Case report

Severe myalgia in familial Mediterranean fever: clinical and ultrastructural aspects

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SUMMARY Severe myalgia is an uncommon feature of familial Mediterranean fever (FMF). A patient is presented in whom acute myalgia and high fever were the sole clinical findings during an FMF attack. The ultrastructural picture of the muscle tissue during the acute stage was characterised by a large deposition of collagen fibrils. The myalgia subsided during colchicine treatment. The clinical and ultrastructural features of myalgia in FMF are discussed in the light of the relevant literature.

Key words: periodic fever, muscle pain, collagen fibrils.

Familial Mediterranean fever is a disease characterised by paroxysmal and self limiting attacks of fever, peritonitis, synovitis, and pleuritis. Sephardic Jews, Armenians, Turks, and Arabs are predominantly affected through a recessive autosomal mode of transmission. In most patients the symptoms start before the age of 20 years.¹ Colchicine has been accepted as an effective therapeutic agent in the treatment of FMF² and in the prevention of its ominous prognostic feature, amyloidosis.³

We present a patient in whom severe myalgia and fever were the sole clinical findings during an FMF attack.

Case report

A 22 year old woman of Iraqi descent was admitted because of severe calf pains. From the age of 6 years multiple episodes of self limiting arthritis of the ankle and knee joints had been recorded. She had not been investigated previously. Five days before admission excruciating pain of both calves and high fever appeared. The pain was so severe that

standing or walking were impossible and a wheelchair was used. On examination the patient was febrile (39°C). Both calves were slightly swollen, warm, and very sensitive; the slightest touch elicited severe pain. The rest of the physical examination and the joint examination were not contributory. The Westergren erythrocyte sedimentation rate was 80 mm/1st h, the C reactive protein + + +, the white blood cell count $12.8 \times 10^9/l$ with normal differential. Blood urea nitrogen, glucose, creatinine, bilirubin, alkaline phosphate, transaminase, calcium, phosphorus, uric acid, total protein and albumin, serum complement, protein electrophoresis, and immunoelectrophoresis were normal. Serum lactic dehydrogenase, creatinine, phosphokinase, and aldolase were normal, and no myoglobin was found in the urine. Serological tests for various infectious diseases, rheumatoid and antinuclear factors, anti-smooth muscle, antimitochondrial and antiparietal cell antibodies were negative. Blood and urinary cultures were sterile. Serum fibrinogen was 6.2 g (normal 2.0-4.0). Roentgenograms of the chest, the lower extremity joints, and the tibial shafts were normal, as was an electromyographic study of the affected areas. A skin and muscle biopsy of the right calf was performed.

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Materials and methods

The tissues for histology were fixed in formalin, embedded in paraffin, and stained with haematoxylin-eosin; phosphotungstic acid-haematoxylin; Congo red. For electron microscopy small pieces of muscle were immediately fixed with ice cold 3% glutaraldehyde in cacodylate buffer, pH 7.3, for one hour, postfixed with 2% osmium tetroxide, dehydrated in alcohol, and embedded in Epon. Sections 1 µm thick were stained with toluidine blue and examined under a light microscope for orientation of muscle fibres. Thin sections were stained with uranyl acetate and lead citrate and examined under a Zeiss 9S electron microscope.

Results

A histological examination of the striated muscle and of the skin did not show signs of vasculitis. There was an increase of the collagen tissue in the interstitium of the muscle and also a few inflammatory cells.

The electron microscopic examination showed that most muscle fibres were of normal size, but atrophic muscle cells with a diameter of 17–20 µm were dispersed among the regular sized cells. The sarcomere pattern was well preserved. Irregularities of the Z band were frequently seen in atrophic and

normal sized muscle cells. The sarcolemma was moderately widened.

The most striking changes occurred in the endomysial and perimysial spaces between muscle fibres. These spaces were occupied by increased amounts of collagen fibrils which often closely applied upon the sarcolemma (Fig. 1). Masses of collagen fibrils occurred also around the wall of the small venules and sometimes appeared between the endothelial layer and the smooth muscle layer of the venular wall (Fig. 2). The perivascular basement membrane of capillaries and of small venules was uniformly and moderately widened (Fig. 2). Small infiltrates composed of fibroblasts, macrophages, and a few mast cells were seen in the interstitial space.

Rectal biopsy was denied by the patient. Treatment with diclofenac sodium 150 mg/day and later with corticosteroids (prednisone 30 mg/day) failed to bring about any improvement. The severe myalgia and the functional disability continued. On the fifth day of hospitalisation arthritis of the right knee appeared. The joint was aspirated and 70 ml of a cell rich fluid (80 000 cells/ml) was evacuated. The fluid was sterile and no crystals were found. The diagnosis of FMF presenting at this stage as severe myalgia was supported by the past history of periodic and self limiting arthritis, by the patient's ethnic origin (non-Ashkenazi Jew), and by an

Fig 1 The electron micrograph shows a large amount of longitudinally sectioned collagen fibrils (O) which occupy the endomysial space. Portions of the striated muscle fibres appear at both sides of the endomysial space. In some areas the collagen fibrils apply upon the sarcolemma (arrow).

Fig. 2 Part of the wall of the venule and the lumen is seen in the upper part of the figure. A concentration of dark collagen fibrils appears between the endothelial layer and the smooth muscle layer of the venule (O). Cross sectioned collagen fibrils are seen in the perivascular space (C) and in close proximity to the widened vascular basement membrane (central arrow) and to the muscle sarcolemma (curved arrow).

appropriate family history (a younger sister suffering from recurrent peritonitis and arthritis). Treatment with colchicine 1.5 mg/day was instituted. Three weeks after the beginning of the attack the myalgia subsided. During the follow up no further episodes of arthritis or muscle pain occurred.

Discussion

The classical clinical manifestations of FMF are well known and have been described in large series of patients.^{4 5} The less common erysipelas-like skin eruptions and non-specific symptoms such as prolonged lymphadenopathy, periodic meningitis, jaundice, cutaneous vasculitis, recurrent pericarditis, severe ovarian and testicular pain and tenderness, pancreatitis, and periodic parotid swelling have also been reported to be associated with the febrile paroxysms.¹

Muscle pain may accompany the other clinical features of FMF. Its presence is usually shadowed by the other impressive manifestations of the disease. Nevertheless, using directed questions it has been detected in up to 20% of the patients.⁶ As in some cases of FMF arthritis, the muscle pain seems to be potentiated by effort and appears usually in the evenings after prolonged standing and walking. The pain subsides in a few hours but sometimes it lasts for a few days. Pain, tenderness, and spasticity have been described in the muscle

area close to the inflamed joints.⁷ The histological picture is that of increased vascularity, atrophy, and fibrosis.⁸

Severe myalgia as the sole feature of the disease or as one of its main clinical manifestations is rare. It has been described in a few studies.^{5 7 9-15} In one patient periodic fever and myalgia were the sole manifestations of the disease.¹⁵ As in our case the diagnosis was supported by the ethnic origin of the patient, by the family history, by the wellbeing between the attacks, and by the excellent response to colchicine therapy. Other authors describe the spectacular response of severe periodic shoulder and hip girdle myalgia to intravenously administered colchicine.¹³ All the authors emphasise the intensity of the attacks, which last two to three weeks. In some patients muscle atrophy was observed after protracted attacks.⁷

Severe myalgia without arthritis is relatively rare in FMF, occurring in two to four of 100 patients.¹⁶ Therefore it is understandable that most histological and ultrastructural studies have been done on the synovia and its related tissues, whereas the changes of the skeletal muscle have been very little investigated.

Biochemical and ultrastructural changes are known to occur in the interstitial tissue matrix in FMF, classically described under the form of amyloid AA deposits. The present case is interesting owing to the fact that no amyloid fibrils could be

detected in our material; deposition of collagen fibrils, however, appeared in increased amounts in the perivascular spaces and in the endomysial and perimysial spaces of the striated muscle. To our knowledge these alterations have not been previously recorded at the ultrastructural level.

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