NECROTIZING MYOPATHY ASSOCIATED WITH STATIN CONSUMPTION: A CASE REPORT

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Abstract

Necrotizing autoimmune myopathies are a group of acquired myopathies with prominent myofiber necrosis, sometimes without significant inflammation. It has been found that some of these patients have antibodies against HMGCR. The presence of this antibody has been associated, most of the time, to the consumption of statins. We present a 57-year-old male with a history of coronary artery disease and intake of Crestor (rosuvastatin). The patient developed a necrotizing myopathy with elevated CPK and rhabdomyolysis. Further tests confirm elevated quantities of anti-HMGCR antibodies and confirmation of a necrotizing myopathy.

Keywords

Autoimmune necrotizing myopathy, rhabdomyolysis, statin-related myopathy, anti- HMGCR antibodies.

Introduction

Immune-mediated necrotizing myopathy is an acute or subacute condition associated with various underlying causes, including malignant tumors, active viral infections, and statin treatment (Dubowitz et al. 535). Statins are medications used to treat or stop cardiovascular disorders, reducing levels of low-density cholesterol by blocking the enzyme HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase, which regulates the rate of cholesterol synthesis (Eckel et al., 2019). Nevertheless, side effects like myalgia and rhabdomyolysis are possible for people on statins.

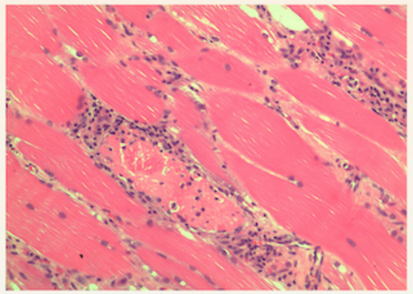
Clinical Presentation

A 57-year-old man with a history of coronary heart disease on Crestor, Lipitor and Zetia treatment was admitted with high CPK levels of 23,506 U/L, aldolase levels of 376 U/L, and creatinine levels of 0.7mg/dL for possible rhabdomyolysis. After taking hour-long walks on consecutive days for two days, the patient exhibits indicators of tiredness, muscle weakness, and trouble raising his arms and walking. CPK levels were reduced to 8,000U/L by steroid therapy, suggesting the possibility of statin-induced myopathy. Muscle biopsy and immunohistochemistry analysis were done. Anti HMGR antibody 125 (Reference: normal range < 20 /strong positive >59)

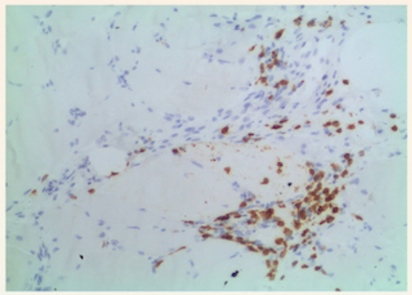
Table 1

2017 ENMC criteria for immune-mediated necrotizing myopathy. Drug/toxin-induced myopathy should be excluded

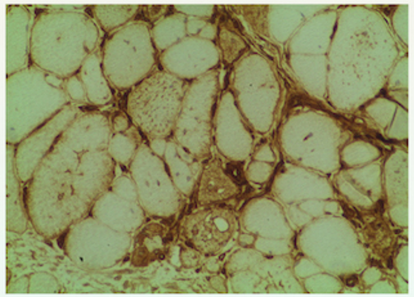
	Serologic criteria	Muscle biopsy features	Clinical criteria
Anti-SRP myositis	Anti-SRP antibody	Not required	High creatine kinase
Anti-HMGCR myositis	Anti-HMGCR antibody		Proximal weakness
Antibody-negative IMNM	No myositis-specific antibody	- Necrotic fibers - Different stages of: Necrosis Myophagocytosis Regeneration - Paucilymphocytic infiltrate	



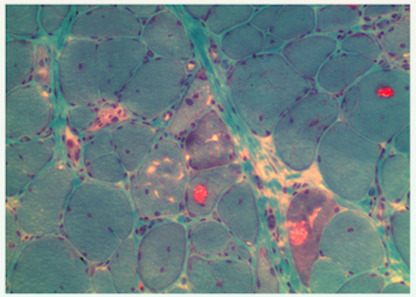
A- Necrotizing myopathy. Necrotic fibers are surrounded by inflammatory cells. H/E x100



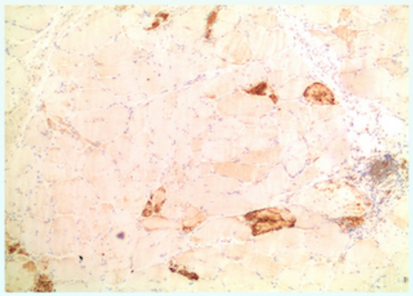
B- The inflammatory infiltrate consists mostly of CD3 T-cells and CD68 macrophages. In this photo de CD3 T-cells are highlighted. CD3 x100



C- HLA is overexpressed in affected fibers. Some of the fibers show rimmed-like vacuoles resembling inclusion body myositis. HLA x100



D- Necrotic fibers are observed. Some of them associated with inflammation. In addition, several fibers present rimmed-like vacuoles. Also there is an increase of endomysial and perymysial fibrosis. Gomori Trichrome x100



E- Abnormal fibers show deposits of P62 protein. In the photo it is also evident the inflammation. P62 x40

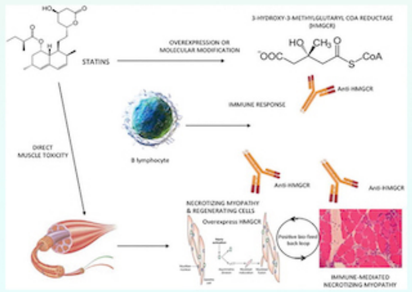


Figure 6: Etiopathogenesis of statin-induced immune-mediated necrotizing myopathy. (Selva-O'Callaghan et al., 2018)

Abstract

Immune-mediated necrotizing myopathy (IMNM), also known as necrotizing autoimmune myopathy (NAM) is a brand-new classification of inflammatory myopathies. These conditions have in common the presence of degenerative muscle fibers and inflammatory cell infiltrates2, and myositis-specific autoantibodies (MSA) such as anti-Jo-1, anti-Mi 2 1 that can help describe the clinical features of the disease. Statin-associated INMN presents the specific autoantibody anti-HMGCR at 100 kDa 7 and 200 kDa (dimerization of the HMGCR protein). Other histological aspects of IMNM include the apparition of major histocompatibility class I antigens (MHC I) in muscle cells, the detection of CD8+ T lymphocyte cells, and the infiltrates of inflammatory cells, round cells, although it can usually be absent. Furthermore, patients with INMN are characterized by high levels of CK levels. In effect, immunohistochemistry and muscle biopsy are useful to diagnose this condition. The findings, in this case, showed skeletal muscle atrophy with distinct type 1 fiber predominance without fiber grouping, which is linked to mitochondrial damage and pathological changes like swollen mitochondria and autophagic vacuoles and can exhibit a phenotype like inclusion body myositis 6. He also had gradual tiredness and low-power contractions over extended periods. Muscle atrophy showed fluctuation in fiber size upon microscopic examination, but it lacked a perifascicular pattern. Moreover, thick-walled blood vessels, fatty replacement, and internal nucleation (10%) were observed. Regenerating muscle fibers and type 1 fiber necrosis, evidence of HMGCR accumulation in the muscle fibers and amplification of the immunological response initially triggered by statin therapy, aligns with the histological data reported in the literature5. The patient also mentioned rhabdomyolysis symptoms such as myoglobinuria, elevated CK values, and muscle discomfort, which are known to be serious side effects of statin therapy 11. Steroid use caused a drop in CPK levels from 23,506 U/L to 8,000 U/L; nevertheless, these CPK levels are still higher than the typical upper limit range, which is consistent with the literature's observation that high CPK levels persist even after statin treatment is stopped 4. Also, the literature presents that eliminating statin consumption does not reverse anti-HMGCR levels or myopathy symptoms and may cause an increment in LDL levels. It is important to discuss therapeutic options for detecting and treating statin-induced myopathies and preventing long-term impairment 7. Immunosuppressive therapy is recommended for patients with symptoms resembling those of muscular dystrophy; the greatest outcomes are achieved with glucocorticoids, intravenous immunoglobulins (IVIG), and immunosuppressive drugs such as azathioprine and methotrexate 11. IVIG functions as a monotherapy for patients who experience side effects after getting steroid treatment 7. Immunosuppressive therapies increase hip flexion and arm strength by lowering CK and Anti-HMGCR levels 14. Also, the use of statins to treat cardiovascular disorders including hyperlipidemia and coronary heart disease is increasing, which will result in an increased prevalence of myopathy and myalgia 9.

Conclusion

1. Elevated CK levels and anti-HMGCR autoantibodies are the hallmarks of statin-induced myopathy, which also displays signs of proximal weakness, fatigue, type I fiber necrosis in muscle biopsies, fiber regeneration, and a low level of i flammatory infiltration, often showing phenotypes of muscular dystrophy and inclusion body myositis.
2. Statins alter the HMGCR protein's structure, exposing new antigenic epitopes that anti-HMGCR antibodies respond to, breaking tolerance to HMGCR. It is significant to highlight that normal maintenance processes involve upregulating HMGCR expression in regenerating muscle fibers.
3. Statins are more often used to reduce the risk of cardiovascular disease, making it crucial to recognize and treat statin-induced myopathies. Some myopathies only respond to intensive immunosuppressive medication, such as intravenous immunoglobulins, steroids, and rituximab.

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