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Re: Manuscript No. 64756 *Muscular atrophy and weakness in proximal parts of lower extremities in Behçet's disease: A case report and review of the literature*

Dear Editor,
My colleagues and I greatly appreciate the comments and critiques of the reviewers and have incorporated their suggestions and recommendations into the manuscript. We wish to acknowledge the reviewers contributions.
We thank you for your consideration and look forward to hearing from you.

RESPONSES TO THE REVIEWERS' COMMENTS:

Reviewer #05516772

The authors described a case of muscular atrophy and weakness in the proximal parts of the lower extremities in a patient with Behçet's disease. It is an interesting case, however, some of the issues must be discussed:

1. *Neurological involvement is rare in BD, especially only peripheral nervous system was involved. Thus, I wonder what was the clinical feature of the patient in regard of the CNS (the MRI? and the cerebrospinal fluid?). This must be described in the main text.*

   As the reviewer's comment, we added the results of MRI of the brain and spinal cord and the cerebrospinal fluid analysis in the main text as following:

   - "Cerebrospinal fluid analysis detected no significant abnormalities" in the part of "***laboratory examinations***".

   - "No significant abnormalities were found in MRI of the brain and spinal cord" in the part of "***imaging examinations***".

2. *What about the differential diagnosis? Any other potential diseases need to be excluded? This should be discussed in the discussion part.*

   As the reviewer's comment, we added discussion about the differential diagnosis in the "***discussion***" part as following:

   - Focal muscular involvement is rarely discussed in reports of other neuromuscular disorders, with the possible exceptions of proximal diabetic neuropathy and Charcot-Marie-Tooth disease[16-18]. Interestingly, these patients also displayed late-onset development of symptoms, similar to our BD patient. However, the pathophysiology of this clinical manifestation has not been explicitly discussed in these reports. The possibility that the

muscle involvement in our BD patient could have been caused by proximal diabetic neuropathy and Charcot-Marie-Tooth disease was excluded through differential diagnosis.

- The possibility that the histopathological findings in our BD patient could have been caused by colchicine or steroid toxicity should also be discussed for differential diagnosis. In the literature on colchicine-induced myotoxicity, most patients showed a history of weakness and myalgia in the proximal parts and displayed significantly elevated CK, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels. In patients receiving long-term therapy, the symptoms generally occur days to weeks, following a change in the BD-related clinical features and symptoms abated within weeks of drug discontinuation[13]. However, in our BD patient, laboratory findings showed normal ALT and AST levels and slightly increased CK levels, and symptoms occurred regardless of changes in the general BD symptomology. Above all, the symptoms continued to progress, even after drug discontinuation. Hence, colchicine-induced myotoxicity cannot fully explain the neuromyopathological involvement in this patient with BD. Steroid-induced myopathy is usually associated with selective type 2 fiber atrophy in muscle biopsies[21]. The histopathological examination in our BD patient showed atrophy of both fiber types, and therefore steroid-induced myotoxicity does not sufficiently explain the muscle involvement in this BD patient.

Reviewer #03003481

Kim KW and colleagues describe a rare case of Behcet's disease with specific set of clinical, radiological, electrophysiological, and histological findings. They focused on the rarity of muscular involvement that has not been often reported previously. The article is well-written with very few grammar mistakes and typos. The logic of the presentation is very clear and easy to read. The introduction is concise and has necessary information for the disease. Presentation of case follows a hospital medical record format, which is informative and easy to catch the main points. The discussion covers most questions relevant to the case, i.e. 1)why it is specific, 2)what is common and what is unique for the case, 3)is the muscular involvement a real symptom or a side effect of therapy. I personally think the discussion is very well-written. I only have a few minor comments on the article:

1. *A few grammar mistakes*

   1) but in a few cases, it presents with arm and generalized weakness "presents" should be "presented"

   2) Denervation atrophy of the involved muscle with superimposed myopathic changes is a distinguishing quality of the neuromyopathy found in our BD patient. "is" should be "was"

   As the reviewer's comment, we revised those grammar mistakes as following:

   - "but in a few cases, it presented with arm and generalized weakness" in the "***introduction***" part

   - "Denervation atrophy of the involved muscle with superimposed myopathic changes was a distinguishing quality of the neuromyopathy found in our BD patient" in the "***discussion***" part

2. *Features of muscular involvement in Table 1 should be summarized and compared more to show*

the common and unique characteristics of its involvement

As the reviewer's comment, we added some more characteristics of involved muscles to the reference by *Afifi et al*.[23] and *Frayha et al*.[15], which have similar muscular involvement to our BD patient as following:

- Muscle weakness and peripheral neuropathy in two cases (Variation in muscle fiber size, electron microscopy: thickened basement membrane of capillaries, myofibrillar loss)

- Progressive weakness in the lower extremities with multiple cranial nerve palsies (Neurogenic atrophy)

We hope that you will find our paper suitable for publication in your journal, and we look forward to hearing from you.

Sincerely yours,
Jae-Heung Cho, MD(DKM), Ph. D.