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Myasthenia and Erdheim-Chester Disease: Causal Relationship, Misdiagnosed, or Accidentally Associated?

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LETTER TO THE EDITOR

We read with interest the article by Golagha *et al*. on a case series of two patients with Erdheim-Chester disease (ECD), clinically affecting the Achilles tendon, abductor hallucis muscle, and medial thigh muscles (patient-1), as well as in the external obturator muscle, extending to the left pectineus and right quadratus femoris muscle (patient-2) [Golagha, M. *et al*., 2024]. Patient-1 initially experienced lower leg pain and pituitary dysfunction and patient-2 had a history of myasthenia and ECD initially manifested in the form of inhomogeneous osteosclerosis [Golagha, M. *et al*., 2024]. The study is impressive, but some points require further discussion.

The first point is that ECD is usually a multisystem disease, either at the onset of the disease or only as the disease progresses [Benson, J. C. *et al*., 2023]. Multisystem involvement can manifest clinically or subclinically [Drier, A. *et al*., 2010]. Therefore, it might be helpful to screen patients with ECD for multisystem involvement, particularly the heart and brain. In the heart, ECD manifests as infiltration of the atrio-ventricular groove (atrial mass), stenosis or occlusion of the coronary arteries, aorta, or venae cava, or as myocarditis and pericarditis with pericardial effusion [Finsterer, J, 2023]. In the brain, ECD can manifest as multiple cerebral artery stenosis or occlusion and therefore can be complicated by ischemic stroke. FDG-PET may not be sufficient to assess multisystem involvement because it may miss arterial involvement.

The second point is that both patients were not genetically tested for the presence of the BRAF variant V600E, which can be found in more than half of the ECD patients [Nelson, D. S. *et al*., 2015]. In addition, mutations in histiocyte genes such as *KRAS*, *NRAS*, *MAP2K1*, or *PIK3CA* [Bartoli, L. *et al*., 2022], are known to be associated with ECD [Nelson, D. S. *et al*., 2015]. CD68 positive histiocytes are a nonspecific finding as they can also occur in Hodgkin lymphoma, xanthogranulomatous disease, Rosai Dorfman disease, or Kikuchi-Fujimoto disease and are therefore not diagnostic, but only an indication of ECD [Benson, J. C. *et al*., 2023].

The third point is that the association with myasthenia in patient-2 was not discussed further. Of particular interest is how myasthenia was diagnosed and whether the orbital masses already had proliferating, foamy histiocytes and whether the myasthenia was actually myasthenia or simply the initial manifestation of ECD. Therefore, we should know whether antibodies to postsynaptic acetylcholine-receptor, muscle-specific kinase (MUSK), LRP4, or titin were elevated, whether low-frequency repetitive nerve stimulation showed an abnormal decremental response, whether thymoma was present, and whether the tensilon-test was positive. It is also imperative to report the treatment the patient received for myasthenia. In addition to glucocorticoids, did he receive acetyl-choline esterase inhibitors, azathioprine, mycophenolate mofetil, or rituximab?

The fourth point is that the long-term results and outcome of the two patients have not been reported. Knowledge of the long-term disease course is crucial in order to be able to assess whether the treatment used (alpha-interferon) actually had a benefit in both patients [Golagha, M. *et al*., 2024]. The treatment of choice for ECD is currently vemurafenib. Have any of the patients ever been switched to this BRAF-kinase inhibitor?

In summary, the interesting study has limitations that put the results and their interpretation into perspective. Removing these limitations could strengthen and support the study's message. ECD patients require a comprehensive workup for multisystem disease, and ECD may initially mimic ocular myasthenia.

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