The Familial Occurrence May Give a Clue to the Pathogenesis of Inclusion Body Myositis

**Key words:** inclusion body myositis (IBM), familial IBM, rimmed vacuole, distal myopathy, steroid therapy

Familial inclusion body myositis (FIBM) is a rare condition belonging to a family of rimmed vacuole myopathies (RVM) which also include distal myopathy with rimmed vacuole (DMRV), hereditary inclusion body myopathy (HIBM), and sporadic inclusion body myositis (SIBM) (1, 2). Oculopharyngeal muscular dystrophy (OPMD) and oculopharyngodistal myopathy (OPDM) may also belong to this category of myopathy (3). RVM is characterized by the presence of many rimmed vacuoles in muscle fibers. Rimmed vacuole (RV) is a light-microscopic feature and muscle fibers with RVs reveal filamentous inclusions by electron-microscopy; this is also a characteristic finding of inclusion body myositis (IBM). IBM has long meant merely a sporadic, inflammatory RVM and viral origin has been suspected. More recently, some hereditary conditions characterized by RV and usually without inflammatory changes were found and the term hereditary inclusion body myopathy (not myositis!) was introduced. Therefore, IBM could mean both inclusion body myositis and myopathy. We should be very careful when we read Western literature. Now, traditional inflammatory and sporadic IBM is called SIBM and hereditary RVM without inflammatory change might be called HIBM. HIBM may be used to describe various forms of RVM.

FIBM is quite distinct from HIBM. FIBM simply means familial occurrence of typical “SIBM”. SIBM was characterized by relatively late onset, slowly progressive proximal and distal weakness, only mild increase of serum CK level, not only myopathic but also some “neuropathic” changes in needle EMG, frequent rimmed vacuoles in muscle histopathology with substantial inflammatory cell infiltration. Muscle weakness and wasting is characteristically prominent in quadriceps, wrist and finger flexors, and ankle dorsiflexors (4). SIBM is the most common myopathy over 50 years of age and unlike polymyositis/dermatomyositis (PM/DM), it is more common in men than in women. Although the presence of inflammatory changes in SIBM is similar to that in PM/DM and is mandatory for its diagnosis, anti-inflammatory therapy and immune therapy have been virtually ineffective. Therefore, SIBM appears quite distinct from polymyositis/dermatomyositis.

As mentioned above, familial cases of RVM or HIBM have been recognized although they are rare. Recently, UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE) gene has been discovered to be causative for HIBM (5) and also DMRV which usually lack inflammatory changes in muscle and is characterized by relative sparing of quadriceps femoris muscle and predominant involvement of the tibialis anterior muscle (6). DMRV or HIBM (hereditary inclusion body myopathy) caused by GNE gene mutation is a genuine degenerative disease in which corticosteroid and other immunotherapies are ineffective.

Contrastively, FIBM appears very unique because it is an inflammatory disorder with a relatively good response to steroid therapy yet it may be a hereditary disease. The recognition of FIBM has two important aspects. From a clinical viewpoint, FIBM may be treatable while familial disorders are usually thought to be degenerative and unresponsive to immunotherapy. From a scientific point of view, if a responsible gene would be discovered, it might provide a clue to the pathogenesis of the myopathic changes characterized by both rimmed vacuole formation and inflammation because molecular genetic studies have been very powerful in the elucidation of various neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis. In this issue of Internal Medicine, two sister cases of FIBM are reported for the first time in Japan (7).

Although FIBM shows some favorable response to corticosteroids, it is not satisfactory. The clarification of the pathogenesis of FIBM is very important and may be very helpful to investigate the more complex version, SIBM. It is sincerely desired that the report would be an important clue to elucidate the pathomechanism of the mysterious entity, rimmed vacuole myopathy or inclusion body myopathy, with or without inflammatory changes.

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