Diagnosis, pathogenesis and treatment of inclusion body myositis
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Purpose of review
We provide an update of progress gained from research into sporadic inclusion body myositis (s-IBM).

Recent findings
Most research on s-IBM has focused on the inflammatory reaction or the accumulation of pathological proteins in vacuolated muscle fibres. The inflammatory reaction is characterized by clonal expansions of lymphocytes, predominantly CD8⁺ cytotoxic T cells, which invade and destroy muscle fibres. That costimulatory molecules have been identified demonstrates that muscle fibres can act as antigen presenting cells, and the expression of various chemokines in muscle indicates their importance in the immunopathogenesis of s-IBM. The region of interest for a susceptibility gene in the major histocompatibility complex has been narrowed, and for the first time it has been demonstrated that a chronic viral infection can trigger the inflammatory process leading to s-IBM. The nature of the accumulated material associated with the vacuoles has been extensively investigated over the past few years. Amyloid-β and phosphorylated tau protein in intracellular inclusions are a characteristic finding in s-IBM, which may lead to calcium dyshomoeostasis and endoplasmic reticulum stress. The proteasomal system is upregulated, including immunoproteasomes. 'Molecular misreading' leading to ubiquitin mRNA mutations and accumulation of pathological ubiquitin in muscle fibres may be associated with proteasomal dysfunction. There is still no efficient treatment for s-IBM, but the effects of new, more specific immunotherapies have begun to be explored.

Summary
Recent findings indicate that both inflammatory reaction and abnormal protein accumulation are important for the pathogenesis in s-IBM. The link between them continues to await elucidation.

Keywords
diagnosis, inclusion body myositis, pathogenesis, treatment

Abbreviations
AβPP amyloid-β precursor protein
CCL CC chemokine ligand
CCR CC chemokine receptor
HLA human leucocyte antigen
HTLV human T-cell leukemia virus
ICOS inducible costimulator
INOS inducible nitric oxide synthase
MHC major histocompatibility complex
PPR prion protein
SDF stromal cell-derived factor
s-IBM sporadic inclusion body myositis
UBB ubiquitin B

Introduction
Sporadic inclusion body myositis (s-IBM) has attracted much interest, partly because it combines features of inflammation and vasculature degeneration with accumulation of pathological proteins, which exhibit many similarities to changes in the brain that occur in Alzheimer's disease. Research into the pathogenesis of s-IBM has followed different lines focusing either on the inflammation or the protein accumulation. Diagnosis of s-IBM is usually based on combined clinical and histopathological features. For a diagnosis of definite s-IBM, certain morphological features should be present. Atypical cases or cases in which the muscle biopsy does not show all of the expected changes are diagnostic problems. Steroid and other immunosuppressive treatments in s-IBM have yielded disappointing results, and the possible beneficial effects of other pharmacological interventions have begun to be explored.

Clinical and diagnostic aspects
s-IBM is considered to be the most common acquired muscle disease in adults, and is characterized by onset at age 50 years or older. In typical cases muscle weakness and wasting are most profound in knee extensors, hip flexors and long finger flexors (Fig. 1). Difficulty with swallowing is encountered by about 50% of the patients [1]. Weakness of the diaphragm is probably an underdiagnosed manifestation of inflammatory myopathies, including s-IBM [2*]. Subacute respiratory failure was reported in one patient with s-IBM who required mechanical ventilation [3*]. Magnetic resonance imaging has been used to visualize inflamed or atrophic muscles in inflammatory myopathies, including s-IBM [4,5]. Whole body turbo STIR (short T1 inversion recovery) magnetic
Figure 1. Muscle wasting in sporadic inclusion body myositis

Shown is atrophy of quadriceps and flexor digitorum profundus muscles in a patient with sporadic inclusion body myositis.

Recent descriptions of diseases that may mimic s-IBM histopathology include a case of Emery–Dreifuss muscular dystrophy and a case with vitamin E deficiency [9,10]. In addition to light microscopic features such as inflammatory infiltrates and rimmed vacuoles, a further clue to the correct diagnosis is upregulation of major histocompatibility complex (MHC) class I, which has been demonstrated to be a valid test for s-IBM and other inflammatory myopathies [11,12*].

Inflammatory reaction and immunogenetics

Although s-IBM is usually grouped among the idiopathic inflammatory myopathies together with polymyositis and dermatomyositis, its aetiology is unknown, and the role played by the inflammation has been questioned [13]. Several factors support the view that the inflammatory reaction is an early "upstream" event. One is that invasion of non-necrotic muscle fibres by mononuclear cells is generally several-fold more frequent than fibres exhibiting any other typical pathological alterations such as rimmed vacuoles [14]. Another is that s-IBM frequently occurs with other autoimmune diseases and is in most cases associated with human leucocyte antigen (HLA)-DRB1*0301 (HLA-DR3) [15*,16,17]. The autoimmune inflammatory cells are predominantly cytotoxic, CD8+, activated T cells, and the invaded muscle fibres consistently express MHC class I on their surface, suggesting an antigen-driven T cell-mediated destruction of muscle fibres. This hypothesis is supported by the fact that the T cells appear in a restricted number of expanded clones that are identical in different muscles of an individual and that these clones persist over many years [18]. The concept that s-IBM is a primary inflammatory myopathy

Figure 2. Typical morphological features of inclusion body myositis

(a) Mononuclear inflammatory cells invade non-necrotic muscle fibres (long arrow), and there are muscle fibres with rimmed vacuoles (short arrows; haematoxylin–eosin staining).
(b) The cytoplasmic filamentous inclusions (arrow) are usually located in association with rimmed vacuoles (electron microscopy).
is also supported by the observation that the patterns of inflammation in polymyositis and s-IBM are identical but different from patterns found in some muscular dystrophies that are known to exhibit inflammation and therefore can be misdiagnosed as polymyositis. One example is the myopathy caused by dysferlin deficiency, in which the inflammatory cell infiltration lacks evidence of T cell mediated muscle fibre degeneration, as is seen in s-IBM and polymyositis [19].

The role played by muscle cells in the initiation and propagation of the immune response in inflammatory myopathies has been debated. Specific stimulation of naïve T cells requires interaction of the T cell receptor with an antigen presented by MHC; interaction between CD28 on T cells with costimulatory molecules belonging to the B7 family, and other factors. Mature muscle cells do not express B7.1/B7.2 either normally or in inflammatory myopathies [20]. The presence of an alternative CD28 ligand (BB-1) on muscle fibres in s-IBM/polymyositis and thus their ability to activate naïve T cells remains controversial [21,22]. More recently, a molecularly defined member of the B7 family, namely inducible costimulator (ICOS) ligand, which has been associated with memory and effector T cell function, was found to be expressed on muscle fibres and upregulated in inflammatory myopathies [23]. ICOS-ICOS ligand interaction may stimulate T cell cytokine production and augment T cell clonal expansion. By combining mRNA and immunohistochemical analyses, it was demonstrated in s-IBM that ICOS ligand and ICOS are upregulated and that the majority of ICOS positive autoinvasive CD8+ T cells contain perforin [24**]. This finding supports the concept that antigen stimulated autoinvasive T cells exert cytotoxic effects in s-IBM. Another novel B7 family protein, namely B7-H1, is also upregulated in muscle fibres in inflammatory myopathies but may act in an inhibitory way by reducing the cytokine production of stimulated T cells [25]. These studies demonstrate that muscle cells may act as antigen presenting cells and have various immune regulatory properties.

Chemokines are chemotactic cytokines that induce directional migration of inflammatory cells into immuno-logically active sites. Families of chemokines are defined on the basis of sequence motifs containing cystein residues at the amino-terminus of the molecule. The families include CXC (α), CC (β), C (γ) and CX3C (fractalkine) chemokines. In idiopathic inflammatory myopathies the expression of various chemokines and their corresponding receptors have begun to be explored [26,27]. Recently, stromal cell-derived factor (SDF)-1 (CXC chemokine ligand 12), a CXC chemokine, was demonstrated to be expressed in normal muscle and upregulated in s-IBM and other idiopathic inflammatory myopathies [28*]. The majority of the inflammatory cells expressed CXC chemokine receptor 4, which is the receptor of SDF-1. CC chemokines attract and activate monocytes and T cells. In s-IBM the CC chemokine monocyte chemoattractant protein-1 (CC chemokine ligand 2) is expressed by endothelial cells near inflammatory foci and by macrophages [27]. An isoform of its receptor, namely CC chemokine receptor (CCR)2B, was found on the majority of invading macrophages, indicating that this receptor is the most important for monocyte chemotactic protein-1 triggered leucocyte activation [29*]. In a study of three additional β chemokines [CCL3 (MIP-1α), CCL4 (MIP-1β) and CCL5 (RANTES)] and their receptors [30*] it was found that CCL4 was upregulated in endothelial cells and that CCR5 (the receptor for CCL3 and CCL4) was upregulated and mainly observed in autoinvasive inflammatory cells. The β chemokine receptor CCR1 was reported to be upregulated in one study [30*] and downregulated in another [29*], illustrating some of the difficulties in the methodologies used in studies of cytokine expression in idiopathic inflammatory myopathies. None of these studies addressed whether the chemokine expression detected in inflammatory myopathies was unique to this pathological process or common to other circumstances of muscle inflammation.

Inducible nitric oxide synthase (iNOS) has been implicated in the pathogenesis of inflammatory diseases because nitric oxide may act as a cytotoxic effector molecule and iNOS is frequently upregulated in inflammatory lesions in various organs. With combined immunohistochemical and in-situ hybridization analyses, it was demonstrated that iNOS is upregulated in a subset of muscle infiltrating inflammatory cells in s-IBM and polymyositis [31]. iNOS was also present at the sarcolemma of muscle fibres invaded by inflammatory cells, indicating an active role for iNOS in the inflammatory lesions.

The strong association of HLA-DR3 (DRB1*0301) with s-IBM has repeatedly been demonstrated and is largely due to an association with the extended 8.1 ancestral haplotype, which also includes HLA-B8 and is associated with a number of autoimmune disorders [32]. Detailed investigation of the MHC region in patients with s-IBM has demonstrated that the association is not directly with HLA-DRB1, because carriage of HLA-DR3 without the central MHC region of the 8.1 ancestral haplotype is less common in s-IBM patients than in control individuals [33**]. According to results from this investigation, the susceptibility gene is likely to lie between HLA-DRB1 and HOX12. A candidate gene would be the butyrophilin-like MHC class II associated gene (BTL1-H1). In a cohort of 52 Dutch s-IBM patients there was a markedly increased frequency of HLA-B8 and HLA-DR3 and of HLA-DR52 and HLA-DQ2 [15*]. The frequency of HLA-DR53 was
significantly reduced, indicating that this might be a protective antigen, and HLA-A1 was associated with an earlier onset of disease in that study.

The antigen that is supposed to initiate and mediate the inflammatory attack on muscle fibres in s-IBM is not known. One possibility is that a viral infection triggers the reaction, s-IBM, as well as polymyositis, has in several cases been associated with human T-cell leukaemia/lymphoma virus (HTLV)-1 infection. Detailed analysis of inflammatory cells in blood and muscle was performed in one HTLV-1 infected patient who developed s-IBM [34**]. HTLV-1 infected CD4+ T cells and CD8+ T cells directed at the HTLV-1 Tax 11-19 peptide were abundantly present in muscle tissue, whereas virus mRNA was not detected in muscle fibres. The anti-Tax 11-19 CD8+ T cells produced perforin, indicating that they were activated and had a cytotoxic function. By reverse transcription polymerase chain reaction analysis, it was demonstrated that there was clonal expansion of the T cells with motifs in the CDR3 region of the T cell receptor that are known to be essential to recognition of the Tax 11-19 peptide. These T cells may correspond to those invading non-necrotic muscle fibres and causing direct muscle damage, or alternatively they may indirectly contribute to muscle damage by perpetuating a chronic inflammatory environment within the muscle. In either case, the report strongly supports the concept that chronic viral infection and immune recognition may be crucial to the inflammatory process that leads to s-IBM.

Abnormal protein accumulation

Rimmed vacuoles with collections of 15–21 nm tubulofilaments and accumulation of amyloid-β, phosphorylated tau and numerous other proteins are important features of s-IBM [13]. Although these typical pathological alterations are not specific for s-IBM, much interest has focused on the inclusions because they may be directly related to the aetiology and pathogenesis of the disease. Following the identification of many of the pathologically accumulated proteins, investigations have focused on the pathogenic events that lead to these changes, which exhibit several similarities to what is found in the brain in Alzheimer’s disease. Recent investigations have addressed questions concerning the handling and degradation of unfolded or misfolded proteins in muscle fibres.

The unfolded protein response – a reaction to endoplasmic reticulum stress – has been studied in s-IBM [35**]. Five studied endoplasmic reticulum chaperone proteins, including calnexin, calreticulin, BIP/GRP78, GRP94 and Erp72, were all increased in s-IBM muscle, and colocalized with amyloid-β precursor protein (AβPP) and amyloid-β. These studies indicate that the excessively synthesized AβPP in s-IBM causes endoplasmic reticulum stress and activation of the unfolded protein response.

The ubiquitin/proteasome system plays a key function in nonlysosomal protein degradation and is involved in multiple cellular functions of the cell. One important function is to degrade misfolded proteins and retro-transposed proteins from the endoplasmic reticulum. Proteasome expression and activity is increased in s-IBM muscle and colocalizes with abnormal aggregates of ubiquitin, phosphorylated tau and other proteins, indicating their involvement in the abnormal protein aggregation [36**]. A special type of proteasome has a central function in processing of antigens for presentation at the cell surface in the context of MHC. Upregulation of such immunoproteasomes, as defined by positive immune staining of the immunoproteasome subunits LMP2, LMP7 and MECL1 and concomitant MHC class I expression in muscle fibres, indicate a possible link between abnormal protein aggregation and antigen presentation by MHC class I [36**, 37].

Somatic mutations of ubiquitin B (UBB) transcripts by 'molecular misreading' cause an abnormal mutated UBB variant termed UBB1, which is related to proteasomal dysfunction and inclusions in nerve cells in some age-related neurodegenerative diseases [37]. UBB1 was identified in s-IBM muscle and colocalized with aggregates containing amyloid-β and phosphorylated tau [38**]. It was proposed that proteasomal inhibition by UBB1, amyloid-β and phosphorylated tau contribute to the pathogenesis of s-IBM. In the brain the level of mutant UBB mRNA is low in demented as well as nondemented individuals, and the accumulation of UBB1 protein appears not to be caused by an increase in the concentration of mutant UBB mRNA [39].

Demonstration of amyloid-β and hyperphosphorylated tau in vacuolated muscle fibres have been important discoveries in research into the pathophysiology of s-IBM [13]. In a recent study into the effect of human viral encoded amyloid-β and tau proteins in murine myotube cultures [40**] it was demonstrated that expression of the amyloid-β-42 peptide and tau resulted in hyperphosphorylation of tau and calcium dyshomeostasis. These findings strengthen the hypothesis that early upregulation and accumulation of AβPP and amyloid-β are important for the pathophysiologial events that lead to muscle degeneration and weakness in s-IBM. A possible link between amyloid-β upregulation, inflammation and ageing may be the increased T cell reactivity to amyloid-β, which is present in older individuals [41].

The tau aggregates in s-IBM are abnormally phosphorylated and muscle exhibits a biochemical profile of tau that is different from that in Alzheimer’s disease and other
"tauopathies" [42]. Further evidence for toxic effects of amyloid-β on muscle cells was obtained by studying the expression of insulin-like growth factor-I in s-IBM muscle [43]. Upregulation of insulin-like growth factor-I and its signalling pathways were observed in s-IBM muscle fibres, especially in association with amyloid-β accumulation, as well as in amyloid-β stimulated myotubes in vitro. These results were interpreted as a reactive upregulation of insulin-like growth factor-I, which may be protective for the muscle fibres. Based on the hypothesis that the accumulation of amyloid-β in muscle in s-IBM is partly dependent on impaired degradation, the influence of age in different muscle fibre types on levels of the amyloid-β degrading proteases insulin-degrading enzyme and nephrilysin were investigated [44]. Both enzymes increased in fast twitch muscle and decreased in slow twitch muscle with age in mice. The significance of this finding is unclear. Morphological studies show that there is atrophy of mainly type 2 (fast twitch) muscle fibres in s-IBM [45].

Several of the genes encoding proteins that are abnormally accumulated in s-IBM muscle have been investigated for mutations or allelic variants but no abnormalities have been found in these genes [46]. Apolipoprotein E and α1-antichymotrypsin polymorphisms were investigated in a cohort of 35 s-IBM patients and 57 control individuals, but no correlation between distinct genotypes and risk for developing s-IBM was found [47]. These findings confirm that there is no association between the apolipoprotein E ε4 allele (APOE-ε4) and s-IBM. Because APOE-ε4 is associated with increased risk for developing AD and with earlier disease onset, these findings indicate that the role played by apolipoprotein E is not the same in s-IBM as it is in Alzheimer's disease.

Prion protein (PrP) was previously described to be accumulated in vacuolated muscle fibres of s-IBM patients and in muscle fibres in other neuromuscular disorders. Extended studies demonstrated abnormal accumulation of the normal cellular form of PrP (PrP(C)) in muscle fibres in a large variety of muscle disorders as well as in lymphocytes in inflammatory myopathies [48]. The PrP(C) accumulation in s-IBM was not particularly associated with rimmed vacuoles. It was suggested that the upregulation of PrP(C) in various myopathies is a cellular stress response. One patient with s-IBM, who developed Creutzfeldt–Jakob disease, exhibited accumulation of pathological PrP (PrP(Sc)) in muscle, which was interpreted as caused by conversion of the abundant PrP(C) that is found in s-IBM muscle [49]. This finding also indicates that muscle may become a potentially infectious tissue when a muscle disease occurs concurrently with a prion disease.

Reactive oxygen species have been implicated in the pathogenesis of s-IBM [13]. They can be derived from several sources, mainly from the mitochondrial oxidative phosphorylation system. Another source, namely semicarbazide-sensitive amine oxidase, was investigated in s-IBM and other myopathies based on the hypothesis that deamination may be increased in myopathies with abnormal protein accumulation [50]. Semicarbazide-sensitive amine oxidase upregulation was found in all investigated myopathies, including s-IBM, but whether this in fact caused damaging production of reactive oxygen species could not be determined.

**Treatment**

Based on the assumption that s-IBM is a primary inflammatory myopathy, several immunosuppressive and immunomodulating therapies have been tried. However, treatment series with corticosteroids, azathioprine and cyclosporine A [1], and trials with methotrexate [51] and high-dose intravenous immunoglobulin [52] have been negative. However, it is our and others' experience that individual patients may respond to treatment with corticosteroids [53], methotrexate, intravenous immunoglobulin or mycophenolate mofetil. A randomized pilot trial on antithymocyte globulin treatment in s-IBM showed a positive response, supporting the concept of a pathogenic role for autoaggressive T cells [54]. A randomized pilot trial of interferon-β-1a at a dose of 60 μg/week intramuscularly found no effect on muscle strength or function [55]. There is still no proven successful immunosuppressive therapy in s-IBM, but future possible immunomodulating treatments may include therapeutic monoclonal antibodies directed at different steps in an autoimmune process (i.e. against T and B cells, cytokines, adhesion molecules and costimulatory molecules). A study with alemtuzumab has been started, and three out of 20 patients have thus far been enrolled (M. Dalakas, personal communication, April 2005).

Another approach to treatment was suggested by Askonas and Engel [13]. This is based on an intervention in a proposed pathogenic cascade and is aimed at reducing the accumulation of harmful unfolded or misfolded proteins, including the amyloid-β-42 peptide.

Because there is no effective medical treatment in s-IBM, all other measures that could possibly be of benefit to patients should be considered. Experience of physical exercise in s-IBM patients has been reviewed [56]. These studies clearly show that resistive and aerobic muscle training or aerobic endurance training can be performed without adverse effects. Although it is not proven that muscle training reduces muscle weakness and wasting in s-IBM, it is our routine to encourage patients to perform physical exercise. Dysphagia, which is commonly encountered in s-IBM, can be relieved either by ericopharyngeal myotomy or alternatively by botulinum toxin A injection into the upper oesophageal...
sphincter, which was shown to be effective in two patients [57]. The physician should be aware of the possibility of hypotension, and application of mechanical ventilation should be considered in such cases.

**Conclusion**

Recent research has added important information and has clearly indicated that inflammation and APBPP upregulation are both essential components of the pathogenesis of s-IBM. There are several interesting and important questions for the future. Where do these two research lines merge? Is the vascular degeneration induced by negative effects of chronic cytokine stimulation in muscle tissue or is it the inflammation triggered by peptides derived from accumulating proteins in degenerating muscle fibres? Which factors trigger the initiation of the inflammatory/degenerative process? Are there additional examples of chronic viral infections associated with s-IBM? Characterizing the precise role played by the clonally expanded, muscle infiltrating 'T' cells would be extremely important. Which is the important susceptibility gene in the MHC gene region? Is it involved in the immune system or other cellular functions?

Before we have precise answers to these questions, it is important to address and treat the consequences of the progressive muscle weakness: in younger s-IBM patients (age < 65 years), to carefully monitor attempts at treatment with one or a few drugs such as meflothrexate, mycophenolate mofetil or intravenous immunoglobulin; and to perform therapeutic trials with potentially effective drugs. Progress has been achieved toward defining a common protocol for treating s-IBM patients. Collaboration toward such a consensus in s-IBM would improve our ability to conduct multicentre trials. Given the low incidence of s-IBM, multicentre recruitment is needed to include enough patients to lend sufficient power to future randomized trials.

**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


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29 Abundant upregulation of SDF-1 by the receptor indicates that they play a significant role in the immunopathology of SIBM and idiopathic inflammatory myopathies. NeuroReport 2004; 15:265—267.


36 The upregulation of several endoplasmic reticulum chaperones in SIBM muscle demonstrates that endoplasmic reticulum stress and the unfolded protein response is in action in SIBM. The localization of endoplasmic reticulum chaperones with AIP provides evidence that these are involved in the AIP folding in SIBM.


The accumulation of abnormal ubiquitin due to multiple mutations of ubiquitin mRNA (UBB-1) was elegantly demonstrated in muscle of SIBM patients. UBB-1 is implicated in protein misfolding in Alzheimer’s disease and other neurodegenerative disorders. The demonstration of UBB-1 in SIBM is the first example of ‘molecular misfolding’ in muscle pathology.


Transgenic expression of the amyloid-β peptide and tau on calcium homeostasis in cultured myocytes was shown to increase the nitric oxide content of calcium and increase the synthesis and secretion of intracellular calcium. Tau was phosphorylated at certain epitopes only in the absence of amyloid-β. Calcium dyshomostasis caused by accumulation of amyloid-β and phosphorylated tau may possibly induce muscle weakness in SIBM.


A careful investigation of tau proteins in SIBM is reported.


The interesting observation that IGFI is upregulated not only in regenerating muscle fibres but also in non-regenerating fibres overexpressing amyloid-β both in vitro in SIBM and in vivo.


This systematic study on the expression of pro-inflammatory (P3) in muscle indicates that it is frequently upregulated as an unspecified reaction in various muscle diseases.


The interesting case report on a patient with Creutzfeldt—Jackob disease and SIBM demonstrates that pathological protein (P3) can be accumulated in muscle when there is pathological accumulation of normal protein (P3) in muscle, which occurs in various diseases (e.g. SIBM).


This case report on the association of SIBM with cancer describes a remarkable positive response to corticosteroids. A different pathogenic mechanism may be suspected to be of importance in a subgroup of SIBM patients.


An interesting and probably safe method to treat a serious condition of SIBM is described.


This report describes an international consensus on outcome measures in inflammatory myopathies with the exception of SIBM.