REVIEW ARTICLE

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Sporadic Inclusion Body Myositis and Other Rimmed Vacuolar Myopathies

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ABSTRACT

PURPOSE OF REVIEW: This article reviews the clinical, laboratory, and histopathologic features of sporadic inclusion body myositis (IBM) and explores its pathogenic overlap with inherited myopathies that have IBM-like pathology.

RECENT FINDINGS: Sporadic IBM is the most common acquired muscle disease in patients older than 50 years of age and is becoming more prevalent because of the increasing age of the population, the emerging development of more inclusive diagnostic criteria, and the advent of a diagnostic autoantibody. No effective therapy is known, and the pathogenic mechanism remains unclear. Some pathogenic insight can be gleaned from other myopathies with pathologic similarities or hereditary inclusion body myopathies. Although clinically distinct from sporadic IBM, preclinical models of hereditary inclusion body myopathy have offered an opportunity to move some therapies toward clinical development.

SUMMARY: Patients with sporadic IBM experience significant morbidity, and the disease is associated with a large unmet medical need. As therapies are developed, improved diagnosis will be essential. Early diagnosis relies on awareness, clinical history, physical examination, laboratory features, and appropriate muscle biopsy processing. Future research is needed to understand the natural history, identify genetic risk factors, and validate biomarkers to track disease progression. These steps are essential as we move toward therapeutic interventions.

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INTRODUCTION

Sporadic inclusion body myositis (IBM) is an insidious and enigmatic myopathy that affects patients late in life. Patients present with slowly progressive disabling weakness that often goes unrecognized early in the disease course, necessitating increased awareness by clinicians, less restrictive yet specific diagnostic criteria, and the understanding of sporadic IBM biomarkers. Recent studies have also demonstrated that hereditary muscle diseases can mimic sporadic IBM both phenotypically and

pathologically, further illustrating the need for improved diagnostic methods. Indeed, two large genetic studies identified that approximately 2.5% of patients previously characterized as having sporadic IBM had pathogenic mutations in two genes (*VCP* and *SQSTM1*) reported in hereditary forms of IBM.[1,2] As therapies are developed, distinguishing between sporadic IBM and hereditary forms of myopathy that can mimic sporadic IBM is critical.

EPIDEMIOLOGY

Published estimates of the prevalence of sporadic IBM range from 5 per million to 71 per million.[3,4] While this variability may relate to geographic location, it seems more likely that challenges in the ascertainment of these data, including inaccuracies and delays in sporadic IBM diagnosis, as well as limitations in insurer-based coding dictionaries, underestimate the true prevalence. It is notable that one study in Japan retrospectively evaluated muscle biopsies between 1990 to 1998 and 1999 to 2007 and found the prevalence of biopsies with pathologic features consistent with sporadic IBM increased from 1.28 per million to 9.83 per million.[5] Whether this is truly due to changes in lifestyle that increase susceptibility to sporadic IBM or is consistent with an aging population and referral patterns for muscle biopsy is not clear. Regardless, it is widely believed that these prevalence data underestimate the true burden of this disease.

CLINICAL FEATURES AND DIAGNOSIS

Patients with sporadic IBM typically present after the age of 45 with slowly progressive weakness of more than 12 months duration (CASE 3-1). The pattern of preferentially affected muscles can be highly distinctive.[6] Specifically, quadriceps weakness is often appreciated early in the disease course (eg, difficulty rising from a chair). Finger flexor weakness manifested by decreased grip strength and ankle dorsiflexion weakness are also common early features. Other clinical features include biceps brachii, triceps, and wrist flexor weakness. Facial weakness, while uncommon, can be prominent in some patients. An atypical pattern of weakness, rapid onset and progression, or onset earlier than age 40 should prompt the clinician to consider alternative diagnoses.

Diagnostic studies can be helpful in confirming or narrowing the differential diagnosis in patients with sporadic IBM. Serum creatine kinase (CK) levels are only modestly elevated, with most patients having a CK level of less than 1500 U/L. A CK level of more than 10 times the upper limit of normal should suggest an alternative diagnosis or other coexisting pathology. Electrodiagnostic studies can be challenging to interpret in some patients with sporadic IBM. Needle EMG often shows abnormal spontaneous activity in the form of fibrillation potentials and positive sharp waves. Motor unit action potentials often vary from large and broad to small and narrow, and recruitment patterns can also vary from reduced to increased (ie, early), suggesting a mixed neurogenic/myopathic process. Of note, these variable findings may even be evident within different regions of the same muscle. Further complicating the interpretation of electrodiagnostic testing in this population is the fact that a concurrent sensory axonal polyneuropathy, in the form of reduced or absent sural sensory nerve action potentials (SNAPs), is common in older patients with sporadic IBM.[7] Muscle imaging can be helpful in establishing the differential pattern of muscle involvement and aid in biopsy site selection but does not replace other testing.[8]

KEY POINTS

- The estimated prevalence of sporadic inclusion body myositis varies from 5 per million to 71 per million but is still likely an underestimate. Diagnostic uncertainty or ambiguity, delays in sporadic inclusion body myositis diagnosis, and the aging population support a higher prevalence.
- Patients with sporadic inclusion body myositis have a slowly progressing preferential pattern of muscle involvement that includes quadriceps, finger flexor, and ankle dorsiflexion weakness.
- An atypical pattern of weakness, rapid progression, or onset younger than 40 years age should prompt the clinician to consider an alternate diagnosis.
- Patients with sporadic inclusion body myositis have modestly elevated creatine kinase levels (≤1500 U/L) and electrodiagnostic studies that may be challenging to interpret because they suggest a mixed myopathic/neuropathic process.
- MRI of the lower extremities can reveal a differential pattern of muscle involvement that selectively affects the anterior thigh muscle. The value of MRI as a diagnostic or prognostic tool in sporadic inclusion body myositis has not been established.

CASE 3-1

A 68-year-old man was referred by his primary care physician for a neurologic evaluation for weakness after a fall and poor response to physical therapy. One year prior, the patient had fallen in his bathroom and needed to call emergency medical services because he was unable to get up off the floor. He did not sustain any injuries and followed up with his primary care physician, who recommended outpatient physical therapy to improve his strength, but the patient felt that it was not beneficial.

On further questioning, the patient described difficulty getting up off the couch for the past 3 years and noted that he would no longer sit in some chairs at home because he could not get up from them. Over the past 6 months, he had stopped going to church because he had to climb seven steps to enter the sanctuary, and he was afraid that he might fall. He also noted that he could no longer loosen the lid of jars.

On examination, he was unable to get up from the chair without using his hands to push up. He had the following pattern on muscle strength testing: neck flexors were 4+/5, bilateral deltoid strength was 4/5, wrist extensor and wrist flexor strength were both 5/5 but strength was 4/5 in his bilateral finger flexors, and notably, he was unable to bury his finger nails when making a fist (FIGURE 3-1). In his lower extremities, he had asymmetric quadriceps weakness that was 4/5 on the right and 5−/5 on the left with obvious wasting of the medial and lateral aspects of his quadriceps bilaterally (FIGURE 3-1). He had bilateral tibialis anterior muscle weakness of 4+/5. His reflexes were intact throughout. He had diminished vibration and pinprick sensation in his lower extremities.

Laboratory studies revealed a mildly elevated creatine kinase level of 479 U/L (normal 20 U/L to 200 U/L). EMG and electrodiagnostic studies were consistent with an irritable myopathy: abnormal spontaneous activity and myopathic motor unit potentials were observed in most tested muscles, and some neurogenic recruitment was seen in the deep finger flexors and vastus medialis. Nerve conduction study was consistent with a sensory neuropathy with small sural sensory nerve action potential amplitudes. An MRI of his lower extremities revealed prominent atrophy and T1 signal abnormalities in the vastus medialis and lateralis with sparing of the posterior compartment of the thigh (FIGURE 3-1). The patient was positive for the anti–5'-nucleotidase, cytosolic IA (NT5C1A) antibody.

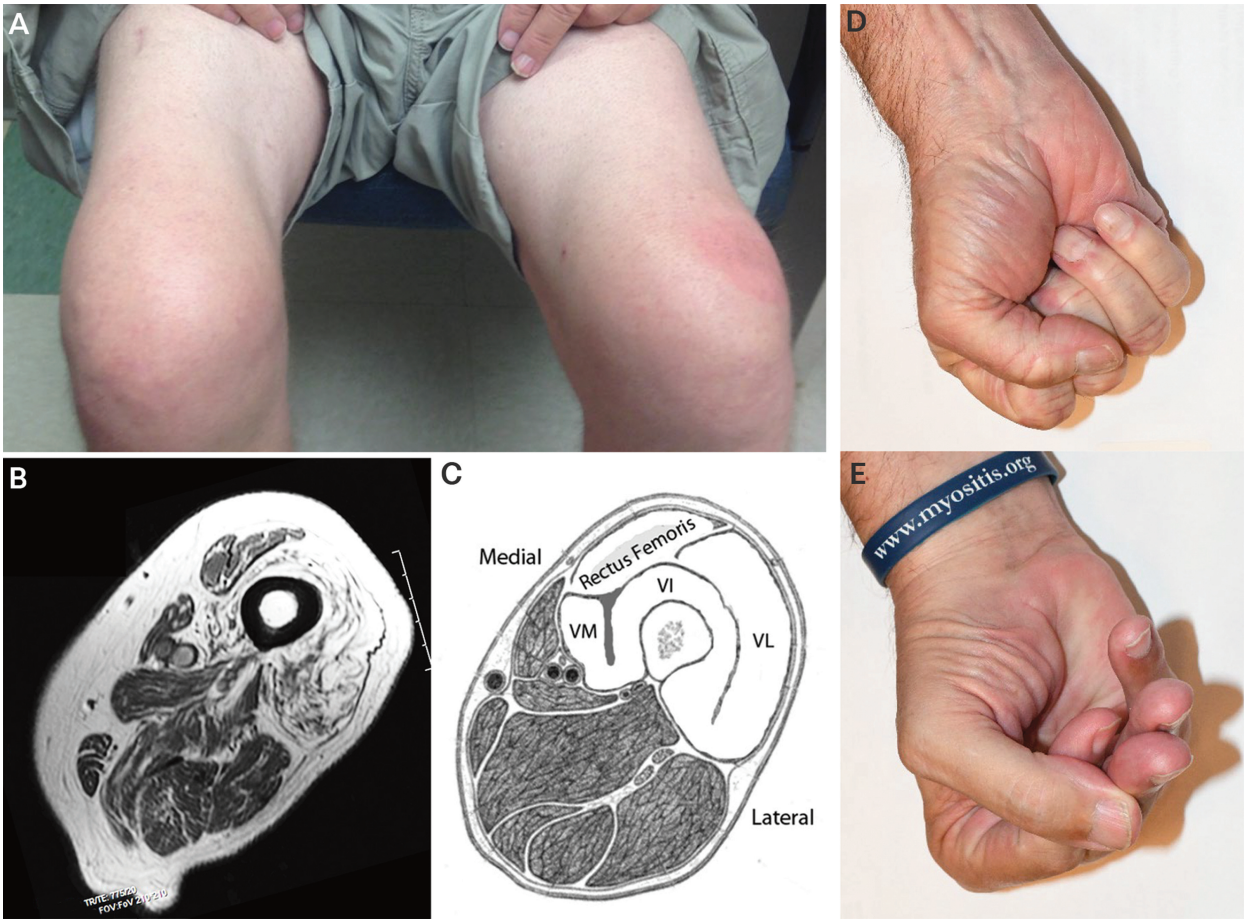

FIGURE 3-1

Clinical features of sporadic inclusion body myositis (IBM) as discussed in CASE 3-1. Asymmetric quadriceps wasting of both the lateral and medial thighs (*A*). T1-weighted MRI of the thigh musculature (*B*) and corresponding diagram of thigh muscle anatomy (*C*). Muscles preferentially affected in sporadic IBM (vastus lateral [VL], medius [VM] and intermedius [VI]) have an increase in T1 signal intensity (*B*); these same muscles are denoted in white on the anatomic drawing (*C*). Finger flexor weakness is shown in two different patients with sporadic IBM (*D, E*). Patients are attempting to make a fist and cannot bury the fingernails completely (*D*) or fully close the hand (*E*).

COMMENT

This patient had a classic pattern of muscle involvement and presented with insidious proximal and distal weakness leading to changes in his lifestyle and loss of independence. Notably, he had frequent falls and was unable to rise from a deep-seated chair, which was initially dismissed as "deconditioning." Questioning and examining the patient at the time of his fall may have facilitated his diagnosis. Although this patient ultimately had a muscle biopsy that demonstrated rimmed vacuoles and endomysial inflammation, which is currently necessary to make even a probable diagnosis of sporadic inclusion body myositis, the pattern of weakness and a positive test for the NT5C1A antibody would have been supportive of the diagnosis.

All current diagnostic algorithms rely on a muscle biopsy to support a definitive diagnosis of sporadic IBM.[9] Several pathologic features such as endomysial inflammation with focal invasion and rimmed vacuoles are present in muscle tissue in patients with sporadic IBM; however, these features can be patchy and easily confounded by the biopsy site, postprocessing of the biopsy, and pathologic interpretation. For example, specific pathologic studies for sporadic IBM, such as electron microscopy, mitochondrial stains, and immunohistochemical analysis for protein inclusions, are often not routinely performed, thus skewing the pathologic interpretation away from sporadic IBM.

A typical biopsy for sporadic IBM has features consistent with a chronic active myopathy (FIGURE 3-2),[10,11] which includes variation in fiber size, with larger hypertrophic fibers and smaller, sometimes clustered, rounded, and angular fibers. Other features consistent with chronicity include an increase in endomysial connective tissue, internal nuclei, and fatty replacement. Endomysial inflammation is an essential feature for sporadic IBM muscle pathology, and although it can vary depending on biopsy site, it is not easily missed in a weak, clinically affected muscle. The endomysial infiltrate is a mixture of acid phosphatase–positive macrophages and lymphocytic T cells. These cells, and

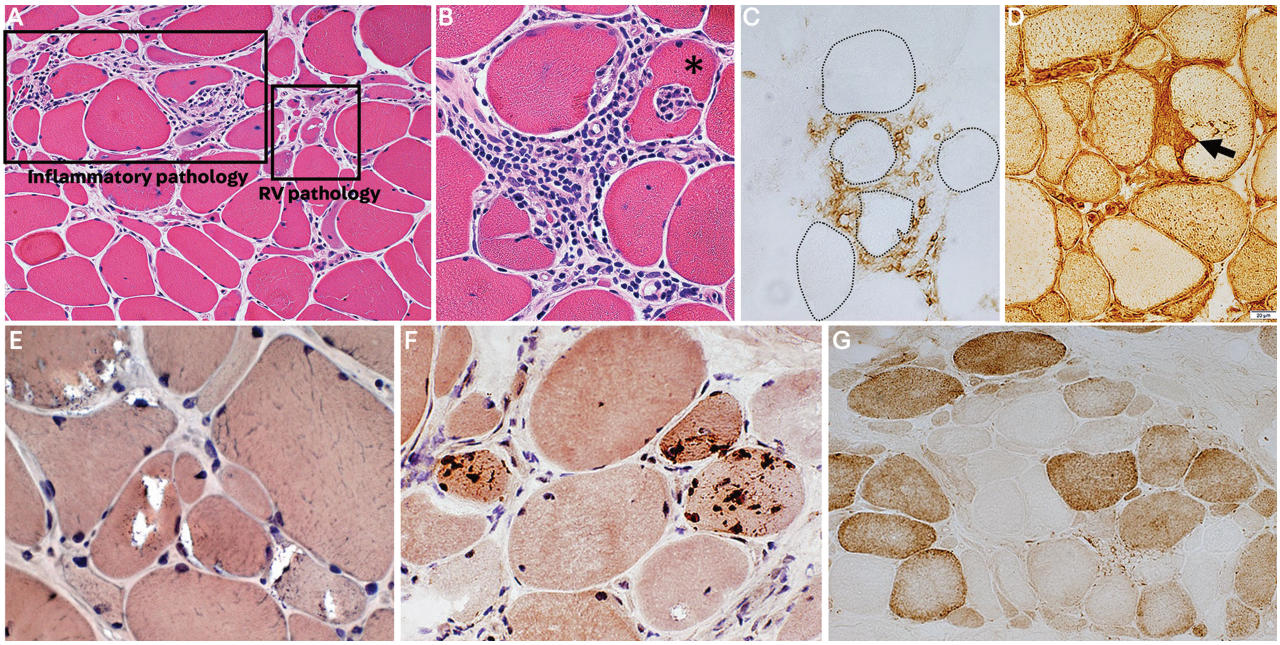

FIGURE 3-2

Sporadic inclusion body myositis (IBM) pathology. *A,* Hematoxylin- and eosin-stained muscle biopsy demonstrates the inflammatory pathology and the rimmed vacuolar (RV) pathology seen in sporadic IBM. Rimmed vacuoles are present in scattered fibers and can be easily missed. *B,* Region of endomysial cellularity consistent with inflammation. *Asterisk* identifies a focally invaded myofiber. *C,* Immunohistochemistry with an antibody recognizing CD8-positive T cells demonstrates that many of the endomysial infiltrates contain this population of cells. Individual myofibers are outlined with a *dotted line*. *D,* Immunohistochemistry for major histocompatibility complex type I demonstrates widespread upregulation on myofibers. The *arrow* denotes an area of focal invasion. *E,* Congo red histochemistry demonstrates fibers with subsarcolemmal, perinuclear, and centrally located rimmed vacuoles. *F,* Immunohistochemical staining for SMI-31 demonstrates protein aggregates in sporadic IBM fibers. *G,* Histochemical analysis with cytochrome oxidase (COX) demonstrates COX-negative fibers.

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more specifically cytotoxic CD8+ T cells, can invade normal-appearing myofibers, a biopsy feature termed *focal invasion*.[12] The mechanism of focal invasion is unclear but may relate to the presence of major histocompatibility complex type I (MHC-I) expression on myofibers. MHC-I on myofiber membranes is absent in normal muscle but is widely expressed in biopsies of patients with sporadic IBM.

Pathologic features often described in muscle biopsies of patients with sporadic IBM include rimmed vacuoles, protein aggregates, and mitochondrial dysfunction. These features have prompted a pathologic categorization scheme to describe sporadic IBM pathology as inflammatory myopathy with vacuoles, aggregates, and mitochondrial pathology (IM-VAMP).[10] Vacuoles, aggregates, and mitochondrial pathology (VAMP) are often striking and specific pathologies but can be rare within a patient biopsy (biopsies in patients with sporadic IBM have rimmed vacuoles in approximately 1% to 6% of fibers) and are often missed.[13] In addition, the ability to see rimmed vacuoles, protein aggregates, and mitochondrial dysfunction can require more specialized histochemical stains and immunohistochemistry that may not be routinely performed by community pathology laboratories. For this reason alone, a reliance on biopsy criteria to make a diagnosis of sporadic IBM is flawed, and a clinical definition with supportive biopsy findings may be more appropriate. Indeed, when using diagnostic criteria that relied heavily on specific pathologic features rather than clinical features, the sensitivity was significantly reduced.[9]

Several consensus diagnostic schemes have been developed since the initial recognition of sporadic IBM as a distinct clinic entity.[9] These criteria use clinical, laboratory, and biopsy features. However, revised diagnostic criteria are needed and should be less restrictive and more clinically focused, with less emphasis on rare pathologic features. A recent study found that the most common sporadic IBM diagnostic categorization schemes had excellent specificity but limited sensitivity and failed to adequately capture all patients with sporadic IBM, suggesting that many patients with sporadic IBM are not diagnosed.[9] For example, using the most recent diagnostic criteria derived from a 2013 European Neuromuscular Centre workshop,[14] only 15% of patients with sporadic IBM would be recognized as clinicopathologically defined (a more stringent categorization), whereas 84% of patients with sporadic IBM would be recognized using the less restrictive categorization of probable sporadic IBM. Regardless, even the least restrictive categorization fails to identify a patient with sporadic IBM 16% of the time.[9] The same study found that clinical measures of strength such as finger flexor weakness and knee extension strength less than or equal to hip flexion strength outperformed many pathologic features necessary to make a definite versus probable diagnosis.[9] As therapies are developed, it will be essential to use less restrictive criteria that rely less heavily on rare biopsy pathologies and more on clinical examination findings.

The recent identification of a serum autoantibody against anti–5'-nucleotidase, cytosolic IA (NT5C1A) in patients with sporadic IBM has offered a new clinical tool.[15,16] Several case series suggest that anti-NT5C1A seropositivity is present in 40% to 60% of patients with sporadic IBM.[15,16] While the presence of anti-NT5C1A seropositivity is low in healthy controls, it can be present in other inflammatory myopathies and systemic autoimmune disorders such as Sjögren syndrome and systemic lupus erythematosus.[17] Thus, in conjunction with clinical history and physical examination, anti-NT5C1A antibody testing may be helpful

KEY POINTS

- At present, muscle histology demonstrating endomysial inflammation, a feature that should be captured when a clinically affected muscle is biopsied, is required for a definitive diagnosis of sporadic inclusion body myositis.
- Overreliance on skeletal muscle histopathology and rare but specific biopsy features such as rimmed vacuoles or electron microscopic identification of proteinaceous inclusions may lead to an underdiagnosis of patients with sporadic inclusion body myositis.
- The most sensitive and specific diagnostic features for sporadic inclusion body myositis are the clinical presentation and physical examination findings.
- Diagnostic criteria that emphasize clinical measures of strength have higher sensitivity and specificity. Specifically, the presence of finger flexor weakness and knee extension strength less than or equal to hip flexion strength has a higher sensitivity for sporadic inclusion body myositis as compared with some pathologic features on muscle biopsy.

in establishing a diagnosis. Whether a positive anti-NT5C1A can replace a muscle biopsy diagnosis remains to be established. Notably, anti-NT5C1A seropositivity may have prognostic implications in patients with sporadic IBM. Anti-NT5C1A seropositivity is found more often in females and may be associated with a more severe phenotype that includes a reduced vital capacity, dysphagia, and higher risk of mortality because of respiratory compromise.[18]

TREATMENT AND MANAGEMENT

Currently, no treatment with proven efficacy slows or reverses sporadic IBM. Supportive care is the mainstay of therapy and includes appropriate introduction of assistive devices such as walkers and wheelchairs. No clear consensus exists regarding the benefit of nutritional supplements or specific exercise protocols. A self-reported calculation of functional status is positively correlated with participation in exercise.[19] Notably, swimming was the exercise reported as associated with the highest functional status when adjusted for age and disease duration. Interestingly, a similar correlation was not seen with participation in physical therapy. These findings emphasize the importance of identifying exercise regimens that minimize a patient's risk of injury and are tailored to the patient's desires.

Disease progression is slow, with an estimated decline of 4% per year in affected muscle groups such as those necessary for knee extension.[20] Loss of ambulation necessitating a wheelchair occurs in most patients 10 to 20 years after disease onset. Some patients develop dysphagia that can respond to pharyngoesophageal dilatation or a cricopharyngeal myotomy. Other complications include aspiration and respiratory compromise.

Falls are a frequent occurrence in patients with sporadic IBM[21]; 98% of patients with sporadic IBM report falling in the past year, and 34% report a fall in the past month.[21] The prevention of falls by patient education or therapy-based fall management programs are essential for patients with sporadic IBM. Patients with sporadic IBM do not have a decreased rate of survival, and preventing falls and aspiration are key to reducing morbidity.[22]

GENETICS

Patients with sporadic IBM have an increased association with coexisting rheumatic diseases such as Sjögren syndrome. Consistent with this association, the strongest genetic associations for sporadic IBM relate to specific human leukocyte antigen (HLA) haplotypes such as HLA-DRB1*03:01.[23] This finding alone lends strong support for autoimmunity in sporadic IBM pathogenesis. A combined genomic/proteomic approach identified an increase in rare missense variants in the autophagic trafficking protein FYCO1.[24] Whether specific HLA haplotypes or *FYCO1* variants alter treatments or prognosis is not established, and genetic assessment for these genes is not recommended.

PATHOGENESIS

The pathogenic mechanism of sporadic IBM remains poorly understood, thus limiting the identification of effective therapies. It is clear that sporadic IBM has an autoimmune component. This is evidenced by inflammatory features on biopsy, an association with specific HLA haplotypes,[23] and the identification of a diagnostic autoantibody (anti-NT5C1A).[15,16] Moreover, the clear identification of patients positive for HIV who develop sporadic IBM–like pathology, a similarly

stereotyped pattern of weakness, and even anti-NT5C1A seropositivity support a dysimmune etiology.[25] A T cell–mediated process has been proposed. This has been further supported by the association of sporadic IBM and T cell large granular lymphocytic leukemia.[26] This observation led to the further identification of clonally expanded CD8+CD57+ cells in the blood and biopsy infiltrates in patients with sporadic IBM, suggesting causality.[27] However, unlike an autoimmune disorder, other inflammatory myopathies, or even T cell large granular lymphocytic leukemia, immunomodulating agents are ineffective, and no therapy has been demonstrated to improve muscle weakness in sporadic IBM. This lack of treatment response has led to speculation that sporadic IBM has additional pathogenic processes unrelated to autoimmunity and is instead an age-associated degenerative myopathy. A more cautious interpretation would suggest that, at the time of patient presentation with clinically apparent muscle weakness, halting the autoimmune response is ineffective, and therapies aimed at reversing muscle degeneration may be more appropriate.

The lack of response to immunomodulation, onset occurring after 45 years of age, and biopsy features demonstrating VAMP features support a degenerative pathogenic mechanism. Moreover, the pathologic similarities of sporadic IBM with rimmed vacuolar myopathies with protein inclusions suggest that the pathogenesis of genetically defined hereditary inclusion body myopathy may inform the pathogenic mechanism of sporadic IBM.[28] The genetic causes of myopathies with rimmed vacuolar pathology are growing with the use of next-generation sequencing platforms. Although these myopathies can be mistaken for sporadic IBM because of biopsy features and slowly progressive weakness (CASE 3-2), these myopathies are clinically distinct from sporadic IBM and often have earlier ages of onset, distinctive patterns of weakness (eg, limb girdle or distal weakness), family history of weakness, and the absence of inflammation on muscle biopsy. The VAMP features in sporadic IBM muscle biopsies are the only unifying feature with other rimmed vacuolar myopathies but can inform the pathogenic mechanism.[28]

Hereditary Myopathies With Pathologic Similarities to Sporadic Inclusion Body Myositis

Several hereditary myopathies have pathologic similarities to sporadic IBM that include protein aggregates and rimmed vacuoles (CASE 3-2). These myopathies have been termed hereditary inclusion body myopathies, myofibrillar myopathies, or rimmed vacuolar myopathies. Distinct from muscle of patients with sporadic IBM, these disorders rarely have evidence of endomysial infiltration or focal invasion. Recently, next-generation sequencing of cohorts of patients with sporadic IBM revealed that approximately 2.5% of patients with a diagnosis of sporadic IBM, as defined by the neuromuscular physician, had a previously reported pathogenic mutation in valosin containing protein (*VCP*).[1,2] Dominantly inherited mutations in *VCP* cause a late-onset rimmed vacuolar myopathy.[29] *VCP*-associated myopathy can also have additional features of Paget disease of bone and frontotemporal dementia. Notably, none of the patients who had been previously diagnosed with sporadic IBM and were found to have pathogenic *VCP* mutations had Paget disease of bone or frontotemporal dementia, nor did they have a family history of weakness. In addition, each had a muscle biopsy with evidence of endomysial inflammation and, in some cases, focal invasion, rimmed vacuoles, and MHC-I upregulation.[1,2] These

KEY POINTS

- Anti–5'-nucleotidase, cytosolic IA (NT5C1A) seropositivity is present in approximately 40% to 60% of patients with sporadic inclusion body myositis. A negative anti-NT5C1A antibody test should not be used to rule out sporadic inclusion body myositis. Moreover, anti-NT5C1A seropositivity can occur in other inflammatory myopathies and should be interpreted with caution. It remains to be determined where anti-NT5C1A seropositivity fits within current diagnostic algorithms.
- Anti–5'-nucleotidase, cytosolic IA seropositivity may predict a more severe sporadic inclusion body myositis phenotype with higher mortality and bulbar symptoms.
- Although not systematically studied, exercise may correlate with a higher functional status in patients with sporadic inclusion body myositis.
- Sporadic inclusion body myositis is a slowly progressive chronic muscle disease. Patients decline at an average rate of 4% per year in affected muscle groups. Most patients with sporadic inclusion body myositis lose ambulation after 10 to 20 years of the disease.
- Of patients with sporadic inclusion body myositis, 98% report falling within the last year. Prevention of falls by patient education is an essential aspect of care of patients with sporadic inclusion body myositis.

findings are not intended to suggest that *VCP* mutations cause sporadic IBM but instead emphasize that some patients with apparent sporadic IBM may be misdiagnosed and have a hereditary muscle disease. The phenotypic variability seen in these hereditary myopathies can even fulfill restrictive diagnostic criteria for sporadic IBM, placing the responsibility on the clinician to consider hereditary disorders when onset is earlier than age 45, the pattern of weakness is atypical, serum CK is more than 10 times the upper limit of normal, muscle biopsy lacks evidence of inflammation or MHC-I upregulation, or when the patient has a family history of weakness, amyotrophic lateral sclerosis, dementia, or Paget disease of bone.

CASE 3-2

A 49-year-old man presented to a neuromuscular specialist because of 3 years of progressive weakness. He initially began noticing weakness with left ankle dorsiflexion that 1 year later progressed to right ankle dorsiflexion, prompting initial medical attention. His family history was notable for dementia in his 75-year-old mother, who lived in a nursing home.

On examination he had symmetric 4/5 bilateral deltoid weakness, mild wrist extensor weakness, asymmetric 4/5 right and 5−/5 left quadriceps weakness, and bilateral 3/5 ankle dorsiflexion weakness.

His creatine kinase (CK) level was 551 U/L (normal 20 U/L to 200 U/L). Nerve conduction studies were normal, while EMG demonstrated small, short-duration, polyphasic motor unit potentials in the upper and lower extremities with some fibrillation potentials, consistent with a myopathy.

The patient had a left deltoid muscle biopsy that revealed chronic myopathic changes; several small, angular fibers with rimmed vacuoles; and a cluster of increased endomysial cellularity with one focally invaded fiber within one region of the biopsy. A presumptive diagnosis of inclusion body myositis (IBM) was made.

He returned to clinic 16 years later at the age of 65 and was nonambulatory. Testing for anti–5'-nucleotidase, cytosolic IA (NT5C1A) serology was negative. Panel-based genetic sequencing for hereditary myopathies identified a p.R159C missense mutation in the *VCP* gene.

COMMENT

This patient has a pathogenic mutation in *VCP* consistent with an autosomal dominantly inherited form of inclusion body myopathy. Notably this patient did not have a family history of weakness but did have a first-degree relative with dementia. Small family structures and varied penetrance of disease phenotypes can often mislead clinicians away from considering a genetic disease. Patients with *VCP* mutations can present with a constellation of diseases that include weakness, dementia, and bone disease. In addition, while not typical, patients with hereditary forms of inclusion body myopathy can have rimmed vacuoles and endomysial inflammation. Considering a diagnosis of hereditary inclusion body myopathy in a patient with early-onset disease (younger than 55 years of age) and with an atypical pattern of weakness (this patient did not have finger flexor weakness early in his disease course) is warranted with panel-based sequencing.

Rimmed Vacuoles as Insight Into Pathogenesis

Rimmed vacuoles are membranous collections of accumulated proteins and organelles found within myofibers. They can be histologically identified by several different stains but are classically identified using modified Gomori trichrome, where they have a red rim and basophilic debris. Rimmed vacuoles are distinct from other vacuoles such as the vacuoles seen in autophagic vacuolar myopathies, which include acid maltase deficiency or Danon disease. The pathologically identified vacuoles in autophagic vacuolar myopathies are lysosomal in origin, stain with acid phosphatase, and are sometimes labeled with sarcolemmal membrane proteins such as dystrophin.[30]

The origin of a rimmed vacuole is less clear. Rimmed vacuoles have been demonstrated to contain autophagic and endosomal proteins as well as nuclear membrane and endoplasmic reticulum proteins.[13,31–33] This suggests a more generalized dysfunction in membrane trafficking. Other proteins that accumulate are structural proteins that include intermediate filaments, RNA-binding proteins, and proteins associated with protein folding and degradation.[24,34–36] Consistent with this, rimmed vacuoles are most commonly a feature of genetic diseases associated with mutations in three categories of proteins: (1) structural proteins such as desmin and filamin C[37,38]; (2) RNA-binding proteins such as TIA1 and HNRNPA1 with aggregation-prone domains[39,40]; and (3) proteins necessary for protein quality control (DNAJB6, VCP, and SQSTM1).[29,41–43] The pathogenic intersection of these proteins is not entirely clear but supports that improving protein quality control may be a reasonable therapeutic intervention.

Indeed, two early-stage clinical trials are using small molecules that may improve protein quality control in sporadic IBM. Interestingly, both of these medications (arimoclomol and rapamycin) were initially tried in mouse models of *VCP*-associated myopathy to support preclinical efficacy.[44–46] Arimoclomol is a heat shock protein inducer and is hypothesized to increase molecular chaperone function. Molecular chaperones help fold proteins within the myofiber, reducing protein aggregation and myodegeneration.[44] Rapamycin may have a twofold function in that it is immunomodulating but can also enhance autophagy.[47] An increase in autophagy may facilitate the clearance of protein inclusions that are deleterious in sporadic IBM. Both of these therapies are focusing on pathomechanisms other than immunomodulation and will address the issue of whether myodegeneration is an effective therapeutic target in sporadic IBM.

KEY POINTS

- Although defined as a sporadic disease, patients with sporadic inclusion body myositis may carry genetic risk factors that are associated with autoimmunity and muscle degeneration such as a human leukocyte antigen DRB1*03:01 allele or *FYCO1* missense variants.
- No treatment has been demonstrated to be clinically effective at reversing or slowing weakness in patients with sporadic inclusion body myositis.
- Patients with hereditary myopathies can be mistaken for sporadic inclusion body myositis because of clinical and biopsy features that overlap.
- Future therapies aimed at correcting muscle degeneration rather than immune dysfunction may be effective in treating patients with sporadic inclusion body myositis.

CONCLUSION

Sporadic IBM is a slowly progressive, late-onset, and currently untreatable degenerative muscle disease. The prevalence of sporadic IBM is underestimated and will likely increase as diagnostic criteria become less restrictive and the population ages. It is essential that novel therapeutic targets are identified that reverse the degenerative component of this disease. Insights gained from hereditary disorders with pathogenic similarities may reveal pathogenic targets and preclinical models for the testing of future therapeutics.

USEFUL WEBSITES

CURE IBM
This is a patient-focused website that provides information on sporadic IBM.
cureibm.org/

CURE VCP DISEASE
On this website, patients and caregivers can find information about VCP-associated muscle disease.
curevcp.org

THE MYOSITIS ASSOCIATION
This website directs patients to resources about myositis, including IBM.
myositis.org/

WASHINGTON UNIVERSITY NEUROMUSCULAR WEBSITE
This is a physician-focused website that provides up-to-date clinical and pathologic information on IBM and other neuromuscular diseases.
neuromuscular.wustl.edu/

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