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## Inclusion Body Myositis

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Updated: Sep 3, 2009

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### Introduction

#### Background

Sporadic inclusion body myositis (s-IBM) and hereditary inclusion body myopathies (h-IBM) encompass a group of disorders sharing the common pathological finding of vacuoles and filamentous inclusions. They collectively demonstrate a wide variation in clinical expression, age of onset, associated diseases, and prognosis. This article focuses on s-IBM. For discussion of h-IBM, the reader is referred to other sources.<sup>1,2</sup>

The term *inclusion body myositis* was originally used by Yunis and Samaha in 1971 for a case of myopathy that phenotypically suggested chronic [polymyositis](#) but showed cytoplasmic vacuoles and inclusions on [muscle biopsy](#). In the subsequent years, s-IBM has been increasingly recognized and reported, primarily because of increased awareness of the condition and improved histologic techniques. A relatively common myopathic process, s-IBM is an important diagnostic consideration in the evaluation of progressive weakness in older Caucasian males.

Expression of s-IBM is variable, but all cases eventually evolve into a syndrome of diffuse, progressive, asymmetric, proximal, and distal weakness that is generally refractory to immunosuppressive treatment.

#### Pathophysiology

s-IBM has been traditionally classified as one of the idiopathic inflammatory myopathies along with [dermatomyositis](#) (DM) and [polymyositis](#) (PM). However, the pathologic findings of sporadic inclusion body myositis (s-IBM) involve both inflammatory and degenerative characteristics, and the true primary pathogenesis of the disease remains a subject of significant debate. Theoretically, the possibilities include (1) a primary T-cell mediated autoimmune response causing muscle damage, (2) a primary degenerative process involving abnormal protein processing leading to a secondary inflammatory response, and (3) separate and independent immune and degenerative processes caused by an external trigger.<sup>3</sup>

#### Inflammatory changes

s-IBM is characterized by the presence of non-necrotic myofibers invaded by mononuclear inflammatory cells, which, as a pathologic phenomenon, is significantly more common than vacuolated, congophilic, and necrotic fibers.<sup>4</sup> It is found at all stages of the disease in both treated and untreated patients.

The endomysial infiltrates in patients with s-IBM are composed primarily of CD8+ T cells and macrophages in a 2:1 ratio.<sup>5</sup> Myeloid dendritic (antigen-presenting) and CD138+ plasma cells are also present in substantial numbers,<sup>6,7</sup> while B cells and natural killer (NK) cells are rare. T cells, macrophages, and myeloid dendritic cells all have the potential to invade non-necrotic muscle fibers.<sup>8</sup> The autoinvasive CD8+ T cells surround major

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histocompatibility complex (MHC) class I-immunoreactive myofibers and express perforin and other markers of activation.<sup>9,10,11</sup>

Identical autoinvasive T-cell clones can persist over time, even in different muscles,<sup>12,13</sup> but the amplified subfamilies sometimes change, which suggests of epitope spreading.<sup>14</sup> Collectively, these observations implicate an antigen-driven, MHC class I-restricted, cytotoxic T-cell-mediated process directed against myofibers. The specific antigens responsible for this reaction are unknown.

Various chemokines, cytokines, and chemokine receptors are upregulated in the inflammatory cell infiltrates, blood vessels, and myofibers in s-IBM.<sup>15</sup> In microarray experiments, cytokine and chemokine genes are differentially upregulated to a significantly greater degree in s-IBM and polymyositis than in dermatomyositis.<sup>16,17</sup>

Humoral immunity may also play a role in the pathogenesis of s-IBM. Microarray studies have shown that many of the highest differentially expressed genes in s-IBM are immunoglobulin (Ig) genes. Indeed, Ig gene transcripts are expressed to a much greater degree in s-IBM and polymyositis than in dermatomyositis.<sup>16,17</sup> Although B cells are rarely encountered in s-IBM muscle, plasma cells occur in the endomysium of patients with s-IBM in numbers 4 times higher than B cells.<sup>6</sup> Moreover, an analysis of antigen receptor H chain gene transcripts of B and plasma cells isolated from s-IBM muscle showed evidence of clonal expansion and variation, isotype switching, and somatic hypermutation, indicative of a local antigen-driven humoral response.<sup>18</sup>

Additional evidence for a primary immune etiology includes the fact that as many as 20-33% of patients with s-IBM have a concomitant systemic or neurologic autoimmune disease.<sup>19,20</sup> [Monoclonal gammopathies](#) are identified with increased frequency in patients with s-IBM compared to age-related controls.<sup>21</sup> In addition, s-IBM is known to occur in association with chronic viral infections known to produce immune dysregulation (eg, [HIV](#), [human T-cell lymphotropic virus I](#) [HTLV-I], and [hepatitis C](#)).<sup>22,23,24,25</sup>

#### Degenerative changes

Despite the preceding arguments in favor of an adaptive immune response in s-IBM, a purely autoimmune hypothesis for s-IBM is untenable because of the disease's resistance to most immunotherapy. Therefore, the alternate theory has arisen that s-IBM is a primarily degenerative disorder related to aging of the muscle, supported by the finding of abnormal, potentially pathogenic protein accumulations in myofibers.

Myofibers in s-IBM exhibit vacuolization, atrophy, abnormal myonuclei,<sup>26,27</sup> and deposits of degeneration-associated proteins. Similar to actions in [Alzheimer disease](#), myofibers in s-IBM accumulate amyloid- $\beta$  (A $\beta$ ), phosphorylated tau (p-tau), apolipoprotein E, presenilin-1, the normal cellular isoform of prion protein (PrP<sup>C</sup>), and many other characteristic proteins.<sup>28,29</sup> Two major types of protein aggregates are found in s-IBM myofibers: (1) rounded, plaque-like, A $\beta$  inclusion bodies; and (2) linear, squiggly, p-tau inclusions (paired helical filaments).<sup>28,29</sup> Both are amyloidogenic.

In general, protein aggregation ensues from the binding of unfolded and misfolded polypeptides.<sup>30</sup> Unfolded and misfolded proteins, in turn, result from increased transcription, impaired disposal, abnormal crowding, or abnormal posttranslational modification of proteins, as might be induced by oxidative stress, various toxins, and aging. A specifically proposed mechanism involved in the formation of protein aggregates in s-IBM is inhibition of the ubiquitin-26S proteasome system, which is the primary degradation pathway for misfolded, unfolded, and other damaged proteins.<sup>30,31</sup>

Of these various alien molecules, A $\beta$  is putatively toxic.<sup>32</sup> Soluble A $\beta$  oligomers are believed to be more cytotoxic than the insoluble  $\beta$ -pleated sheets.<sup>33</sup> A $\beta$  accumulation results from increased synthesis and abnormal processing of amyloid precursor protein (APP) in s-IBM muscle.<sup>34</sup> Askanas and Engel have proposed that overexpression of APP and accumulation of toxic A $\beta$  oligomers are early upstream events in the pathogenesis of s-IBM, predisposing to tau phosphorylation, oxidative stress, proteasomal inhibition, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and, hence, abnormal signal transduction and transcription.<sup>35,36</sup> That said, the accumulation of A $\beta$  in s-IBM myofibers has been challenged.<sup>37</sup>

Accumulation of unfolded or misfolded proteins in the ER triggers the unfolded protein response (UPR), which is a survival mechanism.<sup>38,39</sup> The UPR comprises (1) the transcriptional induction of ER chaperone proteins to facilitate the folding, processing, and export of secretory proteins; (2) translational attenuation to reduce protein overload; and (3) increased retrotranslocation of misfolded proteins into the cytoplasm for ubiquitination and subsequent proteasomal degradation. In s-IBM muscle, expression of ER chaperone proteins is increased, colocalized with A $\beta$  and APP, suggesting that the UPR is activated in s-IBM and promotes proper APP folding.<sup>40</sup> Another protective agent is heat shock protein (HSP) 70, which promotes refolding of A $\beta$  and other misfolded or unfolded proteins.<sup>29</sup>

Several protein kinases are also involved in the s-IBM pathogenic cascade. Kinases that promote tau phosphorylation include cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ). Both

Cdk5 and GSK-3 $\beta$  are strongly expressed in vacuolated myofibers, where they colocalize with p-tau and the paired helical filaments.<sup>41,28</sup> Lithium inhibits GSK-3 $\beta$  and was shown to decrease tau phosphorylation in a transgenic mouse model of s-IBM.<sup>42</sup> Its clinical efficacy in s-IBM is now being investigated in a pilot study.

Most of the rimmed vacuoles in s-IBM are autophagic and composed of lysosomes.<sup>23,43,44</sup> Accumulated A $\beta$  and APP are specific targets of macroautophagy in this disease.<sup>44</sup> However, some of the vacuoles lack lysosomal features and instead contain nuclear proteins, suggesting that they result from the breakdown of myonuclei.<sup>45,46</sup> Nuclear membrane remnants (lamin A/C and emerin), nuclear histones, and the nuclear transcription factor pElk-1 have been found in rimmed vacuoles.<sup>45,47</sup> Thus, the formation of rimmed vacuoles in s-IBM is probably mediated by more than one mechanism.

As a likely secondary phenomenon, various mitochondrial abnormalities have been identified in s-IBM muscle, including ragged red fibers, cytochrome c oxidase-deficient fibers, and multiple mitochondrial DNA (mtDNA) mutations.<sup>48,49,50</sup> These changes might be mediated by aberrant mtDNA replication and maintenance due to oxidative stress, abnormal APP overexpression,<sup>51</sup> or proinflammatory cytokines.<sup>52</sup>

The downstream pathologic effects of the degenerative process were investigated in a recent proteomic, histochemical, and immunohistochemical study, which demonstrated preferential type 2 (fast twitch) myofiber involvement in most s-IBM muscles.<sup>53</sup> In particular, many fast twitch-specific structural proteins were differentially reduced. Expression of the corresponding gene transcripts was relatively preserved, suggesting that the protein loss was not caused by transcriptional failure. Four glycolytic enzymes were also decreased, especially glycogen-debranching enzyme.

#### Possible links between degenerative and inflammatory changes

Theoretically, the abnormal protein accumulations in s-IBM could be linked to the T-cell-mediated immune response by way of self-antigen presentation in MHC I/II-expressing myofibers. For example, immunoproteasome subunits are upregulated in s-IBM myofibers at sites of pathologic protein accumulation, sometimes colocalized with MHC I.<sup>54</sup> The immunoproteasome is specialized to produce antigenic peptides that can be presented by MHC class I molecules to CD8+ T cells.<sup>55</sup> Similarly, autophagosomes process intracellular antigens for MHC II presentation and CD4+ T cell recognition.<sup>56</sup> Thus, A $\beta$  might be presented to CD4+ and CD8+ cells by degenerating myofibers in s-IBM, with an ensuing autoreactive T-cell response.

In addition, ER stress and the UPR can initiate inflammation via multiple intracellular signaling pathways.<sup>57</sup> However, the myofibers invaded by T cells in s-IBM are almost never vacuolated, and the vacuolated fibers are almost never surrounded by mononuclear inflammatory cells, arguing against a cytotoxic T-cell response to A $\beta$  or any other abnormally accumulated protein in s-IBM.<sup>4</sup>

Alternatively, the inflammatory milieu within s-IBM muscle fibers might lead to the accumulation of misfolded MHC-related glycoproteins and trigger the overproduction of APP, A $\beta$ , p-tau, and other such proteins, creating ER stress.<sup>58,3</sup> In s-IBM, proinflammatory cytokines and chemokines correlate with the intramuscular accumulation of APP.<sup>11</sup> Exposure to IL-1 $\beta$  in particular might produce upregulation of APP with subsequent AB-associated degeneration. In a transgenic mouse model of IBM, lipopolysaccharide-induced inflammation increased steady state levels of APP and enhanced tau-phosphorylation in skeletal muscle, possibly secondary to proinflammatory cytokine (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ )-mediated upregulation of the glycogen synthase kinase-3B (GSK-3B) signaling pathway.<sup>42</sup>

Of course, neither APP/A $\beta$ -induced toxicity nor CD8<sup>+</sup> T-cell-mediated cytotoxicity may be the primary event in s-IBM. In this regard, muscle biopsy specimens in patients with s-IBM harbor numerous alpha-B-crystallin-immunoreactive myofibers in the absence of any significant structural abnormality.<sup>59</sup> These "X fibers" are several-fold more frequent than necrotic, regenerating, vacuolated, and non-necrotic/invaded fibers and are many times more frequent than fibers with Congo red-, phosphorylated tau-, or ubiquitin-positive inclusions.

Alpha-B-crystallin is a small HSP, but the expression of other HSPs and markers of oxidative stress are not increased in X fibers, arguing against the presence of a nonspecific stress response or oxidative stress in these fibers. The implication of this finding is that increased expression of alpha-B-crystallin is an early event in the pathogenesis of s-IBM, triggered by an unidentified stressor acting upstream to the development of vacuolated, necrotic, invaded, and congophilic fibers. Engel has speculated that this stressor might be a viral infection or mutated gene.<sup>59,28</sup>

## Frequency

### United States

s-IBM is considered the most common acquired myopathy in patients older than 50 years and accounts for 16-28% of inflammatory myopathies in the United States and Canada.

### International

In 2 population-based studies, a prevalence of 4.9 per million was reported in the Netherlands (which was felt to

be an underestimate) and 9.3 per million in western Australia. The corresponding figures for individuals older than 50 years were 16 and 35.3 per million, respectively.<sup>60,61</sup> A western Australian survey in 2006 revealed a prevalence of 39.5 per million for individuals older than 50 years (unpublished).

## Mortality/Morbidity

- The slow, relentless progression of muscle weakness in s-IBM leads to difficulty with ambulation, frequent falls, and eventual need for assistive-gait devices. Bone fractures and other complications may occur as a result of falls. Patients are often significantly disabled because of finger flexor weakness.
- Dysphagia due to weakness of the cricopharyngeal musculature may predispose individuals to [aspiration pneumonia](#).
- Mortality rate is difficult to assess based on current data. Affected individuals tend to be older, the disease is insidious and chronic, and patients often die of other medical problems. In a population-based study, the mean age of death of patients with s-IBM was not significantly different from that of the general population. Cause of death was disease-related (aspiration pneumonia and respiratory insufficiency) in 2 of 22 reported deaths.<sup>60</sup>

## Race

- No race predilection for s-IBM is known, but the condition has been noted to be uncommon among African Americans, Koreans, and Mesoamerican Mestizos.<sup>62</sup>

## Sex

- Reported male-to-female ratio ranges from 1.4:1 to 3:1.<sup>63,61,60</sup>

## Age

- Age of onset ranges from the late second to ninth decades. Mean age of onset is 56-60 years.<sup>63,60,61</sup>
- While a large majority of individuals develop symptoms when older than 50 years, 17-20% present before the age of 50.<sup>63,64,60</sup>
- The diagnosis of inclusion body myositis is often delayed by a mean of 5-8 years from time of symptom onset.<sup>63,60,65,64,66</sup>

## Clinical

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### History

Since s-IBM is an acquired myopathic process, weakness or impairment of muscle function in the area(s) affected is the presenting symptom. The disease follows a slowly progressive course.

- The distribution of weakness in s-IBM is variable, but both proximal and distal muscles are usually affected and, unlike polymyositis and dermatomyositis, asymmetry is common.
- Early involvement of the knee extensors, ankle dorsiflexors, and wrist/finger flexors is characteristic of s-IBM.
- Weakness of the wrist and finger flexors is often disproportionate to that of their extensor counterparts. Hence, loss of finger dexterity and grip strength may be a presenting or prominent symptom.
- Dysphagia is common, occurring in 40-66% of patients with well-established disease and in 9% of patients at presentation.<sup>63,67</sup> Dysphagia may manifest as a feeling of stasis, a need to swallow repeatedly, regurgitation, or choking.
- Isolated erector spinae weakness or "droopy neck" syndrome has been reported with s-IBM.<sup>68</sup>
- Myalgias and cramping are relatively uncommon.
- Sensory and autonomic dysfunction is not present except in patients with a concurrent polyneuropathy.
- Cardiac disease is common; it is most likely due to the older age of most patients. Direct cardiac muscle involvement by the disease has not been demonstrated.

### Physical

- Clinical suspicion for s-IBM should be very high when the pattern of weakness affects (1) the finger/wrist

flexors out of proportion to the finger/wrist extensors and shoulder abductors or (2) knee extensors disproportionate to the hip flexors.

- Patients have variable degrees of limb weakness and atrophy, which is usually both proximal and distal, and often, but not always, asymmetric.
- Facial muscle weakness may occur, but extraocular muscles are not affected and ptosis is not seen.
- Tendon reflexes may be normal or decreased.
- Decreased sensation in the distal lower extremities and reduced ankle jerks are not uncommon, as some patients have a concurrent polyneuropathy, which may be disease-related.
- Other neurological subsystem involvement (eg, cognitive function, coordination, upper motor neuron dysfunction) is not seen in s-IBM. The presence of such findings should raise suspicion for other processes.
- Examination for skin lesions, joint swelling/tenderness, and other systemic signs suggesting a concomitant autoimmune disorder should be routinely performed.
- Cardiovascular examination should evaluate for [hypertension](#), cardiac dysrhythmia/conduction abnormalities, and [cardiac failure](#).

### Causes

The cause of s-IBM remains unknown. See [Pathophysiology](#).

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## Inclusion Body Myositis: Differential Diagnoses & Workup

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### Other Problems to Be Considered

- Acid maltase deficiency
- Hereditary inclusion body myopathy
- Motor neuron disease
- Post polio syndrome
- Oculopharyngeal muscular dystrophy
- Late-onset distal myopathies
- Overlap myositis
- Sarcoidosis (chronic atrophic sarcoid myopathy)
- Drug-induced myopathies
- Myotonic dystrophy, type 1/2
- Myofibrillar myopathies

Table 1. Clinical Differential Diagnosis of s-IBM

Open [table in new window](#)

Disease	Points of Differentiation
h-IBM	Clinically and genetically heterogeneous group of diseases; positive family history; muscle biopsy features similar to s-IBM, but no inflammation
<a href="#">Polymyositis (PM)*</a>	Weakness usually symmetric and proximally predominant; occasional cardiac and pulmonary involvement; similar to s-IBM, biopsy shows endomysial inflammation with invasion of non-necrotic fibers by CD8 <sup>+</sup> cells, but unlike s-IBM, rimmed vacuoles and ragged red fibers are infrequent and amyloid deposits and tubulofilaments not seen (see <a href="#">Histologic Findings</a> )
<a href="#">Dermatomyositis (DM)</a>	Weakness usually symmetric and proximally predominant; occasional cardiac and pulmonary involvement; characteristic skin lesions; characteristic biopsy findings (eg, perifascicular atrophy, muscle infarcts, microvascular MAC deposits in the endomysium, focal capillary depletion, and conspicuous alterations in endothelial cells of endomysial microvasculature)
Oculopharyngeal muscular dystrophy (OPMD)	Predominant involvement of oculopharyngeal musculature (no extraocular muscle involvement in s-IBM); biopsy shows vacuoles, myopathic changes, and infrequent tubulofilaments (similar to s-IBM) but no inflammation; biopsy also shows

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	pathognomonic intranuclear filamentous inclusions having smaller diameters than s-IBM tubulofilaments in 2-9% of nuclei; genetic testing is available for OPMD ( <i>PABPN1</i> gene); rare, genetically distinct oculopharyngodistal variant in Japan
Late-onset distal myopathies	Clinically and genetically heterogeneous group of diseases; positive family history unless sporadic case; biopsy may show rimmed vacuoles and tubulofilamentous inclusions in Welander, distal myopathy, Nonaka distal myopathy, and tibial muscular dystrophy, all of which can be classified as h-IBM. Gene testing is available for Nonaka distal myopathy ( <i>GNE</i> ) and tibial muscular dystrophy ( <i>titin</i> ).
Overlap myositis	PM- or DM-like clinical and myopathological presentation but with additional systemic and serologic features diagnostic of an underlying connective tissue disease (eg, systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma, or mixed connective tissue disease)
<a href="#">Myasthenia gravis</a>	Unlike s-IBM, extraocular muscles are routinely involved; weakness is usually symmetric and tends to fluctuate, increasing with repeated or sustained exertion; spontaneous remissions can occur; motor unit action potentials (MUAPs) are unstable (increased jitter), whereas jitter is typically normal in s-IBM; repetitive nerve stimulation often shows abnormal decrement (rare in s-IBM); antibodies to acetylcholine receptors or muscle-specific kinase (MuSK) absent in s-IBM
Motor neuron disease	Upper motor neuron signs such as hyperreflexia and extensor plantar responses are not present in s-IBM; EMG in s-IBM may show neurogenic changes (ie, enlarged MUAPs), but these changes are relatively minor compared with predominance of smaller MUAPs, suggesting myopathy; fasciculation potentials are characteristic of motor neuron disease but rarely reported in s-IBM; recruitment is decreased in motor neuron disease and "early" in s-IBM; muscle biopsy in motor neuron disease shows denervation atrophy.
<a href="#">Acid maltase deficiency</a>	Weakness is typically proximal-predominant (torso included); respiratory failure seen in about one third of adults; EMG is myopathic, similar to that of s-IBM, but in acid maltase deficiency, insertional activity is prominently increased, with profuse complex repetitive and myotonic discharges, whereas myotonic discharges are not seen in s-IBM and complex repetitive discharges are uncommon; muscle biopsy shows lysosomal (acid phosphatase-positive), glycogen-laden (PAS-positive) vacuoles, foci of acid phosphatase reactivity in nonvacuolated fibers, and glycogen accumulation by electron microscopy.
<a href="#">Chronic inflammatory demyelinating polyradiculoneuropathy</a>	Weakness is usually both proximal and distal and mildly asymmetric, similar to s-IBM, but more often distally accentuated and lacking in the characteristic quadriceps/deep finger flexor emphasis of s-IBM; almost all patients have sensory signs and symptoms; examination shows diffuse hypo/areflexia; nerve conduction studies are abnormal, consistent with demyelination; EMG shows chronic reinnervational and no myopathic changes; serum creatine kinase (CK) is typically normal.

\*Patients whose polymyositis does not respond to treatment and who have a clinical picture suggestive of s-IBM should be reevaluated. A repeat biopsy should be considered, as they may have s-IBM. Failure to confirm the diagnosis on initial biopsy may have been due to sampling error or insufficient processing.

- Autoimmune and other conditions have been reported in patients, but the relationship to s-IBM is unclear. These included idiopathic interstitial pneumonitis, psoriasis, [primary biliary cirrhosis](#),<sup>69</sup> [sarcoidosis](#), [Sjogren syndrome](#),<sup>70</sup> [celiac sprue](#), and [idiopathic thrombocytopenic purpura](#),<sup>71</sup> macrophagic myofasciitis,<sup>72</sup> [systemic lupus erythematosus](#),<sup>73,74,75</sup> and [dermatomyositis](#).
- [Creutzfeldt-Jakob disease](#) has been described in association with s-IBM.<sup>76</sup>
- Cancer is an uncommonly associated condition. In the series by Lotz et al, 2 female patients were diagnosed as having cancer ([breast](#) and [uterus](#)) within a short period after diagnosis of s-IBM.<sup>63</sup> Arnardottir et al reported a case in association with [chronic T-cell lymphocytic leukemia](#).<sup>77</sup> No established relationship of cancer to s-IBM exists.

## Workup

### Laboratory Studies

- Standard studies pertinent to the evaluation of patients with progressive myopathic weakness include complete blood count, magnesium, calcium, phosphate, creatinine, creatine kinase (CK), erythrocyte sedimentation rate (ESR), antinuclear antibodies, rheumatoid factor, serum protein electrophoresis (+/- immunofixation), vitamin D levels, and thyroid function tests.

- CK level should be assessed prior to the EMG study. In most cases of s-IBM, serum CK level is normal or elevated to a mild-to-moderate degree. Elevation greater than 12 times normal may occur but is rare.
- If polyneuropathy is present based on clinical or electrodiagnostic criteria, then screening for diabetes mellitus and other potential etiologies for a polyneuropathy should be performed.
- Myositis-specific antibodies occur more rarely in s-IBM than in DM or PM, but when present, they may identify a subgroup of immunosuppressive treatment-responsive patients.<sup>78</sup>

## Imaging Studies

- CT or MRI imaging of muscles may be useful in helping diagnose difficult cases. Findings involve selective atrophy of the quadriceps and forearm flexors.<sup>79,80</sup>

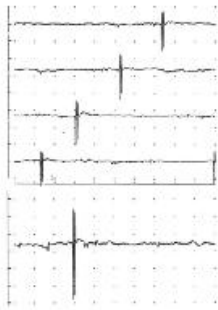
## Other Tests

- Although not routinely indicated, quantitative sensory testing showed abnormal vibratory, thermal, and heat pain thresholds in more than one half of patients with s-IBM in one small series.<sup>81</sup>
- Nerve conduction studies
  - Motor conductions should be performed in at least one lower and one upper extremity.
  - Sensory conductions should include at least one lower and one upper extremity nerve.
- Needle electrode examination
  - A full discussion of electrodiagnostic approaches to myopathy is beyond the scope of this article. The reader is referred to a more extensive discussion. Pictures of some needle electrode examination findings are given at the end of the article.
  - The needle electrode examination aims at demonstrating the presence of a diffuse myopathic process. Conversely, the assumption should not be made that all muscles are affected equally (ie, side-to-side asymmetry, proximal versus distal muscle).
  - The presence of a polyneuropathy on nerve conduction studies should prompt caution in interpretation since 2 different processes may be occurring simultaneously (eg, denervation/reinnervation and myopathy).
  - Therefore, the study's focus should be primarily on weak proximal muscles in 3 extremities, where changes in the MUAPs would most likely reveal changes consistent with a myopathic process. The muscle to be biopsied should be avoided in the needle electrode examination.
  - Insertional activity is variable (ie, normal or mildly increased) but does not show the prominent, complex, repetitive, or myotonic discharges occasionally seen in polymyositis.
  - Spontaneous activity is present in the form of fibrillation potentials or positive sharp waves. In chronic cases, these may be low in amplitude and infrequent or absent.
  - In s-IBM, the MUAPs may be variable in shape and size within the same muscle.



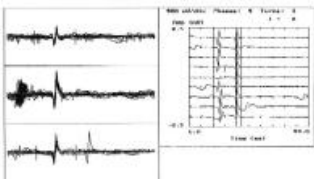
Composite of 20 motor unit action potentials (MUAPs) recorded with a concentric needle electrode from the biceps brachii of a patient with s-IBM. Note the wide range in size and complexity in the MUAPs. Copyright, Paul E Barkhaus, MD, 2000, with permission.

- The MUAPs typically show normal to reduced amplitude—reduced duration for simple (nonpolyphasic) MUAPs and variable increase in complexity (phases and turns). When assessing duration, only simple MUAPs should be measured so as to increase diagnostic sensitivity.
- Increase in complexity (eg, increases in phases, turns, or the presence of late components or satellites) is a nonspecific finding and may be seen as an early abnormal finding in neurogenic or myopathic processes.
- Occasional MUAPs in s-IBM may appear "enlarged" or high amplitude. Careful assessment shows that these are narrow spikes with minimal area.



Top - A large, complex motor unit action potential (MUAP; 5 phases, approximately 2500 microV amplitude and 3 ms duration) firing at a progressively increasing rate (ie, shifting left) at about 13 Hz in apparent isolation. In normal muscle, other motor units typically would be recruited at this threshold (calibration 500 microV/division vertical; 10 ms/division horizontal). In the bottom trace the sensitivity is increased to 100 microV/division vertical (no change in horizontal time base), showing very small motor unit action potentials (MUAPs) in the baseline on either side of the large MUAP. This phenomenon may give rise to a mistaken "neurogenic" impression of the MUAP, as these small potentials are overlooked easily or mistaken for baseline noise or fibrillation potentials. Note also that despite the large amplitude of this MUAP, the spikes include essentially no area, giving them a needle-like appearance. Copyright, Paul E Barkhaus, MD, 2000, with permission.

- In s-IBM, MUAPs are generally stable. In other words, jitter typically is not increased.



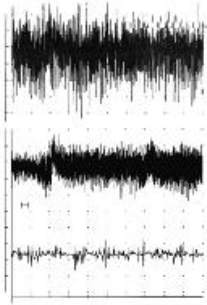
On the left are 3 motor unit action potentials (MUAPs) that have been "captured" from the same site and analyzed using a computer-assisted method. Note that the middle one has a satellite or "early" potential linked to it, characterized by the blackened/blurred area created by their superimposition to the left of the main portion of the MUAP. The reason for this is the increased variability in the interpotential interval on successive sweeps (ie, increased jitter). On the right, this middle MUAP is displayed in faster mode (9 sweeps). Note that on the fifth trace, the early component is absent, indicating a block. This shows the infrequent phenomenon in s-IBM of increased jitter and blocking, Copyright, Paul E Barkhaus, MD, 2000, with permission.

Table 2. MUAP Features in Myopathy

Open [table in new window](#)

Condition	Changes in MUAP Features
Nonspecific abnormality	Increased complexity (ie, phases, turns, late components) Only amplitude reduced
Specific for myopathy	Shortened duration (simple or nonpolyphasic MUAPs) Area reduced

- Recruitment of MUAPs is "early" in myopathic processes. This is interpreted as a more rapid recruitment of motor units for level of effort. Thus, discharging motor units appear to be firing faster and interference pattern (ie, pattern at full effort) appears full but reduced in amplitude.



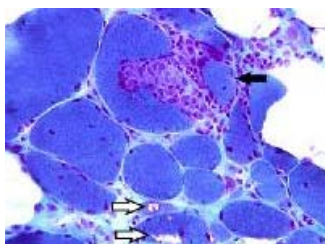
Interference pattern in biceps brachii. Top trace - Normal interference pattern at full effort (calibration - 500 microV/division vertical; 1 s/division horizontal). The middle trace is an interference pattern from a patient with severe s-IBM (calibration - 100 microV/division vertical; 1 s/division horizontal). This epoch of signal actually shows the patient going from minimal activation at the left (beginning of the sweep) to full effort on the far right. The "notch" just to the right of the second division mark shows a baseline shift from needle electrode movement. Overall, no amplitude change of "fullness" is seen going from minimal to full effort, and the amplitude of the signal epoch is less than half of what might be expected in normal muscle. The bottom trace is an expanded segment showing interference pattern from biceps brachii; this trace is from a patient with advanced s-IBM (calibration - 100 microV/division vertical; 10 ms/division horizontal), from the early or far left portion of the middle sweep (see "H" bar position between the middle and lower sweeps). This shows a relatively full baseline of small-amplitude, complex motor unit action potentials (MUAPs). Copyright, Paul E Barkhaus, MD, 2000, with permission.

## Procedures

- [Muscle biopsy](#) is the criterion standard for ascertaining the diagnosis of s-IBM.
- Selection of muscle to be biopsied
  - Findings may be patchy. Therefore, care must be taken in the preparation and examination of sufficient tissue to avoid sampling error.
  - The biopsy sample should be taken from a muscle that is affected moderately (ie, Medical Research Council grade 4 to 4 minus), yet one that is conventionally examined (eg, quadriceps, deltoid, biceps brachii). A severely atrophied, "end-stage" muscle should be avoided.
  - Beyond establishing electrodiagnostic evidence for a myopathic process, the needle electrode examination may be used to determine which muscle would be optimal for biopsy based on electrodiagnostic findings. However, the biopsy sample should not be taken directly from the site of the needle electrode insertion to avoid artifact directly related to changes in the muscle due to insertion of the needle electrode.
  - Polyneuropathy may be present in a number of cases; thus, the sampling of distal muscles should be avoided. Nerve biopsy generally is not indicated in the evaluation of s-IBM.

## Histologic Findings

- Muscle biopsy sample shows myopathic changes with varying degrees of inflammation, predominantly within the endomysium.
- The inflammatory infiltrates consist mainly of T cells and macrophages, which focally surround and invade nonnecrotic MFs.



Modified Gomori trichrome stained section showing (1) 2 muscle fibers (MFs)

containing intracytoplasmic vacuoles (open arrows) and (2) mononuclear inflammatory infiltrates invading a nonnecrotic MF (solid arrow). Copyright, Isabel P Collins, MD, 2000, with permission.

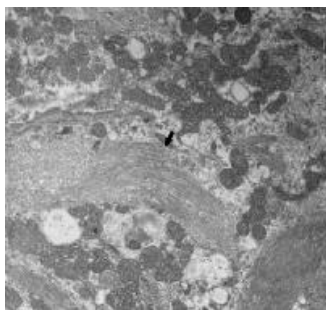
- Fiber size variability is increased with atrophic fibers consisting of both small rounded and angular MFs. Hypertrophied fibers are seen as well.
- Scattered fiber necrosis and regeneration are typically seen.
- The presence of rimmed vacuoles is a characteristic feature of s-IBM. The vacuoles occur singly or in multiples and are either subsarcolemmal or centrally located. These also may be seen in other conditions, such as inherited distal myopathies and oculopharyngeal muscular dystrophy (see [Table 1](#) in Other Problems to be Considered).
- Ragged red fibers and cytochrome C-oxidase (COX) negative fibers are frequently observed to a greater degree than is expected with age.
- Sections stained with Congo red and examined under polarized light demonstrate amyloid as apple green birefringent deposits within MFs.



Congo red-stained section showing apple green birefringent amyloid deposits within muscle fibers (MFs) (arrow). The MF on the right side of the section is focally surrounded and invaded by inflammatory cells. Courtesy of Jerry R Mendell, MD.

If amyloid deposits are not seen with this method, fluorescent technique should be used as an alternate means to detect amyloid. The amyloid deposits tend to occur adjacent to vacuoles and are wispy or plaquelike in appearance. Examination under high power (X40 objective) is often required.<sup>82</sup>

- MHC-1 upregulation is reported in as much as 100% of biopsy specimens and, though nonspecific, it may be helpful in distinguishing s-IBM from noninflammatory conditions.
- Immunohistochemical staining for phosphorylated neurofilament (SMI-31) has been recommended as alternative to electron microscopy.
- Electron microscopy shows intranuclear and intracytoplasmic 15- to 21-nm tubulofilaments. In contrast, oculopharyngeal dystrophy has 8- to 11-nm intranuclear tubulofilaments as a specific marker.



Electron micrograph showing characteristic 15- to 18-nm tubulofilaments (arrow). Copyright, Isabel P Collins, MD, 2000, with permission.

- Proposed morphologic criteria for diagnosis of s-IBM (adapted from Griggs et al)<sup>83</sup>
- Inflammatory myopathy with endomysial mononuclear cell infiltration and invasion of non-necrotic MFs
- Vacuolated MFs
- Intracellular amyloid deposits, 15- to 21-nm nuclear and cytoplasmic tubulofilaments on electron microscopy, or positive SMI-31 staining.
- Recent studies have shown that TDP-43, a nucleic acid binding protein normally located predominantly in

myofiber nuclei, is found in IBM muscle sarcoplasm. TDP-43 immunoreactivity was noted to be more frequent than other biomarkers of IBM, with high sensitivity and specificity for the disease.<sup>84</sup>

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## Inclusion Body Myositis: Treatment & Medication

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### Treatment

#### Medical Care

No definitive treatment has been proven effective for s-IBM.

Early anecdotal reports documented the failure of patients to respond to steroids, methotrexate, azathioprine, and cyclophosphamide. Subsequent clinical studies of various immunosuppressive or immunomodulatory therapies have largely been disappointing. Individual responses, functional improvement, or mild regional improvement in strength have been reported, but sustained remission and improvement in whole-body strength have not been demonstrated.

- An open-label study of high-dose prednisone in 8 patients showed no improvement in strength or functional disability scores despite a decrease in creatine phosphokinase (CPK) and inflammatory cell infiltration. Posttreatment muscle biopsy samples showed increased vacuole formation and amyloid deposition, suggesting that mechanisms other than the inflammatory response play a role in disease propagation.<sup>85</sup>
- A randomized, controlled study of oxandrolone in 19 patients reported a regional improvement in upper extremity strength, but only borderline improvement in whole-body strength.<sup>86</sup>
- A randomized, controlled study of methotrexate in 44 patients likewise showed no improvement in strength despite a significant decrease in CPK levels.<sup>87</sup>
- An early small, uncontrolled study reported improvement in strength in 4 patients following intravenous immunoglobulin (IVIg) treatment.<sup>88</sup> However, subsequent larger and placebo-controlled studies have failed to duplicate these results.<sup>89, 21, 90</sup> Two studies suggest some benefit in patients with severe dysphagia.<sup>91, 92</sup> A subsequent controlled study of IVIg in combination with prednisone likewise showed no treatment response despite a reduction in endomysial inflammation.<sup>93</sup>
- An open-label, randomized study of anti-T-lymphocyte globulin treatment followed by 12 months of oral methotrexate (vs methotrexate alone) reported regional improvement in distal upper extremity strength, but continued deterioration of the proximal muscle groups.<sup>94</sup>
- Beta interferon-1a at standard (30 µg IM/wk) and high-dosage (60 µg IM/wk) regimens were found to be well tolerated but produced no significant improvement in muscle strength or muscle mass.<sup>95, 96</sup>
- A pilot trial of etanercept, a tumor necrosis factor (TNF) alpha blocker, did not show significant benefit in composite muscle strength scores at 6 months. However, with 12 months of treatment, slight improvement in grip strength was noted.<sup>97</sup>

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- A study of alemtuzumab, a T-cell-depleting monoclonal antibody, involved 13 patients who underwent infusion of 0.3 mg/kg/d for 4 days. It reported slowed disease progression, improvement of strength in some patients, and reduction in endomysial inflammation.<sup>98</sup> This preliminary study holds promise for future studies.
- Follistatin, an antagonist of the myostatin pathway, has been shown to produce a dramatic increase in muscle mass in animals.<sup>99</sup> These results are promising for future gene therapy trials to improve muscle mass in patients with neuromuscular disease.
- Arimoclomol, a heat shock protein (HSP) coinducer may slow down the process of protein misfolding and aggregation. A study of its safety and efficacy in IBM is underway.
- Lithium is an inhibitor of the glycogen synthase kinase (GSK) enzyme, the latter of which is involved in the development of phosphorylated tau (p-tau). A study is being conducted to examine its efficacy in slowing muscle degeneration in IBM.
- Empiric therapies include coenzyme Q10, carnitine, and antioxidants. They may provide benefit to some patients, but, to date, none of these has been studied in a controlled clinical trial.
- Routine follow-up visits at intervals contingent upon the progression and severity of involvement are indicated to assess the patient's strength, tolerance of exertion, and compromise in occupation or activities of daily living. Hicks has outlined a strategy for care of patients with inflammatory myopathies, including s-IBM.<sup>100</sup>

## Surgical Care

- Muscle biopsy is performed for diagnosis.
- Severe dysphagia may require cricopharyngeal myotomy or placement of a gastrostomy tube. Chemodenervation with [botulinum toxin A injection](#) into the upper esophageal sphincter has also been shown to be of benefit.<sup>101</sup>

## Consultations

- Depending on degree of weakness, input from physical therapy or physiatry may be useful in optimizing the patient's abilities.
- If dysphagia occurs, referral to a speech therapist would be of benefit for instruction regarding swallowing techniques and aspiration precautions. In patients with severe dysphagia, referral to ear, nose, and throat (ENT) specialist is indicated for consideration of botulinum toxin injections or [cricopharyngeal myotomy](#).

## Diet

No dietary modification is required in most cases unless symptomatic dysphagia occurs.

## Activity

Appropriate activity level depends on the condition of the patient.

Strength training and exercise regimens have been subjects of debate, given concerns that physical activity might instigate increased muscle breakdown and inflammation. However, 3 recent studies have shown that an exercise program can be instituted safely.<sup>102,81,103</sup> In the study by Arnardottir, 6 of 7 patients reported a subjective positive effect on muscle function after a 12-week exercise regimen.<sup>81</sup> No improvement or deterioration in strength was observed, and no increase in inflammation was noted in pretreatment and posttreatment muscle biopsy specimens. In the study by Johnson, 7 patients underwent a combined aerobic and functional exercise regimen.<sup>103</sup> The patients exhibited improved aerobic and functional exercise capacity and strength without significant increase in creatine kinase.

## Medication

Different immunosuppressive treatment regimens have been reported (see [Treatment/Medical Care](#)). The general consensus is that none of these treatments has proven benefits.

Despite lack of responsiveness to treatment, patients may be offered a trial of steroids in the hope of at least slowing progression, but this is controversial (see [Prognosis](#)). Given the variety of empiric treatment protocols, the reader is referred directly to these reports for details.

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## Inclusion Body Myositis: Follow-up

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### Follow-up

#### Further Outpatient Care

- Frequency of follow-up visits is contingent upon the patient's rate of progression and need for symptom control as described above.

#### Complications

- Complications include, but are not limited to, the following:
  - Risk of falls may be assessed best by a physical therapist.
  - If the patient's ability to perform his or her job is questioned, a functional or physical capacity evaluation may be appropriate. This typically is performed through physical therapy or a rehabilitation center. Patients are understandably reluctant to surrender their independence in function. However, patients must not be a danger to themselves or others, whether at their employment or in their activities of daily living.
  - If the patient's ability to operate a motor vehicle is of concern, then this should be noted in the chart and the patient should be advised to seek further evaluation, either through formal assessment at a rehabilitation center or through their local driving licensing authority. Certification for disabled parking should be made when appropriate.

#### Prognosis

- The course of s-IBM is variable but is typically one of slow progression.
- Mean decrease in muscle strength over time was reported to be 15.6% per year in one retrospective study<sup>64</sup> and 7.8% per year in a more recent prospective study.<sup>104</sup>
- Patients with an earlier age of onset tend to have a slower rate of progression than those with onset after age 60 years.<sup>60, 105</sup>
- The mean time between symptom onset and walker use is 10.2 ± 5.8 years in patients with disease onset before 60 years and 5.7 ± 5.0 years in those with disease onset after age 60 years. The wide range reported reflects a significant variability between individuals.

#### Patient Education

- Physician education of patients
  - The treating physician must maintain an ongoing dialogue with patients to keep them informed

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about the status of their disease.

- o While patient issues should be addressed as needed, the physician must be proactive and anticipate issues such as difficulties with driving.
- o The treating physician always should maintain a balance between the reality of the patient's disease progression and a sense of hope and ability for the patient to cope with the disease.
- Information resources for patients
  - o [The Myositis Association](#) provides information on polymyositis, dermatomyositis, and s-IBM.  
Address: 1737 King St, Suite 600; Alexandria, VA 22314  
DC area phone: 703-299-4850  
Toll-free phone: 800-821-7356

## Miscellaneous

### Medicolegal Pitfalls

- In the authors' experience, patients are not often misdiagnosed with s-IBM; the reverse is more likely. The typical scenario is a patient with presumed inflammatory myopathy (ie, polymyositis) who is treated with standard immunosuppressive therapies to no avail. Repeat MBx ultimately may show findings indicative of s-IBM. Whether this represents a true "evolution" in the disease process or a sampling error is not certain (see [Table 1](#) in Other Problems to be Considered). In this instance, the s-IBM patient usually receives the benefit, however dubious, of a trial of immunosuppressive medication.
- Issues regarding employment and driving are covered in [Complications](#).

### Acknowledgments

- Dr. Barkhaus acknowledges support in part from the Department of Veterans Affairs.
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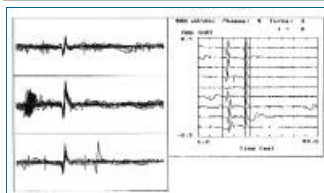
Media file 1: Composite of 20 motor unit action potentials (MUAPs) recorded with a concentric needle electrode from the biceps brachii of a patient with s-IBM. Note the wide range in size and complexity in the MUAPs.

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Media file 2: Top - A large, complex motor unit action potential (MUAP; 5 phases, approximately 2500 microV amplitude and 3 ms duration) firing at a progressively increasing rate (ie, shifting left) at about 13 Hz in apparent isolation. In normal muscle, other motor units typically would be recruited at this threshold (calibration 500 microV/division vertical; 10 ms/division horizontal). In the bottom trace the sensitivity is increased to 100 microV/division vertical (no change in horizontal time base), showing very small motor unit action potentials (MUAPs) in the baseline on either side of the large MUAP. This phenomenon may give rise to a mistaken "neurogenic" impression of the MUAP, as these small potentials are overlooked easily or mistaken for baseline noise or fibrillation potentials. Note also that despite the large amplitude of this MUAP, the spikes include essentially no area, giving them a needle-like appearance.

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Media file 3: On the left are 3 motor unit action potentials (MUAPs) that have been "captured" from the same site and analyzed using a computer-assisted method. Note that the middle one has a satellite or "early" potential linked to it, characterized by the blackened/blurred area created by their superimposition to the left of the main portion of the MUAP. The reason for this is the increased variability in the interpotential interval on successive sweeps (ie, increased jitter). On the right, this middle MUAP is displayed in faster mode (9 sweeps). Note that on the fifth trace, the early component is absent, indicating a block. This shows the infrequent phenomenon in s-IBM of increased jitter and blocking, Copyright, Paul E Barkhaus, MD, 2000, with permission.

Media file 4: Interference pattern in biceps brachii. Top trace - Normal interference pattern at full effort (calibration - 500 microV/division vertical; 1 s/division horizontal).

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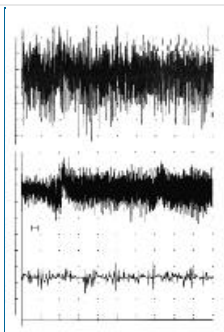
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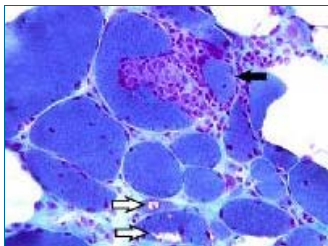
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The middle trace is an interference pattern from a patient with severe s-IBM (calibration - 100 microV/division vertical; 1 s/division horizontal). This epoch of signal actually shows the patient going from minimal activation at the left (beginning of the sweep) to full effort on the far right. The "notch" just to the right of the second division mark shows a baseline shift from needle electrode movement. Overall, no amplitude change of "fullness" is seen going from minimal to full effort, and the amplitude of the signal epoch is less than half of what might be expected in normal muscle. The bottom trace is an expanded segment showing interference pattern from biceps brachii; this trace is from a patient with advanced s-IBM (calibration - 100 microV/division vertical; 10 ms/division horizontal), from the early or far left portion of the middle sweep (see "H" bar position between the middle and lower sweeps). This shows a relatively full baseline of small-amplitude, complex motor unit action potentials (MUAPs). Copyright, Paul E Barkhaus, MD, 2000, with permission.

[\(Enlarge Image\)](#)



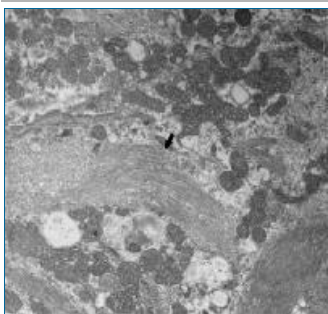
Media file 5: Modified Gomori trichrome stained section showing (1) 2 muscle fibers (MFs) containing intracytoplasmic vacuoles (open arrows) and (2) mononuclear inflammatory infiltrates invading a nonnecrotic MF (solid arrow). Copyright, Isabel P Collins, MD, 2000, with permission.

[\(Enlarge Image\)](#)



Media file 6: Congo red-stained section showing apple green birefringent amyloid deposits within muscle fibers (MFs) (arrow). The MF on the right side of the section is focally surrounded and invaded by inflammatory cells. Courtesy of Jerry R Mendell, MD.

[\(Enlarge Image\)](#)



Media file 7: Electron micrograph showing characteristic 15-to-18-nm tubulofilaments (arrow). Copyright, Isabel P Collins, MD, 2000, with permission.

[\(Enlarge Image\)](#)

## More on Inclusion Body Myositis

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