Adult-Onset Nemaline Myopathy and Monoclonal Gammopathy

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45-year-old man with severe proximal muscle weakness had findings diagnostic of adult-onset nemaline myopathy. He also had a monoclonal gammopathy. This is the fifth report of adult-onset nemaline myopathy in a patient with monoclonal gammopathy, suggesting that the occurrence of these entities may be more than a chance association. Myocyte-bound immunoglobulin or light chains were not detected and immunotherapy was not effective in this patient. Other causes of adult-onset nemaline myopathy were ruled out, including the most common mutations of sarcomeric thin filament genes.

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Nemaline myopathy was described in 1963 as a nonprogressive myopathy of infancy.1,2 On muscle biopsy, characteristic intracytoplasmic granules and rods are found in muscle fibers that appear to arise from the Z-bands of sarcomeres.3 Although the molecular composition of the granules has been partially elucidated (actin filaments cross-linked by α-actinin),4 the pathogenesis of myocyte degeneration remains unclear.3

A unifying genetic feature of nemaline myopathy is the fact that heritable forms of the disease are associated with mutations of sarcomeric thin filament genes including α-tropomyosin (TPM3), α-actin (ACTA1), nebulin (NEB), β-tropomyosin (TPM2), and troponin T1 (TNNT1).4 Although additional genes associated with nemaline myopathy remain to be identified, some cases likely involve nemaline body formation as a nonspecific or secondary response to local pathophysiologic states.4

In 1966, A. G. Engel3 described an adult-onset form of the disease (adult-onset nemaline myopathy) with weakness of proximal limb and trunk muscles and sparing of the bulbar muscles. Most if not all adult-onset cases have been sporadic6 and in only 1 case has a mutation of ACTA1 been identified.7

In 1975, W. K. Engel and Obere8 described a patient with adult-onset nemaline myopathy and monoclonal gammopathy. Since then, 3 similar cases have been reported.9-11 None have had an associated myeloma or identifiable lymphoproliferative disorder. We describe the fifth case of this unusual association.

REPORT OF A CASE

In September 2003, a 45-year-old man with no family history of myopathy noted weakness of proximal limb muscles. The weakness spread and when last seen in January 2005, he could not stand or walk and was totally dependent in all activities of daily living. Weakness was still more severe proximally and he was using noninvasive ventilation. Dysphagia was severe and a percutaneous gastrostomy was performed after he had lost 60 pounds. Eye and tongue movements were normal and his speech was clear. He could not raise his head if supine. Fasciculations were not seen; tendon reflexes and sensation were preserved.
Figure 1. Semi-thin sections (toluidine blue, original magnification × 400) showing numerous granules (arrows).

Figure 2. Electron microscopic image (original magnification × 15 000) showing granules and short rods with disorganized myofibrils.

The clinical and pathological findings in our patient were similar to those of previously described cases of adult-onset nemaline myopathy, which are initial proximal limb weakness without dysphagia, dysarthria or respiratory insufficiency, and lack of affected family members or preceding symptoms. Later, dyspnea, dysphagia, and mild facial muscle weakness have been observed as seen in our patient, 18 months after symptom onset.

Fibers with nemaline rods were scarce in our patient, but the proportion of muscle fibers affected by rod formation and the number of rods per cell are known to vary in muscles of the same patient or in different patients. Moreover, neither rod number, size, or location correlate with clinical severity. In this patient, the typical rod-shaped morphology was not obvious on light microscopic examination of sections stained with the Gomori trichrome method and diagnosis required electron microscopy (Figure 2). Intranuclear rods that are associated with early disease onset and a severe course were not seen.

Disease-causing mutations in 5 different thin sarcomeric filaments have been characterized and other genes are likely to be discovered. Although the vast majority of known mutations have been found in congenital or childhood-onset cases, Agrawal et al described 1 patient with adult-onset disease with an ACTA1 mutation, which was ruled out in our patient. A deletion in exon 55 of the NEB gene, which causes nemaline myopathy in some Ashkenazi Jewish patients, was also excluded in our case. Although it is impossible to be certain, these data, together with the sporadic nature, late onset, and rapid progression of the patient’s nemaline myopathy suggest an acquired rather than a genetic basis for his disease.

Nemaline rods are seen as a minor feature of muscle biopsies in a variety of neuromuscular disorders and rarely even in normal muscle. Nemaline myopathy is diagnosed when nemaline rods are the predominant finding and features of other etiologies are absent.

It is uncertain whether monoclonal gammopathy is causal or coincidental. The previously published histo-
logic findings have suggested an autoimmune etiology. In 2 cases, immunoglobulins of the same type as the circulating protein were seen on the surface of the myofibers by immunohistochemical staining. No sarcomere-bound immunoglobulins were identified by immunofluorescence staining in 2 other cases. However, failure of immunohistochemical or immunofluorescence stains to show immunoglobulin or immunoglobulin light chains does not exclude the possibility of low titer of muscle binding antibodies. Neither immunoglobulin nor immunoglobulin light chains were identified by immunofluorescence staining in our patient, and the incubation of the patient’s serum with frozen sections of his muscle biopsy did not show evidence of sarcomeric or membranous staining.

Symptoms improved partially with plasmapheresis and immunosuppression (prednisone and cyclophosphamide) in 2 of the reported cases, while immunosuppression (prednisone alone) failed in another. In a third patient, plasmapheresis was unsuccessful, but immunosuppression (prednisone and azathioprine) improved symptoms. Unfortunately, all of these therapies as well as treatment with rituximab failed in our patient. Thus, although adult-onset nemaline myopathy with gammopathy may be more than a chance association, immunotherapy may not be effective in all cases.

Author’s Note: After this article had been submitted for publication, Chahin et al described 14 patients with adult-onset nemaline myopathy, including 7 with monoclonal gammopathy. Our patient died in June 2005, 21 months after onset of symptoms.

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REFERENCES


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