Complement-Mediated Muscle Involvement in Juvenile Ankylosing Spondylitis

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Abstract
An 18-year-old Brazilian man had developed ankylosing spondylitis with positive HLAB27 at 13. He had spine and sacro-iliac joint involvement and aortitis with valve regurgitation. He was referred for myalgia and marked increased creatine kinase. Neurological examination did not disclose muscle wasting or weakness. Muscle biopsy demonstrated slight fibre size variability and normal membrane proteins. Immunohistochemical markers of inflammation showed deposition of the membrane attack complex of complement on the walls of some intramuscular blood vessels. This could be of importance for the understanding of the pathogenesis of muscle involvement and possibly for some other clinical manifestations of ankylosing spondylitis.
Key words: ankylosing spondylitis, muscle biopsy, immunohistochemical markers.

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Ankylosing spondylitis is a systemic rheumatic disorder of unknown etiology, characterized by prevalent involvement of the axial skeleton, associated with a number of systemic manifestations, such as uveitis, cardiopathy, lung fibrosis, renal insufficiency [4]. Neurological signs are usually secondary to compression of the spinal chord. Neuromuscular involvement has never been convincingly demonstrated. Neurogenic atrophy of paraspinal muscles was attributed to spinal ankylosis [2, 8]. Studies of serum creatine kinase (CK) are contradictory [6], but only few refer moderate increase [1, 7]. Muscle biopsies performed in some cases demonstrated non-specific alterations, mainly represented by fibre size variability and central nuclei [7, 8]. Only occasional cases showed frank inflammatory changes [9, 10], suggesting a myositic process.

We present the case of an 18-year-old man with ankylosing spondylitis, aortic insufficiency and muscle pain with hyperCKemia.

Case report

An 18-year-old Brazilian patient was referred because of muscle pain and persistent increase of serum CK. Family history was unknown, as he had been adopted at 12 months. At that time he suffered of severe malnutrition; psychomotor milestones were delayed and deambulation began at 20 months. At age 13 he began to present arthritis of the peripheral joints. HLAB27 was positive and a diagnosis of juvenile oligoathritis was made. He was placed on non-steroid antiinflammatory drugs and then on steroids at low dosage (prednisone 5 mg daily) and sulphasalazine. At 16 years of age the spine involvement was typical and both computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated bilateral sacroiliac joint inflammation. There was also calcaneal enthesitis. Bone Tc^{99} scintigraphy showed hyperfixation of the isotope on multiple joints. Puncture of the right knee joint showed marked inflammation; the synovial fluid contained 4100 cells/mm^3 with 72% polymorphonuclear. There was neither ocular nor skin involvement, but the clinical examination disclosed systolic and diastolic murmurs on the base of the heart and on the aortic area; ECG demonstrated first degree atrioventricular block, ecocardiography and MRI showed aortitis with valve regurgitation. Laboratory examinations disclosed increased ESR (80 mm/h) and polyclonal increase of gamma globulins. Immunological tests, thyroid hormones, electrolytes were normal. Infectious and parasytic diseases were excluded by serum tests. Increase of serum CK up to 2000 U/l (normal up to 190) was noted several times, independently of muscle exercise. The patient complained of

occasional myalgias in the legs. Steroid treatment did not modify serum CK. Electromyography (EMG) was unremarkable.

The patient was referred to us when 18, because of persistence of hyperCKemia. Neurological examination showed normal muscle strength without atrophy. Lactic acidemia was normal. EMG was again normal. Quadriceps muscle biopsy was performed and processed with routine histological and histochemical methods on cryostat sections. There was slight muscle fibre size variability, with several atrophic fibres and increase of internal nuclei (Fig 1a). Staining for myofibrillar ATPase showed predominance of type II muscle fibres. Oxidative enzymes (NADH-diaphorase, lactate–dehydrogenase, succinate dehydrogenase, cytochrome c oxidase) were normal. Glycogen and lipid contents were normal. Muscle phosporylase and myoadenylate deaminase were present. Immunohistochemical study of the sarcolemmal membrane did not show alterations of dystrophin, sarcoglycans, merosin, caveolin. Emerin was demonstrated in muscle nuclei. Immunohistochemical markers did not detect macrophages and CD8 lymphocytes. On the contrary the immunohistochemical stain for the membrane attack complex of complement (MAC) demonstrated positive walls in muscle small blood vessels and capillaries (Fig 1b).

Discussion

The interest of this case lies in the muscle involvement with marked increase of serum CK associated with ankylosing spondylitis. CK is usually normal in ankylosing spondylitis [6], even in the few patients with overt inflammatory changes in muscle biopsy [10]. Only Calin et al [1] reported increased CK in several patients, but the elevation was very modest. No histopathological study was performed. In our case serum CK was markedly and repeatedly increased in spite of normal muscle strength; muscle biopsy excluded genetical diseases with minimal clinical expression, which could coexist with the rheumatic disorder: all the proteins of the muscle membrane were normally distributed and emerin was present. Metabolic alterations were ruled out by normal glycogen and lipid contents and by normal activities of muscle enzymes tested by histochemistry.

Muscle alterations described in ankylosing spondylitis are not specific and therefore not supporting an inflammatory involvement of muscle by the rheumatic disease. Contrariwise muscle abnormalities have been considered secondary to the spinal pathology and to its impingement on nerve roots and peripheral nerves. Inflammatory changes consistent with myositis are exceptional [10] and must have been quite focal to explain normal CK. Actually the possibility of focal abnormalities is typical of myositides and therefore a normal muscle biopsy or a biopsy with not specific changes does not exclude inflammatory involvement. The use of specific markers of inflammation has improved the sensitivity of muscle biopsy in inflammatory muscle diseases. Many different markers are utilized to determine the type of immune response [5]: as a general rule in polymyositis the effector response is mediated by T-cell cytotoxicity against muscle fibres, whereas in dermatomyositis it is predominantly mediated by humoral factors. In dermatomyositis the immunolocalization of the membrane attack complex of the complement (MAC) to the walls of intramuscular arterioles and capillaries suggests that the microvascular injury is mediated by complement and that the lytic complement pathway is triggered by an antibody binding to the blood vessels or by the deposition of immune complexes on the vessel walls [5]. Muscle fibres can then suffer because of ischemia or be also directly attacked by the immune complexes. Nothing definite is known about myopathies associated with rheumatic diseases [5], but similar cellular or humoral factors might play a role in the pathogenesis of muscle damage. Even less is known about ankylosing spondylitis and the relative importance of cellular and humoral factors in the physiopathology

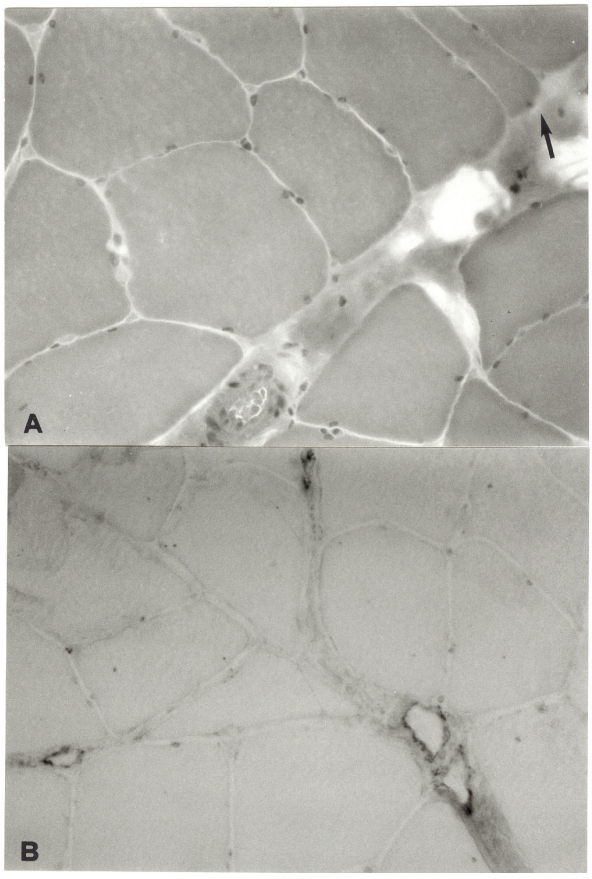

Figure 1. Muscle biopsy.
A. Slight fibre size variability with an atrophic fibre (arrow). HE 265x.
B. Some small intramuscular vessel walls are positive with anti-MAC antibody demonstrated by PAP reaction. 108x.

of the clinical manifestations [4]. In our case the presence of MAC-positive intramuscular blood vessel walls seems to indicate a role of the complement in the pathogenesis of muscle involvement. This could lead to a minimal damage of muscle fibres with subsequent leaking of CK into the blood and increase of serum levels. Inflammatory markers have never been studied in muscle tissue from patients with ankylosing spondylitis; this case could therefore give information about the possible pathogenesis of muscle involvement in this condition. It could even be possible that a same mechanism underlies the involvement of small muscle vessels and other vessels in the body; in our patient the aortic attainment, rare in adults [4] and exceptional in children [3], could be due to a similar immune process.

In conclusion, this patient has some unique characters, namely aortitis and a subclinical myopathy, that can be helpful for a better understanding of ankylosing spondylitis; the demonstration of MAC on intramuscular vessel walls can shed some light on the pathogenesis of some clinical manifestations.

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