A case of amyloid myopathy in a patient with familial Mediterranean fever

Sirs,

Amyloid myopathy (AM), an increasingly recognized muscle disorder (1, 2) is reported in familial and AL-amyloidoses, associated with lymphoproliferative disorders (1-3). To our knowledge, AM has not been previously described in familial Mediterranean fever (FMF), though amyloidosis represents its most severe complication, or in other AA-amyloidoses.

We report the case of a 28-year-old Italian male patient with AM in FMF. He complained of previously undiagnosed recurrent episodes of fever, lymphadenopathy, monoarthritis, thoracical/abdominal pain over the past twenty years, and presented with persistent myalgia, fatigability and creatine kinase (CK) increase.

The duration of attacks (about 20/year) was 1-2 days; symptom-free intervals lasted up to 3 months.

In his medical history there was no consanguinity, nor autoinflammatory or neuromuscular disorders.

Neurological examination detected mild weakness of the leg muscles. Electrodiagnostic studies showed normal nerve responses and myopathic changes bilaterally on anterior tibialis muscles.

Laboratory investigations showed, during attacks, leukocytosis (15.65 x 10^3/mm^3), ESR 120 mm/hour (v.n< 25), CRP 4.13 mg/dl (v.n<0.5), CK 1465 U/l (v.n<170). Acute phase serum amyloid A (SAA) was 141 mg/L (v.n<10). CK decreased to 250 U/l between fever episodes. Kidney function and urinalysis were normal. Antinuclear and antineutrophilic cytoplasmic antibodies were absent. No cardiac abnormalities nor organomegaly were present.

PCR analysis for mutations in *MEFV* and *TNFRSF1A* genes identified a heterozygous K695R *MEFV* mutation.

Fulfilling the Tel-Hashomer criteria, the patient was diagnosed with FMF (4).

Tibialis anterior muscle biopsy showed myopathic changes, sarcolemmal deposits of the terminal complex of complement and amyloid deposition on endomysium and around vessels, confirmed by transmission electron microscopy (Fig. 1).

Colchicine treatment (1 mg/daily) was started and led to a complete resolution of fever attacks, thus confirming the clinical diagnosis of FMF, SAA decrease to normal values after 2 months and CK decrease to 250 U/L.

Skeletal muscle involvement in FMF is rarely reported as protracted febrile myalgia syndrome, i.e. prolonged severe disabling myalgia with fever, elevation of inflammatory markers and frequent association with M694V mutation, typically with normal CK (5). Clinical myopathy may occur as a toxic side effect of colchicine treatment (6).

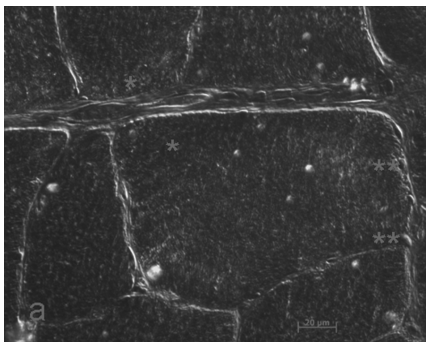


Fig. 1A. Amyloid deposits (*) surrounding vessels and at the periphery of muscle fibres, with tracts of typical apple green birefringence (Congo-Red, polarized light). Connective tissue aspecific birefringence is white (**).

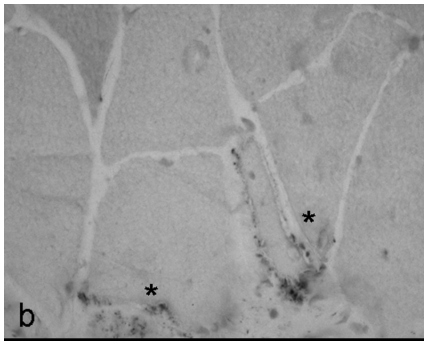
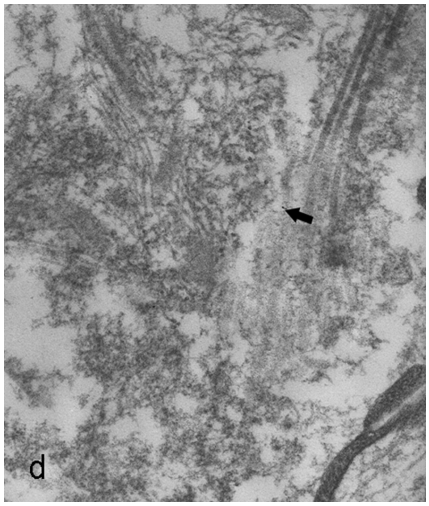


Fig. 1B. Deposition of the terminal complex of complement (C5-b9) on sarcolemma (*). (Immunoperoxidase for C5-b9, diaminobenzidine stain, haematoxylin counterstain, o.m x400).

Proximal weakness is the most common clinical presentation of AM (2, 7), though distal weakness, as in our patient, and nodules within muscle are also recognized (2). Respiratory muscles involvement is sporadic; macroglossia and muscle pseudohypertrophy are characteristic but inconstant features (2, 7). Unusual phenotypes, with a slow evolution over decades, are described in juvenile cases (2). A significant CK increase, as in our report, occurs in 30% of cases and rhabdomyolysis is described (2, 3). Histopathology shows amyloid deposits in perimysium/endomysium, as well as surrounding vessels and myopathic changes of variable severity with possible neurogenic changes and inflammation (1, 2, 7). The mechanisms of myofiber damage are not fully elucidated; they may involve ischaemia, impaired diffusion of nutrients, sarcolemma dysfunction or disruption (8). Cytotoxicity of the complement cascade is also suggested by sarcolemmal localisation of the terminal complex on non-necrotic fibres (3). AM can be the first or rarely the only organ manifestation of genetic transthyretin (7) or gelsolin (1) amyloidosis and AL systemic amyloidosis (2, 7). Speculating why AM occurred in our patient, the prolonged diagnosis delay (20 years) and the subsequent lack of treatment may have been determinant. Country of origin,



Figs. 1C-D. Transmission electron microscopy. Endomysial deposits of amyloid fibrils (arrow) adjacent to collagen fibres (original magnification x39000). The rectangle in Fig. 1C highlights the field of Fig. 1B (o.m. x11500).

M694V homozygous mutation, disease duration, and consanguinity are risk factors for development of renal amyloidosis in FMF (9, 10). It is yet to be determined if these factors, or different *MEFV* mutations, may also be relevant to other organ localisations, such as AM. However, it has been proposed that selective tissue deposition of amyloid may depend on the types or folding of amyloid proteins and AA type might have a low affinity to skeletal muscle (11). Our case suggests that AM may occur as a presenting manifestation of amyloidosis in FMF, therefore we propose that clinical involvement of skeletal muscle, with CK elevation, is to be investigated in FMF, for a possible AM.

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