The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine

eJIFCC



# Anti-HMGCR myopathy without exposure to statins: a case report

Jorge Ferriz Vivancos, Marta Fandos Sánchez, Pilar Teresa Timoneda Timoneda, Goitzane Marcaida Benito

*Department of Clinical Biochemistry, Hospital General Universitario Valencia, Valencia, Spain*

ARTICLE INFO

***Corresponding author:***
Jorge Ferriz Vivancos
Department of Clinical Biochemistry
Hospital General Universitario Valencia
Valencia
Spain
E-mail: ferriz_jor@gva.es

***Key words:***
myopathy, elevated CK values, HALIP, statins

ABSTRACT

Anti-HMGCR, which was first identified in 2010, has emerged as an important mechanism of myopathogenesis in patients with exposure to statins. The availability of new detection methods has expanded the phenotypic spectrum with a subtype of population that hasn't been exposed to the drug and whose clinical, analytical, and pathological manifestations are similar. The observation by immunofluorescence of a highly specific pattern known as HALIP (HMGCR Associated Liver Immunofluorescence Pattern) can be useful in the detection of these antibodies.

## INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of low-prevalence diseases resulting from autoimmune inflammation and muscle damage. They can be categorized into polymyositis, dermatomyositis, autoimmune necrotizing myopathy, and inclusion body myositis based on clinical and myopathological features (1).

More than 15 myositis-specific antibodies (MSA) are considered important in the mechanism underlying IIMs. Among the antibodies responsible for these diseases, we find anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (anti-HMGCR), an enzyme involved in cholesterol synthesis. Statins, a medication frequently used to treat hypercholesterolemia and other lipid metabolic disorders, are typically linked to the development of these antibodies in patients who have received this pharmacotherapy.

The association of anti-HMGCR and statins gives rise to a myopathy histologically compatible with immune-mediated necrosis, whose clinical manifestations are proximal, symmetric, and progressive muscle weakness with hight creatine kinase (CK) values (>1,000-10,000 U/L) (2).

The new chemiluminescence tests (CIA) available on the market, which allow quantifying of anti-HMGCR levels, have increased the determinations of these antibodies, which has resulted in the appearance of new subsets of patient populations, such as children and young people not exposed to statins. The identification of a new immunofluorescence pattern, called HALIP (HMGCR Associated Liver Immunofluorescence Pattern), can also guide its diagnosis.

We present the case of a 17-year-old male where incidental finding of hypertransaminasemia and HALIP led to the diagnosis of anti-HMGCR myopathy. This myopathy in persons not taking statins is an infrequent finding.

## CASE REPORT

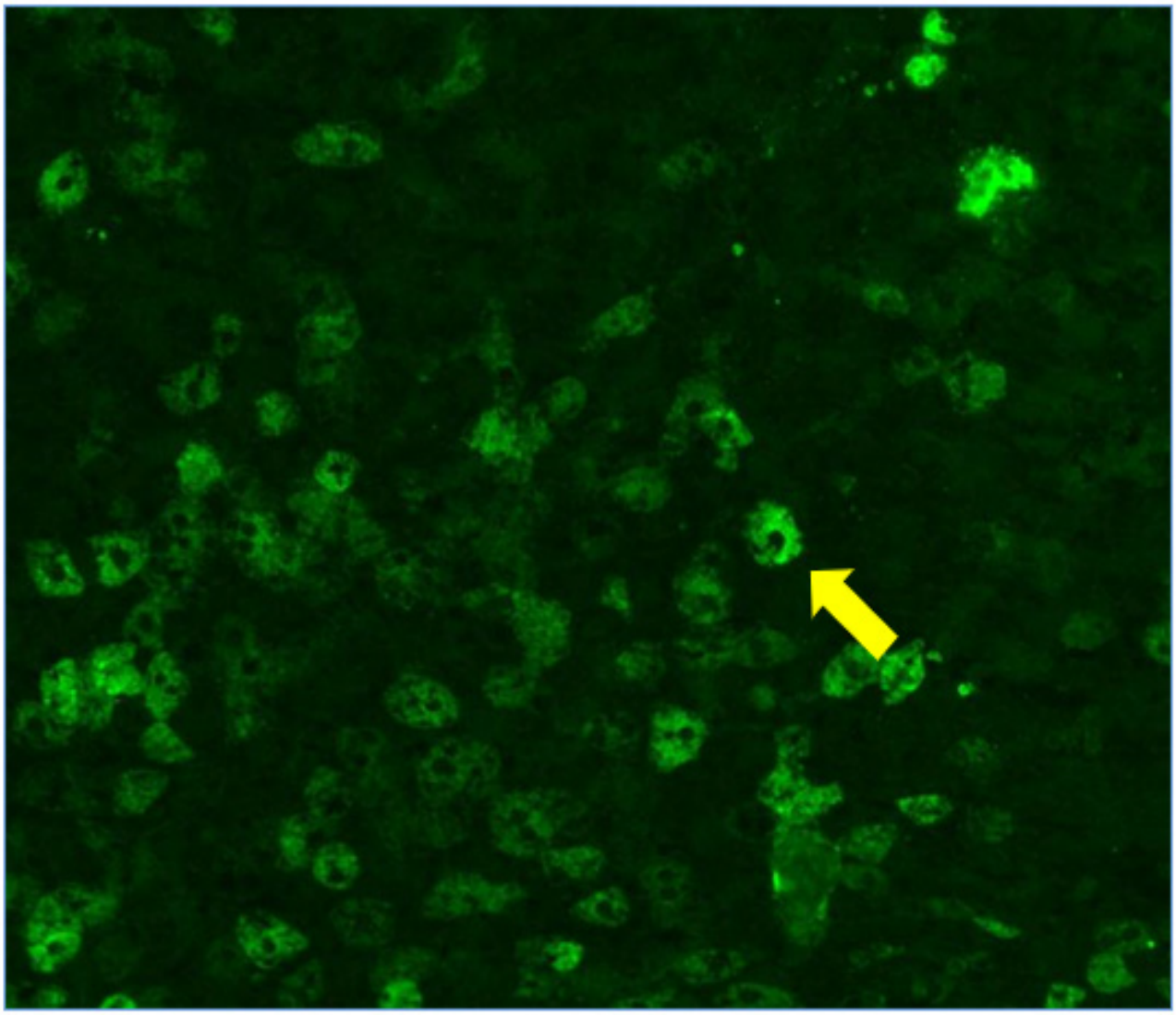
A 17-year-old male with no clinical history or treatment of interest went to Urgent Care due to abusive alcohol intake. Neurological, cardiovascular, and imaging exams without alterations. Laboratory tests revealed moderate leukocytosis (19.500/mL) and increased alanine transaminase (ALT) of 199 U/L (reference interval 3-50 U/L), so he was referred to Gastroenterology Service.

In the analytical liver function follow-up, elevated values of transaminase were maintained with an ALT value of 233 U/L and aspartate aminotransferase (AST) value of 161 U/L (reference interval 5-50 U/L), although total bilirubin (TB), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) levels were normal. Other analytical parameters and infectious serology were without significant alterations. A liver biopsy was performed in which minimal inflammatory infiltrates were found, with dilation, sinusoidal congestion, and slight dilation of the centrilobular veins.

To exclude the possibility of autoimmune liver disease, a study of antinuclear antibodies (ANAs) was performed by IFA using HEp-2 cells (ANA-Mosaik 1A EUROPattern, Euroimmun®) where no pattern was detected at 1/80 titer. Autoimmune liver blot (EUROLINE Autoimmune Liver Diseases, Euroimmun®), which was negative, and triple tissue IFA (Mosaic Basic Profile 3C EUROPattern, Euroimmun®) were also requested. The presence of immunofluorescence in the cytoplasm of dispersed hepatocytes of rat liver was evidenced with a centrilobular distribution, a pattern known as HALIP (Figure 1).

Given this finding, CK (4738 U/L, reference interval 46-171 U/L) and aldolase (42.8 U/L, reference level<7.6 U/L) were determined. Anti-HMGCR (321.6 CU, reference level<20 CU) were also quantified by Quanta Flash CIA assay® HMGCR (Inova, Werfen®).

**Figure 1** HALIP: pattern of immunofluorescence in the cytoplasm of hepatocytes with centro-lobular distribution (yellow arrow) in rat liver stain (dilution 1/80)



The patient was finally treated by the Neurology Service and a neurological evaluation revealed a loss of scapular strength with unusual movements during the examination.

A muscle MRI and electromyography were performed with no pathological findings, and a muscle biopsy, with a report of "Unequivocal immunostaining with autoimmune necrotizing inflammatory myopathy: C5b9 deposits in necrotic fibers and preserved myofiber membrane" (Figure 2).

Anti-HMGCR led to the diagnosis of autoimmune necrotizing myopathy and the patient was treated with immunoglobulins and low-dose corticosteroids with favorable evolution. During follow-up, CK and anti-HMGCR levels were monitored. Although concentrations decreased after treatment, they remained elevated (Figure 3).

**Figure 2** **(I) Hematoxylin and eosin stain of muscle biopsy with necrotic and regenerative muscle fibers (orange arrow). (II) Immunostaining with sarcolemmal C5b–9 (MAC) deposits in necrotic fibers (red arrow)**

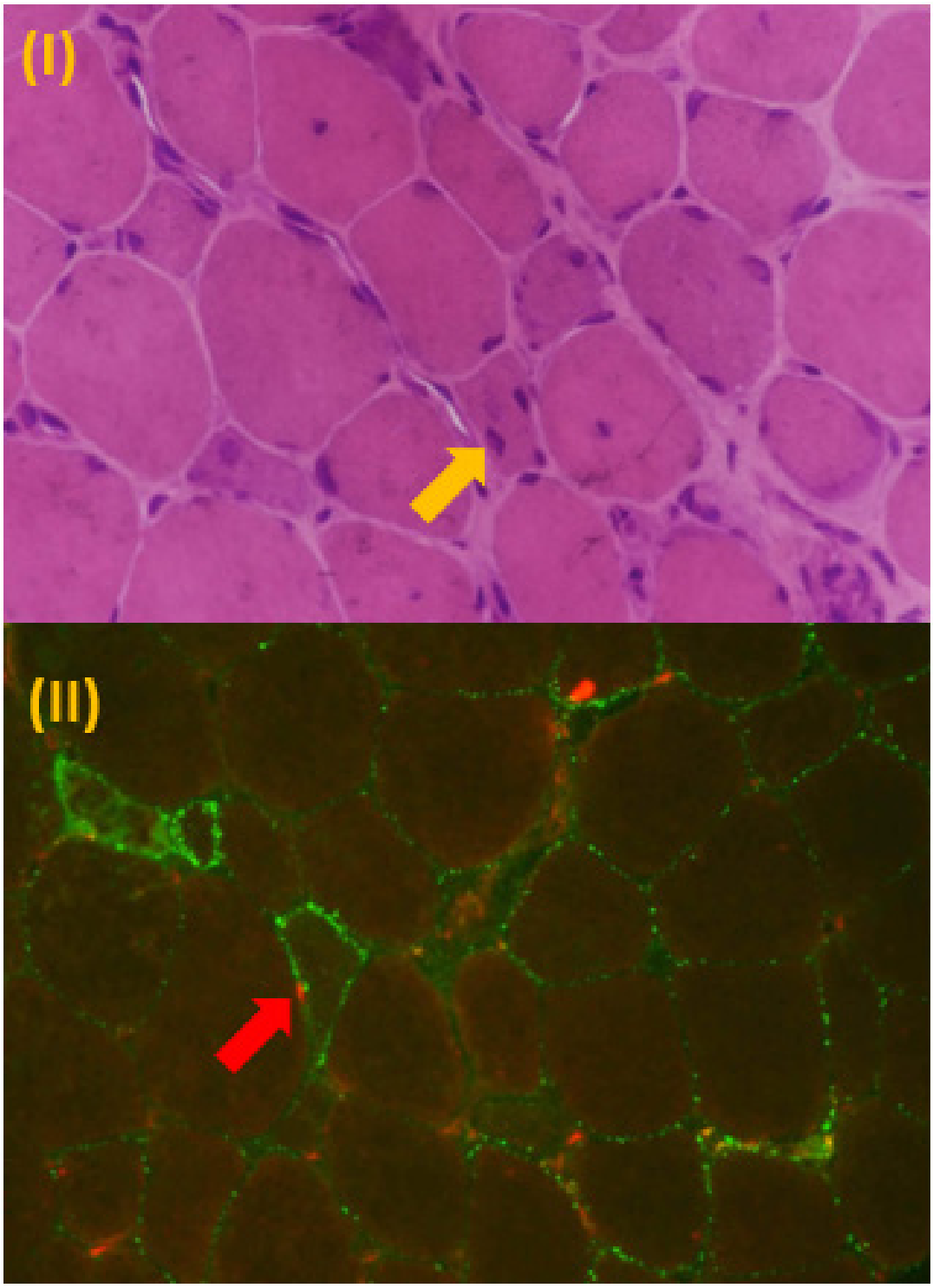
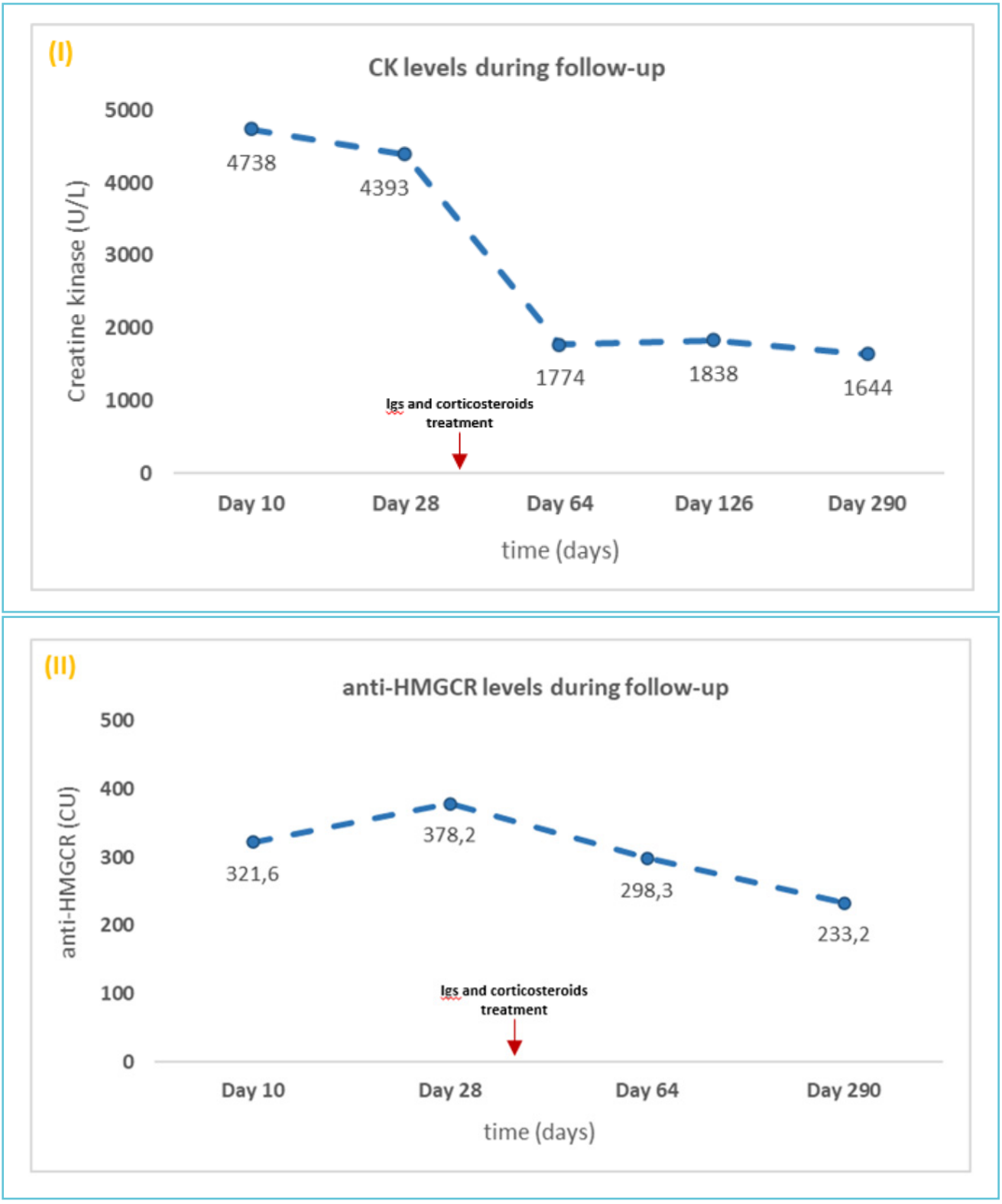


**Figure 3** **CK levels (I) and anti-HMGCR levels (II) during follow-up after Urge Care (Day 1)**



## DISCUSSION

The intake of statins, one of the most frequently prescribed drugs, has increased worldwide in recent years, which has also caused an increase in the incidence of its intolerance, which is around 9.1% (3). One of its most frequent side effects is muscular toxicity (4), which includes anti-HMGCR myopathy, a rare condition that is caused by the action of antibodies against this essential enzyme of cholesterol synthesis. An increase in the HMGCR expression as a consequence of HMGCR inhibition by statins has been suggested as a possible cause of muscle toxicity (5).

Anti-HMGCR antibodies were first described in 2010 in a population of patients with a biopsy consistent with necrotizing myopathy and negative for other autoantibodies (6). Although they were initially associated with taking statins, due to their higher prevalence in this type of patient compared to other myopathies (2-3 of every 100,000 patients treated with statins), new subtypes of patients such as unexposed adults, adolescents, and even children were emerging (2). The estimated incidence of anti-HMGCR is 1.94-10.3 per million adults per year, depending on the testing criteria (7) and the proportion of patients who have been exposed to statins and have anti-HMGCR antibodies positive varies by geographic region, ranging from 44.4% to 72.7% in the European population, with a similar percentage in the North American population, and a lower association in Asian populations (8), where higher consumption of foods rich in natural statins, such as mushrooms or red tea, may act as triggers of non-drug anti-HMGCR myopathy (2).

Genetics can also play a role in anti-HMGCR myopathy. A higher predisposition has been observed in adults with the MHC class II allele DRB1∗11:01, whereas this risk is associated with DRB1∗07:01 in pediatric patients (9-10). However, given the high prevalence of this loci in the general population (7-15%), its determination in this type of patient does not seem useful.

Patients without exposure to statins have similar clinical symptoms to patients exposed to these drugs, although it has been shown that young patients have more severe disease and slower recovery (11). The titers of anti-HMGCR antibodies in IIM patients were also significantly higher in statin users (12). Some patients may have sustained elevated CK levels without muscle weakness, and in both groups, CK levels correlated with muscular strength (13). Although the appearance of HALIP could suggest the presence of autoimmune hepatitis due to immunofluorescence in hepatocytes, few cases have been described in the literature associating these antibodies with liver disease (14).

Unlike other mechanisms of intolerance to statins, drug withdrawal does not usually resolve patient symptoms, and immunosuppressants and intravenous immunoglobulins are necessary to prevent disease progression. The measurement of CK is useful during the monitoring of the disease, but not anti-HMGCR, which usually does not normalize despite clinical improvement (2).

Anti-HMGCR were initially discovered by immunoprecipitation, which remains the gold standard technique, but other techniques such as ELISA and CIA are currently used for their determination. A more common alternative to the above tests is indirect immunofluorescence on triple tissue with rat liver, in search of the characteristic HALIP (HMGCR-Associated Liver Indirect Immunofluorescence Pattern). This pattern has demonstrated high specificity (98.7%) (15-16), making it a fast and cheap alternative for screening myopathies in patients treated with statins.

The determination of anti-HMGCR is a highly specific test (99.7%) and it is not found in patients with other related diseases. Its study, either by CIA or HALIP, should be included in the differential diagnosis of IIM that includes a population of any age with suspected myopathy and not limited to statin users.

## TAKE-HOME MESSAGES

- In patients treated with statins, anti-HMGCR antibodies may develop with symptoms of necrotizing autoimmune myopathy. This condition has also been observed in patients without exposure to statins.
- The finding of the HALIP pattern, specific to this type of myopathy, constitutes a fast and cheap alternative in its diagnosis.

❖❖❖❖❖

### *Compliance with ethical standards*

*Conflict of interest:* The authors have declared that no conflict of interest exists.

*Author contributions:* All authors were involved in the diagnosis and management of this case.

*Funding:* The authors have not declared a specific grant for this research from any funding agency or source in the public, commercial or not-for-profit sectors.

❖❖❖❖❖

## REFERENCES

1. Cheeti A, Brent LH, Panginikkod S. Autoimmune Myopathies. In: StatPearls. Treasure Island (FL): StatPearls Publishing; November 22, 2021.

2. Mohassel P, Mammen AL. Anti-HMGCR Myopathy. J Neuromuscul Dis. 2018;5(1):11-20. doi:10.3233/JND-170282

3. Bytyçi I, Penson PE, Mikhailidis DP, et al. Prevalence of statin intolerance: a meta-analysis [published online ahead of print, 2022 Feb 16]. Eur Heart J. 2022;ehac015. doi:10.1093/eurheartj/ehac015

4. Toth PP, Patti AM, Giglio RV, et al. Management of Statin Intolerance in 2018: Still More Questions Than Answers. Am J Cardiovasc Drugs. 2018;18(3):157-173. doi:10.1007/s40256-017-0259-7

5. 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(3):713-721. doi:10.1002/art.30156

6. Christopher-Stine L, Casciola-Rosen LA, Hong G, Chung T, Corse AM, Mammen AL. A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. Arthritis Rheum. 2010;62(9):2757-2766. doi:10.1002/art.27572

7. Joseph VMK, Rose EC, Edwards CJ, et al. Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies: incidence using different testing criteria, and case series. Clin Exp Rheumatol. 2022;40(2):298-303. doi:10.55563/clinexprheumatol/5y19bb

8. Allenbach Y, Drouot L, Rigolet A, et al. Anti-HMGCR autoantibodies in European patients with autoimmune necrotizing myopathies: inconstant exposure to statin. Medicine (Baltimore). 2014;93(3):150-157. doi:10.1097/MD.0000000000000028

9. Mammen AL, Gaudet D, Brisson D, et al. Increased frequency of DRB1*11:01 in anti-hydroxymethylglutaryl-coenzyme A reductase-associated autoimmune myopathy. Arthritis Care Res (Hoboken). 2012;64(8):1233-1237. doi:10.1002/acr.21671

10. Kishi T, Rider LG, Pak K, et al. Association of Anti-3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Autoantibodies With DRB1*07:01 and Severe Myositis in Juvenile Myositis Patients. Arthritis Care Res (Hoboken). 2017;69(7):1088-1094. doi:10.1002/acr.23113

11. Tiniakou E, Pinal-Fernandez I, Lloyd TE, et al. More severe disease and slower recovery in younger patients with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. Rheumatology (Oxford). 2017;56(5):787-794. doi:10.1093/rheumatology/kew470

12. Musset L, Allenbach Y, Benveniste O, et al. Anti-HMGCR antibodies as a biomarker for immune-mediated necrotizing myopathies: A history of statins and experience from a large international multi-center study. Autoimmun Rev. 2016;15(10):983-993. doi:10.1016/j.autrev.2016.07.023

13. Werner JL, Christopher-Stine L, Ghazarian SR, et al. Antibody levels correlate with creatine kinase levels and strength in anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. Arthritis Rheum. 2012;64(12):4087-4093. doi:10.1002/art.34673

14. Palamuthusingam D, Mantha M, Dheda S. HMG CoA reductase inhibitor associated myositis and autoimmune hepatitis. Intern Med J. 2017;47(10):1213-1215. doi:10.1111/imj.13561

15. Alvarado-Cardenas M, Marin-Sánchez A, Martínez MA, et al. Statin-associated autoimmune myopathy: A distinct new IFL pattern can increase the rate of HMGCR antibody detection by clinical laboratories. Autoimmun Rev. 2016;15(12):1161-1166. doi:10.1016/j.autrev.2016.09.005

16. Baucells A, Martínez MA, Alvarado-Cardenas M, et al. Anti-HMGCR Specificity of HALIP: A Confirmatory Study. J Immunol Res. 2020; 2020:6292631. Published 2020 Jul 16. doi:10.1155/2020/6292631