Progressive proximal muscle weakness with subacute onset in an elderly patient: a case report

Ana Martins, Goreti Nadais, Miguel Pinto, Ricardo Taipa, Lúcia Costa, Sofia Pimenta

Introduction. Statins are some of the most widely prescribed medications. Although statins are generally well tolerated, they can lead to musculoskeletal side effects. Statin-induced necrotizing autoimmune myositis (SINAM) is a rare condition and the prevalence is only 1 per 100,000 people. This disorder is characterized by progressive and severe symmetric muscle weakness, marked elevation of creatine kinase and persistent symptoms despite statin discontinuation. Electromyography commonly shows a nonspecific irritable myopathy pattern indistinguishable from other inflammatory myopathies. Muscle biopsy shows the presence of necrotic fibers, regenerating fibers without significant inflammatory cells and diffuse or focal upregulation of major histocompatibility complex class I expression. The anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies represent a characteristic serological feature of SINAM.

Case report. We present a patient who developed progressive muscle weakness after taking simvastatin for the last seven years. At initial presentation, her creatine kinase level was 2,954 U/L and anti-HMGCR antibodies were positive. The biopsy showed a profound myopathic features with numerous necrotic fibers, some regenerating fibers and perimysial inflammatory cell infiltrate, combined with a diffuse overexpression of major histocompatibility complex class I products. She was diagnosed with SINAM, statin was suspended and a high dose of systemic corticosteroids, intravenous immunoglobulin therapy and methotrexate was started. At three-month follow-up, she had significant improvement in muscle strength and creatine kinase level returned to normal.

Conclusion. In this case, exclusion of inflammatory myopathies, metabolic muscle disorders and other neurological diseases is necessary for establishing a reliable diagnosis. In SINAM, simply discontinuing statin is often insufficient and aggressive immunosuppression or immunomodulation therapy is needed to achieve disease remission. This case aims to demonstrate that statins can induce serious muscular diseases that require aggressive immunosuppression.

Key words. Anti-HMGCR. Muscle disorder. Musculoskeletal side effects. Myopathy. Necrotizing autoimmune myositis. Statin.

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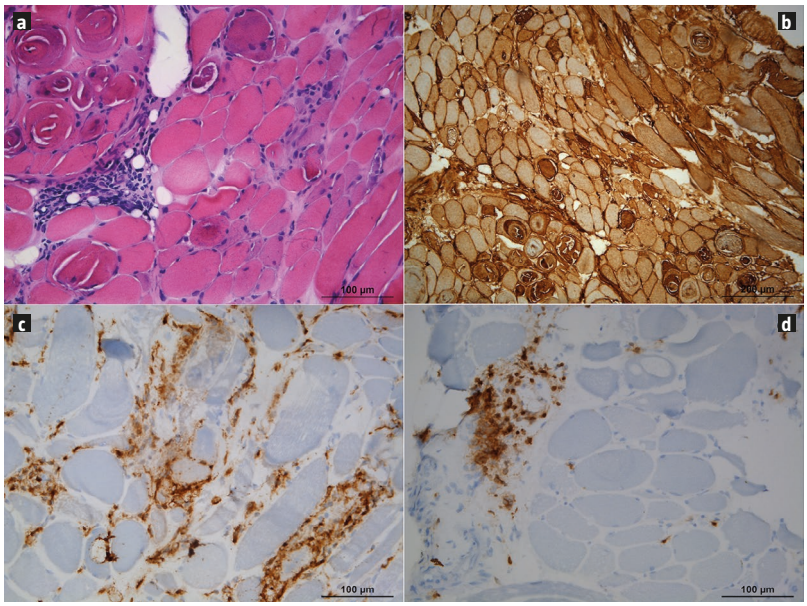
Introduction

Statins are some of the most widely prescribed medications. Although statins are generally well tolerated, they can lead to musculoskeletal side effects, with a relative risk of myalgia versus placebo of 1.01-1.1, depending on the dose [1]. The clinical spectrum of statin-induced myotoxicity varies greatly from asymptomatic elevation of creatine kinase levels to muscle pain, toxic myopathy, necrotizing autoimmune myositis (NAM) and rhabdomyolysis. Statin-induced necrotizing autoimmune myositis (SINAM) is a rare condition and the prevalence is only 1 per 100,000 people [2]. This disorder is characterized by progressive and severe symmetric muscle weakness, marked elevation of creatine kinase and persistent symptoms despite statin discontinuation, if no other treatments are given [3]. The time of onset is variable and may occur several years after statin exposure. Regarding the treatment, simply discontinuing statin is often insufficient and aggressive immunosuppression or immunomodulation therapy is needed to achieve disease remission.

Case report

A 70-year-old female with a past medical history of hypertension, diabetes, hyperlipidemia, ischemic heart disease and degenerative joint disease presented with several months of progressive proximal muscle weakness and myalgia. The patient current medication was tramadol plus acetaminophen 75 + 650 mg every eight hours, fluoxetine 20 mg/day, furosemide 40 mg/day, metformin 1,000 mg/day, linagliptin 2.5 mg/day and simvastatin 20 mg/day (for the last seven years).

Figure. Histological and immunohistochemical analysis of muscle biopsy. Numerous necrotic and regenerating fibers are shown in hematoxylin and eosin stain among a background of round atrophic and whorled fibers. A single perimysial inflammatory infiltrate is discernible (a). Diffuse major histocompatibility complex class I upregulation was documented (b). CD68 and CD3 immunohistochemistry reveals, respectively, an increase of endomysial macrophages (c) and the T lymphocyte predominant perimysial inflammatory cell population (d).



She started having trouble climbing steps and getting out of chair. Gradually, her weakness progressed until she was unable to walk unassisted, comb her hair and take a bath without support. She reported anorexia and weight loss of 15% in the past 10 months. She denied any associated fever or chills, rashes, oral ulcers, shortness of breath, chest pain, dysphagia or any recent vision changes. There was no family history of neuromuscular disease.

Physical examination revealed significant proximal upper and lower extremity muscle weakness (shoulder abduction 3/5, elbow flexion 4/5, hip flexion 3/5, knee flexion 4/5 bilaterally, according to the Medical Research Council muscle strength scale) and she was unable to rise from a seated position. Deep tendon reflexes, sensation and coordination were intact. Heart and lung auscultation and abdominal examination didn't reveal abnormalities. No cutaneous manifestations suggestive of dermatomyositis were found in physical examination.

Laboratory workup showed an elevated creatine kinase (2,954 U/L, ref. 10-149), aldolase (45.6 U/L, ref. <7.6), aspartate transaminase (124 U/L, ref. 10-31 U/L), and alanine transaminase (95 U/L, ref. 10-31 U/L). Serologic tests for herpes simplex, Epstein-Barr, cytomegalovirus, varicella-zoster, human immunodeficiency and hepatitis C were negative. Serology test for hepatitis B revealed a past infection (hepatitis B *virus DNA* was negative). Thyroid function was normal.

Nerve conduction studies and electromyography showed abnormal spontaneous muscle activity in proximal muscles of upper and lower extremities suggestive of an irritable myopathy. A right deltoid muscle biopsy was performed and showed profound myopathic features with numerous necrotic fibers, some regenerating fibers and perimysial inflammatory cell infiltrates (predominantly composed of macrophages and T cells), combined with a diffuse overexpression of major histocompatibility complex class I products (Figure). Results for myositis-associated and connective tissue disease antibodies, including antinuclear antibody, anti-dsDNA, anti-SSA, anti-SSB, anti-Sm, anti-RNP, PR3 antineutrophil cytoplasmic antibodies, MPO antineutrophil cytoplasmic antibodies and myositis panel for Mi2, Ku, SRP (signal recognition particle), PL7 (anti-threonyl-tRNA synthetase), PL12 (anti-alanyl-tRNA synthetase), EJ (anti-glycyl-tRNA synthetase), OJ (anti-isoleucyl-tRNA synthetase), TIF1-γ (anti-transcription intermediary factor 1 gamma), *MDA5* (anti-melanoma differentiation-associated gene-5), SAE (anti-small ubiquitin-like modifier-1 activating enzyme), PM-Scl100, PM-Scl75 and Jo 1 (antihistidyl-tRNA synthetase), were negative. The anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies were positive (>200, ref. <20).

Given the association between inflammatory myopathies and malignancy, cancer screening was reviewed. Colonoscopy, mammogram and cervical cancer screening performed in the past did not show any significant abnormalities. Computed tomography of the chest and abdomen, thyroid ultrasound and positron emission tomography were negative for malignancy.

She was diagnosed with SINAM and statin was suspended. She started on methylprednisolone 1 g/day, for three days followed by prednisolone 60 mg/day (0.75 mg/kg/day). Due to minimal improvement in her symptoms, intravenous immunoglobulin therapy was initiated for five consecutive days (0.4 g/kg/day).

This combination of treatment resulted in a significant improvement in muscle strength and myalgia and a substantial reduction in the creatine kinase level down to 1,029 U/L. After 21 days of hospitalization, she was discharged on a tapering dose

of steroids and methotrexate was started. After three months of follow up, neurological examination was normal and creatine kinase level returned to normal (15 U/L). At that time, she was medicated with methotrexate 10 mg/week and prednisolone 20 mg/day.

Discussion

Necrotizing autoimmune myositis is an autoimmune muscle disease pathologically characterized by prominent myofiber necrosis and minimal lymphocytic infiltration. This condition can be associated with connective tissue disorder but can also be triggered by viral infections (such as human immunodeficiency virus) or malignancy, be statin induced or be idiopathic.

SINAM is an extremely rare and severe form of statin myopathy, which can lead to debilitating weakness. The pathogenesis of SINAM has not been clearly elucidated yet. The current proposed mechanism involves a damage to muscle cells by autoantibodies directed against HMG-CoA reductase, an enzyme constitutively expressed at low level by mature muscle cells [4]. Statins block the activity of HMG-CoA reductase, but also increase the production of this enzyme. This can lead to abnormal protein processing in genetically susceptible patients, with the subsequent production of antigens and antibodies [2]. These autoantibodies were recognized as anti-HMGCR antibodies by Mammen et al [5]. Anti-HMGCR antibodies represent a characteristic serological feature of SINAM and have a sensitivity and specificity of 94.4% and 99.3%, respectively [5].

Predisposing factors for SINAM include advanced age, female sex, physical disability, low body mass index, high statin doses, other medications and substances with toxic muscle effects (for example colchicine and alcohol) and drugs metabolized by cytochrome P450 3A4, such as azole antifungals, macrolides, tricyclic antidepressants, protease inhibitors, calcium-channel blockers and warfarin [6]. There is also a link to a genetic predisposition for this condition, suggested by the increased frequency of DRB1*11:01 haplotypes in patients with positive anti-HMGCR antibodies [7].

A systematic literature review of 100 SINAM cases by Nazir et al found that the mean duration of statin use prior to the onset of myopathy symptoms was 40.48 months [3]. Different statins may produce different risk of myotoxicity, with atorvastatin and simvastatin being associated with higher rates of myopathy than rosuvastatin [8]. However, there is no established association between specific statins and the occurrence of SINAM.

SINAM generally presents with an acute or subacute onset of severe proximal muscle weakness and marked elevation of creatine kinase levels, often 10 times greater than the upper normal limit [4]. Extramuscular involvement including pulmonary fibrosis, skin manifestation and arthritis do not typically occur. Electromyography commonly shows a nonspecific irritable myopathy pattern indistinguishable from other inflammatory myopathies [9]. Muscle biopsy shows the presence of necrotic fibers, regenerating fibers without significant inflammatory cells and diffuse or focal upregulation of major histocompatibility complex class I expression [9].

Differential diagnosis that should be considered include other inflammatory myopathies, metabolic and genetic muscle disorders, and toxic statin myopathy.

In our case, toxic statin myopathy was ruled out because symptoms continued after statin discontinuation, anti-HMGCR antibodies were positive and biopsy revealed increase of major histocompatibility complex class I expression [10]. Major histocompatibility complex class I expression also helped to differentiate SINAM from metabolic and genetic muscle disorders. Dermatomyositis was ruled out by the absence of skin lesions and absence of perifascicular atrophy in the muscle biopsy. The absence of significant endomysial mononuclear infiltrate in the biopsy makes the diagnosis of polymyositis less probable. The absence of rimmed vacuoles and ragged-red fibers excluded inclusion body myositis.

Once the diagnosis of SINAM is established, discontinuation of the offending agent is the most important step in the management of these patients. However, most patients also require treatment with corticosteroids, immunosuppressive agents and, in severe cases, intravenous immunoglobulin (as in our case). Observational studies have shown that the majority of patients required two or more immunosuppressants [3]. Therapy is usually needed for a prolonged period to prevent relapses. A close monitoring, that should include patient reported functional changes, muscle strength testing and serum creatine kinase levels, is fundamental.

In conclusion, necrotizing autoimmune myositis is a rare event related to statin therapy. Exclusion of inflammatory myopathies, metabolic muscle disorders and other neurological diseases is necessary

for establishing a reliable diagnosis. SINAM should be considered in patients exposed to statin that present with typical proximal myopathic weakness and a very high creatine kinase level, even after statin discontinuation. In these cases, screening with HMGCR antibodies and biopsy should be carried out. This will allow an early diagnosis, an appropriate treatment and a better outcome.

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Debilidad muscular proximal progresiva de inicio subagudo en un paciente anciano: descripción de un caso

Introducción. Las estatinas son de los medicamentos más recetados. Aunque las estatinas generalmente se toleran bien, pueden provocar efectos secundarios musculoesqueléticos. La miopatía autoinmune necrotizante inducida por estatinas (SINAM) es una afección rara y la prevalencia sólo es de 1 de cada 100.000 personas. Este trastorno se caracteriza por debilidad muscular simétrica progresiva y grave, elevación marcada de la creatincinasa y síntomas persistentes a pesar de la interrupción de la estatina. La electromiografía suele mostrar un patrón de miopatía irritable inespecífico, indistinguible de otras miopatías inflamatorias. La biopsia muscular muestra la presencia de fibras necróticas, fibras en regeneración sin células inflamatorias significativas y una regulación positiva difusa o focal de la expresión del complejo mayor de histocompatibilidad de clase I. Los anticuerpos anti-3-hidroxi-3-metilglutaril-coenzima A (anti-HMG-CoA) reductasa representan un rasgo serológico característico de la SINAM.

Caso clínico. Presentamos a un paciente que desarrolló debilidad muscular progresiva después de tomar simvastatina durante los últimos siete años. En la presentación inicial, su nivel de creatincinasa fue de 2.954 U/L y los anticuerpos anti-HMG-CoA reductasa fueron positivos. La biopsia mostró rasgos miopáticos profundos con numerosas fibras necróticas, algunas fibras en regeneración e infiltrado de células inflamatorias perimisial, combinado con una sobreexpresión difusa del complejo mayor de histocompatibilidad de clase I. Se le diagnosticó SINAM, se suspendió la estatina y se inició una dosis alta de corticoides sistémicos, inmunoglobulina intravenosa y metotrexato. Después de tres meses de seguimiento, tuvo una mejora significativa en la fuerza muscular y el nivel de creatincinasa volvió a la normalidad.

Conclusiones. En este caso, la exclusión de miopatías inflamatorias, trastornos musculares metabólicos y otras enfermedades neurológicas es necesaria para establecer un diagnóstico fidedigno. En la SINAM, la simple suspensión de las estatinas a menudo es insuficiente, y es necesaria una terapia de inmunosupresión o inmunomodulación agresiva para lograr la remisión de la enfermedad. Este caso tiene como objetivo demostrar que las estatinas pueden inducir enfermedades musculares graves que requieren una inmunosupresión agresiva.

Palabras clave. Anti-HMG-CoA reductasa. Efectos secundarios musculoesqueléticos. Estatina. Miopatía. Miopatía autoinmune necrotizante. Trastorno muscular.