

## Myofibrillar Myopathy – A Case Report –

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Myofibrillar myopathies (MFMs) are a genetically or clinically heterogeneous group of diseases that are characterized by focal myofibrillar dissolution associated with accumulation of myofibrillar degradation products and ectopic expression of multiple proteins. Since MFMs show morphologically distinct features but consist of genetically and clinically heterogeneous diseases, muscle biopsy is important for the diagnosis. A 20-year-old man complained of progressive weakness and atrophy of both legs for two years. He had a dysmorphic face and short stature. The light microscopic examination of his muscle biopsy showed mixed myopathic and neurogenic changes. Many myofibers with multiple clusters of blue red rod-like structures and cytoplasmic inclusions were noted. Immunohistochemistry showed a focal positive reaction in sarcoplasm to desmin and myotilin antibodies. An electron microscope study revealed variable abnormalities of myofibrillar structures. To the best of our knowledge, this is the first reported case of MFM with pathology findings in Korea.

**Key Words :** Myofibrillar myopathies; Desmin; Pathology

Myofibrillar myopathies (MFMs) are a genetically and clinically heterogeneous group of chronic neuromuscular disorders that are characterized by focal myofibrillar dissolution associated with accumulation of myofibrillar degradation products and ectopic expression of multiple proteins including desmin,  $\alpha$ B-crystallin, dystrophin, myotilin, filamin, congophilic amyloid material, sarcoglycans, and many others.<sup>1-13</sup> In the 1970s and 1980s, the light microscopic features of MFM were described under various names.<sup>1,4,8,10</sup> Since some inclusions or material around them were immunoreactive for desmin, the terms 'desmin storage myopathy' and 'desmin-related myopathies' were proposed. In the late nineteen nineties, immunohistochemical studies revealed that other proteins also accumulated in the abnormal myofibers, which led to the use of the non-committal term MFM.<sup>8,10,13</sup> In addition to the poor correlation between genetic changes and clinicopathological findings, the abnormalities cannot be identified in more than 50% of patients with the clinicopathological phenotype of MFM.<sup>1,4,5,10,14</sup> Since the diagnosis of MFM depends on pathological manifestations, the recognition of light microscopic and electron microscopic features is very important for the diagnosis.

## CASE REPORT

A 20-year-old man presented with a history of weakness of both legs and difficulty in going upstairs for last two years. Two years ago, after bumping into a wall to avoid an approaching motorcycle, he felt pain in his left back and pelvic area. Six months later, he noticed mild symmetric weakness of both legs, which had been slowly progressive over the period. Four months before admission, he felt severe pain in the left medial knee and numbness of both legs. His family history was negative for neuromuscular disorders. He was born by normal vaginal delivery without any perinatal problems and his developmental milestones were normal.

The physical examination revealed that he had a dysmorphic face including an elongated face, micrognathia, and high-arched palate with short stature (height of 167.5 cm and weight of 76.5 kg). Mild gynecomastia, atrophy of both scrotums and testicles, and diffusely reduced muscle bulk of both calves were also noted. His cognitive and cortical functions were normal. Cranial nerve function and sensory tests were intact. Motor examination revealed mild proximal and distal weakness of both legs

(Medical Research Council [MRC] grade IV to IV+) and both knee jerks were hypoactive. Motor and sensory nerve conduction studies were normal. Electromyography showed short duration and small amplitude motor unit action potentials with abnormal spontaneous potentials in several muscles of the right leg. The blood chemistry test revealed normal creatine kinase (CK) and lactate dehydrogenase. All other tests including hormones were normal. Screening for mtDNA deletion or point mutation was negative.

A muscle biopsy was done on the vastus lateralis muscle under the clinical impression of congenital myopathy. Light microscopic examination showed pronounced fiber size variation, internalization of sarcoplasmic nuclei, irregular sarcoplasmic eosinophilic inclusions, fiber splitting, and rare necrotic myofibers with focal endomyseal fibrosis and fatty replacement (Fig. 1A). There

were many variable-sized clusters of small angulated or round fibers, which consisted of both type 1 and type 2 fibers on the ATPase reaction with different pH preincubation. Fiber type grouping and a predominance of type 1 fibers were also noted (Fig. 1B). Many myofibers with multiple clusters of rod-like structures and cytoplasmic inclusions were well-documented by modified Gomori's trichrome stain (Fig. 1C). Myofibers with blue-red amorphous inclusions and vacuoles were frequently noted. NADH-tetrazolium reductase (NADH-TR) reaction showed target fibers or mini-core like structures. Immunohistochemistry showed focal positive reaction in sarcoplasm to desmin (1 : 200, monoclonal, NCL-L-DES-DERII, Leica Microsystems, Newcastle Upon Tyne, UK) and myotilin (1 : 20, monoclonal, NCL-MYOTILIN, Leica Microsystems) antibodies (Fig. 1D). Electron microscopic examination showed

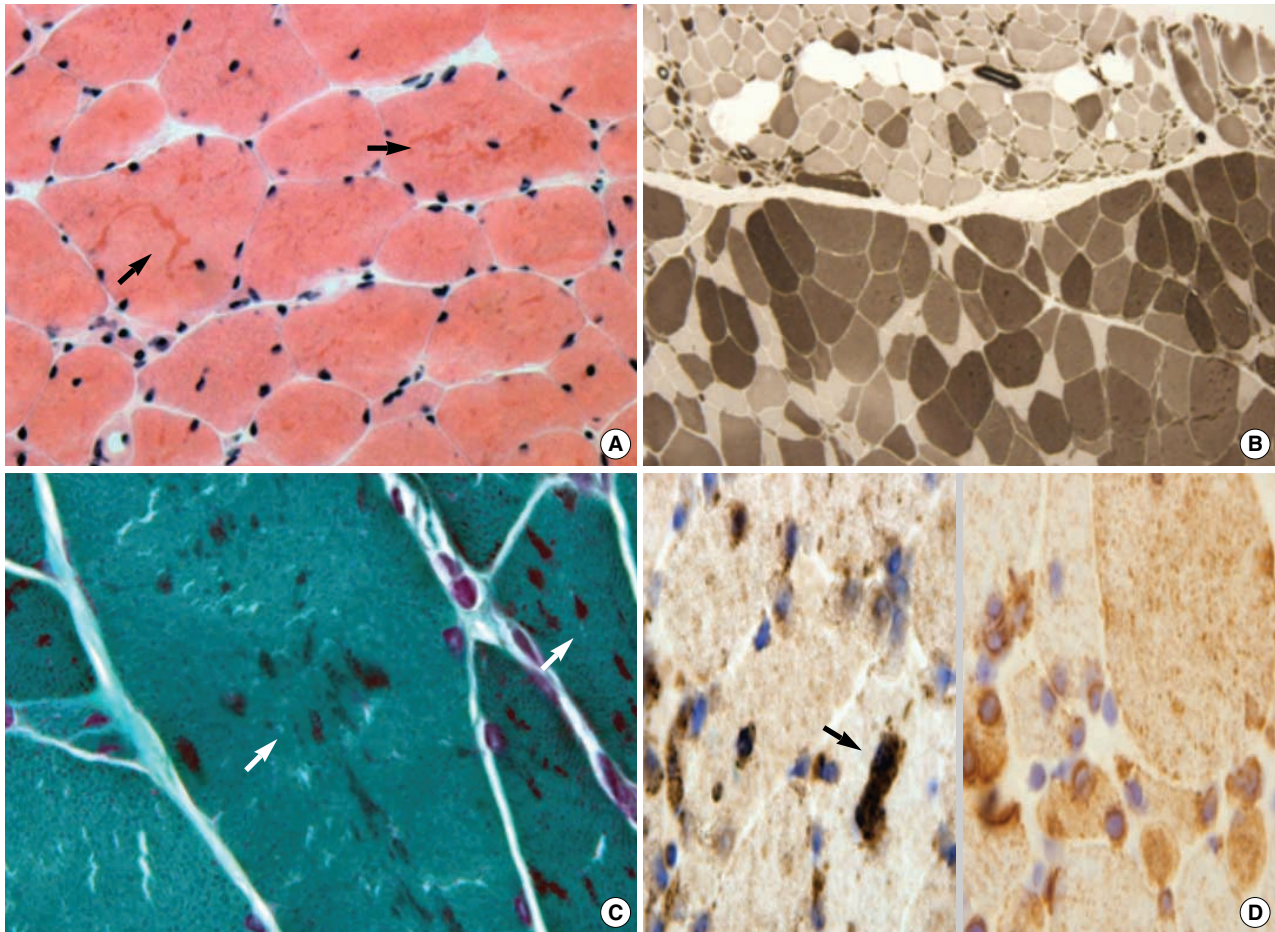
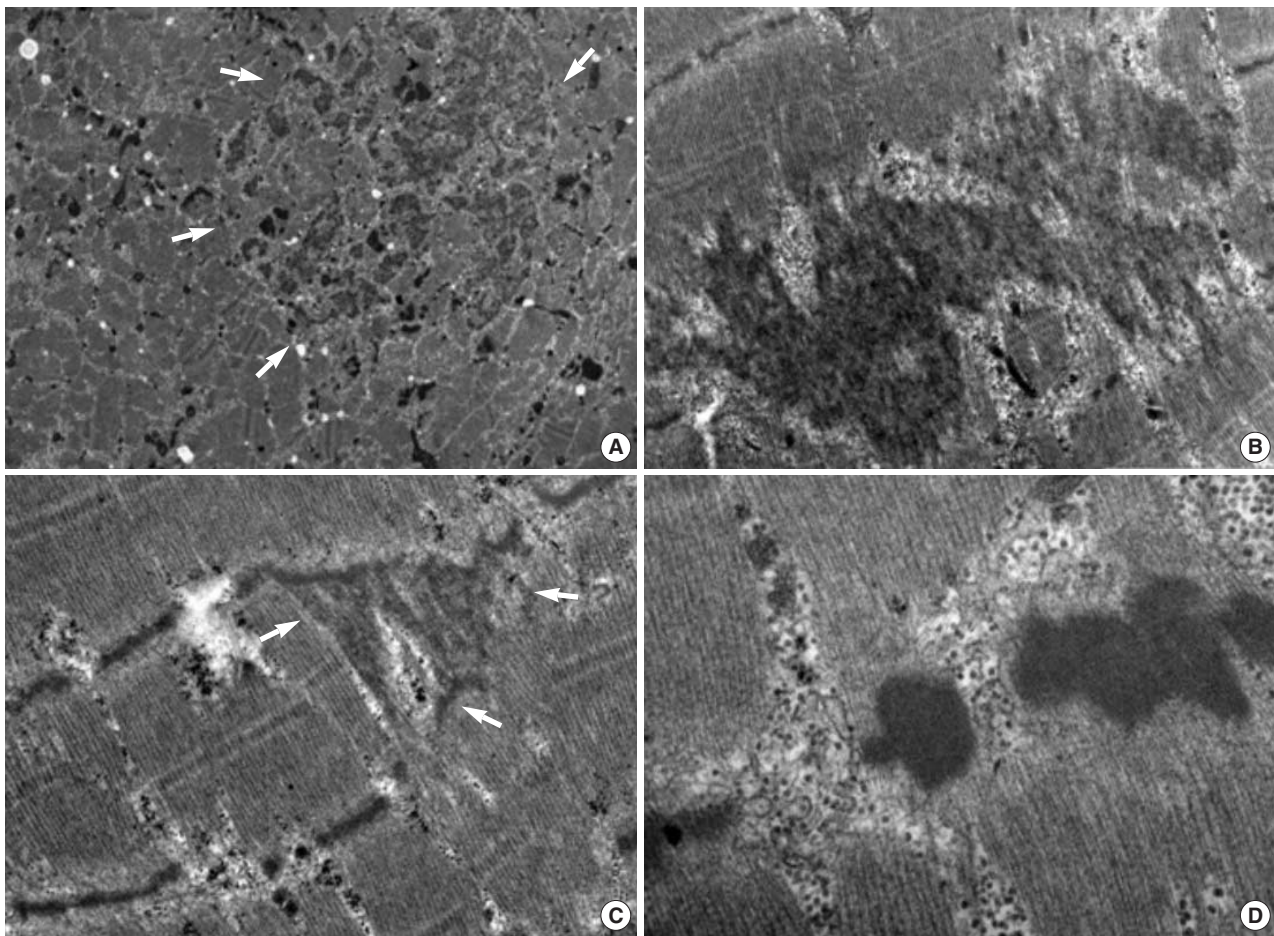


Fig. 1. Light microscopic examination of the muscle biopsy shows marked fiber size variation with internalization of sarcolemmal nuclei and irregular eosinophilic sarcoplasmic inclusions (A, arrows), variable-sized clusters of small angulated fibers consisting of both type 1 and 2 fibers and fiber type grouping (B), myofibers with unevenly distributed variable sized clusters of dark blue-green or red sarcoplasmic inclusions (C, arrows), and a focal positive reaction to anti-myotilin antibody (left in D, arrow) and anti-desmin antibody (right in D). (A) Hematoxylin and eosin stain, (B) ATPase with pH 9.4 preincubation, (C) modified Gomori's trichrome stain, (left in D) immunostain with anti-myotilin antibody, (right in D) immunostain with anti-desmin antibody.



**Fig. 2.** Electron microscopic examination of the muscle biopsy shows localized areas of myofibrillar destruction containing remnants of myofibrils mixed with electron-dense materials of Z-line origin (A, arrows), myofibrillar degeneration with granulofilamentous material (B), Z-disc streaming and flag-like semidense extensions of Z-lines (C, arrows), and cones of dense material that emanate from the Z-disc (D) (A,  $\times 10,000$ ; B,  $\times 25,000$ ; C,  $\times 40,000$ ; D,  $\times 80,000$ ).

myofibers with varying degrees of disorganization, disorientation, and disruption of normal patterns. The myofibers showing diffuse or localized myofibrillar destruction contained remnants of myofibrils, irregular electron-dense material of Z-line origin, large or small autophagic vacuoles including myeloid structures, debris, and abnormal mitochondria (Fig. 2A, B). In addition, variable Z-disc abnormalities such as Z-disc streaming, cones of dense material and dappled dense bodies emanate from and replace normal Z-discs, and variable sized rods were noted (Fig. 2C, D). These findings were consistent with MFM, the genetic cause of which was undetermined because the family refused to allow a genetic study.

## DISCUSSION

Since the clinical features noted in the presenting patient as

well as the myopathic changes were compatible with those of various congenital myopathies as well as MFM,<sup>1,2</sup> a muscle biopsy was done under the clinical impression of congenital myopathy. Congenital myopathies and MFMs are clinically, genetically, and pathologically a heterogeneous group of disorders that are defined by characteristic morphological features on muscle biopsy and characterized by clinical manifestations.<sup>1,2,4</sup> Most of the structural changes and clinical manifestations that characterize these disorders are non-specific and occur to a variable extent in several disorders. There is also considerable pathological overlap between the various congenital myopathies as well as between the MFM cases with different genetic changes.

The occurrence of peripheral neuropathy in a significant proportion of MFM patients has been well documented in previous studies.<sup>1,4,8,10,11</sup> The histopathological features of peripheral neuropathy in the muscle biopsy were also noted in this case. In addition to non-specific pathological features of myopathy

seen on light microscopy, previous studies on MFM described two types of inclusions - hyaline structures and non-hyaline lesions - as specific findings for the diagnosis of MFM.<sup>1,5-8,10</sup> Hyaline structures are cytoplasmic granular inclusions (composed of compacted and degraded remnants of thick and thin filaments), which appear eosinophilic on hematoxylin and eosin stain and dark blue-green or occasionally red on modified Gomori trichrome stain. Non-hyaline lesions consist of disrupted myofilaments, Z-disk-derived bodies, dappled dense structures of Z-disk origin, streaming of Z-disk and the appearance of dark green areas of amorphous material on modified Gomori trichrome stain. The presenting case showed many clearly identified hyaline structures on both light microscopic examination (in trichrome stain-stained sections) and electron microscopic examination. The electron microscopic examination showed the various components of non-hyaline lesions. In addition, the presence of variable-sized autophagic vacuoles including granular material, myeloid structures, and glycogen mixed with abnormal mitochondria was compatible with the findings of MFM. The presence of target fibers or mini-core like structures noted on the NADH-TR stain in this case was compatible with findings of disrupted normal myofibrillar architecture and displacement of mitochondria. Similar findings were previously reported in MFM.<sup>1,7,8,13</sup> The significance of abnormal and ectopic expression of multiple proteins in abnormal myofibers has not been well defined and the increased expression of any one protein does not point to an underlying mutation.<sup>10,11,14</sup> Previous studies suggested the possibility of a mitochondrial abnormality in patients with MFM.<sup>7,15</sup> The negative result in this case from screening for a mtDNA deletion or point mutation suggested the possibility that mitochondrial abnormalities noted in this case were secondary degenerative changes.

The differential diagnosis of this case from muscular dystrophies such as myotonic dystrophy and limb-girdle muscular dystrophies (LGMDs) and dysferinopathies depends on differences in clinical manifestations and pathological findings on muscle biopsy.<sup>16</sup> Myotonic dystrophy (DM1 and DM2) shows myotonia, facial/neck weakness, ptosis, cardiac conduction defects, frontal balding, and gonadal atrophy. In addition to common dystrophic features of skeletal muscle (such as degeneration, necrosis, and regeneration of myofibers, marked variation of fiber size and shape, split fibers, excessive endomyseal and perimyseal connective tissue or adipose tissue), numerous internal nuclei (often in long chains), ring fibers, sarcoplasmic masses with disorganized myofibrillar material, and dilated sarcoplasmic reticulum are frequently noted features in DM. The LGMDs

are a heterogeneous group of disorders with common clinical features of progressive weakness of the pelvic and shoulder muscle, fast clinical progression, and markedly increased serum CK. The muscle pathology shows the dystrophic changes common to all muscular dystrophies with necrosis and fibrosis as well as certain differences (such as the presence of inflammatory cells or vacuoles) according to various subtypes. LGMD2B and Miyoshi distal dystrophies are caused by defects in the dysferin gene. These two entities show clinically distinct features, but with considerable overlap between them. The clinical presentation consisting of gross elevation of serum CK with rapid progression of weakness has often led to a presumptive diagnosis of inflammatory myopathy. In addition to degenerative dystrophic changes in muscle biopsy, inflammatory cell infiltrates and overexpression of sarcolemmal major histocompatibility complex class I antigens on mature fiber are common.

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