the onset of symptoms. The pattern of weakness in IBM is unique in that the clinical hallmark is early weakness and atrophy of wrist and finger flexors, quadriceps, and ankle dorsiflexors (Fig. 7A and B). Toe flexors are also frequently weak, sometimes producing a position of chronic great toe extension, or a pseudo-Babinski sign (Fig. 7C). Some degree of asymmetry in muscle weakness is the rule. Because of the dramatic knee extensor involvement, it is not exclusively a distal myopathy, although distal upper extremity flexor weakness is an invariable component of the disease. Both knee extensor and forearm and finger flexor weakness are included in the new clinical diagnostic criteria for IBM (105). Severe weakness in these muscle groups is so characteristic of IBM that even if the classic histologic findings are not present on muscle biopsy, a presumptive diagnosis of “possible” IBM should be considered (106).

Classic light microscopy features are endomysial inflammation with invasion of nonnecrotic muscle fibers, eosinophilic cytoplasmic inclusions, and rimmed vacuoles within the muscle fibers that contain amyloid deposits (Fig. 8A) (105). On electron microscopy, there is an accumulation of cytoplasmic and intranuclear 15- to 21-nm filaments (Fig. 8B). Although inflammation is nearly always present, the other pathologic features may not be identified on the initial muscle biopsy, often requiring a second or third biopsy for confirmation (106). The histologic similarities between IBM and both Welander and Nonaka

**FIG. 7.** Inclusion body myositis. **A:** Note bilateral atrophy of the flexor forearm muscles. **B:** Same patient as in A. Note inability to flex fingers completely in the left hand. **C:** Pseudo-Babinski sign with chronic toe extension due to weakness of toe flexors.
myopathy have already been described. Mendell et al. (108) found amyloidogenic green-birefringent deposits with Congo red stain in IBM biopsies. However, in that series, the single case of distal myopathy with rimmed vacuoles in the control group also showed these deposits. On histologic grounds, the presence of inflammation may be the only pathologic findings to differentiate IBM from distal muscular dystrophies.

On the other hand, despite the presence of inflammation in IBM, the disease is typically refractory to immunosuppressive therapy. The lack of response to immunosuppressive treatment distinguishes IBM from polymyositis and dermatomyositis. When patients with IBM are placed on prednisone therapy, strength continues to deteriorate, despite a decrease in serum CK and the suppression of inflammation on repeat muscle biopsy (109). In addition, although the inflammation decreases, the number of fibers with vacuoles and amyloid deposits increases over time (109). Finally, it has been shown that there is an accumulation of “Alzheimer-characteristic” proteins in vacuolated muscle fibers such as β-amyloid and paired helical filament-tau in IBM tissue (105). These observations suggest that IBM may be a degenerative rather than an autoimmune inflammatory myopathy and that the inflammation is a secondary response. Seen in this way, it may not be surprising that there are many pathologic similarities between the distal muscular dystrophies and IBM.

AR familial inclusion body myopathy (47) was described in the section regarding Nonaka distal myopathy as recent linkage analyses support that they are the same myopathic disorder (51,52).

Table 3 lists the diseases that have been reported to have both vacuoles and 15- to 18-nm filaments. These filaments can be seen in both the cytoplasm or nucleus in all disorders except oculopharyngeal dystrophy and its distal variant, oculopharyngodistal dystrophy. In the oculopharyngeal dystrophies, the nuclear filaments are 8 to 10 nm and the cytoplasmic filaments are 15 to 18 nm.

**Metabolic and Congenital Myopathies**

Debrancher enzyme deficiency has been reported with severe distal leg weakness (110). We have recently observed a 30-year-old man with adult-onset acid-maltase deficiency who presented with a scapuloperoneal pattern of weakness (111).

Patients with nephropathic cystinosis develop a distal myopathy as a late complication of the disease. This is an AR lysosomal storage disorder in which cystine accumulates and leads to renal failure. Patients who survive child-

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**FIG. 8.** Inclusion body myositis. A: Apple green birefringence indicating amyloid deposition (Congo red under polarized light, ×675). B: Electron microscopy showing the edge of a vacuole (with adjacent normal sarcomeres) containing cytoplasmic debris and 15- to 18-nm filaments (arrowheads) (×10,800). (Courtesy of Dennis Burns, MD.) C: Higher magnification of 15- to 18-nm filaments (×20,000) (Courtesy of Dennis Burns, MD.)
TABLE 3. Myopathies with vacuoles and 15 to 18 nm filaments

<table>
<thead>
<tr>
<th>Inclusion body myositis</th>
<th>Welander myopathy</th>
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</thead>
<tbody>
<tr>
<td>Nonaka myopathy/familial inclusion body myopathy/quadriceps sparing myopathy</td>
<td>Oculopharyngeal/amyotrophy</td>
</tr>
<tr>
<td>Oculopharyngodistal dystrophya</td>
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aIntracellular nuclear filaments 8–10 nm also present.

hood due to renal transplantation develop weakness and wasting in the hand muscles. Electrodagnostic studies are consistent with a myopathic process, and muscle biopsy of hand muscles shows a vacuolar myopathy (112).

Nonprogressive congenital muscle diseases such as nemaline rod (113–115), central core (116), and centronuclear myopathy (117) can have significant involvement of distal muscles. AD nemaline myopathy has been shown to be due to a mutation of the α-tropomyosin gene on chromosome 1 (114,115). In the Australian pedigree, patients first develop symptoms in late childhood, and ankle dorsiflexion weakness is the initial and most significant manifestation of the disease (114,115).

Myasthenia Gravis

Most patients with myasthenia gravis present with ocular, bulbar, and proximal limb muscle weakness (118). Rarely, their weakness can be distally prominent. We identified 7 of 234 (3%) patients with myasthenia gravis and primarily distal muscle weakness, mainly in finger extensors, followed by finger interossei. One patient had distal lower extremity weakness of the ankle dorsiflexors. In addition to the distal weakness, all had ocular and/or bulbar involvement and circulating antibodies to the acetylcholine receptor. The distal weakness in six patients improved with immunosuppressive therapy.

REFERENCES


