



Revision

Dermatomyositis

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ABSTRACT

Dermatomyositis is a form of idiopathic inflammatory myopathy that involves skeletal muscle and skin. The objectives of this review are to briefly describe the cutaneous manifestations of the disease, to raise some questions still debated about amyopathic dermatomyositis, and to reflect current knowledge of an interesting aspect in dermatomyositis as it is the risk to develop malignancy. Although clear evidence for a significant dermatomyositis-cancer association exists, optimal clinical or biological factors that predict an association with cancer have not been identified. Recently, some specific autoantibodies in dermatomyositis have been shown to be associated with internal malignancy. They open up the possibility to have available serological markers for detecting cancer-associated myositis in the near future.

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Dermatomiositis

RESUMEN

La dermatomiositis es un tipo de miopatía inflamatoria idiopática que afecta al músculo esquelético y a la piel. Los objetivos de esta revisión son, en primer lugar, dar una pincelada breve sobre las manifestaciones cutáneas de la enfermedad para los que no estén tan familiarizados con éstas; en segundo lugar, plantear algunas cuestiones aún debatidas sobre la dermatomiositis amiopática, y, en tercer lugar, revisar un aspecto muy interesante como es el de la dermatomiositis y el riesgo de desarrollo de neoplasia. Respecto a este último punto, está claro que los pacientes con dermatomiositis tienen un mayor riesgo de desarrollo de una neoplasia y si bien no hay marcadores clínicos o biológicos claros de la presencia de ésta, es posible que en un futuro próximo se pueda disponer de autoanticuerpos que puedan desempeñar este importante papel.

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Dermatomyositis is an inflammatory disease that affects the skin and muscle. It is included with the inflammatory myopathies or idiopathic myositis, which constitute a heterogeneous group of muscle diseases of unknown etiology characterized by the appearance of progressive muscle weakness and inflammation.¹

Classification

With the intention of putting order in the classification of these processes, several attempts have been made. The first clinical classification is one that distinguishes specific groups of inflammatory myopathies that differ clinically, by microscopy, in its prognosis and, most likely, in its etiopathogenesis (Table 1).² In this

sense, the most current includes, in addition to the entities proposed by Bohan and Peter in 1975,³ other myopathies described later, such as inclusion-body myositis or clinical situations that dermatologists have recognized for some time but had not been included in these classifications until recently. This is the case of amyopathic dermatomyositis or dermatomyositis sine myositis; a diagnosis of great interest for the clinician due to its impact on prognosis and therapy.

A second classification contemplates the presence of antibodies directed, for the most part, against enzymes that participate in protein synthesis and that seem to define certain groups with homogeneous clinical, epidemiological and prognostic findings, especially those associated to antibodies that are myositis-specific (Table 2).^{4,5,6} Their

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Table 1
Clinical classification of idiopathic inflammatory myopathies

Polymyositis
Dermatomyositis
Dermatomyositis sine myositis
Childhood-onset polymyositis and dermatomyositis
Inclusion body myositis
Cancer-associated myositis
Connective tissue disease associated myositis
Eosinophilic myositis
Granulomatous myositis
Focal or nodular myositis
Ocular or orbital myositis

sensitivity is not very considerable and their absence does not exclude the diagnosis of an inflammatory myopathy but their presence in itself does have an elevated predictive value. Among the myositis specific antibodies, the most important ones are the anti-synthase (antiaminoacyl-transferase ribonucleic acid [RNAt] synthase) antibodies directed against cytoplasmic enzymes that catalyze the covalent binding of aminoacids to its tRNA. The anti-histidil-RNAt or anti-Jo-1 antibody is the most frequent. This antisynthase antibody limits, next to anti-Mi-2 and anti-signal recognition particle antibodies, different clinical manifestations with a well defined progression and

response to treatment (Table 2). Anti-Mi-2 antibodies are associated to dermatomyositis, both the childhood associated as well as the adult form and, to a lesser extent, to interstitial lung disease and a relatively good prognosis⁷. This antibody recognizes 2 antigens, Mi-2 α (240 kD) and Mi-2 β (218 kD), which probably belong to the same protein family (nuclear helicases) which have a regulating function of transcription.^{8–10} It might possible that, in a near future, clinical differences are identified between patients with different reactivity against the 2 Mi-2 molecules or against certain fragments of them, as has been reviewed in a recent paper.¹¹ Signal recognition particle (SRP) is a cytoplasmic complex of protein and ribonucleic acid that consists in 7 SL-RNA and 6 polypeptides of 72, 68, 54, 19, 14, and 9 kD. This complex mediates the translocation of polypeptides through the endoplasmic reticulum.

Patients in which antibodies are developed against this particle (anti-SRP) can present an acute onset myositis, generally resistant to standard treatment with steroids and characterized by frequent relapses, myocardial affection, and dysphagia.^{12,13} From a microscopic point of view, this myositis is characterized by the necrosis of muscle fibers almost without any inflammatory infiltrates.¹⁴ Therefore, antiSRP antibodies can constitute a marker of a myopathy syndrome that is different from the typical polymyositis which, although it rarely responds to conventional steroid treatment, may respond to other treatments such as rituximab (monoclonal anti-CD20

Table 2
Antibodies in idiopathic myositis and clinical and progression characteristics of the associated inflammatory myopathy^a

Antibody	Antigen	Patients with antibodies, %	Characteristics of the antigens	Associated clinical syndrome	Progression and prognosis
<i>Myositis specific antibodies</i>					
<i>Antisynthase</i>					
			Cytoplasmic enzymes that catalyze the covalent binding of aminoacids to the RNAt	Onset during springtime as an acute myositis, arthritis, interstitial lung disease, fever, "mechanic's hands" and Raynaud's phenomenon	Moderate response to treatment and relapses characterize progression. Five year survival 65% (respiratory failure and cor pulmonale)
Anti-Jo-1	Histidil-RNAt synthase	20			
Anti-PL-7	Treonil-RNAt synthase	5–10			
Anti-PL-12	Alanil-RNAt synthase	<5			
Anti-OJ	Isoleucil-RNAt synthase	<5			
Anti-EJ	Glycil-RNAt synthase	5–10			
Anti-KS	Asparaginil-RNAt synthase	<5			
Anti-Zo	Phenylalanil-RNAt synthase	<1			
Anti-YRS<Tyrosil-RNAt synthase	<1				
Anti-signal recognition particle	Signal recognition peptide	5	Cytoplasmic complex that mediates the translocation of polypeptides through the endoplasmic reticulum	Acute and severe onset during the fall, with severe muscle, myocardial affection, and dysphagia. Necrotizing myopathy	Poor response to treatment. Five year survival 25% to 30% (due to cardiac affection)
Anti-Mi-2	Nuclear helycase (218/240 kD)	5–10	Nuclear helycase with a transcription-regulating function	Acute and mild onset with classic skin lesions	Good response to treatment. Five year survival 95%
Anti-CADM-140	Unknown (140 kD protein)	50 with DMA	Unknown	Specific of DMA	
Anti-p155/p140	TIF-1- γ	20 with DM		DM, associated to neoplasia	
Anti-MJ	Unknown (140 kD protein)	<5		Childhood DM	
Anti-PMS1	AND repairing enzyme	<5			
<i>Myositis associated antibodies</i>					
Anti-U1 ribonucleoprotein	U1 nuclear ribonucleoprotein	10		Overlap myositis, mixed connective tissue disease	
Anti-Ku	Regulatory subunit DNA-PK (70/80 kD)	20–30		Overlap polymyositis-scleroderma syndrome in japanese	
Anti-PM-Scl	Nuclear complex of 11 to 16 proteins	8–10		Overlap polymyositis-scleroderma syndrome in caucasians	

DMA indicates amyopathic dermatomyositis; DNA, desoxyribonucleic acid; DNA-PK, protein kinase desoxyribonucleic acid; RNAt, transferase ribonucleic acid; DM, dermatomyositis; TIF-1- γ , intermediate transcriptional factor 1- γ .

^a Adapted from Mimori T et al.⁵

antibody).¹⁵ As will be seen later other, more recently identified antibodies may be associated to other clinical situations within the context of dermatomyositis.

Skin manifestations

In addition to muscle, the skin plays a protagonic role in this disease. Skin lesions are very characteristic and precede or may be concomitant to the development of myositis in an elevated percentage of patients, which in many occasions can allow the dermatologist who first encounters the patient to perform the diagnosis of the disease.

This rash is characterized by its violaceous coloration and its distribution around the eyes and bony prominences, forming a heliotrope erythema and Gottron's papules, respectively. To this one must add the intense nail bed affection with thickening and the presence of small hemorrhagic infarct zones.¹⁶⁻¹⁹

Heliotrope lesions, named after their characteristic violaceous coloration, almost always affects both eyelids symmetrically and is accompanied by a certain degree of edema. The unusual clinical manifestation characterized by intense edema that leads to ampoules must not be mistaken with the more common mild skin lesions. A mild erythema should not be overlooked either, present as a slight skin coloration on the edge of the eyelids.

When faced with asymmetric eyelid edema and erythema without a purplish coloration, other diagnosis must be suspected such as lupus profundus, thyroid ophthalmoplegy or an orbital pseudotumor, among other²⁰ (Tabla 3).

Gottron's sign refers to purplish papules and plaques accompanied by mild scaling or, on occasion, of prominent desquamation similar to psoriasis, especially located over bony prominences over the metacarpophalangeal and interphalangeal joints (Figure 1). They can also appear over the elbows, knees, or any other joint. These lesions can be clinically mistaken for lupus erythematosus, psoriasis, or lichen planus. In the latter 2, a helpful test is a microscopic analysis of the skin biopsy.¹⁹

In the case of lupus erythematosus, microscopic changes can be very similar to those of dermatomyositis, but small details such as the localization of the lesions can be of interest. In systemic lupus, when the lesions are over the back of the hands, these are normally found between the fingers and respect the knuckles.

From these pathognomonic, or very characteristic localizations, erythema can extend to the rest of the face (Figure 2) and fundamentally occupy the central zone or seborrheic areas, the scalp, trunk (especially over the anterior part of the neck and the neckline V), the back of the neck, shoulders and upper third of the back, configuring the typical "shawl" appearance of the erythema or the surface of extension of the extremities. It is not uncommon to find poichylodermia (understood as the presence of small areas of atrophy with telangiectasia and pigmentation abnormalities).¹⁹ Occasionally, ulcers or scarring can be seen that indicate skin necrosis due to ischemia (Figure 3) (see Dermatomyositis and neoplasia).

Table 3
Differential diagnosis of edema and unilateral eyelid erythema

Acute	Chronic
Eye infections	Lymphedema
Insect bite	Eyelid or orbital tumor (primary or secondary)
Contact eczema	
Urticaria	Granulomatous dermatosis
Skin infections	Lupus profundus
Thrombosis of the longitudinal sinus	Orbital pseudotumor
Vascular face pain	Facial paralysis
	Localized scleroderma
	Blepharochalasia
	Thyroid ophthalmoplegy

Skin and muscle calcinosis is infrequent in adults but can occur in up to 40% of children and teenagers with dermatomyositis. Skin calcinosis is manifested as hard, yellowish or skin colored nodules which are frequently found over bony prominences. Occasionally, nodules can open to the surface with the risk of a secondary infection. Muscle calcification tends to be asymptomatic and may only be a radiological finding. In severe cases, calcinosis can be a cause of functional limitation of the affected members.^{19,21}

Other lesions, described as infrequent in dermatomyositis are vesicles and ampoules,²² panniculitis,²³ and a curious eruption known as flagellated erythema.^{24,25} The latter consists in the appearance of lineal bands which are non-pruriginous, persistent and found on the trunk and extremities of patients that, on the other hand, have the typical skin findings of dermatomyositis. Patients deny scratching



Figure 1. Erythema of the back of the hand which predominates on the knuckles and the nail bed, a characteristic of dermatomyositis.

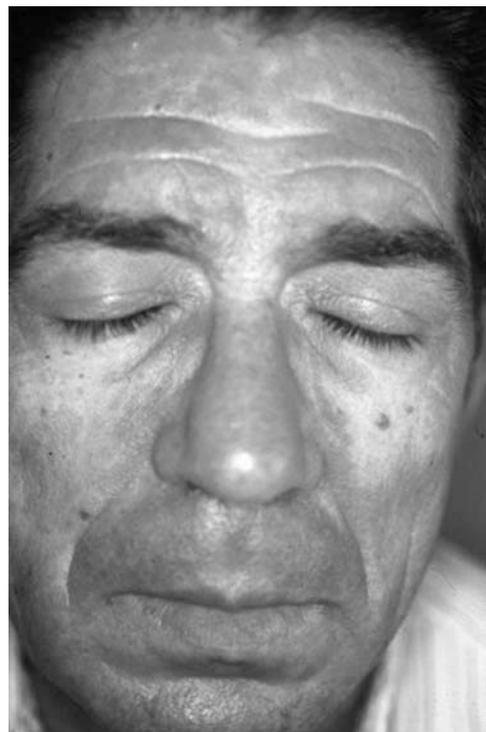


Figure 2. Facial erythema with purplish tonality that predominates on seborrheic areas. Note the eyelid affection that constitutes a heliotrope erythema.

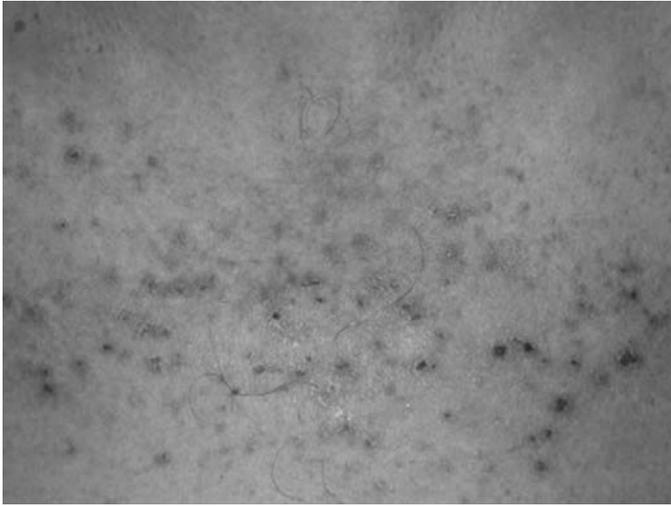


Figure 3. Erythema and scarring on the neckline of a patient with dermatomyositis. These lesions are secondary to the existence of capillary ischemia and, according to some authors, their presence is associated to neoplasia.

and it is not possible to demonstrate dermographism. Lineal bands seem to follow a centripetal distribution and do not lead to interruptions in the continuity of the tissue with the erythematous areas on the back or neckline. These lesions, similar to these that can be found in patients receiving bleomycin, have not been observed in any other autoimmune connective tissue disease, making them very characteristic of dermatomyositis. Although there is no plausible explanation for the development of this peculiar eruption, it is accepted as one more clinical manifestation of this disease from the moment in which microscopy has shown changes similar to those described as typical of dermatomyositis.

The presence of mucin on the dermis is a microscopic finding of the skin lesions of dermatomyositis. However, the clinical translation of these especially intense deposits has only been occasionally described in the form of infiltrated papules or purplish plaques, localized on the trunk, extremities or that follow the flexion line on the palms and fingers.^{26,27} These lesions can be the only skin lesion, therefore constituting a particularly difficult diagnosis.

Finally, in patients with dermatomyositis there are other changes to be seen, such as thickening, hyperkeratosis, and fissures on the lateral and palmar sides of the fingers, a lesion known as “mechanics hands.” These very curious and evident changes which were initially described in patients affected by different connective tissue diseases (mixed connective tissue diseases, dermatomyositis, and systemic lupus erythematosus) but with the common denominator of being accompanied by myositis.²⁸ However, it has been seen associated to the presence of interstitial lung disease, myositis, arthritis, and Raynaud’s phenomenon (in a variable percentage), all of this under the common denominator of the presence of circulating anti-Jo-1 antibodies. This justified the term “anti-synthase syndrome” coined in order to identify patients that presented with these symptoms.^{29,30} Finally, “mechanics hands” have been described next to typical lesions of classic dermatomyositis in patients with polymyositis³⁰ or in overlap syndromes, such as scleromyositis.³¹ Because of this, “mechanics hands” are currently considered a skin marker of myositis, independent of the antibody or associated myopathy.

Dermatomyositis sine myositis

In a low percentage of patients, described between 2% and 18%, a skin eruption indistinguishable from that of classic

dermatomyositis can develop, but with the absence or minimal expression of muscle manifestations. This group of diseases is known as dermatomyositis sine myositis, amyopathic dermatomyositis, or clinically amyopathic dermatomyositis as has recently been proposed by Sontheimer et al.³²

This clinical situation is of great interest and controversial because there are no definite criteria to guide its diagnosis. In addition, it is unknown if patients have the same risk than those with classic disease of developing severe complications, such as neoplasia or interstitial lung disease, and there is no agreement on the best course of therapy.

In relation to its diagnosis, one must remember that there are no clinical or microscopic differences of skin lesions of amyopathic dermatomyositis with respect to classic dermatomyositis and that in more than 50% of patients with classic dermatomyositis, skin lesions precede muscle affection by 3 to 6 months.³³ It is accepted that if it occurs within the first 2 years since the onset of the eruption then this is considered as the common progression of classic dermatomyositis. After this period of time and if only the skin lesions exist, it is referred to as dermatomyositis sine myositis.^{34,35}

It is more controversial to define the absence of muscle disease and up to which point the muscle must be examined to determine if the organ presents inflammatory activity or not. It has been seen that patients with skin lesions of dermatomyositis without clinical signs of muscle weakness and CK (creatine kinase) within the normal range may have electromyographic, magnetic resonance and muscle biopsy alterations, leading to conclude that a clinically asymptomatic myositis exists.^{36,37} However, as demonstrated in a recent study in which a systematic review of the literature was performed,³² these findings are not useful to predict future muscle activity and, therefore, should not necessarily lead to a more intense therapeutic strategy. It can be argued that beyond the clinical examination of the muscle and the determination of CK levels, other muscle examinations in the absence of muscle weakness would be unnecessary to make a therapeutic decision. The onset of muscle affection is frequently preceded by an elevation in CK levels, underlying the importance of performing periodic determinations of this muscle enzyme in patients with clinically amyopathic dermatomyositis, especially during the first 2 years.

It is evident that when faced with the difficulty of defining, from a clinical standpoint, amyopathic dermatomyositis, characterizing a serologic marker that would permit the identification of these patients would be of great clinical and prognostic interest. In this sense, in patients with clinically amyopathic dermatomyositis and not classic dermatomyositis, some antibodies against new autoantigens have been identified and could play this role; among those stand out an anti-CADM-140 antibody directed against a cytoplasmic antibody of 140 kD which is associated, at least in Japanese population, to amyopathic dermatomyositis and, within this context, to rapidly progressive lung disease.³⁸ With respect to this complication, a review of the literature shows that up to 15% of clinically amyopathic dermatomyositis can develop interstitial lung disease with a mortality of up to 40% of cases.³² Until the identification of anti-CADM-140 antibody associated to classic dermatomyositis, such as anti-Jo1, had been identified.

With regard to the therapeutic approach, Euwer and Sontheimer demonstrated in 1991³⁹ that a more intensive treatment of skin disease (understood as the management that would be given to a case of classic dermatomyositis) could prevent the ulterior development of muscle inflammation. However, several series were published afterward in which patients diagnosed with amyopathic dermatomyositis did not develop muscle disease in spite of not undergoing treatment with immunosuppressants^{37,40,41} suggesting that oral steroids or other immunosuppressive drugs should only be administered in the presence of obvious muscle affection.

Dermatomyositis and neoplasia

The association between dermatomyositis and neoplasia was first described in 1916. In the first epidemiological studies, diverse clinical and methodological aspects precluded confirmation.⁴²⁻⁴⁹ Among these aspects are the difficulty in diagnosing myositis and, overall, the distinction between dermatomyositis and polymyositis, the reference bias of the cases, studies with small sample sizes, the short duration of follow up on treatment or the lack of an adequate control group, among others. However, more recent and better designed cohort studies have shown a significant association between myositis and neoplasia; the risk for this association is greater for dermatomyositis than for polymyositis.

In 2001 an Australian group published one such study in which they included a total of 537 patients, all of them with a biopsy-proven inflammatory myopathy.⁵⁰ The standardized incidence rate that was found in the group of patients with dermatomyositis was 6.2, indicating that the risk of neoplasia is 6 times higher in this process than in the general population. They also observed that this risk was 2.4 times higher in patients with dermatomyositis than in patients with polymyositis.

Hill et al⁵¹ demonstrated, in a large group of patients with dermatomyositis and polymyositis, that both entities were associated with a higher risk of cancer, but this risk was even higher in patients with dermatomyositis than those with polymyositis.

Therefore, there seems to be a clear association between dermatomyositis and cancer. However, the best strategy for searching for the disease remains undefined. In this sense, 3 important questions, which are still unanswered, arise. First, are there any predictive factors or neoplastic markers in adult dermatomyositis?; second, should the study of dermatomyositis be performed with minimal examination or, on the contrary, be complete and exhaustive?; and third, how long must follow up of a patients who was found to be cancer free in the first evaluation, continue?

The first question is one of the most important to the clinician because it is obvious that the identification of certain clinical or biological parameters that could serve as neoplastic markers would allow for a selective and meticulous investigation in search of neoplasia only in those patients with positive findings. However, there are unfortunately few that permit the suspicion of cancer. The first one to take into account is age. The frequency of neoplasia in patients with dermatomyositis increases with age^{42,52-56} and the presence of neoplasia is extremely rare in childhood dermatomyositis.¹⁹ However, the risk of neoplasia has been found to be increased even in patients less than 45 years of age. Therefore, age should not be a dissuading argument to the clinician when opting for a thorough search for cancer.

Some authors have pointed out, in several publications in the French medical literature,⁵⁷⁻⁵⁹ that necrotic lesions on the skin of patients with dermatomyositis might be associated to cancer. In one of the studies, the predictive value of the association was calculated to be 70%.⁵⁹ This clinical parameter is easy to evaluate for the dermatologist and its observation could probably justify an exhaustive search for neoplasia.

Finally, it has been shown that the presence of interstitial lung disease by itself or accompanied by anti-synthase antibodies is negatively associated to neoplasia.^{4,60,61}

With respect to the biological parameters, some common laboratory determinations can be distinguished, such as tumor markers and autoantibodies. It has been seen that patients with dermatomyositis and an associated neoplasia have a higher frequency of normal CK values⁶²⁻⁶⁴ although some authors have shown the contrary is also true^{65,66} in addition to finding an increased erythrocyte sedimentation rate.⁶⁵

It has been well established that the determination of a series of tumor markers can provide useful information before the start

of an exhaustive search for neoplasia. In patients with myositis, markers CA 125 and CA 19.9 can be especially interesting, because according to Amoura et al⁶¹ the serum elevated levels of these 2 markers as well as the serial elevation of CA 125 are associated to a greater risk of developing cancer of the ovary and other types as well.

From a serological standpoint, no myositis-specific antibody had been identified as a marker for neoplasia until a few years ago. The medical literature even suggested that the presence of these antibodies reduced the probability of cancer.^{4,67} However, in the past few years, new specific antibodies have been identified in patients with dermatomyositis,^{38,68} some of which seem to be associated to the presence of cancer. One of these antibodies is directed against a 155 kD protein (anti-p155). According to Targoff et al,⁶⁹ anti-p155 was present in 75% of cases of myositis and neoplasia and cancer developed in 37.5% of patients with dermatomyositis and positive anti-p155 antibodies. The target antigen of this antibody is the 1- γ ⁷⁰ intermediary transcriptional factor. Other authors, almost simultaneously, have described a similar antibody that reacts not only with a 155 kD protein but also with another 140 kD protein.^{71,72} This double band of precipitation is mentioned in the previous study,⁶⁹ making it likely that it is the same antibody. In any case, these 2 workgroups^{71,72} identified this antibody as dermatomyositis-specific and proved it shows a good correlation with the presence of neoplasia and the absence of lung disease. In that manner, anti-p155/140 positivity provides high specificity (96%), moderate sensibility (50%), and an elevated negative predictive value (97%) for dermatomyositis associated to cancer. The presence of this antibody also increases sensitivity (94%) and negative predictive value (99%) when other myositis-specific antibodies are negative.⁷² It is obvious that the clinical application of these findings requires confirmation through large prospective studies, but they definitely open the near future to the possibility of having serologic markers of dermatomyositis associated to neoplasia.

With respect to the second question contemplated, how to approach a neoplasia in a patient with dermatomyositis is still under discussion. One must part from the fact that the type of cancer that can be encountered is manifold (the most frequent are ovarian, lung, gastrointestinal, pancreas, and breast cancer) and that most will be initially hidden.⁵¹ From a clinical perspective, it seems reasonable to advise the asymptomatic patient on the search for any process whose early detection and treatment lead to a better prognosis. On the other hand, it is evident that the presence of a neoplasia is a poor prognostic indication in the context of dermatomyositis.

There are 2 traditional and opposing attitudes with respect to the number and type of examinations that must be performed in search of neoplasia. One of them is limited to a complete history and thorough examination as well as a review of systems, routine laboratory analysis, and complementary exams in accordance to the findings, while the other, in addition, includes a wide spectrum of exams such as a thoracic and abdominal computerized tomography (CT), a gastrointestinal endoscopic examination, a mammogram, a bone marrow aspirate, serum electrophoresis, among others.^{65,73} But all of these examinations are probably something that will suffer variations as new medical knowledge and better and more comfortable diagnostic techniques are introduced. For example, the role of the positron-emission tomography would be something to be discussed here.

Currently, and according to a study by Hill et al,⁵¹ it seems reasonable for a male Caucasian with dermatomyositis undergo, in addition to a thorough clinical examination and the usual tests, a search for tumor markers and fecal blood as well as an abdominal CT. In women, a CT would also be justified as well as a pelvic ultrasound and a mammogram. Endoscopic studies of the upper and lower gastrointestinal tract may be indicated according to the age of the

patient.^{54,55,65} Finally, nasopharyngeal cancer is quite common in Asian patients residing in southeast Asia, therefore a careful evaluation of the nose and throat would be recommended.^{64,73}

Although many isolated cases of cancer associated to amyopathic dermatomyositis have been described, there is no population data that confirms the increase in the risk of cancer in this subtype of dermatomyositis.³² However, it is recommended that a vigilant attitude is taken with respect to the possibility of an associated neoplasia.

In between 26% and 70% of cases, the development of neoplasia occurs in the first year since the diagnosis of myositis. This reflects that a meticulous search for neoplasia must be performed especially during this period of time. However, several studies have shown that the risk is higher during the first 3 years, but remains high 5 years after the diagnosis of myositis. This late risk for neoplasia should not be attributed to a long term effect of immunosuppressive therapy. In any case, it is recommended that the clinician who cares for patients with dermatomyositis performs a meticulous annual search for neoplasia during the first 3 or 4 years after the onset of myositis.^{50,51}

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