Male With Chronic Progressive Painless Muscle Weakness

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A 60-year-old man presented with painless, slowly progressive muscle weakness and atrophy of the extremities over a 2-year period. His past medical history was significant for asthma, atrial fibrillation, and a myocardial infarction in 1987. There was no family history of myopathy or neuropathy. Initially affecting only his right hand, the weakness progressed in a stepwise fashion to involve the remainder of his extremities, unaccompanied by sensory symptoms. Physical examination revealed diffuse, asymmetric proximal and distal muscle weakness and atrophy, primarily affecting the upper extremities. Upper extremity and patellar reflexes were absent or reduced, and there were no sensory deficits. His erythrocyte sedimentation rate (Westergren) was 32 mm/h, his creatinine phosphokinase level was 345 IU/L (normal < 157 IU/L), and his antinuclear antibody titer was positive at 1:80. Electromyography and nerve conduction testing showed evidence of widespread muscle disease with fibrillations, high-frequency repetitive discharges, and myotonic potentials consistent with widespread primary muscle disease. Histologic sections of the left deltoid and forearm muscles were obtained and showed a moderate variation of muscle size, scattered degenerating and regenerating muscle fibers, and multifocal chronic endomysial inflammation (Figure 1). Several muscle fibers contained rimmed or autophagic vacuoles (Figure 2). Occasional scattered cytochrome c oxidase–negative muscle fibers were observed. Electron microscopic evaluation of muscle specimens confirmed the presence of prominent rimmed (autophagic) vacuoles (Figure 3). In addition, there were tubulofilamentous cytoplasmic inclusions (15–18 nm in diameter [arrow], Figure 4).

What is your diagnosis?
Pathologic Diagnosis: Inclusion Body Myositis

Inclusion body myositis (IBM) is one of the most frequent types of acquired inflammatory myopathy, typically affecting white men older than 50 years. The vast majority of cases are sporadic, but familial cases of variable phenotype and of autosomal dominant or recessive inheritance have been described. Inclusion body myositis is marked by painless, slowly progressive, asymmetric muscle weakness and atrophy affecting proximal muscles in a limb-girdle distribution. Some patients display equal weakness and atrophy affecting proximal muscles in a limb-girdle distribution. Patients may also be useful in differentiating IBM from polymyositis.

The pathogenesis of IBM is not known, but it is likely to be both multifactorial and multigenic. The term hereditary inclusion body myopathy (h-IBM) was introduced in 1993 to designate a familial form of muscle disease similar pathologically to sporadic IBM (s-IBM), except for the lack of lymphocytic mononuclear cell inflammation. In addition, most of the vacuolated muscle fibers in h-IBM do not stain positively for Congo red and do not contain ragged red fibers or cytochrome c oxidase–negative fibers. The different forms of h-IBM are likely the result of differing genetic defects.

Both viral- and immune-mediated mechanisms have been postulated as putative etiologic agents in s-IBM. Because s-IBM and h-IBM share several pathologic characteristics, a common pathologic cascade ultimately resulting in fiber vacuolation has been proposed. The accumulation of β-amyloid precursor protein, β-amyloid protein, or both in muscle fibers via abnormal signal transduction and transcription is felt to be an early step in this common cascade. This overexpression induces cellular disturbances that lead to oxidative stress and the expression of free radicals, culminating in the pathologic muscle fiber abnormalities and mitochondrial alterations described. Oxidative stress is postulated to augment abnormal signal translation and transduction in a self-perpetuating fashion.

References