The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

EASi™
European Autoimmunity
Standardisation Initiative


ThermoFisher
SCIENTIFIC

The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

Pabst Science Publishers
Lengerich, Berlin, Bremen, Miami,
Riga, Viernheim, Wien, Zagreb

Bibliographic information published by Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

http://www.pabst-publishers.de

Printing: MercedesDruck, Berlin
Typesetting: Hilmar Schlegel, Berlin
Cover: Agentur für zeitgemäße Kommunikation Kaner Thompson
www.kanerthompson.de

ISBN 978-3-89967-770-6

Polymyositis and dermatomyositis

Jiří Vencovský, Ingrid E. Lundberg, Cees Kallenberg, Rudolf Mierau

1 Introduction

Polymyositis (PM) and dermatomyositis (DM) are characterized by chronic inflammation of striated muscles leading to altered muscle function. The main clinical symptom is muscle weakness and low muscle endurance, which is localised predominantly in the proximal portions of upper and lower extremities (Table 1). Other muscles may be involved, such as upper oesophageal and breathing muscles causing difficulties in swallowing and respiratory problems. The systemic nature of the disease is underlined by a possible presence of extramuscular involvement including involvement of the skeletal, pulmonary and cardiac systems and constitutional symptoms. DM patients have a typical cutaneous rash (Fig. 1), but also differ from PM by muscle biopsy characteristics, which suggests a possibility of different pathogenic pathways in these two diseases. Autoantibodies are present in up to 80 % of patients and are frequently associated with particular clinical manifestations. The disease may lead to muscle atrophy and permanent damage of different organs and systems.

The annual incidence of PM and DM is reported to be around 7 per million people and latest figures estimate the prevalence at 21.5/100 000. The overall female:male incidence ratio is 2.5 : 1. In about 15 % of cases, the disease is associated with various malignancies, this is particularly true for dermatomyositis. Myositis with inclusion bodies recognized on muscle biopsy (inclusion body myositis, IBM) occurs mainly in men and usually after 50 years of age.

2 Diagnostic measurements for experts

Muscle inflammation leads to muscle weakness, which can be measured by manual muscle strength test (MMT). This test uses a standardised grading system for measurement of muscle strength in individual muscles or muscle groups. It is recommended to perform the test serially in order to evaluate disease activity over time.

Table 1. Signs and symptoms of polymyositis and dermatomyositis.

Affected organ	Clinical manifestation	Frequency
Skeletal muscles	Muscle weakness, particularly proximal extremities	100 %
Oesophageal muscles	Dysphagia	30 %
Pharyngeal muscles	Nasal voice	< 30 %
Breathing muscles	Respiratory difficulties	< 30 %
Lungs	Alveolitis, interstitial pulmonary fibrosis	30–80 %
Heart	ECG abnormalities, myocarditis, rhythm disturbance	< 30 %
Joints	Arthralgia, arthritis	50 %
Skin	Cutaneous rash	100 % in DM
	– Pathognomonic	
	– Gottron's papules	60–80 %
	– Heliotrope rash	< 50 %
	– Other skin changes include "mechanics hands", "V sign" chest rash, "Shawl sign", erythroderma, nailfold capillary changes and cuticular overgrowth, panniculitis and others.	
Skin	Calcinosis	More frequent in juvenile DM
Vascular	Raynaud's phenomenon, vasculitis in children	< 30 %
Constitutional	Fatigue, fever, weight loss	< 30 %

Inflammation within the muscles causes oedema which can be visualized by magnetic resonance imaging (MRI). It is necessary to use an MRI technique which suppresses the signal of fat to recognise the changes. Because the inflammation can be only focal, MRI may be used to select the optimal biopsy site. MRI may also show atrophy and fibrosis in the advanced stages of disease and therefore helps in distinguishing between active disease and accumulated damage.

Muscle biopsy is the most valuable tool to confirm the diagnosis of PM or DM [1]. This method is particularly important for a definitive diagnosis of polymyositis and to exclude other myopathies that may mimic polymyositis. Classical PM has endomysial inflammatory cell infiltrate composed particularly of $CD8^+$ T-cells that surround and sometimes invade non-necrotic muscle fibres. Macrophages

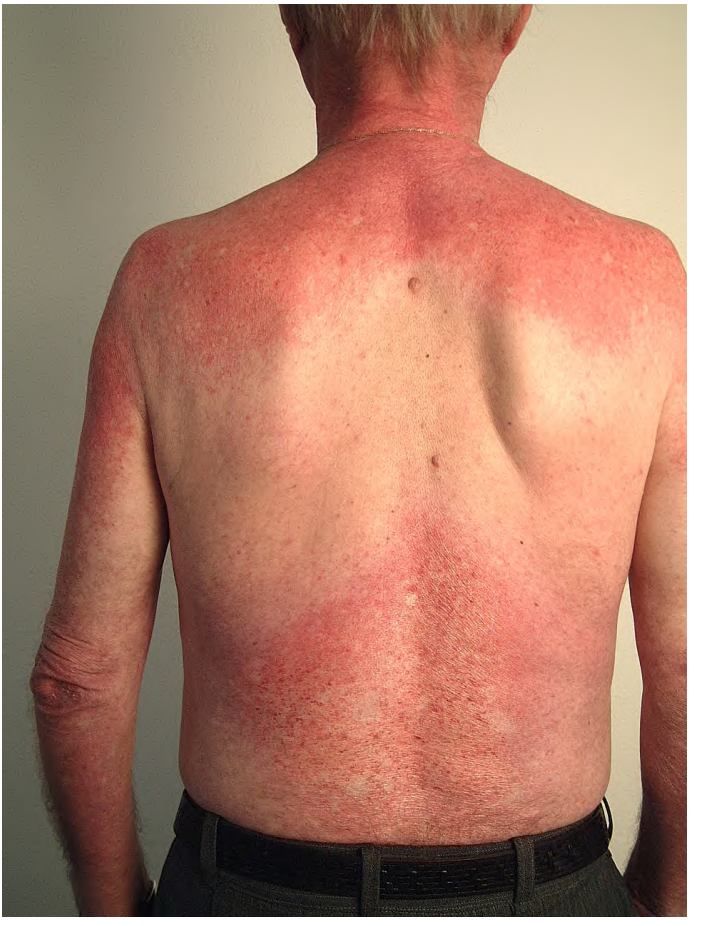

Figure 1. Typical rash in dermatomyositis.

and $CD4^+$ T-cells may also be present. Muscle fibres display ubiquitous MHC-I expression, and this is sometimes seen even in the absence of inflammatory infiltrate, which could be helpful in the diagnostic procedure. Inflammatory cells in dermatomyositis are localized mainly in the perivascular and perimysial space and mostly macrophages, $CD4^+$ T-cells and occasional B-cells are present. Frequently membrane attack complex (MAC) depositions are found on small blood vessels. Muscle histology in inclusion body myositis is similar to PM, but rimmed vacuoles, ragged red fibres, and cytochrome oxidase-negative fibres suggest IBM.

Table 2. Diagnostic criteria.

Clinical criteria
– Symmetric weakness of limb-girdle muscles and anterior neck flexors progressing over weeks to months, with or without dysphagia or respiratory muscle involvement
– Typical skin rash of DM including a heliotrope rash, Gottron's sign, Gottron's papules and involvement of the knees, elbows and medial malleoli as well as the face, neck, and upper torso
Laboratory criteria
– Elevation in serum of skeletal-muscle enzymes (particularly creatine phosphokinase and often aldolase), serum aspartate and alanine aminotransferases, and lactate dehydrogenase
– Electromyographic triad of short, small, polyphasic motor units, fibrillations, positive sharp waves and insertional irritability, and bizarre, high-frequency repetitive discharges
– Muscle biopsy abnormalities of degeneration, regeneration, necrosis, phagocytosis, inflammatory infiltration and atrophy in perifascicular distribution

Definite disease requires 4 criteria (three plus rash) for dermatomyositis and 4 criteria for polymyositis; probable disease must include 3 criteria (two plus rash) for DM and 3 criteria for PM; and possible disease requires 2 criteria (one plus rash) for DM and 2 criteria for PM.
For these criteria to be applied, the exclusion of number of situations: central or peripheral neurologic disease, muscular dystrophy, granulomatous myositis, infections, use of toxins or drugs, rhabdomyolysis, metabolic disorders, endocrinopathies, and myasthenia gravis is required.

Most but not all patients with PM and DM have characteristic autoantibodies present in their serum, whereas these autoantibodies are usually lacking in inclusion body myositis and are less frequent — with one exception (see Table 3) — in cancer associated myopathy.

Some of the antibodies are specific for myositis and cannot be found in other diseases, some are myositis-associated and may be detected in other connective tissue diseases [2, 3], but are still helpful in making the diagnosis and categorising patients (Table 3).

3 Requirements for family practitioners

Polymyositis and dermatomyositis are chronic inflammatory disorders of striated muscles. The leading clinical symptom is muscle weakness and, in particular, low

muscle endurance and easily fatigued muscles, accompanied by a variety of systemic manifestations. The history often includes difficulties walking up stairs, needing to rest after one set before continuing or walking uphill. Muscle weakness is predominantly seen when testing pelvic muscles and neck flexors. Getting up from a squatting position is a simple test that is often impossible to perform for myositis patients. Muscle pain may be present in some patients, but is usually not the main symptom. Diagnosis of dermatomyositis is somewhat easier than polymyositis owing to presence of the typical skin changes. The onset of disease is usually acute or subacute with weakness and fatigue causing patients to see a general practitioner. Notably some patients may present with predominating pulmonary symptoms such as dyspnoea or cough, and with signs of interstitial lung disease on chest radiography. In such patients an underlying rheumatic disease like myositis should be considered.

ESR and CRP are usually within normal range, although CRP may be elevated in some patients with acute inflammation. Often the first serum chemistry shows highly elevated amino-transferases, which, when CK levels are not measured, may be misinterpreted as hepatic injury. To establish a correct diagnosis it is necessary to verify muscle weakness by an appropriate test, measure serum levels of muscle enzymes and/or myoglobin and perform electromyographic testing. Muscle biopsy should always be done in polymyositis and is highly recommended in dermatomyositis to confirm the correct diagnosis, since many conditions may mimic PM and DM. It is advisable that the biopsy is processed by a pathologist experienced in muscle diseases. Testing for serum autoantibodies is often helpful as well as muscle MRI. When a patient presents with muscle weakness and has elevated muscle enzymes, he or she should be referred for further diagnostic specification to a specialist in inflammatory muscle diseases, which may be rheumatologist, neurologist or dermatologist, depending on the local situation and also on the presentation of the disease.

The severity of disease varies from patients confined to bed or to a wheelchair in the acute stage to patients with more subtle manifestations, such as difficulties in climbing stairs or raising hands. When present, dysphagia and interstitial lung disease are usually associated with a worse prognosis. The majority of myositis patients have a chronic disease with exacerbations and remissions, requiring treatment and regular follow up over many years. In some patients, more often with DM, the disease may improve to the extent that long-term remission without the need for treatment is achieved. Since the association with malignancy exists, patients should be evaluated for a possible tumour occurrence by different screening methods, including chest X-ray, abdominal ultrasonography, laboratory examinations and, in selected cases, by positron emission tomography. If pathology occurs, then this should be thoroughly investigated by appropriate and more sophisticated methods.

4 Follow up

Clinical observations

Disease activity should be assessed periodically. The use of Core set measures developed by IMACS (International myositis assessment and clinical studies group) is recommended [4]. These include visual analogue scale (VAS) for physician and patient, manual muscle testing (MMT), health assessment questionnaire (HAQ), muscle enzymes and specific tools to assess extramuscular activity. In clinical studies, a positive response to therapy is achieved, when 3 of any 6 measures improve by 20 % or more, with no more than 2 worsened by 25 % or more, one of which cannot be MMT. Similarly, disease damage can be assessed once a year using core set measures which include VAS by patient and physician, MMT, HAQ and myositis damage index for extramuscular involvement [5].

Expectations

A majority of patients have relapsing-remitting course or chronically progressive illness, although some may have monophasic disease and go into full and permanent remission. Generally, patients with anti-SRP antibodies have a poor prognosis. Patients with anti-synthetase antibodies, where interstitial lung disease may predominate the clinical features, often respond to immunosuppressive treatment, but they also often have a protracted course with a high risk of relapse when attempts are made to stop treatment.

Blood tests

Serum levels of "muscle enzymes" particularly CK, but also LDH, aldolase, ALT, AST are periodically measured. Serum myoglobin levels may also be used. Although frequently helpful, it is accepted that serum levels of these proteins only partially assess the activity, and should not be used as a sole measure of disease activity. Cases of patients with low levels of CK despite active disease exist and other patients may have an elevated CK despite a low degree of disease activity.

5 Management

The mainstay for pharmacological treatment is glucocorticoids. Prednisone is usually given at a dose of around 0.75- 1 mg/kg/day and the treatment is continued for a prolonged period of time with tapering over months, guided by disease activity. Prognosis is worse if the effective treatment is delayed and side effects of the high doses of glucocorticoids are common, therefore it is recommended that glucocorticoids are combined with another immunosuppressive drug. The most frequently used are methotrexate or azathioprine. If these are not effective or not tolerated,

there are reports where cyclosporine, cyclophosphamide, mycophenolate mofetil have proven efficacious. Alternatively combinations of methotrexate with azathioprine or cyclosporine could be used when a single therapy is not effective [6]. For patients with interstitial lung disease there are case reports or case series to suggest that cyclophosphamide, cyclosporine or tacrolimus may be effective. Intravenous immunoglobulins are advocated for resistant cases, but not all reports are positive. Plasmapheresis and leukapheresis have not shown efficacy. Several small series or case reports suggest that rituximab may have good potential, but a recent large controlled trial has not reached the primary endpoint. Anti-TNF drugs were initially described as effective, but more recent studies are negative and worsening of disease has even been described. Exceptionally, some patients may benefit from autologous stem cell transplantation. Inclusion body myositis is usually unresponsive to glucocorticoids and also to other immunosuppressive drugs. Pharmacological treatment is combined with exercise, which should be supervised by experienced physiotherapists and individualised to the patient's situation.

Most patients with myositis respond to treatment to a certain extent. When treatment-resistant inflammatory myopathy presents, it is always necessary to reconsider the original diagnosis [7].

6 Diagnostic tests

There is no single diagnostic test in myositis, and although detection of autoantibodies is helpful, they are present only in about 60–80 % of cases.

Various techniques are employed in the detection of autoantibodies specific for or associated with myositis. Indirect immunofluorescence on HEp-2 cells detects antinuclear or, frequently, anticytoplasmic autoantibodies (Table 3). These autoantibodies must be subsequently identified by specific tests, e.g., the Elisa technique with purified or recombinant antigens. Line or dot-blot immunoassays with spotted autoantigens on nitrocellulose paper are increasingly popular. Immunodiffusion or counterimmunoelectrophoresis can also be used; these techniques require comparison of a precipitin line with one obtained using standard serum of known autoantibody specificity. Some laboratories use Western blotting for autoantibody detection, where nuclear or cytoplasmic cell extracts are electrophoresed in the polyacrylamide gel and transferred to nitrocellulose paper. Strips of nitrocellulose are then incubated with patients' sera and bound autoantibody detected using enzyme immunoassay (Fig. 2). Several of the myositis autoantibodies do not react in these assays and immunoprecipitation of proteins or nucleic acids is used in their detection. In the protein assay, serum antibodies are bound to protein A-Sepharose beads, which are then mixed with ^{35}S-methionine-labeled cell extract. Immunoprecipitated proteins on the beads are subjected to polyacrylamide gel electrophoresis and developed by autoradiography. In the case of RNA assay the resulting immunoprecipitates are electrophoresed in the gel and subsequently

Table 3. Autoantibodies in myositis.

	Antigen	Frequency in myositis	Clinical association
Myositis specific			
Anti-ARS			
Anti-Jo-1	Histidyl-tRNA synthetase	15–30 %	ASS
Anti-PL-7	Threonyl-tRNA synthetase	5–10 %	ASS
Anti-PL-12	Alanyl-tRNA synthetase	< 5 %	ASS
Anti-EJ	Glycyl-tRNA synthetase	5–10 %	ASS
Anti-OJ	Isoleucyl-tRNA synthetase	< 5 %	ASS
Anti-KS	Asparaginyl-tRNA synthetase	< 5 %	ILD, arthritis
Anti-Zo	Phenylalanyl-tRNA synthetase	< 1 %	ASS
Anti-YRS	Tyrosyl-tRNA synthetase	< 1 %	ASS
Anti-SRP	Signal recognition particle 6 peptides	5–10 %	Necrotising myositis
Anti-Mi-2	218/240 kDa helicase family proteins	5–10 %	DM
Anti-p155(/140)	Transcriptional intermediary factor 1γ	9–21 %	Only DM, frequently CDM (50–75 %)
Anti-CADM- 140	RNA helicase encoded by MDA-5	19 % of DM	C-ADM (ILD)
Anti-SAE	Small ubiquitin-like modifier	4 % (8 % in DM)	Severe skin in DM, ILD
Anti-p140 (Anti-MJ)	Nuclear matrix protein (NXP-2)	23 % of JDM	JDM, Calcinosis
Myositis associated			
Anti-PM-Scl	Nucleolar protein complex of 11–16 proteins	8–10 %	PM, DM, overlap with Scl
Anti-U1-RNP	Small nuclear RNP	10 %	MCTD
Anti-Ku	70/80 kDa DNA-PK regulatory subunit	< 20	Overlap with scleroderma
Anti-Ro (52, 60)	hY RNA + peptides	10–40 %	

ASS, antisynthetase syndrome; **PM**, polymyositis; **DM**, dermatomyositis; **CDM**, cancer associated DM; **Scl**, scleroderma; **ARS**, aminoacyl-tRNA synthetase; **SRP**, signal recognition particle; **RNP**, ribonucleoprotein; **DNA-PK**, DNA dependent protein kinase; **hY**, human cYtoplasmic; **ILD**, interstitial lung disease; **MCTD**, mixed connective tissue disease; **C-ADM**, clinically amyopathic dermatomyositis

silver stained. These tests are used only by few specialized laboratories. They can be considered as the most reliable techniques for confirmation. This approach has enabled discovery of several new autoantibodies in myositis sera.

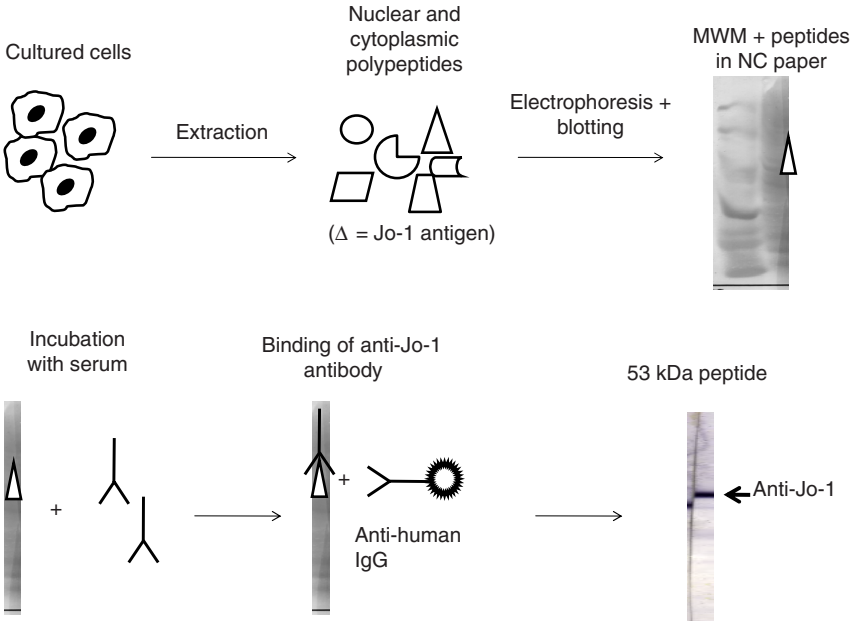

Figure 2. Test principle for detection of autoantibodies by Western blotting. Polypeptides are extracted from the cells (e.g. HeLa cells) and then divided by electrophoresis in polyacrylamide gel according to their molecular weight. Peptides are then blotted from gel to nitrocellulose paper, which is cut into strips. Every strip is incubated with patient's serum and antibody bound to peptide is then visualized with labelled anti-human IgG and developed with substrate. As an example, Jo-1 antigen (△) is delineated. The result then shows a positive band on the strip of the molecular weight typical for Jo-1 antigen.
MWM, molecular weight markers; **NC**, nitrocellulose.

7 Testing methods

Benefits

A positive test for an autoantibody which is myositis-specific or associated with myositis greatly contributes to the diagnostic workout and in many cases also helps in prediction of prognosis. Since typical autoantibodies cannot be found in all myositis patients, a negative result for autoantibodies does not, however, exclude the diagnosis.

The fact that several different assays to detect myositis autoantibodies are available, may be considered a limitation, since different tests differ greatly in their sensitivity and, although not formally compared, our experience suggests there may be discrepant results between individual assays. Therefore, for detection of autoantibodies related to myositis, extra caution is recommended in interpretation of the results and comparison of several detection methods should be used for a final declaration of positivity. Immunoprecipitation techniques usually require the use of radioactivity or a sophisticated procedure and therefore are not routinely available in clinical practice.

References

[1] Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet 2003; 362: 971–82.
[2] Mimori T, Imura Y, Nakashima R, Yoshifuji H. Autoantibodies in idiopathic inflammatory myopathy: an update on clinical and pathophysiological significance. Curr Opin Rheumatol 2007; 19: 523–9.
[3] Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology (Oxford) 2009; 48: 607–12.
[4] Isenberg DA, Allen E, Farewell V, et al. International consensus outcome measures for patients with idiopathic inflammatory myopathies. Development and initial validation of myositis activity and damage indices in patients with adult onset disease. Rheumatology (Oxford) 2004; 43: 49–54.
[5] IMACS (The International Myositis Assessment and Clinical Studies Group) web site (Accessed — for members only — November 22, 2011, at https://dir-apps.niehs.nih.gov/imacs/index.cfm?action=security.login)
[6] Vencovsky J. Therapeutic strategies in polymyositis and dermatomyositis. Drug Discov Today: Therapeutic Strategies 2004; 1: 369–374.
[7] Mann HF, Vencovsky J, Lundberg IE. Treatment-resistant inflammatory myopathy. Best Pract Res Clin Rheumatol 2010; 24: 427–40.