

Diagnosis of Statin-Induced Necrotizing Myopathy: Contribution of Anti-HMGCR Antibodies

Diagnóstico da Miopatia Necrotizante Induzida por Estatinas: Contribuição dos Anticorpos Anti-HMGCR



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ABSTRACT

Over the last few years, several cases of statin-induced necrotizing myopathy have been described. This myopathy is characterized by the necrosis of muscle fibers and the presence of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies. Although the diagnosis of myopathies relies on muscle biopsy, which is considered the gold-standard, the search for autoantibodies has proved to be an essential contribution to the diagnosis of immune-mediated myopathies. The detection of anti-HMGCR antibodies in the patient's serum can be performed by enzyme immunoassays, and more recently, by immunofluorescence. As for the latter, the detection of anti-HMGCR antibodies is performed on tissue sections by indirect immunofluorescence and is characterized by a typical fluorescence pattern called "HMGCR Associated Liver IFL Pattern". The authors present two case reports that show the importance of diagnosing statin-induced necrotizing myopathy as quickly as possible and the contribution of anti-HMGCR antibody detection for the diagnosis.

Keywords: Autoimmune Diseases/chemically induced; Hydroxymethylglutaryl CoA Reductases; Hydroxymethylglutaryl-CoA Reductase Inhibitors/adverse effects; Muscular Diseases/chemically induced

RESUMO

Nos últimos anos foram descritos vários casos de miopatia necrotizante induzida por estatinas. Esta miopatia caracteriza-se por necrose das fibras musculares e pela presença de anticorpos anti-3-hidroxi-3-metilglutaril-coenzima A redutase (anti-HMGCR). Apesar do diagnóstico das miopatias depender da biópsia muscular, considerada a *gold-standard*, a pesquisa dos auto-anticorpos tem-se revelado uma contribuição fundamental para o diagnóstico das miopatias imuno-mediadas. A pesquisa dos anticorpos anti-HMGCR no soro do doente pode ser efetuada por recurso a imunoensaios enzimáticos e mais recentemente foi descrita a possibilidade da sua deteção por imunofluorescência. Neste caso, a pesquisa de anticorpos anti-HMGCR é efetuada em seções de tecido, por imunofluorescência indireta e caracteriza-se pela deteção de um padrão de fluorescência típico denominado "HMGCR Associated Liver IFL Pattern". Os autores apresentam dois casos-clínicos que evidenciam não só a importância de diagnosticar o mais rapidamente possível a miopatia necrotizante induzida por estatinas como também a contribuição da deteção de anticorpos anti-HMGCR para o diagnóstico desta miopatia.

Palavras-chave: Doenças Autoimunes/induzidas quimicamente; Doenças Musculares/induzidas quimicamente; Hidroximetilglutaril-CoA Redutases; Inibidores de Hidroximetilglutaril-CoA Redutases/efeitos adversos

INTRODUCTION

Immune mediated necrotizing myopathy (IMNM) is characterized by progressive and disabling proximal muscle weakness, high serum levels of creatine kinase (CK) and the presence of necrotic fibers with minimal inflammatory cell infiltrate on muscle biopsy.^{1,2} The European Neuromuscular Centre has recognized three serologically different subtypes of IMNM: autoantibody negative, anti-signal recognition particle and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) myopathy. Recently, several cases of anti-HMGCR myopathy associated with statins exposure were described, which raised the profile of this IMNM and the need to diagnose it as soon as possible.

Statins competitively inhibit HMGCR and have a well-established role in the secondary prevention of cardiovascular events.³ However, clinical data suggests that the adverse reactions of statins may affect at least 30% of patients.⁴ Among the several possible adverse reactions, statin-associated myopathy is the most common, with anti-HMGCR IMNM being the most severe subtype.⁵ The exact incidence

of statin associated myopathy is not known. However, recent studies reported that the incidence may vary from 15% to 72% depending on age, geographic location and eating habits as anti-HMGCR could be associated with both the medicine and natural statins occurring in food such as red yeast rice.⁶

The diagnosis of myopathy relies on muscle biopsy, which is considered the gold-standard. Nevertheless, in IMNM, the screening of serum antibodies is changing the diagnostic algorithm. Serology studies are now considered as important as histological studies, with the detection of anti-HMGCR antibodies considered the hallmark in the diagnosis of anti-HMGCR IMNM.

During a 24-hour period, the detection of antibodies could be achieved by immunoassays such as immunoblot and enzyme linked immunosorbent assay. In 2016, Alvarado-Cardenas *et al* used indirect immunofluorescence in rat tissue sections to evaluate serum antibodies of IMNM patients and identified a new specific pattern which was

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called HMGCR Associated Liver IFL Pattern (HALIP).⁷ This pattern is characterized by the presence of stained hepatocytes (no more than 10%) with a centro-lobular distribution. Moreover, the staining was limited to the cytoplasm and spared the nuclei.⁷

In order to emphasize that anti-HMGCR IMNM may present a rapid and fatal course, as well as to highlight the role of antibody detection in the diagnosis of this myopathy, we present two patients with anti-HMGCR statin-induced IMNM.

CASE REPORTS

Patient 1 was a 72-year-old man admitted to the emergency department due to a 4-week history of myalgia and decrease of muscle strength in the lower limbs, without other neuromuscular symptoms. One month before the

onset of symptoms the patient started taking pitavastatin 4 mg, in addition to atorvastatin 40 mg. The patient had been taking atorvastatin for a few months but since he was not achieving the therapeutic goal, atorvastatin was switched to pitavastatin. Due to a misunderstanding, the patient kept taking both statins. The patient had a clinical history of dyslipidemia, arterial hypertension, and type 2 diabetes mellitus. As for family history, the patient's daughter had a multimicore congenital myopathy. At the time of the daughter's myopathy diagnosis, the patient did not undergo genetic testing since he presented normal CK values. On admission, he was found to have CK levels of 9764 U/L (reference range (rf) < 171 U/L), lactic dehydrogenase (LDH) of 1046 U/L (rf < 248 U/L), aspartate transaminase (AST) of 376 U/L (rf < 35 U/L), alanine transaminase (ALT) of 444 U/L (rf < 45 U/L) and increased inflammatory parameters, (Table 1).

Table 1 – Summary of patient characteristics and diagnostic test results

	Patient 1	Patient 2
Patient's characteristics		
Age	72	59
Sex	Male	Male
Symptoms	Myalgia and decrease of muscle strength in the lower limbs	Decrease of muscle strength and episode of rhabdomyolysis
Statin	Pitavastatin 4 mg + Atorvastatin 40 mg ¹	Atorvastatin 20 mg
Medical history	Dyslipidemia, arterial hypertension, type 2 diabetes mellitus, benign prostatic hyperplasia	Dyslipidemia, knee osteoarthritis
Family history	Daughter with multimicore congenital myopathy	Irrelevant
Blood tests		
Leucocytes ²	15.2 x 10 ⁹ /L	9.5 x 10 ⁹ /L
Neutrophils ²	14.14 x 10 ⁹ /L	5.45 x 10 ⁹ /L
CK ²	9764 U/L	8635 U/L
LDH ²	1046 U/L	908 U/L
AST ²	376 U/L	217 U/L
ALT ²	444 U/L	196 U/L
C-reactive protein (CRP) ²	11.46 mg/dL	0.49 mg/dL
Anti-HMGCR antibodies ³	HMGCR antibodies detected	HMGCR antibodies detected
Other autoimmune myositis autoantibodies ⁴	Not detected	Not detected
Other diagnostic tests		
EMG	Acute signs of muscle fiber injury	Acute signs of muscle fiber injury
Muscle biopsy	Extensive necrotic areas	Muscle cell necrosis
Treatment and evolution		
Treatment	Prednisolone and immunoglobulin	Prednisolone
Evolution	Infectious complications that led to death	Good; maintenance of low dose corticosteroid therapy

¹ Due to misunderstanding the patient kept taking atorvastatin concomitantly with pitavastatin.

² Levels at admission; Leucocytes reference range (rf) 4.0 – 10.0 x 10⁹; neutrophils rf 2.0 - 7.0 x 10⁹; CK rf < 171 U/L; LDH rf < 248 U/L; AST rf < 35 U/L; ALT rf < 45 U/L; CRP rf < 0.50 mg/dL.

³ IgG antibodies detection by immunodot assay. Detection of IgG antibodies against Jo-1, PL-7, PL-12, EJ, SRP, Mi-2, MDA-5, TIF1γ, HMGCR, SSA/Ro-52, SAE1/2 and NXP-2. BlueDot Myositis¹² IgG – D-tek®.

⁴ IgG antibodies detection by immunoblot assay. Detection of IgG antibodies against Mi-2α, Mi-2β, TIF1γ, MDA-5, NXP-2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ and Ro-52 antigens. EUROLINE Autoimmune Inflammatory Myopathies 16 Ag - EUROIMMUN®.

CONCLUSION

Statin-induced IMNM is an autoimmune disease associated with the presence of anti-HMGCR antibodies that may present with a rapid, aggressive and fatal clinical course if not rapidly diagnosed. The clinical course of this myopathy seems to be associated with the statin dose, which is in agreement with previous studies.^{6,9} The detection of anti-HMGCR antibodies may contribute to the early diagnosis of this IMNM and to the development of a successful therapeutic strategy.⁷

AUTHORS CONTRIBUTION

CF: Case description and discussion.
AM, RC, FR: Critical review of the work.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Re-

search and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

INFORMED CONSENT

Obtained.

COMPETING INTERESTS

The authors declare that there are no competing interests.

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REFERENCES

- Mohassel P, Mammen AL. Anti-HMGCR myopathy. *J Neuromuscul Dis*. 2018;5:11–20.
- Baucells A, Martínez MA, Alvarado-Cardenas M, Mariscal A, Martínez-Martínez L, Juárez C, et al. Anti-HMGCR specificity of HALIP: a confirmatory study. *J Immunol Res*. 2020;2020:1–4.
- Liu Y, Lv X, Xie N, Fang Z, Ren W, Gong Y, et al. Time trends analysis of statin prescription prevalence, therapy initiation, dose intensity, and utilization from the hospital information system of Jinshan Hospital, Shanghai (2012-2018). *BMC Cardiovasc Disord*. 2020;20:1–13.
- Ward NC, Watts GF, Eckel RH. Statin toxicity: mechanistic insights and clinical implications. *Circ Res*. 2019;124:328–50.
- Baptista B, Tavares J, Marto N, Horta A, Roque R, Mascarenhas V. Miopatia imunomediada por anticorpos anti-HMGCR: revisão da literatura com base num caso clínico. *Med Interna*. 2019;26:314–9.
- Anquetil C, Boyer O, Wesner N, Benveniste O, Allenbach Y. Myositis-specific autoantibodies, a cornerstone in immune-mediated necrotizing myopathy. *Autoimmun Rev*. 2019;18:223–30.
- Alvarado-Cardenas M, Marin-Sánchez A, Martínez MA, Martínez-Martínez L, Pinal-Fernandez I, Labrador-Horrillo M, 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;15:1161–6.
- Selva-O'Callaghan A, Alvarado-Cardenas M, Pinal-Fernández I, Trallero-Araguás E, Milisenda J, Martínez M, et al. Statin-induced myalgia and myositis: an update on pathogenesis and clinical recommendations. *Expert Rev Clin Immunol*. 2018;14:215–24.
- Moita C, Mendonça A, Leite R, de Vasconcellos A. Statin-associated necrotizing myopathy: a rare etiology. *Rev Port Clínica Geral*. 2020;36:503–6.