Mushroom supplements triggering a flare of HMGCR immune mediated necrotising myopathy

Brittany Adler, Lisa Christopher-Stine, Eleni Tiniakou

SUMMARY
Hydroxyl-methyl-glutaryl-Co-A reductase (HMGCR) immune mediated necrotising myopathy (IMNM) is a rare autoimmune myositis that is thought to be triggered by statins and responds to immunomodulation. We report a case of a woman in her 30s with HMGCR IMNM without a history of statin exposure who had a clear flare of her myositis after beginning mushroom supplements. Mushrooms are natural HMGCR inhibitors, and this is the first case to demonstrate a flare triggered by mushrooms in a patient with known HMGCR IMNM. This case highlights the importance of reviewing diet and supplements in patients with IMNM. It also emphasises the importance of strict statin avoidance for patients with IMNM even when the myositis is under good control.

BACKGROUND
Hydroxyl-methyl-glutaryl-Co-A reductase (HMGCR) immune mediated necrotising myopathy (IMNM) is a rare autoimmune myositis that is thought to be triggered by statins and responds to immunomodulation.1 Although the majority of patients with autoantibodies targeting the enzyme HMGCR have a history of statin exposure in the USA, a subset of cases occur without a history of statin use.2 There are reports of HMGCR IMNM developing in statin-naive patients who consume significant amounts of mushrooms,3 a natural source of statins which have HMGCR-inhibitory activity.4 However, these reports are anecdotal and mushrooms have never been definitively proven to be an environmental risk factor for HMGCR IMNM. Intriguingly, the prevalence of statin-naive IMNM is significantly higher in East Asia compared with North America, which has been attributed to dietary differences in consumption of mushrooms and other natural HMGCR inhibitors such as red yeast rice or tea made from the Camellia sinensis plant.3

CASE PRESENTATION
We report a case of a woman in her 30s with Graves’ disease and smouldering IgA multiple myeloma who developed HMGCR IMNM without a history of statin exposure. She initially presented with proximal muscle weakness and elevated creatine kinase (CK), and the diagnosis was confirmed by muscle histopathology showing a necrotising myopathy and positive HMGCR autoantibodies. She met all of the criteria for IMNM based on the 2003 ENMC International Workshop Criteria.6 She was successfully treated with intravenous immunoglobulin (IVIG) and her CK and strength normalised. Seven months after initiation of treatment and while under good control, she started supplementing her regimen with a Mushroom Complex composed of 200 mg Maitake (Grifola frondosa), 200 mg Reishi (Ganoderma lucidum) and 200 mg Shiitake (Lentinus edodes) as well as the mushroom Cordyceps. After starting mushroom supplements her CK began to rise on routine bloodwork, and within 3 months she became weaker and her CK peaked at 1696 units/L (reference range 29–143 units/L). Objective strength testing was not performed because this occurred during the COVID-19 pandemic. The mushroom supplements were at that point stopped and over the course of 6 months her CK gradually returned to her baseline (figure 1) without any other intervention.

OUTCOME AND FOLLOW-UP
The patient remains with good disease control on IVIG 1.5 years later.

DISCUSSION
This is the first reported case of mushrooms triggering a flare of known HMGCR IMNM. To date there have been several reports of HMGCR IMNM occurring among patients who consume significant amounts of mushrooms,3 although the link with this environmental exposure has been anecdotal. Here, we clearly demonstrate a flare of HMGCR IMNM that coincided with the initiation of intake of mushroom supplements, and which resolved after the supplements were discontinued without any additional intervention. One proposed mechanism for autoimmunity is that the HMGCR inhibitor, like the pharmacological statins, may change the conformation of the HMGCR protein, thereby affecting its processing by antigen presenting cells and thus leading to the generation of cryptic epitopes which generate an autoimmune response.7 Additionally, statins increase HMGCR expression in muscle, thus propagating the inflammatory response by increasing the antigen load. Lentinus edodus, and less Grifola and Ganoderma, have an inhibitory effect on HMGCR comparable to pravastatin, which could in part be explained by measurable amounts of statins detected in these mushrooms (up to 316 mg/kg).8

This case emphasises the importance of strict statin avoidance in any form in HMGCR IMNM.9 There has been a question about statin reintroduction in this disease, and this case suggests that this should not be considered even if the patient has good disease control. Other cholesterol-lowering agents should be considered as first-line therapy.10
agents should be considered based on the cardiovascular risk benefit analysis and medication availability. This case also emphasises the importance of taking a detailed medication and dietary history including supplements when evaluating patients with IMNM. All patients with HMGCR IMNM should be counselled about avoiding mushrooms, including mushroom supplements, as well as red yeast rice and other dietary HMGCR inhibitors.

Learning points

► Mushrooms are natural hydroxyl-methyl-glutaryl-Co-A reductase (HMGCR) inhibitors that can trigger a flare of HMGCR immune mediated necrotising myopathy (IMNM).
► Patients with HMGCR IMNM should be counselled about the importance of avoiding mushrooms.
► A careful dietary and supplement history should be obtained for all patients with IMNM, particularly when they have poor disease control.

REFERENCES

1. Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum 2011;63:713–21.
2. Liang W-C, Uruha A, Suzuki S, et al. Pediatric necrotizing myopathy associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies. Rheumatology 2017;56:3654–66.
3. Yoshida T, Chikazawa H, Kumon Y. Did shiitake mushrooms induce immune-mediated necrotizing myopathy?
4. Gil-Ramírez A, Clavijo C, Palansamy M, et al. Screening of edible mushrooms and extraction by pressurized water (PWE) of 3-hydroxy-3-methyl-glutaryl CoA reductase inhibitors. J Funct Foods 2013;5:244–50.
5. Gil-Ramírez A, Smiderle FR, Morales D, et al. Water-Soluble polysaccharide extracts from the oyster culinary-medicinal mushroom Pleurotus ostreatus (Agaricomycetes) with HMGCR inhibitory activity. Int J Med Mushrooms 2017;19:879–92.
6. Hoogendijk JE, Amato AA, Lecky BR, et al. 119th ENMC International workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10-12 October 2003, Naarden, the Netherlands. Neuromuscul Disord 2004;14:337–45.
7. Mohassel P, Mammen AL. Anti-HMGCR myopathy. J Neuromuscul Dis 2018;5:11–20.
8. Gil-Ramírez A, Caz V, Smiderle FR, et al. Water-Soluble compounds from Lentinula edodes influencing the HMG-CoA reductase activity and the expression of genes involved in the cholesterol metabolism. J Agric Food Chem 2016;64:1910–20.
9. Lin S-Y, Chen Y-K, Yu H-T, et al. Comparative study of contents of several bioactive components in fruiting bodies and mycelia of culinary-medicinal mushrooms. Int J Med Mushrooms 2013;15:315–23.