Review

Phenotypic spectrum of inclusion body myositis

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Received on January 4, 2024; accepted in revised form on February 15, 2024.

Clin Exp Rheumatol 2024; 42: 445-453.

Key words: inclusion body myositis, axial myopathy, dysphagia, distal myopathy, proximal myopathy

Competing interests: see page 451.

ABSTRACT

Inclusion body myositis (IBM) is a progressive, debilitating muscle disease commonly encountered in patients over the age of 50. IBM typically presents with asymmetric, painless, progressive weakness and atrophy of deep finger flexors and/or quadriceps muscle. Many patients with IBM develop dysphagia. However, atypical presentations of IBM with isolated dysphagia, asymptomatic hyper-CKemia, foot drop, proximal weakness, axial weakness, and facial diplegia have been reported. Other acquired and some inherited disorders may present similar to IBM, and this list gets more expansive when considering atypical presentations. In general, disease progression of IBM leads to loss of hand function and impaired ambulation, and most IBM patients become wheelchair dependent within 13-15 years of disease onset. Hence, IBM impacts negatively patients' quality of life and reduces longevity compared to the general population. Acknowledging the complete clinical spectrum of IBM presentation and excluding mimics would shorten the time to diagnosis, lead to prompt initiation of supportive management and avoid unproven therapy. Ongoing advanced phase studies in IBM provide hope that a therapy may soon be available. Therefore, an added potential benefit of early diagnosis would be prompt initiation of disease-modifying therapy once available.

Introduction

Inclusion body myositis (IBM) is a debilitating idiopathic inflammatory myopathy (IIM) which unlike other IIMs has no proven therapy. IBM is typically encountered in patients over the age of 50, with a mean age of symptom onset ranging from 61 to 68 years (1-5). In one study, approximately 20% of patients developed initial symptoms of IBM in their forties (6). IBM is more common in males, with a mean male-to-female sex ratio of 1.6:1 (reports ranging from 1.1 and 6.5) (4, 6-8).

Asymmetric painless progressive weakness of deep finger flexors and/or quadriceps muscle is considered the typical clinical presentation of IBM, and many patients develop dysphagia at some stage of their disease (1, 5, 9-11). However, there can be significant variability in terms of clinical presentation, and some patients may present with weakness beyond finger flexors and knee extensors (12). Hence, a delay in diagnosis is common ranging between 4.7 and 5.6 years, with nearly half of IBM patients initially misdiagnosed initially as having another disease (3, 4, 13). As a result, the prevalence of IBM is probably underestimated (1, 4, 14). However, awareness of IBM is rising with a steady increase in the reported prevalence over the last two decades, starting from 16 per million in 2000 (from the Netherlands) to 182 per million in 2021 (Olmsted County, USA) in individuals 50 years of age or older (2, 15-17). Another contributing factor to the variability in the reported prevalence is the difference in the used diagnostic criteria as well as geographic variation in incidence (1, 17).

In the last two decades, ongoing research has helped to expand clinical phenotype of IBM, and it has become crucial to recognise both typical and atypical presentations of IBM to make a timely diagnosis. Timely diagnosis can prevent unnecessary immunosuppressive or immunomodulatory therapies, limit unnecessary diagnostic testing, enhance the potential to participate in research whether through natural history studies or therapeutic trials, and help plan future management plans and monitor for complications. Furthermore, early initiation of appropriate supportive therapy may also improve quality of life of patients with IBM (1, 12, 18).

In this review, we provide a detailed account of the typical and atypical presentations of IBM, highlighting disease course and long-term outcomes. Furthermore, we discuss the mimickers of IBM and the diagnostic dilemmas associated with them (Table I).

Histopathological findings of IBM

Endomysial inflammatory infiltrates, predominantly with highly-differentiated, clonally-restricted, cytotoxic CD8 T cells, are observed in muscle biopsy of IBM (19, 20). Rimmed vacuoles and protein deposits are considered to be hallmark of IBM diagnosis in histopathology, but they can be absent in about 25% of cases with classical presentation of IBM (21). Lastly, cytochrome c oxidase negative fibres are almost always present suggesting mitochondrial dysfunction in IBM (22-25). Histopathology of IBM provides a window into its complex pathogenicity (22, 23). The pathophysiology of IBM is not clearly understood and remains controversial. A detailed discussion of pathophysiology of IBM is beyond the scope of this review (1, 22, 23).

Typical presentations of IBM

Early symptoms of IBM can be subtle, leading to a delay in seeking medical attention, and often mistakenly attributed to arthritis or old age (1, 4). Difficulty with walking, taking the stairs, and standing up, are typical early presentation symptoms of IBM related to lower extremity involvement (1, 4, 7). Impaired hand function from a weakened grip may lead to difficulty with using a golf club or other hand-held tools, and weakness of the finger flexors can lead to difficulty using a spray can or picking up small objects (1, 4). Knee extension weakness can lead to knee buckling and ambulation becoming affected. Similarly, ankle dorsiflexion weakness can lead to foot drop, and frequent tripping can occur when walking (1, 4, 7, 12, 16). Lastly, dysphagia is a common feature of IBM, although excluded from all IBM diagnostic criteria. Most importantly, resulting aspiration pneumonia is the leading cause of death in IBM patients (17, 27, 28). Nevertheless, dysphagia remains underrecognised in IBM, and unless asked specifically about it, patients may not even report symptoms of dysphagia. It has been used as an outcome measure only in three randomised clinical trials in IBM (10, 11, 29).

Physical examination can provide several clues in diagnosing IBM (1, 30). Quadriceps weakness is the most common finding on clinical exam, noted in more than 60% of patients, and can be associated with atrophy of the anterior thigh (4, 7, 26, 31). There is often asymmetric involvement, and usually, quadriceps are the most affected muscles in the lower extremities (Fig. 1-3) (32, 33). In early cases, knee extensor weakness can be subtle, and manoeuvres such as standing from kneeled position or deep squat, hopping on one leg, or climbing stairs can help to elicit mild weakness (1). Hip flexors can also be affected, but knee flexors are usually relatively spared early in the disease (4). Ankle dorsiflexion weakness can also be present in some patients (32, 33). Hip adductors and abductors are generally not affected even late in the disease course, and hip extensor strength may also be relatively preserved (4, 32).

In classical cases of IBM, flexor digitorum profundus (FDP) is usually the most affected muscle in the upper extremities, and the FDP of digit five is more affected than the FDP of digit two (4, 34). Flexor digitorum superficialis (FDS) is generally less affected than FDP, at least in the earlier stage of the disease (Fig. 2) (6, 34). Lumbricals are usually spared in IBM, leading to the classic end-stage IBM hand appearance with straight fingers at the proximal and distal interphalangeal joints with about 80° flexion at the metacarpophalangeal joint (Fig. 1). Flexor pollicis longus is often the second most affected muscle in the upper extremities; however, adductor pollicis is commonly spared (6, 34). The sparing of adductor pollicis and lumbricals allows IBM patients to maintain a form of incomplete functional (albeit weak) grip with these muscles (6). Even after taking the relatively old age of patients with IBM, the interosseus muscles are also generally spared without any definitive visible atrophy (4, 6, 34). Generally, the dominant hand is less affected than the non-dominant hand (6, 34). Among the proximal muscles, triceps is more affected than biceps, and deltoid is less affected. While, biceps can be visibly atrophied, sparing of brachioradialis may help maintaining some arm flexion strength (4, 6, 34).

While involvement of deep finger flexors and quadriceps are the most typical presentation of IBM, they are not pathognomonic and can be seen in other myopathies as well (35, 36). Granulomatous myositis can also present with weakness of quadriceps and finger flexors, sometimes asymmetric, thus mimicking IBM (37-39). Polymyositis with mitochondrial pathology (PM-Mito) patients may present with myalgia, proximal weakness, and IBM-like presentation (40). Muscle biopsies in PM-Mito show inflammatory infiltrates and marked mitochondrial pathology, without rimmed vacuoles (40). It remains unclear whether this is a separate entity from IBM as rimmed vacuoles and/or protein inclusions may not be present in all cases of IBM. In one study, patients with IBM reportedly had higher expression of guanylate-binding protein (GBP)6 and T-cell function-related KLRG1 in muscle tissue than PM-Mito (40). Light chain amyloid myopathy may present similar to IBM (41, 42). In addition, several other inherited myopathies may have overlapping or similar clinical phenotype with IBM (35). Prominent finger flexion weakness and knee extension weakness can be present in myotonic dystrophy type 1 & 2 (43, 44) dysferlinopathies (45, 46), dystrophinopathies (47), limb-girdle muscular dystrophy (D3) (48), myofibrillar myopathy (49) and VCP myopathy (50) usually along with weakness of other muscles groups and often symmetric in nature (35, 43-45). There are reports of GNE myopathy presenting with initial symptoms of weakness of deep finger flexors, but usually along with intrinsic hand muscle involvement (51). Rarely some inherited myopathies with distinct phenotype, such as Pompe disease, MYH7 myopathy, or ACTA1 myopathy may mimic clinical presentation of IBM (36, 52-54). Family history of a myopathy, very longstanding course or onset

Table I. Mimickers of inclusion body myositis.

Clinical presentation	Mimicking diseases	**Comments**
Quadriceps and/or finger flexion weakness	Granulomatous myositis	Patients with IBM may have granulomas on muscle biopsy. Search for sarcoidosis involving other tissues or organs.
	Polymyositis with mitochondrial pathology	Patients may still have IBM. No clear diagnostic biomarkers.
	Light chain amyloidosis	Screen for a monoclonal gammopathy. Autonomic failure and/or rapid progression are common in amyloidosis but not IBM.
	Inherited myopathy	Family history, muscle MRI, muscle histopathology, genetic testing, and clinical examination (*e.g.*, presence of action or percussion myotonia) can help differentiating from IBM.
Isolated dysphagia	Myasthenia gravis	Electrodiagnostic and serological testing can help establish the diagnosis of myasthenia gravis.
	Motor neuron disease	Progression is typically rapid, unlike in IBM. Electrodiagnostic testing would demonstrate a motor neuron disorder.
	Oculopharyngeal muscular dystrophy	Ptosis, common in OPMD but not typically seen in IBM. Genetic testing can establish the diagnosis.
	Toxic myopathies	Patients with hydroxychloroquine myopathy may present with severe dysphagia.
	Other immune mediated myopathies	Other idiopathic inflammatory myopathies, graft versus host disease, and sporadic late onset nemaline myopathy may present with dysphagia. Clinical, histopathological and serological evaluation is warranted.
Foot drop	Neuropathic foot drop	Electrodiagnostic testing for localization and differential diagnosis based on findings (*e.g.*, fibular mononeuropathy, lumbosacral plexopathy or radiculopathy, motor neuron disorder)
	Inherited distal myopathy	FSHD and other distal myopathies are to be considered.
Axial weakness	Various acquired and inherited myopathies	Wide spectrum of acquired and inherited disorders may present as such, including other inflammatory myopathies, sporadic late onset nemaline myopathy, graft versus host disease, radiation-induced myopathy and others. Clinical, serological and histopathological correlation is warranted.
Proximal weakness	Various acquired and inherited myopathies	Wide spectrum of mimicking disorders. Rate of progression and age of onset would help narrowing down the differential diagnosis as IBM is unlikely to present rapidly or in childhood/early adulthood. Clinical, serological, histopathological, muscle imaging, and genetic testing, when applicable, can help establish a diagnosis.

earlier in life, rapid progression with autonomic failure (*e.g.* amyloid myopathy), or associated clinical features (action or percussion myotonia) help raise suspicion for a mimicker when present. Muscle biopsies, genetic testing and imaging studies can help differentiating them from IBM (35, 36).

Atypical presentations of IBM

IBM may present with weakness beyond finger flexors and knee extensors in about 14-23% of patients (6, 12). These presentations include isolated dysphagia, foot drop, proximal limb weakness, axial weakness and facial diplegia. Furthermore, IBM may present as asymptomatic or paucisymptomatic hyper-CKemia (6, 12).

Isolated dysphagia is the most common presentation after knee extension and finger flexion weakness (12, 55-57). Such presentation is more common in females than in males (12), and the majority of patients with IBM develop dysphagia at some point (17, 28). Evaluating a patient with isolated dysphagia is more challenging as these muscles are not accessible for manual testing or for a biopsy. Evaluation by a skilled speech therapist along with imaging, such as a barium swallow, is key to determine if the experienced difficulty swallowing is due to oropharyngeal weakness and whether there is an associated cricopharyngeal bar (Fig. 1). Cricopharyngeal muscle biopsy, when performed, may show similar histopathology as other affected muscles in IBM (1, 58). Complications of dysphagia, including aspiration pneumonia and requiring PEG tube placement to maintain nutrition is common in IBM, and the probability of such complications is about 3 times higher compared to other IIMs (59).

Differential diagnosis includes other motor disorders presenting with dysphagia such as myasthenia gravis and motor neuron disorders, other forms of immune-mediated myopathies (*e.g.* graft versus host disease or sporadic late onset nemaline myopathy) (60, 61), toxic myopathies (*e.g.* hydroxychloroquine-induced myopathy (62) or inherited disorders such as oculopharyngeal muscular dystrophy or oculopharyngodistal myopathy. In patients presenting with isolated dysphagia, electrodiagnostic testing (EMG) and muscle MRI or muscle ultrasound, may help identifying subclinical muscle involvement elsewhere, confirming the myopathic nature of the process (EMG), and

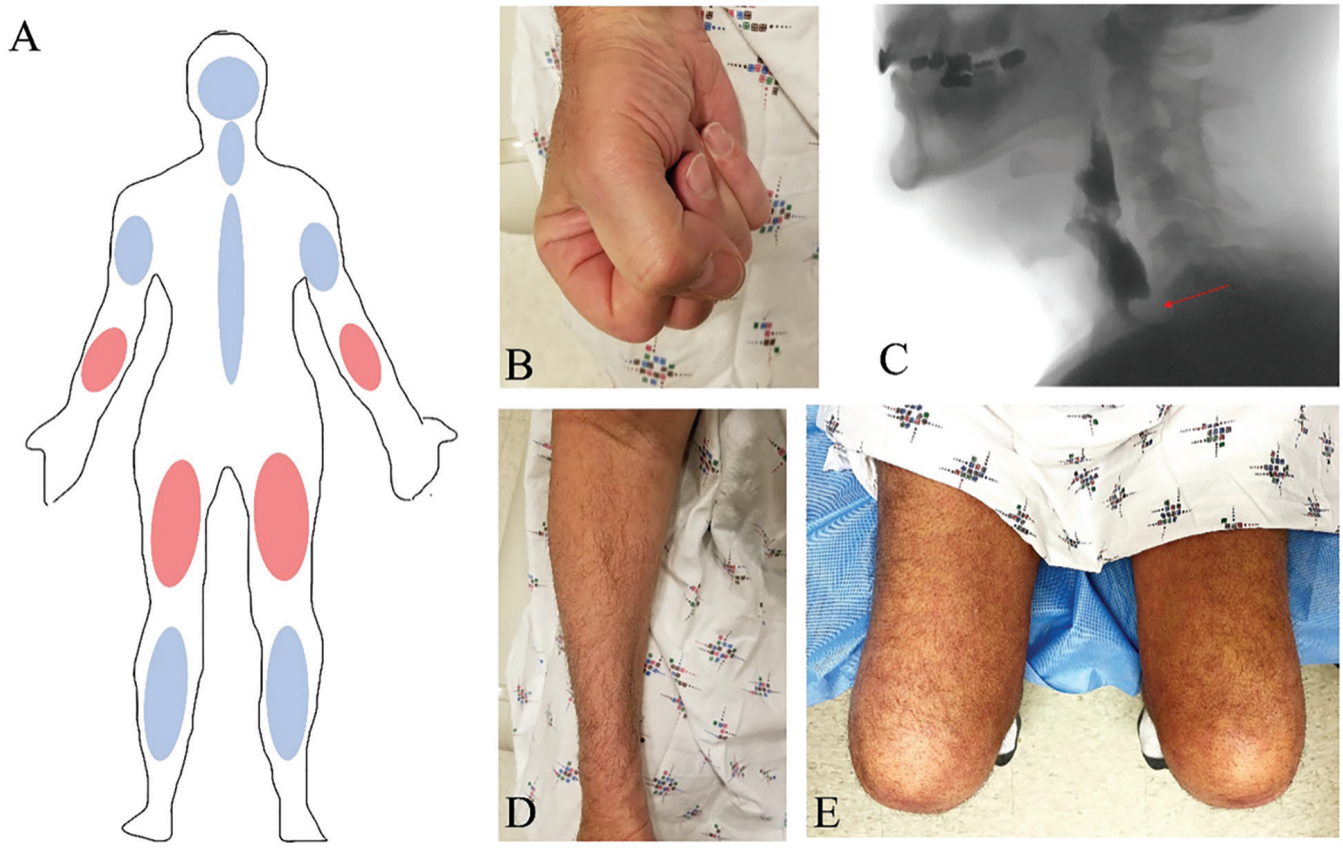

Fig. 1. Clinical presentation of inclusion body myositis (IBM).
A: Schematic representation of typical (represented in red, knee extensors and finger flexors weakness, usually asymmetric) and atypical presentations (represented in blue, facial, swallowing, axial, proximal upper limb and anterior leg compartment muscle weakness). **B**: Weak handgrip: the patient cannot bury fingers into the palm. **C**: Barium swallow evaluation demonstrating a cricopharyngeal bar (arrow) obstructing the esophageal lumen. **D**: Anterior forearm muscle atrophy. **E**: Quadriceps muscle atrophy.

choosing a muscle for biopsy. Furthermore, positive cN-1A antibodies would help raise suspicion for IBM. However, the diagnosis of IBM requires histopathological confirmation. If no suitable target is identified, watchful observation could be considered versus blinded muscle biopsy of the distal vastus lateralis or medialis.

Foot drop is one of the most often misdiagnosed presentations, especially when unilateral or asymmetric, as it can be mistaken for a fibular mononeuropathy or L5 radiculopathy (4, 12). EMG is particularly helpful excluding focal entrapment neuropathy, determining the myopathic nature of the underlying process, as well as searching for subtle involvement of muscles beyond the anterior leg compartment. Among myopathies, inherited myopathies, such as *TTN* myopathy, fascioscapulohumeral dystrophy (FSHD), distal myopathies, or myofibrillar myopathies are to be considered.

The differential diagnosis of IBM presenting with proximal or limb girdle weakness is wide and encompasses several inherited and acquired myopathies. A particularly challenging scenario is that of patients with an associated connective tissue disorder, as they may be clinically diagnosed with other forms of myositis and treated accordingly. A comprehensive clinical and serological evaluation as well as correlation of clinical and histopathological findings is highly relevant in this group.

Patients with axial weakness at onset may present with head drop or camptocormia (12, 63, 64). An inflammatory myopathy is the most common diagnosis in myopathic dropped head syndrome (65). This includes overlap myositis, especially with scleroderma, and inflammatory myopathy not otherwise specified (65-67). In one series, about 2% of patients with myopathic dropped head syndrome had inclusion body myositis (66). Of note, the histopathological diagnosis of myopathy with rimmed vacuoles, without other features of IBM, is common in myopathic dropped head syndrome (66). Patients with IBM presenting with axial weakness are relatively older than those with other presentations (12).

Facial weakness is common but often mild, predominantly involving orbicularis oris and oculi (1, 4); two independent case series reported facial involvement in more than 40% of cases (6, 26). However, extraocular muscles, jaw and lingual muscles are not affected, and ptosis is not seen in IBM (4, 6).

Facial diplegia is an intriguing presentation as it has been exclusively reported in females (12, 68, 69). Dysphagia and bulbar weakness are common in this group, and tongue abnormalities may occur, with either tongue wasting or macroglossia (12, 69).

Several of the atypical presentations may mimic FSHD (*e.g.* facial weakness, axial weakness, foot drop).

Furthermore, rare IBM patients with prominent scapula winging have been reported (70).

Lastly, patients with IBM may be diagnosed at a pre-clinical (or very early) stage presenting with isolated hyperCKemia or vague symptoms such as myalgia and fatigue. Despite being asymptomatic or paucisymptomatic, these patients displayed all canonical histopathological features of IBM on muscle biopsy (12). Close monitoring and recognition of this group of pre-clinical IBM is important if effective treatments were to be developed with intervention at earlier disease stages.

When grouped together, patients with atypical presentation are more likely to be females, unlike those with typical presentation. This is mostly driven by the female predominance in the isolated dysphagia group and facial diplegia. Age of onset is relatively similar to typical IBM with median age of onset of 62 years in one study, however, patients with axial weakness were older at presentation. Most patients reported oropharyngeal dysphagia at some point (12). Elevated creatine kinase (CK) level was seen in 84% of patients and 56% had positive cN-1A antibodies, though these antibodies may be detectable in some rheumatologic diseases (SLE and SS), other diseases (ALS) or even in other IIMs (12).

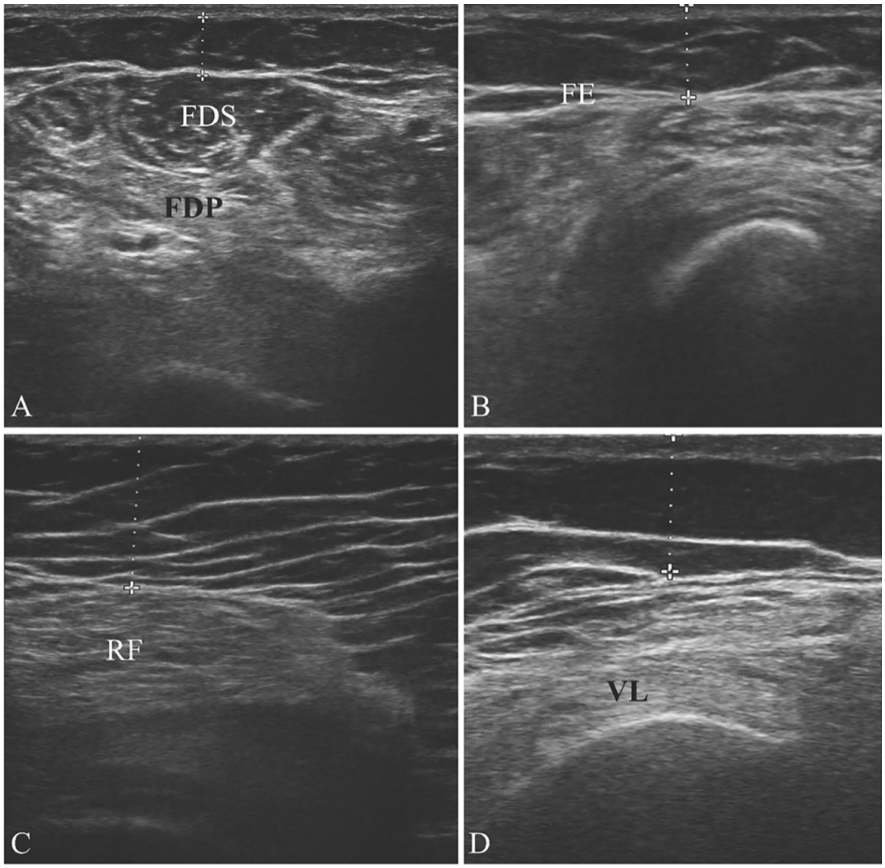

Fig. 2. Muscle ultrasound in an IBM patient.
A: more involvement of flexor digitorum profundus (FDP) compared to flexor digitorum superficialis (FDS); **B**: minimal involvement of forearm extensor (FE) muscles; **C-D**: more severe involvement of vastus lateralis (VL) compared to rectus femoris (RF) muscles. All the images were captured at the same gain and frequency, at the depth of 4 cm, except for depth of 6 cm for rectus femoris as per standard neuromuscular ultrasound protocol. The dotted line showing the skin and subcutaneous tissue depth.

Implications of clinical characteristics in diagnostic criteria of IBM

Multiple diagnostic criteria for IBM were proposed either based on an individual expert opinion (1987-2002) or based on a consensus expert opinion (1995-2013) (1, 30, 71-74). Several changes and adaptations over time, reflecting on the existing knowledge of clinical phenotype of IBM, have helped to increase the diagnostic sensitivity and specificity of these diagnostic criteria, and at present the ENMC 2011 criteria is most commonly used in clinical trials in IBM (30). Among the major changes in demographic aspects of diagnostic criteria have been to increase the age of onset to over 45 years, and disease duration of at least 12 months to increase the specificity of the diagnostic criteria (72-74). Among clinical features, accepting knee extensor weakness greater than or equal to hip flexor weakness (instead of strict greater than hip flexor weakness), increased sensitivity without any major compromise to specificity (74). Earlier diagnostic criteria of IBM used several non-specific clinical features of IBM, such as distal and proximal extremity weakness with wrist flexor>finger extensor weakness, finger flexor weakness alone, or quadriceps weakness with Medical Research Council (MRC) grade score of less than or equal to 4. However, such clinical features compromised the specificity of diagnostic criteria, and were not incorporated in the ENMC 2011 criteria, which had the unintended consequence of not including those phenotypic variants. For example, finger flexors and quadriceps weakness without them being weaker than comparative muscles occurred in 9/51 IBM cases (1, 57, 72-74). Similarly, amyloid deposition, necessity of electron microscopy in all cases, and other degenerative features on muscle biopsies were included in earlier diagnostic criteria, but were later excluded from updated diagnostic criteria due to lack to sensitivity (1, 72-74). Overall, all IBM diagnostic criteria erred on the high specificity side with varying sensitivities ranging from 11% to 84% (74). There is a critical need to improve IBM diagnostic criteria sensitivity without markedly impacting specificity. Hence, a European Neuromuscular Center meeting was convened in June 2023 to revise the ENMC 2011 criteria and the revised guidelines are to be published in 2024.

Disease progression in IBM

Similar to clinical presentation, disease progression in IBM can also be vari-

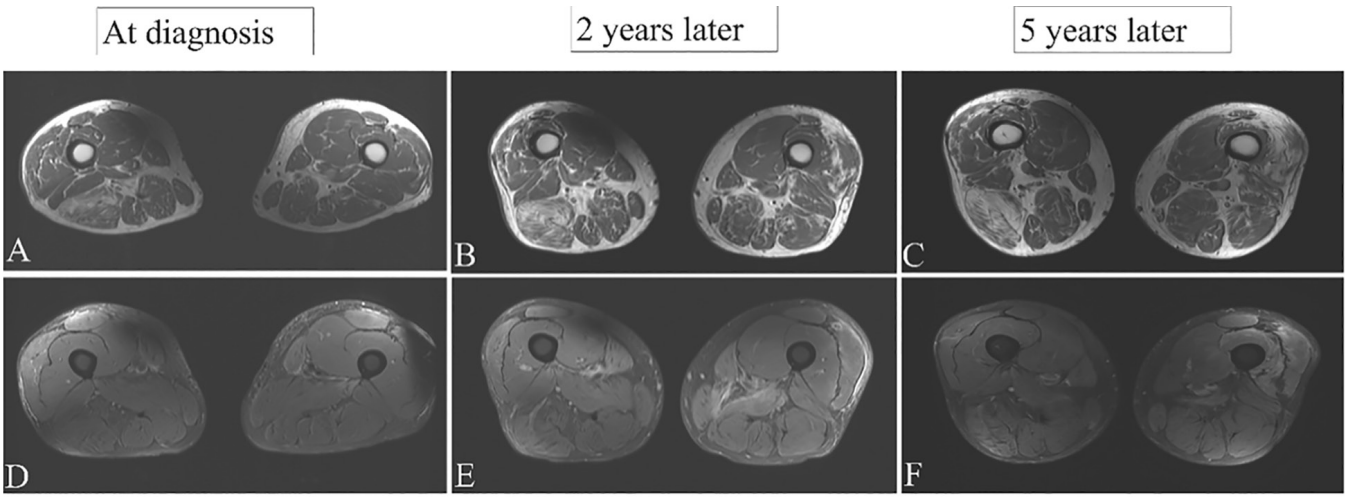

Fig. 3. Muscle MRI from a patient with inclusion body myositis presenting with asymptomatic hyper-CKemia. Axial T1 (top row) and T2 (bottom row) sections from the thigh. At diagnosis, the patient had no demonstrable weakness of the knee extension on manual testing and was able to stand from kneeled position. He had mild fatty replacement of the right long head of the biceps femoris (**A**). 2 years later, he continued to have no weakness, and developed mild fatty replacement in the distal left vastus lateralis (**B**) with mild T2 hyperintensity (**E**). 5 years later, he developed mild to moderate weakness of the deep finger flexors and mild left quadriceps weakness. He became unable to stand from kneeled position on the left. MRI showed further progression of the fatty replacement in the distal quadriceps (**C**), most pronounced on the left side, with increased T2 hyperintensity (**F**) and relative sparing of rectus femoris.

able with different trajectories being observed based on initial muscle group involvement, age of onset and sex (6, 33). Quadriceps, forearm flexors, and pharyngeal muscles are the most common muscle groups affected in IBM, and irrespective of initial presentation, with disease progression, all these muscle groups eventually get involved (1, 6, 12). In general, all muscle groups show deterioration of muscle strength over time with relative sparing of wrist extensors in upper extremities, and hip adductors and abductors in lower extremities (4, 6, 33). Although several longitudinal studies are available on disease progression in IBM, majority of them are limited by small sample size, relatively shorter duration of follow up, and use of different outcome measure parameters; however, some larger scale multicentre longitudinal studies were reported in the recent past (6, 7, 26, 32, 33, 75-77).

The reports on the influence of age of onset in disease progression of IBM is conflicting. Previous studies suggested that earlier age of onset is associated with lower rate of disease progression from one muscle group to another (6), and more rapid deterioration in IBM-functional rating scale score with late disease onset but not in terms of manual or quantitative muscle strength testing (77), but another recent report demonstrated more rapid progression of disease with earlier age of onset (33). The disease progression in IBM may not be perfectly linear, as one study reported relatively more rapid progression of weakness earlier in the disease course, with prominent loss of muscle strength in knee extensors (31, 33, 77, 78). However, it remained unclear whether this is due to limitation (floor effect) of the used outcome measures versus a change in the disease progression rate. Sex may also influence disease progression, with more rapid loss of pinch strength in men and more rapid loss of grip strength in women (33, 77).

The majority of patients with IBM will eventually require assistive device for ambulation (7, 31, 77). Unilateral cane is the most commonly used assistive device, followed by ankle foot orthosis (77). Typical duration of initial use of assistive device can vary, ranging between 3.6-9.2 years, with a shorter time to use an assistive device in patients with late disease onset (31, 77, 79). Eventually, most patients become wheelchair dependent, usually around 13-15 years from symptom onset (7, 77).

Previous reports had identified IBM as a non-fatal disease with only relatively mild effect on mortality (6, 7). However, recent studies on IBM have confirmed increased mortality in IBM patients compared to other inflammatory myopathies and control patients, with a 10-year survival rate of 37% (compared to 67% in IIM and 59% in population control), with respiratory failure and aspiration pneumonia being the most common cause of death (17, 59, 80).

Similar to those with typical presentation, patients with atypical presentations do not generally respond to treatment with corticosteroids or other immunosuppressants (12). There have been anecdotes of immunosuppressive treatment altering certain features of the disease without changing the overall disease course (12, 69): patients experience slowly progressive decline of their motor function (12). In one series, 76% of patients with atypical presentations eventually fulfilled 2011 ENMC diagnostic criteria for IBM and 7 out of 9 patients in the hyper-CKemia group eventually developed typical IBM weakness (12). An additional patient with asymptomatic hyper-CKemia developed typical weakness after the study was published, 5 years from diagnosis (Fig. 3).

Conclusion

Recognition of the atypical presentations of IBM has increasingly been reported in the last decade. The pleomorphic presentation of IBM is important to identify for many reasons, and most important is the ongoing hunt for ef-

fective therapy. While these therapies are currently being evaluated in typical IBM phenotypes, the hope of future discovery is that successful therapies will benefit all IBM patients, regardless of their uniqueness and phenotype.

Competing interests

B. Roy has acted as a consultant for Takeda Pharmaceuticals, Argenx, Alexion Pharmaceuticals (now part of AstraZeneca). He has stocks in Cabaletta Bio, is teh site principal investigator for clinical trials from Abcuro, Immunovant, Argenx, Takeda Pharmaceuticals; none of these financial disclosures have any direct relation to this manuscript.

M.M. Dimachkie seves or recently served as a consultant for Abata/Third Rock, Abcuro, Amicus, Argenx, Astellas, Cabaletta Bio, Catalyst, CNSA, Covance/Labcorp, CSL-Behring, Dianthus, Horizon, EMD Serono/Merck, Ig Society, Inc., Janssen, Medlink, Octapharma, Priovant, Sanofi Genzyme, Shire Takeda, TACT/Treat NMD, UCB Biopharma, Valenza Bio and Wolters Kluwer Health/UpToDate. He has received research grants or contracts or educational grants from Alexion/AstraZeneca, Alnylam Pharmaceuticals, Amicus, Argenx, Bristol-Myers Squibb, Catalyst, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, The Myositis Association and UCB Biopharma/Ra Pharma.

E. Naddaf has declared no competing interests.

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