



Immune-mediated necrotizing myopathy due to statins exposure

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Statin-induced necrotizing autoimmune myopathy (IMNM) is an autoimmune disorder induced by anti-3-hydroxy-3-methylglutaryl-coenzyme-A reductase (anti-HMGCR) antibodies. We performed a retrospective clinical, histological, and radiological evaluation of 5 patients with a 3-year therapeutic follow-up. All patients used statins and then experienced proximal weakness that persisted after drug cessation. Muscle biopsies revealed a primary necrotizing myopathy without inflammatory infiltrates. All patients required immunomodulant combination therapy to achieve clinical remission. Magnetic resonance imaging (MRI) showed the presence of edema in the medial gastrocnemius, posterior and central loggia of the thigh, posterior loggia of the arm, and the infraspinatus and subscapularis muscles, as well as extensive inflammation of the subcutaneous tissues and muscolaris fasciae. Serum analysis, muscle biopsy, and MRI are fundamental for IMNM diagnosis and follow-up. The growing use of statins in the general population raises the importance of acquaintance with this disease in clinical practice.

Key words: HMGCR autoantibodies, muscular MRI, necrotizing myopathy

Introduction

Inflammatory myopathies constitute a heterogeneous group of disorders targeting skeletal muscle. Different inflammatory myopathies vary with regards to prognosis and response to pharmacological therapy. Immune-mediated necrotizing myopathy (IMNM) is a recently recognized category of idiopathic inflammatory myopathy. The autoimmune nature of IMNM is suggested by

its frequent association with two specific autoantibodies: 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and signal recognition particle (SRP) (1). Among patients using statins, the estimated IMNM incidence rate is 2-3 per 100,000 patients, with increased risk among patients over 50 years of age (2, 3).

Histological characteristics of IMNM include the presence of necrotic fibers without inflammatory cell infiltrates. The underlying pathogenesis remains unclear, but statins appear to play a major role. Statins can trigger the expression of anti-HMGCR antibodies. This induces muscle synthesis of HMGCR enzyme, which is normally poorly expressed in mature muscle cells, potentially maintaining inflammatory activity even after statin discontinuation (4-6). First-line treatment of IMNM involves steroids, which is generally effective although steroid treatment usually must be administered in combination with other immunosuppressive agents (9, 10).

Over the last decade, muscle magnetic resonance imaging (MRI) has become a very useful tool in the diagnosis and follow-up of patients with myopathies. Muscle MRI provides information regarding skeletal muscle structure and function, such as the presence of edema and/or fatty infiltration, and it is a good technique for monitoring disease progression (7). To date, only one study has analyzed the muscle involvement pattern in patients with IMNM, reporting widespread muscle involvement and a trend towards atrophy and fatty replacement (8). The predominantly involved muscles are the lateral obturators, glutei, and the thigh medial and posterior compartment (8).

The widespread use of statins in the general population increases the importance of being familiar with IMNM in daily clinical practice. In the present study, we aimed to describe the clinical and histological characteristics of 5 patients affected with IMNM, as well as their post-treatment outcomes, and to illustrate a new MRI pattern for IMNM recognition that may be helpful in early diagnosis.

Methods

Patients. This study included 5 patients belonging to a database approved by the local Ethical Committee. They were diagnosed with IMNM and followed at our Institute from 2014 to 2017. Inclusion criteria were exposure to statins, progressively increasing CK serum activity despite therapy discontinuation, clinical presentation involving subacute onset of severe proximal hyposthenia, necrotizing pattern at muscle biopsy, and serum positivity for anti-HMGCR antibodies.

Each patient was clinically evaluated at the onset of symptoms, as well as during treatment to assess the response to therapy. All patients underwent anti-HMGCR antibody screening tests, EMG, neoplastic screening, muscle biopsy, and muscle MRI.

Diagnostic Imaging. Muscle MRI images of the legs and right arm were acquired using Turbo Spin Echo (TSE) sequences T1, fat sensitive, and Short tau-inversion-recovery (STIR) T2-weighted, fluid sensitive, on a Philips Achieva 1.5T MRI system. Axial images were contiguously acquired throughout the pelvic girdle, thigh

and leg to allow for evaluation of the full extent of each muscle. In the arm study, images partially include shoulder girdle.

MRI scanning was performed before therapy in 4 of the 5 patients, and after treatment in all 5 patients. Each muscle was graded according to the degree of fatty substitution apparent on T1WI sequences using the scale proposed by Mercuri et al. (11) Similarly, muscle edema was graded based on the T2-STIR sequences using a 4-point scale (none = 0, mild = 1, moderate = 2, severe = 3) (12). We also assessed the presence of both soft-tissue and perifascicular edema.

Muscle Biopsy and Serum Analysis. After all patients signed the specific informed consent, skeletal muscle biopsy was performed. Muscle biopsy samples were prepared and analyzed using standard light microscopy techniques (13). Serum concentration of anti-HMGCR antibodies was screened for the presence of by the ELISA method using a commercial kit (QUANTA Lite® HMGCR ELISA; Inova Diagnostics, San Diego, Ca, USA) on a Quantalyser® 160 instrument (Inova Diagnostics, San Diego, Ca, USA) as previously described (14).

Treatment. All patients underwent immunosuppression with a combination of multiple drugs (Table 1).

Results

Demographics and Clinical Features. All patients showed moderate to severe proximal and trunk weakness and myalgia. Only Patient 2 showed occasional dysphagia. The patients exhibited extremely high CK levels with

Table 1. Clinical features, instrumental examination, and drug treatments of patients with statin-related IMNM.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age and sex	67, W	65, M	59, M	76, M	63, W
Statin (years of use)	Simvastatin, atorvastatin (6 years)	Atorvastatin (5 years)	Atorvastatin (3 years)	Atorvastatin (10 years)	Atorvastatin (5 years)
EMG findings	Myopathic, fibrillation, repetitive discharges	Myopathic, fibrillation	Myopathic, fibrillation potentials, repetitive discharges	Myopathic, fibrillation	Myopathic, fibrillation, repetitive discharges
Autoantibodies	Negative	Negative	Negative	Negative	Negative
Treatment	PRD, AZA, IVIg, MTX, MFN	PRD, AZA, IVIg	PRD, AZA	PRD, IVIg, MTX, MFN	PRD, MTX, IVIg
Treatment period before recovery	2 years	1 year	1 year	2 years	2 years
Clinical follow-up	Normalization of muscle strength	Improvement of muscle strength	Normalization of muscle strength	Normalization of muscle strength	Improvement of muscle strength

The autoantibodies tested were: ANA, ENA, ANCA, Mi2, Ku, PM-Scl, 100 and 75, Jo1, SRP, PL 7, 12, EJ, and OJ. PRD, prednisone; AZA, azathioprine; IVIG, intravenous immunoglobulin; MTX, methotrexate; MFN, mycophenolate mofetil.

peak values between 5900 and 9584 U/L. All patients had a medical history of long-term statin use (3 to 18 years). Patient 1 had history of hypertension, diabetes mellitus and dyslipidaemia. EMG revealed a myopathic pattern with fibrillation activity and bizarre high frequency discharges in all patients. All patients started steroid treatment for at least 6 months, after the ineffectiveness of this therapy we performed three cycles of IVIg one month apart from one another. If patients still had symptoms or signs of myopathy, we had another immunosuppressive therapy.

Table 1 shows the patients' detailed clinical features, instrumental examinations, and treatments.

Histology. Muscle examination showed several, scattered necrotic fibers in all specimens, without evidence of inflammatory infiltrates or perifascicular atrophy (Fig. 1). All samples exhibited fiber size variability. Cell typing re-

vealed a scattered presence of CD4+ or CD8+ cells, with no clear distribution pattern. Human leukocyte antigen type I (HLA I) autoantibodies positivity was detected only in necrotic fibers except for patient 3 muscle biopsy which showed membrane positivity also in some scattered non-necrotic fibers (Fig. 1). Anti-membrane attack complex autoantibodies negative in all muscle biopsies.

Serum Antibody Analysis. Anti-HMGCR autoantibodies were markedly positive in all patients at the time of diagnosis before treatment. After one month of treatment and at six months after CK normalization, anti-HMGCR autoantibodies were still detectable in all patients,.

MRI Imaging. Pre-treatment MRI showed several grades of edema at the level of the central and posterior loggia of the thigh and pelvic girdle, and a mild trend towards atrophy and fatty replacement. The most affected

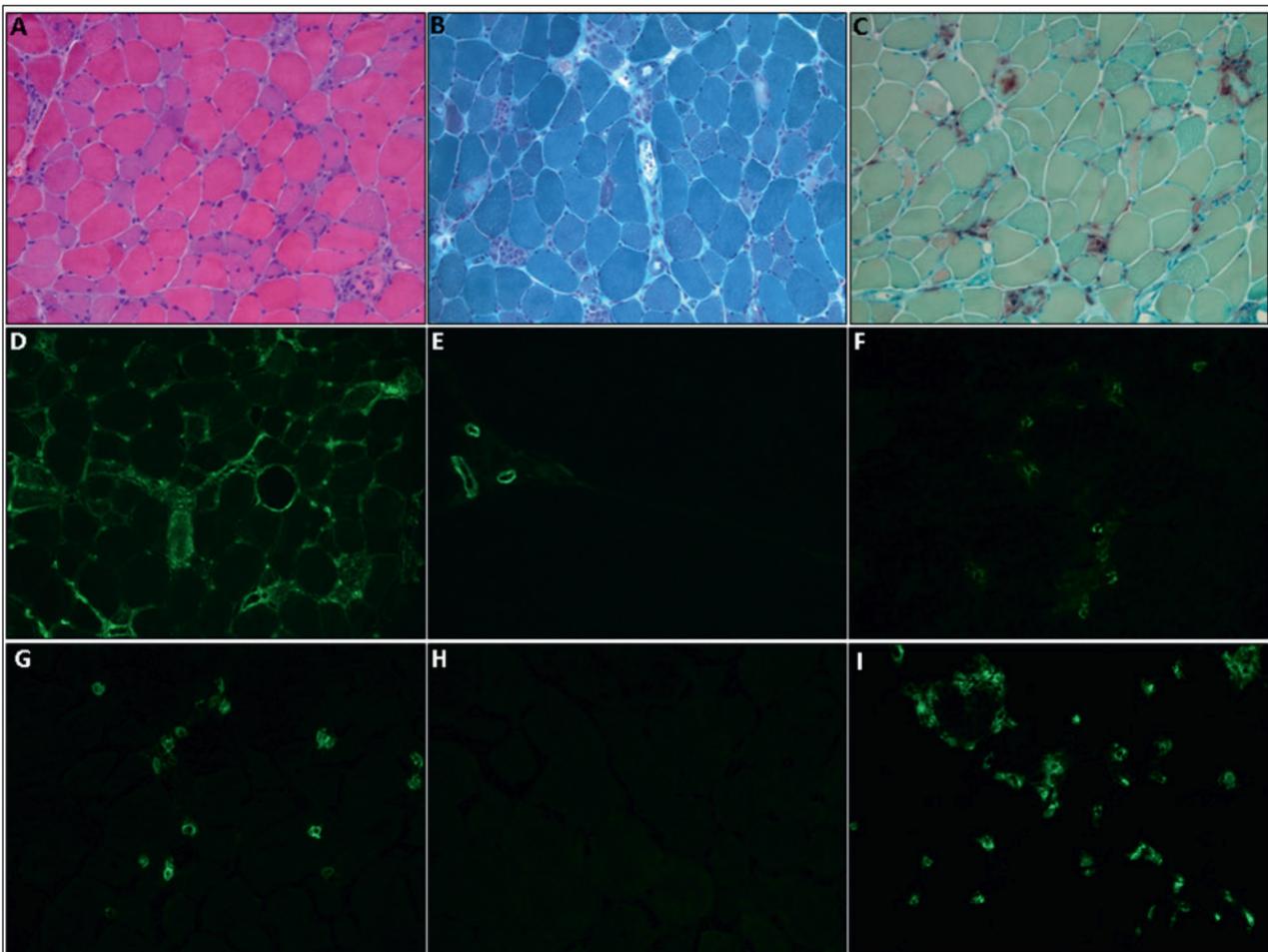


Figure 1. Histological findings with hematoxylin-eosin staining (A) and Gomori trichrome (B) and histochemical findings with acid phosphatase (C) revealing necrotic muscle fibers without any cellular infiltrates. Immunohistochemical evidence of HLA autoantibodies positivity present only in necrotic fibers. MHC class I are expressed only in the cytoplasm of necrotic muscle fibers (D,E). We observed also a variable prevalence of CD8+ cells (F) or CD4+ cells (G,H,I) with no clear distribution pattern.

muscles were the adductor muscles, particularly the adductor brevis, semimembranosus and long head biceps, as well as the obturators and gluteus maximum. At the leg level, the most affected muscle was the medial gastrocnemius whereas at the arm level triceps and deltoid,

followed by infraspinatus and subscapularis, were mostly involved. Figure 2 shows the different grades of fatty replacement and levels of edema documented in the thighs, legs, and arms in pre-treatment MRI scans. Inflammation of the subcutaneous tissue and the muscular fascia was

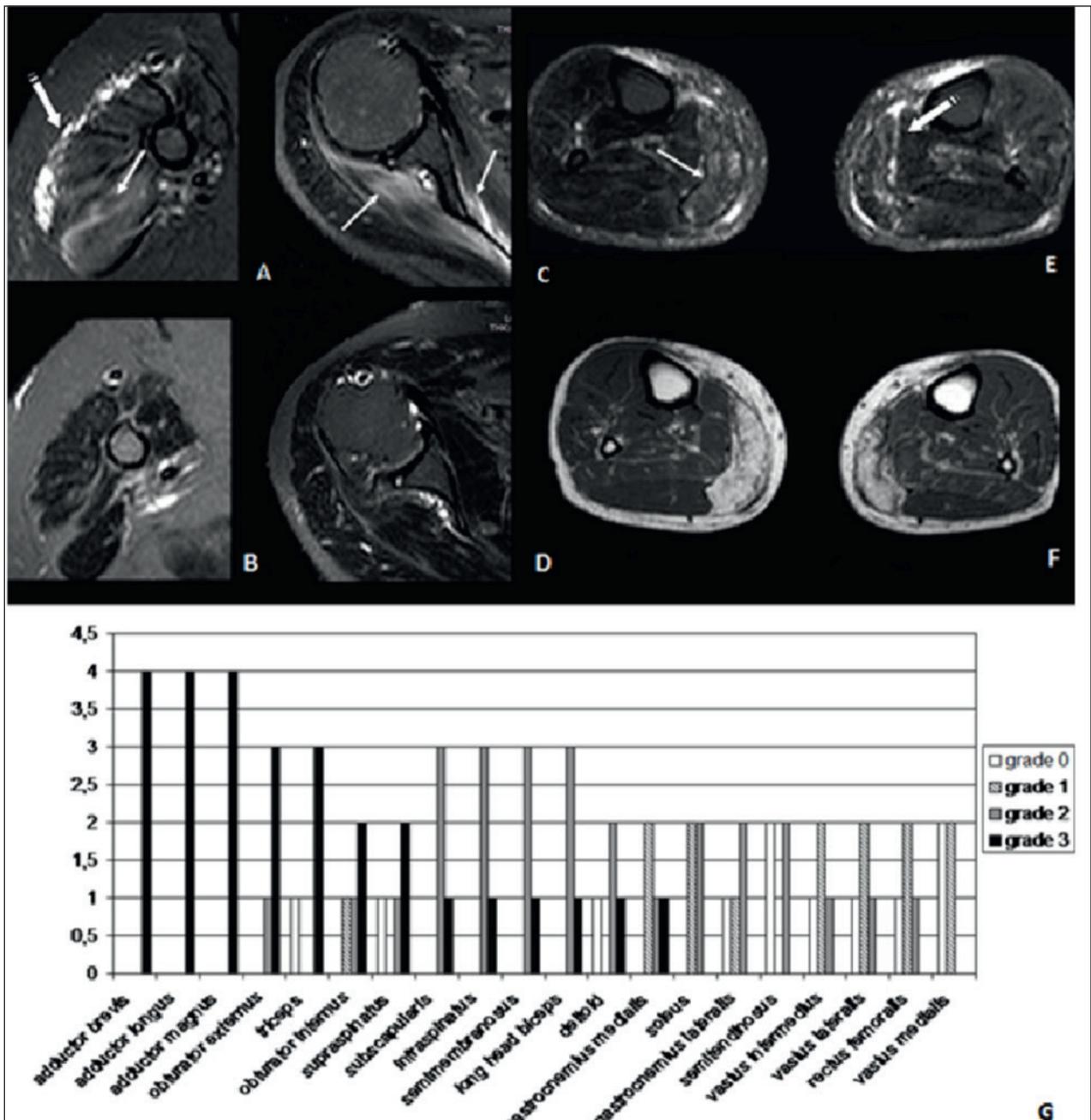


Figure 2. Figure A-C-E. Pre-treatment axial T2 STIR images show edema respectively at the level of the deltoid, subscapularis and infraspinatus muscles and the medial heads of the gastrocnemius muscles bilaterally. Edema is seen at the level of the subcutaneous tissue and the fascia (dotted arrows). Figure B-D-F. Post-treatment axial T2 STIR images document complete resolution of the oedema in the corresponding compartments. Figure G: Extension of oedema of individual muscles on pre treatment MRI, assessed on axial T2WI STIR images. A 4-point scale graduation represent an average of the individual score of the 5 patients for each muscle.

observed in 3 of 4 patients. Post-treatment MRI revealed complete resolution of edema. The grades of fatty replacement remained largely unchanged.

Discussion

Statin use has consistently increased in the last twenty years and has led to more frequent toxic neuromuscular complications, usually self-limiting after drug discontinuation. Quite often, however, statin use induces an autoimmune reaction and causes the development of an aggressive IMNM. The disease is quite rare and, also due to the lack of a validated commercial diagnostic kit, often still under-diagnosed.

In our study all patients had taken atorvastatin. However, due to the small number of examined patients, further studies are certainly needed to validate this association. The 5 patients affected with statin-induced IMNM with serum positivity for anti-HMGCR antibodies and typical pattern of severe necrotizing muscular biopsy, showing acute weakness of trunk flexor and limb girdle muscles, whereas the bulbar muscles were generally spared. Axial involvement is not common among other types of inflammatory myopathies (15). Indeed, in statin-induced myopathies, MRI imaging reportedly shows involvement of the dorsal muscle groups of both the thighs (8, 16). Compared to others toxic and drug-induced myopathies, MRI imaging in our IMNM patients revealed more extensive edema and a trend towards fatty muscle replacement. These findings are in agreement with the recent literature (8). Moreover, extending the study to leg, arm and shoulder girdle, we found a new pattern recognition involving also the medial gastrocnemius and, at the arm level, triceps and deltoid followed by infraspinatus and subscapularis. We also observed inflammation of the subcutaneous tissues and of muscolaris fasciae of both arms and legs, which has not been previously reported to our knowledge (Fig. 2). These findings suggest that patients affected with IMNM may exhibit a wider systemic inflammatory response that is not limited to skeletal muscles.

These new MRI findings allow to improve the differential diagnosis between IMNM myopathy and other inflammatory myopathies and to distinguish IMNM from the toxic myopathy related to statin intake. This distinction is important because toxic myopathy usually improves and then resolves following interruption of statin intake; conversely, IMNM myopathy progressively worsens even after statin suspension and causes a very severe, sometimes hardly or non-reversible, damage to the muscles. Ultimately, muscle MRI may be a useful tool to monitor the evolution of muscle disease over time, but it can be used also as a first-line screening to identify the

most affected muscle and therefore increase the diagnostic accuracy of the skeletal muscle biopsy.

Appropriate therapeutic control is tricky in this type of inflammatory myopathy. Each patient required several immunosuppressive treatments before achieving clinical control. Indeed, all patients were initially treated with IV steroids, followed by high-dose oral steroid therapy, with concomitant superimposition of additional immunosuppressive drugs. Moreover all patients achieved normalization of CK levels and improved muscle strength, albeit with different drug associations and time intervals until response. In two patients, tapering attempts were followed by immediate increase of CK levels that required drug restoration.

In our present study, we aimed to provide a systematic comprehension of this currently under-diagnosed disease in terms of both diagnostic tools and therapeutic options, and to help define the MRI pattern for IMNM recognition to improve its diagnosis.

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