Immune-mediated necrotizing myopathy (IMNM) and overlap syndrome

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Introduction: *The inflammatory myopathies (IMs)* are a rare and heterogeneous group of acquired autoimmune muscle disorders that *comprises: polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), immune-mediated necrotizing myopathy (IMNM), myositis associated with collagen vascular desease, myositis associated with malignancy.* Clinical assessment, muscle biopsy findings and serotype are factors to consider in stratification of the 'IIM spectrum'. *IMNM is associated with autoantibodies directed against signal recognition particle (SRP) and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) in the majority of patients. Statin use is strongly associated with anti-HMGCR-positive myopaty. IMNM generally present with the subacute onset of symmetric proximal muscle weakness, elevated muscle enzymes, myopathic findings on electromyography. Characteristic features on muscle biopsy are myofibers necrosis without prominent inflammation in IMNM.*

Case presentation: *We describe a woman of 77 years, who was suffering only from dyslipidemia (on statin therapy) and osteoporosis until 2 months before. She manifested gradually, within a year, progressive tingling in the fingers, acrocyanosis, fatigue, exertional dyspnea, dysphagia, dysphonia, nonproductive cough, proximal myalgia, lower limb and truncal weakness.*
Neurologic examination showed only mild proximal muscle weakness (S 4/5).
Laboratory testing: creatine kinase 578 U/l(<167), myoglobin 860 mcg/l (<82), troponin T HS 186 ng/l (14), CPK MB 47 micg/l (<5), LDH 730 U/l (240), mild polycythemia, inflammatory and tumor markers normal, ANA absent->1:320->1:640 (nucleolar pattern), anti-ENA, ANCA, anti-phospholipid negative. Anti Mi-2, Ku, PM-scl100-75, Jo1, SRP, PL-7-12, EJ, OJ, Ro-52 negative (met. Immunoblot).
Electromyogram (EMG) showed increased insertional activity, rare polyphasic MUP of low amplitude and short duration in proximal muscles. Capillaroscpy showed microangiophaty. Interstitial pneumonitis and aspiration pneumonia, nonischemic *cardiomyopathy until congestive hear failure emerged over 5 months*

METHOD: vastus lateralis FQ muscle biopsy was performed under local anesthesia.

OBJECTIVE: To elucidate a different pathogenesis of IMNM spectrum, associated with a distinct clinical phenotype. Severe limb muscle weakness, neck weakness, dysphagia, respiratory insufficiency and muscle atrophy were more frequently observed in patients with anti-SRP antibodies than in those with anti-HMGCR antibodies. Serum creatine kinase levels were markedly higher in the patients with autoantibodies than in those without. Histology was characterised by necrosis and regeneration of muscle fibres and was consistent in IMNM. The treatment is initially with corticosteroids and subsequently with immunosuppressive drugs, intravenous immunoglobulin. Rates of unsatisfactory neurological outcome were similar in the 2 autoantibody groups.

RESULTS: The muscle biopsy showed a necrotizing myopathy and modest neuropathic signs. It was performed histologic and histochemical examination. H&E, Gomori's trichrome: atrophic fibers polygonal and angled, isolated and in small groups; rare nuclear morulae; some fibers are necrosis, some with grainy cytoplasm; rare fibers atrophic basophilic; absent inflammatory infiltrates; endomysial connective normal.
ATP ase pH 4.3-4.6-10.3: normal differentiation of the types of fibers; and atrophic fibers are predominantly type 2B. NADH-TR,SDH: normal oxidative reactivity of muscle fibers and the small vessel wall. Cytochome oxidase: reactivity absent in a fiber. Sudan black: normal intracellular lipid content. PAS: no positive PAS material accumulation. Acid phosphatase: widespread activity in a few atrophic fibers. Serum creatine kinase levels were moderatly higher . Serum myositis-related antibodies were negative. She has partially responded to corticosteroids and intravenous immunoglobulin: improvement of dysphagia and fatigue

Discussion: **IMNM can present in a restricted form. Our case, presented with acrocyanosis, fatigue, dysphagia, dysphonia, proximal myalgia, lower limb and truncal weakness, exertional dyspnea and nonproductive cough in interstitial pneumonitis/aspiration pneumonia, nonischemic cardiomyopathy. This clinical phenotype, moderatly elevated muscle enzymes, inflammatory and tumor markers normal, ANA borderline, myositis specific ab negative, electromyography minimal abnormalities, picture of microangiophaty to capillaroscopy and histopathology of muscle biopsies appear suggestive of necrotizing myopathy in undifferentiated connective or future malignancy**

***Conclusions**: immune-mediated necrotizing myopathy (IMNM) associated with severe striatal and extrastriatal-muscular symptoms appears a distinct form, an overlap syndrome (OS), with normal inflammatory markers, common myositis-related-autoantibodies negative and resistance to conventional therapy*

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