Inclusion Body Myositis

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ABSTRACT

PURPOSE OF REVIEW: **This article highlights the clinical and diagnostic features of inclusion body myositis (IBM) and provides recent insights into the pathomechanisms and therapeutic strategies of the disease.**

RECENT FINDINGS: **IBM is an often-misdiagnosed myopathy subtype. Due to the insidious onset and slow progression of muscle weakness, it can often be dismissed as a sign of aging as it commonly presents in older adults. While challenging to recognize upon initial clinical evaluation, the recent recognition of specialized stains highlighting features seen on muscle pathology, the use of diagnostic tools such as the anti-cytosolic 5′-nucleotidase 1A antibody biomarker, and the ability of muscle imaging to detect patterns of preferential muscle involvement seen in IBM has allowed for earlier diagnosis of the disease than was previously possible. While the pathogenesis of IBM has historically been poorly understood, several ongoing studies point toward mechanisms of autophagy and highly differentiated cytotoxic T cells that are postulated to be pathogenic in IBM.**

SUMMARY: **Overall advancements in our understanding of IBM have resulted in improvements in the management of the disease and are the foundation of several strategies for current and upcoming novel therapeutic drug trials in IBM.**

INTRODUCTION

Affecting individuals over age 45 years, inclusion body myositis (IBM) is the most common acquired muscle disease of the aging population. The characteristic features of muscle weakness and atrophy often asymmetrically predominantly affect the quadriceps and finger flexors; however, as the disease progresses, all limb, facial, and diaphragmatic muscles may become involved in advanced cases. The disease is characterized by high disability and morbidity, often due to the weakness of the diaphragm and pharyngeal muscles, resulting in respiratory insufficiency, dysphagia, and risks of aspiration pneumonia. However, no proven therapy is known to effectively stop or even slow progression of the disease.

Published estimated prevalences of the disease have varied based on country, ranging from 33 to 182 per million[1,2]; however, since IBM often affects the older adult population, the symptoms of weakness may be attributed to aging, resulting in underrecognition and underreporting of the disease. Consequently, the true prevalence may be much higher. IBM is often initially misdiagnosed as

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polymyositis or another condition in 40% to 50% of patients, leading to a diagnostic delay of up to 5 years, with the average patient undergoing a diagnostic odyssey and unwarranted immunosuppressive therapies.[3] While features of both inflammatory and neurodegenerative processes are seen on histopathology the pathogenesis of the disease remains unclear, and thus far the disease has been refractory to standard immunotherapy. Several newer diagnostic studies may improve our understanding of the disease and aid in earlier recognition and diagnosis, thus reducing the risk of side effects due to unnecessary immunosuppression and increasing the potential for drug discovery, all of which are reviewed in this article.

CLINICAL FEATURES

Muscle weakness in IBM is insidious in onset, painless, and slowly progressive. Weakness is often attributed to and dismissed as a sign of aging, making it difficult to recognize in individuals over the age of 45 years. Some of the first symptoms often described are difficulty rising from a chair (requiring a push up from the armrest) or climbing stairs (requiring the assistance of a railing to pull themselves up), related to the quadriceps weakness that develops. Gait changes frequently occur, with high risk of falls due to knee buckling (secondary to quadriceps weakness) and tripping (from dorsiflexion weakness). Grip weakness or changes in fine coordination of the hands (manifested as difficulty buttoning, tying shoelaces, writing, or opening jars) result from the finger flexor weakness that progresses over time. Dysphagia, another underreported symptom that may be elicited upon direct questioning of the patient during the history, is initially characterized as a "stuck" sensation when swallowing pills, which progresses to choking and coughing, or even frank aspiration. While dysphagia is a self-reported symptom in 46% of patients with IBM, if formally evaluated through videofluoroscopy, it may be detected in up to 79% of these patients.[4] This discrepancy is important to note as complications from dysphagia are one of the leading causes of mortality in IBM.

On examination, notable asymmetric atrophy of the quadriceps (**FIGURE 5-1A**) and medial forearm flexors occurs, associated with knee extensor and

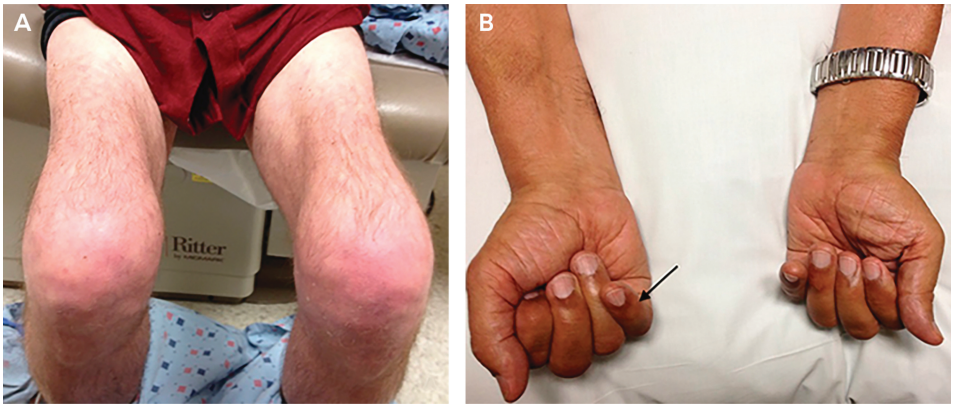

FIGURE 5-1

Clinical features of inclusion body myositis. *A*, Profound muscle atrophy seen on visual examination of the vastus lateralis and medialis muscles of both thighs. *B*, Asymmetric weakness of the deep finger flexors, most predominantly affecting the fifth digits (*arrow*), when attempting to make a fist.

wrist/finger flexor weakness, which can be disproportionately greater than that of the hip flexors and shoulder abductors. This pattern of muscle weakness associated with profound muscle atrophy helps distinguish the disease from other myositis subtypes such as polymyositis, dermatomyositis, and necrotizing myopathy. While frequently overlooked, a clinical pearl lies in the astute attention to the examination of the deep finger flexors or flexor digitorum profundus with detection of weakness in the flexion of the distal fingertips, often frequently involving the fifth digit (FIGURE 5-1B). Early in the disease, the flexor digitorum profundus muscle is disproportionately weaker than other hand muscles (including the flexor digitorum superficialis and interosseous and abductor pollicis muscles). This finding of flexor digitorum profundus weakness may alert the physician to a possible diagnosis of IBM over other subtypes of myositis or amyotrophic lateral sclerosis (ALS). Later in the disease course, both the deep and superficial finger flexors are essentially paralyzed, making it difficult to hold objects and resulting in the end-stage hand appearance of IBM (FIGURES 5-2A and 5-2B). The examination of the lower extremities may also reveal dorsiflexion weakness early on, in addition to the knee extensor weakness. Advanced stages of the disease are characterized by diffuse involvement of all skeletal muscles with profound muscle atrophy and muscle weakness, even affecting the facial, pharyngeal, and diaphragmatic muscles.

Several disease mimics may mislead the evaluating physician to another diagnosis. These conditions include polymyositis (a common misdiagnosis due to the proximal muscle weakness seen in both conditions, especially when finger flexor weakness is overlooked), ALS (as muscle atrophy may be pronounced but the rapid progression in ALS should argue against IBM), and myotonic dystrophy (given the findings of finger flexor weakness) (FIGURE 5-3). Additional clinical features that argue against IBM include very young age of onset (as in 30 years or less) or a family history, which can be seen in inherited myopathies such as glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (*GNE*) or valosin-containing protein (*VCP*) myopathy.

KEY POINTS

- Inclusion body myositis is the most common acquired muscle disease of the aging population, affecting individuals over age 45.
- Inclusion body myositis is often initially misdiagnosed as polymyositis or another condition in 40% to 50% of patients, leading to a diagnostic delay of up to 5 years with the average patient undergoing a diagnostic odyssey and unwarranted immunosuppressive therapies.
- Notable asymmetric atrophy of the quadriceps and medial forearm flexors, associated with knee extensor and wrist/finger flexor weakness, occurs in inclusion body myositis.
- The flexor digitorum profundus muscle is disproportionately weaker than other hand muscles in inclusion body myositis. This finding of flexor digitorum profundus weakness may alert the physician to a possible diagnosis of inclusion body myositis over other subtypes of myositis.

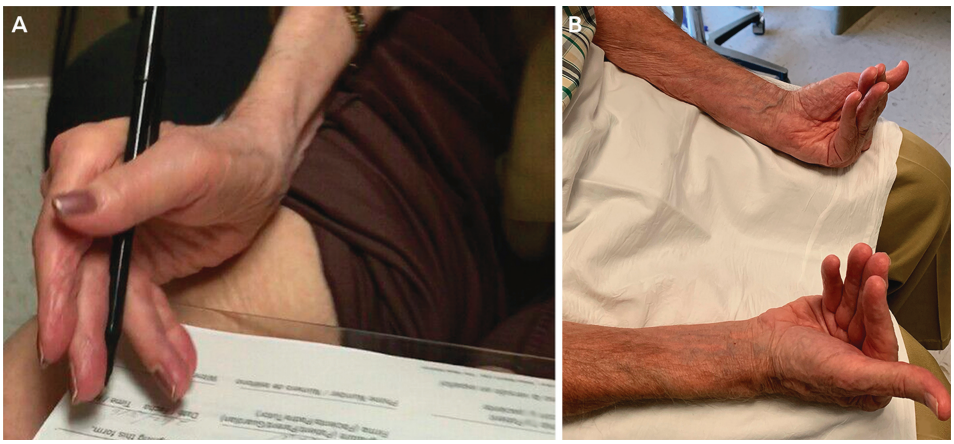

FIGURE 5-2
Advanced weakness of the hand in inclusion body myositis. *A*, As weakness progresses, both the distal and proximal finger flexors become involved, making it difficult to write and hold objects. *B*, Over time, all finger flexors are essentially paralyzed.

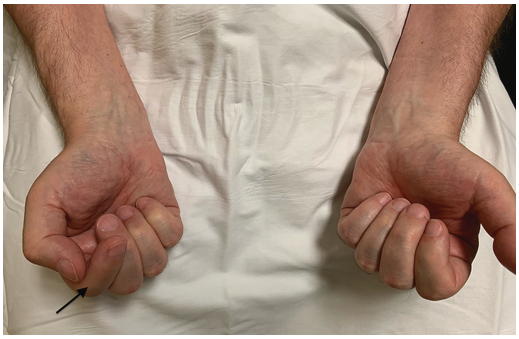

FIGURE 5-3
Finger flexor weakness in myotonic dystrophy. Finger flexor weakness is also seen in myotonic dystrophy type 1 and should be considered in the differential diagnosis when evaluating patients for possible inclusion body myositis (IBM). Interestingly, in this patient with myotonic dystrophy type 1, the second digit (*arrow*) is more affected than the commonly affected fifth digit in IBM.

DIAGNOSTIC EVALUATION

Several diagnostic studies are available to help confirm the diagnosis of IBM, including blood tests, electrodiagnostic studies, muscle MRI, and muscle biopsy.

Serum Creatine Kinase and Electrodiagnostic Studies

While the history of slowly progressive weakness and the hallmark clinical examination findings of asymmetric weakness preferentially affecting the deep finger flexors and knee extensors can be sufficient to raise strong clinical suspicion of IBM, the diagnosis is confirmed with muscle histopathology. Additional studies such as serum creatine kinase (CK), electrodiagnostic studies, autoantibody testing, and muscle imaging may also provide supportive evidence, which is important as the clinical or pathologic features are not always present early in the disease course. Serum CK levels may be modestly elevated; however, in some patients with IBM CK levels may be normal, confusing the clinician who may expect elevated CK levels in all myopathic processes. Electrodiagnostic studies often reveal normal sensory and motor nerve conductions; however, some patients may have an underlying polyneuropathy reflected by low sensory nerve action potentials. Needle EMG may show abnormal spontaneous activity with fibrillation potentials and positive sharp waves in weak muscles. With activation of the muscle, the needle examination reveals short-duration, low-amplitude motor unit potentials, with an early recruitment pattern indicative of a myopathic process. In some muscles, however, a mixed subpopulation of long-duration, high-amplitude, polyphasic motor unit potentials (which are typically expected in a neurogenic condition) may be seen, further adding to the diagnostic uncertainty if physicians do not recognize this electrodiagnostic feature.

Autoantibody in Inclusion Body Myositis

In 2013, two different groups of researchers identified the anti-cytosolic 5'-nucleotidase 1A (anti-NT5C1A) antibody in the sera of patients with IBM as a potential diagnostic biomarker.[5,6] While the presence of the anti-NT5C1A antibody was initially reported to have a sensitivity of 60% to 70%, it had a specificity of up to greater than 90% in IBM, as the antibody was detected in only 5% to 10% of other myositis subtypes (ie, dermatomyositis and polymyositis).[5,6] Subsequently, other groups reported a wide range of diagnostic sensitivity of the anti-NT5C1A antibody assays in IBM, ranging from 37% to 76%,[7,8] possibly related to the assay testing methodology used. Additionally, the presence of the anti-NT5C1A antibody has been reported in other autoimmune diseases (Sjögren syndrome and systemic lupus erythematous) and even motor neuron disease.[9–11]

Interestingly, conflicting reports exist regarding potential phenotypic differences between seropositive and seronegative patients with IBM. Some groups have reported that patients who are seropositive for the antibody may have a poorer prognosis and overall reduced survival[12,13]; however, a 2021 study of 249 patients with IBM found that seropositivity for the NT5C1A antibody did not correlate with any prognostic factors or survival.[14] Despite the controversial concerns about sensitivity and utility, many experts agree that this antibody is a useful noninvasive and complementary assessment that may aid in earlier and more reliable diagnosis of IBM when clinical suspicion is high. The anti-NT5C1A antibody test is especially valuable in patients who clinically appear to have IBM when their muscle histopathology does not fulfill the pathologic diagnostic criteria to confirm an IBM diagnosis.

Muscle Imaging

MRI has become a useful noninvasive modality in evaluating patients with inflammatory myopathy. MRI serves several purposes, as it can (1) delineate the extent and severity of muscle involvement based on signal intensity, with muscle edema (detected by hyperintensity on short tau inversion recovery [STIR] sequences) suggesting an active inflammatory disease process versus muscle atrophy or fatty infiltration (seen as hyperintense on T1-weighted sequences) implying a chronic or end-stage process; (2) characterize the pattern of muscle involvement, giving insight into the subtype of myopathy; and (3) provide guidance on the affected muscle to biopsy.[15] One study reported that using muscle MRI as an add-on test in patients with a previously nondiagnostic muscle biopsy was shown to decrease the false-negative rate of biopsy from 0.23 to 0.06.[16]

In IBM, certain distinct patterns of muscle involvement on MRI may be predictive of the disease, aiding in differentiation of IBM from other myopathy subtypes, particularly when overlap is seen clinically or pathologically. Fatty infiltration on MRI is more common than inflammation, with muscles most frequently involved including the flexor digitorum profundus in the forearm and anterior compartment muscles of the thigh with sparing of the rectus femoris, and severe involvement of the medial compartment of the gastrocnemius. This pattern of involvement can be indicative of IBM (FIGURE 5-4).[17] Another study found a diagnostic accuracy of 95% (with 100% specificity) when applying the typical pattern recognition of MRI findings in distinguishing IBM from other late-onset acquired (inflammatory) or genetic myopathies with overlapping features.[18] Interestingly, early in the disease course, these MRI patterns of muscle abnormalities may be seen subclinically, even preceding detectable weakness of the flexor digitorum profundus.[17] The use of MRI has additionally garnered attention as a potentially useful biomarker to monitor neuromuscular disease progression in clinical trials of IBM, with the possible ability to detect a therapeutic effect on muscle prior to visible functional improvement in patients.[19]

Given the advantages of being easily accessible, portable, and cheap, ultrasound has been studied in IBM; however, the main limitation with ultrasound is the heavy operator dependence in interpreting the various factors that affect the echogenicity of the muscle. In a small study of patients with IBM, ultrasound of the flexor digitorum profundus showed significantly higher echogenicity and was the most discriminating muscle (over the vastus lateralis)

KEY POINTS

- Serum creatine kinase levels may be modestly elevated in inclusion body myositis; however, in some patients with inclusion body myositis, the creatine kinase levels may be normal.
- The needle EMG of a weak muscle in patients with inclusion body myositis may show a mixed population of both short-duration, low-amplitude and long-duration, high-amplitude motor unit potentials.
- The anti-cytosolic 5′-nucleotidase 1A antibody in the sera of patients with inclusion body myositis is a potential diagnostic biomarker.
- The anti-cytosolic 5′-nucleotidase 1A antibody is a useful noninvasive and complementary test that may aid in an earlier and more reliable diagnosis of inclusion body myositis when clinical suspicion is high.
- Fatty infiltration on MRI is more common than inflammation in patients with inclusion body myositis, with muscles most frequently involved including the flexor digitorum profundus in the forearm, anterior compartment muscles of the thigh with sparing of the rectus femoris, and severe involvement of the medial compartment of the gastrocnemius.

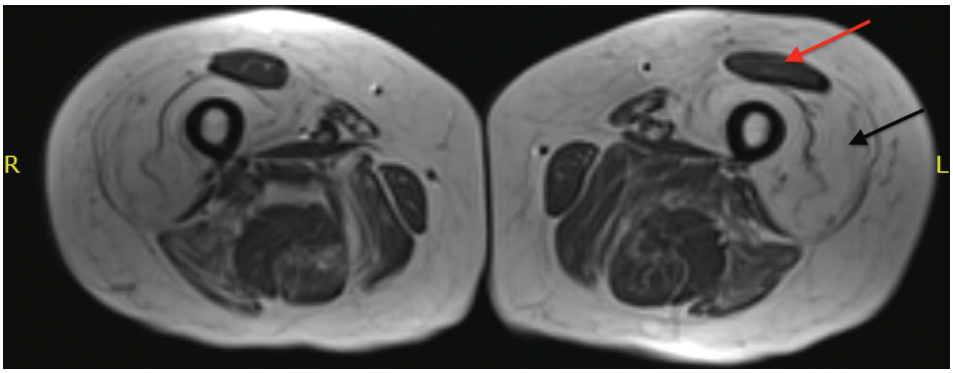

FIGURE 5-4
Axial T1-weighted MRI of the thigh muscles of a patient with inclusion body myositis. Significant hyperintensity indicative of fatty infiltration is seen in the anterior compartment muscles of the thigh, predominantly affecting the vastus lateralis (*black arrow*) and vastus medialis, yet with relative sparing of the rectus femoris (*red arrow*) and the posterior compartment muscles.

in helping to distinguish IBM from other inflammatory myopathies and controls.[20] A 2021 study of 12 patients with IBM who underwent ultrasound and MRI on the same day found significant accuracy of ultrasound compared with MRI for the detection of muscle abnormalities (with sensitivity of 84% and specificity of 100%).[21] These studies have indicated that ultrasound may be a valuable bedside tool if its technical limitations can be overcome.

Muscle Histopathology

The biopsy of a muscle affected by IBM may reveal several pathologic findings (FIGURE 5-5). Inflammatory mononuclear cell infiltration of the endomysium

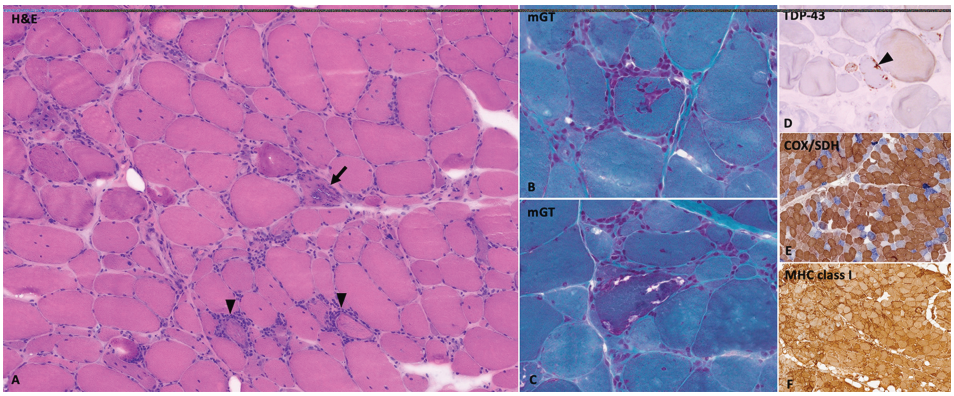

FIGURE 5-5
Histopathology of inclusion body myositis. Hematoxylin and eosin (H&E) stain showing endomysial inflammatory infiltrate (*A*, *arrowheads*) and rimmed vacuoles (myofiber containing rimmed vacuoles, *A*, *arrow*) with severe myopathic features including significant fiber size variation, endomysial fibrosis, and necrosis and regeneration (*not shown*). Modified Gomori trichrome (mGT) stain showing lymphocytes invading a non-necrotic myofiber (*B*, *image center*) and rimmed vacuoles (*C*, *image center*). Presence of protein accumulation detected by TAR DNA-binding protein 43 (TDP-43) immunohistochemistry (*D, arrowhead*). Mitochondrial pathology demonstrated by many blue cytochrome c oxidase–negative/ succinate dehydrogenase–positive (COX/SDH) myofibers (*E*). Strong and diffuse sarcolemmal and sarcoplasmic upregulation of major histocompatibility complex (MHC) class I (*F*).
Figure courtesy of Mari Perez Rosendahl, MD.

with lymphocytes specifically surrounding or invading a non-necrotic myofiber is an important feature seen in IBM on hematoxylin and eosin (H&E) stain; when immunohistochemistry shows that the mononuclear cells are $CD8^+$ T cells, these findings are suggestive of IBM.[22] A key finding that is sought after in making the pathologic diagnosis of IBM is the presence of rimmed vacuoles within myofibers (seen on H&E or trichrome stain); the challenge, however, is that rimmed vacuoles are absent in 20% to 40% of muscle biopsies from patients with IBM, despite typical clinical features.[22,23] Mitochondrial pathology is often detected in IBM, characterized by findings of scattered fibers showing absent or reduced cytochrome c oxidase activity and increased succinate dehydrogenase staining, as well as ragged red fibers seen on trichrome. Additional nonspecific features on H&E staining include fiber size variability, internalized nuclei, type 2 fiber atrophy, and occasional cytoplasmic inclusions.[3] Congophilic inclusions can be seen on Congo red staining. Electron microscopy may help reveal tubulofilamentous and intranuclear inclusions.

Immunohistochemical stains show characteristic findings of major histocompatibility complex (MHC) class I (MCH-I) and MHC class II (MHC-II) staining in IBM. MHC-I molecules play a role in antigen-specific T cell–mediated cytotoxicity, mediating a response against the surface antigens on myofibers,[24] and MHC-II expression is needed to activate T helper cells to initiate an immune response.[25] In IBM, MHC-I and MHC-II overexpression is well reported, with MHC-I being dense and diffusely staining the sarcoplasm in addition to the sarcolemma, and MHC-II being patchy or diffusely staining the sarcolemma of myofibers.[26] While MHC-I overexpression shows a high sensitivity in inflammatory myopathies, it has a very low specificity (demonstrated in both inflammatory and noninflammatory myopathies as well as neurogenic disorders); conversely, MHC-II staining has a much higher specificity to inflammatory myopathies, especially IBM.[25] The p62 immunostain, a marker for the autophagy adapter protein, shows p62-positive coarse aggregates localized within vacuoles, perinuclearly, and in subsarcolemmal regions in IBM muscles, suggesting that a process of autophagic dysregulation of protein homeostasis may occur in IBM.[27] Additionally, other autophagy-related protein stains for microtubule-associated proteins 1A/1B light chain 3B and TAR DNA-binding protein 43 can demonstrate protein aggregation.[28,29]

Diagnostic Criteria for Inclusion Body Myositis

Over the years, several diagnostic criteria have been published for research purposes based on meetings involving consensus expert opinions and developed from 1995 to 2011. These criteria have been based on clinical, pathologic, and laboratory features. While these diagnostic criteria have been traditionally used to define inclusion criteria for IBM clinical trials, a study evaluating the construct categorization schemes noted that many of these published criteria had excellent specificities (97% or greater) but a wide range of sensitivities (some as low as 11%),[30] suggesting that when these criteria are used clinically, many patients with IBM could be underdiagnosed, misdiagnosed, or have a diagnostic delay. The most recently published criteria, the European Neuromuscular Centre (ENMC) 2011 criteria, defines three categories: clinicopathologically defined IBM, clinically defined IBM, and probable IBM, with the last two categories placing greater emphasis on clinical and laboratory features and with less stringent pathologic criteria due to the recognition that pathologic features may

KEY POINTS

- **Inflammatory mononuclear cell infiltration of the endomysium with lymphocytes specifically surrounding or invading a non-necrotic myofiber is an important pathologic feature seen in inclusion body myositis.**
- **A key finding that is sought in making the pathologic diagnosis of inclusion body myositis is the presence of rimmed vacuoles within myofibers; the challenge, however, has been that rimmed vacuoles are reported to be absent in 20% to 40% of muscle biopsies from patients with inclusion body myositis despite typical clinical features.**
- **Major histocompatibility complex (MHC)-I overexpression shows a high sensitivity in inflammatory myopathies but has a low specificity. Conversely, MHC-II staining has a much higher specificity to inflammatory myopathies, especially inclusion body myositis.**

be absent in some patients with IBM.[31] The ENMC 2011 criteria had one of the best performing categories, with 84% sensitivity for the probable IBM category (combining finger flexor and quadriceps weakness with one pathologic finding of either endomysial inflammation or rimmed vacuoles), but only 15% sensitivity for the clinicopathologically defined IBM category (which requires all pathologic features of endomysial inflammation, rimmed vacuoles, and either protein accumulation or 15 nm to 18 nm filaments), suggesting that the specialized pathologic features in this category may be too restrictive.[30] Neither the anti-NT5C1A antibody blood test nor muscle MRI have been incorporated into the current diagnostic criteria to date (CASE 5-1).

PATHOPHYSIOLOGY

It has been repeatedly suggested that the pathomechanism in IBM is quite complex, with a potential interplay between cellular stress, inflammation, protein accumulation, and degeneration fueling a vicious cycle, ultimately leading to muscle fiber damage.[32] The key question that remains is whether the inflammation is a primary autoimmune process or a secondary process that is a consequence of the degenerative pathway. The lack of a current answer to this question has made it difficult to identify therapeutic targets. Compelling arguments supporting both sides of the question have been proposed. The autoimmune features are supported by the presence of inflammatory cytotoxic ($CD8^+$) T cells invading non-necrotic fibers, upregulation of MHC-I class antigens and inflammatory mediators, and the presence of the anti-NT5C1A antibody; on the other side, the degenerative features are supported by the pathologic findings of rimmed vacuoles with associated myonuclear degeneration, myofiber cytoplasmic protein aggregates, and mitochondrial abnormalities, along with the clinical evidence of an increased incidence of IBM seen in the aging population and the lack of responsiveness to standard immunotherapy.[33] Additionally, the histochemical degenerative markers of p62, microtubule-associated proteins 1A/1B light chain 3B, and TAR DNA-binding protein 43 in IBM muscle have provided insight into potential mechanistic roles from cellular stress, activation of the autophagic pathway, and alterations in RNA metabolism.[28,34,35]

In recent years, increasing evidence supports a T-cell-mediated process with description of clonal expansion of T cells and $CD4^+$ and $CD8^+$ T cells driven into highly differentiated effector T-cell populations in the blood and muscle of patients with IBM.[36,37] $CD8^+CD57^+$ cell subpopulations, with CD57 being a marker of T-cell exposure to antigen and T-cell aggressiveness, have been detected invading myofibers in IBM and have been correlated with aberrant populations of large granular lymphocytes, leading to the association of IBM with T cell large granular lymphocytic leukemia.[37] Furthermore, a study evaluating killer cell lectinlike receptor G1 (KLRG1), a marker of highly differentiated effector memory and terminally differentiated effector cells, demonstrated the correlation of KLRG1 gene expression with lymphocyte cytotoxicity and identified that $CD8^+KLRG1^+$ cells appear pathogenic in IBM.[38]

Lastly, a viral etiology has been speculated to play a role in the pathogenesis of IBM. Several reports exist of associations between the development of IBM clinical features in patients infected with human immunodeficiency virus (HIV), human T-cell lymphotropic virus type 1 (HTLV-1), or hepatitis C, suggesting a pathomechanistic link between the conditions.[39–41] Interestingly, the patients who

are HIV positive may present with characteristic polymyositis features, including being under age 45, high CK levels, and proximal weakness; however, over time the findings evolve to more classic IBM features with finger flexor weakness, rimmed vacuoles on biopsy, and anti-NT5C1A antibodies.[39] It has been hypothesized that these chronic retroviral infections may trigger viral-specific $CD8^+$ cells to invade muscle fibers in IBM; however, attempts to amplify HIV retroviruses directly from the muscle have failed and more conclusive data is still warranted.[42]

Genetics

As the pathogenesis of IBM may be multifactorial, it has also been shown that genetic factors may predispose individuals to a risk of developing disease. A large genetic study analyzing immune-related genes in IBM identified strong associations with variants within the human leukocyte antigen (HLA) locus reaching genome-wide significance, with HLA-DRB1*03:01 showing the most significant association with IBM and specific amino acid positions in HLA-DRB1 alleles that may explain the risk.[43] Because IBM shares degenerative pathologic features with other conditions, such as inclusion body myopathy with Paget disease and frontotemporal dementia (a multisystem proteinopathy) and hereditary inclusion body myopathy, interest has been generated in studying a possible commonality between mutations of genes regulating protein homeostasis. This concept led to a candidate-based gene sequencing study evaluating the overlap of inherited muscle and neurodegenerative disorders that uncovered rare missense variants in several genes, including valosin-containing protein (*VCP*) and sequestosome 1 (*SQSTM1*, also known as p62), which play an integral role in autophagy.[44] Additionally, an unbiased proteomics approach using whole exome sequencing of genes encoding rimmed vacuole proteins identified variants in the *FYCO1* gene, another gene implicated in microtubule transport of autophagosomes.[45] Due to the known mitochondrial pathology seen on muscle histology of patients with IBM, a mitochondrial protein under investigation has been the translocase of outer mitochondrial membrane 40 (*TOMM40*). Through the International IBM Genetics Consortium, a study involving a cohort of 158 patients with IBM found no association between an apolipoprotein E (*APOE*)-*TOMM40* genotype and the risk of developing IBM; however, the study did find that patients with IBM carrying the very long *TOMM40* allele were noted to have a later age of onset in developing disease.[46] Further studies are needed regarding the role of these potential genetic implications, which may improve our knowledge of disease causation in IBM.

MANAGEMENT AND RECENT CLINICAL TRIALS

Several immunotherapeutic strategies have been trialed in IBM; however, thus far none have shown robust sustained efficacy or even effectively slowed the rate of disease progression. While no clear evidence exists that life expectancy is affected in IBM, patients do have increased disability, increased use of wheelchairs, and high morbidity as a result of an increased risk of aspiration pneumonia due to dysphagia.[47] Currently, the mainstay of treatment for patients with IBM involves a multidisciplinary approach to care with goals to improve quality of life, provide greater access to assistive devices, and reduce hospitalizations. In addition to the treating neurologist who monitors disease progression (with muscle strength testing and assessing overall health), the

KEY POINTS

- Of the different diagnostic criteria for inclusion body myositis, the European Neuromuscular Centre 2011 criteria had one of the best performing categories, with 84% sensitivity for the probable inclusion body myositis category.
- The key question that remains is whether the inflammation in inclusion body myositis muscle is a primary autoimmune process or a secondary process that is a consequence of the degenerative pathway.
- A study evaluating killer cell lectin-like receptor G1 (KLRG1), a marker of highly differentiated effector memory and terminally differentiated effector cells, has demonstrated the correlation of KLRG1 gene expression with lymphocyte cytotoxicity and identified that $CD8^+KLRG1^+$ cells appear pathogenic in inclusion body myositis.
- A large genetic study analyzing immune-related genes in inclusion body myositis identified strong associations with variants within the human leukocyte antigen (HLA) locus reaching genome-wide significance, with HLA-DRB1*03:01 showing the most significant association with inclusion body myositis.
- Several immunotherapeutic strategies have been trialed in inclusion body myositis; however, thus far none have shown robust sustained efficacy or effectively slowed the rate of disease progression.

CASE 5-1

A 47-year-old man presented for evaluation of a 2-year history of his left leg "giving out" and falling when playing tennis. He described that his left knee would buckle, and he developed left knee pain accompanied by left thigh muscle atrophy. He denied pain or weakness in his upper extremities. Due to the muscle atrophy and 2-year history of falls, he was referred by his neurologist for a neuromuscular subspecialty consultation for a question of amyotrophic lateral sclerosis (ALS).

On neuromuscular examination, the patient had prominent muscle atrophy affecting his left anterior thigh muscles but also mildly affecting his right thigh. Strength testing revealed weakness in the following areas (right/left): elbow flexors 4+/5, elbow extensors 4+/5, hip flexors 5/4+, knee extensors 4+/4, and dorsiflexors 5/4+. No grip or deep finger flexor weakness was detected. Grip dynamometry measurements were 80 pounds on the right and 90 pounds on the left. Deep tendon reflexes were 1+ at the right triceps, 2+ in the rest of the arms, and 1+ at both the patella and ankles.

The patient's creatine kinase (CK) level was initially mildly elevated at 301 U/L; however, when repeated 9 months later, it was normal at 167 U/L. Due to his knee pain, he had initially been seen by an orthopedic surgeon; MRI of his knee showed no joint abnormality but did reveal significant fatty infiltration of his vastus lateralis and vastus medialis muscles on T1-weighted sequences with relative sparing of his posterior thigh muscles.

Needle EMG showed fibrillation potentials with a mixed population of short-duration, low-amplitude motor unit potentials and long-duration, high-amplitude motor unit potentials in several lower extremity muscles. Muscle biopsy of his vastus lateralis performed prior to referral was initially reported as possible polymyositis with

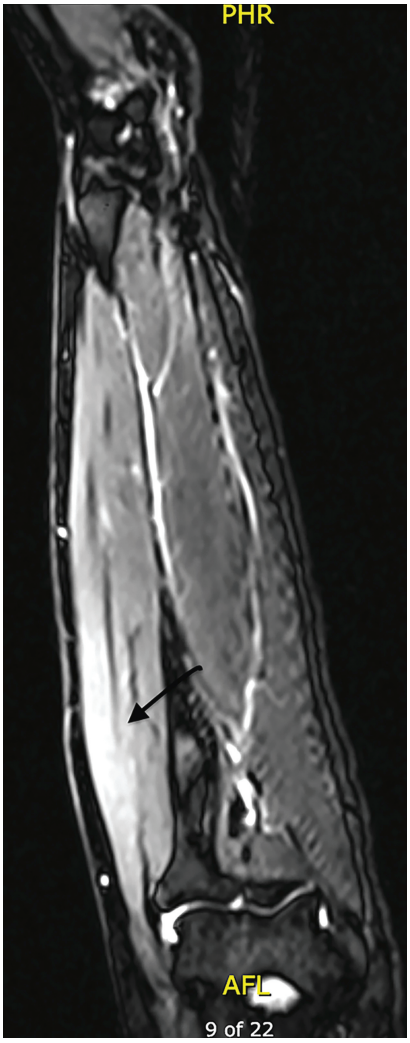

FIGURE 5-6
Coronal section, short tau inversion recovery (STIR) MRI of the forearm muscle in a patient with inclusion body myositis at an early disease stage. Subtle hyperintensity suggestive of edema is seen in the medial forearm flexor compartment muscles (*arrow*). These findings were present prior to the patient developing clinical weakness.
PHR = posterior/head/right; AFL = anterior/foot/left.

endomysial inflammation seen surrounding non-necrotic fibers; however, upon rereview during this neuromuscular consultation occasional myofibers with rimmed vacuoles were seen. Muscle MRI of the forearm showed mild short tau inversion recovery (STIR) signal hyperintensity in the muscles of the medial forearm flexor compartment (FIGURE 5-6). The anti-NT5C1A antibody test was sent and was positive. The patient was diagnosed with inclusion body myositis (IBM).

COMMENT

This case highlights several of the diagnostic dilemmas that a patient with IBM often encounters. ALS was initially raised as a possible diagnosis because of the relatively young age of onset, short duration of symptoms, profound muscle atrophy seen on examination, lack of marked CK elevation, and large, possibly neurogenic motor units (due to the large motor units) seen on needle examination, all features that may raise concern for ALS. In contrast, the lack of upper motor neuron features and recognition that a mixed population of both small and large motor unit potentials were red flags against a diagnosis of ALS kept IBM in the differential. Subsequently, the muscle pathology report had initially only highlighted the endomysial inflammation and was read out as possible polymyositis; however, upon rereview very occasional but present rimmed vacuoles were noted, further raising suspicion of IBM. Interestingly, while the patient did not have symptoms of grip weakness or detectable weakness of the flexor digitorum profundus muscles, muscle MRI showed subtle hyperintensity of the medial forearm flexor compartment muscles, highlighting the ability and utility of MRI to detect subclinical involvement of the muscle even before the clinical examination is able to elicit weakness.

Six years later, the patient did develop clear finger flexor weakness, and his grip dynamometry on the right decreased from 80 pounds to 45 pounds. The positive anti-NT5C1A antibody test also provided further assurance to the patient that his diagnostic workup was complete.

optimal care team often involves a physical therapist to evaluate the need for mobility devices (eg, ankle-foot orthotic braces, cane, walker, wheelchair) and guide exercise regimens; a speech therapist to evaluate the risk of swallowing changes and recommend diet modifications as dysphagia progresses; a pulmonologist or respiratory therapist to perform pulmonary function tests and monitor the need for noninvasive ventilation (such as bilevel positive airway pressure [BiPAP]) when diaphragmatic insufficiency arises; a nutritionist to advise on optimal sources for caloric intake in patients with severe dysphagia; and a social worker to assist in caregiving resources. Additionally, the benefits of exercise should not be underestimated, as combining aerobic and resistance training could positively affect metabolic pathways, promoting muscle fiber regeneration and repair.[48]

Because of the increasing prevalence of the disease within the aging population and the high morbidity associated with IBM, a significant unmet need exists for the development of therapeutic interventions. Several novel investigational agents have recently been tried or are being tested in clinical trials. Bimagrumab, a monoclonal antibody that binds competitively to activin type II receptors with greater affinity than activin and myostatin, resulting in skeletal muscle hypertrophy, was a promising agent trialed in IBM due to its potential to treat profound muscle atrophy seen in the disease. A phase 2b randomized placebo-controlled study of over 250 patients, the largest trial to date in IBM, evaluated the safety and efficacy of three doses of bimagrumab. While the drug showed a dose-dependent effect on lean body mass, confirming its biological activity, it did not show a significant change in the 6-minute walk distance or other functional measures from baseline to week 52 in any of the bimagrumab-treated groups versus placebo, ending the sponsor's pursuit of an indication for the drug in IBM.[49] Arimoclomol, another agent investigated in IBM, postulated to increase heat-shock protein expression and improve cell survival and protein mishandling, was tried in a proof-of-concept placebo-controlled trial of 24 patients and was shown to be safe and well tolerated.[50] These findings led to the recently completed phase 2 study of arimoclomol in 150 subjects with IBM (NCT02753530). Topline results of the study released in March 2021 revealed that the study did not meet the primary end point (IBM functional rating score) or other secondary functional outcome measures.[51]

Attention and hope have now shifted to two other drugs that are currently undergoing trials. Sirolimus (also known as rapamycin), an agent believed to restore aberrant autophagic (protein degradation) pathways, was tested in a randomized placebo-controlled phase 2b study in France with 44 patients with IBM. While the study did not show a significant difference in the primary outcome (quadriceps strength) at 12 months, the treated group did show significantly less fatty replacement in the quadriceps muscle (by quantitative MRI) and significant beneficial effects on the 6-minute walk distance and forced vital capacity.[52] These encouraging results led to the evaluation of the efficacy of sirolimus further in a large phase 3 trial, which is ongoing (NCT04789070). Lastly, the recent findings indicating that highly differentiated cytotoxic CD8+ T cells express KLRG1 and are pathogenic in IBM[38] have made KLRG1 an attractive therapeutic target. A phase 1 study using ABC008, an anti-KLRG1 antibody capable of depleting the highly differentiated cytotoxic T cells found in IBM, is underway in Australia (NCT04659031).

CONCLUSION

IBM is a common acquired muscle disease in older adults that is associated with significant morbidity and disability. Historically, patients frequently undergo a diagnostic odyssey, sometimes for years, before a diagnosis of IBM is made and, in some cases, with years of unwarranted immunosuppression. With improved recognition of the salient clinical features, attention to the careful examination of the deep finger flexors, and the use of newer diagnostic tools (NT5C1A antibody and muscle MRI) when examination and muscle biopsy are not definitive, the rate of misdiagnosis for IBM can decrease. While current interventional therapies have not shown sustained improvement, patients have benefitted from multidisciplinary care and exercise. In recent years, several studies have aimed to enhance understanding of the pathomechanisms of the disease, which have resulted in several novel agents being trialed in IBM. As these efforts continue, the development of promising therapies is foreseen.

KEY POINT

- **The mainstay of treatment for patients with inclusion body myositis is supportive care which involves a multidisciplinary team approach.**

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