

## Extensive inflammatory reaction in facioscapulohumeral muscular dystrophy

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In facioscapulohumeral muscular dystrophy (FSHD), prominent inflammatory cellular infiltrates mimicking inflammatory myopathies are often observed in muscle biopsies. We report extensive inflammatory changes in a 16-year-old girl who was genetically confirmed as to have FSHD. Immunohistochemical staining revealed that this could be clearly distinguished from inflammatory myopathies, both in terms of cell subsets and the expression of antigenic targets. Our observations strongly suggest that the inflammatory cellular infiltrates in FSHD differ from those observed in inflammatory myopathies.

**Key words:** Facioscapulohumeral muscular dystrophy; Inflammation; Immunohistochemistry

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Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal-dominant disorder that predominantly affects the facial and scapular stabilizer muscles. It is considered a relatively benign disease, but its clinical spectrum is highly variable.<sup>1</sup>

In muscle histopathology, most FSHD patients show nonspecific dystrophic features, but some patients may show prominent inflammatory changes that can lead to a misdiagnosis of polymyositis.<sup>2</sup> Although some studies have analyzed inflammatory cellular subsets in FSHD with inflammation,<sup>2-5</sup> the role and significance of these cellular infiltrates in FSHD remain unclear.

Here we describe the clinical, pathologic, and molecular genetic findings for a patient with FSHD in whom a muscle biopsy revealed unusually extensive inflammatory reactions.

## CASE

A 16-year-old girl visited us with generalized muscle weakness. Her weakness started at 11 years of age when she began to experience difficulties running and raising her arms. She denied any preceding febrile illness or trauma at that time. Her weakness slowly worsened,

and she had difficulty climbing upstairs when she presented. Her parents and younger brother did not have any muscle weakness, and her parents denied any familial members with muscle weakness.

An examination revealed bilateral winged scapulae, kyphosis, and facial muscle weakness. Limb weakness was predominant in elbow extension, ankle dorsiflexion, and trunk flexion (Medical Research Council [MRC] grade 2), and in arm abduction, elbow flexion, and leg adduction (MRC grade 3). The power in other muscle groups was MRC grade 4 to 5. Muscle atrophy was observed in bilateral shoulder and upper arm muscles.

Laboratory tests indicated that her serum creatine kinase level was slightly elevated (410 U/L, normal: 5–217 U/L). The results of other tests including chest roentgenography, electrocardiography, and blood tests were normal. Electromyography showed many small polyphasic motor unit potentials with abnormal spontaneous activity in the limb muscles tested, and was compatible with active myopathy.

Despite her typical clinical features suggesting FSHD, a negative familial history prompted us to carry out a muscle biopsy on her left biceps muscle. This revealed extensive inflammatory cellular infiltration in the endomysial and perivascular space, suggesting inflammatory myopathy. In addition, marked variation in fiber diameters, many fibers undergoing necrosis and regeneration, and markedly increased connective tissue were also observed. No perifascicular atrophy was observed (Fig. 1).

Immunohistochemical staining was subsequently performed to identify the phenotypes of the infiltrates and the expression patterns of major histocompatibility complex (MHC) class I and C5b-9 membrane attack complex (MAC). Most of the cellular infiltrates consisted of CD4<sup>+</sup> T cells and

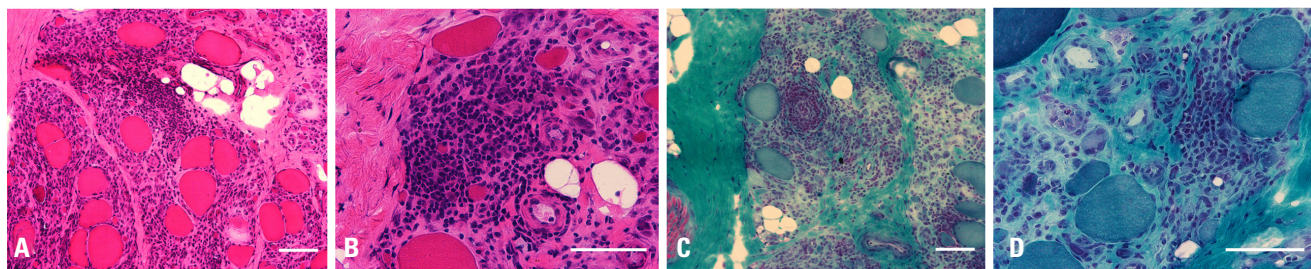
macrophages. A few CD8<sup>+</sup> T cells were also scattered in the endomysial spaces, but they did not surround or invade normal-appearing muscle fibers. MHC class I was expressed on the sarcolemma as well as in the extracellular matrix and vascular endothelium, and MAC deposits were observed in necrotic fibers but not in vessel walls (Fig. 2).

Southern blot analysis using the *EcoRI/BlnI* double digestion method was performed as described previously.<sup>6</sup> The smallest DNA fragment digested by *EcoRI*, which had been 14 kb in size, was reduced to 10 kb after subsequent digestion by *BlnI*, which confirmed the diagnosis of FSHD.

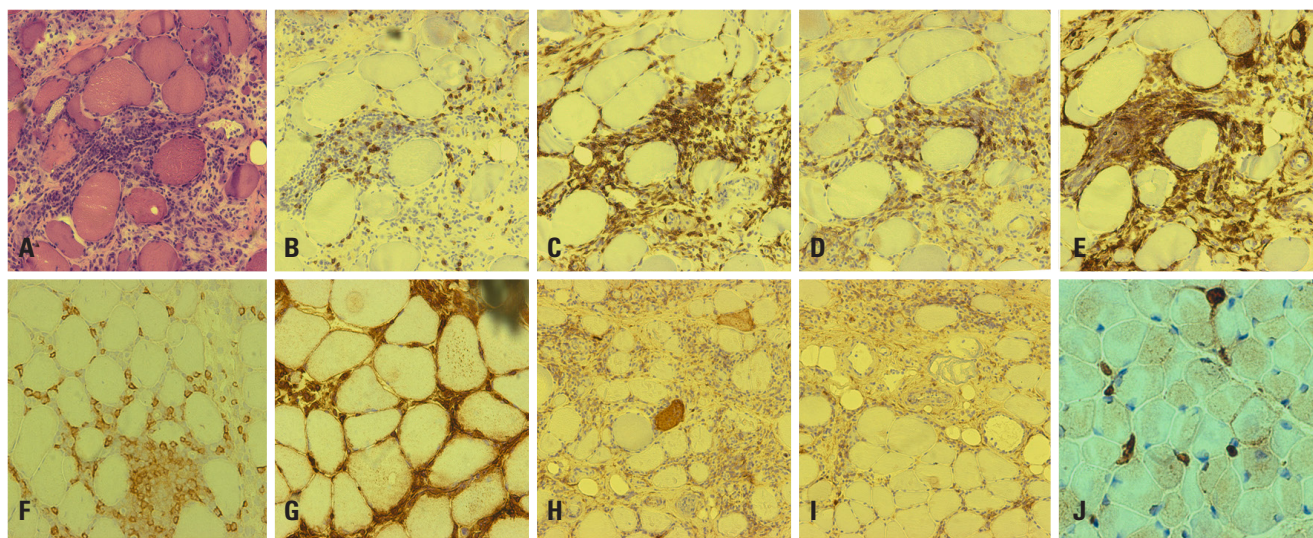
We started prednisolone at an initial dose of 1 mg/kg/day, and then slowly reduced the dose every 3–4 weeks. After 2 years of therapy she had been taking 5 mg of prednisolone every other day. During the follow-up period of longer than 3 years, neither her objective muscle power nor serum creatine kinase level changed from the baseline. The prednisolone was finally discontinued because we concluded that there was no overall beneficial effect.

## DISCUSSION

Inflammatory cellular infiltrates are not uncommon in the muscles of patients with various types of muscular dystrophies, including dystrophinopathy, dysferlinopathy, and FSHD. Although our patient showed typical clinical features of FSHD such as facial weakness and predominant shoulder girdle weakness, a muscle biopsy revealed inflammatory changes that were among the most extensive ever reported, and this could not be distinguished from inflammatory myopathies in routine histopathology. However, an immunohistochemical study revealed some significant differences from inflammato-



**Fig. 1.** Muscle biopsy with routine histochemistry. Muscle biopsy specimen stained with hematoxylin-eosin (A, B) and Gomori trichrome (C, D). Extensive inflammatory cellular infiltrations are evident in the endomysial and perivascular space. There are also marked variations in fiber size and the proliferation of connective tissue. White bars indicate 100  $\mu$ m.



**Fig. 2.** Muscle biopsy with immunohistochemistry. Cellular composition of inflammatory infiltrates in the patient's biceps muscle (A–E). Staining with hematoxylin-eosin (A) and immunostaining for CD8<sup>+</sup> T cells (B), CD4<sup>+</sup> T cells (C), B (CD20) cells (D), and macrophages (CD68) (E). CD4<sup>+</sup> T cells and macrophages are mainly evident. A few CD8<sup>+</sup> T cells are also scattered in the endomysial spaces, but they do not surround or invade any normal-appearing muscle fibers, while normal-looking muscle fibers are focally surrounded and invaded by CD8<sup>+</sup> T cells in polymyositis (F). Immunohistochemical localization of MHC class I (G). MHC class I reactivity is evident on the sarcolemma of muscle fibers as well as in the extracellular matrix and endothelium. Immunohistochemical localization of MAC deposits (H–J). MAC deposits are evident within necrotic fibers (H) but not on vessel walls (I). However, in dermatomyositis (J), the vessels including endomysial capillaries are strongly stained with MAC. The black bar indicates 100  $\mu$ m. MHC, major histocompatibility complex; MAC, membrane attack complex.

ry myopathies.

The inflammatory reaction in polymyositis is characterized by a cytotoxic T-cell-mediated immune response against the muscle fibers expressing MHC class I antigen, and thus CD8<sup>+</sup> T cells predominate.<sup>7</sup> However, such findings were not observed in the present patient. Although MHC class I antigen was expressed on the sarcolemma of nonnecrotic muscle fibers, they were neither surrounded nor invaded by CD8<sup>+</sup> T cells, suggesting that no cytotoxic T-cell-mediated immune response occurred in the patient. Considering that most inflammatory infiltrates are CD4<sup>+</sup> T cells and macrophages, a cell-mediated immune response with activation of helper T cells was present in this patient. Moreover, the expression of MHC class I antigen might have resulted from a nonspecific response to muscle degeneration or regeneration, and could have been induced by proinflammatory cytokines such as IFN- $\gamma$  and TNF- $\alpha$ .<sup>8,9</sup>

On the other hand, our case shared several features with dermatomyositis due to the presence of perivascular inflammation and the high proportion of CD4<sup>+</sup> T cells, macrophages, and B cells among the inflammatory cellular

infiltrates. However, unlike dermatomyositis, no C5b-9 MAC deposition on the capillary endothelium was observed in the patient.<sup>7</sup>

While an inflammatory response is one of the specific features of FSHD, its roles and significance remain unclear. It was postulated that inflammatory reactions may develop during the initial subacute phase of FSHD, followed by a chronic dystrophic phase.<sup>3,4</sup> However, this hypothesis is questionable for the following reasons. Firstly, this type of pathologic evolution is also observed in chronic polymyositis, and no significant correlation is observed between age, duration of symptoms, and the presence of mononuclear inflammatory infiltrations in patients with FSHD. Secondly, the absence or presence of inflammatory changes was consistent in the affected members belonging to the same families, which strongly suggests that it is genetically determined.<sup>10</sup>

In conclusion, the present case report demonstrates that some patients with FSHD can show prominent inflammatory changes in muscle biopsies. However, a detailed immunohistochemical analysis also suggested that its nature differs from those observed in inflammatory myopathies.

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