A hard pill to swallow – statin-induced necrotizing autoimmune myopathy manifesting as dysphagia

Rita Veiga, Nuno Cotrim, Catarina Coelho, Beatriz Andrade, Kevin Domingues

Hospital Distrital de Santarém, Santarém, Portugal

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SOUHRN

Kontext: Statiny indukovaná nekrotizující autoimunitní myopatie (statin-induced necrotizing autoimmune myopathy, SINAM) je velmi vzácná a devastující komplikace léčby statiny.
Kazuistika: Popisujeme případ 70letého muže přivezeného na oddělení akutních příjmů s progredující slabostí proximálního svalstva, dysfagií a myalgií v posledních čtyřech měsících. V předchozích dvou letech užíval atorvastatin v dávce 40 mg. Při příjmu prokázalo vyšetření krve vysoké hodnoty CPK (22 086 U/l). I po přerušení léčby statiny zůstávaly hodnoty CPK vysoké a symptomy přetrvávaly. Vyšetření autoimunity prokázalo významnou pozitivitu protilátek anti-HMGCR. Biopsie vzorku odebraného z deltového svalu prokázala nekrózu a regeneraci svalových buněk. Zjištěné klinické, analytické a histologické důkazy se shodovaly s diagnózou SINAM.
Závěr: U pacienta byla zahájena léčba perorálními steroidy s následným podstatným zlepšením klinických a analytických hodnot. Nekrotizující myopatie s nástupem v dospělosti je rovněž těsně spojena se zvýšeným rizikem rozvoje nádorového onemocnění.

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Keywords:
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ABSTRACT

Background: Statin-induced necrotizing autoimmune myopathy (SINAM) is a very rare and devastating complication of statin therapy.
Case presentation: We report a case of a 70 year-old-male who presented in the ER with progressive proximal muscle weakness, dysphagia, and myalgia for the past 4 months. He was medicated in the previous 2 years with 40 mg atorvastatin. On admission, his blood analysis revealed elevated CPK (22086 U/L). Although the patient suspended statin therapy, CPK values remained high and his symptoms persisted. The autoimmune study was notable for strongly positive HMGCR antibody. Deltoid muscle biopsy revealed muscle-cell necrosis and regeneration. These clinical, analytical, and histologic features were consistent with a diagnosis of SINAM.
Conclusions: The patient was started on oral steroids with substantial clinical and analytical improvement. Adult-onset necrotizing myopathy is also strongly associated with an increased risk of cancer.

Background

Dyslipidaemia is a major risk factor for cardiovascular morbidity and mortality. Statins are the first-choice therapy for this condition in both primary and secondary prevention and work by inhibiting the hepatic 3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR). Although they are well tolerated in the vast majority of cases, clinical data suggests that the side-effects of statins may affect at least 30%[1] of patients and range from myalgia, myopathy to myositis and myonecrosis. A very small subset of patients may develop statin-induced necrotizing autoimmune myopathy (SINAM),[2] a devastating complication of this therapy that can occur at any time after initiation.

Case presentation

We present the case of a 70 year-old male that presented in the emergency department with a progressive proximal muscle weakness, dysphagia, and myalgia for the past 4 months. He was medicated in the previous 2 years with

Address: Rita Veiga, Av. Bernardo Santareno, 2005-177 Santarém, Portugal, e-mail: anaritasveiga@gmail.com
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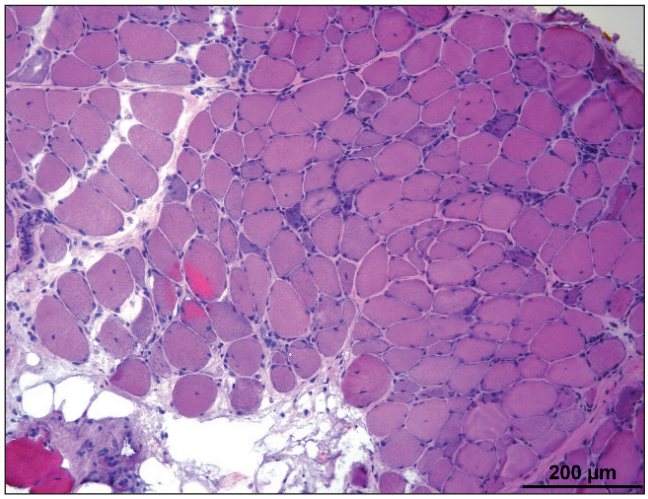

Fig. 1 – Muscle-cell necrosis.

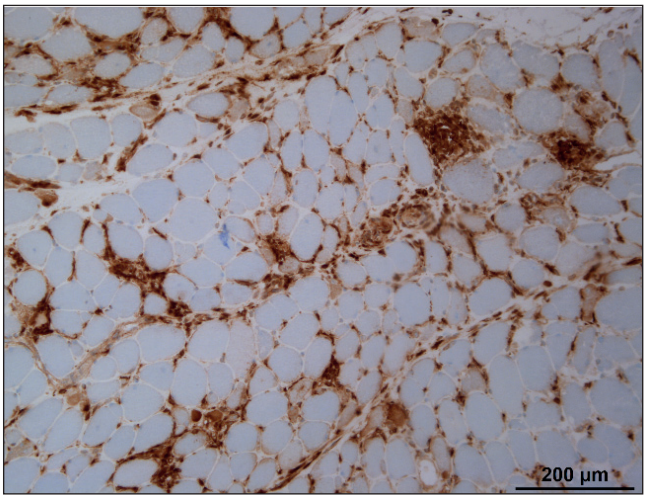

Fig. 2 – Muscle regeneration.

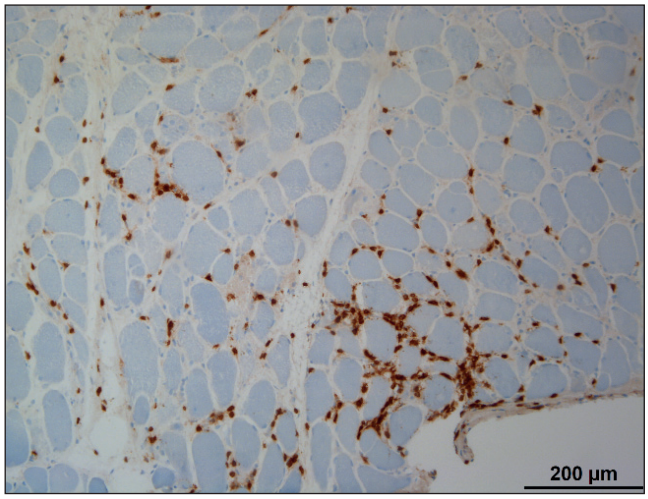

Fig. 3 – Macrophage infiltration in endomysial region and small numbers of lymphocytes.

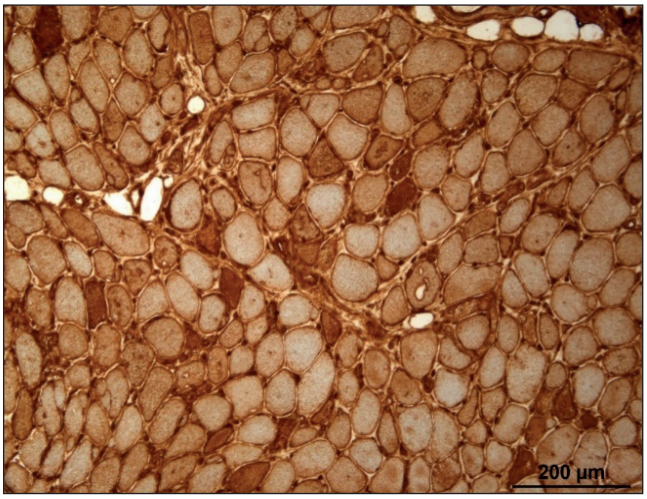

Fig. 4 – Diffuse up-regulation of major histocompatibility complex class I molecules.

40 mg atorvastatin once daily. His personal and family history were negative for muscular disorders. On admission, his blood analysis revealed elevated creatine kinase (CPK 22086 U/L, normal 38–174 U/L). Although the patient suspended statin therapy, muscle-enzyme levels remained high and his symptoms persisted. The autoimmune study was notable for strongly positive anti-HMGCR antibody. Deltoid muscle biopsy revealed muscle-cell necrosis (**Fig. 1**) and regeneration (**Fig. 2**), macrophage infiltration in endomysial region and small numbers of lymphocytes (**Fig. 3**) and diffuse up-regulation of major histocompatibility complex class I molecules (**Fig. 4**). These clinical, analytical, and histologic features were consistent with a diagnosis of SINAM.[3] The patient was started on oral corticosteroids with substantial clinical and analytic improvement.

Discussion and conclusions

The postulated mechanism underlying the development of SINAM remains unknown. Some hypothesis include overexpression of anti-HMGCR triggered by statins in genetically susceptible patients through a complement-mediated mechanism.[4] Patients who seem to be at increased risk include age >50 years and African American descent, with the latter presenting with a higher serum CPK level and less responsive to treatment.

Although SINAM diagnosis is very rare and requires a high index of suspicion, it should be suspected in those with acute and severe onset of progressive and symmetric proximal muscle weakness, markedly and persistently elevated muscle-enzyme levels despite discontinuation of statins and confirmed with an anti-HMGCR autoantibody test.[4] On the other hand, statin-related myositis resolves following discontinuation of the drug. The gold-standard for SINAM diagnosis remains the muscle biopsy.

As it is a devastating and disabling condition, statins should be discontinued and immunosuppressive therapy with intravenous and/or oral steroids, intravenous immune globulin (IVIG) or even methotrexate should be initiated without a delay to induce remission and prevent morbidity and mortality. Some case reports have described mortality due to respiratory complications in

the setting of bulbar involvement.[5] More severe cases requiring intensive care or in refractory patients, plasma exchange, cyclophosphamide and/or cyclosporine may be considered.[6] Some patients may relapse and require long-term treatment with chronic IVIG.

Notably, adult-onset necrotizing myopathy is strongly associated with an increased risk of cancer,[7] particularly within the 3 years prior to and the 3 years after diagnosis. According to recent guidelines, it is highly recommended that all patients continue to participate in population-level cancer screening programmes. Additionally, cancer risk should be stratified according to autoantibody status and clinical features to tailor the following investigations and follow-up.[8]

Conflict of interest
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Data availability
No data were generated or analysed for or in support of this paper.

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