REVIEW

Inflammatory Myopathies with Cutaneous Involvement: from Diagnosis to Therapy

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Received: 08 March 2016

Accepted: 19 July 2016

Published Online: 22 Nov 2016

Published: 27 March 2017

Key words: idiopathic inflammatory myopathies, cutaneous involvement, clinical variants, diagnosis, therapy

Citation: Dourmishev LA. Inflammatory myopathies with cutaneous involvement: from diagnosis to therapy.

Folia Medica 2017;59(1):7-13.
doi: 10.1515/folmed-2017-0003

The group of idiopathic inflammatory myopathies (IIM) include various disorders of skeletal muscles with or without skin involvement. The most common types are dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) and necrotizing autoimmune myopathy (NAM). Dermatomyositis subdivides into various clinical forms such as juvenile, amyopathic or paraneoplastic dermatomyositis, scleromyositis, overlap or anti-synthetase syndromes, etc.

Recently, numerous new antibodies defining the characteristic clinical phenotype have been described as anti-MDA5 antibodies associated with interstitial lung disease and amyopathic dermatomyositis or anti-TIF1γ antibodies as markers for paraneoplastic dermatomyositis. Moreover, new clinical entities as drug-induced dermatomyositis are presumed, since some medications may induce, or trigger inflammatory myopathies.

Knowledge of the complex methods and techniques required to diagnose the disease is of great importance in clinical practice. The variety of clinical variants needs diagnosis because of the differing prognosis and therapeutic modalities.

INTRODUCTION

The group of idiopathic inflammatory myopathies (IIMs) include various disorders of skeletal muscles with or without skin involvement such as dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) and necrotizing autoimmune myopathy (NAM).¹ Dermatomyositis is a rare idiopathic inflammatory myopathy with a specific skin syndrome. The disease itself expresses heterogeneity not only in clinical presentation, but also in the course and prognosis. Some of the patients may have concomitant neoplastic disorders and features of other connective tissue diseases or markers of autoimmunity varying from absence of auto-antibodies to very high titres of auto-antibodies.² Various auto-antibodies found in dermatomyositis may distinguish certain clinical variants as anti-synthetase antibodies in anti-synthetase syndrome (ASS), anti-TIF1γ in paraneoplastic dermatomyositis³ or anti-MDA5 antibodies in amyopathic dermatomyositis⁴. Finally,

some medicaments may induce or trigger clinical variants of myositis.⁵ This heterogeneity presumes different pathogenesis and reflects on clinical course and therapeutic response.⁶

In polymyositis (PM), patients present with a muscle syndrome, laboratory signs of skeletal muscle inflammation but no skin lesions. In contrast to other non-inflammatory myopathies, PM patients have no family history of neuromuscular disease, exposure to myotoxic drugs or toxins, and clinical features of endocrinopathy.²

Inclusion body myositis is a rare inflammatory myopathy which is prevalent in men. It presents with asymmetric muscle affection and atrophy of distal muscles, lack of peripheral reflex, rarely associates with malignancy and therapeutic resistance.⁷ In IBM, muscle biopsy and electron microscopy show basophilic vacuoles of ectopic beta-amyloid and ubiquitin found in myofibrils. Familial cases of IBM with VCP gene mutation and specific antibod-

ies against 43-kDa muscle antigen in sera suggest different aetiology and pathogenesis of IBM from those of other IIMs.⁸

Necrotizing autoimmune myopathy is characterized with myositis, necrotic changes in muscle biopsy, highly elevated creatine kinase (CK) levels, and anti-HMGCR or other myositis specific antibodies (MSA) in sera, and is frequently associated with malignancy or treatment with statins and other drugs.⁹

Dermatomyositis is a relatively rare disorder, with incidence varying between 2 and 19 cases per 1 million population.^{10,11} It affects women about twice as frequently as it does men.^{11,12} The age distribution shows a bimodal pattern with an initial peak at 10 years of age for juvenile DM and a second larger peak between 40 and 60 years of age.^{11,12}

The aetiology of DM and PM remains unclear; however, various exogenous factors as climate, geographic latitude and sun exposure are found to be important in disease onset. An increasing relative prevalence of DM in southern Europe (Greece and Italy) and higher incidence of PM in northern European countries (Finland, Iceland, and Sweden) has been reported, presuming the ultraviolet irradiation is an important triggering, aggravating factor for DM but not for PM.¹³ Epidemiological studies in the USA demonstrated an increased frequency of adult and juvenile DM onset in spring and summer months.¹⁴ Various infectious agents as viruses, bacteria or protozoa (*Toxoplasma gondii*) were discussed in the past as the disease triggers.^{15,16} Other proposed factors as vaccines, immunoglobulins against various viruses, as well as NSAIDs, anti-neoplastic and anti-infectious drugs could be responsible for triggering an autoimmune process.⁵ Cholesterol-lowering statins have been found to be associated in some cases with the development of necrotizing autoimmune myopathy.⁹

Genetic factors are also found to be of major importance, as in other autoimmune diseases. HLA DRB1*0301; DQA1*0501 have been determined to be risk factors for all of the major clinical forms of PM and DM.¹⁷ HLA-DRB1*03 is significantly associated with anti-Jo-1-positive DM and PM.¹⁸ Some TNF-308 A promoter gene polymorphisms have been found significantly increased in both juvenile and adult DM.^{19,20}

DIAGNOSIS

Diagnosis of IIMs is made following the criteria modified by Targoff et al.²¹ These include: 1) symmetric proximal muscle weakness; 2) eleva-

tion of serum levels of skeletal-muscle enzymes; 3) electro-myographic features of muscle affection; 4) inflammatory infiltration, degeneration or atrophy in muscle biopsy; 5) presence of myositis specific auto-antibodies in sera; and 6) typical skin rash of dermatomyositis.

Cutaneous lesions in DM are subdivided into pathognomonic (highly specific and typical of disorder), characteristic and occasional.^{2,21} Pathognomonic lesions are heliotrope erythema and edema of the eyelids, Gottron papules and Gottron sign. Heliotrope erythema is most frequently observed; however, it is a less specific sign than Gottron's papules. It usually is associated with periorbital oedema and clinically presents as violaceous dusky macular erythema involving symmetrically the eyelids, the upper cheeks and forehead.²² Gottron's papules express as bluish-red, slightly elevated violaceous papules or plaques overlying the proximal or distal dorsal interphalangeal or metacarpophalangeal joints, elbow, or knee joints.²² Characteristic but less specific cutaneous manifestations include: Shawl sign; nailfold telangiectasias; scalp scaly disease and photosensitive poikiloderma. Rarely observed skin lesions such as cutaneous vasculitis, panniculitis, ulcerations, calcinosis, hands hyperkeratosis (mechanic's hands), follicular hyperkeratosis, centripetal linear or flagellate erythema, Holster sign, erythroderma, and vesiculo-bullous lesions are compatible with DM.²²

Clinical or minimal erythema dose tested photosensitivity is observed in about half of patients with DM.²³ Nailfold capillaroscopy features of the patients with dermatomyositis include giant capillaries, microhemorrhages, capillary loss and avascular areas that are barely distinguishable from systemic sclerosis.²⁴ Histological features of skin biopsy include vacuolar (hydropic) degeneration of the basal cell layer of the epidermis, necrotic keratinocytes, vascular dilatation and a superficial, perivascular lymphocytic infiltrate.²⁵

Muscles are almost always affected with myalgia and symmetric progressive muscle weakness involving proximal muscle groups of extremities. Serum muscle enzymes as creatine kinase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and aldolase are usually elevated and mark the disease activity. Muscle histology in DM reveals myofiber necrosis, perifascicular atrophy, inflammatory lymphocytic infiltrate in the endomysium and perivascular inflammation in the perimysium.²⁶ Histopathology

from muscle in PM shows myofiber necrosis, an endomysial inflammatory infiltrate, perimysial and perivascular inflammation but no evidence of perifascicular atrophy and no invasion of inflammatory cells in normal muscle fibres.²⁶

Lung involvement presents with interstitial pneumonia, diffuse alveolitis or bronchiolitis obliterans pneumonia. Cardiac affection includes electrocardiographic changes, valve disease, coronary vasculitis, ischemic abnormalities, heart failure and myocarditis.²⁷ Arthralgia and arthritis are observed in about half of patients.²²

Auto-antibodies in patient's sera have important diagnostic value for IIM. As much as 80% of patients with DM or PM have significant ANA titers in sera.²⁸ The myositis-specific autoantibodies (MSAs) include anti-synthetase group, the most important of which is anti Jo-1 (histidyl-tRNA synthetase) antibodies, anti Mi-2, and anti SRP antibodies.²⁹ In sera of patients with PM predominate anti Jo-1 antibodies (up to 50%), while in dermatomyositis more frequent are anti Mi-2 antibodies (found in about 25% of patients).^{29,30} Antibodies to nuclear matrix protein NXP2 (MJ Ab), are among the most common MSAs in juvenile DM, but are also found in patients with paraneoplastic DM.³¹ In overlap syndromes, anti Ku, PM-Scl and U₁RNP antibodies have been found to prevail.^{29,30} Anti-MDA5 (or anti-CADM-140) antibodies are strongly associated with rapidly progressive interstitial lung disease in patients with amyopathic dermatomyositis.^{6,32} New anti-TIF1 γ (formerly termed anti-155/140) antibodies are found in ~75% of sera from patients with paraneoplastic DM.^{33,34} Anti-HMGCR (3-hydroxy-3-methylglutaryl-coenzyme reductase) antibodies are reported as marker for statin-related myopathy in immune mediated necrotizing myopathy.³⁵

CLINICAL VARIANTS

A variety of clinical variants have been reported in the relevant literature of IIMs with cutaneous involvement depending on the clinical manifestations and laboratory findings.

Juvenile dermatomyositis (JDM) usually occurs in adolescents as a severe, persistent eruption over photo exposed areas accompanied by mild fatigue and fever usually before the age of ten. Latterly, the muscle weakness, myalgia, tenderness, cutaneous vasculitis appear and the risk of calcinosis in patients with NXP-2 autoantibodies increases.³⁶ JDM may cause severe disabilities due to flexural contractures, but hopefully almost never associates

with neoplastic disorders.³⁷

In 1916 Stretz introduced the association of dermatomyositis and cancer³⁸ as *paraneoplastic dermatomyositis (PDM)*. The frequency of the PDM varies between 10 - 30% of dermatomyositis patients.³⁹⁻⁴¹ Malignancy can precede occurring simultaneously with or follow the clinical expression of DM.³⁹ DM associates more often with breast, ovarian, colorectal and lung carcinomas in Europe and America and with nasopharyngeal carcinoma in East Asia.³⁸⁻⁴² The proposed predictive factors for underlying malignancy in patients with DM include cutaneous necroses, vasculitis, ulcers or bullous formations on skin, elevated ESR, C-reactive protein and anti-TIF1 γ antibodies in sera.³⁹⁻⁴² In contrast, PM seldom associates with cancer.⁴³

Patients with *amyopathic dermatomyositis (ADM)* have the same cutaneous manifestations as those with classic DM, but without clinical or laboratory evidence of myopathy for at least 6 months.^{4,10} Some authors even propose the term "hypomyopathic dermatomyositis" for those DM patients who have no subjective muscle weakness, but with objective evidence of subclinical muscle affection in electromyography or muscle biopsy.¹⁰ Later, ADM in some patients may transform to classic DM, and if these patients have anti-MDA5 antibodies in sera they are potentially at risk for developing interstitial lung disease.^{32,44} It is estimated that approximately 75% of adolescents with amyopathic juvenile DM will remain free from muscle disease after years of follow-up, while the other 25% of them will cover the typical clinical features of classic juvenile DM.⁴⁵

Overlap syndromes (OS) comprise the features of DM/PM and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome etc. OS strictly predominates in females (male/female ratio is 1:9), and usually associates with auto antibodies against anti-PM-Scl, U₁RNP and Ku antigens.⁴⁶ A distinct clinical variant is scleromyositis, an overlap of DM and systemic sclerosis.

Since DM or PM could be triggered by various medical substances as NSAID, lipid-lowering or antineoplastic agents⁴⁷ and even TNF α inhibitors^{48,49}, we proposed the term "drug-induced myositis"^{5,50} Different groups of drugs may also trigger DM-like only cutaneous syndrome; or in opposite, induce PM, myalgia or necrotizing autoimmune myopathy.^{50,51} A similar form is the necrotizing autoimmune myopathy, which presents with proximal weakness, highly elevated CK, myalgia, active myopathy with necrotic or degenerating muscle fibers and absence

of inflammatory infiltrate in muscle biopsy, and anti-HMGCR antibodies in sera.⁵¹ NAM is found to be an adverse effect of lipid-lowering statin therapy and may not resolve upon medication discontinuation without treatment. Other drug-triggered IIM include eosinophilic myositis defined by presence of eosinophilic infiltrates in muscle biopsy, or macrophagic myofasciitis due to aluminum-adjuvant vaccines.⁵²

Anti-synthetase syndrome (ASS) is an OS with the criteria mainly for PM and rarely DM. The clinical and laboratory features of anti-synthetase syndrome of nonerosive arthritis, interstitial lung disease, Raynaud's phenomenon, mechanic's hand cutaneous lesions, carpal tunnel syndrome, and anti-synthetase antibodies (anti Jo-1, PL-7; PL-12; OJ, EJ, KS and ZO) are found in sera.^{53,54}

TREATMENT OF INFLAMMATORY MYOPATHIES

The first line therapy of DM and PM includes delta corticosteroids (prednisolone, prednisolone or methylprednisolone) since fluorinated glucocorticoids cause more often steroid myopathy. Different therapeutic regimens with moderate doses ranging from 1 mg/kg prednisone (or prednisolone) per day to pulse therapy exist. Systemic corticosteroids are recommended as an initial therapeutic agent for the treatment of DM, while immunosuppressors have been effective in inducing or maintaining a remission or in case of intolerable side effects of steroids in patients with DM.⁵⁵⁻⁵⁷ Azathioprine, methotrexate and mycophenolate mofetil are the most commonly chosen immunosuppressors.⁵⁷

High-dose intravenous immunoglobulins (IVIG) are used for refractory myositis unresponsive to conventional therapy or to avoid relapses with excellent clinical response in up to 70% of patients.^{58,59} Aminoquinolone antimalarials (chloroquine, hydroxychloroquine) are effective in controlling cutaneous lesions as well as a steroid-sparing agent in the treatment of myositis and in some cases in juvenile DM for prevention and treatment of cutaneous calcinosis.⁵⁹

New therapeutics as signal transduction blockers (tacrolimus), TNF α blockers (infliximab, etanercept, adalimumab)⁶⁰ and anti-receptor antibodies (rituximab, eculizumab)⁶¹ although promising are still the second line treatment and could not be used as monotherapy. Moreover, clinical cases with paradoxical aggravation after TNF α blockers treatment have been reported.^{48,49}

Local treatment with photoprotectors, topical steroids and symptomatic treatment of complica-

tions are also of importance. Topical therapy with broad-spectrum sunscreens and amino quinolone antimalarial drugs are a first line treatment for patients with ADM and adjuvant one for IIM patients with cutaneous involvement.

CONCLUSION

Knowledge of clinical variants, laboratory investigations and immunology tests is of importance for clinicians to achieve accurate diagnosis of inflammatory myopathies as well as to administer the proper therapy. The diversity of clinical forms with or without cutaneous and muscle affection require distinction, as they have different prognoses and require specific therapeutic approaches. The relative rarity of IIMs makes the double blind, placebo controlled studies with large cohort of patients difficult to organize. Nevertheless, evidence based investigations are of mutual importance in finding the exact treatment regimens in all clinical forms of the inflammatory myopathies.

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Воспалительные миопатии с поражением кожи: от диагноза до терапии

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Дата получения: 08 марта 2016

Дата приемки: 19 июля 2016

Дата онлайн публикации:
22 ноября 2016

Дата публикации: 27 марта 2017

Ключевые слова: идиопатические воспалительные миопатии, поражение кожи, клинические варианты, диагноз, терапия

Образец цитирования: Dourmishev LA. Inflammatory myopathies with cutaneous involvement: from diagnosis to therapy.

Folia Medica 2017;59(1):7-13.
doi: 10.1515/folmed-2017-0003

Группа идиопатических воспалительных миопатий (ИВМ) включает в себя ряд различных повреждений скелетной мускулатуры с поражениями или без поражений кожи. Наиболее распространенными видами являются дерматомиозит (ДМ), полимиозит (ПМ), миозит с внутриклеточными включениями (МВВ) и аутоиммунная некротизирующая миопатия (АНМ). Дерматомиозит встречается в разных клинических формах: ювенильный, амиопатический или паранеопластический дерматомиозит, склеромиозит, перекрёстные и антисинтетазные синдромы и т.д.

В последнее время множество новых антител, определяющих характерный клинический фенотип, описаны как анти-MDA5 антитела, связанные с интерстициальной пневмонией и амиопатическим дерматомиозитом или как анти-TIF1γ антитела в качестве маркеров паранеопластического дерматомиозита. Кроме этого, такие новые клинические единицы как дерматомиозит, связанный с воздействием лекарственных препаратов, являются доказанным фактом, так как некоторые лекарственные препараты могут индуцировать и вызвать воспалительные миопатии.

Познание современных методов и техник, необходимых для диагностирования заболевания, является фактором исключительного значения в клинической практике. Большое разнообразие клинических вариантов необходимо четко диагностировать ввиду наличия различных прогнозов и терапевтических подходов.