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Polymyositis, a very uncommon isolated disease: clinical and histological re-evaluation after long-term follow-up

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Abstract The aim of the present study was to explore whether polymyositis may be considered as an isolated, organ-specific disease or more suitably as a secondary or associated entity. A retrospective re-evaluation of all the muscle biopsies performed at the Hospital Clínic of Barcelona showing histopathological pattern of polymyositis from January 1997 to May 2012 was carried out. The medical records of the patients with the aforementioned pathological pattern were also reviewed. From 1.290 muscle biopsies performed during the period evaluated, 36 with polymyositis pattern were identified. At the time of muscle biopsy, polymyositis pattern was secondary or associated with other disease in 26 patients and was classified as isolated in the remaining ten patients. After pathological re-evaluation and long-term clinical follow-up, only one patient remained with this diagnosis. Overall, the main final diagnosis related to the initial polymyositis pattern was inflammatory myopathy associated with connective tissue disease. Several other associated conditions were also identified. Isolated polymyositis is highly uncommon. Ruling out potential associated or confusing entities, like inclusion body myositis, overlap syndromes, infections, and cancer, is mandatory.

Keywords Polymyositis · Idiopathic inflammatory myopathy · Inclusion body myositis · Necrotizing autoimmune myopathy · Connective tissue disease

Introduction

Polymyositis (PM) has been classified as a separate entity among idiopathic inflammatory myopathies (IIM) [1]. However, recently, it has been considered as a very uncommon disease, even compared to mythological beasts [2–5]. According to the criteria defined by Bohan and Peter [6, 7] in 1975, nowadays still used in a relevant number of epidemiological, observational, and interventional studies, a diagnosis of PM is considered possible in any patient that presents with the nonspecific syndrome of proximal muscle weakness and raised creatine kinase (CK) values. Moreover, such patients may be treated with steroids and likely with immunosuppressants based on weak diagnosis evidence. Drugs, infections, associated connective tissue diseases (CTD) or non-autoimmune systemic diseases, muscle dystrophies, and other conditions were proved to produce the clinical and pathological picture of PM [8–13]. In 1971, inclusion body myositis (IBM) was included in the group of IIM as a distinct entity [14, 15], and in 2002, the term necrotizing autoimmune myopathy was coined [16]. In

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consonance, a decreasing percentage of PM among the IIM has been reported [17, 18].

The evidence provided by longitudinal studies revealed that a diagnosis of primary, isolated, or organ-specific PM is rarely confirmed if careful clinical and histopathological revision and long-term follow-up are performed [3, 19–21]. Only one study disclosed a discrepant result [4, 5]. Moreover, it is important to remark that most of these studies included a low number of PM patients and mainly from cohorts including all the IIM subsets.

In line with this issue, we decided to perform a study including registered patients during a very long period of time (15 years) and, for the first time, focusing exclusively on patients with the pathologic pattern of PM. The objective of the present work was thus to determine whether PM constitutes an isolated or primary disease or it should be more suitably classified as secondary entity that encompasses a wide differential diagnosis.

Methods

The study was performed at the Muscle Research Unit of the Hospital Clínic of Barcelona, a referral center for muscle diseases that attends irrestrictly adult patients from Catalunya and other Spanish cities. A retrospective search in a database of all the muscle biopsies performed at our institution from January 1997 to April 2012 was performed. Samples with a final report of PM histopathological pattern were included. Biopsies were only performed for diagnosis purposes, independently of this study. The samples were sectioned, stained, and reacted systematically with HE, NEE, TCR, ORO, SDH, CCO ATP-ASE, and NADH [22]. Immunohistochemical method to detect upregulation of MHC class I in sarcolemma of muscle fibers was not routinely performed.

Myositis subtypes were classified according to the Dalakas [23] criteria of 2003. Pathological "PM pattern" was considered when focal endomysial inflammatory infiltrates were present. PM was diagnosed by the presence of the pathological pattern along with the clinical picture of proximal muscle weakness, raised CK levels or myopathic electromyography, in absence of mimic conditions. IBM was defined according to the Griggs criteria modified by Dalakas [15, 24]. It was considered definite when complete biopsy criteria (inflammatory myopathy with auto aggressive T cells, rimmed vacuoles, COX-negative fibers, amyloid deposits or filamentous inclusions, and upregulation of MHC class I expression) were present, probable when clinical features were present in the absence of complete biopsy criteria, and possible in the presence of atypical pattern of muscle weakness and incomplete muscle biopsy criteria. Definite pathological criteria were defined by the presence of endomysial inflammatory infiltrate, rimmed vacuoles, amyloid deposits or filamentous inclusions, and upregulation of MHC-1 expression. Incomplete muscle biopsy criteria were defined as the presence of inflammatory myopathy features with T lymphocytes invasion of muscle fiber but absence of rimmed vacuoles, amyloid deposits, filamentous inclusions, and COX-negative fibers. Necrotizing autoimmune myopathy was diagnosed when many necrotic fibers were the predominant histologic feature and inflammatory cells were only scarce, in accordance with previous description. Initial examination of muscle biopsies was performed by the same pathologist (JMG).

In each muscle biopsy sample selected for the study, the following procedures were performed: (1) to confirm the initial histopathological report of PM pattern, (2) to quantify inflammation, necrosis, and invasion of non-necrotic muscle fibers, and (3) to calculate the interobserver agreement. Inflammation and necrosis were scored as: 0 (absent), 1 (low), 2 (moderate), or 3 (high). The intensity of inflammation was graded as follows (per high-power field $\times$ 100): 0/absent, when no inflammatory cells were found; 1/low, when <3 inflammatory cell foci were detected; 2/moderate if 3–5 inflammatory cell foci were detected; and 3/high when >5 inflammatory cell foci were present. On the other hand, the intensity of necrosis was graded as follows (per high-power field $\times$ 100): 0/absent, when no necrotic cells were found; 1/low, when <3 necrotic cells were detected; 2/moderate if 3–10 necrotic cells were detected; and 3/high when >10 necrotic cells were present.

Pathological re-valuation was carried out by two experienced muscle pathologists (JMG and ASO), unaware of the clinical data from each corresponding patient. Patients signed an informed consent authorizing the review of their medical histories for study purposes. This study was performed in accordance with the Spanish laws regulating clinical research.

Clinical data were collected from the patient medical records of the referral institutions or by phone contact. In cases of uncertainty, the patients were invited to come for personal interview and exam. Data regarding diagnosis at the time of biopsy procedure and follow-up were registered. Clinical and laboratory findings were systematically collected, including demographic data, clinical patterns of muscle involvement, initial and final diagnoses, previous medical conditions, drug exposure, viral diseases, neoplasia, pulmonary involvement, and any evidence (clinical or biological) of autoimmunity disturbance. A double revision the medical charts was performed to evaluate the quality of the data collection by the first investigator (VSV).

Results

A total of 1.290 muscle biopsy reports were performed at our institution from January 1997 to April 2012. One

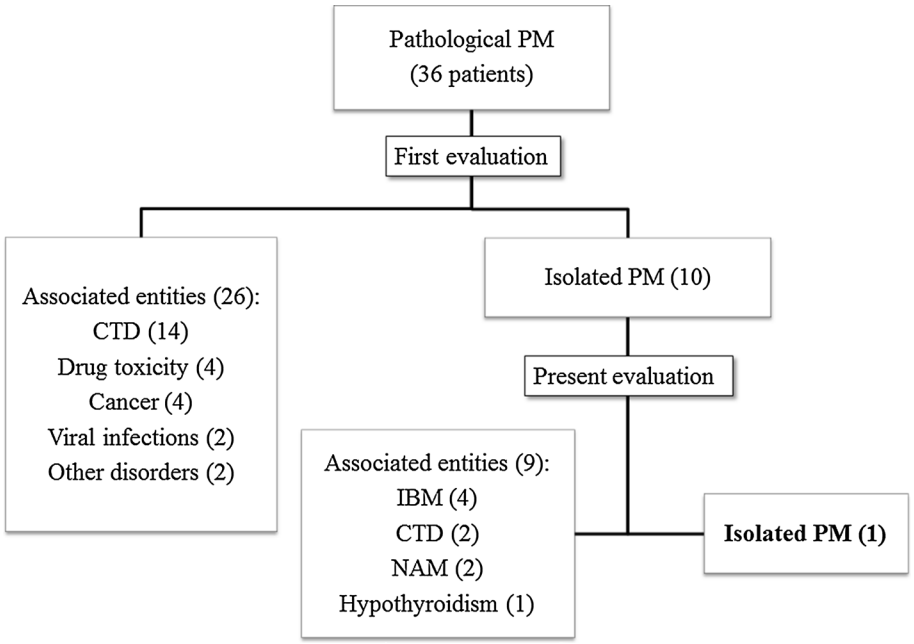

Fig. 1 Flowchart of the present series showing diagnoses at first and present evaluation

hundred and seventy-two biopsies (13.3 % of the entire population) were reported as inflammatory myopathies and classified as the following: dermatomyositis, 86; IBM, 38; necrotizing autoimmune myopathy, 12; and PM, 36. The 36 cases with the final pathological diagnosis of PM were included in the study, representing the 2.8 % of all biopsies performed during this 15-year period. Samples with nonspecific findings or nonspecific myositis were not included as PM pattern. All but one of the biopsies were performed before steroids or immunosuppressant therapy. Inflammation, characterized by focal endomysial inflammatory infiltrates, was present in 100 % of the samples. Inflammation was scored as follows: grade 3, 26.4 %; grade 2, 26.4 %; and grade 1, 47.2 %. Necrosis was present in 73.9 % of the samples. A 100 % interobserver agreement was registered.

Thirty-three patients were Caucasian and three Berber, including 16 males and 20 females. The mean age at the beginning of the muscle disease was 51 years, ranging from 22 to 77 years. Thirty-five patients were followed-up for at least 2 years, and the mean follow-up was 5.5 years. Only one patient was included in last year, but she already had a previous diagnosis of rheumatoid arthritis (RA) at the time of PM pattern detection.

At the initial evaluation, ten patients were diagnosed as isolated PM, and in the remaining 26 patients, other different entities were identified (see flowchart in Fig. 1). Those entities included: inflammatory myopathies associated with CTD, drug toxicity (statins in two cases and neuroleptics in another two), cancer (3 hematologic and one colon), viral infections (hepatitis C in one patient and co-infection hepatitis C with human immunodeficiency virus in another), muscle dystrophy (1 patient), and graft versus host disease (1 patient). CTD diagnosed at that point was: systemic sclerosis (9), anti-synthetase syndrome (2), systemic lupus erythematous (1), Sjogren syndrome (1), and RA (1). In these 14 patients with inflammatory myopathies associated with CTD, the inflammatory myopathy simultaneously developed with the clinical/laboratory features of CTD. In this group of 26 patients, the pathologic revision resulted in unchanged report in all the patients.

Among the ten patients initially diagnosed as isolated PM, after histological re-evaluation and clinical follow-up, only one remained with this diagnose. Table 1 summarizes the evolution of these patients. The patient with primary PM improved with imunossupression and no other diagnose was identified after 7 years of follow-up. Figure 2 discloses the final diagnose of the 36 patients included in the study.

Discussion

In the present series, among a cohort of 172 IIM patients, the most common pathological pattern corresponded to DM (50 %), while a histological pattern of PM was only found in 21 % of the cases. Moreover, at the time of the disease onset and muscle biopsy, PM was related/associated with other entities in 26 patients and classified as isolated in ten patients (0.7 % of the muscle biopsies performed during 15 years at our institution). And finally, after clinical and histological re-evaluation and long-term follow-up, only one patient remained with the diagnosis of isolated or primary PM. Our study revealed that the presence of

Table 1 Clinical, laboratorial and pathologic features, evolution and final diagnosis of the ten patients initially diagnosed as isolated PM

Patient	Initial clinical features (y)	CK (mg/dl)	Biopsy findings (first evaluation)	Clinical follow-up	Biopsy findings (re-evaluation)	Final diagnosis
1	F, 73 Proximal weakness	390	PM	Disabled	Red ragged cell	Definite IBM
2	F, 39 Myalgia and mild weakness	460	PM	RA after 8 years of follow-up	No changes	Rheumatoid arthritis
3	F, 59 Proximal weakness	3,000	PM	Remission with GC	No changes	Isolated PM
4	F, 56 Proximal weakness	7,160	PM	Partial improvement with ciclosporine	Severe necrosis.	NAM
5	F, 51 Proximal with neck weakness	273	PM	Died	Vacuoles	Definite IBM
6	F, 48 Proximal weakness	13,000	PM	Stable with GC and IVIG	Mitochondrial changes	Probable IBM
7	M, 77 Proximal with neck weakness	2,537	PM	Disabled	Ragged red cell	Probable IBM
8	M, 56 Proximal weakness	3,000	PM	Improvement with GC SSc after 10 of follow-up	No changes	SSc
9	F, 29 Asymptomatic (CK rising)	Not available	PM	Improvement with levo-thyroxine	No changes	Hypothyroidism
10	M, 39 Severe proximal weakness	CK 2,600	PM	Anti-SRP Improvement with GC and IVIG	Severe necrosis	NAM

F female, *M* male, *y* years, *CK* creatine kinase, *Anti-SRP Ab* anti-signal recognition particle antibody, *GC* glucocorticoids, *IVIG* intravenous immunoglobulin, *PM* polymyositis, and *SSc* systemic sclerosis

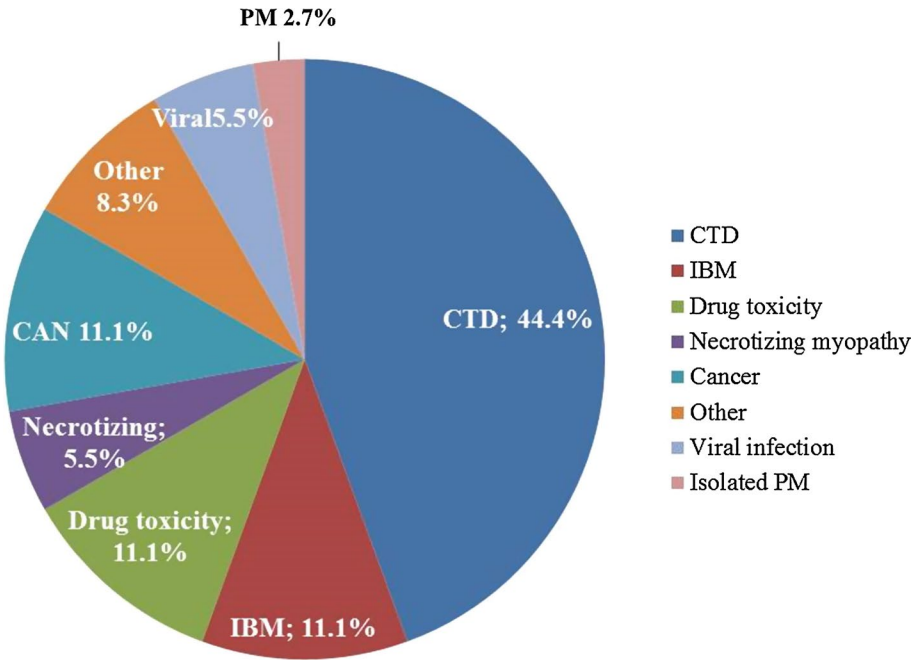

Fig. 2 Overall final diagnoses after clinical and pathological re-evaluation and follow-up

the clinical and pathological picture of proximal weakness raised muscle enzymes and focal endomysial muscular inflammatory infiltrates really needs to consider a wide differential diagnosis.

Inflammatory myopathy associated with CTD was the most frequent final diagnoses of the patients with pathological PM pattern at the time of first evaluation. Among CTD, SSc was the main diagnosis, in accordance with previous series [19]. A mild, indolent myopathy, with no specific pathological findings in muscle biopsy has been described in SSc patients [25, 26, 27]. However, these patients may also develop a clear inflammatory myopathy, clinically and histologically indistinguishable from classic PM, as demonstrated in our study.

When the final diagnosis was different from the initial, it mainly changed from PM to IBM. These data are similar to other longitudinal studies, suggesting that IBM is the disease more frequently misdiagnosed as PM [3, 19–21]. NAM and inflammatory myopathy associated with CTD were the other two alternative diagnoses more frequently found. The first due to the entity was described in 2002 and we included patients from 1997, and the second because myopathy may be the initial manifestation in the CTD setting so long-term follow-up is required before excluding inflammatory myopathy associated with CTD [19].

A recent systematic review revealed that the prevalence of PM among the IIM virtually remains unchanged in transversal studies. However, when longitudinal studies are performed, its prevalence usually decreases [28]. The authors also found that the delay in IBM diagnosis remains long, and the disease is highly underdiagnosed. To date, there still is no consensus about diagnostic criteria for inflammatory myopathies and the Bohan and Peter's ones are commonly used nowadays in epidemiological, observational, and interventional studies. Using these criteria, the incidence and prevalence of PM is probably overestimated since they do not require muscle biopsy for diagnosis of probable PM and do not distinguish IBM from PM. Epidemiological studies showed the global incidence and prevalence of PM, mainly using diagnostic codes, with no information about other related disorders. Extensive chart review and follow-up process, as performed in our work, are necessary to identified or rule out associated entities. According with our results, one epidemiologic study that requested muscle biopsy for PM diagnosis revealed increasing IBM prevalence unlike PM one [29].

We also found cancer, drug-related myositis, viral diseases, and non-inflammatory myopathies as disorders associated to a pathological PM pattern, with a similar prevalence to previous reports [21].

Our study has the limitation of its retrospective nature. However, full data of all the patients were available, and a double revision of the medical records was performed. Moreover, the patients were included from an entire population of patients with myopathies attended in our Muscle Research Unit. Therefore, the results can be extrapolated to the entire external population of patients with myositis.

In conclusion, we can assume that as an isolated disease, PM is extremely rare. Inflammatory myopathy associated with CTD, IBM, and NAM is the main entities misdiagnosed as isolated PM. Infections, drugs, and cancer must be also included in the differential diagnosis. Our work highlights the importance of using combined clinical, pathological, and serological criteria of IIM diagnosis, since nowadays, the criteria from Bohan and Peter [6, 7] are not specific and they are indeed, really obsolete [30].

Conflict of interest The authors declare no conflicts of interest.

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