

## Case 42

# Antibody-Mediated Muscle Disease?

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### History

A 23-year-old man presented with progressive proximal limb weakness. He used to train as a body builder and, over the previous year, he had noticed a rapid decline in muscle strength and bulk. He first noticed weakness of pectoral and periscapular muscles with winging of the scapulae. This was followed a few months later by proximal leg weakness. He also complained of mild dysphagia but reported no ptosis, diplopia or respiratory difficulty. The onset of symptoms was heralded by a non-pruritic rash on his trunk followed by a flu-like illness. He was not on any regular medication and there was no history of toxic exposure, although he had consumed anabolic steroids. His past medical and family history were otherwise unremarkable.

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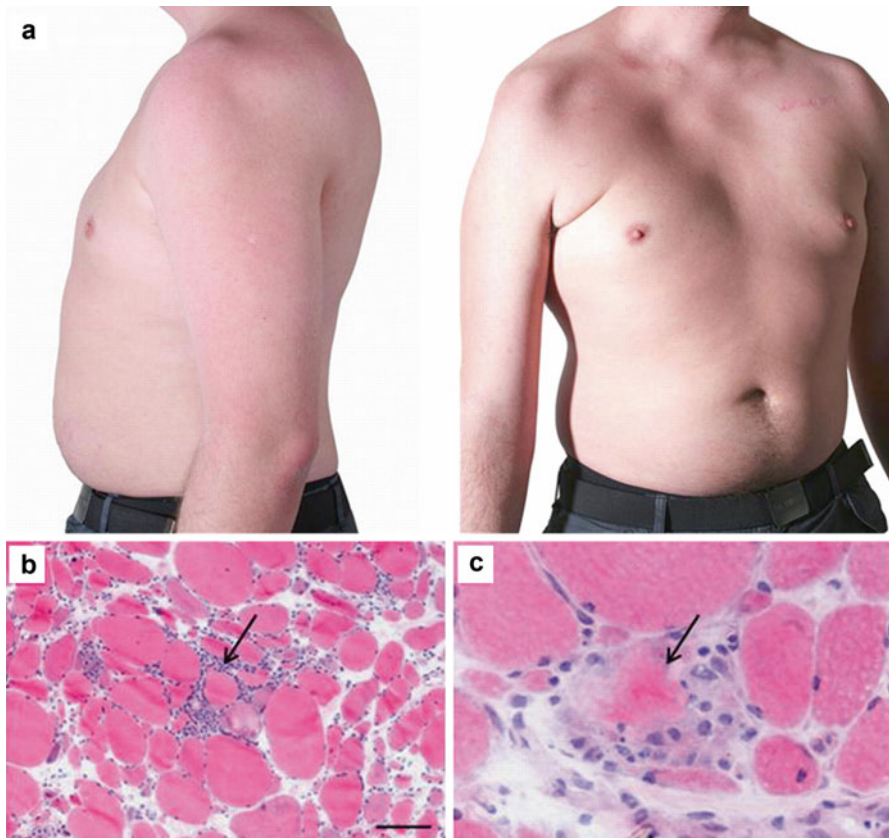
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## Examination

There was no ptosis, ophthalmoparesis or facial weakness. Bulbar function was normal. Neck flexion and extension were weak. Examination of the upper limbs showed bilateral scapular winging, wasting of shoulder-girdle muscles (Fig. 42.1a) with shoulder adduction and abduction weakness (MRC grade 4/5), and elbow flexion weakness (4/5). In the lower limbs, there was weakness of hip flexion (2/5) and knee flexion/extension (4/5). Deep tendon reflexes were preserved. Examination was otherwise normal.



**Fig. 42.1** (a) Wasting of shoulder girdle and infraclavicular muscles. (b, c) Muscle histology (H and E) demonstrating occasional endomysial inflammatory changes (*arrow in b*) and scattered necrotic fibres (*arrow in c*). Bar = 100 microns in (b) and 50 microns in (c) (Courtesy of Zane Jaunmuktane and Sebastian Brandner)

## Investigations

Serum CK and ALT levels were raised at 24,000 IU/L (<204 IU/L) and 212 IU/L (<160 IU/L), respectively. EMG showed a myopathic pattern with increased spontaneous activity. Respiratory function tests showed a mild decrease in the FVC to 71 % of predicted. Cardiac assessment revealed a dilated cardiomyopathy and runs of non-sustained ventricular tachycardia that required insertion of an implantable cardioverter defibrillator (ICD). Chest, abdomen and pelvic CT scans were normal.

### Muscle biopsy

There was increased variation in fibre size, atrophic and regenerating fibres and increased endomysial connective tissue. Small foci of endomysial inflammation and scattered necrotic fibres were present (Fig. 42.1b, c). Immunohistochemical stains revealed small numbers of CD8+ T-cells in the endomysium and CD68+ macrophages in necrotic fibres. Only very sparse CD4+ T-cells and no CD20+ B-cells were observed. There was no increase in the sarcolemmal expression of MHC-I antigen or deposition of complement attack complex in capillaries.

### Genetic testing

Genetic testing for *calpain-3*, *dysferlin*, *FKRP* and *lamin A/C* mutations and for facioscapulohumeral muscular dystrophy was negative.

### Serological tests

Screening for ANA, ANCA and rheumatoid factor was negative. Anti-signal recognition particle (SRP) antibodies were present at high titres.

## Diagnosis

Necrotizing myopathy associated with anti-SRP antibodies.

## Discussion

Four major forms of idiopathic inflammatory myopathy are described: dermatomyositis, polymyositis, immune-mediated necrotizing myopathy (IMNM) and inclusion body myositis. These disorders present with progressive weakness of shoulder and hip girdle muscles except for inclusion body myositis, in which forearm flexor muscles are affected early. A clinically suspected diagnosis is supported by increased levels of CK and myopathic changes on EMG, and confirmed by muscle biopsy. Inflammation is the histologic hallmark, with additional features being specific for each subtype. The differential diagnosis is wide and includes inherited myopathies such as facioscapulohumeral dystrophy and the dysferlinopathies, which may exhibit inflammatory infiltrates on muscle biopsy.

Necrotizing myopathy associated with anti-SRP antibodies is a rare but increasingly recognised form of IMNM with distinctive clinical and pathological features. It typically presents subacutely, although chronic forms are described. Muscle weakness is often severe, symmetrical and predominantly proximal, involving both the upper and lower limbs. Muscle atrophy and dysphagia are common features. Marked elevation of serum CK (3000–25,000 IU/L) is the rule. EMG demonstrates myopathic units, early recruitment and increased spontaneous activity. Muscle biopsy shows scattered necrotic fibres, with or without myophagia, but only rare or absent mononuclear inflammatory cells. Upregulation of sarcolemmal MHC-I expression is absent or weak and focal. Endomysial connective tissue may be increased and capillary density reduced. The capillaries may show increased diameter or deposition of C5b-9 complement. The pathological significance of the autoantibodies against SRP, a cytosolic ribonucleoprotein complex that targets nascent polypeptides into the endoplasmic reticulum, remains to be determined.

The differential diagnosis includes other forms of IMNM such as those associated with neoplasms or with statin use and autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Patients may respond to immunotherapy. However, relapses are common during steroid tapering and most patients require long-term maintenance treatment. Residual muscle weakness is frequent.

In the present case, treatment with intravenous methylprednisolone followed by oral prednisolone and methotrexate was initiated. Muscle strength stabilised and CK levels remained between 2000 and 3000 IU/L. However, no clinical improvement was observed and gradual withdrawal of steroids resulted in worsening symptoms. Five years after the disease onset, treatment with a single dose of intravenous cyclophosphamide and two infusions of rituximab led to clinical improvement and slight reduction in CK levels. This allowed the withdrawal of methotrexate and the reduction in prednisolone dosing. Repeat rituximab treatment was given without further improvement but the patient is clinically stable on a low dose of prednisolone as his only immunomodulatory medication. He also takes low dose ACE inhibitor and bisoprolol. The ICD has sensed very brief runs of ventricular tachycardia that have all self-terminated.

## Reference

- Matthews E, Plotz PH, Portaro S, Parton M, Elliot P, Humbel RL, Holton JL, Keegan BM, Hanna MG. A case of necrotizing myopathy with proximal weakness and cardiomyopathy. *Neurology*. 2012;78:1527–32.