Inclusion Body Myositis

Background

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

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

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

Pathophysiology

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

Inflammatory changes

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

The endomysial infiltrates in patients with s-IBM are composed primarily of CD8+ T cells and macrophages in a 2:1 ratio.[5] Myeloid dendritic (antigen-presenting) and CD138+ plasma cells are also present in substantial numbers,[6, 7] while B cells and natural killer (NK) cells are rare. T cells, macrophages, and myeloid dendritic cells all have the potential to invade non-necrotic muscle fibers.[8] The autoinvasive CD8+ T cells surround major histocompatibility complex (MHC) class I-immunoreactive myofibers and express perforin and other markers of activation.[9, 10, 11]

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

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

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

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

Degenerative changes

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

Myofibers in s-IBM exhibit vacuolization, atrophy, abnormal myonuclei, and deposits of degeneration-associated proteins. Similar to actions in Alzheimer disease, myofibers in s-IBM accumulate amyloid-β (Aβ), phosphorylated tau (p-tau), apolipoprotein E, presenilin-1, the normal cellular isoform of prion protein (PrPc), and many other characteristic proteins. Two major types of protein aggregates are found in s-IBM myofibers: (1) rounded, plaquelike, Aβ inclusion bodies; and (2) linear, squiggly, p-tau inclusions (paired helical filaments). Both are amyloidogenic.

In general, protein aggregation ensues from the binding of unfolded and misfolded polypeptides. Unfolded and misfolded proteins, in turn, result from increased transcription, impaired disposal, abnormal crowding, or abnormal posttranslational modification of proteins, as might be induced by oxidative stress, various toxins, and aging. A specifically proposed mechanism involved in the formation of protein aggregates in s-IBM is inhibition of protein processing of amyloid precursor protein (APP) in s-IBM muscle. Askanas and Engel have proposed that overexpression of APP and accumulation of toxic Aβ oligomers are early upstream events in the pathogenesis of s-IBM, predisposing to tau phosphorylation, oxidative stress, proteosomal inhibition, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and, hence, abnormal signal transduction and transcription. That said, the accumulation of Aβ in s-IBM myofibers has been challenged.

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

Several protein kinases are also involved in the s-IBM pathogenic cascade. Kinases that promote tau phosphorylation include cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase-3β (GSK-3β). Both Cdk5 and GSK-3β are strongly expressed in vacuolated myofibers, where they colocalize with p-tau and the paired helical filaments. Lithium inhibits GSK-3β and was shown to decrease tau phosphorylation in a transgenic mouse model of s-IBM. Its clinical efficacy in s-IBM is now being investigated in a pilot study.

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

http://emedicine.medscape.com/article/1172746-overview#showall
As a likely secondary phenomenon, various mitochondrial abnormalities have been identified in s-IBM muscle, including ragged red fibers, cytochrome c oxidase-deficient fibers, and multiple mitochondrial DNA (mtDNA) mutations.\[48, 49, 50\] These changes might be mediated by aberrant mtDNA replication and maintenance due to oxidative stress, abnormal APP overexpression,\[51\] or proinflammatory cytokines.\[52\]

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

**Possible links between degenerative and inflammatory changes**

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

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

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

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

Alpha-B-crystallin is a small HSP, but the expression of other HSPs and markers of oxidative stress are not increased in X fibers, arguing against the presence of a nonspecific stress response or oxidative stress in these fibers. The implication of this finding is that increased expression of alpha-B-crystallin is an early event in the pathogenesis of s-IBM, triggered by an unidentified stressor acting upstream to the development of vacuolated, necrotic, invaded, and congophilic fibers. Engel has speculated that this stressor might be a viral infection or mutated gene.\[59, 28\] Muth et al demonstrated an association between alpha-B-crystallin and APP/Aβ in X-fibers, supporting an early inflammatory response, with subsequent degenerative Aβ accumulation and vacuolar changes.\[60\]

**Epidemiology**

**Frequency**

**United States**

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

**International**
In 2 population-based studies, a prevalence of 4.9 per million was reported in the Netherlands (which was felt to be an underestimate) and 9.3 per million in western Australia. The corresponding figures for individuals older than 50 years were 16 and 35.3 per million, respectively.[61, 62] A western Australian survey in 2006 revealed a prevalence of 39.5 per million for individuals older than 50 years (unpublished).

**Mortality/Morbidity**

- The slow, relentless progression of muscle weakness in s-IBM leads to difficulty with ambulation, frequent falls, and eventual need for assistive-gait devices. Bone fractures and other complications may occur as a result of falls. Patients are often significantly disabled because of finger flexor weakness.
- Dysphagia due to weakness of the cricopharyngeal musculature may predispose individuals to aspiration pneumonia.
- Mortality rate is difficult to assess based on current data. Affected individuals tend to be older, the disease is insidious and chronic, and patients often die of other medical problems. In a population-based study, the mean age of death of patients with s-IBM was not significantly different from that of the general population. Cause of death was disease-related (aspiration pneumonia and respiratory insufficiency) in 2 of 22 reported deaths.[61] In a 12-year follow-up study in the Netherlands, life expectancy was normal (81 years), although activities of daily living were restricted.[63] The most common cause of death was respiratory system disorders.

**Race**

- No race predilection for s-IBM is known, but the condition has been noted to be uncommon among African Americans, Koreans, and Mesoamerican Mestizos.[64]

**Sex**

- Reported male-to-female ratio ranges from 1.4:1 to 3:1.[65, 62, 61]

**Age**

- Age of onset ranges from the late second to ninth decades. Mean age of onset is 56-60 years.[65, 61, 62]
- While a large majority of individuals develop symptoms when older than 50 years, 17-20% present before the age of 50.[65, 66, 61]
- The diagnosis of inclusion body myositis is often delayed by a mean of 5-8 years from time of symptom onset.[65, 61, 67, 66, 68]

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References


5. Engel AG, Arahata K. Monoclonal antibody analysis of mononuclear cells in myopathies. II: Phenotypes of


25. Matsuura E, Umehara F, Nose H, Higuchi I, Matsuoka E, Izumi K. Inclusion body myositis associated with


66. Lindberg C, Persson LI, Bjorkander J, Oldfors A. Inclusion body myositis: clinical, morphological,


112. Askanas V. 1996.


attack in idiopathic inflammatory myopathies.