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Before a Statin-Induced Myopathy is Diagnosed, All Differential Diagnoses Must be Thoroughly Ruled Out

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LETTER TO THE EDITOR

We were interested to read the article by Gomez-Perez *et al*. about a 71-year-old woman who was diagnosed with subacute immune-mediated necrotizing myopathy (IMNM) after taking atorvastatin and bezafibrate for five years [Gómez-Pérez, F. J. *et al*., 2025]. The diagnosis was based on medical history, clinical presentation, hypercreatine kinase (CK)emia, muscle biopsy findings, increased tracer uptake on positron emission tomography of muscle (PET-CT), decrease in muscle mass on dual-energy X-ray absorptiometry and the presence of antibodies against 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) [Gómez-Pérez, F. J. *et al*., 2025]. The patient was treated with methotrexate (MTX), intravenous immunolgobulins (IVIGs) and rituximab (RTX) and made a full recovery from weakness and hyperemia, but not from muscle wasting [Gómez-Pérez, F. J. *et al*., 2025]. The study is noteworthy, but several points should be discussed.

The first point is that we disagree with the diagnosis of IMNM [Gómez-Pérez, F. J. *et al*., 2025]. There are several arguments against IMNM: 1. the patient took the statin and the fibrate for 5 years without any major side effects. Why would the statin and fibrate suddenly trigger IMNM, why didn't it occur earlier? 2. the muscle biopsy revealed enlarged mitochondria with impaired cristae formation and “electron lucid changes”, indicating that the patient actually had a mitochondrial myopathy. Diagnosis of mitochondrial myopathy requires determination of serum lactate at rest and during mild exercise (lactate stress test) [Finsterer, J, 1998], immunohistochemical examination of the muscle biopsy and biochemical examination of the muscle homogenate to determine whether the function of the respiratory chain complex is normal or reduced [Mordekar, S. R. *et al*., 2025]. A panel test for mutations in muscular dystrophy-associated genes, which was apparently performed in the index patient due to diagnostic uncertainty, is not sufficient, as the type and number of myopathies far exceeds that of muscular dystrophies.

The patient should have been screened for pathological mutations in mtDNA or nuclear genes involved in mitochondrial morphology, function, reproduction, fusion, fission and signaling. It would also have been helpful to take a family history, as mtDNA variants are transmitted through the maternal line in 75% of cases [Poulton, J. *et al*., 2017]. Did the mother of the index patient show clinical features of a mitochondrial disorder (MID)? 3. IMNM is usually triggered by extreme muscular exertion, infections, seizures or new concomitant medications, but none of these triggers were identified in the index patient. 4 IMNM is not usually a multisystem disease, but is limited to skeletal muscle. However, the index patient had multisystem involvement that affected not only the muscles but also the thyroid (Hashimoto's), pancreas (diabetes), heart (hypertension), liver (steatosis), and lipid metabolism (hyperlipidemia) [Gómez-Pérez, F. J. *et al*., 2025]. Did the index patient also have other common phenotypic features of MID such as short stature, retinopathy, impaired hearing, ptosis, ophthalmoparesis, thyroid dysfunction, gastrointestinal impairment, cardiomyopathy, cardiac arrhythmias or renal dysfunction? 5 HMGCR-associated IMNM usually also lead to damage to the perimysial connective tissue, which was not observed in the index patient.

The second point is that the presence of HMGCR antibodies does not necessarily mean that the patient has IMNM [Alshehri, A. *et al*., 2015]. HMGCR antibodies can also be positive in patients who regularly take statins but have no clinical manifestations [Torri, F. *et al*., 2021]. HMGCR

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antibodies can also be positive in patients with inclusion body myositis [Alshehri, A. *et al*., 2015].

The third point is that the patient was treated with ezetimibe after stopping statins and fibrates. Since ezetimibe can also trigger the occurrence of IMNM [Slim, H. *et al*., 2018], we recommend discontinuing ezetimibe in the index patient.

In summary, it is essential to rule out mitochondrial myopathy or other primary myopathies before attributing myopathy to statins and fibrates in a multimorbid elderly patient.

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