

Inclusion body myositis a clinical review with illustrative case report

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Keypoints

- Sporadic Inclusion Body Myositis (IBM) is the most common acquired inflammatory myopathy in patients over 50 years.¹
- The diagnosis is very often missed due to the co morbidities associated in older people.
- IBM can present in various ways to the acute admission unit, including falls, aspiration pneumonia and dysphagia.
- Typical clinical features are a slowly progressive painless, proximal lower limb weakness, with muscle wasting and early loss of reflexes.
- Early involvement of the multidisciplinary team is essential to provide support to patients and carers, although no specific therapy has been shown to be effective.
- Corticosteroid therapy is ineffective for treatment of IBM.²

Abstract

Every acute physician has come across elderly patients presenting with muscle weakness and falls. Distinction between normal age related muscle wasting and pathological muscle atrophy can be difficult. It is important for acute physicians to be aware of the differential diagnosis of such a presentation. Inclusion body myositis (IBM) is the most common type of acquired myopathy above the age of 50.¹ This article aims to highlight the diagnosis

and management of this chronic illness. It is frequently misdiagnosed as polymyositis and wrongly treated with steroids.³ The typical symptoms and signs are illustrated by a recent case which presented to our department (see box 1).

Keywords

Inclusion body myositis; Myopathy; Elderly; Muscle atrophy.

A 79 year old woman was referred to our elderly care clinic with a long history of reduced mobility and impaired sensation in her feet. As a result she had several falls, one of them resulting in a wrist fracture. Her main complaint was a heavy achy feeling in her arms and legs. She had numbness in her fingers and toes and was finding it increasingly difficult to perform fine tasks. She had also noticed increasing difficulty with swallowing and required endoscopy with subsequent esophageal dilatation. There was a temporary resolution of her dysphagia, although this recurred quickly. This had resulted in progressive weight loss.

Her symptoms had progressed over ten years. She had gone from being independently mobile to being wheel chair bound during this period.

She lived with her daughter and required help with personal care including feeding. She had undergone several hospital admissions during the past year due to the deterioration in her mobility.

On examination, she had bilateral lower motor neuron facial weakness. The ocular movements were normal and there was no ptosis. The tongue and palate movements were normal. Speech was hoarse. She had marked wasting in proximal and distal group of muscles in upper and lower limbs. Wasting was especially marked around the shoulder joints and in quadriceps. There were no fasciculations. Muscle weakness was more noticeable in proximal muscle groups of the limbs. Tendon reflexes were absent. There was no abnormality on sensory examination.

The distribution of the weakness with facial and swallowing muscle involvement suggested a primary muscle disorder. In view of the prolonged history, the neurologist suggested a possible diagnosis of inclusion body myositis.

Full blood count, CK, autoimmune profile, thyroid function tests, chest X-ray, B12, folate, ESR and nerve conduction studies were normal. Concentric needle EMG showed small polyphasic short duration units in keeping with a myopathic process. There were also some shorter duration larger units reaching neurogenic proportions in the quadriceps. The electrophysiological features were in keeping with inclusion body myositis. Muscle biopsy showed fibrotic muscle fibres and infiltration by adipose tissue. However, some muscle fibres showed either centrally located or subsarcolemmal vacuoles which included granules. The granules represent rimmed vacuoles and lipofuscin. There was also mild inflammation with predominant lymphocytes surrounding the blood vessels. There was no fibrinoid necrosis. Staining showed some COX negative fibres. The histological features supported the clinical diagnosis of inclusion body myositis.

A multidisciplinary team in the form of occupational therapy, speech and language therapist, dietician and physiotherapy were put in place to support this patient. A year following the diagnosis, the patient was admitted to the hospital after a fall and severe chest infection and passed away during this admission.

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Box 1. A Recent Case in our Department.

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History and classification

The term “inclusion body myositis” (IBM) was initially introduced by Yunus and Samaha in 1971.⁴ They describe a case which phenotypically appeared to have chronic polymyositis but had cytoplasmic vacuoles and inclusions on muscle biopsy. Over the past 37 years it has been increasingly recognized and diagnosed due to increased awareness and improved diagnostic tests.

Two main forms of IBM are described:

- *Familial or hereditary IBM* (h-IBM)
- *Sporadic inclusion body myositis* (h-IBM)

Epidemiology

The incidence of IBM is higher in Northern European, North American white and white Australian populations as compared to Korean, African-American, middle Eastern and southern Mediterranean.⁶ The prevalence in an Australian study was 9.3 per million in the general population and 35.3 per million in the above 50 years age group. The condition affects men more commonly than women, in a ratio 1.4:1 to 3:1.² The age of onset is usually over 50 years. More epidemiological studies are required to determine whether the comparative frequencies of sporadic IBM in different geographical regions and ethnic groups are related to genetic or environmental factors.

Several neuromuscular disorders with muscle weakness have an age related incidence. The increased susceptibility of aged muscle to disease probably represents a double hit in which an inciting risk factor acts as a trigger to a normally aging muscle or with another age related disease.⁷

Genetics

The association of sporadic inclusion body myositis with DR3 is one of the most robust HLA –disease connections recorded. It is present in approximately 75% of cases.^{8,9}

Familial or hereditary IBM is classified into autosomal dominant and autosomal recessive forms. They are inherited through mutations on chromosome 9 and 17 respectively.¹⁰

Pathogenesis

Various theories have been proposed to explain how IBM is caused, which suggests that the exact aetiopathogenesis is largely unknown.

Some researchers advocate that an undiscovered virus or an autoimmune disorder is the primary cause with secondary degeneration of muscle fibres.³ The immune system is activated against specific antigens expressed by myocytes and this has an important role in the pathogenesis of the disease. There is a sustained antigen driven immune response during the course of the disease. There is increased expression of cytokines and chemokines. However, the severity of the disease is poorly associated with the degree of the inflammatory changes. Treatment with steroids might reduce the inflammation but it does not stop the degenerative changes and has little or no effect on the degree of weakness.¹¹

An alternative theory is that it is a degenerative disorder related to aging of muscle fibres.

Some investigators suggest that the accumulations of amyloid mRNA, amyloid precursor protein, and amyloid beta are the trigger events leading up to vacuolar degeneration and atrophy of muscle fibres.¹² The reason behind accumulation of amyloid mRNA, precursor and proteins is not clear. One hypothesis suggested is that various insults causing oxidative stress, lead to abnormal signal transduction and transcription, causing over expression of amyloid precursor protein and abnormal processing. Abnormal accumulation of amyloid proteins in turn leads to cell ageing and death.¹³ This is a self perpetuating mechanism, wherein the amyloid beta causes further oxidative stress.

Similarities have been noted between the pathogenesis of s-IBM and Alzheimer's disease because of accumulation of similar proteins, their association with oxidative stress and cellular ageing.¹⁴

A key question is whether the inflammatory and myodegenerative process are interlinked. There is evidence to support that these changes might happen in parallel in different sets of muscle fibres. This might imply that different fibres are affected at the same time by different mechanisms or the same set of muscle fibres showing segmental changes. It is equally plausible that one process (inflammatory) is followed by secondary (degenerative, vacuolation) changes.¹⁵

Clinical features

Sporadic IBM is a slowly progressive disorder and age of onset is usually >50 years although onset has been seen at a young age as 20 years.¹⁶

Clinical presentation is usually that of muscle weakness, such as difficulty in rising from chair, rising from squatting position or climbing up chairs. Unlike polymyositis and dermatomyositis the distribution of muscle involvement can be asymmetrical and tends to involve proximal and distal groups. The earliest involvement is that of wrist/finger flexors, ankle dorsiflexors and knee extensors. Hence the commonest complaint is loss of hand dexterity.

Dysphagia is found in over half of patients with well established disease.

Sub clinical involvement can be found in >80% patients.¹⁷ It may present as need to repeatedly swallow or nasal regurgitation. Pain and sensory involvement is uncommon. Although direct cardiac muscle involvement has not been demonstrated heart diseases are common because of the age group involved. Although facial muscles are involved extraocular muscles are not involved. Presence of other neurology involvement – incoordination, upper motor signs and cognitive impairment should prompt a search for an alternative diagnosis.

Inclusion body myositis usually occurs in isolation, but can be associated with other autoimmune disorders or connective tissue diseases. Occasionally it is associated with HIV, HTLV-1 and hepatitis C infection.¹⁶

The disease is slowly progressive and relentless. Patients continue to lose their mobility and have to rely on aids to support mobility. Dysphagia predisposes to aspiration pneumonia. Falls may lead to fractures. Patients usually die

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of other medical conditions. Overall mortality is no more than in the average population.¹⁸

Investigations

Blood tests include full blood count, renal function, calcium, phosphate, creatinine kinase, thyroid function test, autoimmune profile, protein electrophoresis.

- *Serum creatinine kinase* is mildly or moderately raised but can be normal. The levels fall as the disease progresses.
- *Electromyography (EMG)* is aimed at demonstrating a diffuse myopathic process. In a study of 25 patients with s-IBM, single fibre electromyography was carried out. All of them showed fibrillation, positive sharp waves and small amplitude short duration motor unit potential.¹⁹ The added findings of high amplitude, long duration action potential unit potentials might suggest the possibility of a neurogenic disorder such as motor neuron disease.²⁰
- *Muscle biopsy* provides a definitive diagnosis. IBM is characterized by numerous rimmed vacuoles in atrophic muscle fibres and perivascular and endomyseal infiltrate. Rimmed vacuoles are areas of focal destruction of muscle fibres containing amyloid protein of beta type.²¹ Inclusions due to build up of abnormal proteins e.g. tau protein and beta amyloid are found within the muscle cells. The amyloid inclusions are best seen with Congo red and viewed with Texas red filters. There is an increase in ragged red fibres and cytochrome-c-oxidase (COX) negative muscle fibres.²² Tau protein inclusions are seen with immunohistochemistry. Immunohistochemical stains are useful in detecting endomyseal infiltrate and autoinvasive T cells and MHC-1 expression in muscle fibres. If the main changes are seen on light microscopy, electron microscopy is not essential for diagnosis.

Diagnostic categories¹⁶

Definite inclusion body myositis

- Characteristic features, with biopsy confirmation: inflammatory myopathy with autoaggressive T cells, rimmed vacuoles, COX negative fibres, amyloid deposits or filamentous inclusions and upregulation of MHC-1 expression.
- Atypical pattern of weakness and atrophy but with diagnostic biopsy features.

Probable inclusion body myositis

- Characteristic clinical and laboratory features but incomplete biopsy criteria –e.g., features of necrotizing inflammatory myopathy with T cell invasion of muscle fibres but absence of rimmed vacuoles, amyloid deposits, filamentous inclusions, and COX-negative fibres.

Possible inclusion body myositis

- Atypical pattern of weakness and incomplete biopsy criteria.

Management

No drug treatment had been found to give a sustained or consistent response. It is a relentlessly progressive disorder: most patients require a walking aid after about 5 years and the use of a wheelchair by about 10 years.²³ Steroids, azathioprine, methotrexate and cyclophosphamide have been tried with little success.²⁴

The treatment is largely empirical. Some advocate the use of a steroid and immunosuppressive trial in the initial period for 3–6 months, in patients with associated connective tissue disease or other autoimmune disorders.²⁵

Both corticosteroids and methotrexate have been used in small number of patients over a period of 12 months. Each has shown a fall in serum creatinine kinase concentration but continued progression of the disease.^{26,27}

Intravenous immunoglobulin (IVIG) has shown variable response. It has been tried in three controlled trials, involving 60 patients in total. The primary endpoint of these trials was improvement in muscle strength. Two of these trials lasted 3 months and one lasted 6 months. In one of these 3 month trials, IVIG was compared with placebo and there was no significant improvement in muscle strength in the immunoglobulin group.^{28–30} An improvement was found in swallowing after 3 months of treatment with IVIG in one of these cross over trials.²⁹ These results have not been reproducible in other longer trials.³¹

Antithymocyte globulin has been tried in a 12 month controlled trial in ten patients with inclusion body myositis. There were two treatment arms; Antithymocyte globulin plus methotrexate and methotrexate alone. Those treated with antithymocyte and methotrexate were shown to have a mean increase in their muscle strength.³²

Larger trials are necessary to trial intravenous immunoglobulin and antithymocyte globulins further.

Symptom directed treatment can be used to restore some functioning. Swallowing may improve temporarily following oesophageal dilatation. Other experimental strategies include botulinum toxin injection into upper oesophageal sphincter and cricopharyngeal myotomy.³³

An exercise programme adjusted according to the patient's needs is found to be safe and effective. It does not cause increase in markers of disease activity.³⁴

Orthotic appliances such as ankle- foot orthoses for foot drop and knee locking braces for patients with recurrent falls can be of benefit.

Regular follow up is essential to monitor progress and instill supportive care by a multidisciplinary team. As outlined in our case, physiotherapy, occupational therapy, speech and language therapy are vital to manage this insidious yet relentlessly progressive condition. The disease management spreads across different specialties – geriatricians, neurologists, ENT, gastroenterologists and psychiatrists.

Useful patient support groups are The Myositis Support Group (www.myositis.org.uk) and the Muscular Dystrophy Campaign (www.muscular-dystrophy.org). They are UK wide charity organizations and support over 30,000 people.

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Summary

- Inclusion body myositis (IBM) often presents with non-specific features including reduced mobility in elderly patients
- Early consideration of IBM is essential to prevent inappropriate treatment with corticosteroids if confused with polymyositis.
- Early referral to a multidisciplinary team comprising of physiotherapists, occupational therapists and speech and language therapists is essential to manage this insidious but relentlessly progressive condition.
- Although there is no effective cure, patients find it useful to be provided with a diagnosis to enable them to plan ahead for possible complications.

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