Journal of Autoimmunity 48-49 (2014) 118–121

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

# The diagnosis and classification of polymyositis

J.C. Milisenda [a,b], A. Selva-O'Callaghan [c], J.M. Grau [a,b,*]

[a] Muscle Research Unit, Internal Medicine Service, Hospital Clínic de Barcelona, Villarroel 170, 08036 Barcelona, Spain
[b] Fundació Cellex, University of Barcelona, Villarroel 170, 08036 Barcelona, Spain
[c] Internal Medicine Service, Hospital Vall d'Hebrón, Barcelona, Spain

ARTICLE INFO

*Article history:*
Received 7 October 2013
Accepted 13 November 2013

*Keywords:*
Polymyositis
Idiopathic inflammatory myopathies

ABSTRACT

Polymyositis is classified as a separate entity among idiopathic inflammatory myopathies but it is considered as the least common since it is an exclusion diagnosis. This myopathy usually presents with subacute-chronic symmetric proximal limb weakness, although some extramuscular manifestations are common. Creatine kinase values may be increased up to 50-fold in active disease. Muscle biopsy is characterized by endomysial inflammatory infiltrate consisting predominantly of CD8+ T cells that invade healthy muscle fibres expressing the MHC-I antigen. Although serum autoantibodies, EMG and imaging techniques can help in diagnosis, muscle histopathology is a pivotal value. The clinical picture together with the pathological findings confers the also called PM pattern. A broad differential diagnosis is needed before concluding a diagnosis of pure PM. Sporadic inclusion-body myositis, toxic, endocrine and metabolic myopathies as well as muscular dystrophies are the major categories to be ruled out. Finally, a diagnostic algorithm for suspected cases of PM is also proposed.



## 1. Introduction

Although the term polymyositis (PM) was first introduced by Wagner in 1863, the recognition of PM as a distinct entity was due to Walton and Adams in 1958. In 1975, these observations were confirmed by Bohan and Peter, and the diagnostic criteria for PM and DM [1,2] were established, still remaining in use today, at least partially. Although many investigators agree with the concept that muscle biopsy plays a pivotal role in the diagnosis, it was not until 1984 when histopathological features were clearly established by Arahata and Engel [3]. Finally in 1991 and then again in 2003 Dalakas added the findings on muscle biopsy to the diagnostic criteria [4,5] (Table 1).

In 1971 Yunis and Samaha differentiated the patients who fulfilled the clinical and histopathological features of PM but exhibited vacuoles rimmed by basophilic material and nuclear and cytoplasmic filamentous inclusions in muscle biopsy. They coined the term sporadic inclusion body myositis (s-IBM) with many reports in medical literature since then [6]. Note that this disease must be distinguished from PM, as does immune-mediated necrotizing myopathies (IMNM) also. IMNM has been considered as a PM variant with prominent necrosis and very little T-cell infiltrates [7]. It is known that infectious agents, drugs, congenital dystrophies, endocrine and systemic diseases are associated with the histological findings of the PM pattern.

## 2. Epidemiology

At present PM is considered a rare disease. It is classified as a separate entity among idiopathic inflammatory myopathies (IIM) and is considered to be the least common. It is rare in childhood and occurs mainly after the second decade of life. IIM as a whole have an annual incidence of 2.1–7.7 cases per million while the frequency of PM alone is unknown but is estimated to be of around 4 cases/million population/year of incidence [8–11]. DM and PM are known to have a close relationship and higher risk for cancer in comparison with the general population, being three times more common in DM than in PM, 13.8% and 6.2% respectively around the world. The presentation and diagnosis of cancer can be made during, before or after the onset of myositis. In European and North American population, ovarian cancer is the predominant associated cancer while gastric, nasopharyngeal carcinoma and breast cancer are most common in Asian population. On the diagnosis of PM

*Abbreviations:* PM, polymyositis; DM, dermatomyositis; s-IBM, sporadic inclusion body myositis; IMNM, immune-mediated necrotizing myopathies; MAAs, myositis-associated autoantibodies; MSAs, myositis-specific autoantibodies; ILD, interstitial lung disease; MHC-I, histocompatibility complex class I; CHF, congestive heart failure; PFTs, pulmonary function tests; CTD, connective tissue diseases; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography.

* Corresponding author. Internal Medicine Service, Hospital Clínic de Barcelona, Villarroel 170, 08036 Barcelona, Spain. Tel.: +34 3 932275539.
*E-mail addresses:* jcmilise@clinic.ub.es (J.C. Milisenda), aselva@vhebron.net (A. Selva-O'Callaghan), jmgrau@clinic.ub.es (J.M. Grau).

0896-8411/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jaut.2014.01.025

**Table 1**
Diagnostic criteria for PM (after careful ruling out all the conditions showed in Table 3). MHC: major histocompatibility complex.

| Criterium | Definite | Probable |
|---|---|---|
| Myopathic muscle weakness | Yes | Yes |
| EMG findings | Myopathic | Myopathic |
| Muscle enzymes | High (up to 50-fold normal) | High (up to 50-fold normal) |
| Muscle pathology | Inflammation with CD8+/MHC-1 complex. No vacuoles | Ubiquitous MHC-1, but no CD8+ infiltrates. No vacuoles |
| Rash | Absent | Absent |

screening for cancer is recommended. PET-CT study as the only imaging technique seems to be of the same value as conventional studies [12–14].

## 3. Pathophysiology

### 3.1. Immmunopathogenesis

It is believed that physical, chemical or external infectious agents act upon a genetically predisposed person. The relationship of PM with other autoimmune disorders, the existence of autoantibodies, histocompatibility genes, the presence of T cells in muscle tissue and their response to immunotherapies, has led PM to be considered an autoimmune disease, but no specific target antigens have been identified yet [15].

#### 3.1.1. Adaptive immune mechanisms

*3.1.1.1. Humoral immune response.* More than half of PM patients have positive antinuclear antibodies. These autoantibodies are myositis-associated autoantibodies (MAAs) or myositis-specific autoantibodies (MSAs). Up to 20% of patients have autoantibodies directed against ribonucleoproteins involved in protein synthesis (anti-synthetase) or translational transport (anti-signal-recognition particle) [16]. In some cases these autoantibodies are associated with a clinical picture; for example, anti-Jo-1 (antibody against histidyltRNA synthetase) is associated with myositis, non erosive arthritis, Raynaud's phenomenon and interstitial lung disease (ILD) [17]. The most common shared clinical feature of anti-synthetase autoantibodies is ILD, which may precede myositis or even be present without myositis. Table 2 illustrates the principle myositis-associated autoantibodies.

*3.1.1.2. Cell-mediated immune response.* The PM pattern is characterized by endomysial inflammatory infiltrates of activated CD8 T lymphocytes and macrophages. The CD8 cytotoxic T lymphocytes recognize the major histocompatibility complex class I (MHC-I) expressed on muscle fibres and invade non-necrotic muscle cells inducing necrosis through the perforin pathway [18,19].

**Table 2**
Autoantibodies in IIM. DM: dermatomyositis, SLE: systemic lupus erythematosus, MCTD: mixed connective tissue disease. ILD: interstitial lung disease.

| Myositis specific autoantibodies | Frequency | Antigen | Associations |
|---|---|---|---|
| Anti-aminoacyl-tRNA synthetases | 20-30% | Different synthetases | Myositis, non erosive arthritis, Raynaud's and ILD |
| Anti signal recognition particles (SRP) | 4-5% | SRP-complex | |
| Myositis-associated autoantibodies | | | |
| Anti PM-Scl | 15% | Nuclear complex | DM with scleroderma |
| Anti RNP | | | SLE, scleroderma and MCTD |
| Anti SSA | | | Sjögren syndrome |

### 3.2. Viral triggers

CD8 T cells are associated with repeated antigen stimulation and are increased in individuals with chronic viral infections [20]. Although nobody has been able to demonstrate the presence of virus in muscle, it is well known that some viruses are involved in acute and chronic myositis. It has been demonstrated that HIV-infected persons as well as those infected by human T cell lymphotropic virus (HTLV-1) may develop PM or sporadic inclusion body myositis (sIBM).

## 4. Clinical features

### 4.1. Muscular manifestations

Muscle involvement usually develops over the course of weeks or months. Is characterized by symmetrical and proximal limb weakness [21], affecting the quality of the patient's daily activity. Facial muscles remain unaffected and distal muscles may be affected only in late stages of the disease as may paravertebral muscles, leading to the camptocormia syndrome. Involvement of neck muscles is rare, but if present, dropped head is the principle sign.

### 4.2. Extramuscular manifestations

#### 4.2.1. Joint manifestations

These manifestations are characterized by arthralgia and non erosive arthritis involving the wrists, knees, and the small joints of the hands [22].

#### 4.2.2. Cardiovascular manifestations

Cardiac involvement varies widely between 6% and 75%, depending on whether clinical events or subclinical manifestations are considered. Clinically symptomatic cardiac involvement is relatively rare. In a long-term follow-up study, cardiovascular involvement was found to be a cause of death in 10%–20% of the patients. Cardiac manifestations include arrhythmia, conduction abnormalities, cardiac arrest, congestive heart failure (CHF), myocarditis, pericarditis, valvular heart disease and secondary fibrosis. It is believed that the cause of CHF and arrhythmia is secondary to myocarditis by the same mechanism that results in skeletal muscle involvement.

#### 4.2.3. Pulmonary and gastrointestinal manifestations

Three pulmonary complications have been described: hypoventilation, aspiration pneumonia, and ILD, being a major cause of morbidity and mortality [23]. When the respiratory muscles are involved hypoventilation occurs. As a result, restrictive lung function impairment is noted on pulmonary function tests (PFTs). Some patients may develop aspiration pneumonia, being more frequent when they complain of dysphagia. In addition, when pharyngoesophageal muscle tone is lacking, patients develop nasal speech, hoarseness, nasal regurgitation as well as obstructive sleep apnoea. The reported prevalence of ILD in IIM patients varies from 20% to 65%, possibly because of the lack of standardised diagnostic criteria in most of the studies and is considered a major risk factor for premature death. The presence of anti-synthetase antibodies is a strong predictive marker for ILD [24].