Sporadic inclusion body myositis (sIBM) is but one of the inflammatory myopathies. The inflammatory myopathies are characterized by varying degrees of muscle weakness in the setting of endomysial inflammation and elevations in creatine kinase.\(^1\) sIBM is the most common inflammatory myopathy in people older than 50 years.\(^2\) The term \textit{sporadic} inclusion body myositis is used here to distinguish it from \textit{hereditary} inclusion body myopathy (hIBM), which is a distinct disorder that is not associated with muscle inflammation and presents with a different distribution of weakness. hIBM is not discussed in this article. The interested reader may find it useful to read a review by Askanas and Engel.\(^3\)

For the sake of simplicity, the remainder of this article uses the term inclusion body myositis (IBM) to mean sporadic inclusion body myositis. This review focuses on the clinical presentation of IBM, and discusses its pathogenesis and treatment options.

**EPIDEMIOLOGY**

Relatively few studies have looked at the epidemiology of IBM. The prevalence of IBM in the Netherlands is 4.9 cases per million inhabitants.\(^4\) In Australia, it is reported at 9.3 cases per million inhabitants.\(^5\) In a study population of 9 Caucasian individuals diagnosed with IBM in Olmsted County, Minnesota, researchers estimated the incidence of IBM, adjusted for sex and age to the 2000 US Census population, at 7.9 cases per million inhabitants.\(^6\) In the same study, they estimated the prevalence to be 70 cases per million inhabitants.\(^6\) However, the epidemiology of IBM in non-Caucasian populations is far different. In a study of Mesoamerican, self-classified mestizos, no cases of IBM were reported among the 98 adults diagnosed with an idiopathic inflammatory myopathy.\(^7\)
Differences in worldwide distribution of IBM may be related to genetic or environmental factors. Genetic susceptibility studies have found a strong association between IBM and HLA-DR3 (up to 75% of IBM cases in certain populations). The 8.1 MHC ancestral haplotype (a conserved combination of alleles including HLA-A*01, -B*0801, -DRB1*0301, -DQB1*0201, -DQA1*05) is also associated with IBM in Australian, Dutch and North American white populations. In Japanese individuals, IBM appears to be related to the 52.1 ancestral haplotype (which includes HLA-B*5201 and HLA-DRB*1502). Therefore, although a genetic linkage is evident, more studies are necessary to better understand the role of genes in IBM.

**CLINICAL FEATURES**

IBM tends to primarily affect individuals older than 50 years, but it should be considered in patients with appropriate symptoms who are older than 30. It is more common in men than women. The disease presents insidiously, with a reported mean time to diagnosis ranging from 1 to 9 years. IBM characteristically presents with quadriceps and forearm flexor (especially the flexor digitorum profundus) weakness. Quadriceps and forearm atrophy may be seen as the presenting feature. A finding that helps distinguish IBM from other inflammatory myopathies, such as dermatomyositis and polymyositis, is an asymmetric distribution of weakness.

Lower extremity complaints come typically in the form of difficulty arising from chairs, and walking upstairs or downstairs. As the disease progresses, lower extremity weakness leads to frequent falls. Although one can conclude that falls in IBM patients occur as a result of proximal muscle weakness, distal lower extremity weakness occurs as well. In fact, foot drop is a recognized feature of IBM.

Upper extremity weakness manifests as difficulty with fine motor skills, including buttoning buttons, zipping zippers, or opening jars, given the finger flexor weakness found in this disorder. Some clinicians note that a weak handshake (suggestive of weakness of grip) may be a clue to the diagnosis.

Dysphagia, caused by esophageal and pharyngeal muscle involvement, is reported in anywhere from 40% to 60% of patients. It may even be the presenting symptom. Dysphagia in IBM is reported to affect nutrition in some, but not all patients. Some groups have noted that dysphagia is underreported by patients. Other muscle groups may be affected in IBM. Facial weakness occurs in about one-third of cases. Unusual presentations of IBM have also been reported, including involvement of only the erector spinae muscles.

Peripheral neuropathy may be found on clinical neurophysiological testing. In a series of 12 patients with IBM, morphometric studies of sural nerve biopsies demonstrated varying reductions in myelinated fibers indicative of a neuropathic process. However, the neuropathy observed in patients with IBM is largely asymptomatic. Comorbid autoimmune diseases, such as systemic lupus erythematosus, Sjögren syndrome, scleroderma, and variable immunodeficiency have been reported in IBM patients.

In general, IBM is a slowly progressive disease. In a prospective study by Rose and colleagues of 11 IBM patients, quantitative strength testing demonstrated a 4% decline over 6 months. However, the investigators reported that 4 of their 11 patients demonstrated no change. In a retrospective trial, the rate of functional decline of patients, measured by time to use of an assistive device, was faster in those patients diagnosed after age 60 years compared with those diagnosed when they were younger.
LABORATORY FINDINGS

Elevations in creatine kinase (CK) are common, but they are generally less than 12 times the upper limit of normal. Autoantibodies associated with myositis are usually not found in IBM patients. Paraproteinemia is overrepresented in IBM patients when compared with age-matched controls.

ELECTRODIAGNOSTIC FINDINGS

Electromyographic study of IBM patients demonstrates increased insertional activity and short-duration, polyphasic motor unit potentials (MUAPs) with early recruitment. In one series of 30 patients with biopsy-proven IBM, about a third of the patients demonstrated a mixed pattern of what are commonly referred to as “neurogenic” and “myopathic” MUAPs. Some authorities ascribe these “neurogenic” potentials to a secondary process. As previously noted, nerve conduction studies in IBM patients are consistent with a superimposed peripheral neuropathy.

DIAGNOSIS

IBM presents insidiously and manifests with atrophy of forearm and quadriceps muscles. These findings, along with electrodiagnostic and pathologic findings, have been used to establish diagnostic criteria. One set of criteria were put forth by Griggs and colleagues. More recently, modified IBM criteria were posed during an IBM workshop by the MRC Center for Neuromuscular Diseases. The purpose of modifying the criteria was to help in the diagnosis of patients who clinically appear to have IBM but do not have the pathologic criteria set forth by earlier groups. One should note that both sets of proposed criteria do not include the use of radiographic studies. Magnetic resonance imaging (MRI) of muscle in IBM patients demonstrates involvement of the quadriceps femoris and the medial gastrocnemius along with forearm flexors (especially the flexor digitorum profundus). Some believe that MRI is of limited diagnostic value, as quantitative muscle testing revealed weakness in muscles that did not have signal changes on MRI.

The most helpful diagnostic test of IBM is muscle biopsy. Which muscle to biopsy depends on the clinical presentation. A good rule of thumb is to avoid muscles that are at or are less than antigravity strength, as the biopsy will most likely show fibrosis. Because IBM tends to affect the quadriceps muscles, a muscle often biopsied is the vastus lateralis. However, if the muscle is too atrophied, other muscles including the biceps brachii, deltoid, or even the tibialis anterior can be biopsied. The specific findings seen on muscle biopsy are discussed at greater length in the histopathology section of this review.

DIFFERENTIAL DIAGNOSIS

Perhaps the most common misdiagnosis of a patient with IBM is polymyositis. The error stems partially from the misinformed notion that elevations in CK accompanied by muscle weakness are characteristics only of polymyositis. As stated previously, the pattern of muscle involvement can help guide a clinician toward the right diagnostic path. It is important to mention that the characteristic findings of IBM are not always seen on muscle biopsy. In the authors’ experience it is not uncommon to receive a patient’s muscle pathology report with a diagnosis of “polymyositis” when clinically the patient appears to have IBM.

Given the “neurogenic” findings seen on electrodiagnostic studies along with the asymmetric distribution of weakness, amyotrophic lateral sclerosis (ALS) is in the
differential for IBM. Important features of ALS that help to distinguish it from IBM are hyperreflexia, severe dysphagia, fasciculations, and cramping. Furthermore, atrophy in ALS tends to affect intrinsic muscles of the hand, the so-called split-hand syndrome,\textsuperscript{29} rather than the deep finger flexors.

As briefly mentioned in the introduction, hIBMs are a group of inherited, usually noninflammatory myopathies that affect distal musculature and share some common pathologic characteristics with IBM (mainly vacuolar changes on muscle biopsy).\textsuperscript{3}

Rimmed vacuoles on muscle biopsy of patients with IBM are not specific to the disease. Vacuolar changes are seen in a variety of muscle disorders including oculopharyngeal muscular dystrophy, oculopharyngodistal myopathy, distal myopathy with rimmed vacuoles, inclusion body myopathy, and myofibrillar myopathy.\textsuperscript{30,31} More recently, rimmed vacuoles have been reported in a case series of patients with facioscapulohumeral muscular dystrophy.\textsuperscript{32} There is at least one case report of rimmed vacuoles in a case of dermatomyositis.\textsuperscript{33}

**HISTOPATHOLOGY**

A “definite” diagnosis of IBM includes finding particular abnormalities on muscle biopsy.\textsuperscript{11} Features seen include: (1) mononuclear cell invasion of non-necrotic endomysial fibers; (2) intracellular amyloid deposits seen with Congo Red staining.
techniques; (3) eosinophilic intracytoplasmic inclusions; (4) rimmed vacuoles; and (5) loss of cyclooxygenase (COX) staining of certain fibers.8

Immunohistochemical staining of IBM muscle demonstrates that mononuclear infiltrates are composed of CD8+ T cells.34 MHC-1 expression in muscle fibers is also a feature of IBM muscle pathology.8 Myeloid rather than plasmacytoid dendritic cells are reported to surround non-necrotic areas in affected muscle fibers.35 These findings suggest a role for adaptive immunity in the pathophysiology of IBM. It is interesting that through immunohistochemical techniques, using markers for CD138, plasma cells have been reported in muscle biopsies of IBM patients.36

Rimmed vacuoles, round or polygonal structures that are surrounded by a basophilic rim on hematoxylin-eosin stains (Fig. 1), are a feature of IBM muscle. The make-up of these structures is of interest. Nuclear membrane proteins, including emerin and lamin A/C, are reported to line these structures.37,38 Other myonuclear-associated structures such as histone-138 and valosin-containing protein39 are also found in the lining of rimmed vacuoles. Immunostaining for TDP-43, a nucleic acid binding protein, is reported to yield an abnormal distribution in the cytoplasm of IBM muscle.40 In fact, Salajegheh and colleagues40 reported that more than 1% of myofibers stained for TDP-43 outside of the nucleus, and they were 91% sensitive and 100% specific for the diagnosis of IBM in their study of 50 patients.

Cytoplasmic inclusions are another feature of muscle affected by IBM. Inclusions are reportedly seen by stains for ubiquitin.41 The use of an antibody directed against phosphorylated tau (SMI-31) has been reported to help visualize cytoplasmic inclusions that are not otherwise seen by light microscopy (see Fig. 1).42

At specialized centers, electron microscopy can help in the diagnosis of IBM. The cytoplasmic inclusions reported to stain with the SMI-31 antibodies are seen as 15- to 21-nm paired helical filaments or tubulofilaments.42 Other ultrastructural findings of IBM muscle include 6- to 10-nm amyloid-like filaments.11

PATHOGENESIS

Despite years of dedicated research, the pathogenesis of IBM remains unknown. Immunohistochemical studies as well as ultrastructural studies have yielded postulated mechanisms for the pathogenesis of IBM. Some of the findings point toward an immune-mediated cause, whereas others may indicate a degenerative process.

**Fig. 1.** Selected microscopic fields from muscle biopsy of a patient with IBM. In (panel A) muscle is stained with hematoxylin and eosin. The white arrow points to a rimmed vacuole. The white arrowhead is directed at the mononuclear endomysial inflammatory infiltrates. The (panel B) demonstrates lower field demonstrates a muscle fiber stained with SMI-31. It shows aggregates surrounding rimmed vacuoles (black arrowhead), as well as aggregates scattered within the muscle fiber. (Courtesy of Katherine Lindstrom, MD.)
The presence of CD8⁺ T cells invading non-necrotic fibers has prompted some investigators to think of IBM as a primarily immune-mediated disorder.⁴³,⁴⁴ Evidence supportive of this hypothesis includes identification of clonally expanded T cells in invaded myofibers.⁴⁵ Furthermore, electron microscopy studies demonstrate that invasion of non-necrotic muscle fibers by T cells occurs more frequently than other pathologic hallmarks of the disease, such as rimmed vacuoles and congophilic amyloid inclusions.⁴⁶ Upregulation of inducible costimulator and its ligand add credence to the role of muscle fibers acting as antigen-presenting cells in the pathogenesis of IBM.⁴⁷ This opinion is further supported by the finding of myeloid dendritic cells, which serve as antigen-presenting cells, in tissue samples of IBM affected muscle.⁴⁵ The role of plasma cells, identified in IBM affected muscle via microarray studies, is also suggestive of a possible immune-mediated mechanism.⁴⁶ Furthermore, there is evidence suggestive of a humoral antigen-driven response in tissue samples from IBM patients.⁴⁸ The importance of the overrepresentation of paraproteinemias in IBM patients is also of unclear significance.²⁵

The lack of clinical response, despite reduced evidence of inflammation, to immunomodulatory therapy⁴⁹ argues against IBM as a primarily immune-mediated disease. The lack of clinical response to immunomodulatory therapies has been replicated by many groups.⁴⁹–⁵¹

The degenerative pathogenesis model of IBM stems from the identification of protein aggregates (beta-amyloid, phosphorylated tau, presenilin, and parkin, among others) often associated with other neurodegenerative diseases.⁵²–⁵⁴ These aggregates are postulated to occur due to protein misfolding, thus leading to accumulation of aberrant proteins.⁵³ Protein accumulation is thought to lead to failure of cellular processes geared toward disposing of misfolded proteins.⁵⁴ The postulated mechanisms that falter are the 26 S proteasome system, various heat shock proteins, and disturbances in autophagy.⁵⁴–⁵⁶ Proponents of this theory postulate that the inflammatory changes seen are secondary to aberrant protein accumulation. Critics of the postulated degenerative theories note the lack of critically supported data that demonstrate the presence of phosphorylated tau in IBM muscle specimens.⁵⁷

Links between the mainly immune-mediated and the mainly degenerative theories exist. Colocalization between the proinflammatory cytokine 1LB and the amyloid precursor protein in IBM muscle⁵⁸ suggests such a link. In a murine experimental model of inflammatory myopathy, researchers demonstrated evidence of inflammation leading to tau pathology.⁵⁹ However, other groups argue against such causal links.⁶⁰

The interplay between the two major theories regarding the pathogenesis of IBM remains highly debated. The role of mitochondrial DNA mutations, which occur with greater frequency in patients with IBM when compared with age-matched controls, may be a secondary finding.⁵¹ Myonuclear degeneration, as evidenced by the presence of myonuclear proteins in rimmed vacuoles,⁴⁰ and its role in the pathogenesis of inclusion body myositis is unclear. On a final note, there is a body of literature suggesting that viruses play a role, such as the human immunodeficiency virus, as possible agents in the pathogenesis of IBM.⁶²

**TREATMENT**

There are no proven pharmacologic treatments for IBM. Given the inflammatory infiltrates seen in IBM muscle, oral steroids have been used to treat the disease. In a series of 8 patients followed from 6 to 24 months, Barohn and colleagues⁴⁹ demonstrated reduced inflammatory infiltrates and levels of CK in patients but no improvements in
strength. The use of intravenous immunoglobulin (IVIg) has met with mixed results. Investigators report some improvement in dysphagia but no significant improvement in strength.\textsuperscript{6,51,63} The combination of prednisone and IVIg also proved to be ineffective.\textsuperscript{64} A randomized controlled trial of weekly methotrexate failed to demonstrate improvement.\textsuperscript{50}

Given the potential involvement of T lymphocytes in IBM, an open-label, randomized pilot study using Anti–T-lymphocyte globulin (ATG) was conducted, but failed to provide clear benefit.\textsuperscript{65} In a proof-of-principle trial, Dalakas and colleagues\textsuperscript{66} reported that patients’ strength improved 6 months after treatment with alemtuzumab (a humanized-monoclonal antibody against CD52) when compared with a pretreatment observation period. However, some concerns over the results have been raised by other investigators.\textsuperscript{67}

A pilot trial using the anti–tumor necrosis factor-\textalpha\ drug etanercept showed promise by demonstrating improved handgrip strength after 12 months.\textsuperscript{68} This study has prompted an ongoing double-blind, placebo-controlled trial of etanercept (see clinicaltrials.gov for details).

A randomized trial of high-dose beta interferon-1a (60 \textmu g intramuscularly, weekly) demonstrated significant improvement in grip strength. However, the study failed to show statistical significance in other measured outcomes.\textsuperscript{69}

Ongoing trials aimed at finding treatments for IBM include the aforementioned etanercept trial as well as a recently closed pilot trial studying the use of lithium (see clinicaltrials.gov). The rationale behind the use of lithium is that it serves as an inducer of autophagy, thereby improving clearance of misfolded proteins.\textsuperscript{70} Furthermore, in a transgenic mouse model of inflammatory myopathy treated with lithium for 6 months, animals demonstrated a trend toward improved motor performance, although results were not statistically significant.\textsuperscript{59} With the putative role of heat shock protein abnormalities playing a role in the pathogenesis of IBM, there is a trial of arimoclomol, a heat shock protein inducer, for the treatment of IBM (see clinicaltrials.gov).

**SUMMARY**

IBM is the most common acquired myopathy in people older than 50 years. It typically presents with knee extensor and finger flexor weakness. Asymmetric weakness is not unusual. Associated clinical findings include distal lower extremity weakness and dysphagia. The diagnosis of IBM is made with the aid of muscle pathology, but the clinical impression is very important, as widely accepted pathologic hallmarks are neither always present nor specific to the disease. The pathogenesis of IBM remains unclear. Pharmacotherapy for this condition has not proved to be efficacious.

**REFERENCES**


