

AUTOANTIBODIES IN ADULT PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES IN BUENOS AIRES

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Abstract The idiopathic inflammatory myopathies(IIM) are a heterogeneous group of diseases of the skeletal muscle. On the basis of clinical, serologic and histological differences, they are classified in dermatomyositis (DM), polymyositis (PM), inclusion body myositis and immunomediated necrotizing myopathy. Autoantibodies directed against nuclear and cytoplasmic antigens are present with variable frequencies among studies. Myositis-specific antibodies (MSAs) are useful in IIM because they contribute to the diagnosis, help to identify different clinical subsets, and have prognostic value. This study aimed to explore the frequency of autoantibodies, especially MSAs, and their relationship with clinical features in adult patients with DM, PM and overlap syndrome. Medical records were reviewed. Myositis-associated antibodies (non-specific) and MSAs (anti Jo-1, PL-7, PL-12, Mi-2 and SRP) were measured using commercial kits. Twelve patients had MSAs, an overall frequency similar to those of international series, but PL-12 and Mi-2 were more frequent than Jo-1, which is the most frequently observed elsewhere. All five patients with Mi-2 had classical DM with a favorable response to treatment. Interstitial pneumonia (n: 4) and/or treatment-refractory disease (n: 3) were found in the presence of anti-PL-12, alone or associated with anti-SRP and/or Jo-1. In conclusion, the coexistence of AEM, a rare finding, was found in three patients. The presence of MSAs aided to the diagnosis of IIM, in particular in those patients without available or conclusive biopsy results.

Key words: autoimmune myositis, polymyositis, dermatomyositis, autoantibodies

Resumen *Autoanticuerpos en pacientes adultos con miopatía inflamatoria idiopática en Buenos Aires.*

Las miopatías inflamatorias idiopáticas (MII) comprenden un grupo heterogéneo de enfermedades adquiridas del músculo esquelético. Según sus características clínicas, serológicas e histológicas se las clasifica en dermatomiositis (DM), polimiositis (PM), miopatía necrotizante autoinmune y miositis por cuerpos de inclusión. Los anticuerpos específicos de miositis (AEMs) contribuyen al diagnóstico, permiten distinguir formas clínicas y tienen valor pronóstico. Con el objetivo de explorar la frecuencia de autoanticuerpos, en particular AEMs, y su relación con las características clínicas de las MII del adulto, se revisaron las historias clínicas de 25 pacientes con DM, PM y síndromes de superposición, asistidos en nuestro centro entre 1999 y 2013. La presencia de autoanticuerpos asociados a miositis (no específicos) y AEMs (anti Jo-1, PL-7, PL-12, Mi-2, SRP) se investigó utilizando kits comerciales. Doce pacientes presentaron AEMs, frecuencia global similar a la encontrada en series internacionales, pero a diferencia de lo observado en otros países, anti-PL-12 y anti-Mi-2 fueron más frecuentes que anti-Jo-1. Los cinco pacientes con anti-Mi-2 tuvieron DM clásica y buena evolución clínica. Anti-PL-12, ya sea solo o asociado a anti-SRP y/o anti-Jo-1, estuvo presente en pacientes con neumonía intersticial (n:4) y/o enfermedad refractaria al tratamiento (n: 3). En conclusión, la coexistencia de AEM, hallazgo raro, se encontró en tres pacientes. La presencia de AEMs contribuyó al diagnóstico de MII, en particular en aquellos casos sin resultados concluyentes de biopsia de músculo.

Palabras clave: miositis, polimiositis, dermatomiositis, autoanticuerpos

The idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous diseases of the skeletal muscle of unknown cause and low prevalence (0.5-9.3 cases per million) with geographic and ethnic variations^{1,2}. IIMs are

classified in four distinct subtypes with clinical, serologic and histological differences: dermatomyositis (DM), polymyositis (PM), inclusion body myositis and immunomediated necrotizing myopathy³.

Autoantibodies directed against nuclear and cytoplasmic antigens are present in 60% and 80% of patients with PM and DM, respectively, and their presence is related to clinical features⁴⁻⁹. Autoantibodies are classified into myositis-specific antibodies (MSAs) like anti-synthetase

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antibodies, anti-Mi-2 and anti-SRP which are only found in IIMs, and myositis-associated antibodies (MAAs), which are also described in other connective tissue diseases^{10,11}. Reportedly, anti-Jo-1, one of the anti-synthetase antibodies, is the most prevalent and is present in 11%-33% of patients with PM or DM. Other anti-synthetase antibodies –like anti-PL-12, anti-PL-7, anti-OJ, anti-EJ– are detected in less than 3% of patients with IIM¹². Myositis-specific antibodies (MSAs) are useful tools in patients with IIMs due to their contribution to the diagnosis, as well as their significant prognostic value.

In Argentina, Espada et al.¹³ described in 2009 the frequency of MSAs in a pediatric population. To our knowledge, there is no data about the prevalence of MSAs in adults with IIMs. The purpose of this study was to explore the frequency of myositis-specific antibodies and myositis-associated antibodies and their relationship with clinical features in adult patients with idiopathic inflammatory myopathies.

Materials and Methods

The study included patients older than 18 years with DM, PM, and overlap myositis (overlap with rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis), who had been diagnosed by a rheumatologist, based on Bohan and Peter's criteria, between June 2000 and December 2013¹⁴. There were no patients with inclusion body myositis. The study was approved by the Institutional Review Board. Whenever possible, the patients gave their written informed consent to use their medical records. Patients' medical records were retrospectively analyzed and the following data were collected: demographics, date of diagnosis, disease duration since diagnosis, type of inflammatory myopathy, presence of overlap syndrome, association with malignancy, Raynaud's phenomenon, cardiac or respiratory compromise, presence of characteristic DM lesions, such as a heliotrope rash, Gottron's papules, shawl (or V) sign, mechanic's hands, electromyographic findings if an electromyography had been performed, treatment with steroids glucocorticoids, azathioprine, methotrexate, mycophenolate, intravenous immunoglobulin, or rituximab. Ethnicity was defined according to GLADEL criteria¹⁵. Antisynthetase syndrome refers to a clinical entity characterized by the presence of antisynthetase antibodies, interstitial lung disease, non-erosive arthritis, fever, Raynaud's phenomenon and characteristic hyperkeratotic lesions along the radial and palmar aspects of the fingers known as mechanic's hands⁵. Clinical remission was defined as recovered muscle strength, absence or regression of skin lesions characteristic of the disease, and normal muscle enzymes, without requiring glucocorticoids or requiring less than 5 mg of prednisone per day. Refractory myositis was defined by the intolerance or an inadequate response (no remission) to glucocorticoids and at least one other immunosuppressor or immunomodulatory agent¹⁶. Muscle biopsy stained with hematoxylin and eosin and modified Gomori trichrome was performed in the majority of biopsy specimens, while periodic acid Schiff-PAS and Congo red were applied if necessary.

MSAs and MAAs were measured in samples from the serum bank of the Immunology Unit of *Instituto de Investigaciones Médicas Alfredo Lanari*. The bank contains samples collected to perform routine analyses at the time of diagnosis

from adult patients with IIM who had not been under treatment at the time of the blood specimen collection. In the case of this study, the samples had been kept at -80 °C. MAAs such as anti-Ro, anti-La, anti-ribosomal-P, anti-RNP, anti-Sm, anti-centromere and anti-topoisomerase 1 were measured by a commercial line immunoblot assay (INNO-LIA ANA update 28662 v1). Antinuclear antibodies (ANA) were measured by indirect immunofluorescence (Kallestad HEP-2 Cell line slide, Bio-Rad Laboratory). MSAs were assessed by a commercial kit approved by ANMAT- (*Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*) (Myositis plus ORG 760, Orgentec Diagnostika GmbH), a membrane based enzyme immunoassay for the measurement of IgG class autoantibodies to Mi-2, Jo-1, PM-Scl-100, PL-7, PL-12, Ku (p70/80), and SRP. Manufacturers reported a normal range established with samples from healthy blood donors: 70.7% sensitivity, 93.9% specificity, 86.1% overall agreement, and an acceptable precision measured by intra-assay and inter-assay coefficients of variation. These latter commercial kits only determine the presence of autoantibodies in a qualitative way.

Results

All 25 patients fulfilled the Bohan and Peter classification for definite or probable DM or PM. Mean age was 47 years (SD ± 15); 20 were women and median disease duration since diagnosis was 7.4 years (IQR 0.5-34). Fourteen patients were *Mestizos*, 10 were Caucasian, and no information on ethnicity was retrieved from one patient. Twenty-three patients had proximal muscle weakness and 12 of these 23 had neck muscle weakness and swallowing disturbances. One female patient had involvement of respiratory muscles requiring non-invasive mechanical ventilation.

Fig. 1 shows distribution of cases according to availability and results of muscle biopsy. Two patients with probable DM had associated neoplasia located in ovary and colon, respectively.

Lesions compatible with immune-mediated necrotizing myopathy were present in the biopsy of a female patient. The patient had neither been administered statins nor had anti-SRP antibodies in serum; furthermore she had not been diagnosed with a malignancy. The biopsy showed necrotizing changes with minimal inflammatory infiltrate by hematoxylin and eosin stain but immunohistochemistry was not performed to confirm the presumption of immune-mediated necrotizing myopathy.

Twelve of these 25 patients had positive MSAs. Only two patients had more than one MSA determination, with the same result pre-and post-treatment in both cases. Table 1 summarizes clinical, laboratory, and demographic features in patients with and without detectable circulating MSAs. Seven of the 12 patients with MSAs had positive antisynthetase antibodies, anti-PL-12 (n = 6) being the most frequent. Frequencies of MSAs in patients with DM, PM and overlap syndrome are shown in Table 2. The second most frequent antibody in our series was anti-Mi-2 (n: 5) and all five patients had classical DM. Three

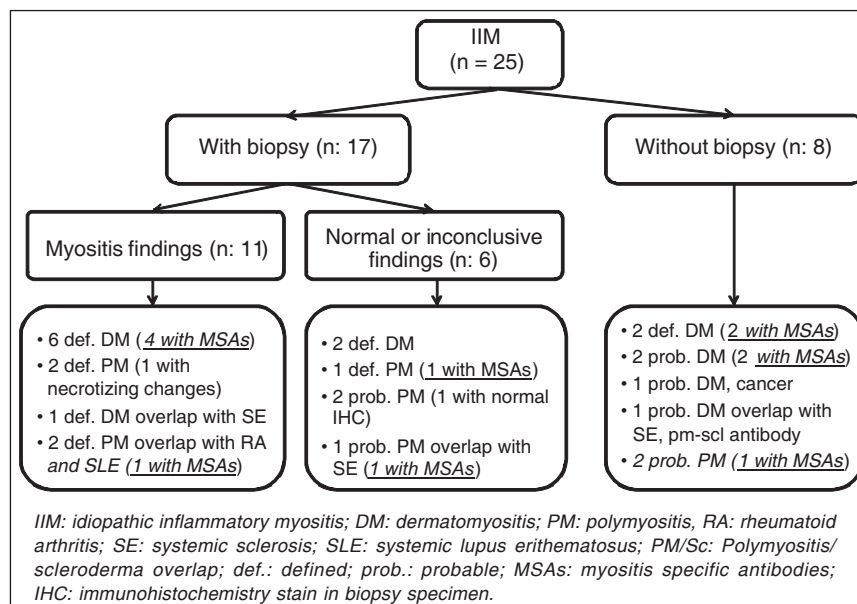


Fig. 1.– Features of 25 patients with idiopathic inflammatory myositis according to biopsies done or not done.

TABLE 1.– Clinical, laboratory and demographic features of patients with and without detectable myositis specific antibodies

	MSAs present (n = 12)	MSAs absent (n = 13)
PM	2	5
DM	8	5
Overlap syndrome	2	3
Median disease duration, yrs (range)	5 (1-23)	5 (0.5-26)
Median age, yrs (range)	37 (20-71)	65 (32-78)
Caucasian	4	6
Mestizo	8	6*
Positive ANAs	6	6
Other MAAs	3	4
Raynaud's phenomenon	6	4
Interstitial lung disease	4	1
Cardiac involvement	0	0

*MSAs: Myositis specific antibodies, MAAs: Myositis associated antibodies, PM: polymyositis, DM: dermatomyositis, ANAs: antinuclear antibodies, *unknown ethnicity for 1 patient.*

patients had coexistence of two or three MSAs at the time of diagnosis, and they also had one or more MAA.

Table 3 presents clinical features of the 12 patients with detectable MSAs. Three out of six patients with anti-PL-12 had interstitial lung disease and five out of seven patients with antisynthetase antibodies had symptoms related to the antisynthetase syndrome.

Of three patients with MSA coexistence (identified as 10, 11 and 12 in Table 3), two had refractory disease with elevated muscle enzymes and physical disability,

received long courses of corticosteroids, failed to second line drugs, and finally received anti-CD 20 therapy. Even though these three patients had anti-SRP, none of them had cardiac compromise.

By the time this paper was being finished, two patients had died, one from cancer associated with DM, and the other, an elderly woman with PM, from sepsis.

In the group of the 13 patients without MSAs, one patient had interstitial lung disease (cryptogenic organizing pneumonia-COP), which only remitted upon corticosteroids therapy.

TABLE 2.– Number of patients with myositis specific antibodies (MSAs) detected in patients with idiopathic inflammatory myositis (IIM)

MSA	Any IIM	DM	PM	Overlap syndrome
Mi-2	5	5	0	0
PL-12	4	2	0	2
PL7	0	0	0	0
Jo-1	0	0	0	0
SRP	0	0	0	0
SRP + PL12	1	0	1	0
SRP + PL12 + Jo1	1	0	1	0
SRP + Jo-1	1	1	0	0
Total	12	8	2	2

DM: dermatomyositis, PM: polymyositis

TABLE 3.– Characteristics of the 12 patients with idiopathic inflammatory myopathies and myositis associated antibodies

Patient	MSA	ANA	Other MAAs	Type of IIM	Raynaud	Remission	Lung involvement
1	Mi-2	+	–	DM	–	Yes	No
2	Mi-2	+	–	DM	–	Yes	No
3	Mi-2	+	–	DM	+	Yes	No
4	Mi-2	–	–	DM	–	Yes	No
5	Mi-2	–	–	DM	–	Yes	No
6	PL-12	–	–	Overlap	+	Yes	non-specific IP
7	PL-12	–	–	DM	+	No	No
8	PL-12	–	–	DM	–	Yes	No
9	PL-12	+	a-DNA	Overlap	+	Yes	usual IP
10	PL-12, SRP	+	Ro, La	PM	+	No	usual IP
11	PL-12, SRP, Jo-1	+	Ro, FR	PM	–	No	No
12	Jo-1, SRP	+	Rnp, Ro, FR	DM	+	MD	non-specific IP

MSA: myositis specific antibodies, MAA: myositis associated antibodies, PM: polymyositis DM: dermatomyositis, Overlap: overlap syndrome, IP: interstitial pneumonia, MD: missing data

Discussion

To our knowledge, this is the first series describing MSAs in adult patients with IIMs in Argentina. The sole antecedent to our work is a work reporting the presence of Jo-1 antibodies in a woman with PM and subluxing arthropathy with apatite deposition¹⁷. The finding of MSAs in near half of the patients in our series is in line with overall frequencies reported elsewhere^{9, 18}.

Most studies worldwide agree in pointing to anti-Jo-1 as the most common antisynthetase antibody found in IIMs. Authors from the Mayo Clinic reported that 20% of the patients with PM and DM had anti-Jo-1, 5% anti-PL-7 and anti-PL-12, 5-10% had anti-SRP, and less than 10% had anti-Mi-2¹⁹. Similar findings were published by Cruellas et

al. in 222 patients from San Paulo, Brazil, where 19% had anti-Jo-1, 8% had anti-Mi-2, 3% had anti-SRP and anti-PL-7, and 2.7% had anti-PL-12 antibodies, without differences between PM and DM patients²⁰. Instead, in an Italian series anti-Jo-1 was present in only 10% of IIM patients²¹.

In our study, only two patients were anti-Jo-1 positive, while the MSA most frequently found was anti-PL-12. Four of our six patients with anti-PL-12 developed interstitial lung disease and/or clinical features of the anti-synthetase syndrome. Our results are in line with results reported by Kalluri's et al., who found the presence of anti-PL-12 antibody to be strongly associated with interstitial lung disease and clinical features of the anti-synthetase syndrome²².

In our series, the second most frequent MSA was anti-Mi-2 and, in line with other studies, it was found to be pre-

sent in patients with DM with a monocyclic disease course whose condition improved upon treatment with first line drugs¹⁸. In a juvenile idiopathic myositis cohort, Lisa Rider found that anti-Mi-2 subgroup patients were Hispanic²³. Association between immunogenetic profiles and ethnicity has also been proposed by other authors but still remains a controversial issue²⁴. Our results did not endorse such association, as we found MSAs similarly distributed between ethnic groups. Differences in results among studies can be attributed to lack of universal agreement in the definition of ethnic groups and differential accuracy of the laboratory assays applied, among other factors.

Anti-SRP antibodies have been associated with myositis of acute disease onset, dysphagia, myocardial involvement and necrosis in muscle biopsies²⁶. None of three patients with anti-SRP antibodies in our series had myocardial disease or acute disease onset, and necrotizing changes were absent in the only patient positive for anti-SRP who had a muscle biopsy performed. Two of the three patients had, however, a severe disease course with frequent clinical exacerbations that responded to rituximab, as described by Basnayake et al. in an Australian cohort with variable degrees of necrotizing myopathy, clinical heterogeneity and refractory disease²⁷.

Allegedly, MSAs are mutually exclusive²⁸. Recent studies, however, have established that, although rare, their coexistence is possible. A meta-analysis including 3487 patients found four cases of MSAs associations and a Japanese study including 166 patients with the anti-synthetase syndrome described anti-PL-7 coexisting with anti-PL-12 in one patient^{29, 30}. Other two studies described the rare coexistence of anti-Jo-1 and anti-SRP antibodies in patients with a severe disease course^{31, 32}. In as many as three patients of our series, two or three MSAs were found to coexist at the time of diagnosis, together with more than one MAA. In all three patients, anti-SRP and at least one anti-synthetase antibody were detected, in the presence of a severe disease course and/or lung involvement. Although the number of cases is small and we did not corroborate the findings by a second antibody detection system, in our series, the coexistence of MSAs at diagnosis was associated with severe disease, as previously reported.

This retrospective series has several limiting factors. First, the small number of patients, which is explained by the low-prevalence of the condition under analysis, and the fact that the study was performed in a single institution. Second, the kit used for MSA detection does not identify all the autoantibodies known to be involved in IIM; for example, it does not detect anti-MJ or anti-155/140 antibodies, which were studied in the pediatric series reported from Argentina¹³. A third limitation is that muscle biopsies were available for only 17 cases, and in none of these cases magnetic resonance imaging had aided to optimization of sampling site. This might explain the failure of biopsy

in finding IIM specific lesions for six of the 17 biopsed cases. Moreover, only two muscle biopsies underwent enzymatic histochemical staining and standardized immunohistochemistry.

In conclusion, relative frequencies of MSAs in our series differed from frequencies reported elsewhere. The presence of MSAs was of value for the diagnosis of IIM, in particular in those patients with unavailable or inconclusive biopsy results. Further studies with a larger number of patients are required to assess the role of different MASs in prognosis and to elucidate the relation of their presence with ethnicity in our population.

Conflict of interests: None to declare

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LA TAPA

Robert Hooke (1635-1702). Mucor, 1665

Grabado, Fig. XX, ilustra la Observación XII: “Of the blue Mold, and of the first Principles of Vegetation arising from Putrefaction”. Tomada de: Robert Hooke MICROGRAPHIA: or Some Physiological Descriptions of Minute Bodies Made by Magnifying Glasses with Observations and Inquiries thereupon. By R. HOOKE. Fellow of the ROYAL SOCIETY. LONDON, Printed by Jo. Martyn, and Jo. Allestry, Printers to the ROYAL SOCIETY. M DC LXV. Preface. Copia facsimilar de Dover Ed: New York, 1961, p 124-31.

Considerada la primera ilustración de un microorganismo; Leewoenhoek ilustró bacterias luego, en 1674 (Gest H. The discovery of microorganisms by Robert Hooke and Antoni van Leeuwenhoek, Fellows of The Royal Society. *Notes Rec R Soc Lond* 2004; 58: 187-201. La figura es la de un hongo de la familia de las Mucoráceas que Hooke encontró creciendo en las tapas de un libro cubiertas, al parecer, con piel de oveja. En el texto Hooke describe en detalle la estructura del hongo, los tallos y los globos que “crecen” en sus extremos: A): globos redondos y lisos; B): oblongos, apenas rotos o hendidos; C): volados en pedazos; D): sin mención en el texto [restos]. Las consideraciones sobre las características físicas, funciones, reproducción, etc. del hongo debemos leerlas con la mentalidad de la época. Hooke olió y probó los hongos: repugnantes. La línea inferior es una escala, 1/32 de pulgada.

La mucormicosis en el hombre la describió, posiblemente, Cohnheim en 1865, aunque Paltauf se cita como el primero [*Medicina (B. Aires)* 1963: 13: 102-6]. Una revisión útil: Spellberg B, Edwards J jr., Ashraf I. Novel Perspectives on Mucormycosis: Pathophysiology, Presentation, and Management. *Clin Microbiol Rev* 2005; 18: 556-69. La incidencia de enfermedades producidas por hongos aumenta después de los desastres naturales (Benedict K, Park BJ. Invasive fungal infections after natural disasters. *Emerg Infect Dis* 2014; 20:349-55). A los ornitorrincos de Australia y Tasmania los afecta una forma de mucormicosis cutánea (Platypus Fungal Disease.- Mucormycosis (En: <http://dpipwe.tas.gov.au/wildlife-management/animals-of-tasmania/mammals/echidnas-and-platypus/platypus-platypus-fungal-disease>; consultado el 16/12/2015).