

Statin-associated necrotizing myopathy: a rare etiology



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ABSTRACT

Introduction: Necrotizing autoimmune myopathy is a rare entity characterized by proximal muscle weakness, elevated creatine kinase levels, potential autoantibody presence, and myofiber necrosis with reduced or absent inflammation.

Case description: We report the case of a 72-year-old female with a 3-week-history of asthenia, increasing proximal tetraparesis, without pain, fever, or other symptoms, and elevated creatine kinase levels. Previous history was remarkable for dyslipidemia controlled with statin therapy. A muscular biopsy was performed, leading to the diagnosis of necrotizing myopathy. A body computed tomography (CT) scan was normal. Corticotherapy was initiated with progressive clinical and analytical improvement.

Discussion: This case depicts an uncommon and underdiagnosed pathology which may be associated with statin treatment or cancer, that requires an early diagnosis and close follow-up for better clinical outcomes.

Keywords: Myositis; Rhabdomyolysis; Hydroxymethylglutaryl-CoA reductase inhibitors; Autoantibodies.

INTRODUCTION

Immune-mediated necrotizing myopathy (IMNM), also termed as necrotizing autoimmune myopathy (NAM) is a type of myositis included in the most recent classifications of inflammatory myopathies.¹⁻² It is characterized by proximal muscle weakness (significant skin or lung involvement should suggest other inflammatory myopathies), elevated creatine kinase (CK) levels – 10-100 times the upper limit –, autoantibody presence, and myofiber necrosis with reduced or even absent inflammation.³

Currently, two autoantibodies have been described in association with IMNM: one targeting the signal recognition particle (SRP)⁴ and more recently, anti-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) autoantibodies.⁵

Autoimmune myopathies are rare, most frequently affect adults but can also occur in children,⁶ with a prevalence of 9-14 cases per 100000 people,⁷⁻⁸ from which ~10% present anti-SRP or anti-HMGCR autoantibodies.^{3,5}

The etiology of IMNM remains elusive, although predisposing and risk factors have been identified. Specifically, the DRB1*11:01 and DRB1*07:01 MHC class II alleles have been strongly associated with anti-HMGCR myopathy.⁹ Also, accumulating evidence established statin exposure as a risk factor for anti-HMGCR myopathy,¹⁰⁻¹¹ in which drug discontinuation fails to improve patient symptoms. Some authors have reported a correlation between anti-HMGCR antibody, CK concentration, and clinical disease activity, suggesting a role for these antibodies in the disease etiology.⁵

Inflammatory myopathies have been associated with cancer; in IMNM this association depends on the disease sub-type: auto-antibody negative pathology has been associated with increased risk of malignancy,¹³ anti-SRP myopathy is not associated with cancer^{3,13-15} and anti-HMGCR has provided conflicting reports on this matter.^{9,13,16} Given these possible associations, some authors speculate that in some cases, IMNM may be triggered by tumors.¹³ In this context, some also recommend chest and abdomen computed tomography (CT) as well as the recommended age and gender cancer screenings.¹⁷

Some reports indicate viral infections as a possible trigger of IMNM, as it has been observed a seasonal pattern to anti-SRP myopathy¹⁸ and SRP and HMGCR

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proteins that share homology regions to varicella-zoster virus and human papillomavirus type 58 which may generate cross-immunity.¹⁷

To this point, no clinical trials have been conducted to establish treatment guidelines for this disease, and as such, the recommendations found in the literature are based on case series, observational studies, and own personal experience.¹⁷ Most authors agree to statin discontinuation and a speedy initiation of treatment which in most cases is an association of corticoid therapy and immunosuppressants (methotrexate, azathioprine, mycophenolate, tacrolimus, cyclosporine, ...).² Some reports suggest the use of rituximab in anti-SRP patients who fail to respond to steroids and other agents.^{3,19} Concerning the anti-HMGCR subtype, intravenous immunoglobulin (IVIG) has been recommended.²⁰

The prognosis for IMNM patients is worse than for other myositis, and the proportion of patients that present persistent muscle weakness even with aggressive immunosuppression is high.^{3,14,16}

This clinical case intends to call attention to an underdiagnosed pathology that should be considered in the differential diagnosis of muscle weakness in patients under statin treatment.

CASE DESCRIPTION

A 72-year-old woman, autonomous, married (Nuclear family – stage VIII Duvall Cycle), retired, without previous known allergies, alcohol, or tobacco consumption. Medicated with atenolol 50mg id, levothyroxine 25µg id, lansoprazole 30mg id, acetylsalicylic acid 150mg id, cinnarizine 75mg id, human basal insulin 40U, metformin 1000mg bid, pentoxifylline 400mg bid, rosuvastatin 20mg id, trazodone 150mg id, hydroxyzine 25mg id and tramadol/paracetamol 37,5mg/325mg (none of which recently initiated). Previous medical history of hypertension, type 2 diabetes, hypothyroidism, dyslipidemia, bilateral knee replacement, left hip replacement, and obesity.

The patient presented to her primary care physician with asthenia, increasing proximal tetraparesis for the previous three weeks, without pain, fever, or other symptoms, without describing any triggers. Physical examination was only notable of muscular strength of the upper limbs of 3/5; muscular strength of the lower

limbs was 2/5 and a weak patellar reflex, with normal remaining reflexes. Polymyalgia rheumatica was considered, besides anemia, thyroid dysfunction, among other hypotheses, and a full blood panel (including C-reactive protein test, CK, and sedimentation rate) was requested and obtained within the same day, that showed a CK value of 9976 UI/L, with no other noticeable changes (including kidney and thyroid function). The patient was immediately referred to the Emergency Room (ER) within the same day for further evaluation and treatment.

Upon ER admission, the increased CK value was confirmed (8336 UI/L) and the patient initiated fluid therapy with diuretics. After neurology observation, electromyography (EMG) was performed which was compatible with an inflammatory myopathy (an anomalous spontaneous activity with fasciculations and a short polyphasic myopathic pattern of the motor unit potentials was observed in the majority of the tested muscles), and therefore iv methylprednisolone was administered (1000mg id).

Echocardiogram, Holter, and chest-abdominal-pelvis CT scan showed no relevant changes. A deltoid biopsy revealed necrotizing myopathy.

The patient completed a 5-day iv corticoid treatment (methylprednisolone 1000mg id), followed by oral therapy (prednisolone 40mg id), with progressive analytical and clinical improvement, having been discharged a week after admission. One month later, the patient took a single dose of iv rituximab (1000mg). She continued with monthly follow-up in neurology, oral corticoid therapy (with progressive dose decrease), and physical rehabilitation. She suspended statin and cinnarizine. Several insulin adjustments were required due to corticotherapy. At the present time, the patient presents a full recovery with apparently no sequelae.

DISCUSSION

Here we report the case of a 72-year old female patient that presented to her primary care physician with a 3-week-history of asthenia and proximal tetraparesis. Upon blood work analysis, increased CK levels were detected and the patient was admitted to the ER with a rhabdomyolysis diagnosis. Further studies confirmed a necrotizing myopathy, probably associated with statin intake. As the patient had initiated statin therapy five



years previously to the episode here described, this was not an acute, self-limited toxic statin myopathy, and statin withdrawal did not improve patient symptoms, which points to IMNM. Unfortunately, it was not possible to determine antibody (SRP and HMGCR) presence which could contribute to therapeutical approaches and future course of action. The GP's prompt diagnosis of myositis and the neurologist's fast intervention was critical for clinical improvement. The primary care doctor should be aware of possible therapeutic alternatives for dyslipidemia in this patient, namely ezetimibe, and if lipidic level control is not sufficiently achieved, PCSK9 inhibitors. At this point, probably due to drastic lifestyle modifications introduced by this patient, the lipidic profile has been within target values, without the need of introducing new therapeutics. Tight glycemic control through insulin adjustments due to corticotherapy was required, which prompted several contacts with the GP. These were crucial to minimize the impact on the patient's quality of life, along with providing support and advice also to the patient's husband (her primary caregiver), through the recovery period which took approximately six months. The need for several GP appointments (which included domiciliary visits) and the informatic constraints between the primary and secondary health providers, were the major difficulties experienced in the follow-up of this patient.

As previously mentioned, this pathology (according to its subtypes) has been associated with cancer, which should also prompt the primary care physician to a strict follow-up of the recommended age and gender screenings in this context.

This case alerts to a rare entity that may be associated with statin treatment, still underdiagnosed, and that requires an early diagnosis for better clinical outcomes. As predisposing genetic factors have been described, one may speculate about the caution of introducing statin therapy in direct relatives.

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REFERENCES

1. Senécal JL, Raynauld JP, Troyanov Y. Editorial: a new classification of adult autoimmune myositis. *Arthritis Rheumatol*. 2017;69(5):878-84.
2. Allenbach Y, Mammen AL, Benveniste O, Stenzel W. 224th ENMC International Workshop: clinico-sero-pathological classification of immune-mediated necrotizing myopathies, Zandvoort, The Netherlands, 14-16 October 2016. *Neuromuscul Disord*. 2018;28(1):87-99.
3. Pinal-Fernandez I, Parks C, Werner JL, Albayda J, Paik J, Danoff SK, et al. Longitudinal course of disease in a large cohort of myositis patients with autoantibodies recognizing the signal recognition particle. *Arthritis Care Res*. 2017;69(2):263-70.
4. Okada N, Mimori T, Mukai R, Kashiwagi H, Hardin J. Characterization of human autoantibodies that selectively precipitate the 7SL RNA component of the signal recognition particle. *J Immunol*. 1987;138(10):3219-23.
5. Mammen AL, Chung T, Christopher-Stine L, Rosen P, Rosen A, Doering KR, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. *Arthritis Rheum*. 2011;63(3):713-21.
6. Suzuki S, Ohta M, Shimizu Y, Hayashi YK, Nishino I. Anti-signal recognition particle myopathy in the first decade of life. *Pediatr Neurol*. 2011;45(2):114-6.
7. Svensson J, Arkema EV, Lundberg IE, Holmqvist M. Incidence and prevalence of idiopathic inflammatory myopathies in Sweden: a nationwide population-based study. *Rheumatol*. 2017;56(5):802-10.
8. Dobloug C, Garen T, Bitter H, Stjärne J, Stenseth G, Grøvlø L, et al. Prevalence and clinical characteristics of adult polymyositis and dermatomyositis: data from a large and unselected Norwegian cohort. *Ann Rheum Dis*. 2015;74(8):1551-6.
9. Ohnuki Y, Suzuki S, Shiina T, Uruha A, Watanabe Y, Suzuki S, et al. HLA-DRB1 alleles in immune-mediated necrotizing myopathy. *Neurology*. 2016;87(18):1954-5.
10. Allenbach Y, Drouot L, Rigolet A, Charuel JL, Jouen F, Romero NB, et al. Anti-HMGCR autoantibodies in European patients with autoimmune necrotizing myopathies: inconstant exposure to statin. *Medicine*. 2014;93(3):150-7.
11. Watanabe Y, Suzuki S, Nishimura H, Murata KY, Kurashige T, Ikawa M, et al. Statins and myotoxic effects associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase autoantibodies: an observational study in Japan. *Medicine*. 2015;94(4):e416.
12. Mohassel P, Mammen AL. Anti-HMGCR myopathy. *J Neuromuscul Dis*. 2018;5(1):11-20.
13. Allenbach Y, Keraen J, Bouvier AM, Jooste V, Champiaux N, Hervier B, et al. High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. *Brain*. 2016;139(Pt 8):2131-5.
14. Watanabe Y, Uruha A, Suzuki S, Nakahara J, Hamanaka K, Takayama K, et al. Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. *J Neurol Neurosurg Psychiatry*. 2016;87(10):1038-44.
15. Suzuki S, Nishikawa A, Kuwana M, Nishimura H, Watanabe Y, Nakahara J, et al. Inflammatory myopathy with anti-signal recognition particle antibodies: case series of 100 patients. *Orphanet J Rare Dis*. 2015;10:61.
16. Tiniakou E, Pinal-Fernandez I, Lloyd TE, Albayda J, Paik J, Werner JL, et al. More severe disease and slower recovery in younger patients with anti-3-hydroxy-3-methylglutarylcoenzyme A reductase-associated autoimmune myopathy. *Rheumatology*. 2017;56(5):787-94.
17. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Immune-mediated necrotizing myopathy. *Curr Rheumatol Rep*. 2018;20(4):21.
18. Leff RL, Burgess SH, Miller FW, Love LA, Targoff IN, Dalakas MC, et al.

Distinct seasonal patterns in the onset of adult idiopathic inflammatory myopathy in patients with anti-Jo-1 and anti-signal recognition particle autoantibodies. *Arthritis Rheum.* 1991;34(11):1391-6.

19. Valiyil R, Casciola-Rosen L, Hong G, Mammen A, Christopher-Stine L. Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series. *Arthritis Care Res.* 2010;62(9):1328-34.
20. Mammen AL, Tiniakou E. Intravenous immune globulin for statin-triggered autoimmune myopathy. *N Engl J Med.* 2015;373(17):1680-2.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

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RESUMO

MIOPATIA NECROTIZANTE ASSOCIADA A ESTATINAS: UMA ETIOLOGIA RARA

Introdução: A miopatia necrotizante autoimune constitui uma entidade rara, caracterizada por diminuição da força muscular proximal, níveis séricos elevados de creatina cinase, eventual presença de autoanticorpos e necrose muscular com inflamação reduzida ou ausente.

Descrição do caso: Apresenta-se o caso de uma mulher de 72 anos com uma história de astenia e tetraparesia proximal com três semanas de evolução, sem dor, febre ou outra sintomatologia e níveis séricos elevados de creatina cinase. Como antecedentes relevantes apresentava dislipidemia controlada com estatina. Foi realizada biópsia muscular, tendo sido estabelecido o diagnóstico de miopatia necrotizante. A tomografia computadorizada toraco-abdomino-pélvica (TC-TAP) não mostrou alterações relevantes. Iniciou corticoterapia com melhoria clínica e analítica progressiva.

Comentário: Este caso relata uma patologia incomum e subdiagnosticada que pode estar associada a tratamento com estatina ou neoplasias, requerendo um diagnóstico célere e um acompanhamento rigoroso para melhores resultados clínicos.

Palavras-chave: Miosite; Rbdomiólise; Inibidores hidroximetilglutaril-CoA reductase; Autoanticorpos.
