Inflammatory Myopathies. Dermatomyositis, Polymyositis, and Inclusion Body Myositis

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Idiopathic inflammatory myopathies are a group of heterogeneous, acquired systemic diseases characterized by progressive symmetrical muscle weakness, elevated serum levels of muscle enzymes, electromyographic abnormalities, and inflammatory infiltrates on muscle biopsy. Characteristic histopathologic features allow classification of idiopathic inflammatory myopathies into polymyositis, dermatomyositis, and sporadic inclusion-body myositis. These are commonly regarded as autoimmune disorders, and various autoantibodies directed to specific nuclear and cytoplasmic antigens are found. Other organs besides the muscle can be involved being the skin and lung the most frequent. Occasionally dermatomyositis and polymyositis can be associated with cancer in a paraneoplastic manner. Corticosteroids and immunosuppressive agents are the mainstay therapy, although in refractory cases biologic therapy can be used. Physical therapy can not be forgotten.

Key words: Inflammatory myopathy. Dermatomyositis. Polymyositis. Inclusion body myositis.

Miopatías inflamatorias. Dermatomiositis, polimiositis y miositis con cuerpos de inclusión

Las miopatías inflamatorias idiopáticas son un grupo heterogéneo de enfermedades cuya principal característica es la debilidad muscular y la identificación de una inflamación subyacente en la biopsia muscular. Se incluyen en este grupo la dermatomiositis, la polimiositis y recientemente la miositis con cuerpos de inclusión, con toda probabilidad la menos inflamatoria y también la miopatía adquirida más frecuentemente a partir de los 50 años. Aunque el principal órgano diana es el músculo, la piel y el pulmón, entre otros órganos internos, se afectan con frecuencia, por lo que las miopatías inflamatorias se consideran enfermedades sistémicas. En ocasiones pueden asociarse a cáncer y la presencia de autoanticuerpos específicos y asociados a estas enfermedades sustenta la etiología autoinmune del proceso y ayuda a categorizar a los pacientes. El tratamiento incluye la administración de glucocorticoides, inmunodepresores y puntualmente terapias biológicas, sin descuidar la rehabilitación incluso en la fase aguda de la enfermedad.

Palabras clave: Miopatías inflamatorias. Dermatomiositis. Polimiositis. Miositis con cuerpos de inclusion.

Introduction and Epidemiology

Inflammatory myopathies constitute a group of diseases characterized by specifically affecting striated muscle and by their inflammatory nature.[1-3] The muscle biopsy identifies an inflammatory infiltrate that, according to its localization and distribution, decidedly contributes to diagnosis. Under this concept, there are 3 fundamental entities grouped[4,5]: dermatomyositis, a well defined disease; polymyositis, which groups several diseases that have muscle inflammation and is considered an exclusion diagnosis; and finally, inclusion body myositis (IBM),[6,7] catalogued as sporadic, because there is an indistinguishable familiar form of the latter. IBM was incorporated into the group in the 1990's and, even when it has an undoubtable clinical presence, for some authors it could only be included in this group in a tangential manner, because the inflammatory infiltrate detected in the muscle biopsy seems more an accompanying epiphenomenon of the characteristic inclusion bodies of this disease and not the true cause of the muscle weakness in these patients. Inflammatory myopathies, especially dermatomyositis and polymyositis, considered systemic diseases, because even when the main target organ is the striated muscle, other structures such as the skin or the joints are often affected. Also internal organs, especially the lung, form a part of the clinical spectrum of these diseases. Occasionally, and mainly in dermatomyositis, they can be associated to cancer and present a paraneoplastic behavior.

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Manuscript received May 6, 2008; accepted for publication July 4, 2008.

Regarding its frequency, they can be considered as rare diseases due to their low incidence. Epidemiological studies carried out in different parts of the world establish a yearly mean incidence of 2.1 to 7.7 new cases per every million inhabitants/year.[8] In Spain, the mean yearly incidence is similar, 2.2 to 10.6 new cases per every million inhabitants/year.[9]

Diagnostic Criteria and Differential Diagnosis

The diagnostic criteria established by Bohan et al[1] are still useful in the daily clinical practice because of their simplicity, as well as a classification proposed by these authors, which divides inflammatory myopathies in 5 groups that include adult onset dermatomyositis and polymyositis, juvenile dermatomyositis, paraneoplastic myositis, and overlap syndromes. This classification has the inconvenience of not including IBM, unknown then, but on the other hand allows the establishment of different prognostic groups.[10]

Muscle biopsy is, to some authors, the gold standard for the diagnosis of inflammatory myopathies.[4,5,11] This, without a doubt, is true in the case of dermatomyositis and, to a lesser degree, of IBM, but not in polymyositis, which is still an exclusion diagnosis. Perifascicular atrophy due to microischemia phenomena and necrosis produced by a reduction of the muscle capillary vessels, next to a perivascular and perimysial inflammatory infiltrate, with predominance of T CD4+ lymphocytes and B cells, is typical of dermatomyositis. Immunohistochemistry techniques allow for the identification of the membrane attack complex of complement (C5b9) such as the cause of this capillary destruction. The biopsy is so characteristic in patients with dermatomyositis that the diagnosis can be reached exclusively through histologic analysis, even when the characteristic skin lesions of this disease are absent. However, the muscle biopsy can be negative because the affection tends to be patchy and the fact that steroid use during at least 2 weeks can minimize pathologic findings. Some authors propose the systematic practice of magnetic resonance imaging (MRI) which would allow the performance of a biopsy of muscles previously identified as altered.[12]

Histologic findings in polymyositis, such as endomysial infiltration with a predominance of T CD8+ lymphocytes and a partial invasion phenomenon, can be observed in other myopathies, mainly muscle dystrophies and IBM.[11,13] The expression of major histocompatibility complex type 1(MHC-I) molecules on unaffected muscle fibers supports the diagnosis of idiopathic polymyositis, although it can occasionally be seen in IBM and some muscle dystrophies, specially dyspherlinopathies. All of this has led to question the individualization of polymyositis itself, converting it into an exclusion diagnosis and obliging a meticulous immunohistochemical study which weeds out other entities

TABLE 1. Diagnostic Criteria for Dermatomyositis and Polymyositis[a]

Systemic weakness of the muscles of the scapular and pelvic regions, the neck flexors, progressing through weeks or months with or without dysphagia and respiratory affection
Muscle biopsy characteristic of inflammatory myopathy
Elevated muscle enxymes (creatinkinase, aldolase, transaminases...)
Characteristic electrophysiologic muscle findings
Pathognomonic skin lesions of dermatomyositis (Gottron´s sign, purple or heliotrope erythema)
Definite disease: 4 criteria; probable: 3 criteria; possible: 2 criteria. In the case of dermatomyositis, the last criteria must always be present

[a]Taken from Bohan et al.[1]

TABLE 2. Diagnostic Criteria for Dermatomyositis[a]

Characteristic aspects
Clinical manifestations
Subacute start (weeks to months) in infancy and adult age
Characteristic skin lesions: Gottron's sign/signo de Gottron/heliotrope erythema
Subcutaneous calcinosis (especially in juvenile forms)
Muscle weakness: diffuse, proximal
Systemic affection (dysphagia, synovitis, Interstitial pneumopathy)
Laboratory alterations
Elevated muscle enzymes (creatinkinases and others), although they could be normal
Electromyographic myopathic pattern with spontaneous discharges
Muscle biopsy
Necrosis and regeneration of muscle fibers
Microinfarctions
Perifascicular atrophy
Mononuclear cell infiltrate (perimisial and perivascular); especially lymphocytes B and T CD4+
Vascular immunoglobulin deposit and membrane attack complex (complement)
Capillary depletion; tubuloreticular inclusions in endothelial cells
Muscle expression of class I antigens of the HLA system
Associated problems
Overlap with scleroderma and other connective tissue diseases
Associated cancer (specially in patients over 50)
Rare: sarcoidosis, HIV, toxoplasmosis
Diagnostic categories:
Definite dermatomyositis
Characteristic skin changes with a muscle weakness pattern and histologic confirmation. If the biopsy is conclusive, no more data is necessary
Probable dermatomyositis
Atypical skin lesions with clinical and laboratory evidence of myositis and histologic confirmation
Possible dermatomyositis
Skin lesions indicative of dermatomyositis with clinical and electromyographic evidence of myositis, but a normal or non-specific biopsy
Amyopathic dermatomyositis
Characteristic skin lesions but no clinical or laboratory evidence of myositis

[a]HIV indicates human immunodeficiency virus; HLA, human leukocyte antigen.

TABLE 3. Diagnostic Criteria for Polymyositis[a]

- Characteristics
  - Clinical manifestations
    - Subacute onset in the adult age (rarely before)
    - Diffuse muscle weakness predominantly proximal
    - Systemic manifestations in some cases (dysphagia, interstitial affection)
  - Laboratory alterations
    - Elevation of muscle enzymes
    - Electromyogram (EMG): myopathic motor unit potentials with spontaneous discharge or not
    - Muscle biopsy
      - Myonecrosis (single-fiber pattern) and regeneration
      - Polyphasic and multifocal
      - Endomisial mononuclear cell infiltrate:
      - T CD8+ lymphocytes
      - Invasion of non-necrotic mononuclear cells: macrophages and T CD8+ lymphocytes
      - Expression of Class I MHC antigens on the muscle fibers
  - Associated problems
    - Connective tissue diseases (MCTD, SA, SLE, RA, SS)
    - Other autoimmune diseases
    - Occasionally due to HIV or HTLV-I
    - Cancer (weaker association then dermatomyositis)
- Diagnostic categories
  - Defined polymyositis
    - Clinical characteristics and confirmation through biopsy
    - Other laboratory findings are not necessary if the biopsy confirms it
  - Probable polymyositis (one of the 2 following)
    - Clinical characteristics, EMG findings and elevation of muscle enzymes with incomplete muscle biopsy criteria (minimal, non-specific inflammatory changes...)
    - Atypical clinical data, compatible EMG, elevation of muscle enzymes and evidence of necrotizing inflammatory myopathy on the biopsy
  - Possible polymyositis
    - Compatible clinical and EMG data, with elevation of muscle enzymes but normal or non-specific biopsy

[a]HTLV indicates human T lymphotrofic virus; MCTD, mixed connective tissue disease; MHC, major histocompatibility complex; HIV, human immunodeficiency virus; RA, rheumatoid arthritis; SA, spondyloarthropathy; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome.

TABLE 4. Diagnostic Criteria for Inclusion Body Myositis[a]

- Characteristics
  - Clinical manifestations
    - Disease lasts more than 6 moths
    - Age at onset >30 years
    - Slowly progressive weakness and atrophy; selective femoral quadriceps and finger-flexor affection
    - May be asymmetric
    - Frequent dysphagia
  - Laboratory alterations
    - Moderately high muscle enzymes
    - May be normal
    - Myopathic or "mixed" electromyographic pattern with long and short lasting motor unit potentials
    - Muscle biopsy
      - Muscle fiber necrosis and regeneration
      - Non-necrotic muscle fiber infiltration by mononuclear cells T CD8+ lymphocytes
      - Endomysial infiltrate by (variable) mononuclear cells
      - Vacuolated muscle fiber (ringed vacuoles)
      - COX-negative muscle fibers (excessive by age)
      - Ubiquitine positive inclusions and amyloid deposit in muscle fibers
      - Nuclear or cytoplasmic tubulofilamentous inclusions of 15-18 nm
      - MHC class I antigen expression in the fibers
  - Associated problems
    - Inclusion body myositis can present isolated but can also be associated to:
      - Other autoimmune problems, connective tissue disease, sarcoidosis
      - VIH or o HTLV-I infection
      - Cancer (weak association)
      - Very infrequently: toxoplasmosis
  - Diagnostic categories
    - Definite inclusion body myositis
      - Clinica characteristics and biopsy confirmation: inflammatory myopathy with autoimmune T cells, ringed vacuoles, COX-negative muscle fibers, tubulointerstitial inclusions and amyloid deposit. No other laboratory findings are needed if the biopsy is diagnostic
      - Atypical pattern of muscle weakness and atrophy as well as diagnostic muscle biopsy
    - Probable inclusion body myositis
      - Characteristic clinical and laboratory data with incomplete morphologic criteria
    - Possible inclusion body myositis
      - Atypical clinical data and incomplete biopsy

[a]HIV indicates human immunodeficiency virus; HTLV, human T lymphotrophic virus; MHC, major histocompatibility complex.

such as dystrophies or IBM, especially in those cases which are resistant to treatment.[11,12,14] The subsarcolemic ribbed vacuoles, rich in amyloid and evidenced through staining with Congo red, or amyloid filaments seen with electronic microscopy allow, in addition to the clinical characteristics, for a diagnosis of IBM.[11,13,15] The different criteria proposed for the diagnosis of the diseases that form the group of inflammatory myopathies are summarized in Tables 1-4. Differential diagnosis is ample[13] and includes hereditary muscle diseases, particularly dystrophies which can present an inflammatory infiltrate in the muscle biopsy, some metabolic diseases such as glucogenosis, among which adult McArdle's disease or microphosphorilase deficit are the most frequent and require exclusion through a forearm ischemia test[16] or a genetic study; thyroid disease, which can not only be mistaken for polymyositis, but can also appear and coexist with inflammatory myopathies leading to a poor progression and an inadequate therapeutic response[17]; parasitic infections, such as toxoplasmosis and trichinosis, and drug-induced states, particularly after the use of drugs for hyperlipidemia, such as statins or fibrates, but also glucocorticosteroids or antimalarials used for the treatment of some of the manifestations of the disease itself. Another aspect to take into account is that sometimes a mistaken diagnosis of hepatitis is reached due to the elevation of transaminases that are also be originated in the muscle and are elevated in concert with

creatinphosphokinase in myopathies. Among the dystrophies, a dyspherlin deficit, a membrane protein of the muscle fiber that participates in cell repair, is most frequently mistaken with polymyositis. The suspicion and diagnostic confirmation of this disease is important, because it appears that steroid treatment has a negative effect on muscle, worsening the clinical picture and its progression.[18,19]

Steroid-induced myopathy is not uncommon, rarely represents a diagnostic problem for the clinician, can be of lesser intensity and the clinical context, and in case of doubt the electromyography, can help to identify it. In our experience, steroid myopathy is sometimes more evident clinically in those diseases in which the inflammatory component is reduced or less relevant (dystrophies, IBM); the toxicity of the drug predominates in the muscle with respect to the supposed benefit of acting on inflammation. Occasionally, antimalarial drugs, also associated to myopathy, are employed for treatment of the skin or joint manifestations of the disease, although with a greater degree of histopathologic relevance in the ultrastructural study than clinical repercussion.[20]

Clinical Manifestations

The commonest form of presentation of these diseases is muscle weakness, that can characteristically affect the proximal skeletal muscles, particularly in the scapular and pelvic girdles, complicating activities that require the normal use of these muscles, such as hanging up clothes, combing ones hair, going up the stairs or getting up from a chair, among others.[21] This weakness is accompanied by a myopathic gait with oscillation of the hips evident on each step. Facial muscles are usually conserved. The flexor muscles of the neck and the striated muscle of the oropharynx is frequently affected; the latter ones cause dysphagia present in patients with myositis, which can occasionally be so intense that it is manifested by nasal regurgitation of food content during swallowing and, occasionally, leads to aspiration pneumonia.[2,3,5] It seems that these patients present sleep apnea syndrome more frequently due to the collapse of the upper airways due to weakness of the oropharynx muscles (unpublished personal observation). Myalgias are a symptom that occurs infrequently.

There does not seem to be any differences with relation to muscle affection between dermatomyositis and polymyositis, but there is when compared to BMI. The clinical suspicion of the latter is highest when progression worsens, does not respond to conventional treatment and, characteristically, the patient presents asymmetric muscle weakness and proximal and distal affection next to important atrophy of the quadriceps, which translates into frequent falls, and when it affects the deep flexors of the fingers, something that contributes to the difficulty of these patients to untie a knot or unscrew an object. In contrast to dermatomyositis and polymyositis, which predominate in women as is the case of most systemic autoimmune diseases, BMI is more frequent in males and is considered the most frequent acquired myopathy after 50 years.[5,22]

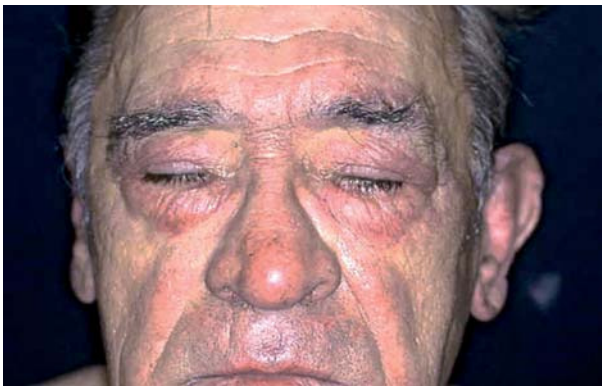

Figure 1. *Heliotrope erythema.*

Skin manifestations are characteristic of dermatomyositis, and there is an ample variety of lesions, most of them with a with a certain photosensitivity component in areas exposed to the sun.[2,3,5] Among the pathognomonic lesions, a lilac discoloration of the eyelids accompanied by edema, or heliotrope (because this is the color of said flower) and Gottron's nodules, slightly descamative and erythematous areas and infiltrations on the knuckles (Figures 1 and 2), have been described. Similar lesions can be observed in extension zones, elbows and knees and also in the intersection of the hairline and the back of the neck. Other skin lesions found on the neckline forming a "V" or on the back, in the form of a "shawl" also have a relationship to sunlight exposure. In general, the skin biopsy is not recommended due to its diagnostic unspecificity. Occasionally, characteristic skin lesions can appear without muscle affection, and when this situation persists for more than 2 years without any signs of myopathy it is called amyopathic dermatomyositis, which is not always benign because it can be associated to cancer or to the development of interstitial pneumonia with a poor prognosis.[23] A subgroup of patients presents a characteristic eccematous lesion on the lateral area of the fingers and the hands that is called "mechanic's hands" (Figure 3) and is related to the presence of anti-Jo1 antibodies. Panniculitis and calcinosis (Figure 4) can become equally important in patients with dermatomyositis, especially in the juvenile form, although occasionally in the adulto.[24,25] It is not infrequent to see pitting edema in the acute phases of disease, which is exclusively attributed to the underlying inflammatory process. Dermatomyositis and polymyositis are considered systemic diseases and as such present the following manifestations.

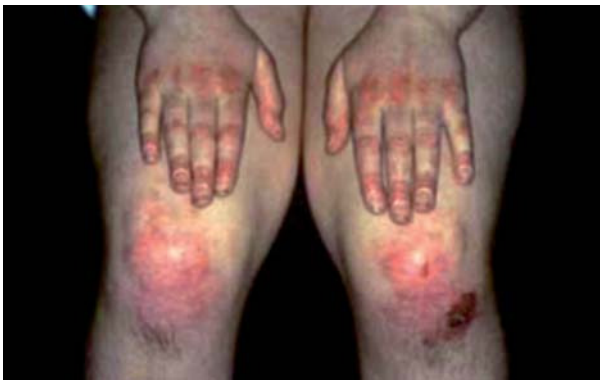

Figure 2. *Gottron's sign.*

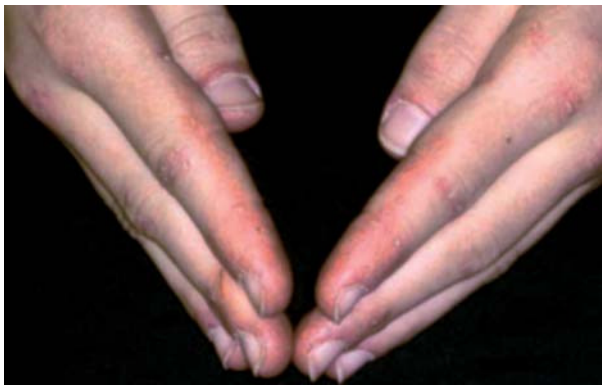

Figure 3. *Mechanic's hands*

Respiratory Affection

It is the most common visceral manifestation and appears almost in half of the patients in one form or the other.[26-31] The most common form of respiratory affection in patients with dermatomyositis and polymyositis is interstitial. In general, its onset is subacute or chronic and the clinical findings upon examination can detect dry rales, similar to the sound of "velcro," characteristic of lung fibrosis. In these cases, antisynthetaze antibodies, especially anti-Jo1 (antihystidil-RNAt synthetaze) are the most frequent, are usually positive and constitute a marker of a clinical syndrome characterized by the presence of inflammatory myopathy (dermatomyositis or polymyositis), interstitial pneumonitis, arthritis, fever, Raynaud's phenomenon and "mechanic's hands," among other minor manifestations. Occasionally, interstitial lung diseases is the main concern and the motive of attention, with myopathy being practically subclinical and its immunologic marker is the presence of other antisynthetaze antibodies different from anti-Jo1.[32] The pathologic substrate seems to lie in most of the cases a non-specific interstitial pneumonia, but there have been cases associated to a common interstitial pneumonia or an organizing cryptogenic pneumonia, formerly known as organizing bronchiolytis with organizing pneumonia (OBON).[26,33,34] These forms of respiratory affection do not seem associated to a worse prognosis.[35] High resolution computerized tomography (CT), an initial bronchioalveolar lavage and, overall, respiratory function tests which include forced vital capacity (FVC), CO diffusion (DLCO), and inspiratory (PIM) and espiratory (PEM) diaphragmatic pressure parameters help in evaluating these patients.

With lesser frequency, an acute interstitial pneumonia can occur with a rapid and fulminant progression, with destruction of lung parenchyma, pneumomediastinum and negative antisynthetaze antibodies, whose pathological background is a diffuse alveolar lesion and can lead to irreversible respiratory insufficiency within a few months in spite of intense immunosupressive treatment; a lung transplant is the only viable therapeutic option.[36-39] This is the most frequent form in oriental patients and this ethnicity has shown to have an autoantibody versus a 140 kD protein that could act as a diagnostic marker in the fulminant form.[40] Respiratory muscles, especially the diaphragm, can also be affected

Figure 4. *Calcinosis cutis*

due to the disease.[28,36] In most of the subjects there is a mild-to-moderate respiratory insufficiency that runs parallel to the course of the disease and that can improve with treatment of the baseline myopathy. A reduction in the PIM and PEM values is characteristic of this situation and can impact the FVC and lead to a false impression when interpreting the low FVC values as secondary to interstitial pneumonitis. In only a few cases the patient progresses to respiratory insufficiency as a consequence of weakness of respiratory muscles. While the effect of immunosupressive treatment is expected, external mechanical ventilation (BiPAP) can help maintain the patient alive, avoiding the necessity for orotracheal intubation.[41] Pulmonary hypertension that accompanies lung fibrosis or happens as a primary disease is infrequent, but it must be considered when the patient presents an increase in dyspnea and a reduction in the DLCO, in spite of a lack of modification of the FVC. Echocardiography would be the first step in reaching the diagnosis.

Cardiac Affection

Cardiac affection is infrequent but when present, it normally is manifested as myocarditis, has a poor prognosis and can progress into dilated cardiomyopathy. In some clinical series it constitutes the main cause of death of these patients.[42,43] Conventional treatment with steroids and immunosupressants can revert its progression, but occasionally patients have to undergo cardiac transplantation.[44] Echocardiography, cardiac MR with gadolinium and a radionuclide scan with 99mTc are the most widely employed diagnostic techniques next to electrocardiography.[42,45] It is possible for patients to only present subclinical cardiac manifestations, mainly elevated creatinphosphokinase (CK-MB) in asymptomatic cases with myositis.[46] Anti-SRP (single recognition particle) antibodies have been associated to polymyositis in black women with severe cardiac affection and mainly during the fall,[47] although this association is controversial.

Digestive Tract

Dysphagia appearing during the course of the disease is due to myopathy of the striated muscles of the oropharynx. Intestinal vasculitis and/or hollow-organ perforation have been found in juvenile forms, but rarely in adults.[48] Bowel obstruction and cystoid pneumatosis are uncommon manifestations but have been described in association to dermatomyositis.[49,50] A relationship between celiac disease and antigladin antibodies and myopathy, especially in polymyositis and IBM has been speculated upon.[51,52]

Etiopathogenesis and Autoantibodies

The etiopathogenesis of inflammatory myopathies is not well known.[53] On the basis of an external physical, chemical or infectious agent that act in a genetically predisposed terrain, some theories have been advanced. A multinational study in almost 1000 patients with polymyositis or dermatomyositis, demonstrated that living close to latitude 0° was a risk factor for the development of dermatomyositis. In other words, countries closest to the equator, and therefore exposed to light radiation, presented a greater frequency of dermatomyositis, and in countries farthest away, polymyositis was the most frequent clinical entity. These differences were attributed to the influx of UV radiation as an etiopathogenic stimuli. These results were confirmed by other studies.[54,55] Another theory, which has still to be consolidated, refers to the phenomenon of fetal microchimerism through which immunocompetent cells from the fetus remain nested in the mother womb and activate leading to an authentic graft-versus-host reaction.[56,57] Although epidemiological studies have not been capable of attributing any etiopathogenic role to silicon gel implants in the development of autoimmune diseases in general or in the particular case of polymyositis or dermatomyositis, cases of dermatomyositis have been described in association to the use of silicone prosthesis within a favorable genetic context.[58-60] The endothelium of the capillaries is the main target for attack indermatomyositis and C5b9, or the membrane attack complex of complement, seems to be the main cause of capillary lesion. Cytokines, vascular and interstitial adhesion molecules and metalloproteinases seem to carry out an adjuvant role in the inflammatory process led by T and B cells. The lesion mechanism seems different in polymyositis, where T CD8+ mediated (via perforin) seems to be the main cause.

The presence of autoantibodies is one of the characteristics of autoimmune diseases. In dermatomyositis and polymyositis more than half the patients present positive antinuclear antibodies and up to 20% have specific, myositis-associated antibodies.[47,61-64] In a less frequent manner, the presence of these autoantibodies has been described in IBM.[65,66] Table 5 specifies the main antibodies related to myositis.

Cancer and Inflammatory Myopathies

Several epidemiological studies establish, without a doubt, a close relationship between dermatomyositis and cancer and, in a lesser degree, polymyositis and cancer.[67-69] A third of the patients with dermatomyositis will have cancer or, in other words, a patient with dermatomyositis has a threefold risk of developing cancer than a person without the disease. These values are a bit more moderate for polymyositis. Currently, there does not seem to be enough

TABLE 5. Autoantibodies in Polymyositis/Dermatomyositis[a]

Antigen	Frequency, %	Associated Clinical Characteristics
Myositis specific antigens		
Antisynthetases	20-30	Fever, arthritis, mechanic's hands, Raynauds phenomenon, interstitial pneumopathy, myositis
Hystidil-RNAt synthetase (Jo-1)		
Treonil-RNAt synthetase (PL-7)		
Alanyl-RNAt synthetase (PL-12)		
Isoleucil-RNAt synthetase (OJ)		
Glycil-RNAt synthetase (EJ)		
Asparaginyl-RNAt synthetase (KS)		
Fenilalanyl-ARNt synthetase (Zo)		
Anti-SRP (signal recognition particle)	4-5	Myositis, poor prognosis, treatment resistant, heart affection
Anti-Mi-2 (helycases)	5-14	Dermatomyositis
Myositis associated antibodies		
Anti-PM/Scl (exosome)	5-10	Myositis, sclerodermia
Anti-RNP (U1 ribonucleoprotein)	5-10	Myositis, SLE, MCTD, sclerodermia
Anti-SSA (Ro 60/Ro 52)	10-25	Sjögren's syndrome

[a]MCTD indicates mixed connective tissue disease; SLE, systemic lupus erythematosus.

evidence that allows the association of cancer with IBM, which represents another differential fact of this disease. Among the neoplasia most frequently associated, ovarian cancer stands out, and some authors recommend the yearly determination of tumor markers for this neoplasia during the first 5 years after diagnosis.[70,71] The representation of cancer associated to dermatomyositis, excluding ovarian cancer, seems to follow the normal population distribution. In general, cancer associated to dermatomyositis-polymyositis has a paraneoplastic behavior; it appears 2-3 years before or after the diagnosis of inflammatory myopathy. Although it is generally accepted that the course of dermatomyositis and polymyositis runs parallel to that of cancer, it is difficult to ascertain, because the improvement in the former after chemotherapy can be due to the resolution of the neoplasia or due to the potent immunosupressive action of antineoplastic treatment. A search for this association is recommended at the onset or at the diagnosis of dermatomyositis-polymyositis, performing a basic blood profile and biochemistry, prostate, ovarian and breast tumor markers, a thorax and abdomen CT, a mammogram, and a gynecologic examination. Even then, it is not infrequent that the clinical follow up of the patient surprises us with the appearance of a neoplasia and therefore, new strategies have been developed.[72] Positron emission tomography (PET)-TC with fluorodesoxyglucose, a hybrid technique that combines morphology and cel function data could be a good option, although preliminary results (personal observation, unpublished data) does not seem to show a greater cost-effectiveness than traditional means of detection; in any case, more studies are needed to establish its usefulness in this regard.

Several studies have manifested the existence of shared antigens in tumor cells and myocytes.[73-75] The recent discovery of antibodies versus a 155 kD protein seem to have an elevated negative predictive value, in other words, patients with a negative result for this autoantibody are unlikely to develop cancer.[76-78]

Treatment

Treatment of inflammatory myopathies is based on the administration of glucocorticoids and immunosupressants, without forgetting physical therapy or rehabilitation, even in the acute phase.[79,80] A third of the patients respond to monotherapy with steroids, but most need the addition of an immunosupressant. Among them, azathioprine[81] at a dose of 1-2 mg/kg/day adjusted according to the tiopurine methyltransferase polymorphism result and methotrexate[82,83] at a dose of 7.5-20 mg/week are the most employed. However, calcineurin antagonists, such as cyclosporin or tacrolimus, when the patient is not hypertensive, are well tolerated and especially useful in interstitial disease.[83-85] Also, the administration of cyclophosphamide in monthly pulses of approximately 700 mg with mesna to reduce bladder toxicity, during 6 months, has proven useful for the control of interstitial pneumonitis in these patients.[86] New antimetabolite immunosupressants such as mycophenolate mofetil or mycophenolic acid, have shown their potential usefulness in the treatment of refractory myositis,[87] even if there has been reports of lymphoproliferative diseases associated to their administration. Intravenous immunoglobulin[88,89] act by improving muscle weakness, are rapid in their effect, have little toxicity and are well tolerated, with the main problem being their price and the fact that they act symptomatically, but can be used in any case until the

immunosupressive treatment reaches its desired effect. Plasmapheresis, total body irradiation or oral cyclophosphamide have not proven their efficacy in the treatment of inflammatory myopathies.[90,91] Other, lesser drugs, such as antimalarials, useful in systemic diseases such as, for example, lupus, could be employed as adjuvant drugs in the control of skin and/or joint manifestations, although our experience in this sense leaves somewhat to be desired. Creatine supplements as a coadjuvant therapy has been employed.[92] Multiple trials and treatments used in patients with IBM have failed or proven inconclusive.[93-97] Biologic therapy, such as etanercept, infliximab, or rituximab, has proven efficacious in some clinical cases or observational studies with few patients.[98,99] There is a randomized, double blind trial currently under way with placebo and rituximab, pending results.

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