A Challenging Inflammatory Myopathy Case-Report: Dermatomyositis-Like Rash in an Anti-HMGCR Positive Patient with an Uncertain Muscle Histology

Hugo Parente, Maria Pontes Ferreira, Catarina Soares, Emanuel Costa, Francisca Guimarães, Soraia Azevedo, Daniela Santos-Faria, José Tavares-Costa, Daniela Peixoto, Carmo Afonso, Filipa Teixeira

Mediterr J Rheumatol 2023;34(4):570-2
A Challenging Inflammatory Myopathy Case-Report: Dermatomyositis-Like Rash in an Anti-HMGCR Positive Patient with an Uncertain Muscle Histology

Hugo Parente1, Maria Pontes Ferreira1, Catarina Soares1, Emanuel Costa2, Francisca Guimarães1, Soraia Azevedo1, Daniela Santos-Faria1, José Tavares-Costa1, Daniela Peixoto1, Carmo Afonso1, Filipa Teixeira1

1Rheumatology Department, Unidade Local de Saúde do Alto Minho, Ponte de Lima, Portugal, 2Rheumatology Department, Hospital de Braga, Braga, Portugal

INTRODUCTION
Idiopathic inflammatory myopathies (IIM) are an heterogeneous group of rare immune-mediated diseases characterised by muscle weakness, elevation of muscular enzymes, auto-antibodies (aAbs) and inflammation on the biopsy tissue. They are divided in polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), anti-synthetase syndrome (ASS), overlap myositis (OM) and immune-mediated necrotising myopathy (IMNM).1 IMNMs are expressed with severe proximal muscle weakness (typically progressing faster and with more pain), high creatine kinase (CK) levels, predominant muscle fibre necrosis and no extramuscular features. The associated aAbs are anti-signal recognition (SRP) and anti-3-hydroxy-3-methylglutaryl-coenzyme A (HMGCR). The latter might be triggered by statin exposure. IMNMs’ diagnosis relies on its serological and histopathological aspects, and its treatment is harder to attain. We report herein a rare case of an admissible anti-HMGCR IMNM with DM-like cutaneous features, whose diagnosis was challenging due to its dubious histology.

CASE REPORT
A 67-year-old patient was referred to the Rheumatology consultation for a 2-year proximal muscle weakness and pain, leading to limitation in her daily live activities - mainly brushing her hair and climbing stairs, having prompted some accidental falls. Her clinical background was positive for type 2 diabetes mellitus and dyslipidaemia for which she was treated with atorvastatin 10mg/day for 7 years prior. There was no family history of muscle or autoimmune diseases. The muscle symptoms were neither associated with a specific timing of her physical activities nor with carbohydrate/lipid ingestion. She had no constitutional, mucocutaneous, oesophageal, or microvascular symptoms. Muscle strength examination revealed severe weakness. She had been treated 3 months earlier with intramuscular betamethasone 14mg, followed by a massive improvement in her symptoms. Her laboratory analysis revealed high CK levels (2212U/L), as well as myoglobin (1181U/L) and aldolase (22.3U/L). Inflammatory markers were normal, so were urinalysis, antinuclear aAbs, and myositis-specific (anti-synthetase, anti-Mi2, anti-SAE, anti-MDA5) and associated aAbs (MAA - anti-RNP, anti-Ku, anti-PM-Scl, anti-SSa, anti-Ro52). The electromyography showed myopathic abnormalities, without neuropathic changes. Deltoid biopsy presented frequent muscle fibres at different stages of necrosis and two endomysial mixed CD3+ T lymphocyte inflammatory infiltrates, concluded to be common features of both PM and IMNM. Cancer screening done by thoraco-abdominopelvic computed tomography, mammography, positron emission tomography scan, esophagogastroduodenoscopy and colonoscopy was negative. She was started on prednisolone 1mg/kg/day and, by the end of the first month, her symptoms and lab results had improved (CK 728U/L, myoglobin 646U/L). At that timing, the patient was found to have a bilateral heliotro-
pic rash (Figure 1). The aAbs against TIF1y and NXP2 were negative. At the second month of corticosteroids, while tapering, her symptoms aggravated, so she started azathioprine 50mg/day and stopped atorvastatin. Later, the results for the first-time requested aAbs related to IMNM came negative for SRP and positive for HMGCR. As adverse events for corticosteroids started to compound, namely cataracts, hyperglycaemia, and osteoporosis, she was proposed treatment with intravenous immunoglobulin (IVIg) 2g/kg for 5 days, followed by monthly booster doses of 1g/kg spread over 3 days, while maintaining corticosteroids and azathioprine (started, respectively, 4 and 3 months previously). After only 1 month of treatment, she noted greater muscle strength and better overall functionality, with resolution of the heliotropic rash. The muscle enzymes were normal. At the last follow-up, after almost 9 months, and with an ongoing decreasing corticosteroid dose of 10mg/day, there was no evidence of disease recurrence.

**DISCUSSION**

IMNMs can be subdivided into anti-SRP, anti-HMGCR and seronegative. These last two might be more frequently associated with malignancies. Anti-HMGCR aAb was first identified in 2010 among IMNM patients, aimed at HMGCR antigen, a key enzyme in cholesterol synthesis that is targeted by statins.3 These aAbs' pathogenicity is accepted, as in vitro they induce muscle atrophy impairing muscle regeneration.2 Also, their titres correlate with disease activity.4 They are found to be highly specific for immune-mediated myopathies, since they are not found in the majority of statin-exposed individuals, including those with a self-limited myopathy.2 Anti-HMGCR primarily associates with IMNM and rarely with other idiopathic inflammatory myopathies (IIM) and connective tissue diseases.6,7 Anti-HMGCR IMNM typically affects people between 40 and 60 years old, with a female preponderance.3 Statin exposure covers about 50 to 66% of these patients, and their CK levels remain elevated for a mean duration of 39 months.8 This elevation has been shown to actually precede muscle weakness by months to years in an atorvastatin-associated anti-HMGCR IMNM cohort,9 so that one should prompt HMGCR aAb search if levels are persistent despite statin suspension. Extramuscular manifestations are usually absent.2,4 As for the anatomopathological aspects, it reiterates necrosis, muscle atrophy and variable grades of regeneration, with little to no inflammatory infiltrates.2,4 There are only four9-12 reported cases of statin-induced anti-HMGCR IMNM with typical cutaneous DM rash. Although our patient displays a histology with mixed IIM characteristics, those are not of DM, and it has no other clinical or serological arguments that fully support the OM diagnosis. Overlap myositis includes IIM plus symptoms peculiar of systemic lupus erythematous, systemic sclerosis or Sjögren’s disease, and is usually linked with MAAs like anti-Ku, anti-PM/Scl, anti-Ro52 and anti-U1-RNP.13 This rationale strengthens our confidence in this case's diagnostic assumption of an anti-HMGCR IMNM with DM cutaneous involvement. The previously mentioned cases reported patients between 47 and 61 years old exposed to statins 8 months to 10 years prior to their symptoms. Proximal muscle weakness and DM rashes were observed for 4 weeks to 4 years. None of the muscle biopsies showed any sign of dermatomyositis. Two of these patients were submitted to skin biopsy, showing neutrophilic interface dermatitis.

**Figure 1.** Bilateral heliotropic rash.
sis was, thus, based on the muscle biopsy (albeit the blended inflammation), statin exposure and anti-HMGCR aAb positivity. This validated association between anti-HMGCR IMNM and DM cutaneous traits implies that patients with this kind of rashes should be cautiously evaluated, even more so as anti-HMGCR aAbs are not routinely included in most myositis panels. Cutaneous DM-like highlights might just be the lead to anti-HMGCR IMNM, especially in patients with severe proximal myalgias and weakness, and with statin exposure. Clinical, serological, and histological components have to be integrated altogether.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

FUNDING ACKNOWLEDGEMENTS
There was no financial support associated with this paper.

AUTHOR CONTRIBUTIONS
Hugo Parente conceived of the presented idea. All authors were involved in the case follow-up. All of them provided critical feedback and contributed to the final version of the manuscript.

REFERENCES