Challenges in diagnosis and treatment of sporadic inclusion-body myositis

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Abstract

Sporadic inclusion body myositis (sIBM) is a rare yet increasingly prevalent disease and the most common cause of inflammatory myopathy in people over the age of 50. The exact cause of the disorder is unknown. In sIBM 2 processes, first autoimmune and the other degenerative, parallelly occur in the muscle cells. The inflammation aspect is characterized by the cloning of T cells that appear to be driven by specific antigens to invade muscle fibers. The degeneration aspect is characterized by the appearance of holes in the muscle cell vacuoles, deposits of abnormal proteins within the cells and in filamentous inclusions. The disease has a major impact on patients' motor functionality and their quality of life. The treatment of sIBM still remains a major challenge. Early diagnosis of sIBM (already at the histopathology stage), when one still cannot observe fully developed clinical symptoms, may stop help to the progression of the disease.

Key words: biomarker, early diagnosis, sporadic inclusion body myositis

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Table 1. Sporadic inclusion-body myositis (sIBM) diagnostic criteria from 2011

Classification	Clinical features	Pathological features
Clinicopathologically defined sIBM	1. duration of weakness >12 months 2. creatine kinase $\leq 15 \times$ ULN 3. age at onset >45 years 4. finger flexion weakness > shoulder abduction weakness, and/or 5. knee extension weakness > hip flexor weakness	All of the following: 1. endomysial inflammatory infiltrate 2. rimmed vacuoles 3. protein accumulation or 15–18 nm tubulofilaments
Clinically defined sIBM	1. duration of weakness >12 months 2. creatine kinase $\leq 15 \times$ ULN 3. age at onset >45 years 4. finger flexion weakness > shoulder abduction weakness 5. knee extension weakness > hip flexor weakness	One or more: 1. endomysial inflammatory infiltrate 2. upregulation of MHC class I 3. rimmed vacuoles 4. protein accumulation or 15–18 nm tubulofilaments
Probable sIBM	1. duration of weakness >12 months 2. creatine kinase $\leq 15 \times$ ULN 3. age at onset >45 years 4. finger flexion weakness > shoulder abduction weakness, or 5. knee extension weakness > hip flexor weakness	One or more: 1. endomysial inflammatory infiltrate 2. upregulation of MHC class I 3. rimmed vacuoles 4. protein accumulation or 15–18 nm tubulofilaments

sIBM – sporadic inclusion body myositis; MHC class I – major histocompatibility complex class I; ULN – upper limit of normal.

Sporadic inclusion-body myositis (sIBM) is one of the causes of myopathy that should be considered in rheumatological and neurological diagnosis. The onset of the disease is usually concealed and clinical symptoms develop slowly (over the years), leading to weakness and atrophy of both proximal and distal muscles.¹ The term sIBM was introduced in 1971 by Yunis and Samaha to describe patients with polymyositis, for whom the histopathological examination revealed the presence of rimmed vacuoles and specific intercalations localized in the cytoplasm and nuclei of muscle fibers.^{1,2} Generally, sIBM is taken into consideration in the diagnosis of myopathy when a patient does not respond to the treatment with glucocorticosteroids, or when the clinical symptoms include muscle involvement seen in distal muscles, particularly in the foot extensors or deep fingers flexors.^{1–4} Moreover, the facial and swallowing muscles are affected; hence, one of the clinical symptoms of sIBM could be difficulty in swallowing.⁵ The disease usually manifests itself after the age of 50 and is more common among males (2:1). Its steady progress leads to significant motor impairment. The muscle involvement can be asymmetric and can occur selectively in the quadriceps (muscles of the thighs), iliopsoas muscle, triceps, biceps, and forearm flexor muscles.⁵ Laboratory tests may show elevated or normal levels of creatine kinase (CK). Asymptomatic presentation of sIBM is rare.⁶

Electromyography (EMG) can be used to exclude typical causes of neurogenic disorders and to classify the disease into the group of muscle damage; however, it cannot accurately extract its cause (myositis, toxic or dystrophic myopathic processes).⁵ Therefore, muscle biopsy with histopathologic, immunohistochemical and microscopical examination remains the best method for diagnosing sIBM. In the analysis of the muscle biopsy, sIBM can be signaled by: inflammatory infiltrations, infiltration

Table 2. Sporadic inclusion-body myositis (sIBM) diagnostic criteria from 1995

Clinical features	1. duration of illness >6 months 2. age of onset >30 years old 3. muscle weakness affecting proximal and distal muscles of arms and legs and patient must exhibit at least 1 of the following features: a. finger flexion weakness b. wrist flexion weakness > wrist extension weakness c. quadriceps muscle weakness ($\leq$ grade 4 MRC)
Laboratory features	4. serum creatine kinase <12 times normal 5. muscle biopsy a. inflammatory myopathy characterized by mononuclear cell invasion of non-necrotic muscle fibers b. vacuolated muscle fibers c. either intracellular amyloid or 15–18 nm tubulofilaments 6. electromyography – inflammatory myopathy

MRC – Medical Research Council scale.

of inflammatory cells intact muscle fibers (partial infiltration), rimmed vacuoles, deposits of amyloid, and 15–18 nm tubulofilaments seen in electron microscopy. Moreover, it should be noted that not all of these changes can be observed in every patient simultaneously; this fact is included in the diagnostic criteria from 2011 (Table 1).⁷ So far, the existing diagnostic criteria for sIBM have been mainly based on histopathological changes (Table 2).⁷ In definite IBM, patients must exhibit all muscle biopsy features, including invasion of non-necrotic fibers by mononuclear cells, vacuolated muscle fibers and intracellular (within muscle fibers) amyloid deposits or 15–18 nm tubulofilaments. If the muscle biopsy shows only inflammation (invasion of non-necrotic muscle fibers by mononuclear cells) without other pathological features of IBM, then a diagnosis of possible IBM can be given if the patient exhibits the characteristic clinical and laboratory features.

Fig. 1A. Myelin structure, transmission electron microscopy (TEM)

Fig. 1B. The muscle ultrastructure. Rimmed vacuole is recognized by a lining of granules at the margins of the vacuole, transmission electron microscopy (TEM)

Prognostic factors in sporadic inclusion body myositis

The disease has a major impact on the patients' motor functionality and their quality of life. As the time of disease development is slow, the survival rate of patients with sIBM is probably not comparable to the life expectancy of the general population.⁸ Causes of death associated with IBM mainly include malnutrition, wasting (cachexia), aspiration, respiratory infections as a result of dysphagia, and decreased respiratory muscle function in advanced cases of the disease.⁷ The increased cancer risk was not proven like in other inflammatory myositis.⁹ According to Benveniste et al., a few factors can contribute to the progression of the disease towards disability and they include: male gender, older age (>60 years) and immunosuppressive therapy.¹⁰ Cortese et al. also suggested that advanced age

(>55 years) is associated with an unfavorable prognosis.¹¹ Furthermore, the time to stand up and start the movement was the prognostic factor in patients with sIBM.¹²

The cause of the disease is still not fully understood. So far, the proposed theories suggest a role in the etiology of disease of: viral infection, accumulation of toxic proteins, the autoimmune attack, degeneration of muscle cells (rimmed vacuoles filled with nuclear and lysosomal proteins, and inclusions in the cytoplasm of muscle cells composed of the TDP-43 (TAR DNA-binding protein 43) (Fig. 1A,B); the role of lysosomal membrane protein LAMP1 and LAMP2 in the degeneration of the muscle cells' proteins and the formation of typical vacuole), and impaired proteasome and autophagocytosis function (accumulation of P62 (a protein associated with the nuclear pores-lamin involved in the transportation between the nucleus and cytoplasm), LC3 (microtubule-associated proteins 1A/1B

light chain 3-autophagy membranes) and NBR1 (neighbor of the *BRCA1* gene 1 protein, receptor associated with p62)).^{5,13–15} New insights into the role of p62 in sIBM pathogenesis indicate that p62 join to perform selective autophagy.¹⁶ Furthermore, p62 could be induced by some cellular stresses. Nakano et al. recently published the theory that in sIBM, compromised binding of the p62-ubiquitinated protein complex to LC3 could stop the autophagy process in its initial stages, which causes the formation of aggregates of p62-oligomers with Lys63-ubiquitinated proteins.¹⁶ Also, the upregulation of TGF- β (transforming growth factor- β) signaling may have an important influence on sIBM pathogenesis.¹⁷

Among patients with sIBM, the histopathological muscle biopsy finds: atrophied fibers along with the normal and overgrown fibers with properly preserved differentiation in the types of metabolic, infiltration with mononuclear cells (mainly lymphocytes around blood vessels and muscle fibers that do not show the features of necrosis), presence of rimmed vacuoles in the fibers and eosinophils inclusions in the cytoplasm of muscle fibers, as well as vacuoles comprising basophilic granularities.^{7,18}

The fact that sIBM belongs to the group of autoimmune diseases is indicated by the presence of infiltrates composed of cytotoxic lymphocytes T CD8⁺ that form an immunological connection with major histocompatibility complex class I (MHC-I). This leads to a failure of muscle fibers through the mechanism of special cytolytic proteins-perforins, which provides the reason for the use of immunosuppressive drugs.^{19–25} Additionally, apart from the inflammatory process, in sIBM coexist features of the degeneration of muscle fibers in the form of rimmed vacuoles, and the depositions of congophilic amyloids and other specific proteins.²¹ Rare missense variants in FYCO1 (a protein accumulated at rimmed vacuoles) may impair autophagic function, leading to rimmed vacuoles formation.²⁶ In sIBM there were also observed activated lymphocytes of B type, dendritic cells of plasmacytoid origin in the area of perivascular and perimysium, as well as increased expression of adhesion molecules and significant amount of cytokines and chemokines such as, for example: γ -interferon, interleukin (IL)-1b, tumor necrosis factor alpha (TNF- α), CXCL3-CXCL10, and deregulated expression of mitochondrial proteins in oxidative phosphorylation.^{13,27} Still, there are no established biomarkers for sIBM that could be used in everyday clinical practice.²⁸ The proposed biomarkers of the disease are presented in Table 3. The determination of biomarkers of sIBM is limited by the lack of specific standards for the use of specific biomarkers (medium cut, accountability), the lack of comparable sensitivity and specificity with other than sIBM muscle diseases, and the need to perform invasive muscle biopsy. Nowadays, the most suitable determination method appears to be the use of antigens anti-cN1A (cytosolic 5'-nucleotidase 1A antibodies), described for the first time by Larman et al.²⁹ The antigen localizes itself predominantly in the

Table 3. The biomarkers of sporadic inclusion-body myositis (sIBM)

Biomarker	Mechanism of action
Rimmed vacuoles (1.3–16% of muscle fibers in IBM)	degeneration of muscle cells
Tubulofilaments	theory of viral infection – unconfirmed
Congo red-stained material	protein accumulation
Beta-amyloid accumulation (6–25% of patients with IBM)	theory of molecular toxicity
TDP-43 accumulation (inside and around rimmed vacuoles, sensitivity – 91% and specificity – 77% vs 0% and 8% in polymyositis)	metabolism of nucleic acids, degeneration of muscle cells
Immunoreactive SMI-31 accumulations (initially named phosphorylated tau protein)	unknown
p62 accumulation	protein accumulation, autophagocytosis
cN1A antibodies	metabolism of nucleic acids
Invasion of nonnecrotic fibers	autoimmune etiology
BACE-1 PS-1 sAPP β	amyloidogenic-related molecules

BACE-1 – beta-secretase-1; PS-1 – presenilin-1; sAPP β – soluble A β precursor protein.

perinuclear and rimmed vacuoles region. Their advantage is the determination of blood serum taken from patients. Their sensitivity was between 60% and 70% and specificity was enclosed in the range of 83–92% at low titer and correspondingly 33–34% and 96–98% at high titer.^{29–32} Probably, this antibody could be connected with a more severe phenotype and a higher adjusted mortality risk.³³

Treatment of sIBM still remains a major challenge due to the coexistence of autoinflammatory and degenerative processes. So far, there has not been enough evidence in favor of using glucocorticosteroids, methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, or intravenous immunoglobulin. Even though up to 30% of patients during the initial period of treatment may show some response, the disease is still slowly progressing.^{21,34,35} Recently, it was suggested that the aggressive anti-inflammatory treatment in sIBM might stop the degenerative process. Therefore, a few studies were carried out with the use of alemtuzumab (humanized monoclonal IgG1 kappa causing long-term reduction in lymphocytes). Indeed, the results showed that this antibody significantly reduces the number of T cells in the muscles and inhibits certain molecules associated with degenerative process, which slowed down the progression of the disease in the 6-month period under consideration. However, there was no improvement in muscle strength.^{36,37} Other substance, arimoclomol, has been already used in neurology as it affects the expression of the heat shock proteins (HSP). In the course of therapy, slow improvement was observed in patients' exercise capacity, assessment of manual muscle (MMT) and grip strength in the right upper extremity. However, no effect was found

on the quantitative assessment of muscle tissue with dual-energy X-ray absorptiometry (DEXA) and the level of HSP70 in the muscle biopsy taken at the beginning and at the end of the treatment. The study in question has yet to be fully published.³⁸ Currently, we are expecting the results from 2 other studies that were carried out with the administration of rapamycin.^{21,39,40} The research that was carried out with the use of immunosuppressive drugs represents an introduction to new treatment options and a better understanding of sIBM's pathomechanism. Early diagnosis of sIBM (already at the histopathological stage), when one still cannot observe fully developed clinical symptoms, may help to stop the progression of the disease.

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