Inclusion body myositis
Steven A. Greenberg

Division of Neuromuscular Disease, Department of Neurology, Brigham and Women’s Hospital, and Children’s Hospital Informatics Program, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Steven A. Greenberg, MD, Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115, USA
Tel: +1 617 732 8641; e-mail: sagreenberg@partners.org

Current Opinion in Rheumatology 2011, 23:000–000

Purpose of review
Sporadic inclusion body myositis (sIBM) is a poorly understood immune and degenerative disease of skeletal muscle. Here, current opinion of the nature of this disease is summarized.

Recent findings
Recent findings for sIBM include further characterization of muscle involvement through magnetic resonance imaging, the role of muscle as a host for immune cells, progress in the role of extranuclear TDP-43 in causing cellular injury, and the discovery of a new sIBM autoantibody.

Summary
sIBM understanding continues to advance, with progress regarding the mechanism of this disease.

Keyword
inclusion body myositis

Introduction
Sporadic inclusion body myositis (sIBM) is a slowly progressive degenerative and inflammatory disorder of skeletal muscle of unknown cause beginning in middle or later life. Selective involvement of specific muscles, including finger flexors and quadriceps, together with certain degenerative and immune muscle histopathological changes and refractoriness to treatment are distinctive features of this syndrome.

Epidemiology
sIBM is the most common muscle disease of aging, generally affecting individuals over the age of 50. A number of recent reviews are available [1–6]. sIBM prevalence estimates vary widely across different ethnic populations. Per million estimates include 1.0 in Turkey, 4.7 in the Netherlands [7], 10.7 in Connecticut USA [8], 14.9 in western Australia [9], and 71 in Olmsted County USA [10]. Age 50 or greater prevalence estimates are approximately three-fold higher [11]. sIBM is considered to be rare among Asians and African–Americans [11].

Clinical features
sIBM is a slowly progressive muscle disease with symptoms generally due to a specific pattern of muscle involvement (see for example [12,13]). Involvement of the quadriceps muscle, resulting in difficulty walking and knee buckling, and finger flexors, resulting in grip weakness, are distinctive features (Fig. 1). Finger flexor weakness is commonly worse on the nondominant side [14,15]. Ankle dorsiflexion weakness (‘footdrop’) is common, and dysphagia may occur but is typically not severe. Delayed diagnosis (average time 5.2 years) [15] and misdiagnosis [11] are common observations. Over-reliance on muscle biopsy features relative to clinical features contributes to misdiagnosis, with failure to recognize weakness of flexor digitorum profundus (flexing the finger tips) or flexor digitorum superficialis (flexing fingers at their proximal interphalangeal joints) is likely the most common reason for misdiagnosis. MRI is helpful in delineating specific patterns of muscle involvement [16,17].

Pathology
The muscle pathology of sIBM typically demonstrates extensive endomysial inflammation, with inflammatory cells surrounding myofibers, as well as less specific myopathic features (for example, fibrosis, variation in myofiber size, and atrophic fibers). Although invasion of nonnecrotic myofibers by inflammatory cells has been frequently emphasized, the surrounding of myofibers by these cells without invasion is far more common. Nodular collections are frequently present and often displace myofibers [18]. Rimmed vacuoles, more commonly visible on Gomori trichrome stains than hematoxylin and eosin (H&E) stains, are variably present in approximately 1–6% of myofibers [19]. The rimmed vacuoles seen on frozen sections are in part artifactual, as these empty spaces contain cytomembranous and nuclear material visible in glutaraldehyde-fixed toluidine stained thin sections that better preserve muscle morphology (Fig. 2). Masses of tubulofilaments visible by electron microscopy are often within nuclei or...
2 Myositis and myopathies

Figure 1 Clinical features

(a) Finger flexor weakness in sporadic inclusion body myositis (sIBM). Patient attempting to close both hands. (b) Quadriceps atrophy visible with T1 axial MRI. Severe involvement of vastus lateralis and vastus medialis (white arrows) with relative preservation of rectus femoris (black arrow) and the posterior thigh is characteristic of sIBM.

in clumps suggestive of former nuclei devoid of nuclear membrane (Fig. 2).

Diagnostic criteria
sIBM diagnosis depends foremost on the clinical pattern of weakness, supported by laboratory features (serum creatine kinase that is not too elevated) and pathological features. Among patients with difficulty distinguishing sIBM from polymyositis, an sIBM pattern of weakness (clinical sIBM) is predictive of treatment refractoriness even in the absence of biopsy-evident rimmed vacuoles (biopsy polymyositis) [20]. For research purposes, the European Neuromuscular Centre (ENMC) diagnostic criteria [7] recognize this important point, allowing a diagnosis of probable sIBM if typical clinical features are present but rimmed vacuoles absent.

Immunology: genomic studies, mechanisms, and autoantibody discovery
Immune injury of IBM myofibers has traditionally been viewed as due to cytotoxic T cells. Recent studies have demonstrated expanded roles for other arms of the immune system, including myeloid dendritic cells (mDCs) [21], B cells [18,22–24], and a newly discovered IBM autoantibody [25].

T cells
A role of cytotoxic T cells in IBM myofiber injury has long been recognized and emphasized. Models of such injury are based on observations of the types and locations of T cells present in muscle, the nature of the T-cell antigen receptor present on these cells, and the presence of the cytotoxic T-cell molecules perforin, granzyme A, and granulysin [26]. These models propose that the common final pathway by which the immune system injures IBM muscle is cytotoxic T-cell invasion of myofibers. However, it is noteworthy that the vast

Key points
- Inclusion body myositis (IBM) is a disease with much opportunity for further research and understanding.
- IBM is a highly atrophying disease and the mechanism of this atrophy is unknown.
- An IBM autoantibody was recently reported.

Figure 2 Sporadic inclusion body myositis myonuclear pathology

(a, b) Rimmed vacuoles typically are lined with nuclear membrane proteins, such as emerin (shown here) and lamin A/C. (c) Vacuoles seen on glutaraldehyde-fixed toluidine blue stained thin sections show vacuoles are not empty spaces but contained packed structures including degrading nuclei and membranous material. (d) Electron micrograph showing a mass of tubulofilaments within a nucleus. (e-1, e-2) TDP43 sarcoplasmic deposits in a myofiber whose nuclei are devoid of TDP43 (white arrowheads). Panels a and d reproduced with permission from [19].
majority of immune system cells in IBM muscle biopsy cross-sections appear to surround but not invade myofibers (Fig. 3a). These immune cells may be injuring myofibers through secreted molecules, not visible to the pathologist by microscopy. Very little study of the soluble immune protein compartment of IBM muscle has been performed.

**B cells**

B cells as defined by the surface markers CD19 and CD20 were long thought to be sparse or absent from IBM muscle, based on pivotal immunohistochemical studies performed in 1984 [27]. Surprisingly, microarray studies published in 2002 [22] showed an abundance of immunoglobulin transcripts in IBM muscle and led to the recognition in 2005 that plasma cells (CD138⁺ differentiated B cells) are transcriptionally active, producing and secreting immunoglobulins within IBM muscle [23], and in 2007 that these plasma cells are antigen directed and clonally expanded [24].

**Inclusion body myositis muscle has become an immune cell host**

Recent evidence indicates that IBM muscle has become an immune cell host, a place where B cells mature into plasma cells and mDCs activate T-helper cells (Fig. 3c) [18]. Nodular collections of immune cells (Fig. 3b) studied by serial sections and laser capture microdissection demonstrate the presence of plasma cells producing immunoglobulins with the same antigen specificity, therefore derived from a common precursor, developing in an environment rich in T-helper cells and the cytokine B-cell activating factor (BAFF). These nodular collections are unlike typical germinal center B-cell follicles recognized in other autoimmune disease tissue sites. Skeletal muscle is probably not well suited to function as both a force-generating contractile tissue and a lymphoid tissue supporting an environment for immune-cell interaction and maturation. The presence of this activity in IBM-diseased tissue provides a rationale for targeting molecules involving mDC/T-cell and T-cell/B-cell interactions in therapeutic trials of inflammatory myopathies.

**Anti-IBM-43: an inclusion body myositis autoantibody**

Recognition that a B-cell-specific response was present in IBM muscle and characterization of this response suggested that a search for circulating IBM autoantibodies might be fruitful. Since 1980 [28,29], autoantibodies have been recognized associated with polymyositis and dermatomyositis (reviewed in [30,31]) but no IBM autoantibody has been identified. In 2011, an autoantibody against a 43 kDa muscle protein (anti-IBM-43) was identified [25]. Plasma samples from 50 patients with myositis (25 with IBM, 10 with dermatomyositis, 10 with polymyositis, and five with myasthenia gravis) and 15 normal samples were examined by western blot for their binding to human muscle proteins from biopsy specimens. An autoantibody to an approximately 43 kDa protein was present in 52% (13/25) of the IBM samples and 0% (0/40) of all other samples (Fig. 4). For patients with myositis, this antibody, thus, had 52% sensitivity and 100% specificity for IBM. The identity of the 43 kDa protein has not been established.

**Nuclear degeneration: from rimmed vacuoles to TDP-43**

Myonuclear degeneration was emphasized as a prominent part of IBM pathology in the earliest studies by Chou in 1967 [32] and by Carpenter, Karpati, and coworkers in 1978 [33], and 1993–1996 [34–36]. These investigators formulated a hypothesis that rimmed vacuoles, a pathological feature that distinguishes IBM from other inflammatory myopathies on H&E and trichrome stained muscle sections, derived from the...
breakdown of myonuclei. This hypothesis was neglected in the medical literature between 1996 and 2007. There are at least 31 review papers on IBM written during this period [37]; none mentioned the existence of these data regarding myonuclear degeneration, the theory advocated by Chou, Carpenter, and Karpati, or its implications.

A resurgence of interest in IBM myonuclear degeneration has developed since recognition in 2006 that the vast majority of rimmed vacuoles are lined with nuclear membrane proteins, suggesting they derive from myonuclear breakdown (Fig. 2) [19,37]. One study found that 73% of H&E-defined rimmed vacuoles are lined with the nuclear membrane protein emerin. Recent studies continue to observe myonuclear degeneration [38]. The tubulofilaments that have been long recognized in IBM are frequently intranuclear (Fig. 2).

The recent discovery of the nucleic acid-binding protein TDP-43 in IBM nonnuclear sarcoplasm by four independent laboratories [39–42] is a major advance in this long-ignored theory. TDP-43 is a predominantly nuclear heterogeneous nuclear ribonucleoprotein (hnRNP) that undergoes nucleocytoplasmic shuttling and associates with translation machinery in the cytoplasm. TDP-43 has two RNA-recognition motifs (RRMs) capable of binding both DNA and RNA [43].

In IBM, 23% of myofibers contain nonnuclear sarcoplasmic TDP-43 accumulations; these fibers contain nuclear TDP-43 in only 12% of their nuclei, compared with TDP-43’s presence in 99% of normal muscle myonuclei (Fig. 2) [40]. TDP-43 has, thus, redistributed from nuclei to sarcoplasm in a large percentage of IBM myofibers. In western blot studies, abnormal TDP-43 degradation products are unique to sIBM among other inflammatory myopathy samples. TDP-43 sarcoplasmic accumulation is a highly sensitive and specific biomarker for IBM; the presence of more than 1% of affected myofibers was 91% sensitive and 100% specific to sIBM among 50 samples with inflammatory myopathies [40].

The consequences of TDP-43 redistribution have been unknown until recently. It is now clear that aberrant extranuclear accumulation of TDP-43 is toxic to cells, and that this toxicity depends on the TDP-43 nucleic acid-binding domain [44]. In a Drosophila model, targeting TDP-43 to cytoplasm by mutating its nuclear localization signal resulted in cellular cytotoxicity that was rescued after additionally mutating TDP-43’s RRM nucleic acid-binding domain. These studies suggest that accumulation of extranuclear TDP-43 is toxic through its binding to RNA.

**Other theories**

Many theories of pathogenesis of sIBM have been proposed over the four decades since its pathological delineation [32]. A potential viral etiology has repeatedly intrigued researchers, bolstered by the existence of HIV and human T-lymphotropic virus type I (HTLV-1)-associated sIBM [45]. The presence of mitochondrial abnormalities has been studied [46,47]. Toxicity theories of various molecules have dominated the field for two decades [48], with one such molecule forming the basis for at least 13 animal model publications (reviewed in [2]). This literature has been reviewed from the perspective of citation and belief [49].

**Conclusion**

sIBM remains a poorly understood inflammatory, atrophying muscle disease for which there is a major need for effective treatment. Of the inflammatory myopathies, it has the most intense and refined adaptive immune system response, yet remains refractory to all immune treatments reported tried to date. There is currently no understanding as to the cause and mechanism of the myonuclear and sarcoplasmic degeneration resulting in loss of myofibers and disability in patients with sIBM.

**Acknowledgements**

The author thanks the Muscular Dystrophy Association for inclusion body myositis research support through grants MDA186627 and MDA4353.

**Conflicts of interest**

There are no conflicts of interest.
References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

**of special interest**
**of outstanding interest**

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

17. A study of muscle selectivity as determined by MRL.