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Review

Diagnosis and classification of sporadic inclusion body myositis (sIBM)

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ABSTRACT

Sporadic inclusion body myositis (sIBM) is the most common acquired muscle disease in elderly individuals, particularly men. Its prevalence varies among ethnic groups but is estimated at 35 per one million people over 50. Genetic as well as environmental factors and autoimmune processes might both have a role in its pathogenesis. Unlike other inflammatory myopathies, sIBM causes very slowly progressive muscular weakness and atrophy, having a distinctive pattern of muscle involvement and different forms of clinical presentation. In some cases a primary autoimmune disease coexists. Diagnosis is suspected on clinical grounds and is established by typical muscle pathology. As a rule sIBM is refractory to conventional forms of immunotherapy.

Contents

1. Introduction

Sporadic inclusion body myositis (sIBM) is a progressive degenerative inflammatory disorder in skeletal muscle of unknown etiology. In addition, is one of the three main subsets of inflammatory myopathies, the other two being polymyositis and dermatomyositis. Although all of these conditions include inflammation in the endomysium, muscle fiber necrosis, elevation of serum muscle enzymes and varying degrees of muscle weakness, sIBM is often misdiagnosed as polymyositis. sIBM should be distinguished from hereditary inclusion body myopathies (hIBM) in which histologic and ultrastructural findings resemble those of sIBM with one clear exception: the absence of inflammation.

2. Epidemiology

The prevalence of sIBM is estimated at between 4.5 to 9.5 per one million rising to 35 per million for people over 50 years old. Recent studies have reported differences in prevalence with respect to geographical location, being 1.0 in Turkey [1], 4.7 in Netherlands [2], 9.8 in Japan [3] or 50 in Western Australia [4]. A number of discrepancies

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suggest that these numbers underestimate the true prevalence of this myopathy. On the basis of clinical reports from reference centers worldwide, it seems that sIBM is the most common acquired myopathy in patients above 50 years, affecting men slightly more frequently than women [5,6].

3. History

In 1971 Yunis and Samaha coined the term IBM for the definition of a myopathy that clinically resembled a chronic polymyositis but was pathologically characterized by the presence of vacuoles containing cytoplasmic degradation products with fibrillary nuclear and cytoplasmic inclusions [7]. A few years previously some authors had reported clinical cases suggestive of IBM. Since then, large series of patients have been described.

4. Pathogenesis

Although the underlying cause of sIBM is unclear, it seems that at least three processes might occur in parallel: a primary immune process due to T-cell mediated cytotoxicity, a non-immune process characterized by vacuolization and intracellular accumulation of amyloid-related molecules probably due to MHC-class I-induced stress [6,8], and mitochondrial dysfunction.

Choi et al. [9] demonstrated the elevated expression of transglutaminases 1 and 2 in the vacuoles of sIBM, co-localizing with amyloid-related proteins. They suggest that these enzymes participate in the formation of insoluble amyloid deposits and may thereby contribute to progressive debilitating muscle disease. This topic has been explored by Selva-O'Callaghan et al. [10] with interesting results. Genetic factors are presumed to play a role in sIBM based on an association between sIBM and certain HLA genes, in particular HLA — DR3. This association is present in nearly 75% of the cases, but this figure may vary in different ethnic groups [6,11,12]. Many recent studies have shown parallelism between sIBM and Alzheimer's disease, focusing on similarities between brain and muscle cells of Alzheimer and sIBM, respectively. These similarities include cellular aging, oxidative and endoplasmic reticulum stresses, mitochondrial abnormalities, proteasome inhibition and multiprotein aggregates [13–15].

5. Clinical manifestations

sIBM causes weakness and atrophy of the distal and proximal muscles and involvement of the quadriceps and deep finger flexors are clues to early diagnosis. The pattern is sometimes asymmetric resembling a motor neuron disease. Neck flexors and extensors are frequently affected. Heat drop and camptocormia (selective atrophy and weakness of paraspinal muscles) may occur, even as a form of clinical presentation. Facial involvement is rare but can be observed in HIV-related cases. Dysphagia occurs in up to 60% of patients with sIBM and again may be the form of presentation in rare cases. Sensory function is normal as well are tendon reflexes, but they become diminished or absent as the atrophy of major muscles occurs. The clinical course is always chronic or very chronic, lasting for years after the onset of symptoms and the diagnosis of the disease. Disease progression is slow but steady resembling that of a muscular dystrophy.

6. Differential diagnosis

sIBM is often misdiagnosed as polymyositis or other diseases and is frequently only suspected retrospectively when a patient with presumed polymyositis does not respond to therapy. In a patient complaining of falls due to weakness at the knees and feet with atrophic thighs and without paresthesias or cramps the most plausible diagnosis is sIBM. Useful data regarding differential diagnoses are shown in Table 1.

Table 1
Differential diagnoses (prominent data for each condition).

Motor neuron disease:	Hyperreflexia, cramps, fasciculations Typical EMG
Polymyositis:	Subacute (weeks to months) Proximal and symmetrical muscle weakness High CK levels
Vacuolar myopathies: (myofibrillar myopathies, hIBM)	Lack of inflammation, negative MHC HLA-class I

7. Pathological features

The common findings in muscle biopsy are perivascular and endomisial inflammatory infiltrates of varying degrees, rimmed vacuoles in atrophic fibers (Fig. 1), the presence of partial cellular invasion by CD8 cells, frequent cytochrome oxidase (COX)-negative cellules, β-amyloid and tau deposits and the upregulation of MHC class I antigens in healthy muscle cells. In addition abnormal mitochondrial changes such as ragged-red fibers are frequently observed. Some of theses features can be observed in Fig. 1. Nuclear and/or cytoplasmic filamentous inclusions of 16–20 nm are seen in electron microscopy examination [16]. Recent studies suggest that abnormal accumulation of extranuclear TDP-43, a nucleic acid-binding protein, in sarcoplasm of IBM muscle cells may be toxic through its binding to RNA [17,18]. On some occasions an additional muscle biopsy must be performed if pathological changes are suggestive but not consistent.

8. Biochemical features

Creatine kinase (CK) serum levels are moderately elevated but can be normal. Unlike other inflammatory conditions acute phase reactants are normal in sIBM.

9. Serological features

Different autoantibodies can be detected in a percentage of sIBM patients. Antinuclear antibodies (20%), rheumatoid factor (13%), anticardiolipin antibodies (10%), antiRo antibodies (10%) are the most frequently reported. In 2011, an autoantibody to an approximately 43 kDa human muscle protein was identified in 52% of IBM samples, 0% of other autoimmune myopathy samples and 0% of normal samples [19,20]. In about 10% of the cases dysproteinemia can also be detected [21].

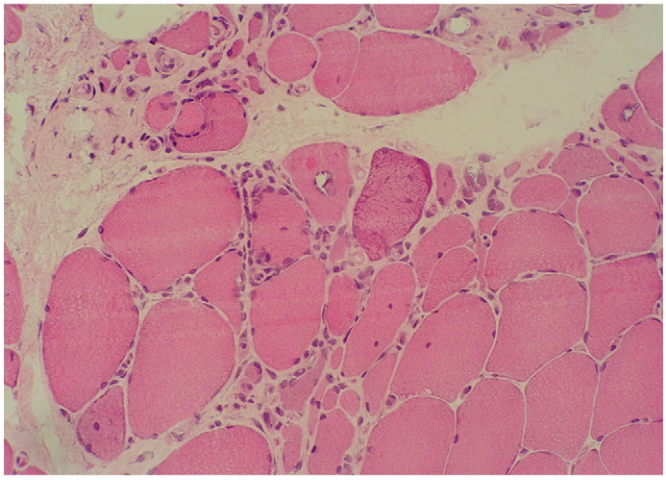

Fig. 1. Variability in fiber size with prominent connective tissue. Mononuclear cells in the endomysium as well as invading a healthy muscle cell can be observed. Rimmed vacuoles are present on at least two fibers. A typical ragged-red fiber is also observed in the center of the picture. HE on frozen muscle biopsy from an sIBM patient.

Table 2
Diagnostic criteria proposed for sIBM.

Clinical features:
- Duration of illness >6 months
- Age at onset > 30 years
- Slowly progressive muscle weakness and atrophy: selective pattern with early involvement of quadriceps femoris and finger flexors (frequently not symmetric)
- Dysphagia
Laboratory features:
- Serum CK levels might be high but can be normal
- EMG: myopathic or mixed patterns, with both short and long duration motor unit potentials and spontaneous activity
Muscle biopsy:
- Myofiber necrosis and regeneration
- Endomysial mononuclear cell infiltrate (in variable degree)
- Mononuclear cell-invasion of non-necrotic fibers (mainly CD8)
- MHC class I expression in otherwise morphologically healthy muscle fibers
- Vacuolated muscle fibers (rimmed vacuoles)
- Ubiquitin-positive inclusions and amyloid deposits in muscle fibers
- Nuclear and/or cytoplasmic filamentous inclusions of 16–20 nm on electron microscopy
- COX-negative fibers

10. Associated disorders

Several autoimmune disorders have been reported in association with sIBM [6,21–23], including pernicious anemia, dermatitis herpetiformis, psoriasis, Sjögren syndrome, SLE, rheumatoid arthritis, common variable immunodeficiency, idiopathic thrombocytopenic purpura, Hashimoto's thyroiditis, dermatomyositis and gluten sensitivity enteropathy. In a recent study Ray et al. demonstrated the evidence of humoral autoimmunity in sIBM [24]. Unlike dermatomyositis, sIBM should not be considered as a paraneoplastic condition. In addition HIV infection can be associated with sIBM with progressive muscular disease despite the good control of the infection (normal CD4 values as well as viral load).

11. Diagnostic criteria

The definite diagnostic procedure is a biopsy of the muscle. Although individual pathological features are all non specific and can also be seen in other myopathies and neurogenic disorders, their co-occurrence in the same biopsy allows the diagnosis of sIBM. Table 2 shows the diagnostic criteria for sIBM. The criteria for diagnosis of sIBM were first proposed by Griggs et al. in 1995, with minor modifications in 2002 and were finally reviewed by Dalakas in 2007. Table 3 presents the diagnostic categories (definite, probable and possible sIBM) [5,6,25].

12. Prognosis

The severity of the disease is poorly associated with the degree of inflammatory changes found in muscle biopsies and although treatment with corticosteroids might reduce the inflammation, it does not stop the degenerative changes and has little or no effect on the degree of weakness. sIBM is a relentlessly progressive disorder: most patients requiring a walking aid after 5 years and the use of wheelchair after about 10 years. sIBM patients often die due to a complication of their debilitating progressive disease (aspirative pneumonia) or because an unrelated condition.

Table 3
Diagnostic categories.

Definite sporadic inclusion body myositis:
· Characteristic clinical features with biopsy confirmation: inflammatory myopathy with autoaggressive T cells, rimmed vacuoles, COX-negative fibers, amyloid deposits or filamentous inclusions and upregulation of MHC class I expression. With these pathlogical findings the presence of other laboratory features are not mandatory.
· Atypical pattern of weakness and atrophy but with diagnostic biopsy features.
Probable sporadic inclusion body myositis:
· Characteristic clinical and laboratory findings but incomplete biopsy criteria (e.g. features of necrotising inflammatory myopathy with T cell invasion but absence of rimmed vacuoles, amyloid deposits, filamentous inclusions and COX-negative fibers).
Possible sporadic inclusion body myositis:
· Atypical pattern of weakness and incomplete biopsy criteria

13. Therapy

Most patients do not respond to antiinflammatory, immunosuppressant or immunomodulatory drugs currently available. Corticosteroids, cytotoxic drugs, intravenous immunoglobulins, antithymhocyte globulin and cytokine-based therapies have been used with poor results in follow-up [5,6]. Some authors have reported reliable data about inefficacy of immunotherapy in sIBM [26]. A small proportion of patients do respond, at least initially, and this probably represents a subgroup in whom the disease is diagnosed early and/or is associated with a primary autoimmune condition [27]. In some centers an initial 3–6 month trial of prednisone and methotrexate or azathioprine is recommended.

Other empirical therapies such as coenzyme Q10, carnitine, myostatin inhibitors and even statins have been used or are under investigation. Exercise therapy and orthotic appliances have confirmed their efficacy in stabilizing muscle strength and functional ability [28].

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