Inclusion body myositis: an underdiagnosed myopathy of older people

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Abstract

Inclusion body myositis (IBM), a condition characterised by progressive muscle weakness and inclusion bodies visible on muscle biopsy, is the most common type of myopathy in patients over 50 years of age. However, it is not only underdiagnosed but frequently misdiagnosed as polymyositis and hence wrongly treated with steroids [1, 2, 3]. In the evaluation of progressive weakness in older Caucasian males, IBM should be an important diagnostic consideration. Treatment-resistant ‘polymyositis’ in patients over 50 years of age is often IBM. If there is no histological confirmation, the diagnostic criteria allow for a category of ‘possible IBM’. Sometimes, the diagnosis is missed because of the slow progression of the disease and a lack of suspicion on the part of physicians. The following case report and literature review will explore many of these issues.

Keywords: myopathy, inclusion body myositis, older people, elderly

Introduction

Inclusion body myositis (IBM), a condition characterised by progressive muscle weakness and inclusion bodies visible on muscle biopsy, is the most common type of myopathy in patients over 50 years of age. However, it is not only underdiagnosed but frequently misdiagnosed as polymyositis and hence wrongly treated with steroids [1, 2, 3]. In the evaluation of progressive weakness in older people, IBM should be an important diagnostic consideration. Treatment-resistant ‘polymyositis’ in patients over 50 years of age is often IBM. If there is no histological confirmation, the diagnostic criteria allow for a category of ‘possible IBM’ [4]. Sometimes, the diagnosis is missed because of the slow progression of the disease and a lack of suspicion on the part of physicians. The following case report and literature review will explore many of these issues.
Case report

An 81-year-old Caucasian man was admitted, on several occasions, to our hospital with a multitude of problems (urinary retention, chronic obstructive pulmonary disease, ischaemic cardiac events, gastrointestinal bleeds and stroke) over a span of 3 years. On each occasion, he complained of muscular weakness. This complaint did not receive much attention as the weakness was attributed by the patient and his GP to residual deficits from his stroke and other comorbidities. His old medical records showed mildly elevated creatinine kinase (CK) levels in the range of 677–996 IU/l (normal values = 25–200 IU/l).

His recent hospital admission was due to recurrent falls, necessitating the use of a frame and a mobility scooter. Two years earlier, he had been independent but now required assistance for most activities of daily living such as transfers from bed to chair, climbing stairs, toileting and washing. Fine motor skills of his hands and fingers were affected significantly, making him unable to hold a glass of water or even a spoon. Clinical examination showed an asymmetrical, generalised wasting of quadriceps, tibialis anterior and finger and wrist flexors along with weakness and minimal tenderness.

Tests revealed that the elevated CK was predominantly of the CK MM type. EMG showed no evidence of myositis or myopathy but did show features consistent with an axonal neuropathy. Tests for any possible internal malignancy (chest X-ray, tumour markers, GI endoscopy, abdominal ultrasound, LFT, immunoglobulin and protein electrophoresis) proved inconclusive. A muscle biopsy from the quadriceps was taken and a short course of steroids (normal values = 25–200 IU/l).

Instituted. The skeletal muscle biopsy confirmed ‘IBM’ (Figure 1) and the steroids were withdrawn. He stabilised briefly with physiotherapy but over the subsequent year deteriorated slowly.

Historical features, epidemiology and classification

The term IBM was introduced in 1971 by Yunis and Samaha to describe a subset of patients with chronic polymyositis whose muscle fibres showed inflammation and vacuoles and characteristic filamentous inclusions within the cytoplasm and nuclei [1]. Two main forms have been described: (i) familial or hereditary IBM and (ii) sporadic IBM.

Familial or hereditary IBM (h-IBM) is different from sporadic IBM because muscle biopsies from such individuals do not show inflammation, common in IBM. Therefore, these are better termed as ‘myopathies’ [5]. Two types, namely the autosomal recessive and autosomal dominant forms, have been described which are inherited through mutations on chromosomes 9 and 17, respectively. A few of these individuals live beyond the fifth decade.

Sporadic IBM (s-IBM) is now recognised as the most common acquired inflammatory myopathy in patients over 50 years and is usually just designated as ‘IBM’ [2]. There are several theories as to its cause, but none have been conclusively proved. It may be a degenerative muscle disorder, or triggered by a virus or an autoimmune disorder, and is found to be two to three times more common in males than in females and in Whites than in Blacks or Asians [5]. The relative prevalence of IBM is found to be 16–28% among all of the inflammatory myopathies [6]. While population-based studies are scarce, studies from Sweden and Netherlands have shown prevalences of 2.2–4.9 per million, but age-adjusted rates above 50 years may be as high as 16 per million [7, 8]. s-IBM is classified along with polymyositis, dermatomyositis and the rarer eosinophilic polymyositis and focal myositis under what is known as the ‘idiopathic inflammatory myopathies’ (IIM). These myopathies are pathogenically, histologically and clinically distinct entities. The differences among the three conditions are shown in Appendix I.

Pathogenesis and aetiology

The aetiopathogenesis of IBM is largely unknown. Mitochondrial DNA deletions, protein accumulations and altered transcriptions have all been implicated [4]. The roles of oxidative stress, ageing, genetic factors and viruses have also been highlighted. Within the vacuolated muscle fibres of IBM, abnormal amounts of prion protein, acetylcholine receptor and proteins that are typically characteristic of Alzheimer brain (β-amyloid, N- and C-terminal epitopes of β-amyloid precursor protein, alpha 1 antichymotrypsin, phosphorylated tau, apolipoprotein E and ubiquitin) are found. An unanswered question is what triggers this characteristic muscle pathology and why IBM patients do not have Alzheimer’s disease, despite similar pathological changes in the muscle and brain. Similar pathological changes have been described in oculopharyngeal muscular dystrophy.

Pathology

Light microscopic features include lymphocytic mononuclear cell inflammation, muscle fibres with vacuoles containing red and green staining material with the Congo-Red stain (60–
80% of the vacuolated muscle cell fibres and denoting amyloid), ragged-red fibres and atrophic muscle fibres. Repeated biopsies are essential because there is patchy involvement of the muscles. By electron microscopy, the characteristic feature of the vacuolated muscle fibres is the presence of cytoplasmic 15–18 nm diameter paired helical filaments.

**Clinical features of s-IBM**

Sporadic IBM is slowly progressive and affects proximal and distal muscles, the weakness and atrophy often being asymmetric [4]. Characteristic features consist of early involvement of quadriiceps, ilio-psosas, ankle dorsiflexors and volar forearm muscles. Because of the distal weakness and the early loss of the patellar reflex resulting from the severe weakness of quadriceps muscle, a neurogenic disease is often suspected [5, 6].

Dysphagia is common in s-IBM. Subclinical involvement on swallowing studies is seen in >80% patients, but clinically about 40–50% complain of swallowing difficulties. As the disease progresses, the majority of the patients develop symptoms [9]. Some patients develop mild facial weakness, peripheral neuropathy and vasculitis [7, 10]. Immune-mediated conditions such as SLE, mixed connective tissue disease, scleroderma, thyroid dysfunction, sarcoidosis and/or mitochondrial diseases may co-exist. Other significant associated illnesses include diabetes mellitus (20%) and diffuse peripheral neuropathy (18%) [11–13]. IBM may mimic motor neuron disease. Muscle biopsy and quantitative electromyographic analysis are indicated in patients with atypical motor neuron disease, especially those with slow progression, isolated swallowing involvement or early and disproportionate weakness of the finger flexors [14, 15]. IBM is also noted to be associated with HIV and HTLV infection [16]. Unlike other IMIs, there is no associated cardiac disease or malignancy, and typically these patients have lower CK levels [4]. The disease is usually slowly but relentlessly progressive.

Two types of diagnostic criteria have been described to define s-IBM (Mendel's diagnostic criteria and the European neuromuscular centre diagnostic criteria, see Appendices IV and V) [6, 17]. None of the clinical or laboratory features are mandatory if the muscle biopsy is diagnostic.

**Disease progression, prognosis and treatment**

Older individuals progress at a rate much faster than those who develop symptoms at a younger age [18]. Patients with progressive dysphagia have a significantly worse functional class rating, poor prognosis and poorer quality of life than patients with non-progressive dysphagia. Cricopharyngeal myotomy and local injection of Botulinum A have been found to be useful in selected older patients with dysphagia [19]. Intravenous immunoglobulin (IVIg) + prednisolone therapy has been demonstrated to be beneficial in life-threatening oesophageal involvement [20, 21].

Therapy of IBM has been less than satisfactory and mostly unsuccessful. Immunosuppressive agents, such as prednisone, azathioprine, chlorambucil and methotrexate, have been tried with minimal improvement, and the effects were usually unsustained. They seem to decrease inflammation on biopsy and decrease CK levels, but patients show no clinical improvement. Treatment with IVIg and plasma exchange has also been tried, with mixed results.

As with all disabling conditions, the role of allied professionals such as physio- and occupational therapists and speech therapists is of the utmost importance. The Myositis Support Group (www.myositis.org.uk) and the Muscular Dystrophy Campaign (www.muscular-dystrophy.org) are UK-wide charities that provide support for the 30,000 people and the 120,000 friends and family also affected by these conditions in the UK through: Fact Sheets, Family Care Officers, Occupational Therapy, Specialist Medical Services, Training and Employment and Grants for Equipment to Individuals. The Myositis Association of America (www.myositis.org) has also been doing tremendous work over the years, having provided all kinds of support to patients, families, carers and researchers throughout the world.

**Recent advances in IBM**

A trial of oxandrolone showed a significant effect in improving whole body strength measured by maximal voluntary isometric contraction testing [19]. A home exercise programme on muscle function found it to be a useful method of preventing loss of muscle strength due to disease and/or inactivity [22]. Interferon beta-1a given intramuscularly has also been tested with variable results.

A new autosomal dominant myopathy (OMIM 605637 inclusion body myopathy 3) associated with a missense mutation in the myosin-heavy chain (MyHC) IIa gene has been described recently. MyHC IIa gene mutation E706K is pathogenic and its expression increases with age [23]. The demonstration also in recent studies of the presence in muscle fibres of potentially toxic aberrant protein transcripts (e.g. ubiquitin UBB+1) that can interfere with proteasomal degradative mechanisms provides another possible explanation for the abnormal protein accumulation and for the generation of antigenic peptides that could be driving the T-cell response [24–26].

Future research in IBM should include population-based studies in order to determine disease prevalence and determine the predisposing environmental or genetic factors (in retrospective or prospective trials), to be able to modify them to stop the disease progression. Attempts to define the natural course of the disease and advances in molecular immunology may help the development of new therapeutic approaches, such as blockade of the signal transduction in T lymphocytes (e.g. by cyclosporin, rapamycin and specific monoclonal antibodies) and agents against immunomodulating cytokines (e.g. anti-TNF-α strategies).

**Key points**

- s-IBM is the most common myopathy in patients over 50 years and most often misdiagnosed.
A high index of suspicion along with knowledge of the diagnostic criteria is essential to avoid misdiagnosis.

The co-morbidities of older people may render clinical diagnosis difficult.

s-IBM should be considered in treatment-resistant polymyositis over 50 years, disproportionate quadriceps, finger/wrist flexor weakness, unexplained dysphagia and in atypical motor neuron disease.

Repeated biopsies may have to be done to demonstrate the features of IBM.

Steroid treatment must not be continued for more than 3–6 months as it is not effective and also carries a risk of steroid-induced myopathy, which worsens the condition.

In life-threatening oesophageal impairment, a course of IVIg + steroids is beneficial.

References

The very long list of references supporting this article has meant that only the ten most important are listed here and are represented by bold type throughout the text. The full list of references is available in the supplementary data on the journal’s website (http://www.ageing.oxfordjournals.org) along with a description of the diagnostic criteria and mechanisms and the theories of pathogenesis of IBM (Appendices II and III).

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An unusual cause of pleural effusion

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Abstract

Primary effusion lymphoma (PEL) is a unique clinicopathological entity associated with human herpesvirus-8 (HHV-8) infection, occurring almost exclusively in human immunodeficiency virus (HIV)-infected individuals. We report a rare case of HHV-8-negative PEL in an HIV-negative elderly patient who presented with pleural effusion. The patient was treated with CHOP and Rituximab. As opposed to the general poor outcome of this disease, our patient achieved complete remission and is still without signs of disease 11 months after the last treatment.

Keywords: primary effusion lymphoma, human herpesvirus-8, Rituximab, human immunodeficiency virus, CHOP