Review

Inclusion body myositis: A review of clinical and genetic aspects, diagnostic criteria and therapeutic approaches

Frank L. Mastaglia *, Merrilee Needham

Institute of Immunology and Infectious Diseases, Murdoch University, Murdoch, WA, Australia
Western Australian Neuroscience Research Institute, Queen Elizabeth II Medical Centre, Verdun Street, Nedlands, WA 6009, Australia

1. Introduction

The first description in the literature of the condition now referred to as inclusion body myositis (IBM) appears to have been that of Adams, Kakulas and Samaha in 1965 [1], although the name was not suggested until 1971 [2]. It is now recognised that sporadic inclusion body myositis (sIBM) is the most common primary myopathy presenting after the age of 40 years and the form of inflammatory myopathy most likely to be encountered in adult neurological practice. The prevalence of IBM varies, being highest in Caucasian northern European, North American and Australian populations in which prevalence figures of 4.9–14.9 per million have been reported [3,4]. It is distinguished from other inflammatory myopathies by its insidious and progressive course and selective pattern of muscle involvement, and pathologically by the combination of inflammatory and myodegenerative features and abnormal protein aggregates in affected muscles. Because of this, and the fact that the condition is poorly responsive to conventional forms of immune therapy, there is still debate as to whether IBM is primarily autoimmune in origin or a degenerative myopathy with a secondary inflammatory/immune response.

2. Clinical aspects

Typically, the quadriceps femoris and long finger flexors are preferentially affected and there is progressive wasting of the thighs and forearms (Fig. 1). Other muscle groups such as the finger extensors, upper arm muscles and ankle dorsiflexors are often also affected to varying degrees in patients with more advanced disease, and some patients may also develop weakness of the paraspinal muscles resulting in dropped-head or camptocormia, and of the facial muscles (Fig. 2). Because of the insidious nature of the disease and nonspecific initial symptoms many patients only seek medical attention once they start to have falls, and by then the degree of weakness and atrophy of the quadriceps is already quite advanced. Early symptoms which should raise suspicion of the diagnosis include difficulty in climbing stairs or rising from a chair or squat, aching in the thighs and knees with exercise, weakness of the oropharyngeal muscles is also common due to weakness of the oropharyngeal muscles and of the facial muscles (Fig. 2). Because of the insidious nature of the disease and nonspecific initial symptoms many patients only seek medical attention once they start to have falls, and by then the degree of weakness and atrophy of the quadriceps is already quite advanced. Early symptoms which should raise suspicion of the diagnosis include difficulty in climbing stairs or rising from a chair or squat, aching in the thighs and knees with exercise, weakness of grip and difficulty using spray cans or other utensils and tools. Dysphagia is occasionally an early symptom but more often develops later in the course of the disease [5,6]. Obstructive sleep apnoea due to weakness of the oropharyngeal muscles is also common [7]. Other clues to the diagnosis include the finding of selective weakness of the flexor digitorum profundus and flexor pollicis longus in the early stages with sparing of the flexor digitorum superficialis and intrinsic hand muscles, and an asymmetric pattern of muscle involvement with the weakness usually being more severe in the non-dominant arm and leg (Fig. 1).
Several studies have investigated the natural history of sIBM [8–12]. The rate of progression of weakness has been shown to be around 4% per year and is more rapid in the lower limbs, but varies from patient to patient. As the condition progresses, patients have increasing difficulty with everyday activities such as handwriting, cutting up food, dressing, personal hygiene and mobility and become increasingly dependent. Most patients need to use a walking stick or walker after 5–10 years, but only a minority become wheelchair-bound. A 10 point IBM functional rating scale has been developed to quantify and monitor the severity of these disabilities over time [13].

3. Immunological associations

In some cases sIBM is associated with another autoimmune disease such as Sjögren’s syndrome [14], systemic lupus erythematosus, scleroderma, rheumatoid arthritis or thrombocytopenic purpura [15]. In addition, the frequency of non-organ specific auto-antibodies such as antinuclear antibody, anti-Ro 52/60 and anti-ribonucleoprotein, and monoclonal gammopathy is increased [16,17]. sIBM has also been reported to occur in association with retroviral infections (human immunodeficiency virus or human T-cell lymphotrophic virus I), chronic lymphocytic leukaemia [18] and immunodeficiency states [19,20]. These findings are all suggestive of an underlying disturbance of immune control and support the hypothesis of an immune basis for the myopathy. The recent demonstration of serum antibodies to cytosolic 5-nucleotidase (anti-cN1A) with a high specificity for sIBM provides further evidence of an underlying immunological process and a possible link between the autoimmune and myodegenerative components of the disease [21,22].

4. Genetics

Most cases of IBM are sporadic, but there are rare reports of familial cases with a recessive or dominant pattern of inheritance [23–26]. In Caucasian populations there is a strong association with the HLA-DRB1*0301 allele and 8.1 major histocompatibility complex (MHC) ancestral haplotype (HLA-A1, B8, DR3) in sporadic cases, and HLA-DRB1*0301 carriers have more severe muscle weakness [17,27–30]. It has been estimated that in Western Australia, carriers of HLA-DRB1*0301 have a 10-fold higher risk of developing sIBM [3]. Carriers of the HLA-DRB1*0301/*0101 diplotype were found to have the highest disease risk and more severe muscle weakness [30,31]. In contrast, carriage of the secondary HLA-DRB loci DRB4 and DRB5 is protective and is associated with a reduced risk of developing IBM [32]. Although apolipoprotein E (APOE) alleles do not influence the risk of developing sIBM [33], the rs10524523 polymorphism in the TOMM40 gene, which is in linkage disequilibrium with APOE and encodes an outer mitochondrial membrane translocase, has recently been shown to be protective and is associated with a reduced disease risk and a later age at the onset of symptoms [34].

5. Electrophysiological studies

Electromyography (EMG) can provide a clue to the diagnosis of sIBM, and typically shows a mixture of low amplitude short duration and large longer duration motor unit potentials, as well as spontaneous fibrillations and positive sharp waves in affected muscles such as the flexor digitorum profundus [35]. In some patients these findings may lead to a mistaken diagnosis of a neurogenic disorder such as amyotrophic lateral sclerosis [36]. While large polyphasic potentials can also be seen in other chronic myopathic conditions, this “mixed” EMG pattern with myopathic and neuropathic-appearing motor unit potentials is very typical of sIBM. A neurogenic component has in fact been excluded by quantitative EMG and single fibre EMG studies [37–39]. However, some patients may develop a mild peripheral neuropathy and electrophysiological evidence of a subclinical neuropathy may be found in some cases [40,41].

6. Muscle imaging

Muscle MRI can provide useful information that may help in the diagnosis of sIBM, particularly in cases in which the muscle biopsy is
inconclusive, and allows recognition of the selective pattern of muscle involvement in the upper and lower limbs and degree of involvement of the paraspinal muscles. Proton-density weighted images demonstrate atrophy and signal change in the deep flexor muscles of the forearms and in the quadriceps femoris and calf muscles (Fig. 3, 4) [42] which are also seen with T1- and T2-weighted and fat-suppressive short tau inversion recovery sequences. MRI also demonstrates the preferential involvement of the vasti with relative sparing of the rectus femoris, and of the medial head of gastrocnemius and flexor digitorum profundus [42–45].

A recent ultrasound study of the forearm muscles has shown that a contrasting pattern of echogenicity in the flexor digitorum profundus and flexor carpi ulnaris muscles can be helpful diagnostically [46].

Preliminary studies using $^{11}$C Pittsburgh Compound-B positron emission tomography scanning to detect deposition of $\beta$-amyloid in skeletal muscles have been carried out [47], but it remains to be determined if this will be reliable enough to be of diagnostic value.

### 7. Muscle pathology

The major pathological features on which the diagnosis of sIBM is based are summarised in Table 1. The endomysial inflammatory infiltrate is mixed and comprises mainly CD8$^+$ T cells, but also variable numbers of CD4$^+$ T cells, myeloid dendritic cells, macrophages and plasma cells [48,49]. CD8$^+$ T cells surround and invade non-necrotic muscle fibres and are thought to cause perforin-mediated cytotoxic injury as a result of the interaction between antigen presenting MHC class I molecules on muscle fibres and co-stimulatory molecules on the CD8$^+$ cells. Serial T cell receptor spectratyping on muscle tissue has shown that the CD8$^+$ T cells are clonally expanded in situ and persist over time, suggesting an antigen-driven immune response [50,51], as does the finding of upregulation of both MHC Class I and II antigens in muscle fibres [52] (Fig. 5).

In addition to the inflammatory infiltrate, degenerative changes are present in variable numbers of muscle fibres. These include rimmed vacuoles, eosinophilic inclusions, and greater than expected numbers of cytochrome oxidase deficient (COX-negative) muscle fibres for the patient’s age, suggesting that there is an acceleration of the normal aging process in sIBM muscle (Fig. 6). The rimmed vacuoles represent areas of autophagic degeneration and are ubiquitin-positive. Amyloid-like inclusions can be identified in sections stained with crystal violet (Fig. 5), or Congo red viewed with Texas red filters. Immunohistochemical staining techniques demonstrate pathological aggregates of a variety of proteins in muscle fibres including $\beta$-amyloid, TDP-43, $\alpha$B-crystallin, myotilin and p62 (Fig. 6) [53], suggesting that protein degradative mechanisms in muscle fibres are dysfunctional [54].

Whilst the combination of inflammatory and myodegenerative changes is characteristic of sIBM, not all of the histological changes are necessarily found together in all biopsies and the findings may vary according to when the biopsy is performed. Thus, in the earlier stages inflammation tends to be more florid while rimmed vacuoles and other changes may be inconspicuous or even absent and tend to become more prominent as the disease progresses.

### 8. Diagnostic approach

The approach to the diagnosis of sIBM has evolved over the past three decades, beginning with an emphasis on the presence of key pathological features on muscle biopsy (Table 1), [55] particularly the combination of a CD8$^+$ T-cell lymphocytic endomysial infiltrate with invasion of non-necrotic fibres, MHC-I and II upregulation, together with rimmed vacuoles, congophilic inclusions and protein aggregates, and mitochondrial changes. More recently the importance and specificity of clinical criteria such as the characteristic pattern of muscle involvement, with selective and severe weakness of the long finger flexors and quadriceps, has been emphasised [56]. Over this period, more than 10 different sets of diagnostic criteria have been proposed [55,57–66]. These have recently been evaluated by Lloyd et al. [57], and many have been found to lack sensitivity. There is no doubt that over time the diagnosis of sIBM becomes clear by its slowly progressive clinical course with resistance to treatment, characteristic pattern of muscle weakness and...
wasting, and muscle biopsy changes that evolve over time, but not all of these features occur simultaneously or are present at the initial presentation. The key is to be able to correctly diagnose patients early to avoid the risks associated with unnecessary immunosuppression, and to enable eligibility for current and future clinical trials of new therapeutic agents.

In clinical practice the diagnosis of sIBM should be considered when a patient over the age of 50 years (occasionally younger) presents with slowly progressive weakness over a period of months to years (compared with weeks to months for other inflammatory...
myopathies), with selective involvement of the long finger flexors (which is often more severe on the non-dominant side and easy to miss unless specifically looked for), and of the quadriceps, anterior tibial, neck flexor and bulbar muscles. An MRI will confirm the specific pattern of muscle involvement [42], and an EMG may show changes in keeping with an inflammatory myopathic process. The presence of anti-cN1A antibodies, which are 70% sensitive and 92% specific at moderate reactivity [21], in the presence of the

**Fig. 5.** Histological findings in sporadic inclusion body myositis muscle biopsies: (A) Endomysial mononuclear cell infiltrate and invasion of non-necrotic muscle fibre (arrow) (haematoxylin and eosin, original magnification × 640). (B) Rimmed vacuoles in muscle fibres (arrows) (haematoxylin and eosin, original magnification × 400). (C) Amyloid protein deposit in muscle fibre (arrow) (crystal violet stain, original magnification × 400). (D) Cytochrome oxidase stain with counterstaining for succinic dehydrogenase showing increased numbers of cytochrome oxidase deficient muscle fibres (blue).

**Fig. 6.** Immunohistochemical staining: (A) CD8+ T cells surrounding and invading muscle fibres (original magnification × 640). (B) Focal and more diffuse staining for p62 protein in muscle fibres (original magnification × 400). (C) Diffuse sarcolemmal and sarcoplasmic staining for major histocompatibility complex (MHC) I (original magnification × 400). (D) Sarcolemmal and sarcoplasmic staining for MHC-II (original magnification × 400).
characteristic clinical findings may be diagnostic. However, in most cases a muscle biopsy is still necessary for confirmation of the diagnosis.

The controversy surrounding the diagnostic criteria has often been related to cases in which one or more of the pathological features of sIBM are absent in the biopsy, making a definite pathological diagnosis difficult. A recent retrospective study investigated which pathological features were most sensitive and specific for the diagnosis of sIBM [53], and found that in tissue sections that had rimmed vacuoles, the morphology and distribution of p62 aggregates in combination with the inflammatory changes was 93% sensitive and 100% specific for the diagnosis of sIBM. In sections where rimmed vacuoles were absent, the combination of inflammatory changes with mitochondrial changes was 100% sensitive and 73% specific for sIBM.

A proposed diagnostic algorithm based upon this clinical approach to a patient with suspected sIBM is shown in Figure 7.

9. Treatment

There have been many clinical trials of immunosuppressive and immunomodulatory drugs, but none have yet shown clear benefit for patients with sIBM. However, most trials have been underpowered and of relatively short duration, and it is possible that there are subgroups of patients with sIBM who may benefit from some of these medications. In particular, there has been some evidence that patients suffering with both sIBM and Sjögren's syndrome may derive at least short-term benefit from immunosuppressive therapy [14].

Medications that have been investigated include prednisone, intravenous immunoglobulin (IVIG), methotrexate, azathioprine, interferon-β-1A, etanercept, arimoclomol and alemtuzumab. To further support the lack of clinical trial evidence for immunosuppression, there was a suggestion in a long-term observational study of sIBM that patients who had been tried on immunosuppression had an accelerated degree of disability [10]. Only exercise therapy has been shown in uncontrolled trials to not only be safe, but to result in improved muscle strength over a short period of time [68–70]. Currently bimagrumab (BYM338), a monoclonal antibody which binds to activin-II receptors in muscle and blocks the growth inhibitory effect of myostatin, is undergoing a multinational multicentre Phase III clinical trial, including two Australian centres. Whilst this will not be a cure for sIBM, it is hoped that it will help maintain or build muscle strength and improve function in affected individuals (ClinicalTrials.gov identifier: NCT01925209).

In clinical practice it is accepted that trials of immunosuppression are not generally recommended, as the risks of such treatment appear to outweigh any clinical benefit. However, it may be that some patients, such as those with a high degree of inflammation on the biopsy, those with another associated autoimmune disorder such as Sjögren’s syndrome, or those with rapid clinical deterioration or severe dysphagia may warrant a trial of prednisolone and an immunosuppressive agent such as methotrexate, or IVIG. IBM with rapid progression or severe dysphagia has been an approved indication for IVIG in Australia since July 2012 (National Blood Authority, Australia).

There is a need for adequately powered randomised clinical trials to determine whether treatment with conventional or newer forms of immune therapy over sufficiently long periods (of at least 12 months) can alter the natural history of the disease. Similarly, the possibility of developing therapies which target the abnormal protein aggregation in the muscles, and the use of combined therapies, also warrant further investigation.

Fig. 7. Proposed diagnostic algorithm for sporadic inclusion body myositis. Anti-cN1a Ab = antibody to cytosolic 5’-nucleotidase, CK = serum creatine kinase level, COX = cytochrome oxidase, MHC = major histocompatibility complex, N = normal numbers, RV = rimmed vacuoles, sIBM = sporadic inclusion body myositis, ULN = upper limit of normal, –ve = negative, +ve = positive. Derived in part from Brady et al. [56].
10. Concluding remarks

Further prospective studies of large cohorts of patients with sIBM are needed to more fully define the phenotypic spectrum and natural history of the disease, to refine and validate current diagnostic criteria, to identify disease biomarkers that can be useful diagnostically, and to monitor disease activity and response to therapy. In particular, further studies are needed to confirm the sensitivity and specificity of the anti-cN1A antibody in the diagnosis of sIBM. In addition, further genetic studies in different ethnic and racial groups using exonic sequencing and genome wide association studies are needed to confirm the importance of the known HLA and non-HLA loci and to identify additional genetic loci that have an association with disease susceptibility and pathogenesis. Large multicentre randomised control trials will also be necessary to resolve the issue of whether subgroups of sIBM patients are more responsive to immune therapies and whether the disease is likely to be more responsive if these therapies are commenced early in the course of the disease and continued for prolonged periods.

Conflicts of Interest/Disclosures

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References


