# Pitfalls in Diagnostic Myopathology of Sporadic Inclusion Body Myositis (SIBM)

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## ABSTRACT

Sporadic inclusion body myositis (SIBM) is the most common idiopathic inflammatory myopathy in Caucasians over the age of 50 years. The prevalence of SIBM in the Asian population was initially thought to be very low, although the recent study showed that the prevalence of SIBM in Japan is in fact similar to the prevalence in Australia and the USA. SIBM is a refractory myositis with associated myodegenerative features mimicking the neuropathology of Alzheimer's disease. The diagnosis of definite SIBM requires the typical clinical features and the presence of an autoaggressive inflammatory reaction, rimmed vacuoles, and congophilic deposits or tubulofilamentous inclusions. About one-fourth of patients with the typical clinical features of SIBM did not fulfill the pathological criteria of the definite SIBM. These canonical biopsy features may be absent in the early stage of the disease. Here we review the typical findings and the diagnostic pitfalls of the muscle biopsy in SIBM.

**Keywords:** Amyloid-β, PM/IBM, PM-Mito, SIBM, sporadic inclusion body myositis

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Immune-mediated myopathy refers to a clinically and pathologically heterogeneous group of myopathies due to the dysimmune process. Immune-mediated myopathies are divided into 2 groups: non-inflammatory (necrotizing) and inflammatory myopathies. Inflammatory myopathies are characterized by the biopsy findings of inflammatory changes and necrotic and regenerating fibers. Inclusion body myositis (IBM), polymyositis (PM) and dermatomyositis (DM) are 3 major categories of idiopathic inflammatory myopathy.[1] These inflammatory myopathies are clinically and pathologically distinct (Table 1). Idiopathic inflammatory myopathy sometimes occurs in patients with other well-characterized connective tissue disease forming overlap syndromes or in patients suffering from viral infections especially HIV. Despite the clinical differences among various types of inflammatory myopathies and the recent knowledge on myositis-related antibodies, muscle biopsy remains the essential diagnostic procedure. Some muscular dystrophies or myopathies may have biopsy findings mimicking inflammatory myopathy. A history of affected family members and distribution of muscle weakness should guide the clinicians to reach a correct diagnosis (Table 2).[2-11]

IBM is a unique inflammatory myopathy with myodegenerative features mimicking the neuropathology of Alzheimer's disease. It is the most common idiopathic inflammatory myopathy in Caucasians over the age of 50 years and accounts for nearly one-third of all inflammatory myopathies.[12] The prevalence of IBM in the Asian population including Thailand and other non-Caucasian ethnic groups has not been reported, but it is considered to be uncommon.[13] These racial and ethnic variations were thought to be due to the low frequency of the IBM susceptible alleles, HLA-DRB1*0301 (DR3) in the non-Caucasian population.[13] However, the recent preliminary study from Japan showed that the prevalence of IBM in Japan in 2005 was 11.8 per million which is similar to the prevalence of IBM in the USA and Australia.[13,14] In Japan, there was a 4.7-times increase in the prevalence over a 10-year period (1995-2005).[14]

SIBM is a slowly progressive, refractory inflammatory myopathy. Early atrophy and weakness of quadriceps (Fig 1A) and finger flexors are the typical clinical features of IBM. The canonical biopsy findings include autoaggressive inflammatory reaction, rimmed vacuoles, and congophilic

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**TABLE 1.** Idiopathic inflammatory myopathies.

| *Characteristics* | | *Sporadic inclusion body myositis* | *Polymyositis* | **Dermatomyositis** |
|---|---|---|---|---|
| Onset | | Late adulthood (> 50 years) | Adulthood | Childhood, juvenile or adulthood |
| Clinical presentations | Neuromuscular | Symmetrical or asymmetrical proximal and distal weakness with predominant quadriceps and finger flexors involvement; dysphagia | Symmetrical limb-girdle weakness; dysphagia | Symmetrical limb-girdle weakness; dysphagia |
| | Extra-neuromuscular | - | Myocarditis; interstitial lung disease | Rash; myocarditis; interstitial lung disease |
| Serum CK level | | Normal to mildly elevated | Moderately to markedly elevated | Normal to markedly elevated |
| Electrodiagnostic study | | Variable but mixed myopathic and neurogenic MUPs with fibrillations are typical. | Myopathic MUPs with fibrillations | Myopathic MUPs with fibrillations |
| Response to immunosuppressive therapy | | None or minimal | Yes | Yes |
| Associated conditions | Malignancy | None | Yes | Yes (adult-onset) |
| | Others | Neuropathy, Sjogren syndrome or Sarcoidosis | Connective tissue diseases | Connective tissue diseases or vasculitides |
| Light microscopic pathology | Site of inflammation | Predominant endomysial exudates | Predominant endomysial exudates | Predominant perivascular perimysial exudates |
| | Autoaggressive exudates | Common | Common | Uncommon |
| | Lymphocyte subtypes | CD8-positive T cells | CD8-positive T cells | CD4-positive and B cells |
| | Perifascicular atrophy and other changes | - | - | + |
| | COX-negative fibers | + (scattered fibers) | - | + (perifascicular fibers) |
| | Vacuolated fibers | + (rimmed vacuoles in scatted fibers) | - | + (non-rimmed vacuoles in rare perifascicular fibers) |
| | Congophilic inclusions | + | - | - |
| Immunohistochemical analysis | MHC class I | + (scattered fibers) | + (scattered fibers) | + (perifascicular fibers) |
| | αB-crystallin | + (scattered fibers) | + (scattered fibers) | + (perifascicular fibers) |
| | Microvasculature | Normal | Normal | Capillary depletion and C5b-9 complex deposits in the remaining capillaries |
| Electron microscopic analysis | Tubulofilmentous inclusions (16-20 nm) in myonuclei and sarcoplasm | + | - | - |
| | Tubuloreticular inclusions in capillary endothelium | - | - | + |
| Myopathies with similar pathology | | Hereditary inclusion body myopathy and myofibrillar myopathy | Anti-synthetase syndrome, polymyositis with mitochondrial pathology and PM/IBM | Anti-synthetase syndrome, anti-SRP myopathy and necrotizing myopathy with pipestem capillaries |

CK, creatine kinase; COX, cytochrome C oxidase; IBM, inclusion body myositis; MUP, motor unit potential; PM, polymyositis; SRP, signal recognition particle

**TABLE 2.** Myopathy or muscular dystrophy with pathologic features resembling myositis.

| *Diagnosis* | *Mode of inheritance* | *Gene* | *Onset* | **Phenotypes** |
|---|---|---|---|---|
| 1. Dystrophinopathies | XR | *DMD* | Childhood to adulthood onset | Duchene or Becker muscular dystrophy, manifesting carrier, muscle cramps or X-linked dilated cardiomyopathy |
| 2. Merosinopathy | AR | *LAMA2* | Neonatal or infantile onset | Congenital muscular dystrophy (MDC1A) |
| 3. Alpha-dystroglycanopathies | AR | *FKTN, FKRP, POMT1, POMT2, POMGnT1, and LARGE* | Neonatal to early adulthood onset | Congenital muscular dystrophy with neuronal migration defects or LGMD2 |
| 4. Calpainopathy* | AR | *CAPN3* | Childhood or early adulthood onset | LGMD2A or presymptomatic hyperCKemia |
| 5. Dysferlinopathy | AR | *DYSF* | Early adulthood > infantile onset | Congenital muscular dystrophy, distal myopathy with anterior tibial onset, LGMD2B, Miyoshi myopathy, presymptomatic hyperCKemia or rigid spine syndrome |
| 6. Hereditary inclusion body myopathy | AR | *MYH2* | Neonatal to early adulthood onset | Congenital transient joint contracture, childhood onset ophthalmoparesis and adult-onset limb-girdle or scapuloperoneal weakness |
| | AR | *GNE*** | Early adulthood onset | Distal myopathy with anterior tibial onset (distal myopathy with rimmed vacuoles or DMRV) |
| | AD | *VCP* | Early adulthood onset | Limb-girdle, scapuloperoneal or axial weakness associated with Paget disease of bone and frontotemporal dementia (inclusion body myopathy with Paget disease of bone and frontotemporal dementia or IBMPFD) |
| 7. Facioscapulohumeral muscular dystrophy | AD | D4Z4 contraction or hypomethylation | Early adulthood > childhood > infantile onset | Axial myopathy, camptocormia or scapuloperoneal myopathy with or without facial involvement, |
| 8. Myofibrillar myopathies | AD | *BAG3* | Childhood onset | Congenital muscular dystrophy with cardiomyopathy, neuropathy and rigid spine syndrome |
| | AR | *PLEC1* | Childhood onset | Epidermolysis bullosa simplex with congenital myasthenic syndrome, congenital muscular dystrophy, LGMD or pyloric atresia or isolated LGMD, |
| | X-linked | *FHL1* | Childhood onset | EDMD, reducing body myopathy, rigid spine syndrome, and scapuloperoneal myopathy |
| | AD>AR | *CRYAB, DES, FLNC, MYOT,* and *ZASP* | Childhood to late adulthood onset | Distal myopathy or LGMD with associated cardiomyopathy, neuropathy or cataracts (*CRYAB*) |

AD, autosomal dominant; AR, autosomal recessive; EDMD, Emery-Dreifuss muscular dystrophy; LGMD, limb-girdle muscular dystrophy; MDC, congenital muscular dystrophy;*, biopsy resembling eosinophilic myositis; **, biopsy showing inflammatory changes in some patients

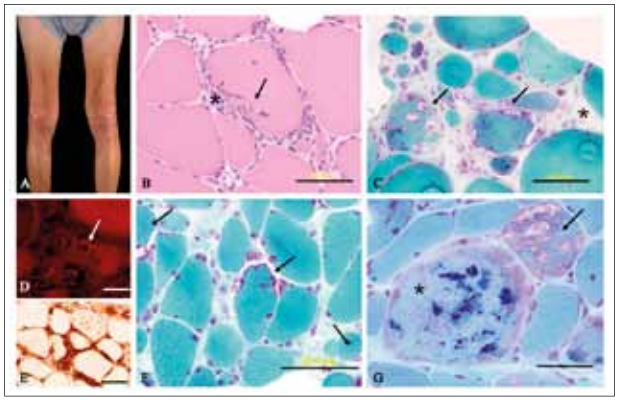

**Fig 1.** Clinical and pathologic features of sporadic inclusion body myositis and its mimickers.
(A-E) Sporadic inclusion body myositis (SIBM). (A) Photograph of definite SIBM patient showing atrophy of quadriceps. (B) H&E stained section revealed a marked variation in fiber size and an inflammatory exudate concentrated at the endomysial site (asterisk), where it invaded non-necrotic muscle fibers (arrow). (C) Trichromatically stained section showed rimmed vacuoles (arrow) and endomysial fibrosis (asterisk). (D) Congo-red stained section viewed under rhodamine optics displayed congophilic deposits in vacuolated fiber (arrow). (E) MHC-I immunoreactivity is present at the sarcolemma of non-necrotic muscle fibers. (F) Inclusion body myopathy with Paget disease of bone and frontotemporal dementia (IBMPFD). Trichromatically stained section revealed rimmed vacuoles (arrow) which were identical to those seen in SIBM. (G) Myofibrillar myopathy. Trichromatically stained section displayed a fiber containing rimmed vacuoles (arrow) and another fiber harboring amorphous hyaline material and multiple small cytoplasmic bodies (asterisk). Bar, 50 μm

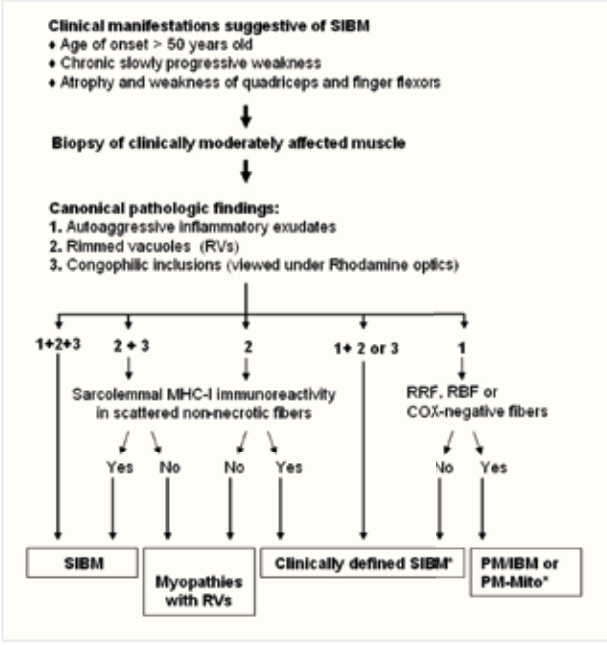


**Fig 2.** Diagnostic algorithm of the muscle biopsies in patients with clinical features of sporadic inclusion body myositis (SIBM). COX, cytochrome c oxidase; PM-Mito, polymyositis with mitochondrial pathology; RBF, ragged blue fibers; RRF, ragged red fibers; RV, rimmed vacuoles; SIBM, sporadic inclusion body myositis; * PM/IBM, PM-Mito and clinically defined SIBM may be the same entity and represent an early stage of SIBM (see text).

deposits or 16- to 20-nm tubulofilamentous inclusions.[12] Griggs and colleague defined definite IBM patients as having all canonical biopsy findings regardless of the clinical presentations (Table 3).[15] These biopsy features were originally thought to be IBM-specific, but they are also present in other myopathies including hereditary inclusion body myopathy (HIBM) and myofibrillar myopathy (MFM). HIBM is a group of clinically and genetically heterogenous, hereditary myopathies with the common pathological features which include rimmed vacuoles, congophilic deposits and tubulofilamentous inclusions. The onset of HIBM is typically earlier than IBM and the pattern of muscle weakness is also different between HIBM and IBM. An inflammatory exudate is normally absent in HIBM, but rare patients with the *GNE* variant of HIBM were reported with inflammatory changes mimicking IBM.[16,17] To avoid the confusion, IBM is sometimes referred to as sporadic inclusion body myositis (SIBM), although in rare occasions SIBM occurs in the same family.[13,18] For myofibrillar myopathy, the authors have described it in detail elsewhere.[19]

SIBM patients typically respond poorly to immunosuppressive therapy.[12] One of the possible explanations is that most SIBM patients were diagnosed late in their clinical course.[12-14,20] In the Japanese SIBM cohort, only 38% of patients were initially diagnosed as SIBM. The mean time to diagnosis was 4.6 years after the onset.[14] To achieve the correct diagnosis early, it is vital for clinicians and pathologists to be familiar with the typical clinicopathological features of SIBM. Diagnosis of SIBM can be made easily when all characteristic pathological features are present, and difficulties arise when some of the typical changes are absent and it requires clinicopathological correlation, special immunohistochemical studies or even a repeat biopsy to reach the correct diagnosis. Herein, we review the typical findings and the diagnostic pitfalls of muscle biopsy in SIBM.

## Pathology of Sporadic Inclusion Body Myositis (SIBM)

As mentioned earlier, SIBM is pathologically characterized by an autoaggressive inflammatory reaction, rimmed vacuoles, congophilic deposits and 16- to 20-nm tubulofilamentous, nuclear or sarcoplasmic inclusions.[21] Each pathological feature individually is nonspecific, although a combination of all 4 features increases the specificity toward SIBM. It is important to keep in mind that the inflammatory and myopathic changes in inflammatory myopathy can be focal and often these may be absent at an early stage or in patients who receive immunosuppressive therapy.

### I. Autoaggressive inflammatory reaction:

Invasion of non-necrotic muscle fibers (Fig 1B) by CD8+ T cells indicates autoaggressive inflammatory changes.[22] The similar autoaggressive feature also presents in PM, but the number of invaded fibers per unit biopsy area was significantly lower than in SIBM.[21] The distribution and degree of inflammatory changes in inflammatory myopathies vary from muscle to muscle, therefore careful selection of the biopsied muscle is the first step to avoid a false-negative biopsy. A clinically moderately affected muscle or a muscle showing moderate signal abnormality offers the proper choice for the biopsy. Open biopsy is

**TABLE 3.** Diagnostic criteria of sporadic inclusion body myositis.

| *Diagnostic criteria* | | *Clinical and laboratory features* | **Pathological features** |
|---|---|---|---|
| Griggs et al, 1995[15] | Definite SIBM | None of clinical and laboratory features are mandatory if biopsy features are diagnostic | Fulfill all pathological characteristics of SIBM including (1) autoaggressive inflammatory exudates, (2) rimmed vacuoles and (3) either congophilic deposits or tubulofilamentous inclusions |
| | Possible SIBM | Fulfill all clinical and laboratory characteristics of SIBM including (1) age of onset > 30 years, (2) duration of weakness > 6 months, (3) predominant wrist flexors, finger flexors or quadriceps weakness, (4) CK < 12 times normal, and (5) EMG findings consistent with inflammatory myopathy | Only autoaggressive inflammatory exudate |
| Needham et al, 2007[25] | Definite SIBM | Fulfill all clinical and laboratory characteristics of SIBM including (1) age of onset > 30 years, (2) duration of weakness > 6 months, (3) predominant finger flexors and quadriceps weakness, (4) normal or high CK, and (5) EMG showing myopathic or mixed MUPs but the distribution of weakness can be atypical if biopsy findings are diagnostic | Fulfill all pathological characteristics of SIBM including (1) autoaggresive inflammatory exudates, (2) rimmed vacuoles, (3) COX-negative fibers, (4) upregulation of MHC-I expression and (5) amyloid deposits or tubulofilamentous inclusions |
| | Probable SIBM | Fulfill all clinical and laboratory characteristics of SIBM | Incomplete biopsy criteria |
| | Possible SIBM | Atypical pattern of weakness | Incomplete biopsy criteria |
| Benveniste et al, 2010[20] | Pathologically defined SIBM | Consistent with SIBM | Fulfill all pathological characteristics of SIBM including (1) autoaggressive inflammatory exudate, (2) rimmed vacuoles and (3) amyloid deposits (Congo-red or crystal violet) or hyperphosphorylated tau (SMI-31 or p62) or TDP-43-positive aggregates or tubulofilamentous inclusions |
| | Clinically defined SIBM | Fulfill all of clinical and laboratory characteristics of SIBM including (1) age of onset > 30 years, (2) duration of weakness > 6 months, (3) predominant finger flexors and quadriceps weakness, and (4) EMG findings consistent with inflammatory myopathy | Autoaggressive inflammatory exudate or upregulation of MHC-I without congophilic deposits or SMI-31-positive aggregates or tubulofilamentous inclusions |
| | Possible SIBM | Similar to clinically defined SIBM but weakness predominantly involves either finger flexors or quadriceps | Similar to Clinically defined SIBM |

CK, creatine kinase; COX, cytochrome c oxidase; MUP, motor unit potential; SIBM, sporadic inclusion body myositis

preferable over needle biopsy because it provides a larger sample.

Major histocompatibility complex class-I (MHC-I) is normally expressed in intramuscular blood vessels, inflammatory cells and the sarcoplasm of necrotic or regenerating fibers.[23] Sarcolemmal immunoreactivity of otherwise morphologically healthy muscle fibers is a key feature of inflammatory myopathies (Fig 1E) (Table 2) and is present even when the inflammatory exudates are subtle or absent.[24,25] However, this aberrant expression of MHC-I should be interpreted in the appropriate clinical context, because it also presents in other myopathies, muscular dystrophies and in some patients with statin-induced myopathy.[23-26]

**II. Rimmed vacuoles and congophilic inclusions:**

On H&E stained sections, rimmed vacuoles appear empty and mostly located at the subsarcolemmal areas. A vacuole is typically rimmed by hematoxophilic material, hence the name rimmed vacuole. It is best seen on a trichromatically stained section (Fig 1C). Rimmed vacuoles were also reported in HIBM, MFM, oculopharyngeal muscular dystrophy (OPMD), reducing body myopathy, Marinesco-Sjogren syndrome, some variants of distal myopathies or limb-girdle muscular dystrophies and in rare patients with facioscapulohumeral muscular dystrophy (FSHD) or X-linked Emery-Dreifuss muscular dystrophy (EDMD).[27-31] In SIBM, only about 3% of muscle fibers harbor rimmed vacuoles.[32]

SIBM differs from PM and DM because it features not only an inflammatory reaction, but also a myodegenerative process characterized by ectopic expression of several proteins in muscle fibers resembling the brain pathology of Alzheimer's diseases.[33] Abnormal protein aggregates are a composite of misfolded proteins (e.g. amyloid- and phosphorylated tau) and key molecules of unfolded protein response (UPR) and endoplasmic reticulum associated degradation (ERAD) (e.g. ubiquitin and proteosome).[33,34] Amyloid aggregate is visualized by Congo-red (Fig 1D), thioflavin or crystal violet, but it is often that these special stains are not included in the routine set of biopsy analysis. Moreover, these amyloid deposits can easily be missed if examined only through polarizing filters. Amyloid deposits often are very small and typically present in only 60-80% of vacuolated fibers or about 0.75% of all myofibers.[20,35] Viewing a Congo-red stained section under rhodamine optics greatly facilitates identification of amyloid deposits.[36] Amyloid aggregate itself is non-specific and has been reported in a variety of myopathies.[11,28,36-41] The intramuscle fiber amyloid deposits observed in SIBM, HIBM, MFM, OPMD, and in rare patients with X-linked EDMD differ from the interstitial or vascular amyloid aggregates observed in dysferlinopathy and immune-mediated or hereditary systemic amyloidosis.[11,28,36-41]

**III. Nuclear or sarcoplasmic tubulofilamentous inclusions:**

The characteristic ultrastructural feature of SIBM are 16- to 20-nm tubulofilamentous, nuclear or sarcoplasmic inclusions resembling paired helical filaments (PHFs) of neurofibrillary tangles seen in Alzheimer's disease brain.[33] Similar to the tangles, these inclusions contain phosphorylated tau. PHFs are present in 2-6% of myonuclei.[33] The similar tubulofilamentous inclusions were also reported in other myopathies, muscular dystrophies, neurogenic disorders and congenital myasthenic syndromes.[23,42] PHFs differ from amyloid- aggregates which are 6- to 10-nm filaments or flocculomembranous or amorphous material.[33]

**IV. Other pathological features of SIBM:**

There are other pathological features of SIBM that are important, but not diagnostic. These encompass type 1 fiber preponderance (Liewluck T, unpublished data), with the pathological alterations suggestive of mitochondrial dysfunction (ragged-red, ragged-blue and cytochrome c oxidase-negative fibers), and small angular fibers over-reactive for nonspecific esterase indicative of recent dener vation.[20] The myopathological finding of denervation atrophy is consistent with the electrodiagnostic feature of mixed neurogenic and myopathic motor unit potentials and with the axonal degeneration seen in the nerve biopsy of some SIBM patients.[43-45]

**Recent developments in diagnostic myopathology of SIBM**

SIBM was initially recognized as a specific subset of inflammatory myopathies based on the identification of rimmed vacuoles and tubulofilamentous inclusions in patients with steroid-unresponsive PM.[46] It was later realized that SIBM patients had a unique distribution of muscle weaknesses different from PM patients and the pathological changes were not as specific as initially thought.[15] In clinical practice, about 1/4 of patients with characteristic clinical presentations of SIBM do not fulfill the pathological diagnostic criteria of definite SIBM based on Griggs criteria (Table 3).[15] This may reflect sampling error or the currently recognized canonical pathologic alterations are late features of SIBM, and not the sensitive biomarkers of the disease. An attempt has been made to identify a new specific marker for SIBM that is more sensitive than rimmed vacuoles, amyloid deposits or tubulofilamentous inclusions in order to identify SIBM patients at an early stage of the disease.

Salajegheh et al., reported sarcoplasmic TDP-43 immunoreactivity as the most sensitive histologic marker of SIBM identified in nearly 25% of myofibers in definite SIBM cases.[32] However, the amount of TDP-43 may vary from patients to patients as suggested by the lower sensitivity of TDP-43 immunoreactivity observed in other series of SIBM patients.[20,47] SMI-31 and p62 antibodies detect phosphorylated tau and a shuttle protein in ERAD, respectively. Both SMI-31 and p62-positive inclusions occur in the similar proportion of fibers harboring rimmed vacuoles.[20,35,47] Some experts consider electron microscopy as a nonessential study, because the presence of SMI-31 or p62-positive inclusions is equally sensitive and specific, and is more practical in routine laboratories.

Banwell et al., detected enhanced expression of αB-crystallin, a small heat shock protein, in approximately 10% of myofibers in definite SIBM patients.[35] Most of these αB-crystallin–positive fibers did not harbor other structural changes. The similar fibers were also present in PM, DM, MFMs and critical illness myopathy but less frequent. Although αB-crystallin is the most sensitive histologic marker for SIBM to date, its lack of specificity does not permit distinction between SIBM and PM. Currently, the list of aggregated proteins found in SIBM continues to expand and this may provide the future direction to identify the more sensitive and specific histologic marker for SIBM.[34]

**Clinically defined SIBM, PM/IBM and PM-Mito**

As described earlier, about 25% of patients with typical clinical features of SIBM demonstrate only the

autoaggressive inflammatory changes without rimmed vacuoles or amyloid deposits.[21] This group of patients was originally designated as "possible SIBM" based on Griggs criteria.[15] Currently, it is known that some of possible SIBM patients behaved clinically like definite SIBM patients and a repeat biopsy a few years later revealed the canonical pathological findings of SIBM.[20] Therefore it is recommended to classify these possible SIBM patients as "clinically defined SIBM" or "PM/IBM".[20,21]

In 1997, Blume et al., reported a new entity of inflammatory myopathy, PM with mitochondrial pathology (PM-Mito).[48] Characteristic distribution of muscle weakness as in SIBM and PM/IBM were reported in 60% of PM-Mito patients.[49] All PM-Mito patients, either with or without predominant quadriceps or finger flexors weakness, shared the similar clinical course to SIBM and PM/IBM patients.[49] It is known that mitochondrial pathology is common in SIBM and PM/IBM,[21] therefore PM-Mito may in fact be the same entity as PM/IBM and both reflect the early stage of definite SIBM. To date, all randomized clinical trials recruited only definite SIBM patients, hence patients with an advanced disease, and all drugs tested appear to be ineffective.[20] Several experts postulated that a clinical trial in early SIBM patients (e.g. PM/IBM or PM-Mito) may yield a better result.[20] Fig 2 showed the diagnostic algorithm of muscle biopsies in patients with clinical features of SIBM.

## CONCLUSION

SIBM has unique clinical and pathological features. It is a refractory inflammatory myopathy with associated myodegenerative features. Some SIBM patients were not initially diagnosed as definite SIBM, because the biopsies lacked some of the canonical pathological findings. In order to diagnose SIBM at the early stage of the disease, it is important to find the specific histologic markers that have higher sensitivity than rimmed vacuoles, congophilic deposits and tubulofilamentous inclusions. Clinically defined SIBM, PM/IBM and PM-Mito may represent the early stage of definite SIBM and should be included in the study of any new histologic markers or novel therapeutic agents in the future.

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