated, myocardial impairment, particularly endocarditis and myocarditis should have been ruled out. Myocarditis has been repeatedly reported as a complication of SARS-CoV-2 vaccinations.[5]

Overall, the interesting study has some limitations and inconsistencies that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the validity of the study. More conceivable than exclusively vaccine-induced muscle damage is a scenario of propacetamol-induced or -enhanced muscle damage leading to rhabdomyolysis. This speculation should be substantiated by further relevant studies.

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The Author's Response: COVID-19 Vaccine-Induced Inflammatory Myositis

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We received valid questions from Finsterer J regarding our previous report of COVID-19 vaccine-induced inflammatory myositis.[1] We agree that the concerns that need to be discussed and respond to his comments point by point.

Dr. Finsterer J commented that we interpreted the myopathy as rhabdomyolysis as being due to immune myositis. However, we described the characteristics of vaccine-induced inflammatory myositis, different from rhabdomyolysis. The patient was just once administrated with propacetamol at ER but the patient's muscle enzymes continued to show increased level. There are no comments about muscle enzymes in the article cited as saying that propacetamol can elevate muscle enzymes.[2] The article showed that there was no statistically significant difference in elevated liver enzymes[2] and there was liver function test within normal range after receiving propacetamol in the manuscript. The patient did not take any other drugs between first and second presentation. We showed the maximal serum values of creatine-kinase and myoglobin in Supplementary **Fig. 1**. Dr. Finsterer J indicated if there was myoglobinurea or not. To assess myoglobin in urine is important under the impression of rhabdomyolysis. Therefore, we mentioned that "The urinalysis results were unremarkable. And the patient did not have darkened urine." Because myopathy is common in hereditary myopathies, we investigated the past medical and family history and described "The patient denied any previous medical history, current allopathic or herbal medication, excessive exercise, trauma, and alcohol consumption in case presentation. He had no family history of autoimmune or musculoskeletal diseases."

Brain MRI was performed to differentiate brain and neurologic problems from dysphagia and dysarthria. In this process, diffuse muscular enhancement of the head and neck muscles was confirmed. There was no evidence of brain damage or neurologic deficit on the MRI reading, which was confirmed through consultation with a neurologist. In addition, after immunomodulatory treatment, the muscular pain, swelling, heating sense, and weakness of both extremities, as well as dysphagia and dysarthria have almost recovered. Dysphagia and dysarthria are clinical symptoms that can often occur in inflammatory myositis.[3]

Since the patient's clinical feature, biopsy results, and treatment course are more appropriate for inflammatory myositis than rhabdomyolysis, the patient's symptoms of dysphagia and dysarthria should be regarded as symptoms of worsening myositis and weakness.

Dr. Finsterer J wonder that muscle biopsy show muscle cell necrosis, a typical feature of rhabdomyolysis. We described the unique histological features that multifocal infiltration of macrophages, intermingled with a few lymphocytes, different from rhabdomyolysis. Inflammation in toxin induced rhabdomyolysis shows 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. We mentioned these contexts in discussion.

In dermatology consultation, it was decided to perform a skin biopsy when symptoms worsen since skin symptoms were non-specific. However, myositis aggravated and we decided to differentiate dermatomyositis through muscle biopsy pathology. After steroid treatment started following to muscle biopsy and skin symptoms improved. Therefore, no additional skin punch biopsy was performed.

Myocarditis as a complication of COVID-19 vaccinations was previously reported in many papers. Because the patient had the elevated CK-MB, we tested for cardiac disease and described about this in the manuscript; there were no specific findings on chest radiography, abdominal computerized tomography, echocardiography, or transthoracic echocardiogram.

In conclusion, we agree with Duruisseaux that our study has several limitations and inconsistencies that call the results and their interpretation into question. However, we emphasize that this myopathy is COVID-19 vaccine-induced inflammatory myositis with unique clinicopathological features, rather than rhabdomyolysis.

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