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Polymyositis with mitochondrial pathology or atypical form of sporadic inclusion body myositis: case series and review of the literature

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Abstract

Polymyositis with mitochondrial pathology (PM-Mito) is a rare form of idiopathic inflammatory myopathy with no definite diagnostic criteria and similarities to both PM and sporadic inclusion body myositis (s-IBM). The aim of this study is to address the dilemma of whether PM-Mito is a subtype of inflammatory myopathy or represents a disease falling into the spectrum of s-IBM. Herein, we report four female patients diagnosed with PM-Mito, highlighting their rather atypical clinical and histopathological characteristics that seem to indicate a diagnosis away from s-IBM. Muscle weakness was rather proximal and symmetrical and lacked the selective pattern observed in s-IBM. Patients had large-scale deletions in mtDNA, reflecting the mitochondrial component in the pathology of the disease. Conclusively, our study adds to the limited data in the literature on whether PM-Mito is a distinct form of myositis or represents a prodromal stage of s-IBM. Although the latter seems to be supported by a substantial body of evidence, there are, however, important differences, such as the different patterns of muscle weakness, and the good response to treatment observed in some patients. Larger-scale studies are certainly needed to clarify pathogenesis and clinical characteristics of PM-Mito patients, especially in therapeutic and prognostic terms.

Keywords Polymyositis · Mitochondria · mtDNA · Inclusion body myositis

Introduction

The idiopathic inflammatory myopathies (IIMs) are acquired autoimmune disorders characterized by progressive proximal muscle weakness and can be mainly grouped into four categories: dermatomyositis (DM), polymyositis (PM), sporadic inclusion body myositis (s-IBM) and necrotizing autoimmune myopathy (NAM). Overlap syndromes refer to these disorders in association with cancer or with another connective tissue disease [1]. The absence, until recently, of diagnostic criteria for inflammatory myopathies with high sensitivity and specificity and the increasingly recognized new subcategories led to the development of the new EULAR–ACR classification criteria [2]. However, the underlying pathomechanisms still remain to be elucidated.

PM and s-IBM share some common histopathological features, including endomysial inflammation and invasion by CD8 + T cells of non-necrotic fibers expressing MHC-1 complex. However, the additional presence of rimmed vacuoles and cytoplasmic and/or intranuclear 15–18 nm tubulofilamentous inclusions is characteristic for s-IBM

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[1]. Mitochondrial pathology may be also observed in IIMs, especially in s-IBM with a variable extent of cytochrome c oxidase (COX) deficiency and ragged red fibers (RRFs) due to mitochondrial DNA (mtDNA) deletions [3–6]. In dermatomyositis, widespread mitochondrial abnormalities may be observed in perifascicular regions, distinguishing it from other inflammatory myopathies, along with skin alterations and perimysial connective tissue pathology [6, 7]. Polymyositis with COX-deficient fibers, also called PM with mitochondrial pathology (PM-Mito) was first reported in 1997 by Blume et al. [3] as a rare form of inflammatory myopathy sharing common clinical and pathological features with s-IBM, such as later age of onset, slow progressive selective weakness of the quadriceps, poor response to corticosteroids, endomysial inflammation with focal invasion of intact muscle fibers and severe mitochondrial pathology, but lacking the characteristic rimmed vacuoles [3]. Thus, several reports considered the disease as a possible variant of s-IBM [3, 8] with common pathogenic mechanisms including disordered autophagy [9].

There is a scarcity of cases with PM-Mito in the literature to date, and only a few patients have been reported so far [3, 8, 9]. So, the aim of the present study is to further expand the limited existing literature regarding PM-Mito, by reporting four patients with slow progressive muscular weakness and myopathological findings suggestive of the disease and discuss.

Materials and methods

A retrospective review was carried out at the Department of Myology of the Aeginition University Hospital on muscle biopsies performed in the period from 2010 to 2016, to identify cases diagnosed as PM-Mito. Since the above diagnosis is primarily histologic, the selection of patients was based on strict pathological changes, as previously defined [10]. More specifically, the muscle biopsy should reveal lymphocytic endomysial infiltrates, especially of CD8+ T cells and/or macrophages invading non-necrotic fibers, diffuse HLA-1 increase and > 1% COX-negative fibers. Rimmed vacuoles and cytoplasmic inclusions should be absent. Muscle biopsies review was performed by two experienced myopathologists (GKP and CP). The study revealed 4 such patients with the aforementioned diagnosis out of 805 (Suppl. Fig. 1), whose clinical data were retrospectively analyzed. The patients' evaluation was based on muscle strength, laboratory testing and neurophysiological studies. They all had a negative family history for neuromuscular diseases and had been investigated for slow progressive muscle weakness. The diagnostic work up included routine laboratory investigations, screening for chronic viral infections such as HIV and Hepatitis C, blood tests for autoimmune diseases, a panel of myositis-specific antibodies (jo-1, Mi-2, SRP, PL-7, PL-12, EJ, OJ) and myositis-associated antibodies (anti-Ro/SSA, anti-La/SSB, anti-PM/Scl, anti-Ku, anti-U1RNP), electrodiagnostic studies with ENMG (electroneuromyography) and muscle biopsy. The muscle specimens were obtained by open biopsy under local anesthesia and were snap frozen in liquid nitrogen-cooled isopentane. Six micrometer thick cryostat sections were used for histological, histochemical, and immunohistochemical studies, using conventional techniques. Muscle biopsy was performed for all patients prior to any corticosteroid use.

Ethical approval was obtained from the Aeginition Hospital Ethics Committee and all patients have signed written informed consent for their data to be used for research purposes and/or to be published in a scientific journal.

Mitochondrial DNA analysis

Total DNA was isolated from skeletal muscle biopsy specimens of the four patients and eight age-matched controls (individuals without evidence of mitochondrial disease) using a salting-out method based on the procedure described by Miller et al. [11], after written informed consent. The presence of mtDNA rearrangements was examined with long-range PCR in the major arc, using primers F6951 (6951-6972) and R15997 (15997-15975) generating a wild-type product of 9047 bp (primer numbers refer to NCBI Reference Sequence NC_012920.1). PCR amplification was carried out on a Veriti Thermal Cycler (Applied Biosystems) using Phusion DNA Polymerase (ThermoFisher Scientific) according to the manufacturer's recommendations. The PCR products were electrophoresed on a 0.8% agarose gel and imaged using a UVIdoc Gel Documentation System (UVItec Ltd, UK).

Case reports

Clinical/paraclinical manifestations and outcome

The clinical history, the laboratory findings and the results of the neurophysiological studies for each patient are summarized in Table 1. A modified Medical Research Council (MRC) scale was employed, with grade 5 representing normal strength and grade 0 no muscle movement [12]. A sum score ranging from 0 to 100 was calculated for each patient by bilateral examination of shoulder abduction, elbow flexion, elbow extension, wrist flexion, wrist extension, hip flexion, knee flexion, knee extension, dorsal foot flexion and plantar foot flexion.

Patient 1, a 46-year-old female, was referred with a slowly evolving proximal lower limb muscle weakness with difficulty in climbing stairs and rising from a chair over the

Table 1 Clinical, laboratory and neurophysiological findings

Patient number	Gender	Age at symptoms' onset (years)	Age at biopsy (years)	Symptoms	Modified MRC (sum score)	Comorbidities	CK (max value) (U/L)	EMG
1	F	40	46	Swallowing difficulties, muscle weakness initially in proximal lower and later in upper legs	94	–	697	Myopathic changes and rare complex repetitive discharges
2	F	35	38	Muscle weakness (proximal and distal) of lower and upper extremities, mild drop head	90	Primary Sjogren's syndrome	538	Myopathic changes and spontaneous activity
3	F	50	52	Swallowing difficulties, nasal speech, muscle weakness of lower legs (distal > proximal), drop head	84	Hypothyroidism	943	Mixed myopathic and neurogenic changes
4	F	57	67	Mild slowly progressive proximal muscle weakness	97	Hypothyroidism, depression	453	Mild myopathic changes

previous 6 years. In the last 2 years, she also developed proximal upper limb weakness and occasionally dysphagia. Clinical examination showed symmetrical mild proximal muscle weakness of shoulder abduction, elbow flexion and hip flexion reduced to 4/5 bilaterally. Creatine kinase (CK) was mildly elevated (normal values 26–180 U/L) on repetitive measurements (max value: 697 U/L). Testing for myositis-specific and myositis-associated antibodies was negative. ENMG showed myopathic findings (defined as small amplitude, short duration, polyphasic motor unit action potentials, with early recruitment) with rare complex repetitive discharges in proximal muscles and polyphasic motor unit potentials in rectus abdominis muscle. NCS (nerve conduction studies) were normal. The patient was initially treated with prednisone up to 50 mg/day (equivalent cortisone dose of 5 mg/kg/day) for 3 months and prophylactic calcium/vitamin D treatment with a relative good response especially in upper limbs. Thereafter, oral methotrexate was instituted with a gradual increase up to 25 mg weekly, while prednisone was tapered down to 5 mg every alternate day. 3 years after the diagnosis, dysphagia is still occasionally present, but without worsening and a very mild bilateral hip flexion weakness.

Patient 2 was a 38-year-old female who was admitted with a 3-year history of slowly progressive weakness of the lower limbs following her third uncomplicated pregnancy. She was also diagnosed with primary Sjögren's Syndrome (pSS) since the age of 35, initially suspected from the xerostomia and arthralgias she suffered for several years. The neurological examination revealed mild drop head and a symmetrical mild proximal and distal muscular weakness of the upper and lower extremities (bilateral elbow flexion, wrist flexion/extension, hip flexion 4/5, right foot dorsiflexion 4/5, left foot dorsiflexion 4/5). ENMG revealed myopathic changes in most muscles examined, with spontaneous discharges of fibrillation potentials and positive sharp waves in tibialis anterior bilaterally, while NCS were normal. Serum CK levels were moderately elevated in consecutive measurements (max value: 538 U/L), erythrocyte sedimentation rate was moderately increased (45; normal, < 10), anti-nuclear antibodies (1/320) and anti-La/SSB antibodies were positive, while anti-DNA antibodies, rheumatoid factor and anti-Ro/SSA antibodies were absent. The panel of myositis-specific autoantibodies was negative. The patient started methylprednisolone at a dose of 64 mg/day (equivalent cortisone dose of 6 mg/kg/day) and calcium supplementation with the concurrent administration of methotrexate, which progressively increased at a maximum total dose of 25 mg/week, based also on the consultation of the patient's rheumatologist. A gradual clinical improvement was definitely observed and 4 years after treatment initiation the patient is almost asymptomatic and she receives 4 mg of methylprednisolone daily.

Patient 3, a 52-year-old woman with a history of hypothyroidism presented with slowly progressive dysphagia, nasal speech, mild drop head and mild proximal lower limb muscle weakness over the last 2 years. Clinically, the patient had bilateral symmetrical weakness of hip flexion (3/5) and a more severe distal involvement with bilateral weakness of foot plantar flexion and dorsiflexion (2/5). CK was moderately elevated (max value: 943 U/L), while the

immunological laboratory findings were normal. ENMG revealed myopathic changes and spontaneous activity in the muscles of lower extremities with normal NCS. The patient was initially put on treatment with prednisone 50 mg/day (equivalent cortisone dose of 5 mg/kg/day) and calcium/vitamin D prophylaxis with a gradual improvement of muscle weakness and dysphagia over the following months. The steroid dose was then slowly tapered down, but after an attempt to further lower the dose below 15 mg/day, the patient complained about the reappearance of mild dysphagia. Thereafter, mycophenolate mofetil at a final dose of 1500 mg/day was added with a clinical improvement that subsequently permitted prednisone reduction to 10 mg on alternate days. On last examination, 4 years after the disease onset, the patient still receives the same treatment and remains the same with just a mild waddling gait.

Patient 4 was a 67-year-old woman who presented with a 10-year history of slowly progressive proximal lower and upper limb weakness with characteristic difficulty getting out from a chair, climbing stairs and lifting her arms above the head. Other comorbidities included a history of a well-controlled hypothyroidism and depression. Clinical examination showed symmetrical mild proximal weakness with shoulder abduction 4/5 and hip flexion 4/5. Laboratory investigations revealed a mildly increased CK (max value: 453 U/L). Immunological investigations were unremarkable. ENMG showed myopathic changes, especially in proximal muscles of upper and lower limbs and normal NCS. The patient was put on prednisone up to 50 mg daily (equivalent cortisone dose of 4 mg/kg/day) and calcium/vitamin D prophylactic treatment for 2 months with a subsequent tapering and methotrexate (gradual increase up to 20 mg weekly). Due to lack of substantial improvement after 6 months, the patient received two cycles of 2 g/kg IVIg over 5 days, given 6 weeks apart. Unfortunately, there was no response to any therapeutic intervention and she gradually stopped any treatment. However, the patient was advised to perform mild aerobic exercise and was also instructed to come to regular follow-up visits. The last clinical examination did not reveal any meaningful deterioration.

Histopathological study

A left biceps brachii biopsy from patient 1 showed myopathic changes with increased variation of muscle fiber diameter, regeneration, necrosis, phagocytosis, endomysial inflammatory infiltrates, many RRFs and a high percentage of COX-deficient fibers (15.5%) as measured by randomly selected region of approximately 250 muscle fibers cut in cross-section and evaluated at ×10 magnification. An increased MHC-1 sarcolemmal expression was also observed in many muscle fibers. Muscle biopsy of patient 2 (Fig. 1) taken from left vastus lateralis revealed inflammatory cell infiltrates (mainly CD4+ and fewer CD8+ cells) in the endomysium and myopathic changes mainly consisting of muscle fiber size variation and a mild increase in central nucleation. There was also evidence of disease activity with necrosis, phagocytosis of both necrotic and non-necrotic muscle fibers and few regenerating fibers. Increased sarcolemmal expression of MHC-1 antigen was also observed in multiple fibers. The muscle specimen also showed scattered RRFs, a high amount of fibers with enhanced subsarcolemmal succinate dehydrogenase (SDH) activity and multiple fibers with deficient COX activity. The percentage of COX-deficient muscle fibers was estimated at 20.3%. Patient's 3 muscle biopsy of the right vastus lateralis showed mild myopathic changes with increased internal nucleation, inflammatory cell infiltrates (both CD4+ and CD8+ cells),

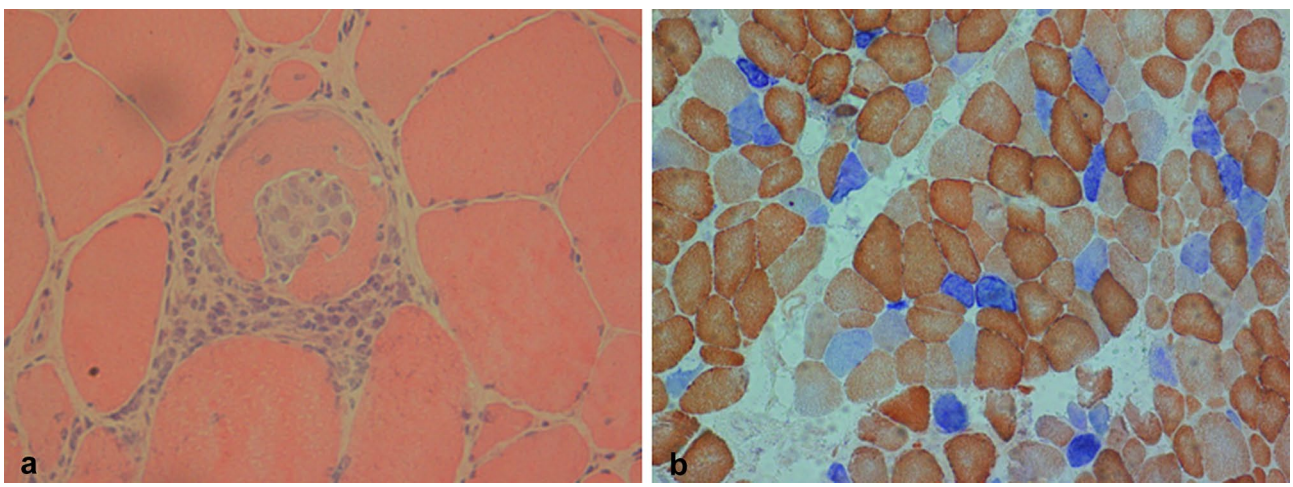

Fig. 1 Muscle biopsy sections from patient 1 stained with hematoxylin–eosin, **a** showing endomysial infiltrates and inflammatory cells invading a non-necrotic muscle fiber and COX-SDH staining (×40), **b** revealing many COX-deficient muscle fibers (×20)

increased sarcolemmal MHC-1 in many muscle fibers, regeneration, necrosis phagocytosis, few ragged red/blue fibers and multiple COX-deficient muscle fibers (8.8%) measured as described above. Similarly, a muscle biopsy of left deltoid from patient 4 showed endomysial inflammatory infiltrates, increased sarcolemmal expression of MHC-1 in few fibers, RRFs and COX-deficient fibers estimated at 7.9%.

Muscle biopsy findings for each patient are summarized in Table 2.

Mitochondrial DNA analysis

Long-range PCR revealed the presence of multiple large-scale mtDNA deletions in all four patients, while the aged-matched controls exhibited only the ~ 9 kb wild-type species (Fig. 2).

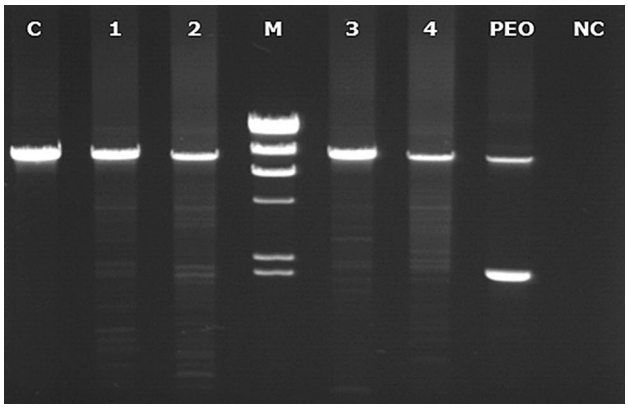

Fig. 2 Agarose gel analysis of the long-range PCR products. C, one of the age-matched control subjects; NC, PCR negative control; 1, patient 3; 2, patient 1; 3, patient 2; 4, patient 4; PEO, patient diagnosed with cPEO; M, λ-*Hind*III molecular size marker

Search strategy

We conducted a search on PubMed, MEDLINE, EMBASE, Web of Science and Scopus using combinations of the terms "polymyositis", "inflammatory myopathies", "myositis" with "COX-negative fibers" or "mitochondrial pathology". The search period was extended until November 2018 and the articles should be written in English. In fact, very few articles were specifically published on the degree of mitochondrial pathology especially in polymyositis. One of the first systematic studies, reporting a frequent occurrence of mitochondrial dysfunction in inflammatory myopathies, involved 30 patients with different types of myositis compared to an equal number of age-matched controls [6]. The term PM-Mito was used, a little later, as a distinct form of myositis. That study involved ten patients with histologically confirmed polymyositis associated with multiple COX-negative fibers, while mitochondrial DNA analysis showed multiple deletions in the majority. The patients' clinical presentation and the poor treatment outcome resembled s-IBM [3]. The progress in immunohistochemistry using autophagic markers has helped to distinguish s-IBM from other types of inflammatory myopathies and especially PM [9, 10]. In another report of two patients with PM-mito, the response to treatment was poor, while one patient had also an immunological profile compatible with SS [8].

Discussion

PM-Mito is a rare and probably controversial form of IIMs with significant mitochondrial pathology being one of its histopathological hallmarks. Definite diagnostic criteria for this disorder are still lacking and it has even been considered as an early form of s-IBM falling within the broad spectrum of the disease, without the presence of characteristic rimmed vacuoles [9, 10]. Mitochondrial abnormalities, such as muscle fibers lacking COX activity and RRFs may be frequently observed in patients with IIMs, but they are more striking in s-IBM patients [3, 7, 8, 13].

The first report of PM with COX-deficient muscle fibers as a distinct recognizable subtype of myositis included ten patients with COX deficiency in 4.2–27.4% of the total

Table 2 Muscle biopsy findings

Patient number	Muscle biopsy (other findings)	%COX-negative fibers
1	Endomysial inflammatory infiltrates, myopathic changes, regeneration, necrosis, phagocytosis, multiple RRFs and COX-negative, increased MHC-1 expression	15.5
2	Endomysial inflammatory cell infiltrates, myopathic changes, necrosis, phagocytosis, regeneration, increased MHC-1 expression, RRFs, multiple COX-negative fibers	20.3
3	Endomysial inflammatory infiltrates, myopathic changes, regeneration, necrosis phagocytosis, multiple COX-negative fibers, few RRFs, increased MHC-1 expression	8.8
4	Endomysial inflammatory infiltrates, mildly increased MHC-1 expression, RRFs, many COX fibers	7.9

muscle fibers. The patients were characterized by a median age at disease onset at the 7th decade, moderately elevated CK levels, a slowly progressive course and muscle weakness most prominent in knee extension [3]. Two other reported PM-Mito patients had a later disease onset, but one of them had a rather asymmetrical proximal muscle weakness of lower legs and a more severe distal involvement [8]. Termiz et al. [9] compared the clinical and pathological features of 23 PM-Mito patients with 26 s-IBM and 12 PM patients and showed that PM-Mito and s-IBM patients shared many commonalities, involving a selective weakness in the quadriceps or finger flexors, a history of resistance in corticosteroid treatment and the presence of LC3 autophagic marker and αB-crystallin containing aggregates in muscle biopsy. However, it should be stressed that when LC3-positive fibers are < 14%, s-IBM can be excluded and a similar cutoff of 7% can be also used for TDP43 [10]. On the other hand, unlike s-IBM patients, weakness in PM-Mito progressed more slowly [9]. Overall, the aforementioned clinical and laboratory features of PM-Mito highly resemble those of s-IBM, which is a slowly progressive, late onset disease, with a propensity to asymmetrically affect quadriceps, finger flexors and swallowing [14–16]. Nevertheless, the lack of rimmed vacuoles and granular debris in PM-Mito in combination with more elaborate immunohistochemical antibody panels for autophagy could be of value in the histopathological distinction from s-IBM [9, 10]. However, the latter might not, even under these conditions, be definitely excluded as a potential diagnosis, since the absence of these findings may be due to their rarity or patchy distribution or may just not be present at a pre-degenerative stage of the disease. In fact, 44% of patients with PM-Mito who had repeat biopsies, because of increasing disability, showed vacuoles typical of s-IBM [9].

The four female patients of the present study had a negative family history for neuromuscular diseases. They were diagnosed with PM-Mito mainly based on histopathological features showing endomysial inflammation and invasion of non-necrotic muscle fibers by cytotoxic T lymphocytes associated with a variable high extent of mitochondrial pathology. On clinical grounds, they presented with a relatively indolent onset of muscle weakness, slowly progressing over the years and a persistent, mild to moderate CK increase. Muscle weakness was rather proximal and symmetrical with sparing of knee extensors even in the oldest patient with the longer 10-year course of the disease (patient 4), lacking the selective pattern observed in s-IBM. However, patients 2 and 3 also had distal foot weakness reminiscent of s-IBM, but without the concomitant characteristic of distal hand involvement. Previous studies of patients with inflammatory myopathy and mitochondrial pathology supported that selective weakness is almost invariably present in s-IBM, relatively less frequent in PM-Mito and absent in patients with polymyositis [7, 9]. Clinical manifestations of patients with s-IBM may also include other symptoms such as dropped head or camptocormia due to paraspinal muscle weakness and dysphagia [17, 18]. Interestingly, bulbar signs and dropped head that are quite common in our patients, are absent in all the PM-Mito patients described in the literature, so far.

The large-scale deletions in mtDNA found in all four cases correlated well with the presence of the excess of COX-deficient fibers, reflecting the mitochondrial component in the pathology of the disease. They may be due to a primary defect leading to myopathy or the result of inflammation and an increase of the mutational load with age. The presence of clonally expanded mtDNA deletions has been frequently observed in a high percentage of s-IBM patients [5, 19–21] and in patients diagnosed with PM-Mito [3], which may be an indication of a similar pathogenetic mechanism. They are by no means specific for these disorders, as they are commonly encountered in mitochondrial diseases resulting from mutations in nuclear DNA genes involved in the biogenesis or maintenance of mtDNA integrity and follow Mendelian inheritance, such as autosomal dominant/recessive progressive external ophthalmoplegia and mitochondrial neurogastrointestinal encephalomyopathy [22]. Nuclear factor involvement in the pathogenesis of s-IBM has been proposed more than 20 years ago [23, 24]. Recently, a number of such nuclear DNA genes were examined in s-IBM patients [13], but further studies involving a wider range of genes are needed to elucidate the genetic component causing the mtDNA rearrangements. Large mtDNA deletions have also been associated with the normal aging process and age-related diseases in various post-mitotic tissues, such as brain and muscle [25], but were not observed in our age-matched controls.

One patient of the present study (patient 2) was also diagnosed with pSS. Sjögren's syndrome has been associated with a diversity of neurologic manifestations with peripheral neuropathy due to an underlying vasculitis being the most common [26]. The emergence of another autoimmune disease secondary to pSS seems to be higher in the presence of SSA/SSB-positive antibodies, which are indicative of an active immunological profile [27]. The co-existence of inflammatory myopathy and Sjögren's syndrome is already well established, but the most common association seems to be with s-IBM, possibly attributed to a common genetic predisposition linked to the MHC [28]. In a large cohort of patients with pSS and long-term follow up, polymyositis developed in few patients with a mean occurrence delay of 78 months [27]. Increased Sjögren's syndrome-related anti-nuclear antibodies have recently been reported in one PM-Mito patient without any rheumatic-related symptoms or positive diagnostic tests for pSS [8]. Although the limited number of patients prevents drawing general conclusions, it

seems that PM-Mito might be also part of an overlap syndrome. Hypothyroidism, which was also another comorbidity in two patients (pts 3 and 4), may be associated with increased CK levels and occasionally myopathic changes in muscle biopsy [29, 30]. However, both patients had normal thyroid function at the time of the biopsy and it is not therefore expected to generate any impact on histologic appearance, which also differs a lot from PM-mito.

Three out of four patients had a satisfactory outcome after treatment, while one patient did not show any sign of improvement. At first glance, the relatively good therapeutic response in three patients may not be in line with the notion that PM-Mito is refractory to treatment [10], but concrete conclusions cannot yet be drawn due to lack of experience from broad-scale studies. Theoretically, if PM-Mito is considered an intermediate form between PM and s-IBM, it could be expected that treatment may occasionally be beneficial and probably inversely related to the extent of the degenerative component and the chronicity of the disease. This latter explanation may contribute to the treatment failure in patient 4, who was the oldest case with the longest course before diagnosis.

The main limitations of the present study are the small number of patients, which is explained by the rarity of this entity and the lack of immunohistochemical autophagic markers, such as p62, due to the retrospective nature of the study. Overall, it tries to explore the dilemma of whether PM-Mito is a distinct form of inflammatory myopathy or represents a prodromal stage of s-IBM. Although the latter seems to be supported by a substantial body of evidence, there are, however, some issues, that would question this premise. More specifically and based on the present work, the involvement of iliopsoas and not of vastus lateralis, even after many years from disease onset in patients 1 and 4, a relatively early age of the first symptoms in patient 2 and the good response to treatment in patients 1, 2 and 3, raise the suspicion of a more PM-like disorder. The diagnostic challenge becomes more relevant nowadays, due to the increasing skepticism about the strict diagnostic criteria initially proposed by Griggs et al. [24], since a plethora of patients lacking the characteristic clinical pattern and/or the key pathological features on muscle biopsy, will prove over time to have s-IBM [31]. It has recently been proposed that rimmed vacuoles, a cardinal histopathological finding representing the degenerative component of the disease, may be a later finding and possibly absent in younger patients [32]. On the other hand, mitochondrial abnormalities were 100% sensitive and 73% specific for s-IBM. Therefore, they significantly increase the diagnostic yield of the disease and are considered as the second most common histopathological finding after inflammation [13, 24]. Thus, some practical considerations should be taken into account, when evaluating patients with IIMs. Mitochondrial pathology must be always critically evaluated and may be revealed either in PM-Mito or s-IBM, while assessing autophagy may add value to distinguishing these entities. PM-Mito is primarily a histologic diagnosis and the clinical pattern may be quite variable. Given the limited experience so far and the different response to treatment, as also observed in this small cohort, it should be recommended to follow the general therapeutic principles in such patients, but with close and thorough monitoring. Especially in case of treatment failure, there should be a high suspicion index for s-IBM, where repeating muscle biopsy may prove useful.

In conclusion, there are still several gray areas that need to be addressed, such as whether the presence of mitochondrial abnormalities is a primary or a secondary phenomenon triggered by inflammatory infiltrates, how the inflammation is linked to mitochondrial dysfunction and if there is an association between clinical severity and the extent of mitochondrial pathology. Further studies on a larger series of patients are needed to clarify whether PM-Mito is a subset within the s-IBM spectrum or whether it constitutes a different entity with potentially separate therapeutic approach and prognosis.

Author contributions GKP: study concept and design, writing, revising the manuscript, accepts responsibility for all research, giving final approval. CK: study concept, mtDNA analysis and interpretation of data, revising the manuscript, giving final approval. SX: acquisition, analysis and interpretation of data. MC: analysis and interpretation of data. EK: study design, drafting, revising the manuscript, giving final approval. CP: study concept, drafting, revising the manuscript, giving final approval.

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Compliance with ethical standards

Conflict of interest All authors declare that there are no conflicts of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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