Diagnosis and Clinical Development of Sporadic Inclusion Body Myositis and Polymyositis With Mitochondrial Pathology: A Single-Center Retrospective Analysis

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Abstract

To review our diagnostic and treatment approaches concerning sporadic inclusion body myositis (sIBM) and polymyositis with mitochondrial pathology (PM-Mito), we conducted a retrospective analysis of clinical and histological data of 32 patients diagnosed as sIBM and 7 patients diagnosed as PM-Mito by muscle biopsy. Of 32 patients identified histologically as sIBM, 19 fulfilled the 2011 European Neuromuscular Center (ENMC) diagnostic criteria for “clinico-pathologically defined sIBM” at the time of biopsy. Among these, 2 patients developed sIBM after years of immunosuppressive treatment for organ transplantation. Of 11 patients fulfilling the histological but not the clinical criteria, including 3 cases with duration <12 months, 8 later fulfilled the criteria for clinico-pathologically defined sIBM. Of 7 PM-Mito patients, 4 received immunosuppressive treatment with clinical improvement in 3. One of these later developed clinico-pathologically defined sIBM; 1 untreated patient progressed to clinically defined sIBM. Thus, muscle histology remains important for this differential diagnosis to identify sIBM patients not matching the ENMC criteria and the PM-Mito group. In the latter, we report at least 50% positive, if occasionally transient, response to immunosuppressive treatments and progression to sIBM in a minority. The mitochondrial abnormalities defining PM-Mito do not seem to define the threshold to immunosuppression unresponsiveness.

Key Words: Diagnosis, Differential, Immunosuppression, Inclusion body, Mitochondria, Myositis, Polymyositis.

INTRODUCTION

Sporadic inclusion body myositis (sIBM) is a slowly progressive inflammatory muscle disorder with a characteristic pattern of muscle weakness (1). Typically, the onset of symptoms is after the age of 50 years and there is no favorable response to immune treatments (2, 3). Despite this, there are marked inflammatory tissue changes based on expanded, persistent clones of CD8-positive cytotoxic T cells targeting myofibers as found in the generally treatment responsive polymyositis (PM) (4–6). The features of sIBM that differ from those of other idiopathic inflammatory myopathies, including PM, are degenerative findings, in particular pathological protein aggregation (7–9), rimmed vacuoles, and more frequent mitochondrial changes. The latter include ragged red fibers, cytochrome c oxidase (COX)-negative fibers and mitochondrial DNA (mtDNA) deletions (10). Diagnostic criteria for sIBM now use a combination of the inflammatory and the degenerative—but not the mitochondrial—histological changes as well as clinical signs (11) (see Table 1).

Due to the similar autoinflammatory process in PM and reports of the frequent occurrence of various autoimmune diseases in the sIBM population (up to 33%) (12), one line of thought is that sIBM might be a primary autoimmune inflammatory disorder then converting (at least in part) into a degenerative process (13). Recent data point toward changes in accord with secondary effects of chronic inflammatory (over)stimulation, in particular detection of peripheral regulatory T-cell deficiency (14), T-cell large granular lymphocyte expansion (15), and increased expression levels of markers for T-cell exhaustion and senescence (16). Some argue that a causative population of highly differentiated cytotoxic T cells (TEMRA) is unaffected, possibly selected, by all conventional immunosuppressive and immunomodulatory treatments (17).

Among the observations cited to support the view of a primary inflammatory trigger (13) are also PM cases that show limited sIBM-like histological changes and may respond to immunosuppression, but later develop typical sIBM, or that show a sIBM-like clinical presentation but only later fulfill the histological criteria. However, there are few reports concern-
ing these and the patients’ outcome and response to treatment does not appear to be homogeneous.

In brief, 10 PM patients with >4% fibers negative in COX enzyme histochemistry and multiple mtDNA deletions were reported in 1997 (18). These “polymyositis with mitochondrial pathology (PM-Mito)” cases were found to be somewhat older than other PM patients, to have selective quadriceps weakness and poor response to immunosuppressive therapy, thus sharing features with sIBM, but missing rimmed vacuoles or congophilic material. The following year, 1998, a meaningful clinical improvement of 5 out of 7 such patients (“inflammatory myopathy with COX-negative muscle fibers”) to methotrexate treatment was reported (19). Chahin and Engel choose a different approach correlating clinical and histological signs to define a population without the histological diagnosis but with the clinical features of sIBM (“PM/IBM”) that did not respond well to immunosuppressive treatment and showed more COX-negative fibers per centimeter square biopsy area than their PM group (20). In a follow-up to the first report (18), 9 of the original PM-Mito patients had had a further muscle biopsy and 4 were reclassified as sIBM due to the presence of rimmed vacuoles (21). An expanded group of PM-Mito cases (threshold now defined as >1% COX-negative fibers), shared aggregates reactive with anti-LC3 and anti-zB-crystallin with sIBM, but not abnormal anti-SMI-31 or anti-TDP43 immunohistochemistry (IHC) (21). Two PM-Mito patients’ samples underwent ultrastructural analysis without demonstration of sIBM pathology (22). Of these 2 patients, 1 improved with steroid treatment and 1 did not. In a recent study, of 4 patients classified as PM-Mito by histology, 3 showed long-term improvement with immunosuppressive treatments (23).

To provide further data for clinicians charged with setting the course for treatment in PM-Mito cases and as clinical feedback on the debate about the immunological genesis and treatability of sIBM, we present details of our case series of PM-Mito (Table 1).

MATERIALS AND METHODS
Ethics Approval
Approved as a retrospective study by the local ethics committee (349/20), thereby waiving the need for further consent.

Case Selection
In order to guarantee standardized work-up of muscle biopsy samples, we restricted our retrospective analysis to patients whose muscle biopsy had been investigated in our laboratory from January 2007 to January 2020 (more than 1500 samples) and who had been seen in our department around the time of biopsy. Cases not seen in our neuromuscular clinic or those treated in our clinic but with external histological diagnosis were excluded. However, no fixed follow-up time was required. The first step in selecting cases was based on the histopathology. To be included in the PM-Mito group, >1% COX-negative fibers and predominately endomysial inflammatory infiltrate surrounding—preferably invading—in individual non-necrotic muscle fibers had to be present in the absence of rimmed vacuoles and pathological protein accumulation as determined by Congo red stain and anti-p62 immunoreactivity. For the histological diagnosis of sIBM, upregulation of major histocompatibility complex I (MHC-I), endomysial inflammatory infiltrate, rimmed vacuoles, and pathological protein accumulation had to be present. We then screened the clinical files of patients fulfilling either histological criteria with particular regard to the symptoms at first presentation, course of clinical signs and alternative causes (i.e. overlap of defined mitochondrial disorder and other inflammatory myopathy) based on clinical picture as well as further investigations (family history, laboratory data, genetic analysis) if present. This included clinical notes from outside our clinic as well as notes or oral reports from patients or their relatives concerning the course of disease after patients had last been seen in our clinic. Because data on myositis-specific/-associated antibodies were not available in all patients, these were not included. Patients in whom a cause different from sIBM or PM-Mito, respectively, had to be assumed were not included.

Histology
Muscle Material
Muscle specimens were obtained by standard open biopsy during diagnostic work-up for neuromuscular complaints. The muscles were frozen in melting isopentane and stored in liquid nitrogen. Cryosections were cut at 6-μm thickness and transferred onto silanated glass slides. The sections were then fixed in acetone for 5 minutes at −20°C and air-dried, either to be stained directly or stored at −20°C for subsequent staining.

For histology, diagnostic biopsies underwent standard work-up, including hematoxylin and eosin, modified Gomori trichrome, adenosine triphosphatase (pH 4.2, 4.6, and 9.4), reduced nicotinamide adenine dinucleotide, periodic acid Schiff, oil-red-O, acid phosphatase, Congo red, myoadenylate deaminase, phosphofructokinase, succinate dehydrogenase (SDH), COX, and myophosphorylase stainings. Histochemical and enzyme histochemical staining procedures were conducted by standard protocols. IHC employing antibodies against MHC-I (1:1000; W6/32; DAKO, Hamburg, Germany), membrane attack complex of complement (MAC/C5b9; 1:100; aE11; DAKO), cluster of differentiation 3 (CD3; 1:50; T3-4B5; DAKO), cluster of differentiation 68 (CD68; 1:80; EBM11; DAKO), and anti-p62 (SQSTM1; 1:800; D-3; Santa Cruz Bio-technology, Heidelberg, Germany), respectively, was used for all samples. In some cases, antibodies against CD8 (1:50; NCL-CD8, Novocastra, United Kingdom) and MHC-II (1:200; L243, BD Biosciences, Heidelberg, Germany) were used. The percentage of COX-negative fibers was determined by count of 3 random fields of view at 10-fold primary magnification of combined COX/SDH enzyme histochemistry.
RESULTS

Between January 2007 and January 2020 biopsies of 33 patients fulfilled all histological criteria of sIBM (endomysial inflammatory infiltrate, upregulation of MHC-I, rimmed vacuoles, and protein accumulation); 27 patients were male and 6 were female. Of these, 1 male case had to be excluded as no clinical data were available for all. All patients were older than 45 years and all had clinical signs of muscle disease for 12 months or longer. At first clinical assessment in our clinic of these 32 patients, 3 had knee extension weakness ≥ hip flexion weakness and finger flexion weakness > shoulder abduction weakness; 19 had knee extension weakness ≥ hip flexion weakness or finger flexion weakness > shoulder abduction weakness; and 10 showed neither. Two patients had creatine kinase (CK) values >15× the upper limit of normal; 1 had a normal CK value.

From the same time, 7 patients’ biopsies were found to fulfill our criteria for PM-Mito, 1 male and 6 females, and initial clinical data were available for all. All patients were older than 45 years and all had clinical signs of muscle disease for 12 months or longer. At first clinical assessment, none of these patients had knee extension weakness ≥ hip flexion weakness and finger flexion weakness > shoulder abduction weakness; 2 had knee extension weakness ≥ hip flexion weakness or finger flexion weakness > shoulder abduction weakness (patients 2 and 6 in Table 3), thereby conforming to European Neuromuscular Center (ENMC) diagnosis of “probable sIBM” (11). Five patients showed neither. All patients had elevated CK below 15× the upper limit of normal. One of these patients (patient 7) had a second biopsy 57 months later fulfilling the histological criteria for sIBM and therefore one of her biopsies was included in either count. We considered excluding another patient due to chronic hepatitis C under interferon treatment as an alternative cause (patient 3). However, as hepatitis C virus infection has also been discussed as being associated with sIBM, we decided against this (24).

Comparison of the 2 groups for age at biopsy and CK values showed a statistically significant difference for the former (p < 0.05; 2-tailed t-test as data normally distributed) but not for the latter (Mann-Whitney U test as data not normally distributed). Further data on both groups are found in Table 2; data on the individual cases in Table 3.

In PM-Mito, Partial Response to Immunosuppression is Frequent but May Not Preclude Later sIBM

Of the 7 patients, all complained about problems linked to proximal leg weakness, that is, climbing stairs and walking uphill, but only 4 showed manifest weakness in the initial neurological exam in our department. Myalgia and muscle cramps were complaints in 4 cases. The muscle biopsies of 6 patients showed invasion of non-necrotic fibers in addition to predominately endomysial inflammatory infiltrates, all had >1.3% COX-negative fibers and no rimmed vacuoles (Fig. 1A). Antip62 IHC did not show protein aggregation typical for sIBM, but occasionally mild and more diffuse reactivity (Fig. 1I). Ubiquitous upregulation of MHC class I on the muscle fibers was found in all biopsies (Fig. 1C).

Patient 1 is lost to follow-up. Patient 2 choose to have no further medical treatment or follow-up, but reports progressive weakness in typical sIBM distribution in the following

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TABLE 1. 2011 European Neuromuscular Centre Research Diagnostic Criteria for sIBM (11)

<table>
<thead>
<tr>
<th>Clinical and Laboratory Features</th>
<th>Pathological Features</th>
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<tbody>
<tr>
<td>Clinically and pathologically defined IBM</td>
<td>All of the following:</td>
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<tr>
<td>– Duration &gt;12 months</td>
<td>– Endomysial inflammatory infiltrate</td>
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<tr>
<td>– Age at onset &gt;45 years</td>
<td>– Rimmed vacuoles</td>
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<tr>
<td>– Knee extension weakness ≥ hip flexion weakness and/or finger flexion weakness &gt; shoulder abduction weakness</td>
<td>– Protein accumulation* or 15–18 nm filaments</td>
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<td>– CK no &gt;15× ULN</td>
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<tr>
<td>Clinically defined IBM</td>
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<td>– Duration &gt;12 months</td>
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<td>– CK no &gt;15× ULN</td>
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<td>Probable IBM</td>
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*Demonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid, Congo red, crystal violet, thioflavin T/S; immunohistochemistry for other proteins, p62, SMI-31, TDP-43).
years. Patient 3 with chronic hepatitis C and interferon treatment that had already been discontinued 6 months prior to the biopsy chose to have no further neurological treatment or follow-up, but is reported to have died 6 years after the biopsy without developing further muscle complaints or immobility.

Patient 4 received 3 monthly i.v. pulses of 3/C2 1 gm ethylprednisolone and treatment with azathioprine (approximately 2 mg/kg body weight/day). No improvement of her muscle weakness resulted, but apart from the onset of mild neck flexion weakness 27 months into the treatment, her symptoms did not progress either. However, increased immobility due to polyneuropathic signs was reported by her treating neurologist (suspected diabetic polyneuropathy). She was lost to follow-up 40 months after the start of treatment. Three further patients (patients 5, 6, and 7) were treated with orally administered steroids (1 mg/kg body weight daily) after making the diagnosis and all responded with reduction of their muscle complaints with impact on their daily activities. Patient 5 discontinued treatment due to side effects and has been undecided about further immunosuppression. In clinical follow-up after 18 months without treatment, her complaints had returned and were slightly more severe than before. Patients 6 and 7 received methotrexate in addition to decreasing dose steroids and showed further improvement including amelioration of manifest weakness in follow-up neurological exams in our neuromuscular clinic. However, both patients experienced side effects (worsening of asthma and liver toxicity, respectively) and immunosuppression was changed to mycophenolate mofetil. Patient 6 is stable more than 2 years after biopsy but still has some proximal muscle weakness and developed weakness of the flexion of the middle and distal joints of her left fourth and fifth finger for which no alternative cause was found. The condition of patient 7 worsened under mycophenolate mofetil, in particular with severe dysphagia. Escalation of immune-treatments first with intravenous cyclophosphamide, then rituximab and finally high dose intravenous immunoglobulins did not stop progression. When she developed finger flexor weakness a second muscle biopsy was performed more than 4 years after the first. This fulfilled the histological criteria of sIBM (Fig. 1B, D, H, J) and her diagnosis was changed to clinico-pathologically defined sIBM (11).

**Primary sIBM Developed Under Long-Term Immunosuppression After Organ Transplantation**

Unlike patient 7 in whom the sIBM phenotype developed from a previously diagnosed inflammatory myopathy under treatment, patients 8 and 9, diagnosed as having clinico-pathologically defined sIBM (11) with fulfillment of all histo-
logical criteria (Fig. 2), developed their muscle complaints under long-term immunosuppression after organ transplantation.

Patient 8 developed muscle weakness 15 years after a kidney transplantation due to a mesangioproliferative glomerulonephritis. He had an immunosuppression with cyclosporine, mycophenolate mofetil, and steroids. He already showed predominate finger flexor and knee extensor weakness at first presentation in our clinic and his CK value was elevated 3.5× the upper limit of normal. Muscle biopsy was performed under ongoing immunosuppressive therapies and showed typical sIBM findings (Fig. 2A, C, E, G). However, the infiltrate was rather sparse and we found no invasion of non-necrotic fibers (Fig. 2E). The disease course was typically progressive and 6 years after the sIBM diagnosis he died from complications of surgery due to a gall bladder adenocarcinoma with hepatic metastases.

Patient 9 had a liver transplantation for cirrhosis related to primary sclerosing cholangitis and had immunosuppressive treatment with first cyclosporine, later with OKT3 and tacrolimus, briefly sirolimus and everolimus. Six years after organ transplantation he developed a mild dysphagia and equal

**FIGURE 1.** Histology of PM-Mito patient 7 later diagnosed as sIBM. Modified Gomori Trichrome stain (A, B), anti-MHC-I (C, D), anti-MHC-II (E, F), anti-CD8 (G, H), anti-p62 (I, J) immunohistochemistry and cytochrome c oxidase/succinate dehydrogenase double enzyme histochemical staining (K, L) of first (A, C, E, G, I, K) and second (B, D, F, H, J, L) biopsy of patient 7 who was first diagnosed as PM-Mito and later fulfilled the criteria of clinico-pathologically defined sIBM. Note that rimmed vacuoles are absent in (A) and frequent in (B). Anti-p62 IHC indicated pathological protein accumulation typical for sIBM in (J), while only a single deposit was found in the first biopsy (arrowhead in I). Note eosin counter stain in (G–J). Primary magnification for (A), (B), (I), and (J), ×20; scale bar in (B) = 50 μm. Primary magnification for (C–H), (K), and (L), ×10; scale bar in (D) = 100 μm.
weakness of hip flexion and knee extension as first muscle symptoms and developed finger flexor weakness later. Serum CK was elevated 11.4× the upper limit of normal. His muscle biopsy was taken under tacrolimus treatment and showed typical sIBM histopathology (Fig. 2B, D, F, H).

The Majority of Patients Fulfilling the Histological but not the Clinical ENMC sIBM Criteria at the Time of Biopsy Later Fulfilled Both Criteria

Of 13 patients with histological findings for sIBM but not fulfilling the ENMC criteria at the time of biopsy, 8 could...
be classified as clinico-pathologically defined sIBM upon clinical follow-up (11). In 7 patients, this was due to development of weakness (2–38 months after biopsy), and one was due to the time course (6 months after biopsy). Of the remaining, 3 are lost to follow-up, including 1 case with CK >15× the upper limit of normal and disease duration at time of biopsy <12 months. Two cases still did not fulfill the criteria for clinico-pathologically sIBM, that is, 1 did not show the weakness pattern at only 6-month follow-up and 1 fulfilled the weakness criteria but with a CK <15× upper limit of normal.

**DISCUSSION**

The PM-Mito cases in this report are in accord with the majority of existing literature on the condition concerning the patients’ age (18, 19, 21, 22), the higher portion of affected females (18, 19, 21, 23) than in sIBM (25), and in the frequent complaint of muscle discomfort (21). As reported, the 2 patients later developing a “sIBM phenotype” did show neither rimmed vacuoles nor pathological protein aggregation in their (first) biopsy (21). In line with some of these reports, at least half of the patients treated with immunosuppression (3 out of 4) did show a positive response (19, 22, 23). This could be an argument to at least attempt to treat patients without pathological protein aggregation (and rimmed vacuoles) with immunosuppressive agents regardless of mitochondrial changes in their biopsy unless they show sIBM-typical distribution of weakness.

The clinical response to methotrexate in our patient 7, with transient but clear improvement of muscle strength but later descent into progressive weakness of sIBM phenotype, illustrates that, however, this response does neither guarantee continuous treatability nor justify treatment escalation once sIBM diagnostic criteria are fulfilled. Mild and transient responses of sIBM to immune treatments are known (26, 27), but long-term beneficial effects have so far not been found (2). The clinical sIBM phenotype seems to be specific and some histological changes, in particular rimmed vacuoles, may develop while the patient already shows typical clinical signs (1, 20). Thus, at least concerning fulfillment of the histological criteria, the age at biopsy may play a role. It is noteworthy that this was statistically significant lower in our PM-Mito compared with our sIBM group, although hardly to an extend useful in clinical diagnostics (Table 2).

There are no consensus criteria for the diagnosis of PM-Mito and indeed a robust definition of PM-Mito in itself is not easy to reach as both parts of the compound term are independently under debate. The diagnostic category of polymyositis has been criticized as early definitions were far too broad and the histological signs indicating the attack of CD8-positive cytotoxic T cells on myofibers, that is, predominately endomyosial and CD8-positive infiltrate encircling and preferably invading non-necrotic myofibers, that were later defined as rimmed vacuoles, were rarely found (28). Recent approaches to sort idiopathic inflammatory myopathies subtypes did not identify a corresponding group either (29). However, the cases presented here all showed this type of infiltrate and all but patient 7 showed invasion of non-necrotic fibers. Thus, except for patient 5 with CK <2× the upper limit of normal, they all fulfill the PM criteria of van der Meulen et al (28), which so many cases previously diagnosed as PM did not.

In addition, the lowering of the threshold percentage of COX-negative fibers as indicative of mitochondrial pathology from 4% (18, 19) to 1% (21, 23) can be criticized as too close to normal values. While some diagnostic criteria suggested in the literature point in this direction, for example (30), it should be noted that definitive, age- and inflammation-adapted values are not available. In fact, some available data suggest a very relevant age-dependence of the percentage of COX-negative fibers in inflammatory myopathies. For example, a range of 0–4.7% and a mean of 1.2% COX-negative fibers in a group of 15 dermatomyositis (DM), 12 PM and 3 sIBM cases were reported but this dropped to a mean of 0.8% in DM and 0.2% in PM when only the cases younger than 65 years were included (31). As PM-Mito seems to be a rare condition with little available data so far, our choice had to be to adhere to the 1% threshold currently in use. In our group, patient 2 with more than 4% COX-negative fibers converted to sIBM as did patient 7 with <4% in both biopsies and transient response to immunosuppression.

Rightly, diagnostic criteria for sIBM were over time adapted to further include the clinical presentation as purely histological criteria were found to lack sensitivity (11). Yet, the observation of histological changes more often found in sIBM than other inflammatory myopathies, in particular COX-negative fibers, has led to speculation about a “prestage” of sIBM, that is, patients about to convert from a (polymyositis treatable with conventional immunosuppressive agents to sIBM no longer responding to these treatments. The view that such derailment of an inflammatory process might lead to the refractoriness of sIBM for immunosuppressive treatments (13), if not the degenerative changes, has been supported by the findings of immune cell populations in sIBM patients’ muscle and blood that indicate chronic activation and loss of control mechanisms (14–17). Indeed, a causative cell population like this could explain the development of sIBM under prolonged immunosuppressive treatments in our patients 8 and 9 just as in the other 28 cases we considered “primary” sIBM. A somewhat similar case under sustained rheumatological treatment has been reported (32). It should be noted that all 3 cases had autoimmune diseases prior to immunosuppression as a possible starting point of chronic activation. Furthermore, control of disease activity or immunotolerance of the transplant, respectively, but not total suppression of immunological activity are the aims of these treatments and each of the substances used may have immunological side effects.

Should such pre-existing autoimmune activity lay the seed of later sIBM, these cases could point to a remarkable latency of this process as well as to an extramuscular disease origin, at least based on their clinical manifestations. In such a scenario, “secondary” sIBM could arise from an inflammatory myopathy responsive to immunosuppression, but it seems harder to understand why these cases should show an increased number of COX-negative fibers. An interaction of this particular immunological development with the mechanisms driving mitochondrial as well as the further histological changes of sIBM would be one explanation (13). Alternatively, the PM-Mito group could contain at least 2 entities. On the one hand, sIBM cases where the further histological changes—rimmed vacuoles and/or protein accumulation—cannot yet be found
hand, cases of inflammatory myopathies with >1% COX-negative fibers that later may or may not have the misfortune of their autoimmune activity steering toward sIBM but are yet within reach of conventional immunosuppression.

Finally, while the clinical presentation appears to have a better prognostic value for the development of sIBM than the histological criteria and thereby may make a muscle biopsy redundant in some cases (1), the number of patients in our retrospective analysis that were classified as sIBM by histology without showing the typical distribution of weakness at the time (10/32) but later fulfilling the ENMC criteria for clinicopathologically defined sIBM (7/10) demonstrates that muscle biopsy remains an essential tool in this differential diagnosis with implications on pharmacotherapy.

Our study has the obvious limitations of a retrospective analysis spanning many years as we have quantitative data on some, but not all aspects and have to rely on data from many sources, despite the inclusion criterion of at least having the core data established in our center. There is the ongoing need for the collection of defined, large, multicenter data sets. However, securing corresponding longitudinal data will obviously take time.

ACKNOWLEDGMENTS

The authors thank the patients and patients’ relatives for giving additional information. We gratefully acknowledge the help of the colleagues who send their patients to us, the many who cared for them here over the years and thereby provided a large part of the material and file notes used.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The retrospective and single-center nature of our study restrict availability of further patient data as this may require further consent and/or make the identification of individuals possible.

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