## One biopsy, two diagnoses: statin-induced autoimmune myopathy in combination with extranodal marginal zone lymphoma

Sirs,

A 64-year-old white male visited our department with chronic proximal muscle weakness. His medical history consisted of type 2 diabetes, hyperlipidaemia treated with atorvastatin and morbid obesity. Shoulder and pelvic girdle weakness appeared one year ago and persisted after atorvastatin discontinuation. Musculoskeletal examination showed weak neck flexors, deltoid and gluteus muscles, with preserved distal muscle strength. Several thoracic livid-red maculae were present. No lymphadenopathies were present.

Laboratory tests showed a normal white blood cell count, mild thrombocytopenia (127,000/µL, reference 150,000-450,000/µL) and an erythrocyte sedimentation rate of 6 mm/hour. C-reactive protein was normal (1.0 mg/L, reference <5.0 mg/L). Creatine kinase (CK) was 1256 U/L (reference <190 U/L) with slightly elevated transaminases. Antinuclear antibodies, assessed by indirect immune fluorescence were negative. Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies (anti-HMGCR-antibodies) were detected at high titer (132 SGU, reference <20 SGU). Electromyography of the left quadriceps muscle showed myogenic alterations (muscle membrane instability at rest and small short polyphasic action potentials at contraction). Pulmonary function tests were consistent with a restrictive pattern (TLC 58% of predicted; diffusion capacity TLco 76% of predicted). High resolution computed tomography of the thorax revealed limited reticulations in basal areas suspect for non-specific interstitial pneumonia. Pathological examination of the quadriceps muscle (Fig. 1A-E) showed an active necrotising myopathy with endomysial inflammatory infiltrates invading skeletal muscle fibres and active myophagia. Surprisingly, small cell lymphoid infiltrates were identified in both muscle and surrounding adipose tissue. Additional immunohistochemistry showed intense CD20 expression. Heavy and light chain rearrangement analysis confirmed the monoclonal nature of the B-cell population. A clonally related monoclonal B-cell population was identified in the skin biopsy specimen (Fig 1F-H). Further screening showed multiple bilateral cervical and peri-clavicular lymph nodes, with low to absent metabolic activity. Bone marrow aspirate and biopsy were normal.

The patient was diagnosed with both necrotising autoimmune myopathy (NAM) and an indolent B-cell non-Hodgkin's lymphoma, type extranodal marginal zone lymphoma. In this subtype, a watchful waiting approach is recommended in the asymptomatic patient. However, hypothesising this NAM as a lymphoma-related paraneoplastic phenomenon, we considered B-cell targeting therapies as preferential therapeutic approach. He was treated with rituximab 375 mg/m$^2$ for 4 consecutive weeks and a tapering scheme of 48 mg methylprednisolone. This resulted in a significant decrease in CK-levels (247 U/L) and recovery of muscle strength.

Statins can cause serious muscle damage with weakness and elevated CK levels, although this remains rare (approximately 1/10,000 treated persons per year). Most patients recover spontaneously after statin discontinuation. However, a small subgroup (2-3/100,000 treated persons) develops a statin-induced NAM with the presence of anti-HMGCR-antibodies which persists after statin cessation and must be controlled with immunosuppressive therapy (1, 2).

A subset of inflammatory myopathies is associated with malignancy. Cancer-associated dermatomyositis is associated with antibodies to NXP2 or TIF1γ (3). More recently, Chun *et al*. reported on 18 patients with anti-HMGCR-positive statin-induced NAM and identified two concurrent neoplasias (4). Allenbech *et al*. described a malignancy risk of 17.3 % in 52 anti-HMGCR-positive patients. Two-thirds of malignancies occurred within 3 years of or before the diagnosis of myositis (5). A broad range of cancers may be associated: gastrointestinal, lung, breast, ovarian and renal cancers (4, 5). We did not find any reports on HMGCR-positive NAM associated with lymphoma.

In this case, one sole biopsy revealed the presence of an anti-HMGCR-positive NAM and a coexistent extranodal marginal zone lymphoma. To the best of our knowledge, this is the first report on statin-induced NAM in the context of lymphoma. This triggers the question whether the abnormal B-cell population could drive anti-HMGCR-antibody production. Unfortunately, at present, this remains an intriguing but unproven hypothesis.

S. MICHIELS[1]
D. DIERICKX[2]
V. TAELMAN[1]
T. TOUSSEYN[3,4]
J. LENAERTS[1]
E. DE LANGHE[1,5]

*[1]Division of Rheumatology, [2]Laboratory for Experimental Haematology, Department of Oncology, and [3]Department of Pathology, University Hospitals Leuven, Belgium; [4]Imaging and Pathology, Translational Cell and Tissue Research, and [5]Laboratory of Tissue Homeostasis and Disease, Skeletal Biology and Engineering Research Center, Department Development and Regeneration, KU Leuven, Belgium.*

*Address correspondence to:*
*Dr Ellen De Langhe,*
*Division of Rheumatology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.*
*E-mail: ellen.delanghe@uzleuven.be*

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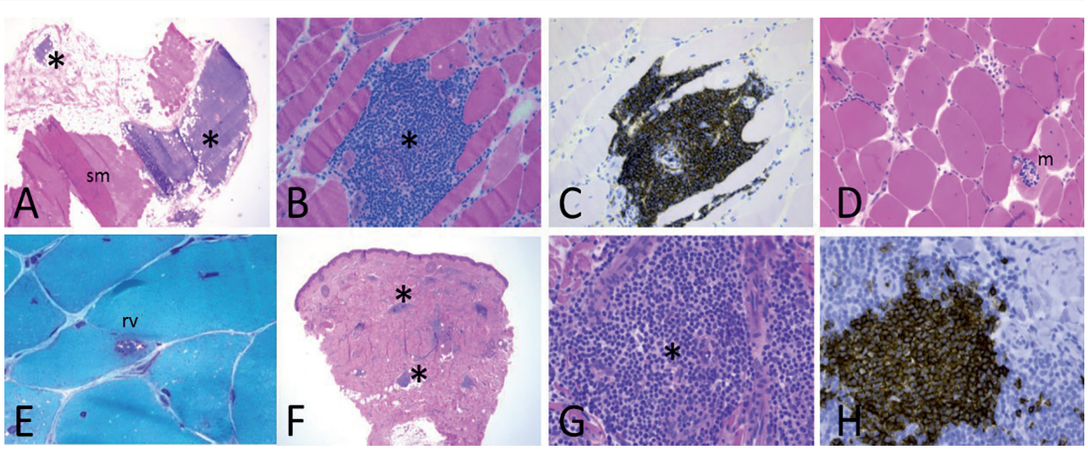


**Fig. 1. A-E**. Muscle biopsy.

**A**: Large sheets of monotonous lymphoid cells (*) in adipose tissue, surrounding the skeletal muscle (sm)**. B**: Endomysial lymphoid infiltrates; **C**: expressing CD20; **D**: with focal invasion of skeletal muscle fibres and accompanying active myophagia (m); **E**: Focal presence of a rimmed vacuole (rv) in the muscle fibre.
**F-H**. Punch biopsy of the skin. **F-G**. Presence of multiple interstitial dermal lymphoid infiltrates (*), consisting of monotonous (H) CD20-expressing lymphoid cells. (A, B, D, F, G: haematoxylin and eosin stains, at magnification 25x, 400x, 400x, 25x, 400x; **C**, **H**: immunohistochemical staining using anti-CD20 antibody at 400X; **E**: Gomori Trichrome staining at 400x; photographs are taken using a Leica DFC290HD camera).