VCP-related Multisystem Proteinopathy Presenting with Lobulated Myofibers

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Valosin-containing protein (VCP)-related multisystem proteinopathy (MSP1) is a rare genetic disorder marked by abnormal protein accumulation. This study presents the case of a 52-year-old woman with MSP1, showing progressive weakness, gait disturbances, and respiratory muscle weakness over five years. The clinical examination revealed diverse presentations, including neurogenic changes in electrophysiologic study, multifocal fatty changes of muscle, and cognitive impairment with a confirmed VCP gene mutation through genetic testing. Notably, we identified lobulated myofibers in the muscle biopsy, an unusual finding in MSP1. This is the first report of lobulated myofibers in MSP1 with multisystem involvement. Identifying unique muscle biopsy results in suspected MSP1 patients through careful neurological examinations and timely genetic testing may help in early diagnosis and appropriate management.

Multisystem proteinopathy (MSP) is a rare genetic disorder characterized by the formation of abnormal protein aggregates and their accumulation in various tissues and organs. Valosin-containing protein (VCP) related multisystem proteinopathy, suggested as multisystem proteinopathy 1 (MSP1), is caused by mutations in the VCP gene on chromosome 9p13–p12; also known as inclusion body myopathy with Paget's disease of bone (PDB) and frontotemporal dementia (FTD) or IBMPFD (Inclusion Body Myopathy With Early-Onset Paget Disease). MSP1 leads to the accumulation of cytoplasmic proteins in vacuoles and inclusion bodies in muscles, bones, and the central nervous system. While the diversity of mutations and clinical phenotypes, there is a paucity of research on this disease. A recent study suggests that MSP1 may coexist with other neurological disorders. Moreover, its prevalence may be higher due to misdiagnosis with diseases having similar symptoms. This study aims to report an unusual muscle biopsy finding in an MSP1 patient with VCP mutations presenting with var-

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ious phenotypes in the context of multisystem involvement.

Case

A 52-year-old woman presented with a gradual onset of proximal weakness and gait disturbance for five years along with muscle atrophy. She had no chronic disease or family history of neuromuscular disease. On examination, she showed weakness in the shoulder, thigh, and knee (Medical Research Council [MRC] grade 4+). Her elbow, wrist, and ankle were MRC grade 5-, showing weakness mainly in the proximal region. Her facial muscles were normal, and she had mild dysarthria. Her sensory modalities were intact, and she showed no upper motor neuron signs such as limb spasticity, brisk jaw jerk, or hyperreflexia. She presented fasciculations in both lower limbs, and the Gower's sign was positive. There were no skin lesions or bone/joint pain. Her serum creatine kinase (153 IU/L) and alkaline phosphatase (86 IU/L) were within the normal range. Pulmonary function tests showed that her vital capacity was reduced by 36% of predicted, and her maximal inspiratory pressure and maximal expiratory pressure were also reduced, indicating respiratory muscle weakness. Nerve conduction studies were normal. Electromyography showed widespread neurogenic changes; however, no myopathic potentials were identified. She showed memory impairment with stubbornness and poor hygiene maintenance. Her Mini-Mental State Examination score was 23, and the Frontal Assessment Battery score was 13. Brain magnetic resonance imaging showed atrophy of the frontal and temporal lobes, suggesting FTD. Muscle computed tomography showed diffuse atrophy with multifocal fatty changes, mainly in the limb-girdle muscles. Biopsy of the right vastus lateralis muscle revealed marked size variation of myofibers with rimmed vacuoles (Fig. 1A) and frequent observation of lobulated myofibers (Fig. 1B). Gomori-trichrome staining confirmed the presence of rimmed vacuoles in muscle fibers (Fig. 1C), with TDP 43 inclusions and ubiquitin-positive aggregates (Fig. 1E, 1F). Electron-microscopy showed rimmed vacuoles (Fig. 1D) along with myofilament disarray. Using a targeted Next-Generation Sequencing focused on limb-girdle muscular dystrophy in response to suspected proximal weakness, genetic testing identified heterozygote c.463C>T resulting in p. Arg155Cys substitution in the VCP gene, previously reported as a pathologic variant of MSP1. The patient showed gradual deterioration of respiratory function and limb weakness.

Discussion

MSP is defined by the presence of two or more of the fol-
lowing conditions: inclusion body myositis, Paget’s disease of bone, and amyotrophic lateral sclerosis (ALS)/FTD (ALS and FTD are regarded as a single spectrum). In a previous study, only 10% of patients satisfied the symptom triad, and the most common findings were myopathy (89%), PDB (43%), and FTD (29%). Muscle weakness mainly occurs in the limb-girdle region, but axial, distal dominant, and facial/tongue weakness may also be observed. In most cases, FTD is behavioral variant FTD with personality change and behavior problems. Our patient showed impairment in word fluency and the Go-No-Go test, indicating a problem in executive function. The muscle pathology in MSP1 varies from nonspecific myopathy to rimmed vacuoles containing TDP-43 (TAR DNA binding protein 43) and p62 aggregates, with appearance of neurogenic/myopathic changes in some cases. The c.464G>A (p.Arg155His) heterozygous mutation was found in one case of a Korean individual who presented with axial muscle weakness; another case series included a Korean family and had the same mutation (c.463C>T, p.Arg155Cys), as reported in the current study. Muscle biopsy results in the above cases ranged from normal to demonstrating fiber size variation, fat infiltration, and angulated atrophic fibers. A lobulated myofiber exhibits an irregular cytoarchitectural pattern wherein normal lattice-shaped fibers form an abnormal spatial distribution of the intermyofibrillar mitochondria network. This finding is observed in various neuromuscular diseases such as limb-girdle muscular dystrophy type 2A, facioscapulohumeral muscular dystrophy, and nemaline myopathy. Regarding the VCP gene, Liewluck et al. first reported a patient with heterozygous c.1160G > A resulting in p. Asn387Ser substitution who presented myopathic symptoms; another case series included a Korean family and had the same mutation (c.463C>T, p.Arg155Cys), as reported in the current study. Muscle biopsy results in the above cases ranged from normal to demonstrating fiber size variation, fat infiltration, and angulated atrophic fibers. Thus, this is the first report on the possibility of lobulated myofibers in MSP1 patients with multisystem involvement.

Because of the diversity of clinical manifestations of MSP1 involving multiple systems, diagnosis can be challenging. However, acknowledging that unique muscle biopsy findings may be present when MSP1 is suspected through careful history-taking and neurological examinations, patients could benefit from timely genetic testing for early diagnosis and effective management.

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Conflicts of Interest

All authors have no conflicts of interest.

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