

NOVELTIES IN DERMATOLOGY

New Antibodies in Dermatomyositis

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Abstract. Dermatomyositis is an idiopathic inflammatory myopathy that affects skeletal muscle and the skin. Idiopathic inflammatory myopathies are characterized by the production of autoantibodies directed against different cell structures. Some of these autoantibodies are specific to idiopathic inflammatory myopathies (myositis-specific antibodies) whereas others are found in a range of overlap syndromes (myositis-associated antibodies). Although they are all associated with certain clinical and physiopathological characteristics of myositis, myositis-specific antibodies are essentially the most useful markers for clinical diagnosis, classification, and prognosis in idiopathic inflammatory myopathies. In recent years, two new myositis-specific antibodies—in clinically amyopathic dermatomyositis (CADM), CADM-140 and, in cancer-associated dermatomyositis, anti-p155/p140—have been identified. This is of great importance as no myositis-specific antibodies had previously been detected in these clinical subgroups. The identification of target antigens that are recognized by these antibodies is essential for a better understanding of the pathogenesis of these diseases.

Key words: idiopathic inflammatory myopathy, polymyositis, amyopathic dermatomyositis, cancer-associated dermatomyositis, myositis-specific antibodies.

NUEVOS AUTOANTICUERPOS EN LA DERMATOMIOSITIS

Resumen. La dermatomiositis es un tipo de miopatía inflamatoria idiopática que afecta al músculo esquelético y a la piel. Las miopatías inflamatorias idiopáticas se caracterizan por la producción de autoanticuerpos que se dirigen frente a diversas estructuras de la célula. Algunos de estos autoanticuerpos resultan específicos de las miopatías inflamatorias idiopáticas (anticuerpos específicos de miositis), mientras que otros se encuentran en diversos síndromes de solapamiento (anticuerpos asociados a miositis). Todos ellos determinan ciertas características clínicas y patofisiológicas de miositis, pero son principalmente los anticuerpos específicos de miositis los que constituyen marcadores muy útiles para el diagnóstico clínico, la clasificación y la predicción del pronóstico en las miopatías inflamatorias idiopáticas. En los últimos años se han identificado dos nuevos anticuerpos específicos de miositis, el anti-CADM-140 en la dermatomiositis amiopática y el anti-p155 y anti-p155/p140 en la dermatomiositis asociada a cáncer. Ello tiene una gran trascendencia ya que en estos subgrupos clínicos no se detectaban anticuerpos específicos de miositis. La identificación de los antígenos diana que reconocen estos anticuerpos resultará fundamental para comprender mejor la etiopatogenia de estas enfermedades.

Palabras clave: miopatía inflamatoria idiopática, polimiositis, dermatomiositis amiopática, dermatomiositis asociada a cáncer, anticuerpos específicos de miositis.

Dermatomyositis is an inflammatory disease that affects both muscle and skin. It is a member of the group of idiopathic inflammatory myopathies (idiopathic myositis), which are a heterogeneous group of muscle diseases of

unknown origin that are characterized by progressive muscle weakness and inflammation.¹

Several classifications have been proposed in an attempt to order these processes. One is a clinical classification, which distinguishes between specific groups of inflammatory myopathies that differ in terms of clinical symptoms, microscopic appearance, prognosis, and, probably, pathogenesis (Table 1).² In addition to the entities proposed by Bohan and Peter in 1975,³ the more recent of these classifications include other myopathies that were not described until later, such as inclusion-body myositis, and clinical conditions that, although they have been recog-

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nized for some time by dermatologists, were not incorporated into these classifications until just a few years ago. Such is the case of amyopathic dermatomyositis, or dermatomyositis sine myositis, an extremely interesting diagnosis for clinicians, given its impact on prognosis and therapy.

A second classification is based on the presence of antibodies, most of which are directed against enzymes that participate in protein synthesis.^{4,5} These antibodies seem to be found in groups of patients with homogeneous clinical, epidemiologic, and prognostic characteristics, especially those associated with myositis-specific antibodies (Table 2). Their sensitivity is low, with the result that their absence does not rule out a diagnosis of inflammatory myopathy; however, their presence does have a high predictive value. The most important myositis-specific antibodies are antisynthetase antibodies (antiaminoacyl-tRNA synthetase), which target cytoplasmic enzymes that catalyze covalent bonding of amino acids with their transfer RNA (tRNA). The most common is antihistidyl-tRNA or anti-Jo1.⁶ Apart from the 6 classic antisynthetase antibodies, there are 2 additional antibodies—anti-Zo (phenylalanyl-tRNA synthetase) and anti-YRS (tyrosyl-tRNA synthetase)—that were recently identified in the serum of 2 separate patients.^{7,8} With few exceptions, patients present only 1 of these antisynthetase antibodies, and the clinical manifestations are broadly similar in all of them. The presence of myositis, interstitial lung disease, arthritis, Raynaud phenomenon, and mechanic's hands is characteristic. Hence the term antisynthetase syndrome, which was coined to refer to patients with these symptoms.⁹ The real interest in antisynthetase antibodies lies in their ability to predict interstitial lung disease in patients with myositis and vice versa, namely, the late onset of myositis in patients whose first manifestation is interstitial lung disease.¹⁰

The clinical changes that define mechanic's hands are thickening, hyperkeratosis, and fissures on the margins and palms of the hands.^{11,12} However, these cutaneous changes were later described alongside lesions that are typical of classic dermatomyositis in patients with polymyositis or in overlap syndromes, such as scleromyositis.¹⁴ Therefore, mechanic's hands are currently considered a cutaneous marker of myositis irrespective of the associated antibody or myopathy.

Two other well-known myositis-specific antibodies are anti-Mi-2 and the anti-signal recognition particle (anti-SRP). Anti-Mi-2 is associated with both juvenile and adult dermatomyositis. It indicates a low risk of interstitial lung disease and a relatively good prognosis.¹⁵ This antibody recognizes 2 antigens, Mi-2 α (240 kDa) and Mi-2 β (218 kDa). These antigens are presumed to belong to the same family of proteins, the nuclear helicases, which have a transcription-regulating function.¹⁶⁻¹⁸ According to a recent report,¹⁹ in the near future, clinical differences could

Table 1. Clinical Classification of the Idiopathic Inflammatory Myopathies

Polymyositis
Dermatomyositis
Dermatomyositis sine myositis
Childhood dermatomyositis and polymyositis
Inclusion-body myopathy
Myositis associated with cancer
Myositis associated with connective tissue disease
Eosinophilic myositis
Granulomatous myositis
Focal or nodular myositis
Ocular or orbital myositis

be identified between patients with different degrees of reactivity to the 2 Mi-2 molecules or specific fragments of these molecules. SRP is a protein-RNA cytoplasmic complex consisting of the 7SL RNA molecule and 6 polypeptides (72, 68, 54, 19, 14, and 9 kDa). This complex mediates translocation of polypeptides across the endoplasmic reticulum. Patients who develop antibodies against this particle usually present an acute-onset myositis that is generally refractory to standard treatment with corticosteroids and involves frequent exacerbations, myocardial disease, and dysphagia.^{20,21} Microscopy reveals that muscle fiber necrosis predominates in this myositis, with almost no inflammatory infiltrates.²² Therefore, anti-SRP may be the marker of a necrotizing myopathy syndrome that is different from classic polymyositis, which, while not responding to conventional corticosteroids, does respond to other treatments such as rituximab, an anti-CD20 monoclonal antibody.²³

New myositis-specific autoantibodies have recently been described, and these seem to be associated with clinical conditions that are particularly interesting for the dermatologist (eg, amyopathic dermatomyositis and dermatomyositis associated with cancer).

Amyopathic Dermatomyositis

A small percentage of patients (2%-18%) are affected by a rash that cannot be distinguished from classic dermatomyositis, but in which muscle disease is minimal or absent. The condition affecting this group is known as dermatomyositis sine myositis or amyopathic dermatomyositis or, as recently proposed by Sontheimer et al,²⁴ clinically amyopathic dermatomyositis. This condition is both inter-

Table 2. Antibodies in Idiopathic Myositis and Clinical and Prognostic Characteristics of Associated Inflammatory Myopathy

<i>Antibody</i>	<i>Antigen</i>	<i>Patients With Antibodies, %</i>	<i>Characteristics of the Antigens</i>	<i>Associated Clinical Syndrome</i>	<i>Outcome and Prognosis</i>
Myositis-Related Antibodies					
Antisynthetases	Histidyl-tRNA synthetase	20	Cytoplasmic enzymes that catalyze covalent bonding of amino acids with their tRNA	Acute onset in spring with myositis, arthritis, interstitial lung disease, ever, mechanic's hands, f and Raynaud phenomenon	Moderate response to treatment and recurrences. Five-year survival of 65% (due to respiratory failure and cor pulmonale)
Anti-PL-7	Threonyl-tRNA synthetase	5-10			
Anti-PL-12	Alanyl-tRNA synthetase	< 5			
Anti-OJ	Isoleucyl-tRNA synthetase	< 5			
Anti-EJ	Glycyl-tRNA synthetase	5-10			
Anti-KS	Asparaginyl-tRNA synthetase	< 5			
Anti-Zo	Phenylalanyl-tRNA synthetase	< 1			
Anti-YRS	Tyrosyl-tRNA synthetase	< 1			
Anti-Signal recognition particle	Signal recognition particle	5	Cytoplasmic complex that mediates translocation of polypeptides through the endoplasmic reticulum	Very acute and severe onset in autumn, with severe muscle involvement, myocardial involvement, and dysphagia. Necrotizing myopathy	Poor response to treatment. Five-year survival of 25% to 30% (due to cardiac involvement)
Anti-Mi-2	Nuclear helicase (218/240 kDa)	5-10	Nuclear helicase that regulates transcription	Acute and mild onset with classic cutaneous lesions	Good response to treatment. Five-year survival of 95%
Anti-CADM-140	Unknown (140-kDa protein)	50 in ADM	Unknown	ADM-specific	
Anti-p155 (p140)	TIF1- γ	20 in DM		DM, especially DM associated with cancer	
Anti-MJ	Unknown (140-kDa protein)	< 5		Juvenile DM	
Anti-PMS1	DNA repair enzyme	< 5			
Myositis-Related Antibodies					
Anti-U1RNP	Nuclear U1RNP	10		Myositis overlap syndrome, mixed connective tissue disease	
Anti-Ku	DNA-PK regulatory subunit (70/80 kDa)	20-30		Polymyositis-scleroderma overlap syndrome in Japanese patients	
Anti-PM-Scl	11-16-protein nucleolar complex	8-10		Polymyositis-scleroderma overlap syndrome in white patients	

Adapted from Mimori T et al.⁵Abbreviations: ADM, amyopathic dermatomyositis; DM, dermatomyositis; DNA-PK, DNA-dependent protein kinase; TIF1- γ , transcriptional intermediary factor 1- γ

esting and controversial, since the criteria for its diagnosis remain undefined. In addition, we do not know whether the patient is at the same risk as in classic dermatomyositis of developing severe complications such as malignant neoplasms or interstitial lung disease, and there is no consensus on the most suitable treatment.

As far as diagnosis is concerned, there are no differences in symptoms or microscopic appearance of skin lesions between amyopathic dermatomyositis and classic dermatomyositis. Furthermore, skin lesions precede muscle involvement by between 3 and 6 months in more than 50% of patients with classic dermatomyositis.²⁵ If muscle

disease develops during the first two years after onset of the rash, then it must be considered the usual course of classic dermatomyositis. If the condition remains restricted to the skin after this initial period, it can be described as dermatomyositis sine myositis.^{26,27}

Defining the absence of muscle disease is somewhat more controversial, as is the extent to which the muscle should be explored in order to determine whether or not there is involvement. Patients with dermatomyositis skin lesions and no symptoms of muscle weakness and creatine kinase levels within the normal range could have abnormal findings in the electromyogram, magnetic resonance image, and muscle biopsy, suggesting the existence of a clinically silent myositis.^{28,29} However, a recent systematic review of the literature²⁴ showed that these findings cannot predict subsequent onset of frank muscle disease and, therefore, their presence does not necessarily imply a change in treatment. Indeed, one might argue that, beyond a clinical search for muscle disease and determination of creatine kinase levels, additional muscle examinations would be unnecessary when deciding on the treatment to prescribe in the absence of muscle weakness. Notwithstanding, it is true that the onset of muscle disease is often heralded by increased creatine kinase levels, thus stressing the interest in periodic testing for this muscle enzyme in patients with clinically amyopathic dermatomyositis, especially during the early phase.

Therefore, given the difficulty in defining amyopathic dermatomyositis in clinical terms, characterization of a serum marker enabling these patients to be identified would be of enormous clinical and prognostic interest. Patients with clinically amyopathic dermatomyositis (but not those with classic dermatomyositis) have been shown to harbor antibodies targeting new autoantigens that could act as such a marker. The most relevant of these is anti-CADM-140, which targets a 140-kDa cytoplasmic antigen and is associated, at least in the Japanese population, with amyopathic dermatomyositis and, in this setting, with rapidly progressive lung disease.³⁰ The literature review mentioned above²⁴ showed that up to 15% of patients with clinically amyopathic dermatomyositis can develop interstitial lung disease with a mortality of almost 40%. Until anti-CADM-140 was identified, these patients were observed not to harbor any classic myositis-specific antibodies such as anti-Jo-1, unlike patients with classic dermatomyositis associated with lung disease. Perhaps future studies will be able to characterize new antibodies, such as anti-CADM-140, that can identify patients with amyopathic dermatomyositis associated—or not—with lung disease.

In 1991, Euwer and Sontheimer³¹ suggested that adopting a more aggressive approach—understood as that applied in classic dermatomyositis—when treating cutaneous disease could prevent subsequent development of

muscle inflammation. Nevertheless, the subsequent publication of several series in which patients diagnosed with amyopathic dermatomyositis did not develop muscle disease despite not receiving immunosuppressive agents^{29,32,33} suggests that oral corticosteroids or another immunosuppressive agent should only be administered in the presence of frank muscle disease.

Dermatomyositis Associated With Cancer

Another interesting aspect of some of the new antibodies identified in dermatomyositis is the greater risk of cancer. The link between the two was first posited in 1916, although it was difficult to confirm this association in the first epidemiologic studies because of various clinical and methodologic hurdles, including the difficulty in diagnosing myositis (especially in differentiating between dermatomyositis and polymyositis), case reference bias, small study samples, short follow-up, and absence of suitable control groups.³⁴⁻⁴¹ More recent, well-designed cohort studies, on the other hand, have demonstrated a significant association between myositis and cancer, and the risk of such an association is greater in dermatomyositis than in polymyositis.

One of these studies was published by an Australian group in 2001 and included 537 patients, all of whom had biopsy-proven inflammatory myopathy.⁴² The standardized incidence ratio obtained in the group of patients with dermatomyositis was 6.2, which indicates that the risk of cancer is 6 times greater in these patients than in the general population. The risk was also observed to be 2.4 times greater in patients with dermatomyositis than in those with polymyositis.

In a large group of patients with dermatomyositis and polymyositis, Hill et al⁴³ demonstrated that both conditions were associated with a greater risk of cancer, although this risk was greater in patients with dermatomyositis.

The association between dermatomyositis and cancer, therefore, seems clear. However, the most suitable strategy for identifying cancer associated with dermatomyositis remains undefined. Three key questions do not yet have a clear answer: First, are there any predictors or markers of cancer in adult dermatomyositis? Second, should a cancer workup be limited to a few examinations, or should it be complete and exhaustive? And, third, how long should the patient be followed if cancer is not found at the first examination?

The first question is one of the most important for physicians, since identification of specific clinical findings or biologic parameters that could act as tumor markers would clearly make it possible to carry out a selective and thorough study of the tumor only in those patients

who were carriers of these markers. Regrettably, few clinical alterations enable us to suspect the presence of cancer. The first factor to be taken into consideration is age. We know that the frequency of cancer in patients with dermatomyositis increases with age,^{34,44-48} and that the presence of cancer is exceptional in childhood dermatomyositis.⁴⁹ However, the risk of cancer has been shown to be increased even in dermatomyositis patients aged under 45 years. Therefore, age should not deter the physician from carrying out a thorough search for cancer.

Several publications in the French-language medical literature⁵⁰⁻⁵² reveal the interest in observing necrotic lesions on the skin of patients with dermatomyositis, since they could be a tumor marker. In one of these studies, the predictive value of the association between skin necrosis and cancer was 70%.⁵² This clinical parameter is easily evaluated by the dermatologist, and it could probably justify an exhaustive cancer workup.

Finally, the presence of interstitial lung disease alone or with antisynthetase antibodies is negatively associated with the risk of cancer.^{4,53,54}

With regard to biologic parameters, a distinction can be made between some routine laboratory tests, tumor markers, and autoantibodies. Patients with dermatomyositis and cancer more commonly have normal creatine kinase levels⁵⁵⁻⁵⁷—although some authors have reported the opposite^{58,59}—and an increased erythrocyte sedimentation rate.⁵⁸

It is well known that a battery of tumor markers can provide useful information before an exhaustive cancer workup is undertaken. The markers CA125 and CA19-9 could be of special interest in patients with myositis, since Amoura et al⁵⁴ reported that high serum titers of these markers, as well as increasing CA125 levels in serial determinations, were associated with a greater risk of developing not only ovarian cancer, but also other types of cancer.

As for serology, no myositis-specific antibodies had been identified as a marker of malignancy until very recently. Moreover, there had been reports in the literature that the presence of myositis-specific antibodies reduced the likelihood of cancer.^{4,60} Nevertheless, in recent years, new specific antibodies have been identified in patients with dermatomyositis,^{30,61} and some of these seem to be associated with cancer. One such antibody is anti-p155. According to Targoff et al,⁶² anti-p155 was present in 75% of cases of myositis and cancer, and cancer developed in 37.5% of patients with dermatomyositis who were positive for anti-p155. The target antigen of this antibody is transcriptional intermediary factor 1- γ (TIF1- γ).⁶³ Almost simultaneously, other authors reported a similar antibody, which reacts not only with a 155-kDa protein, but also with a 140-kDa protein.^{64,65} This double precipitation

band had already been mentioned in the study by Targoff et al⁶²; therefore, it is probably the same antibody. In any case, this antibody was identified as dermatomyositis-specific by both groups,^{64,65} and it correlates well with the presence of cancer and absence of lung disease. Thus, positivity for anti-p155/140 has a high specificity (96%), moderate sensitivity (50%), and high negative predictive value (97%) for dermatomyositis associated with cancer. Moreover, the presence of this antibody together with a negative myositis-specific antibody panel result increases sensitivity (94%) and negative predictive value (99%).⁶⁵ The clinical application of all these results clearly requires confirmation by broad studies with a prospective follow-up, although the way has been paved for serum markers of dermatomyositis associated with cancer.

As for the second question posed, let us say that the approach to a cancer workup in a patient with dermatomyositis continues to be a matter of debate. First, we must recognize that a variety of cancers can occur (the most common involve the ovaries, lung, gastrointestinal tract, pancreas, and breast) and that most are occult.⁴³ From a clinical viewpoint, it seems reasonable to advise the asymptomatic patient of the need to screen for disorders whose early detection and treatment lead to a better outcome. Second, the presence of a neoplasm is an indicator of poor prognosis in the context of dermatomyositis.

There have traditionally been 2 opposing approaches to the number and type of workup that should be performed when screening for cancer in patients with this disease. One limits the investigation to an exhaustive history, a detailed physical examination, routine laboratory tests, and complementary tests depending on the signs and symptoms revealed by the clinical history. The other approach includes both these examinations and a wide range of imaging tests such as thoracoabdominal computed tomography (CT), gastrointestinal endoscopy, and mammography, as well as bone marrow biopsy and serum immunoelectrophoresis.^{58,66} However, these recommendations probably cannot be considered definitive, rather they may vary in time as new medical knowledge is gained and more sensitive and patient-friendly examination techniques are developed. Positron emission tomography could play a role here.

According to Hill et al,⁴³ today it seems reasonable that a white male patient with dermatomyositis should undergo both a thorough clinical examination and routine analysis and determination of tumor markers, as well as determination of blood in feces and a CT scan of the chest and abdomen. Women should also undergo CT, pelvic ultrasound, and mammography. Endoscopy of the upper and lower intestinal tract could also be indicated depending on the patient's age.^{46,47,58} Finally, cancer of the nasopharynx is very common in patients living in Southeast

Asia; therefore, they should undergo a careful examination of this area.^{57,66}

Although isolated cases of cancer associated with amyopathic dermatomyositis have been reported, there are no population data to confirm the increased risk of cancer in this subtype of dermatomyositis.²⁴ Nevertheless, the possibility of an associated neoplasm should always be monitored.

Between 26% and 70% of cases develop cancer during the first year after the diagnosis of myositis, thus confirming the need for exhaustive screening during this period. However, several studies have shown that the risk is higher during the first 3 years, and that it continues to be high 5 years after the diagnosis of myositis. The possibility that this late risk of cancer is due to a long-term effect of immunosuppressive therapy cannot be ruled out. In any case, physicians caring for patients with dermatomyositis should perform thorough annual screening for cancer for the first 3 or 4 years after the onset of myositis.^{42,43}

Conflict of Interest

The authors declare no conflicts of interest.

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