Differences in the pattern of muscular and extramuscular involvement in patients with inflammatory myopathy according to the clinical groups and specific autoantibodies

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To my husband, Iago.

To my parents and sister.

To the memory of my grandparents, Lalo and Lala.

To my mentors.

"Science, my lad, is made up of mistakes,

but they are mistakes which it is useful to make,

because they lead little by little to the truth"

Jules Verne

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ABBREVIATIONS

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A-V blocks	Atrioventricular blocks
APC	Antigen presenting cell
ASyS	Antisynthetase syndrome
AZA	Azathioprine
BAL	Bronchoalveolar lavage
CADM	Clinically amyopathic dermatomyositis
CHD3	Chromodomain Helicase DNA Binding Protein 3
CHD4	Chromodomain Helicase DNA Binding Protein 4
CTL	Cytotoxic T cells
CYA	Cyclosporine
CYC	Cyclophosphamide
DLCO	Diffusing capacity for carbon monoxide
DM	Dermatomyositis
EMG	Electromyography
ENMC	European Neuromuscular Centre
FEV1	Forced expiratory volume in one second
FHLF	Four and a half LIM domain
FVC	Forced vital capacity
HLA	Human leucocyte antigen
HMGCR	3-hydroximethyl-3-methyl-glutaryl CoA reductase
HRM	High resolution manometry
HRCT	High resolution computerized tomography
IBM	Inclusion bodies myositis
IDL	Interstitial lung disease

IL	Interleukin
IM	Inflammatory myopathy
IMNM	Immune-mediated necrotizing myopathy
INF	Interferon
IVIg	Intravenous immunoglobulins
JDM	Juvenile dermatomyositis
MAA	Myositis-associated autoantibody
MAC	Membrane attack complex
MCTD	Mixed connective tissue disease
MDA5	Melanoma Differentiation-Associated protein 5
MHC	Major histocompatibility complex
MMF	Mycophenolate mophetil
MRI	Magnetic resonance image
MSA	Myositis-specific autoantibody
MSG	Muscle Study Group
MTX	Methotrexate
NF-kβ	Nuclear factor-kappa beta
NSIP	Non-specific interstitial pneumonia
NT5C1A	5'-nucleotidase, cytosolic IA
NuRD	Nucleosome Remodeling Deacetylase
OP	Organizing pneumonia
PAH	Pulmonary arterial hypertension
PFT	Pulmonary functional tests
PM	Polymyositis

PDM/SSc	Overlap syndrome between PM/DM and scleroderma
RP	Raynaud´s phenomenon
RTX	Rituximab
SLE	Systemic lupus erythematosus
SnRNPs	Small nuclear ribonucleoproteins
SSc	Scleroderma
SUMO	Small ubiquitin-like modifier activating enzyme heterodimer
STIR	Short tau inversion recovery
tMRI	Thigh magnetic resonance image
TAC	Tacrolimus
TGF- β	Transforming growth factor beta
Th	T helpers
TIF1 γ	Transcriptional intermediary factor 1-gamma
TLC	Total lung capacity
TLRs	Toll –like receptors
TNF	Tumor necrosis factor
Treg	T regulator
UIP	Usual interstitial pneumonia
U1RNP	U1 ribonucleoprotein
UV	Ultraviolet

I. INTRODUCTION

1. Concept, history, and classification of inflammatory myositis

Inflammatory myositis (IM) is a heterogeneous group of diseases primarily characterized by muscle weakness and inflammatory infiltrates on the muscle biopsy. But muscle involvement is not always present and other organs and tissues like the lung, skin, and joints are also commonly affected**.**

Early period:

In 1863[1], Wagner documented the first case of myositis. The patient that he described had both muscle and skin features. In the next thirty years, other authors published similar cases[2-4] naming the syndrome myositis universalis acuta, pseudotrichinosis or polymyositis (PM)[5-8] At the end of the 19th Century, Unverrich coined the term dermatomyositis (DM) to define the specific syndrome combining muscle and skin inflammation[9].

The 20th Century:

Along the early 20th Century, various authors reported several clinical features and conditions highly associated with the IM, like neoplasms (mainly described in DM patients), subcutaneous calcinosis or the typical erythematous lesions covering the knuckles, known as Gottron's papules and considered as a pathognomonic sign of DM[5-7,10].

The first case of DM in children was published in 1940[11]. Thirteen years later, Wedgewood et al. described for the first time the vascular pathology of DM in a case series of 26 children, observing involvement of muscle arteries and arterioles with a proliferation of the internal and media of the small vessels[12]. Later on, Banker and Victor described a series of 8 cases of children between 2.5 years and 7 years and 8 months, with

typical DM skin changes accompanied by anorexia and fatigue as the first symptoms, followed by weakness, muscle pain, and stiffness. Characteristically, these juvenile cases of DM had low-grade fever, muscle contractures, dysphagia and subcutaneous calcinosis, occasionally accompanied by gastrointestinal involvement with abdominal pain, hematemesis, melena and/or ulceration, which frequently lead to intestinal perforation and death. In children, the most striking pathological findings were the inflammation of the blood vessels of the connective tissue of the skin, muscles, gastrointestinal tract, fat and small nerves. Denervation atrophy and infarction of the muscle were also common lesions in juvenile DM (JDM). Moreover, in contrast to adults, no association between childhood form of DM and cancer was found. Due to those differences between DM in children and adults, juvenile and adult DM were differentiated[13].

Attempts to classify the IM:

During the last forty-five years, several authors have developed different classifications for IM. In 1975, Bohan and Peter developed five major criteria to define PM and DM and classifying them into five groups: Group I: Primary idiopathic PM; Group II: Primary idiopathic DM; Group III: DM or PM associated with neoplasia; Group IV: Childhood DM or PM associated with vasculitis; and Group V: PM or DM associated with associated collagen-vascular diseases[14] (Tables 1 and 2).

However, at that time it was observed that some patients presented skin manifestations without muscular disease[15] and Pearson named this entity amyopathic dermatomyositis (ADM)[12]. Later, in 1991, Sontheimer et al. published a case series of 6 patients with cutaneous manifestations but not muscle involvement during the two first years of follow-up[16]. Finally, in 2002, Sontheimer proposed the most widely accepted criteria for ADM so far[17] (Tables 1 and 2).

Simultaneously, experts started to be concerned about a group of PM patients with marked distal weakness that was refractory to immunosuppressant treatment. This disease was first described by Chou et al. in 1968[18] after observing myxovirus-like inclusions in the muscle biopsy of some PM patients. But it was not until 1991 that Dalakas et al. coined the term inclusion body myositis (IBM), defined the diagnostic criteria for IBM and included this entity in the IM classification[19]. In the following years, some diagnostic problems arose for lack of some of IBM-defining features in patients with the disease and thus, in 1995 new IBM criteria based on pathological findings were defined[20] (Tables 1 and 2).

The myositis-specific autoantibodies (MSA) in the IM classification:

The MSA, target cytoplasmic and nuclear proteins. Their specificity is higher than 90%[21] and they are, generally, mutually exclusive[22,23]. It has been suggested that most IM subsets can be defined by a specific MSA with singular clinical features, response to treatment, and prognosis.

The classical MSA are 1) the anti-aminoacyl tARN synthetases (targeting the aminoacyl tRNA synthetases, a family of cytoplasmic proteins), 2, anti-DNA helicase or anti-Mi2 (against the Chromodomain Helicase DNA binding protein 4 [CHD4] and Chromodomain Helicase DNA binding protein 3 [CHD3]) antigens, a component of the NuRD (Nucleosome remodeling deacetylase) complex that participates in transcription regulation), and 3) the anti-signal recognition particle or anti-SRP (against the signal recognition particle, a RNA-protein complex that is in charge of the protein translocation across the endoplasmic reticulum[24-26].

More recently, scientists have discovered novel MSAs. Some of them, target nuclear components like MJ/NXP2 (nuclear matrix protein NXP2), p155/140 (TIF1γ,

transcriptional intermediary factor 1-γ) and SAE or SUMO (Small ubiquitin-like modifier activating enzyme). Others, like MDA5 (CADM-140) and anti-HMGCR (200/100 kDa) target cytoplasmic proteins[27-30].

After observing that the MSA status might be more useful than the clinical groups to evaluate patients with IM, some authors proposed classifying myositis patients based on the MSA[31]. Later on, a modification of the Bohan and Peter´s criteria included the MSA and the MRI imaging[32]. Finally, in 2005, Troyanov et al, suggested using a clinic-serological classification by modifying Bohan and Peter´s criteria by adding the results of the MSA and the myositis-associated autoantibodies (MAA) tests[33] (Table1). MSA and MAA will be discussed in more detail in section 2.

Histopathology and immunopathology in the classification of IM:

In 2003, Dalakas and Hohlfeld observed that markers as CD4, CD8, expressed in the inflammatory cells that infiltrate the muscle, and the major histocompatibility-complex (MHC) class I, expressed on muscle cells, could be used to distinguish PM from DM. Therefore, they proposed classifying myositis patients based on the histopathology and immunopathology as they thought that it would be the best way to separate PM from other myopathies[34] (Table1).

The ENMC:

Since 2003, the European Neuromuscular Centre (ENMC) and Muscle Study Group (MSG) have met on several occasions to reach a consensus on different aspects of IM and its classification. Amato proposed a new classification based on pathogenesis and included the immune-mediated necrotizing myopathy (IMNM) as a different myositis subgroup[35] (Tables 1 and 2).

Recent years:

In 2011, Pestronk presented an alternative classification based exclusively on muscle biopsy features[36] and more recently, in 2016, Allenbach et al. proposed an IM classification including the autoantibody profile and incorporating clinical, morphological and molecular data[37] (Table1).

Table 1. History of myositis classification

Authors	Year	Characteristics
Medsger et al.	1970	Based on personal experience. Proposed 5 criteria as a guideline (weakness, biopsy, EMG, enzyme criteria and response to corticosteroids)
Bohan and Peter	1975	Classified PM and DM into 5 groups
Dalakas	1991	Modification of Bohan and Peter's criteria by including IBM by the first time. This classification was based on immunopathological features on muscle biopsy.
Love et al.	1991	Suggested using MSA. Included IBM
Griggs et al.	1995	Defined new IBM criteria
Tanimoto et al.	1995	PM and DM, childhood IM and cancer-associated IM are excluded. Preserved Bohan and Peter's criteria and added 4 more: arthritis or arthralgias, systemic inflammatory signs, muscle pain and anti-Jo1 positive.
Targoff et al.	1997	Modified Bohan and Peter's criteria including for the first time the MSA
Mastaglia and Philips	2002	Proposed new criteria for PM, DM and IBM and separate autoimmune from infectious muscle disease
Sontheimer	2002	Set criteria for ADM
Dalakas and Hohlfeld	2003	Classification based on histopathology and immunopathology. They incorporated the idea that CD4, CD8 and MHC I infiltrating the muscle surface can be used to help classify PM vs. DM
Hoogendijk, Amato et al.	2003	IMNM was included by the first time
Troyanov et al.	2004	Proposed a clinicoserological classification by modifiying the Bohan and Peter's criteria and adding the MSA and MAA.
Pestronk	2011	Proposed a new classification based on muscle biopsy features

Table 2. Myositis subsets

IM subtype	Clinical characteristics	Laboratory	Biopsy features	Prognosis
DM	Proximal weakness, typical rash: Gottron´s papules, heliotrope rash, V-Shawl sign. May associate ILD, vasculitis and malignancy	CK levels may be normal or up to 50 times normal	Perivascular and perimysial infiltration with CD4+ T cells and B cells. MAC deposition in the microvasculature	Good survival at 5 years with treatment
PM	Proximal weakness, no rash. May associate ILD, malignancy, MCTD and myocarditis	CK levels up to 50 times normal	Non-necrotic fibers invaded by CD8+ T cells and macrophages	Good survival at 5 years with treatment
IBM	More frequent in men > 50 years. Insidious onset of proximal and distal weakness; facial muscles may be involved. Early atrophy of the quadriceps and forearm flexor muscles. May associate dysphagia (40%), MCTD and SSc	CK levels may be normal or up to 10 times normal	Accumulation of beta amyloid and tau protein within fibers. Rimmed vacuoles. Inflammation mediated by macrophages and CD8+ T cells	Poor prognosis even with treatment
IMNM	Proximal muscle weakness. May associate malignancy and CTD	CK up to 100 times normal. Anti-HMGCR or anti-SRP autoantibodies positive	Necrotic fibers invaded by macrophages. MAC deposition in microvasculature	Highly refractory to treatment
JDM	Childhood onset and female predominance. Symmetric proximal weakness, Gottron´s papules, heliotrope rash, malar erythema, V-Shawl-sign, small vessel vasculopathy, dilated and tortuous periungual capillaries. Patients may present calcinosis (20-47%), lipodystrophy (10%) and gastrointestinal ulcerations (25%)	Mild elevation of CK levels	Muscle atrophy 45%	Prognosis is variable. 50-60% of patients experience chronic illness. 24–40% have a monocyclic course of illness Mortality 2-3%
ADM	Typical rash: Gottron´s papules, heliotrope, Shawl sign. No muscle involvement. May associate rapidly progressive ILD	CK levels are normal	Normal biopsy	Poor prognosis if ILD
Hypomyopathic DM	Typical rash: Gottron´s papules, Heliotrope, Shawl sign. May have sub-clinical evidence of muscle involvement on laboratory, electrophysiologic, and/or radiologic evaluation. May associate rapidly progressive ILD	CK levels may be mildly elevated	May have pathological findings	Poor prognosis if ILD
CADM	ADM + hypomyopathic DM	CK levels may be normal or mildly elevated	Normal or pathological finding	Poor prognosis if ILD

2. Autoantibodies in inflammatory myositis

The autoantibodies that can be found in IM patients are usually classified in two groups, myositis specific (MSA) and myositis associated autoantibodies (MAA).

2.1 Myositis specific autoantibodies and their clinical manifestations

As it has been explained before, MSA target cytoplasmic and nuclear proteins, and they are 90% specific for IM[21]. The classical, and more recently discovered MSA, already mentioned will be discussed in this section.

2.1.2 Anti-aminoacyl-tRNA synthetase autoantibodies

Anti-ARS antibodies are the most common MSAs and are found in 25–35 % of patients with PM or DM[21].

Aminoacyl-tRNA synthetases are enzymes localized in the cytoplasm of the cell. Their mission consists in catalyzing the binding of each amino acid to its specific tRNA during protein synthesis. So far, eight different autoantibodies targeting the anti-aminoacyl-tRNA synthetases have been identified: histidyl (Jo-1), threonyl (PL-7), alanyl (PL-12), glycyl (EJ), isoleucyl (OJ), asparaginyl (KS), tyrosyl (Ha), and phenylalanyl (Zo) synthetases. Among these autoantibodies, the most common and the first to be described was the anti-Jo-1[38]. It is found in 20–30 % of patients with adult PM, 8% of patients with adult DM[21], 4.4% of JDM patients[39]. Overall it is found in 50-85 % of those with ILD[21,40]. In contrast, anti-PL-7 and anti-PL-12, are found in less than 5 % of the patients, and anti-KS, -OJ, -EJ, -Zo, -Ha, in less than 2 % of PM or DM[41].

The anti-ARS antibodies are the serologic marker of the so called antisynthetase syndrome (ASyS), that was described for the first time in 1990 by Marguerie et al. It is

characterized by antisynthetase autoantibodies and clinical characteristics including myositis, arthritis, ILD, fever, RP and mechanic's hands[42].

The clinical manifestations of the ASyS can differ according to the type of anti-ARS autoantibody[40]. The course of the lung involvement may be acute and rapidly progressive or, more frequently, appears as a chronic interstitial pneumonia. In general, patients with anti-Jo1 show more muscle involvement (90%), arthralgia and arthritis, and less ILD and gastrointestinal manifestations, than patients positive for anti-PL7 and anti-PL12[40,43,44]. Frequently, anti-ARS coexist with anti-Ro52 autoantibodies (up in 70% of the anti-Jo1 patients); in those patients with concomitant anti-Ro52, the muscle and joint involvement has been reported to be more severe[45] (Table 3).

2.1.3 Anti-Mi2 autoantibodies

Mi-2 is a nucleosome helicase, which forms part of a complex called Mi-2/nucleosome remodeling and histone-deacetylase complex (NuRD complex). NuRD regulates gene transcription via chromatin modifications by histone deacetylase and ATP-dependent nucleosome remodeling[46]. More recent investigations indicate that the Mi-2, as well as other proteins that are part of the NuRD complex, may have specific functions in development[47], especially of the skin[48].

Mi-2 autoantibodies can recognize two homologous proteins called Mi-2 alpha (CHD3) and Mi-2 beta (CDH4) and both are part of the NuRD complex[49]. Mi-2 beta is thought to be the predominant form in vivo.

The prevalence of anti-Mi-2 antibodies in IM patients is 4-18%. They are more frequent in DM (up to 31%)[24] and are considered to be specific of this type of IM[50]. Thus, the majority of patients with anti-Mi-2 antibodies present with clinical features of DM such as Gottron's sign or papules, heliotrope rash, involvement of the neck and upper

back ("V" and "shawl" rashes), and cuticular overgrowth[51]. Patients with anti-Mi-2 antibodies typically develop mild to moderate myositis[39]. Signs and symptoms of SSc or ASyS (ILD, polyarthritis) are uncommon in these patients[31]. The association of anti-Mi-2 DM with cancer development seems to be lower compared with other DM patients and the response to corticosteroid´s treatment is better[24,52]. All of the abovementioned characteristics are signs of good prognosis[31,53]. It has been shown that a relationship exists between the lower latitudes and a higher frequency of anti-Mi-2 antibodies among IM patients[54,55]. Some studies demonstrated increased of Mi-2 protein expression in keratinocytes when these were exposed to a UV treatment for 30 minutes[56]. However, other studies have demonstrated differences in the autoantibody frequency in two Mexican cohorts, with similar UV exposures. These discoveries suggest that the UV radiation is not the only factor that influences anti-Mi-2 development[57] (Table 3).

2.1.4 Anti-NXP2 autoantibodies

Anti-NXP2 autoantibodies target a 140-kDa nuclear protein called nuclear matrix protein 2 (NXP2), which is involved in the regulation of p53-induced cellular senescence in response to oncogenic signals[58].

The anti-NXP2 autoantibody, originally named "anti-MJ", was described the first time in patients with JDM who presented with very severe myositis and calcinosis, polyarthritis, joint contractures and intestinal vasculitis[59]. Anti-NXP2 is known to be present in 20-25% of JDM patients and has a lower frequency in adult PM/DM (1-17%)[60]. In adult DM patients, but not in children, there is an association between anti-NXP2 antibodies and cancer[61]. Alternatively, calcinosis in anti-NXP2 myositis is common in children, but rare in adults[62] (Table 3).

2.1.5 Anti-TIF1γ (p155/140) autoantibodies

In 2006-2007, two independent groups reported a new autoantibody targeting a 155/140-kDa doublet protein in about 20–30 % of adults as well as juvenile forms of DM[29,63]. Later on, scientists discovered that the above-mentioned autoantigen is composed by multiple proteins that are part of the human transcription intermediary factor 1 (TIF-1 or TRIM 33) family, including TIF1γ, TIF1-α, and also TIF1-β proteins[64]. These proteins are implicated in various cellular pathways including cell proliferation, development, apoptosis and innate immunity[65].

In terms of clinical manifestations, studies show that both juvenile and adult patients with anti-TIF1γ, have an increased risk of severe skin disease[39,65,66]. Adult patients frequently have psoriasiform lesions, 'red on white' skin changes and hyperkeratotic, verruca-like papules[60]. Symptoms like RP, calcinosis, arthritis and ILD are less frequent in patients with anti-TIF1γ autoantibodies than in those who are negative[65].

Anti-TIF autoantibodies have been associated with cancer associated myositis in adults[67] but this association has not been found in children or younger adults[65,66] (Table 3).

2.1.5 Anti-small ubiquitin-like modifier activating enzyme autoantibodies (Anti-SAE)

Anti-SAE autoantibody targets an activating enzyme heterodimer called SUMO-1. This protein, composed of two subunits, SAE1 and SAE2 (with molecular weights of 40 kDa and 90 kDa, respectively)[68], is located in the cell nucleus. The function of SUMO-1 is to "sumolynate" the target proteins, which is a type of post-translational modification[21].

Anti-SAE autoantibodies were first described by Betteridge et al. in 2 patients with DM. They presented widespread skin involvement, dilated nailfold capillaries, dysphagia, and limited nonspecific interstitial pneumonia (NSIP)[30]. The prevalence of anti-SAE is different in European cohorts (6-8%)[30,69,70] than in Asian studies (around 2%)[71].

Since the discovery of the anti-SAE autoantibody, several authors have reported that these patients may present skin involvement before the onset of muscle weakness [69,72-74]. Also, these patients show occasional dysphagia (75-78%), and ILD. However, the prevalence of ILD is lower in European cohorts (0-18%)[69,72] than in Asian cohorts (71%)[71], where ILD seems to be milder[71] (Table 3).

2.1.6 Anti-MDA5 (CADM-140) autoantibodies

Anti-MDA5 autoantibodies were first described in 2005 and originally called anti-CADM-140 autoantibodies[28]. MDA5 is a cytoplasmic RNA-specific helicase that recognizes single-stranded RNA viruses[75].

The first studies showed that anti-MDA5 positive patients presented scarce or absent muscle involvement[28,76] with marked DM-skin involvement and a high risk of developing a rapidly progressive and highly lethal form of ILD (dermato-pulmonary syndrome)[77-79]. Some years later, additional clinical features in patients positive for anti-MDA5 autoantibodies, including Gottron´s papules, skin ulceration, palmar pustules and tender palmar papules typically affecting the lateral nailfolds, were described[77,78,80]. These patients have more risk of developing arthritis or arthralgia and also oral pain and ulceration[80] (Table 3).

2.1.7 Anti–signal recognition particle autoantibodies (Anti-SRP)

The signal recognition particle complex (SRP complex) is a cytosolic ribonucleoprotein composed of six polypeptides (72, 68, 54, 19, 14, and 9 kDa) and a single 7SL RNA molecule. Its function is to recognize newly formed proteins and help to translocate them across the rough endoplasmic reticulum[81]. In 2005 Satoh et al. demonstrated that the anti-SRP autoantibodies can target one or more of the six polypeptides that form the SRP complex as well as the 7SL RNA[82].

The most typical clinical presentation of a patient with anti-SRP antibodies is acute or subacute proximal weakness associated with high creatine kinase levels and dysphagia due to weakness of the pharyngeal muscles. Usually, these symptoms progress fast, leading to a severe disability. The muscle biopsy of these patients shows a severe necrotizing myopathy with abundant necrosis and regeneration and scarce inflammatory cells as the main histopathological features[83].

Skin involvement, RP, arthritis, ILD and even arrhythmia and cardiomyopathy can also be present, but their frequency varies between studies[25,83,84]. Specifically, cardiac involvement was highly prevalent in the earliest anti-SRP reports[84], but very low or nonexistent in more recent studies[25,83], suggesting that treatment of this type of disease may have significantly modified the clinical phenotype of these patients (Table 3).

2.1.8 Anti-HMGCR (200/100-kDa) autoantibodies

3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) is a 100 kDa protein which plays an important role in the cholesterol biosynthesis. The existence of an antibody against this protein was reported in 2010 in 64% of necrotizing myopathy

patients without any known MSA or MAA[27]. Later on, it was discovered that the target of this new autoantibody was HMGCR[85].

Anti-HMGCR antibodies were first described predominantly in patients exposed to statins, but eventually it was also found that many anti-HMGCR have no history of statin exposure[27,85]. Patients with no statin exposure, as well as younger patients, were identified as presenting more severe forms of the syndrome[86]. The Class II allele DRB1*11:01 was identified as a strong genetic risk factor for developing anti-HMGCR-associated myopathy[87].

Patients who have this autoantibody present with proximal muscle weakness, markedly elevated creatine kinase levels (over 10,000 IU/l), and generally, a good response to immunosuppressive therapy. Autoantibody titers and CK levels are highly correlated. The muscle biopsy is characterized by prominent myofiber necrosis; this is why these individuals are included within the IMNM group, together with anti-SRP myopathy patients[27] (Table 3).

Table 3. Myositis specific autoantibodies

Name	Target	Frequency	Characteristics
Anti-aminoacyl tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo)	Aminoacyl tRNA synthetases	25-35% of all IM	Antisynthetase syndrome: ILD, myositis, Raynaud's phenomenon, mechanic's hands, non-erosive arthritis, fever
Anti-Mi2	Nucleosome remodeling-deacetylase	20% DM 10% JDM	Classical DM skin features, mild to moderate myositis, low frequency of joint involvement and ILD
Anti-SRP	Signal recognition particle	5% of all IM	Proximal weakness, high CK levels (over 10 times normal), dysphagia. Necrotizing myopathy
Anti-NXP2	Nuclear matrix protein 2	20-25% JDM 1-17% PM/DM	Increased risk of cancer. High risk of calcinosis
Anti-p155/140 (TIF1-γ)	Transcriptional intermediary factor 1-γ	Adult PM/DM 13-21% Adult DM 15-25% JDM 22-29%	Severe skin disease distributed among scalp, face, upper chest and upper back. Palmar hyperkeratosis, Gottron's papules, telangiectasia. Increased risk of cancer
Anti-SAE	Small ubiquitin-like modifier activating enzyme	Caucasian adult PM/DM 6-8% Asian adult PM/DM 2% JDM<1%	Skin features appear before muscle involvement (amyopathic onset)
Anti-MDA5	Melanoma differentiation-associated protein 5	6% of all IM Caucasian adult DM 0-13% Asian adult DM 10-48% JDM 7-38%	Severe ILD. Serious skin features: and oral ulcers, arthritis/arthralgia. Minimal muscle involvement or ADM. Poor prognosis
Anti-HMGCR	3-hydroxy-3-methylglutaril-coenzyme A reductase	6% of all IM	Progressive weakness and high CK. Muscle biopsy: necrosis and little inflammation. MHC I upregulation and MAC deposit on non-necrotic fibers

2. 2 Myositis associated autoantibodies and their clinical manifestations

Alternatively, MAA are present in up to 50% of the IM patients[26,41]. Terminology is still confusing, but generally, among myositis associated autoantibodies we can find both non-specific autoantibodies that can be detected in various autoimmune syndromes and combined with MSAs, (e.g., anti-Ro52 autoantibodies), or syndrome-specific autoantibodies associated with highly characteristic overlap syndromes, (e.g., anti-Pm/Scl autoantibodies[26,41]). I am going to go into detail in the upcoming paragraphs.

2.2.1 Anti-PM/Scl

Anti-PM/Scl was first described by Wolfe et al. in 1977 as a precipitin against calf thymus nuclear extract present in sera of PM and PM/SSc overlap patients[88]. Several years later, Reichlin et al. proposed the name PM/Scl to indicate that the patients who were positive for the autoantibody had PM and the majority had also SSc features[89]. Later on, and based on their molecular weight, scientist identified the two main components of the PM/Scl autoantigen: PM/Scl 75 and PM/Scl 100[90,91].The PM/Scl complex was discovered to be a 11-16 protein complex[92,93] analogue to the yeast exosome that is in charge of the RNA degradation and processing[94].

Patients with anti-PM/Scl autoantibodies are characterized by muscle and lung involvement as well as RP, arthritis, mechanic´s hands and dysphagia[95-100]. These patients have a good prognosis and a good response to treatment with corticosteroids[96,99,101,102] (Table 4).

2.2.2 Anti-small ribonucleoprotein

In 1972, Sharp et al. discovered an antibody against the U1 ribonucleoproteine (U1RNP) and described a new disease in which patients had higher titers of the above-

mentioned autoantigen as well as clinical features similar to those in SLE, SSc and PM. They coined the disease as mixed connective tissue disease (MCTD)[103].

The U1RNP is part of a group of small nuclear ribonucleoproteins (snRNPs) composing spliceosome along with other snRNP subunits, U1, U2, U4, U5 and U6, and several protein factors[104]. The spliceosome´s function is to remove the noncoding introns from precursor messenger RNAs (pre-mRNAs)[105].

Patients with this syndrome present combined features of scleroderma (sclerodactyly, Raynaud´s syndrome, pulmonary hypertension), inflammatory myopathy (mechanic´s hands or myositis) and/or systemic lupus erythematosus (glomerulonephritis). In fact, anti-U1RNP patients may modify their immunologic profile and clinical phenotype during the evolution of the disease and some of these patients may behave as pure SLE after an initial period showing mixed clinical features. Regarding the pathogenicity of anti-U1RNP, some authors reported the possibility that this autoantibody could bind endothelial cells, leading to RP, sclerodactily, puffy hands, PAH and ILD. Moreover, it has been proposed that anti-U1RNP autoantibodies could form immunocomplexes that may activate complement leading to myositis, arthritis and ILD[106,107] (Table 4).

2.2.3 Anti-Ku

Anti-Ku autoantibodies were first described by Mimori et al. in Japan in 1981[108]. Later on, in 1985 and 1986, Reeves et al. and Francoeur et al. described antibodies against p70/p80 and Ki66/Ki86 that were found to be the same as anti-Ku in USA patients[109,110]. The authors reported differences between the two groups with the Japanese patients having more prevalent overlap syndrome[108], while the patients from the USA had more SLE[109,110].

Ku (Ku70/Ku80) is a DNA-binding protein that plays an important role in double-stranded DNA repair and has also been implicated in DNA replication and the regulation of gene transcription[111,112]. Anti-Ku antibodies may be found in several types of autoimmune diseases like MCTD, SLE, Sjögren´s syndrome, idiopathic lung fibrosis or overlap syndromes with SSc and myositis; the main symptoms of the patients that are positive for this autoantibody are RP and muscular and articular features, but these autoantibodies are not associated with any specific clinical manifestation[113] (Table 4).

2.2.4 Anti- Cytosolic 5'-nucleotidase 1A

Anti-Cytosolic 5'-nucleotidase 1A (anti-NT5C1A) was first described as an antibody that recognized a 43 kDa protein in sera of patients with IBM[114], and two years later, the 43 kDa protein was identified as the NT5C1A[115].

NT5C1A is part of a family of 7 enzymes that convert noncyclic nucleoside monophosphates to nucleoside and inorganic phosphate by dephosphorylation,[116] and is known to play a role in cell metabolism and replication[117,118].

The prevalence of anti-NT5C1A among the different subtypes of IM varies. Thus, in DM the prevalence is 4-21%, 4-11% in PM, and 33-70%[115,119,120] in IBM patients, so anti-NT5C1A may be used to distinguish PM from IBM, which is important due to the different response to treatment between this two entities[120]. Apart from IM, anti-NT5C1A has also been found in other autoimmune diseases like SSc and systemic lupus erythematosus (SLE).[120]

Anti-NT5C1A has been associated with a more severe IBM phenotype[121,122] and Lloyd et al. reported a lower prevalence of rimmed vacuoles in IBM patients with anti-NT5C1A positive compared to negative ones. Besides this, no phenotypical differences were found between the patients with and without this autoantibody.[120] (Table 4).

2.2.5 Anti-Ro60/Ro52

Anti-Ro/SSA autoantibodies were described for the first time in 1961 by Anderson et al[123]. Its double name "Ro" and "SSA" is due to the separate discovery of the antigen by two different groups; so "Ro" was the name of the first prototype serum positive for this autoantibody and "SS" was named for the association of these autoantibodies with Sjögren syndrome[124]. Later on, Alspaugh and Tan also reported two antibodies found in patients with Sjögren´s syndrome that they named "SSA", corresponding with anti-Ro and "SSB", also known as anti-La[125].

The Ro/SSA antigen is a two-polypeptide complex composed by a 52 and a 60 kDa protein. The Ro-52 protein is also known as TRIM 21 and was reported to be a negative regulator for the production of proinflammatory cytokines[126]. The Ro-60 protein was reported to bind misfolded RNA for degradation[127-129]. Both antigens were reported to be located in the same protein complex, but recent studies suggest that Ro-52 and Ro-60 are two different protein systems[130].

Anti-Ro antibodies are mostly detected in SLE and SS patients, but also in patients with IM (4 to 70%)[130-133]. Some authors published that the majority of PM and DM patients that are positive for anti-Ro autoantibodies react only against Ro-52[130-132]. The positivity of anti-Ro52 autoantibodies in anti-Jo1 positive patients is higher than in other types of IM with no anti-Jo1 autoantibodies[132] , and it has been associated with more severe ILD[134] (Table 4).

2.2.6 Anti-cortactin

Anti-cortactin antibody was simultaneously described by Labrador-Horrillo et al.[135] in myositis and Gallardo et al.[136] in myasthenia gravis in 2014. Cortactin is a protein

encoded by CTTN gene and is a substrate of the oncogene Src tyrosine kinase. This protein has been associated with progression of cancer[137,138].

The prevalence of anti-cortactin autoantibodies in IM was found to be 20% in PM, 7.6% in DM, 26% in IMNM and 0% in IBM patients, but this autoantibody was not associated with any specific clinical phenotype[135]. Anti-cortactin is found also in other diseases like myasthenia gravis (Table 4).

2.2.7 Anti-four and a half LIM domain 1

The four and a half LIM domain (FHL) proteins are proteins expressed predominantly in the skeletal muscle. These proteins are critical for muscle cell differenciation[139,140], muscles growth[141] and structural maintenance of the muscle[142]. Mutations in the FHL1 proteins lead to X-linked myopathies with very severe muscle involvement[143].

Autoantibodies against FHL1 protein were identified by Albrecht et al. in sera of IM patients and also in patients with other autoimmune diseases. The prevalence of anti-FHL1 antibodies in IM patients was reported to be 58% in PM, 30% in DM, 9% in IBM and 3% in JDM[143]. Patients positive for this autoantibody presented with more severe dysphagia, muscle atrophy, weakness, muscle fiber necrosis and vasculitis than negative patients for this autoantibody [143] (Table 4).

2.2.8 Anti-decorin

Decorin is a small leucine-rich proteoglycan that is part of the extracellular matrix and is secreted by human skeletal muscle cells[144,145]. The anti-decorin antigen was described for the first time by Al-Lozi et al. in 1997 in a patient with Waldenstrom's macroglobulinemia and myopathy[146]. Patients with anti-decorin autoantibodies are

characterized by slow progression of proximal and symmetrical weakness, high CK, a myopathic pattern in the EMG and endomysial fibrosis in the muscle biopsy[147] (Table 4).

2.2.9 Anti-nucleoporin

Anti-nucleoporin antibodies that recognize the nuclear pore complex proteins (nucleoporins), were described by Senécal et al. in a cohort of French Canadian patients with connective tissue diseases[148]. Those patients had severe myositis characterized as chronic and refractory to corticosteroids, but responsive to a second drug; erosive arthritis with anti-CCP antibodies and positive rheumatoid factor, mild ILD, RP and trigeminal neuralgia. Despite these facts, the prognosis of these patients was good and the long-time survival was 100%[148] (Table 4).

Table 4. Myositis-associated autoantibodies

Name	Target	Frequency	Characteristics
Anti-NT5C1A	Cytosolic 5' nucleotidase 1A	DM 4-21% PM 4-11% IBM 33-70%	Associated with more severe IBM phenotype
Anti-PM/Scl	PM/Scl-75 and PM/Scl-100 proteins	PM 8% DM 11% PDM/SSc 31%	Muscle and lung involvement, Raynaud's phenomenon, arthritis, mechanic's hands, dysphagia
Anti_U1snRNP	U1 small ribonucleoprotein	9% of all IM	Combination of SSc, IM and or SLE features (MCTD)
Anti-Ro52	TRIM21 protein	>30% of all IM PM/DM 76.5%	May be associated to anti-Jo1 (56-72%), being the ILD more severe in these patients.
Anti-Ro60	60kDa RNA-binding protein	Mediterranean patients: PM 37% DM 15% 22% of all IM	Associated with Sjögren's disease
Anti-cortactin	Cortactin	PM 20% DM 7.6%, IMNM 26% IBM 0%	No phenotypic association with anti-CTTN in the IM patients were described
Anti-FHL1	Four and a half LIM domain	PM 58% DM 30% IBM 9% JDM 3%	Associated with a more severe dysphagia, muscle atrophy, vasculitis and weakness
Anti-Ku	Ku protein complex	12-23% of all IM PDM/SSc 25-55%	Raynaud's phenomenon, articular and muscular features. Favorable prognosis.
Anti-Decorin	Decorin	-	Slow progress of proximal and symmetrical weakness, high CK, myopathic pattern in the EMG and endomysial fibrosis in the muscle biopsy.
Anti-nucleoporin	Nucleoporin	IM 4%	Severe myositis refractory to corticosteroids, but responsive to a second drug; erosive arthritis with anti-CCP antibodies and rheumatoid factor positive, mild ILD, RP and trigeminal neuralgia. Overlap syndrome. Good prognosis and prolonged survival

3. Epidemiology of inflammatory myositis

IM is considered a rare disease. The definition of what to consider a rare disease varies according to the geographical region. Thus, in Europe rare diseases are considered those affecting less than 1 in 2,000 people. However, to consider a disease to be rare in the United States of America or in Japan, it should have a prevalence lower than 1 in 1,500 and 1 in 2,500 respectively.

The incidence of IM has been estimated to be around 2.18 and 8.8 cases per 1,000,000 inhabitants per year[149-155] and the prevalence is around 1.4 cases per 1,000.000[156]. However, the incidence and prevalence of the different IM subtypes vary according to epidemiologic features like the gender, sex, and age at onset[152]. Accordingly, the ratio female to male in DM and PM varies between 1.5:1[152] and 2.2:1[149,153], but IBM is more frequent in males[157].

PM and DM prevalence in the United States of America are 9.7 per 100,000 people and 5.8 cases among 100,000 people respectively[158]. PM rarely to occurs during childhood and its onset is usually after the second decade of life[159]. On the other hand, DM is the most common form of myositis in children with two peaks of incidence: one during childhood and another between 50 and 70 years[160]. Alternatively, IBM affects people over the fourth decade of life and is known to be the most common idiopathic inflammatory myopathy occurring in patients over the age of 50 years[161,162]. It has been estimated that IBM comprises around 30% of all IM[163]. Publications studying the incidence and prevalence of IBM are scarce and data is somewhat confusing due to the great number of IBM patients misdiagnosed as PM. However, some reports from Sweden and the Netherlands established the prevalence of IBM to be around 4.9 patients per million inhabitants, with an incidence of 2.2 per million per year[164,165].

Regarding to the life-expectancy of PM and DM patients, the 5-year survival varies from 60% to 77% [152,166,167]. Airio et al. stated that the standardized mortality ratio for both PM and DM is approximately a threefold compared to the general population.[166]. Moreover, PM and DM patients have a 10% increased mortality risk due to diseases related with the autoimmune process, like cancer, and this fact is more frequent to happen after the first year of the IM onset.[168]. Related to the IBM patient's mortality risk, there is some controversy in the literature. On the one hand, it was published that IBM is a disease that, although leads to a progressive disability, it does not increase patients mortality[169]. On the contrary, Prince et al. suggested an increase of the mortality risk in IMB relative to an age-matched comparison population, particularly in those with dysphagia and following aspiration pneumonia[170].

4. Etiology and pathogenesis of inflammatory myositis

The etiology and pathogenesis of the different types of IM remain still largely unknown, but it is believed that a multifactorial combination of genetic and environmental factors may disrupt immune tolerance and trigger the disease. There have been several hypotheses that have tried to shed light on the pathogenesis of this group of diseases.

It is believed that genetic and environmental factors could act as a trigger of the autoimmune response through the activation of polyclonal T and B lymphocytes, or by antigen mimicry[171]. The antigen mimicry theory is based on the evidence that the sequences of some proposed stimuli, particularly viral proteins, share homology with autoantigen sequences[172,173].

The genetic basis of the autoimmune diseases has been a point of interest for several years. Scientists have confirmed the association of autoimmune diseases with some allelic variants from the human leukocyte antigen (HLA) region of the major MHC on chromosome 6p21.3[174]. Specifically, it was demonstrated that patients with myositis show more commonly the HLA 8.1 ancestral haplotype, particularly the *DRB1*03:01*. Also, sporadic IBM has been associated with *HLA-DRB3, HLA-DRA,* and *BTNL2*[175]. More recently, a genome wide association study (GWAS) in myositis patients confirmed HLA as the main genetic risk factor in IMs and stressed that specific MHCs may be associated with particular IMs phenotypes[176].

In terms of environmental factors, several authors have suggested that ultraviolet (UV) radiation may cause an immunomodulatory effect that could trigger DM [54,55,177]. This would explain the latitudinal gradient that the relative incidence of DM seems to follow in the Northern hemisphere. [54,55,177]. Moreover, the UV radiation has been related to the production of anti-Mi2 autoantibodies.[55]

The role of tobacco use in IM etiology and pathogenesis has also been studied. In 2012, Chinoy et al. studied the association of the smoking habit with the development of anti-Jo-1 antibodies in HLA-DRB1*03-positive IIM. They suggested that the risk of developing anti-Jo1 antibodies is increased in IM patients who were smokers and had one or more copies of HLA-DRB1*03.[178]

Apart from tobacco, authors have studied other inhaled substances as possible inductors of IM. Labirua-Iturburu et al. analyzed the association between dust, gases or fume exposure and ASyS[179]. The percentage of ASyS patients that were exposed to the mentioned substances was significantly higher than the one in the control group (50% vs. 22%, $p < 0.005$) and they obtained the same result when analyzed the interstitial lung disease (ILD) frequency. This study supports the idea that occupational exposure could play a role in the pathogenesis of some cases of ASyS-associated ILD[179]. Also supporting the idea that environmental dust exposure could trigger myositis, it was reported that workers in the World Trade Center rescue/recovery after the 9/11 showed an increased risk to develop systemic autoimmune diseases during the years following the incident. Interestingly, from the new autoimmune diseases that were detected, 13.6% were IM (PM and DM)[180].

Continuing with the subject of environmental factors related with the genesis of myositis, a toxic myopathy is the one that is caused by drugs, leading to manifestations of myopathic symptoms such as muscle weakness, myalgia, increase of creatine kinase or myoglobinuria.[181]. Several drugs have been described as a trigger for myopathy, and in these cases, patients develop muscle weakness and tenderness, more frequently of proximal limbs and axial muscles and also histological lesions in muscle biopsies[182].

Steroid myopathy was first described by Dubois[183] in 1959 and being one of the best known causes of drug toxicity. The onset of myopathy is insidious affecting the

lower extremities more than the upper ones[182]. Colchicine is also a well-known cause of toxic myopathy. In these patients, is possible to observe proximal muscle weakness and distal areflexia because of toxic neuropathy. Vacuolar myopathy is a common histological change in the muscle biopsy [182] at patients with colchicine myopathy. Finally, D-penicillamine may also cause muscle involvement[184,185] with clinical features that do not differ from those with autoimmune PM [182].

Other drugs like vincristine, diuretics, antacids, beta blockers or certain antibiotics may induce myopathy[181,182]. Also, in the lasts years, statins, frequently used to low cholesterol levels, have attracted researchers' attention due to its potential to cause toxic myopathy and necrotizing myopathy with positive anti-3-hydroximethyl-3-methyl-glutaryl CoA reductase (HMGCR) autoantibodies. However, the incidence of serious muscle toxicity caused by statins is low, with 5 patients per 100,000 persons-years developing myopathy, 1.6 patients per 100,000 persons-years rabdomyolisis and even less anti-HMGCR immune-mediated necrotizing myopathy (IMNM)[186-188] .

In addition to the above-mentioned causes, viral infections are also suspected to be a trigger for MI, especially, for DM. It has been proposed that the virus could interact with self-proteins and turn them into neo-antigens or that self-proteins may be targeted as viral proteins[189].

Influenced by the aforementioned genetic and environmental factors, both innate and adaptive immune systems are suspected to participate in the pathogenesis of IM.

4.1 Innate immune mechanisms of muscle damage:

When the muscle tissue is injured, it releases damage-associated molecules that bind to toll like receptors (TLRs) in skeletal muscle fibers, macrophages, myeloid dendritic cells, capillaries, plasmacytoid cells, and fibroblasts[190-192]. This binding activates the

innate immune response by inducing the secretion of proinflammatory cytokines and chemokines like type 1 interferons (IFN-α, IFN-β), tumor necrosis factor alpha (TNF-α), interleukins (IL) 1, 12 and IFN-γ. These molecules bind to their receptors on the muscles and capillaries[193-196], leading to vessel damage and muscle hypoxia[197]. Moreover, muscle indirect damage may also be mediated by the action of nuclear factor kappa beta (NF-kβ), activated by TNF. This transcription factor is able to suppress the synthesis of MyoD (a protein which plays a critical role in regulating muscle differentiation) and inhibit the formation of the new muscle fibers[198].

4.2 Adaptive immune mechanisms of muscle damage:

The antigen presenting cells (APC) that are activated by the damage associated muscular pattern via TLRs, are able to activate CD4-T cells via the MHC II complex, and CD8-T cells via the MHC I complex expressed in their membrane[199].

CD8 T-cells can differentiate into cytotoxic T-cells (CTLs). CTLs release cytotoxic enzymes, like perforin-1 and granzyme-B, that directly damage the membrane of muscle cells[200].

Complementarily, the CD4-T cells can differentiate into several types of specialized cells by the action of some cytokines. So, the transforming growth factor beta (TGF-β), IL-4 and IL-12 convert the CD4-T cells into T-helper (Th-17), Th2 and Th1 respectively. In turn, these cells release cytokines that can act on other types of cells[201]. Thus, through interferon gamma (INF-γ), the Th1 cells generate M1 macrophages that produce cell damage by secreting TNF- α, IL6 and IL-1. Complementarily, Th2 cells, through IL-4, TGFβ and IL-10 induce the creation of M2 macrophages, which participate in tissue repair and remodeling[202,203]. Moreover, Th2 cells participate in B-cell maturation and differentiation into antibody-producing plasma cells which initiate a complement-

mediated damage to the capillaries. This capillary damage may induce hypoxia and subsequent tissue damage.

Finally, cytotoxic CD28-/- T cells and regulatory T cells (Tregs) are able to inhibit the function of antigen presenting cells and T-effector cells, which may lead to decrease of inflammation and tissue damage [204,205].

5. Clinical manifestations

IMs are a heterogeneous group of diseases that can affect multiple organs and tissues, mainly the muscle but also the skin, the lung and the joints, among others. Thus, the clinical manifestations in these diseases could be conceptually divided in muscular and extra muscular involvement.

5.1 Muscle involvement

Inflammation of the striated muscle usually causes proximal and symmetrical weakness with no involvement of the facial muscles. This weakness developing over weeks to months[19], unlike the muscular dystrophies which progress slowly over the years[12,206,207]. If poorly controlled, muscle atrophy happens in late stages of the disease[208]. However, myositis clinical spectrum is highly heterogeneous and there are specific forms with characteristic distal, slowly progressive and asymmetric weakness, like IBM[209 210-212], others exclusively affecting facial muscles, like orbital myositis[213,214], and forms of IMNM with an extremely rapid onset and early muscle atrophy, like anti-SRP associated myositis[83].

As the pharynx and the upper third of the esophagus contain skeletal muscle[215], myositis can compromise swallowing. Dysphagia in myositis can lead to bronchoaspiration and secondary pneumonia. Esophageal involvement is not equally common in all different types of IM. Thus, in PM, 30-60% of the patients present with dysphagia; while in DM, the percentage of patients who have been reported to have swallowing problems is around 18-20%. The highest incidence of dysphagia is found in IBM (65-86%), where it responds less well, if at all, to treatment than the same symptom in PM or DM[216,217]. Moreover, the weakness of the diaphragm and thoracic muscles,

together with ILD, may cause dyspnea as well as nonproductive cough, aspiration pneumonia and hypoxemia[218-221].

5.2. Extramuscular involvement

As it was mentioned before, the skin, the lungs, and the joints are also frequently affected in patients with IM, but the degree of involvement of these other tissues and organs varies among the different types of IM.

5.2.1 Skin findings

Skin involvement is characteristic in DM, JDM and clinically amyopathic dermatomyositis (CADM) and also, can be found in patients with the ASyS[222,223].

Gottron' papules and sign and heliotrope erythema are the pathognomonic skin sings of DM. Gottron's papules consist at erythematous papular rash over the knuckles, proximal and distal interphalangeal joints. They are observed in 80% of patients with DM. When the rash progresses and the papular lesions converge towards a flaky eruption it is known as Gottron´s sign. The heliotrope rash is a purple discoloration on the upper eyelids, which may associate periorbital edema and telangiectasias. In black patients, the Gottron´s sign and papules as well as the heliotrope rash may appear as a hyperpigmented lesion instead of a violaceous discoloration[204].

Another typical manifestation of DM is an erythematous rash distributed symmetrically over the lower anterior neck and upper anterior chest, known as “V-sign”. If the erythema extends over the upper back, posterior neck, shoulders and lateral arms it is called the “shawl” sign. All above mentioned skin features may appear before, after or coinciding with the muscle symptoms in DM[203] and JDM. However, in CADM, by definition, there is no clinical muscle involvement.

Periungual erythema, cuticular hypertrophy, and periungual telangiectasia are also frequent in patients with DM. Poikiloderma, which corresponds to hypo and hyperpigmented macules with skin atrophy and telangiectasia in between, can be found in photo-exposed areas in DM and it has been described as a manifestation of the disease's chronicity[224]. In some subtypes of DM, other skin symptoms like ulcers, digital necrosis, calcinosis and mechanic´s hands are characteristic. The mechanic´s hands consist of fissuring and cracking of the radial side of the palms and fingers with palm hyperkeratosis[225]. This feature is typical, but not exclusive, of the ASyS associated to other myopathies different from DM. Patients with and without ASyS may present Raynaud's phenomenon (RP). RP consists in three phases of skin color change in the fingers or toes. These colors are white, due to the arterioles spasm; blue, due to the lack of oxygen in the distal parts; and red when the arterioles relax and the blood returns to flow through them. About the 20% of patients with PM or DM can present with RP[226]. 38% of patients positive for anti-Jo1 autoantibodies, which are the most common antibodies found in ASyS, present RP[223].

Although not so common, DM patients may present with subcutaneous edema, defined as pitting or non-pitting edema in the extremities accompanying the active phase of the disease. There are reports associating subcutaneous edema with a typical pattern in the muscle consisting of perifascicular atrophy, necrosis and cell regeneration, perivascular infiltrate, microinfarction, and the punch-out phenomenon.[227]. Moreover, this clinical sign is associated with a more severe disease course and patients with anti-NXP2 autoantibodies are more likely to have edema than those who are negative for this autoantibody[228].

5.2.2 Lung involvement

5.2.2.1 Interstitial lung disease

In 1956, Mills et al. reported the first case of IM associated with ILD in a 52 years old woman who died from the complications of this manifestation of the disease[229]. Since then, it has been clearly established that the lung is, along with the muscle, one of the most affected organs in IM. The prevalence of IM with associated ILD, which is the typical form of lung involvement in IM, is about 78%[230]. PM, DM, CADM and ASyS are associated with ILD and it can be especially severe and rapidly progressive in some forms of CADM[231,232]. It can be also associated with diffuse alveolar damage[233,234] and poor prognosis[235]. In general, ILD increases the morbidity and mortality of patients with IM and in some series, the mortality of myositis patients due to ILD was estimated to be about 50%[236,237].

The most frequent clinical manifestations of lung involvement in myositis are dyspnea and cough. However, some patients may be asymptomatic and the lung involvement can only be detected by complementary exams like high-resolution computer tomography (HRCT) or pulmonary function test (PFT)[238]. The presentation of lung symptoms may occur before, at the same time or after the onset of muscle or skin involvement appears[236,239-241]. The frequency and clinical manifestation of ILD are different according to the autoantibodies. Thus, antisynthetase and anti-MDA5 autoantibodies are highly associated with ILD[74,242], while anti-Mi2, anti-NXP2 and anti-TIF1γ show a very low prevalence of lung involvement[242-245]. The relationship of ILD with different antibodies will be explained in detail in the corresponding section.

The most common findings at the initial HRCT of patients with ILD and IM are peribronchovascular thickening, linear and ground-glass opacities[230,246-248] and the most

frequent anatomopathological finding in patients with ILD and IM is NSIP. These patterns of lung damage will be discussed in detail further on in the text.

5.2.2.2Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is defined as a mean resting pulmonary artery pressure of ≥ 25 mmHg at rest and a pulmonary capillary wedge pressure of ≤ 15 mmHg measured during a right heart [249,250]. PAH is a common lung complication in patients with SSc, but its prevalence is lower in IM and other autoimmune diseases like SLE, MCTD, RA or Sjögren´s syndrome[251]. However, the prevalence of PAH in patients with ASyS is about 8%[252] and it may be up to 29% in patients with anti-PL12 autoantibodies[40].

Although there are some published cases about isolated PAH in IM[253,254], the presence of PAH secondary to ILD, due to chronic hypoxic pulmonary vasoconstriction is more frequent than primary PAH in IM patients[252,255].

The pathophysiological mechanism of pulmonary hypertension is still not well known. Denbow et al. studied the cardiac involvement in PM patients by examining 20 autopsies, finding 4 patients with small vessel disease of the lungs consisting of medial smooth muscle hyperplasia with little or no intimal proliferation[256]. Other studies showed fibrous proliferation of the intima of the small pulmonary arteries[254]. Thus, the early studies in this field revealed occlusive changes as a possible cause of PAH in IM.

5.2.2.3 Pleural involvement

Pleural involvement in myositis can occur as pneumomediastinum or pneumothorax and, less commonly as pleural effusion[257].

Pneumomediastinum and/or pneumothorax are rare complication of CADM, DM and PM[258,259]. However, it is especially frequent in anti-MDA5 patients, where the clinical manifestation is associated with great morbidity and mortality[258]. Pneumomediastinum is typically caused by the rupture of the subpleural and paracardial blebs due to the distortion of the lung architecture in patients with ILD, but isolated cases of pneumomediastinum without ILD have been reported in IM patients[258,259].

Although less common than pneumomediastinum or pneumothorax, several clinical cases have reported pleural effusion as a complication of PM or DM[260-262]

5.2.2.4 Lung Infection

Patients with IM can suffer from pulmonary infections especially during the first year of diagnosis due to aspiration pneumonia and as a consequence of the immunesupression[231,263]. Aspiration pneumonia in IM is caused by dysphagia due to the dysfunction of the pharyngeal muscles. This is known to be a marker of poor prognosis[264]. Opportunistic infections secondary to the steroid treatment alone (*Mycobacterium tuberculosis, Mycobacterium xenopi,*) or in combination with immunosuppressive drugs (*Candida albicans, Aspergillus fumigatus, Aspergillus niger, cytomegalovirus*) have been described in patients with IM[265].

5.2.2.5 Pulmonary drug toxicity

It is known that some of the drugs that are used for IM treatment may cause lung toxicity. Methotrexate is usually prescribed for muscle and joint involvement and, although it is not a common secondary effect, treatment with this drug may lead to pneumonitis[34,266]. Likewise, lung secondary effects as bacterial and fungal infections, chronic pneumonitis or fibrosis, and pulmonary nodules can appear while using anti-TNF

drugs[267]. Moreover, anti-TNF therapy has been reported as a trigger of autoimmune diseases, including IM.[268,269]. It may be complicated to distinguish a drug-induced lung involvement from the ILD caused by the underlying disease. If the lung damage is caused by drugs, bronchioalveolar lavage (BAL) can be helpful by showing an increased eosinophil count or a mixed lymphocytic and neutrophilic cellular pattern[257] and the interruption of the drug often leads to rapid remission of the lung involvement.

5.2.3 Cardiac involvement

Oppenheim was the first author to describe cardiac involvement in IM in 1899[270]. The frequency of heart involvement in patients with IM varies between 6 and 75% depending on the cohorts[271,272]; being the clinically significant heart involvement occurs in only 10-15%[273,274]. Cardiac involvement in IM has been reported as a poor prognostic feature; and mortality in PM is, according to some authors, around 5-20% of patients with this manifestation of the disease[275,276].

The most frequently reported clinically significant symptom of cardiac involvement in IM patients is the development of a congestive cardiac failure (3-45%)[256,276-279]. Other clinical manifestations that may appear in these patients are coronary heart disease with angina pectoris and myocardial infarction.

Subclinical manifestations that can be shown in the electrocardiogram (ECG) are atrial and ventricular arrhythmias, auriculoventricular blocks (A-V blocks), high-grade heart block, bundle branch block, prolongation of PR-intervals, abnormal Q-waves or non-specific ST-T wave changes[280].

However, due to the high frequency of cardiac involvement in the general population and lack of properly controlled studies in myositis, the prevalence and pathophysiology of the cardiac involvement is still not well understood in this group of

patients. Some theories point to the myocarditis or fibrosis leading to left ventricle dysfunction and some autopsies showed a mononuclear inflammatory cell infiltration within the endomysium and perivascular areas, causing degeneration of cardiac myocytes. Similar pathological changes were observed in the conduction system and are thought to be the cause for the electrocardiographic changes[281].

5.2.4 Joint involvement

Arthralgia is common in myositis patients, especially in patients with ASyS who present with anti-Jo-1 autoantibodies and in patients with overlap syndromes with MCTD or rheumatoid arthritis[34].

Arthritis is, on occasions, the predominant feature in ASyS. It follows a symmetrical and non-erosive pattern involving fingers, wrist and knees. An erosive form associating distal fingers calcinosis has also been reported[282].

Patients with anti-MDA5 autoantibody, often present arthralgia and polyarthritis, similar to rheumatoid arthritis. These joint symptoms and signs have been reported as signs of poor prognosis in this group of patients[231].

5.2.5 Esophageal and gastrointestinal involvement

As mentioned before, the pharynx and the upper third of the esophagus, formed by skeletal muscle, are commonly affected in IM[215]. However, some authors have reported involvement of the middle and lower third of the esophagus in patients with IM.[283-285]. Several esophageal motility studies in DM and PM patients demonstrated abnormalities in peristalsis of the lower part and body of the esophagus including diffuse spasm, low amplitude esophageal contractions, and diminished or absent peristalsis[283-

[285]. Moreover, Donoghe et al. reported that esophageal hypomotility in DM patients may be indistinguishable from that seen in SSc[283].

The esophageal and gastric emptying in IM patients was studied by Horowitz et al., who concluded that both are delayed in PM and DM patients and that involvement of these organs are associated with the severity of muscle weakness[286].

Several authors have reported vasculitis of the gastrointestinal tract in JDM patients[287,288]. The SSc patients had abdominal pain with no occult blood in stools and a normal abdominal x-ray[288]. Despite this, some individuals required surgery due to intestinal perforation[287,288]. Consequently, authors suggested including ulcerations and perforation to the differential diagnosis of JDM patients who present abdominal pain[288].

Furthermore, there are several reports in the literature that associate DM and PM with other entities that affect the gastrointestinal tract, such as celiac disease[289-291], primary biliary cirrosis[292,293], viral hepatitis B[294-296] and C[297,298] and pneumatosis intestinalis[299-301] as well as small intestine pseudo-obstruction and pseudomonal necrotizing enterocolitis[302,303].

5.2.6 Neoplasm in IM

Cancer-associated myositis is defined as cancer occurring within 3 years of the myositis diagnosis, and also if the myositis is cured when the cancer is cured[33].

The first report of cancer-associated IM was made in 1916[5,304], and later on, Williams et al. (1956)[305] and Barnes et al. (1976)[306] performed the first large retrospective studies about the topic.

The incidence of cancer in IM was reported to be 5.7-37.5%[63,307-309] and adenocarcinoma is the most common type of tumor among patients with PM and

DM[309,310]. The ovaries, lung, colon and rectum, stomach and pancreas, are the most frequent localizations for this type of cancer[309].

Compared to the general population, DM and PM are associated with a four-fold increase of malignancy[311], and although most of the studies have been done in PM/DM patients, there are several reports describing an association between IBM and malignancy[312-314] and even with chronic lymphocytic leukemia[315,316].

To explain the relationship between IM and cancer, two theories are most favored. The first one proposes that the immune system may find a target in some self-proteins that are mutated in tumors and this anti-tumor response may redirect to the wild type protein leading to tissue injury. According to the second theory, overexpression of myositis autoantigens by tumor cells may trigger a response against the tumor and this response may be also redirected to muscle tissue[317].

The association of some myositis autoantibodies with malignancy has been studied by several authors. Thus, anti-TIF1 γ and anti-NXP2 autoantibodies were reported as a risk factor for malignancy in patients with IM[307,317]. Concerning anti-NXP2 patients, it has been published that 31-37.5% occur in association with cancer[61,244]. Regarding anti-TIF1γ autoantibody, Targoff et al.[63], Kaji et al.[29] and Trallero-Araguas et al. [310] reported a relationship between anti-p155 and cancer myositis association in IM patients. Although some authors have reported a marginal association with cancer[318,319], the association between anti-HMGCR and cancer remains controversial.

6. Diagnosis

Apart from the history and physical exam, several complementary studies can help the clinician to diagnose and monitor the evolution of patients with IM.

6.1 Electromyography:

Electromyography (EMG) is a tool that may help in diagnosing inflammatory myopathies. On the basis of changes in the shape, the size, and the recruitment pattern of the motor unit potential, it is possible to distinguish between denervation and muscle involvement. But no electromyographic finding individually is specific for myositis, making this a sensitive but unspecific technique[19,320].

The EMG of patients with DM, PM, IMNM and IBM consist in polyphasic, short-duration, low-amplitude motor action potentials, with an early recruitment pattern. Moreover, if the disease is active at the moment of the exam, the EMG can reveal fibrillations and positive sharp waves indicating membrane irritability. Immunosuppressant treatment may normalize the EMG findings in myositis patients and this is something to take into account when interpreting results since a normal test does not exclude the diagnosis of IM. The above-mentioned EMG pattern may be seen also in patients affected by other types of muscular diseases as dystrophies, congenital, metabolic and toxic myopathies. In some occasions, patients with IBM can show mixed EMG patterns difficult to differentiate from chronic neurogenic disease[321].

6.2 Pulmonary functional tests

PFTs are very useful test to detect and monitor ILD in IM patients. They are useful also to assess lung disease severity and evaluate response to treatment[322].

The most typical PFT pattern in ILD is a restrictive ventilatory defect with decreased total lung capacity, functional residual capacity, residual volume, forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). The finding of normal or elevated FEV1/FVC ratio with decrease diffusing capacity for carbon monoxide (DLCO) is the most sensitive test to detect ILD. However, a decreased DLCO is not specific for ILD and can be also found in other lung conditions with impaired gas exchange like PAH[323].

Respiratory muscles weakness can lead to reduced FVC, total lung capacity (TLC) and FEV1, which can be easily mistaken by ILD. An increased residual volume with a normal FEV1:FVC ratio suggests respiratory muscle weakness[324].

6.3 High-resolution computerized tomography:

High-resolution computerized tomography (HRCT) of the thorax is the best technique to perform a structural evaluation of the lung in myositis patients. Around 75% of PM/DM patients have evidence of ILD, either clinical or subclinical, on the HRCT[325].

The most characteristic findings in the HRCT of patients with IM ILD are: linear and ground glass opacities, nodules and micronodules, irregularity of interfaces, consolidations, traction bronchiectasis and fibrosis with or without honeycombing[326]. These changes are localized predominantly to the lower lobes[238,327].

Lung HRCT has a higher sensitivity to detect ILD than chest X-ray[323], it is useful for identifying the extent and severity of the disease and can help to distinguish between active lung inflammation and fibrosis[323].

Several HRCT patterns than can be observed in IM ILD. The most common are OP, NSIP or mixed NSIP–OP pattern, and UIP pattern is less frequent[328].

However, lung HRCT uses ionizing radiation and this is why its use as a follow-up technique is limited to patients with a change in their functional status or need to clarify the differential diagnosis[329].

6.4 Lung biopsy

Since it is an unspecific and invasive exam, which entails potential morbidity, the lung biopsy is not a routine test to diagnose ILD in IM patients[219].

The most common histological pattern of ILD in patients with IM is NSIP (44.4-81.8%), followed by UIP (2.3-45.5%) and organizing pneumonia (OP) (0-38.5%). Diffuse alveolar damage is less frequent but, if present, it is associated with a more severe phenotype. Moreover, it is possible to find mixed patterns of OP and NSIP[236,238,246,330-332].

The open lung, as well as the video-assisted thoracoscopic surgery biopsy, does not usually change the management of the disease compared with less invasive procedures (PFTs, HRCT and bronchoalveolar lavage). Thus, it is only indicated in case of clinical uncertainly in the diagnosis of ILD[257,326].

6.5 Bronchoalveolar lavage:

BAL is a less invasive technique that allows to sample the cellular and protein composition of the lower respiratory tract. In healthy patients, alveolar macrophages are the BAL predominant cell. Meanwhile, if local inflammation exists, neutrophils and eosinophils predominate. In some diseases that associate ILD, BAL cytology seems to correlate with poorer lung function, but no correlation with prognosis or response to treatment has been assessed[333-336].

The clinical information given by BAL is often limited due to the differences in the performance of the technique between different operators. Regardless of that, BAL is a good technique to evaluate the abnormal findings of other complementary exams and to rule out diffuse alveolar hemorrhage, opportunistic infection or some drug reactions that may show eosinophilia in this technique[337-339].

6.6 Magnetic resonance imaging:

Magnetic resonance imaging (MRI) is a useful method for the evaluation of neuromuscular disorders. It is known to be the best image technique to investigate soft tissue abnormalities. It has been used to detect unique patterns of muscle edema, muscle atrophy, fatty replacement and fascial edema in different types of IM patients[340]. For example, previous studies have noted that fascial edema seems to be more common in DM than PM or IBM[341,342]. Other studies have revealed that IBM patients have a unique pattern characterized by severe involvement of the anterior thigh compartment with selective sparing of the rectus femoris muscle[343], these patients also tend to have asymmetric muscle involvement on MRI[344]. A more recent study has described a pattern of MRI findings that may be useful for diagnosing IBM and excluding other myopathies, such as PM and DM[345].

Different MRI sequences detect different tissue abnormalities. Thus, on T1 weighted images, fat is shown hyperintense and edema appears as low signal and these sequences are useful to assess the presence of atrophy and the degree of fatty infiltration[346].

As both edema and fatty infiltration appear hyperintense on T2 weighted sequences, using conventional T2 muscular images to evaluate edema is complicated[347,348]. However, in fat suppressed T2 weighted or short-tau inversion

recovery (STIR) sequences[349], fluid appears hyperintense while fat becomes hypointense (the fat signal is eliminated). This fact allows for distinguishing the edema from the fatty infiltration[347].

Even the creatine kinase values are normal, MRI may be useful[32]. In 2004, the European Neuro-Muscular Centre classification criteria, included MRI findings of edema on STIR weighted imaging as one of the laboratory variables[35]. It has been reported that the MRI is a useful tool for guiding muscle biopsies[350,351]. However, ACR and EULAR excluded the MRI from their most recently proposed criteria[352].

In summary, MRI is a useful technique both for diagnosis, guiding muscle biopsy, monitoring disease activity and detecting patterns of muscular damage. Despite this, there is no validated protocol for the evaluation of the MRI in IM patients[353].

6.7 High-resolution manometry:

Thirty-two to eighty-four percent of patients with IM have reported suffering from dysphagia. Swallowing problems in these patients are mainly due to the inflammation of the skeletal muscle of the pharynx and the upper third of the esophagus[215].

Until recently, clinicians have used the barium swallowing study and conventional manometry to assess the causes of dysphagia and its degree of severity. But doctors are increasingly requesting the high-resolution manometry (HRM) to study this symptom.

The differences between the two types of manometry are the number of pressure sensors (8 in the conventional and 20-36 in the HRM), the separation intervals between them (5 cm in the conventional and 1 cm in the HMR); and the importance of the catheter position inside the esophagus (conventional manometry needs accurate positioning of the catheter, while HRM catheter embraces the entire esophagus making positioning not so important)[354].

Normal values for HRM have been well defined both in American and European populations[355-359]. Classification v3.0, released in 2015, was developed to categorize esophageal motility disorders utilizing HRM[356].

6.8 Muscle biopsy:

Muscle biopsy is considered the definitive exam to confirm skeletal muscle inflammation and to exclude other types of myopathy[19]. The most typical muscles to obtain a biopsy in IM patients are the deltoids and the quadriceps. The selection of the muscle to be biopsied is usually made by physical exam (the biopsy should be taken from a muscle that is weak, but not atrophic) or EMG. MRI is also useful to identify an appropriate muscle, decreasing the false negative rate of the technique.

Distinct IM subsets have different pathological features on biopsy. In PM, the inflammatory infiltrate is usually composed of CD8+ cytotoxic T cells, but also macrophages and dendritic cells. This mononuclear infiltrate invades individual muscle fibers in what is called primary inflammation[360]. The expression of class I major histocompatibility complex antigen is increased in the muscle fibers[361].

In DM patients, perifascicular atrophy in the muscle biopsy is the most characteristic pathological finding, being so specific that some authors consider that if it is present it is possible to diagnose DM even in the absence of skin involvement. It is typical to see capillary injury and fibrosis. The inflammatory infiltrate, typically composed of CD4+ cells, macrophages and B cells, is located primarily in the perimisium. Invasion of non-necrotic fibers is uncommon. Even at early stages of the disease, before the appearance of inflammatory cell infiltration, the terminal complement C5b–9 membrane attack complex can be detected in the walls vessels[362].

Alternatively, the typical findings in the IBM biopsy are the presence of endomysial inflammation, eosinophilic cytoplasmic inclusions, angulated fibers and rimmed vacuoles. Rimmed vacuoles are basophilic granular inclusions around the edge of slit-like vacuoles[212,363-366]. A pathognomonic finding that can be detected in IBM using electronic microscopy is the presence of filamentous inclusions in the cytoplasm or nucleus, especially in the proximity of the rimmed vacuoles[19].

Finally, the most common findings in the biopsy of patients with IMNM are the presence of scattered necrotic muscle fibers[367] with scarce inflammatory infiltrate[368]. It is possible to see overexpression of MHC-I in necrotic fibers as well as in the regenerating ones, but this overexpression is not so striking as in other diseases[369,370]. As it happens in DM, it is possible to find membrane attack complex (MAC) depositions on microvessels but not perivascular inflammation or perifascicular atrophy.

6.9 Skin biopsy

The typical findings in the skin biopsy of DM patients involves both, dermis and epidermis. In the dermis, these patients show apoptosis, necrosis of keratinocytes, mucine deposits and perivascular lymphocyte T infiltration[371,372].

It is also common to see vacuolar changes in the basal cell layer of the epidermis as well as an increase in Ki-67+ keratinocytes and decrease of Bcl-2+ cells. These features may indicate the existence of disrupted apoptotic pathways in the skin of DM patients[373].

Unfortunately, it is not possible to distinguish between DM´s and SLE´s rashes by using routine pathologic studies. Thus, the definitive pathological diagnosis of DM cannot be achieved solely based on the skin biopsy[373].

7. Prognosis

The prognosis of the IM depends on the myositis subtype. In general, PM and DM have a good prognosis with a 5-year survival higher than 70% with treatment[166]. Patients with IMNN may have profound muscle weakness which may be occasionally refractory to conventional immunosuppressant treatment, especially in young patients with anti-SRP autoantibodies[374]. The prognosis of IBM is poor, even with intense immunosuppressant treatment, since this disease is characteristically refractory to any type of therapy. However, life expectancy is not significantly altered in this type of IM, probably due to the old age at onset of the patients and slow evolution over time[212,373].

Neoplasm and older age are associated with a poor prognosis in IM patients. Some features associated with an increase of morbidity are pulmonary fibrosis, pulmonary hypertension, pneumonia due to esophageal dysmotility and calcinosis in DM patients[252,375-377]. Autoantibodies are also associated with the prognosis; for example, patients with DM and anti-Mi2 positive autoantibodies have a good prognosis[31] compared to those DM patients with other autoantibodies.

8. Treatment

Treatment of the inflammatory myopathies is complex due to several factors. First, there are little high-quality studies to guide the treatment, there are a considerable number of therapeutic options, and the targets of the immunosuppressant treatment are multiple. Furthermore, the effectiveness of the different therapies in the different types of organ involvement may not be homogeneous.

8.1 First line of therapy:

The first line of treatment is IM is corticosteroid therapy. The starting dose is 60mg/d or 0.75-1.5 mg/kg/d. In the case of severe symptoms at onset or a severe flare of the disease, it may be necessary to use intravenous methylprednisolone at dose of 1g/d during the first 3-5 days. High-dose steroids are maintained until the patient's strength normalizes or an improvement in strength occurs and CK normalizes (what happens usually during the first 2 to 4 months after starting the treatment). Then, the dose is tapered up to the minimum dose that allows the patient to be asymptomatic[378,379]. Corticosteroids have never been compared with placebo, but as they clearly improve most IM subtypes, it is unlikely that such studies will ever be conducted.

Although corticosteroids have demonstrated efficacy in the treatment of PM and DM patients, several studies report that IBM patients are not responsive to this drug[380-382]; indeed one-third of IBM patients remain stable without any treatment or even improve over a 6-month period follow-up[383].

It is necessary to take into account the secondary effects of corticosteroids, especially if the patient is being treated with a high dose. Osteoporosis, high blood pressure, hyper or hypoglycemia, hypokalemia, gastric problems, aseptic femoral necrosis or infection are some of the secondary effects that doctors should be aware of[266].

Thus, is important to monitor the blood pressure, serum glucose, potassium and also measure bone density with dual energy, X-ray densitometry at baseline and if required, prescribe a biphosphonate[384,385]. Also, all patients, independent of their bone mass, should take calcium and vitamin D supplementation daily[266,385]. Moreover, physical activity is important to prevent bone loss and type 2 fibers atropy[266].

Patients with PM and DM have been reported to have increased risk of herpes zoster virus infection[265,386], as well as tuberculosis[387]. Thus, it is recommended that all PM and DM patients to be vaccinated for herpes zoster virus and also tested for tuberculosis, and if necessary, treated before starting corticosteroid treatment or any other immunosuppressant drug [386,387]. Also, patients should be vaccinated against influenza and pneumonia and those receiving high doses of corticosteroids should be considered for prophylaxis of *Pneumocystis carinii* pneumonia[388-390].

Due to the secondary effects of corticosteroids, a second-line agent is often necessary as a corticosteroid-sparing drug.

8.2 Second line of therapy

In addition to corticosteroids, other immunosuppressive and immunomodulatory drugs are useful to treat IM. This include azathioprine (AZA), methotrexate (MTX), cyclosporine (CYA), mycophenolate mofetil (MMF), cyclophosphamide (CYC), tacrolimus (TAC), intravenous immunoglobulins (IVIg), and more recently, biologic agents such as rituximab (RTX) have been used successfully in IM patients[391,392]. Tumor necrosis factor alpha inhibitors (anti-TNF alpha) have also been used to treat IM[393,394], but its use is controversial due to its lack of efficacy in some series and its potential to induce and exacerbate PM and DM[395,396].

8.2.1 Methotrexate:

MTX is a folic acid antagonist developed in the 1940s. It has been used as a therapy for cancer and also has been demonstrated to be useful in the treatment of rheumatoid arthritis[397]**.** Other uses of this drug are the treatment of several other autoimmune diseases like myasthenia gravis, SSc, Chron's disease, Still disease, etc. Molar and ectopic pregnancies can be treated also with MTX. In addition, it can also be used for therapeutic abortion.

There are no randomized controlled trials demonstrating MTX efficacy in PM and DM, but some open-label and retrospective studies as well as case series support the use of this drug in myositis[398-402].

MTX can be given orally or subcutaneously. Starting at 5.0 to 7.5 mg once a week, the dose can be increased up to 25 mg/weekly. The most common side effects of MTX include hepatotoxicity, leukopenia, kidney failure, abdominal discomfort, and pneumonitis. In fact, its potential pulmonary toxicity has been of serious concern when prescribing this drug in patients with ASyS due to the difficulty of differentiating methotrexate pneumonitis from IM ILD. However, as long as the patient does not have IM ILD, MTX can be considered as an effective alternative for patients with muscle and joint manifestations[403].

8.2.2 Azathioprine

AZA is derived from 6-mercaptopurine and is one of the most popular corticosteroid sparing drugs in myositis[404]. It takes longer to be effective than MTX, up to 6 months, but the efficacy is similar. The dose range goes from 1.5 to 3.0 mg/Kg/day orally[266].

The principal adverse effects are thrombocytopenia, anemia, leukopenia or pancytopenia. Patients can also develop nausea, vomiting, hepatotoxicity and an increased risk of malignancy. It should be avoided in combination with allopurinol because this drug is known to increase the risk of liver and bone marrow toxicity[266].

The combination with MTX has shown efficacy in selected patients that were refractory to one of them in monotherapy[405].

8.2.3 Intravenous human immunoglobulin

IVIg is considered an immunomodulatory agent, although its mechanism of action is not well defined. A couple of double-blind placebo-controlled studies and diverse retrospective uncontrolled studies both in DM and PM demonstrated IVIg to be effective in myositis, with an improvement in manual muscle test scores and daily living activity and reduction of CK levels[406-412]. IVIg has also been suggested to be effective in patients with IM-associated ILD[413,414]

Several studies have been conducted in IBM and the majority revealed non-significant improvement of these patients when treated with IVIg[415-417].

The usual dose of IVIg is 2g/Kg/monthly. Headaches, fever, chills, nausea, vomiting, myalgia, flushing and hypotension may occur and are related to the rate of infusion. It is important to check the renal function of the patients before starting the treatment because of the risk of IVIg induced renal failure. Other adverse like stroke, rash or aseptic meningitis may occur[266]. Also, IVIg may increase the risk of thromboembolic events which is of particular concern since myositis patients have already higher incidence of pulmonary and peripheral venous embolism[418].

8.2.4 Mycophenolate mofetil

Mycophenolate mofetil (MMF) inhibits the proliferation of T and B cells by blocking purine synthesis. The starting dose of MMF is 250-500 mg by mouth twice a day. Then, the dose can be increased 250-500 mg every 1 or 2 weeks to reach target dose of 1500-3000 mg/day[419-427].

There are some case series that reported benefits in patients with PM and DM treated with MMF[421,422]. An open label study showed that MFF in combination with IVIg is effective in severe and refractory myositis, and is useful as a steroid-sparing agent[428]. Several case series have suggested that this drug may be useful for refractory cutaneous DM[423,429]. Furthermore, some retrospective studies and case series suggested that MMF could be an appropriate therapy for ILD in patients with dermatomyositis[424-426].

8.2.5 Rituximab

RTX is a monoclonal antibody targeting the CD20 antigen on B cell lymphocytes. Usually, the dose in myositis patients is of 1g repeated 2 weeks apart. Before starting the treatment, patients should be screened for hepatitis B and C. Moreover, patients that have recovered from hepatitis B should be monitored for virus reactivation for 1-2 years after RTX therapy. Cytopenias, infections and infusion-related reactions are the most common secondary effects of RTX.

Several case series and case reports have shown that RTX may decrease CK levels and improve the strength both in refractory DM and PM patients[430-433]. However, several other studies in DM and PM patients showed no improvement in skin rash or CK levels in these patients[434]. Furthermore, the largest randomized, double-blinded, controlled trial in refractory IM treated with RTX, published in 2013, did not show any differences in the time to achieve the IMACS definition of improvement (DOI) between the early-treated group and the late-treated group. However, DOI was met by 83% of patients at the end

of the trial. Moreover, in this study, RTX was associated with a significant steroid-sparing effect[435].

8.2.6 Cyclosporine

Cyclosporine (CYA) is a calcineurin inhibitor that inhibits the production and release of IL-2 and IL-2-induced activation of T lymphocytes. In association with corticosteroids, CYA has been used to treat PM/DM with associated ILD and has shown good results in steroid-resistant patients[330,436-440]. Moreover, the combination of CYA and MTX seem to be beneficial in refractory juvenile DM as well as in rheumatoid arthritis[441].

The usual dose of CYA is 4–6 mg/kg/day, split into two daily doses. The side effects of CYA included high blood pressure, nephrotoxicity, hepatotoxicity, infection, hirsutism, tremor, gum hyperplasia and teratogenicity[266].

8.2.7 Tacrolimus

Like CYA, Tacrolimus (TAC) is a calcineurin inhibitor. The first study to report the efficacy of TAC for the treatment of steroid-resistant PM/DM-associated ILD, was conducted in 1999[442]. Since then, several other studies have suggested the effectiveness of this drug for this purpose[443-447].

The usual dose of TAC is 0.1–0.15 mg/kg/day divided into two doses in adults and 0.15–0.20 mg/kg/day for children, every 12 hours [266].

The secondary effects of TAC are similar to those of CYA, including hypertension, liver enzyme increase, renal failure and hypertrichosis.

8.2.8 Cyclophosphamide

Cyclophosphamide (CYC) is an alkylating agent that was first used for cancer treatment. In IM, is useful to treat severe manifestations like rapidly progressive ILD or

systemic vasculitis[448].

Several studies have shown weakness improvement and a decline of the CK levels in patients treated with CYC[449-451]. Moreover, CYC appears to improve ILD both as assessed by pulmonary function tests and by HRCT imaging in patients with IM ILD[265,448,452-454]. In these patients, using CYC has also has been associated with improved survival[77,455,456].

CYC is reserved as a rescue therapy because it may cause serious adverse effects like bone marrow suppression, cardiotoxicity, infertility, and increase the risk of several tumors, especially Hodgkin lymphoma and multiple myeloma. It may also cause hemorrhagic cystitis; the risk of this can be reduced by using 2-mercaptoetane sodium sulphate (MESNA).

The usual dose of CYC is 0.5-1 g/m^2 monthly for 6 to 12 months intravenously. The oral dose is 1.0-2.0 mg/kg/d. Urinalysis and complete blood count should be monitored during treatment with CYC[266] . IV treatment is usually preferred for the decreased rate of complications and side effects.

8.3 Emerging therapies:

In recent years, new drugs have been reported for IM treatment.

Alemtuzumab is a humanized monoclonal anti-CD52 antibody. It causes a depletion of the peripheral blood lymphocytes. It was suggested in a single study to improve muscle strength in IBM patients as well as slow down the disease progression, but this data has not been reproduced by other authors and this drug is not ordinarily used to treat IBM myositis[457].

Another monoclonal antibody, Belimumab, targets the B lymphocyte stimulator, a TNF-related cytokine implicated in B cell maturation and development. Although this

drug was approved for SLE treatment in 2011[458], its effectiveness to IM treatment remains unknown.

Alternatively, tocilizumab is an antagonist of IL-6. Some studies show that patients with IM have overexpressed interleukine 6 (IL-6) in serum and this cytokine is also observed in the muscle tissue of these patients[459-461]. Narazaki et al. reported the improvement of 2 patients with refractory PM in terms of CK levels and muscle MRI findings after using this drug[462].

Safalimumab is an anti-IFN-monoclonal antibody that neutralizes the type I IFN gene signature. This neutralization leads to a coordinated suppression of T cell-related proteins such as soluble IL-2RA, TNF receptor 2 (TNFR2), and IL-18 (128). Some studies show evidence that type I interferon (IFN alpha/beta)-mediated innate immunity may be implicated in IM pathogenesis[463]. The treatment with Safalimumab has been associated with suppression of the IFN signature in muscle and blood of IM patients and these features correlate with a clinical improvement[464].

TNF-alpha inhibitors are a group of drugs that target tumor necrosis factor alpha receptors, reported to be increased in the serum of IM patients[465]. This family of drugs is extensively used to treat rheumatoid arthritis[466], and includes several pharmaceutical products as infliximab, adalimumab, certolizumab, golizumab and etanercept.

Althought infliximab and etanercept have been used to treat IM, their use in this disease is controversial due its risk of exacerbate PM and DM[395,396].

Finally, ruxolitinib, which is a Janus kinase (JAK) inhibitor, was reported as effective in a single case of paraneoplastic DM [467]

II. HYPOTHESIS AND OBJECTIVES

1. Hypothesis

DM and PM are still the most commonly recognized forms of IM even though they include heterogeneous groups of patients. Surprisingly, the classification of IM has not evolved to recognize homogeneous categories that would be more useful to predict prognosis and select treatment. Furthermore, MSA have proven useful to differentiate homogeneous clinical phenotypes. We hypothesize that an IM classification based on the MSA may be useful to assess the prognosis of patients with IM.

Also, certain epidemiologic factors, like the race or the age at the onset of the disease, have demonstrated to act as modifiers of the disease activity in different types of myositis, but it is not yet well understood how these factors influence the evolution of the disease.

Specific diagnostic techniques, like MRI, are widely used in patients with myositis even though studies systematically analyzing the value of this techniques is scarce. We hypothesize that a systematic analysis of retrospective data using such techniques could provide clear data about the diagnostic and prognostic utility of these technique and help us understand the evolution.

Finally, lower esophageal involvement has been reported occasionally to be highly prevalent in patients with IM, but the type of esophageal involvement associated with the different types of myositis or the relationship between the clinical manifestations with the signs of the disease as this level are to a large extent unknown. We propose that using high resolution techniques to analyze esophageal involvement could shed a light on the pathophysiology of this process in patients with myositis and help to assess the necessity of treating this type of manifestation in patients with myositis.

2. Objectives

2.1 General objective

- To study muscle and esophageal involvement in IM through t-MRI and HRM.
- To define the pattern of muscle and esophageal involvement in IM patients, and compare the differences in those patterns among the IM clinical and serological subtypes.
- To establish the utility of t-MRI to distinguish the IM subsets.
- To study the prevalence, rate of appearance and severity of clinical features in patients with different ASyS autoantibodies, and assess if autoantibodies as well as epidemiological features like sex and race have a role in ASyS prognosis.

2.2 Objectives of the different studies

Study 1

Thigh muscle MRI in immune-mediated necrotizing myopathy: extensive edema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity.

-To use t-MRI to define the pattern of muscle involvement in patients with immune mediated IMNM relative to those with other types of IM.

-To compare t-MRI findings in anti-SRP versus anti-HMGCR IMNM patients.

-To establish the utility of thigh MRI to differentiate the various types of myositis.

Study 2

High-resolution manometry in patients with idiopathic inflammatory myopathy: elevated prevalence of esophageal involvement and differences according to autoantibody status. and clinical subset

-To examine the prevalence of HRM findings as well as esophageal symptoms among clinical and serological groups of patients with PM and DM.

-To define the features of esophageal involvement in IM and compare the prevalence of these features among IM patients with different autoantibodies.

Study 3

A longitudinal cohort study of the antisynthetase syndrome: Increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies.

-To define the prevalence, rate of appearance, and severity of clinical features in patients with different ASyS autoantibodies.

-To compare the clinical features and evolution of these features over time in patients with different types of ASyS autoantibodies.

-To assess if autoantibodies as well as epidemiological features like sex and race have a role in ASyS prognosis.

III. PUBLICATIONS

1. Thigh magnetic resonance imaging in immune-mediated necrotizing myositis

Pinal-Fernandez I*, Casal-Dominguez M*, Carrino JA, et al. Thigh muscle MRI in immune-mediated necrotising myopathy: extensive oedema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity. Ann Rheum Dis 2017;76:681-7.

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EXTENDED REPORT

Thigh muscle MRI in immune-mediated necrotising myopathy: extensive oedema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity

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ABSTRACT

Objectives The aims of this study were to define the pattern of muscle involvement in patients with immune-mediated necrotising myopathy (IMNM) relative to those with other inflammatory myopathies and to compare patients with IMNM with different autoantibodies.

Methods All Johns Hopkins Myositis Longitudinal Cohort subjects with a thigh MRI (tMRI) who fulfilled criteria for IMNM, dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) or clinically amyopathic DM (CADM) were included in the study. Muscles were assessed for intramuscular and fascial oedema, atrophy and fatty replacement. Disease subgroups were compared using univariate and multivariate analyses. Patients with IMNM with anti-signal recognition particle (SRP) autoantibodies were compared with those with IMNM with anti-HMG-CoA reductase (HMGCR) autoantibodies.

Results The study included 666 subjects (101 IMNM, 176 PM, 219 DM, 17 CADM and 153 IBM). Compared with DM or PM, IMNM was characterised by a higher proportion of thigh muscles with oedema, atrophy and fatty replacement ($p<0.01$). Patients with IMNM with anti-SRP had more atrophy (19%, $p=0.003$) and fatty replacement (18%, $p=0.04$) than those with anti-HMGCR. In IMNM, muscle abnormalities were especially common in the lateral rotator and gluteal groups. Fascial involvement was most widespread in DM. Fatty replacement of muscle tissue began early during the course of disease in IMNM and the other groups. An optimal combination of tMRI features had only a 55% positive predictive value for diagnosing IMNM.

Conclusions Compared with patients with DM or PM, IMNM is characterised by more widespread muscle involvement. Anti-SRP-positive patients have more severe muscle involvement than anti-HMGCR-positive patients.

INTRODUCTION

The idiopathic inflammatory myopathies, including polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM), are a heterogeneous family of diseases characterised by muscle weakness, high muscle enzyme levels, autoantibodies and muscle biopsies with prominent lymphocytic infiltrates.[1] As the best imaging technique to investigate soft tissue abnormalities, MRI has been used to detect unique patterns of muscle oedema, muscle atrophy, fatty replacement and fascial oedema in different types of patients with myositis.[2] For example, previous studies have noted that fascial oedema seems to be more common in DM than PM or IBM.[3 4] Other studies have revealed that patients with IBM have a unique pattern characterised by severe involvement of the anterior thigh compartment with selective sparing of the rectus femoris muscle;[5] these patients also tend to have asymmetric muscle involvement on MRI.[6] A more recent study has described a pattern of MRI findings that may be useful for diagnosing IBM and excluding other myopathies, such as PM and DM.[7]

In recent years, it has become widely accepted that some patients with autoimmune myopathy have muscle biopsies with prominent muscle cell necrosis and only minimal lymphocytic infiltration. This form of myositis has been termed immune-mediated necrotising myopathy (IMNM) or necrotising autoimmune myopathy and is now recognised to be distinct from PM, DM or IBM.[1] Patients with IMNM typically have very high serum creatine kinase (CK) levels, a relative lack of skin or other organ system involvement and, often, autoantibodies recognising either the signal recognition particle (SRP) or HMG-CoA reductase (HMGCR).[1] Some of these patients, especially those with anti-SRP, may have especially severe disease that responds poorly to immunosuppressive therapy.[1]

To date, no studies have used thigh MRI (tMRI) to analyse the pattern of muscle involvement in patients with IMNM. In this study, we analysed the tMRI features in a large cohort of patients with myositis, comparing IMNM with other disease categories. We also compared the tMRI features of anti-SRP-positive IMNM subject with those who had autoantibodies recognising HMGCR.

MATERIAL AND METHODS

Study population

All patients enrolled in the Johns Hopkins Myositis Center longitudinal cohort from May 2008 to April 2015 with an available tMRI, routinely performed at the first visit, were sequentially included in the study.

Standard protocol approvals and patient consents

This study was approved by the Johns Hopkins Institutional Review Board, and written informed consent was obtained from each participant.

Demographic and clinical features

The date of the tMRI and demographic features, including the sex, race and date of symptom onset, were collected through retrospective chart review. Also, patients were classified in one of five mutually exclusive clinical subgroups by retrospective chart review. Thus, patients were classified as having IMNM if they met the 2003 European Neuromuscular Centre (ENMC) criteria,[8] IBM if they fulfilled Griggs' criteria[9] or clinically amyopathic DM (CADM) if they met Sontheimer's criteria.[10] If none of these three criteria were met, patients were evaluated for Bohan and Peter criteria and classified accordingly as possible, probable or definite DM or PM.[11]

Autoantibody analysis of patients with necrotising myositis

Testing of sera for anti-HMGCR autoantibodies was performed by ELISA and confirmed by immunoprecipitation in vitro-transcribed and translated (IVTT) HMGCR protein as previously described.[12] Anti-SRP testing was performed by immunoprecipitation of IVTT-generated SRP subunits at the Johns Hopkins Rheumatic Disease Research Core Center as previously described,[13] by testing at the Oklahoma Medical Research Foundation using immunoprecipitation, and/or by using Quest Diagnostics myositis panels. Other myositis-specific autoantibodies, including the antisynthetase autoantibodies, anti-MDA5, anti-Mi2 and anti-NXP2 were also tested using these methods.

Image acquisition

MRI was performed on a 1.5T (Avanto, Siemens Medical Solutions, Erlangen, Germany) or 3T (Verio, Siemens Medical Solutions, Erlangen, Germany) depending on scanner availability with standardised protocol of coronal and axial T1-weighted and short-tau inversion recovery (STIR) images.[14] The type of image 'weighting' employed during image acquisition determines the MRI contrast, with T1 being fat sensitive and STIR being fluid sensitive. The imaging sequences were performed with parameters to optimise image quality and yield with similar contrast resolution irrespective of field strength.[2] The field of view was from the hips to knees. Axial images were contiguously acquired throughout the thigh to allow for evaluation of the full extent of each muscle (see online supplementary appendix 1).

Image evaluation

Image analysis was performed by two experienced musculoskeletal radiologists at the Johns Hopkins Radiology Department as part of routine clinical care. One of the musculoskeletal radiologists (JAC) had more than 10 years of experience reading MRI (and interpreted the majority of cases ~75%), and the other musculoskeletal radiologist (SA) had 3 years of experience reading MRI (in addition to a musculoskeletal fellowship).

The radiologists interpreting the scans were masked to disease activity and subgroup of inflammatory myopathy. The presence of oedema, fatty replacement, atrophy and fascial oedema was evaluated in 15 muscles of both thighs (figure 1). Muscles were grouped according to online supplementary table S1.

The readings were standardised using predefined MRI definitions and pulse sequences. Consensus training was arranged by using the MRI definitions document (see online supplementary appendix 1).

Statistical analysis

Dichotomous variables were expressed as percentages and absolute frequencies, and continuous features were reported as means and SDs.

Pairwise comparisons for categorical variables between groups were made using χ^2 test or Fisher's exact test, as appropriate. Student's t-test was used to compare continuous variables among groups and correlation was studied using Pearson's coefficient.

The asymmetry of each tMRI feature in each patient was quantified by calculating the percentage of muscles that showed that feature in one side but not in the other.

We defined the extent of a tMRI feature as the percentage of muscles showing each feature. We determined whether certain muscle groups were more likely to be affected by MRI abnormalities depending on the disease category.

The influence of non-modifiable risk factors (sex, race, length of illness and age at the onset of the first symptoms) on the percentage of muscles showing each of the tMRI features were assessed using fractional probit models, reporting the marginal effects (dy/dx) of each of the predictor variables (equivalent to the predicted per cent change in the dependent variable per unit of the predictor variable).[15] The administration of corticosteroid, intravenous immunoglobulins, rituximab, methotrexate, azathioprine and mycophenolate were used as adjusting covariates in the models comparing anti-HMGCR with anti-SRP-associated myositis.

Also, forward multiple logistic regression was used to select which muscles and tMRI features were most informative for each clinical group. A likelihood ratio test significance of 0.01 was selected to include variables in the model to maintain a manageable number of items in each formula. The area under the receiver operating characteristic (ROC) curve of the resulting models was internally validated using 100 bootstrap samples, obtaining the optimism-corrected area under the curve (AUC).[16]

All statistical analyses were performed using Stata/MP V.14.0. To account for the number of statistical tests performed, a two-sided p value of 0.001 or less was considered statistically significant for the univariate analysis while 0.05 was considered significant for the multivariate analysis.

RESULTS

Patients

Eight hundred and ninety-one patients underwent tMRI and 666 of these fulfilled the criteria for one of the defined myositis groups. Among these, 101 had IMNM, 219 had DM, 176 had PM, 17 had CADM and 153 had IBM. From the 101 patients with IMNM, 50 were positive for anti-HMGCR (50%) and 22 for anti-SRP autoantibodies (22%) (figure 2). Other myositis-specific autoantibodies were detected in <3% of the patients with IMNM. As expected, there were marked differences in the age at onset, duration of disease and demographic factors among the different groups of patients. Patients with anti-SRP were younger and were more commonly under immunosuppressant treatment at the time of the tMRI (68% vs 40%, p=0.03) than those with anti-HMGCR (38.4 vs 53.3 years old, p<0.001); there were no differences between these two groups of patients with IMNM with regard to the duration of disease at the time of tMRI, race or gender (table 1).

Extent and laterality of tMRI features by univariate analysis

MRI revealed that patients with IMNM had more extensive oedema (56%) than those with either PM (29%) or DM (30%) (all p<0.0001). Moreover, patients with IMNM showed a trend

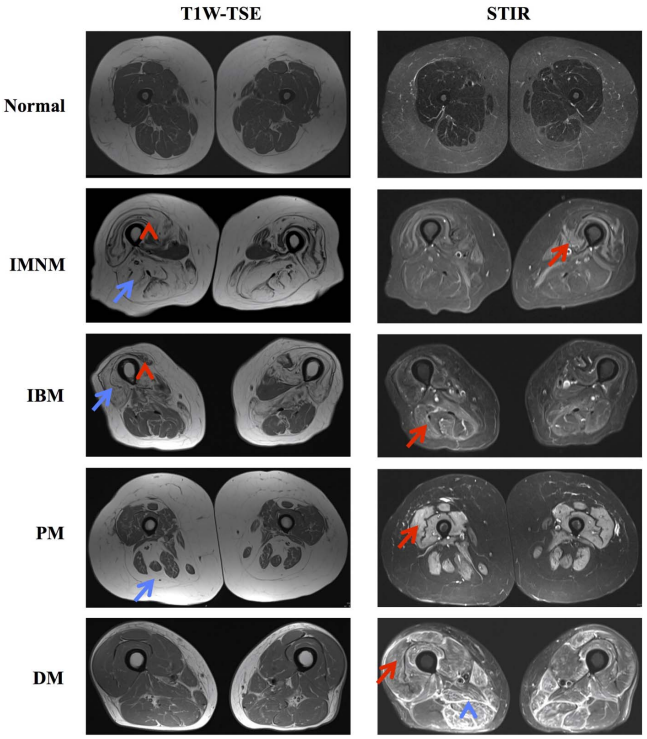

Figure 1 Examples of T1-weighted (T1W) turbo spin echo (TSE) and short-tau inversion recovery (STIR) sequences showing oedema (red arrows), atrophy (red arrow heads), fatty replacement (blue arrows) and fascial oedema (blue arrow heads) in patients with immune-mediated necrotising myopathy (IMNM), inclusion body myositis (IBM), polymyositis (PM) and dermatomyositis (DM).

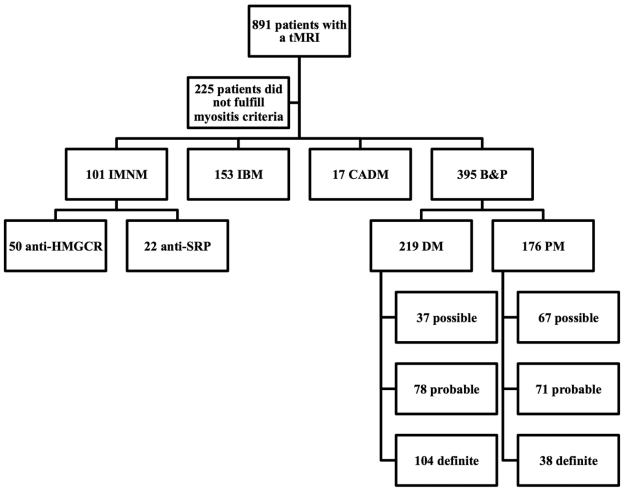

Figure 2 Patient flow chart. B&P, Bohan and Peter criteria; CADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; IBM, inclusion body myositis; IMNM, immune-mediated necrotising myopathy; PM, polymyositis; SRP, signal recognition particle; tMRI: thigh MRI.

Table 1 General features of the patients included in the study

	IMNM							
	Total (n=101)	HMGCR (n=50)	SRP (n=22)	IBM (n=153)	PM (n=176)	DM (n=219)	CADM (n=17)	Total (n=666)
Age at onset	48.9 (16.0)	53.3 (13.1)***	38.4 (13.1)***	58.4 (10.8)***	50.8 (15.9)	45.4 (14.2)***	48.7 (14.9)	50.4 (15.0)*
Length of illness (years)	4.3 (5.8)	4.3 (5.8)	3.5 (4.0)	7.8 (6.7)***	5.6 (7.2)	3.8 (4.7)***	2.2 (3.0)*	5.2 (6.3)*
Female sex	65% (66)	64% (32)	86% (19)	38% (58)***	66% (116)	76% (167)***	82% (14)	63% (421)
White	69% (70)*	78% (39)	59% (13)	88% (134)***	69% (122)**	81% (177)	71% (12)	77% (515)
Black	19% (19)*	14% (7)	36% (8)	7% (10)*	20% (35)***	8% (17)*	6% (1)	12% (82)
Other races	12% (12)	8% (4)	5% (1)	6% (9)*	11% (19)	11% (25)	24% (4)	10% (69)

Continuous variables are expressed as mean (SD) and bivariate variables as percentage (absolute number). The value of each major clinical group (IMNM, IBM, PM, DM and CADM) was compared with the rest of the sample. In separate analyses, patients with anti-HMGCR and anti-SRP were compared with each other only. The χ^2 test and Fisher's exact test were used to compare bivariate variables. Continuous variables were compared using Student's t-test. The length of illness was measured from the onset of first symptoms to the date of the thigh MRI.
*<0.05; **<0.01; ***<0.001.
CADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; HMGCR, HMG-CoA reductase; IBM, inclusion body myositis; IMNM, immune-mediated necrotising myopathy; PM, polymyositis; SRP, signal recognition particle.

Table 2 Extent of thigh MRI findings among clinical subsets

	IMNM							
	Total (n=101) Mean (SD)	HMGCR (n=50) Mean (SD)	SRP (n=22) Mean (SD)	IBM (n=153) Mean (SD)	PM (n=176) Mean (SD)	DM (n=219) Mean (SD)	CADM (n=17) Mean (SD)	Total (n=666) Mean (SD)
Oedema	55.5 (32.2)***	58.9 (31.8)	65.8 (28.9)	48.1 (24.6)***	29.4 (30.5)***	30.1 (36.7)***	6.1 (18.5)***	37.3 (33.5)
Atrophy	23.2 (28.7)**	21.7 (28.9)*	38.2 (30.2)*	32.2 (26.7)***	12.7 (24.6)*	5.7 (16.7)***	2.5 (7.4)*	16.2 (25.5)
Fatty replacement	38.0 (33.1)*	34.4 (30.9)	49.1 (31.2)	50.1 (27.3)***	28.3 (31.1)	17.5 (27.0)***	7.1 (12.8)**	30.7 (31.6)
Fascial oedema	6.2 (15.1)*	5.1 (15.2)	6.0 (12.2)	6.0 (12.0)**	5.8 (11.8)**	16.5 (24.3)***	8.6 (17.0)	9.5 (18.1)

Mean percentage of each major clinical group (IMNM, IBM, PM, DM and CADM) compared with the rest of the sample using Student's t-test. In separate analyses, patients with anti-HMGCR and anti-SRP were compared to each other only.
*<0.05; **<0.01; ***<0.001.
CADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; HMGCR, HMG-CoA reductase; IBM, inclusion body myositis; IMNM, immune-mediated necrotising myopathy; PM, polymyositis; SRP, signal recognition particle.

towards more atrophy (23%) and fatty replacement (38%) than those with either PM or DM (all p<0.02). As expected, CADM showed the least extensive muscle involvement by tMRI (table 2).

Interestingly, patients with IMNM showed a trend towards having more asymmetry in the percentage of muscles showing fatty replacement (2.6%, SD 6%, p<0.01) than those with DM or PM. Patients with anti-SRP showed more asymmetry than those with anti-HMGCR for all the tMRI features, but the difference did not reach statistical significance. Similar to IMNM, IBM also showed greater asymmetry in the percentage of muscles with atrophy (2.5%, SD 5.2%, p<0.001) compared with PM or DM. Of note, DM showed a trend towards more asymmetry in fascial oedema compared with all the other groups (2.2%, SD 4.7%, p<0.05). These differences in the laterality of muscle involvement did not seem to have a preference for a particular side (see online supplementary table S2).

Overall, fatty replacement extent was moderately correlated with the extent of atrophy (R=0.5, p<0.001) and oedema (R=0.4, p<0.001) while the extent of oedema was associated with the extent of atrophy (R=0.3, p<0.001) and fascial oedema (R=0.3, p<0.001). IBM did not show a significant association between oedema and atrophy or fascial oedema (both p>0.05), while in DM oedema was more correlated with fascial oedema than in the rest of the clinical groups (R=0.5, p<0.001) (see online supplementary table S3).

tMRI features by muscle group

Next, we determined whether certain muscle groups were more likely to be affected by MRI abnormalities depending on the disease category. Indeed, IMNM subjects had atrophy and fatty replacement preferentially in the lateral rotators, glutei, medial compartment and posterior compartment. In contrast, patients with IBM had oedema, fatty replacement and atrophy predominantly in the anterior, medial and posterior compartments. Patients with DM had more prevalent fascial oedema in the anterior, medial and posterior compartments compared with the rest of the patients. Finally, patients with PM showed no defined pattern of involvement for any of the tMRI features. Within the IMNM subgroups, patients with anti-SRP showed a trend towards more extensive oedema, atrophy and fatty replacement in the lateral rotator group, more atrophy and fatty replacement in the anterior compartment, and more atrophy in the medial compartment compared with those with anti-HMGCR (all p values between 0.001 and 0.05) (see online supplementary table S4).

Multivariate analysis of tMRI features

Multivariate analysis demonstrated that IMNM had significantly more extensive oedema, atrophy and fatty replacement than DM, PM or CADM (all p<0.01) independent of the age at onset, duration of illness, sex or race of the subject (table 3); tMRI features were not statistically different between patients with IMNM and IBM (all p>0.05). Within the IMNM subgroup, anti-SRP-positive patients had more extensive atrophy (19%, p=0.003) and fatty replacement (18%, p=0.04) than anti-HMGCR-positive patients independent of the age at onset, duration of the disease, sex, race and treatment at the time of the tMRI (table 4).

Not surprisingly, in all myositis subgroups, as the length of time between disease onset and imaging increased, the extent of oedema decreased and both atrophy and fatty replacement increased (all p<0.01). Moreover, graphical analysis revealed that these changes were faster immediately after the onset of the

Table 3 Multivariate analysis of the extent of the different thigh MRI features (percentage of muscles involved) among different clinical subsets using fractional probit regression

	Oedema dy/dx (95% CI)	Atrophy dy/dx (95% CI)	Fatty replacement dy/dx (95% CI)	Fascial oedema dy/dx (95% CI)
Clinical subset (referenced to IMNM)				
IBM	−5.82 (−13.31 to 1.66)	0.92 (−4.23 to 6.06)	1.52 (−5.56 to 8.61)	1.68 (−3.87 to 7.23)
PM	−23.72 (−30.63 to −16.80)***	−10.92 (−16.38 to −5.46)***	−10.77 (−17.69 to −3.86)**	0.05 (−4.53 to 4.64)
DM	−22.14 (−29.36 to −14.93)***	−18.24 (−24.00 to −12.47)***	−17.39 (−24.21 to −10.57)***	8.82 (4.53 to 13.11)***
CADM	−61.46 (−85.87 to −37.05)***	−25.76 (−39.13 to −12.39)***	−31.18 (−46.55 to −15.80)***	1.85 (−6.86 to 10.57)
Age at onset (10 years)	0.73 (−1.10 to 2.56)	2.41 (0.84 to 3.97)**	2.05 (0.34 to 3.77)*	−0.88 (−1.76 to 0.00)
Time from onset to MRI (logarithm of months)	−8.83 (−14.34 to −3.33)**	10.44 (6.13 to 14.74)***	13.90 (8.90 to 18.89)***	−4.82 (−7.39 to −2.26)***
Sex (female)	−9.60 (−14.58 to −4.61)***	3.24 (−0.45 to 6.92)	−8.61 (−13.11 to −4.11)***	−2.92 (−5.72 to −0.11)*
Race (referenced to white patients)				
Black	6.11 (−1.70 to 13.92)	0.84 (−5.26 to 6.95)	8.18 (1.59 to 14.77)*	−0.49 (−4.77 to 3.80)
Other races	2.26 (−5.86 to 10.37)	4.08 (−1.70 to 9.86)	−0.02 (−7.69 to 7.66)	−0.51 (−4.74 to 3.73)

dy/dx, marginal effect (% change of the dependent variable for each one point of the predictor variables).
*<0.05; **<0.01; ***<0.001.
CADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; IBM, inclusion body myositis; IMNM, immune-mediated necrotising myopathy; PM, polymyositis.

Table 4 Multivariate analysis of the extent of the different thigh MRI features (percentage of muscles involved) in patients with anti-HMGCR-associated myositis compared with those with anti-SRP-associated myositis using fractional probit regression

	Oedema dy/dx (95% CI)	Atrophy dy/dx (95% CI)	Fatty replacement dy/dx (95% CI)	Fascial oedema dy/dx (95% CI)
IMNM autoantibody group (anti-SRP vs anti-HMGCR)	6.92 (−9.74 to 23.58)	19.18 (6.52 to 31.84)**	17.64 (0.59 to 34.70)*	6.59 (−1.38 to 14.56)
Age at onset (10 years)	−2.04 (−7.33 to 3.25)	0.28 (−4.69 to 5.25)	0.06 (−5.53 to 5.65)	1.35 (−1.85 to 4.56)
Time from onset to MRI (logarithm of months)	−21.98 (−35.02 to −8.93)***	11.21 (−2.96 to 25.38)	20.50 (6.34 to 34.66)**	−2.32 (−9.08 to 4.45)
Sex (female)	−10.63 (−26.29 to 5.04)	5.06 (−8.39 to 18.50)	−2.68 (−17.65 to 12.30)	−6.19 (−13.14 to 0.76)
Race (referenced to white patients)				
Black	8.41 (−8.93 to 25.75)	4.42 (−8.56 to 17.40)	11.98 (−4.41 to 28.37)	−4.47 (−10.05 to 1.10)
Other races	6.18 (−16.62 to 28.97)	16.62 (−11.24 to 44.48)	−24.72 (−48.05 to −1.39)*	−3.18 (−9.81 to 3.45)

dy/dx, marginal effect (% change of the dependent variable for each one point of the predictor variables).
Multivariate analysis adjusted for treatment (administration of corticosteroid, intravenous immunoglobulins, rituximab, mycophenolate, methotrexate or azathioprine).
*<0.05; **<0.01; ***<0.001.
HMGCR, HMG-CoA reductase; IMNM, immune-mediated necrotising myopathy; SRP, signal recognition particle.

disease than later on (and required a logarithmic transformation of the length of illness to linearise its relationship with the tMRI features) (table 3).

Excluding the patients with only 'possible' DM and PM from the analysis did not change the results (see online supplementary table S5).

tMRI features most associated with each myositis subgroup

We used forward logistic regression to select individual muscles and tMRI features that were most uniquely associated with IMNM compared with the other clinical subgroups. This analysis revealed that adductor brevis oedema and obturator externus atrophy were especially common in IMNM. In contrast, fascial oedema in the semitendinosus was particularly rare in IMNM compared with the other subgroups.

We performed similar analyses to identify tMRI features that are preferentially associated with the other myositis subgroups. In IBM, fatty replacement of the vastus lateralis and atrophy of the vastus medialis were more prevalent than in other subgroups; in contrast, oedema in the obturator internus was particularly rare in IBM. Patients with PM had no defining pattern of muscle involvement by tMRI; however, oedema and fascial oedema in the rectus femoris were particularly uncommon with this diagnosis. Interestingly, these analyses revealed that fascial oedema is the hallmark tMRI feature of DM. Indeed, fascial oedema surrounding the rectus femoris and the semimembranosus were the most supportive features for DM, while the presence of atrophy in the vastus medialis and oedema in the biceps femoris were the two features most unlikely to be found in this subgroup of patients (see online supplementary table S6).

We next determined how well the patterns of muscle involvement using tMRI could be used to diagnose the different myositis subgroups. However, after selecting the most balanced cut-off for the logistic regression formulas using Youden's index, we estimated that the positive predictive value of these formulas was suboptimal, with a value >60% only in patients with IBM. Nonetheless, the negative predictive values of these formulas were excellent in IBM (94.7%) and IMNM (93.1%) and very good in DM (88.3%). (see online supplementary table S7 and figure S1).

DISCUSSION

Patients with IMNM comprise a significant fraction of patients with idiopathic inflammatory myopathies. Indeed, 15% of patients from Johns Hopkins Myositis Center Longitudinal

Cohort meeting criteria for this study had IMNM. Although a number of prior reports have used muscle MRI to characterise muscle abnormalities in patients with PM, DM, IBM[4 5 7 17–21] and even anti-SRP,[22] no studies have systematically investigated the MRI findings in patients with IMNM compared with the other clinical groups. Here, we demonstrate that patients with IMNM have significantly more widespread muscle oedema, atrophy and fatty replacement compared with those with PM and DM. Our analysis also reveals that patients with IMNM have a characteristic pattern of muscle involvement. Taken together, these findings reinforce the idea that IMNM represents a unique form of myositis that can be distinguished from PM based on autoantibodies and muscle biopsy findings, and on the extent and pattern of muscle involvement. Moreover, comparing the two most common autoantibody groups in IMNM we have found that patients with anti-SRP show evidence of more severe muscle involvement than those with anti-HMGCR, reinforcing that autoantibodies define distinct groups and serve as important prognostic factors in patients with myositis.

In addition to MRI features that were specific to IMNM, we identified some characteristics that apply to all forms of myositis. For example, we found that fatty replacement occurs relatively early in all forms of myositis and spreads to additional muscle groups most quickly during the early phases of disease. This novel observation is consistent with the importance of early therapeutic intervention with immunosuppressive agents so as to maximise the chances of limiting the spread of disease in patients with PM, DM and IMNM. Unfortunately, to date, no therapies have been shown to affect disease progression in IBM.

Several articles have noted that fascial oedema appears to be a characteristic of DM muscle MRI.[3 4] However, the current study is the first to conclusively demonstrate that fascial oedema is more common and widespread in DM compared with other forms of myositis. This finding is consistent with muscle biopsies from patients with DM, which often show inflammation within the perimysium.

We used forward logistic regression models in an attempt to identify diagnostic patterns of muscle involvement in patients with each myositis subtype. Ultimately, these models yielded patterns that had only modest positive predictive values for identifying the different forms of myositis. Of note, we found that models for PM performed especially poorly, which is consistent with PM including an especially heterogeneous population of patients.

This study has a number of limitations. First, because most patients had only one muscle MRI, we were unable to perform longitudinal studies on individual patients. Nonetheless, the large sample size, with patients undergoing MRI at various times during their disease course, allowed us to use statistical methods to model how the duration of disease affects muscle MRI features in different myositis subsets. Second, our study only included information about whether the features analysed here were present within a given muscle; even though the tMRI protocol included semiquantitative assessment at an individual muscle level for each radiologic feature (three levels of extent for all tMRI features), we considered that analysing the presence/absence of each tMRI feature would increase the reproducibility of our findings and simplify the methodology of our analysis. Therefore, we analysed patterns of muscle involvement and the spread of involvement to additional muscles over time, but we did not analyse the extent of the muscle features within a given muscle. Third, only about 50% of the patients (666 out of 1312 patients) had an available tMRI performed at Hopkins. Various reasons lead to the lack of a tMRI, including scheduling issues, availability of a recent tMRI outside Hopkins and patient consent. However, the proportion of patients in each clinical group with a tMRI was similar (IMNM: 55.5%; IBM: 57.1%; PM: 51.2%; DM: 46.3%; CADM: 37.8%). Given the type of features that we analysed and the final large sample size, it is unlikely that selection bias could have significantly influenced our results. Finally, interobserver reproducibility was not formally assessed but the clinical practice for myositis interpretations was to use a standardised set of definitions developed and agreed upon by the two participating radiologists in consensus so as to minimise this bias.

These limitations notwithstanding, this study demonstrates that patients with IMNM have especially extensive muscle involvement compared with other forms of myositis, that patients with IMNM have a characteristic pattern of muscle abnormalities involving hip rotators and glutei, and that patients with DM have the most widespread fascial involvement. Our analysis also revealed that in IMNM the spread of abnormalities (including fatty replacement) to additional muscles within the thigh occurs most quickly near the onset of disease and that patients with anti-SRP have more severe muscle involvement compared with patients with anti-HMGCR.

Correction notice This article has been corrected since it was published Online First. Details of the co-corresponding author have been included.

Contributors All authors listed have contributed sufficiently to the project to be included as authors and to take public responsibility for its content, and all those who are qualified to be authors are listed in the author byline.

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IMAGE ACQUISITION PARAMETERS

T1-weighted coronal (repetition time (TR): 680-790 msec; echo time (TE): 8-12 msec; 12; slice thickness (SL), 5 mm; gap, 1 mm; flip angle (FA) and axial (TR , 680-790 msec; TE, 8-12 msec; SL, 6 mm; gap, 1 mm;)

STIR coronal (TR, 3500-6800 msec; TE, 42-58 msec; SL, 6 mm; gap, 1 mm;) and axial (TR , 3500-6800 msec; TE, 42-58 msec; SL, 7 mm; gap, 1 mm)

MRI DEFINITIONS APPENDIX

Overview:

Several parameters will be used for characterization and analysis of myositis MR images, including edema-like signal (muscle edema), fatty infiltration, atrophy, fascial edema and interfascial edema.

Rationale:

Generation of granular semiquantitative data will allow thorough analysis of myopathy MR images in a systematic, objective and reproducible fashion.

Method:

Each muscle is graded with respect to each parameter, as defined below.

When grading of a muscle is not possible, the following designations are used:

NA = not applicable (e.g. amputation, surgical resection)

NI = not interpretable (e.g. artifact prevents reasonable interpretation)

1. EDEMA-LIKE SIGNAL (MUSCLE EDEMA)

Muscle edema is defined as increased signal intensity within muscle tissues on fluid-sensitive sequences (e.g. STIR or fat suppressed T2 weighted images). As there are no absolute values or standardization for MRI signal intensity, internal references are used for comparison. Signal alteration is characterized by degree and extent.

A 4 point scale is employed to grade degree of muscle edema: normal (0), mild (1), moderate (2), or severe (3). In this scheme, normal muscle signal without edema-like signal is graded as 0, and fluid-like signal (the brightest signal on fluid-sensitive sequences) is graded as 3. Mild muscle edema (grade 1) is defined as increased fluid signal within muscle tissue, up to 1/3 of fluid signal intensity (qualitatively or quantitatively, using ROI signal measurements), with moderate (grade 2) defined as greater than mild and less than severe; that is, more than 1/3rd but not fluid-like signal intensity. Where muscle signal intensity is heterogeneous, the most severe focus of edema is scored.

Extent will be rated on a similar 4 point scale:

0 = none
1 = up to 1/3 of muscle volume involved
2 = 1/3 – 2/3 of muscle volume involved
3 = greater than 2/3 of muscle volume involved

Figures

Grade 0: normal
Grade 1: mild
Grade 2: moderate
Grade 3: severe

2. FATTY INFILTRATION

Fatty infiltration refers to replacement of muscle tissue with fat. On MRI, it is defined as intramuscular T1 hyperintense signal, which suppresses on STIR or fat-saturated images.

Grading is based on the estimated proportion of affected muscle volume using a 4 point scale:

0 = none
1 = up to 1/3 of muscle volume involved
2 = 1/3 – 2/3 of muscle volume involved
3 = greater than 2/3 of muscle volume involved

Figures

Grade 0: normal
Grade 1: mild
Grade 2: moderate
Grade 3: severe

3. ATROPHY

Muscle atrophy is defined as reduced muscle bulk. On MRI, atrophy is graded based on subjective assessment of the cross-sectional area of a muscle, compared to the contralateral side or other muscle groups. Cross sectional area will be estimated at the muscle's greatest area on axial images (typically mid-belly).

Grading is based on the estimated proportion of muscle volume loss using a 4 point scale:

0 = none (no loss of bulk)
1 = up to 1/3 loss of bulk
2 = 1/3 – 2/3 loss of bulk
3 = greater than 2/3 loss of bulk

4. FASCIAL EDEMA

Fascial edema is defined as circumferential fluid-like signal around the periphery of a muscle.

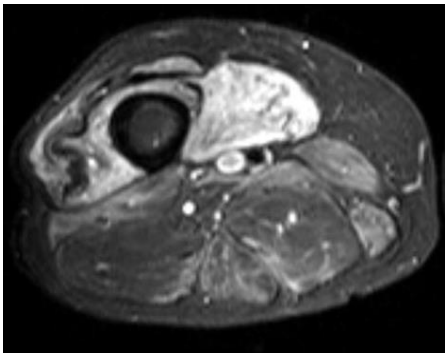
Grading is based on the estimated proportion of perimuscular signal abnormality using a 4 point scale:

0 = none
1 = up to 1/3 of circumference involved
2 = 1/3 – 2/3 of circumference involved
3 = greater than 2/3 of circumference involved

5. INTERFASCIAL EDEMA

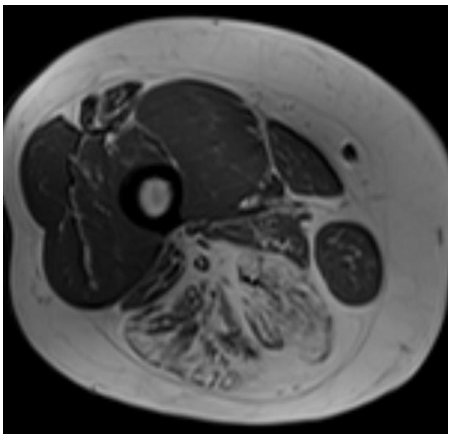
Interfascial edema refers to fluid-like signal between groups of muscles, and is graded subjectively based on reference images for each lower extremity, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Muscle edema



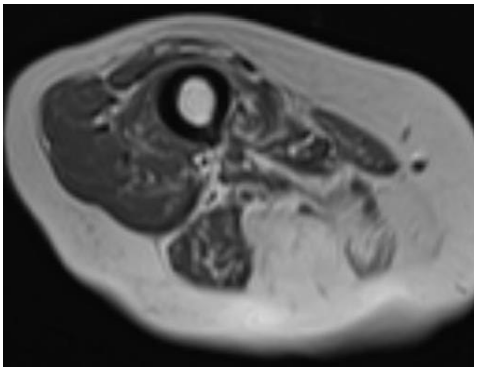
Grade 3 = Right vastus medialis
Grade 2 = Right semitendinosus, gracilis and sartorius
Grade 1 = Right biceps femoris

Fatty replacement



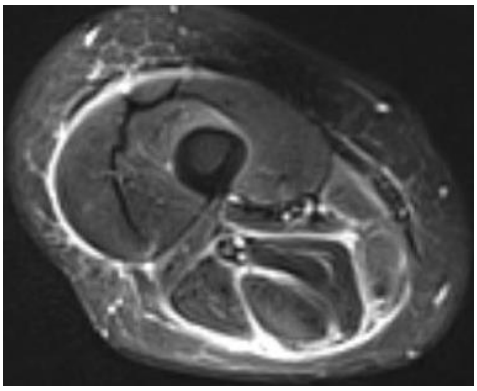
Grade 3 = Semimembranosus, semitendinosus
Grade 2 = Biceps femoris
Grade 1 = Adductor magnus, rectus femoris
Grade 0 = Vastus lateralis, vastus intermedius, vastus medialis, sartorius and gracilis

Muscle atrophy



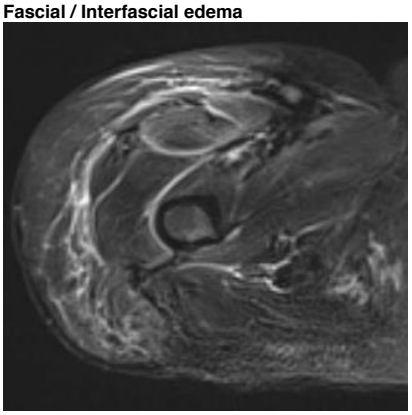
Grade 3 = Vastus medialis, adductor magnus
Grade 2 = Rectus femoris, semimembranosus
Grade 1 = Vastus intermedius
Grade 0 = Vastus lateralis

Fascial edema



Grade 3 = Semitendinosus, semimembranosus, biceps femoris
Grade 2 = Vastus lateralis, rectus femoris, sartorius, gracilis
Grade 1 = Vastus intermedius

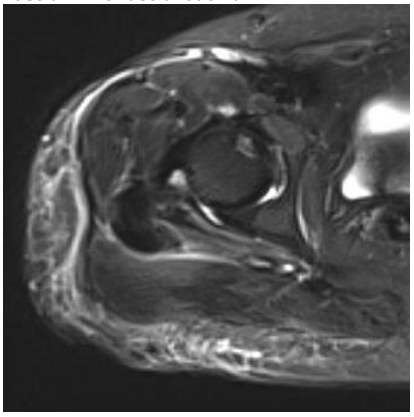
Fascial / Interfascial edema



Fascial edema
Grade 2 = Right obturator externus
Grade 3 = Right rectus femoris, vastus lateralis

Interfascial edema
Anterior compartment right thigh

Fascial / Interfascial edema



Fascial edema
Grade 2 = Right gluteus maximus, obturator internus

Interfascial edema
Anterior and lateral right thigh

MRI SCORE SHEET

History: Evaluate for myositis.

Technique: Coronal T1 and STIR, sagittal T1 and T2 and axial T1 and STIR weighted images of the bilateral femurs.

Findings:

HIP ROTATORS:

RIGHT: The gluteus maximus muscle demonstrates #/# muscle edema, # atrophy, # replacement and # fascial edema. The obturator internus muscle demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The obturator externus muscle demonstrates # muscle edema, # atrophy, # replacement and # fascial edema.

LEFT: The gluteus maximus muscle demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The obturator internus muscle demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The obturator externus muscle demonstrates # muscle edema, # atrophy, # replacement and # fascial edema.

ANTERIOR COMPARTMENT:

RIGHT: The rectus femoris muscle demonstrates #/# muscle edema, # atrophy, # replacement and # fascial edema. The vastus medialis muscle demonstrates #/# muscle edema, # atrophy, # replacement and # fascial edema. The vastus intermedius muscle demonstrates #/# muscle edema, # atrophy, # replacement and # fascial edema. The vastus lateralis muscle demonstrates #/# muscle edema, # atrophy, # replacement and # fascial edema.

LEFT: The rectus femoris muscle demonstrates #/# muscle edema, # atrophy, # replacement and # fascial edema. The vastus medialis muscle demonstrates #/# muscle edema, # atrophy, # replacement and # fascial edema. The vastus intermedius muscle demonstrates #/# muscle edema, # atrophy, # replacement and # fascial edema. The vastus lateralis muscle demonstrates #/# muscle edema, # atrophy, # replacement and # fascial edema.

MEDIAL COMPARTMENT:

RIGHT: The sartorius demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The gracilis demonstrates 0 muscle edema, # atrophy, # replacement and # fascial edema. The adductor longus demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The adductor brevis demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The adductor magnus demonstrates # muscle edema, # atrophy, # replacement and # fascial edema.

LEFT: The sartorius demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The gracilis demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The adductor longus demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The adductor brevis demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The adductor magnus demonstrates # muscle edema, # atrophy, # replacement and # fascial edema.

POSTERIOR COMPARTMENT:

RIGHT: The semimembranosus demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The semitendinosus demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The biceps femoris demonstrates # muscle edema, # atrophy, # replacement and # fascial edema.

LEFT: The semimembranosus demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The semitendinosus demonstrates # muscle edema, # atrophy, # replacement and # fascial edema. The biceps femoris demonstrates # muscle edema, # atrophy, # replacement and # fascial edema.

INTERFASCIAL EDEMA:
RIGHT: #
LEFT: #

COMMENTS:

INTERPRETATION:

IMPRESSION:

Supplementary Table S1. Muscles and muscle groups analyzed in each thigh.

Compartments	Muscles
Gluteal	Gluteus maximus
Lateral rotator group	Obturator internus Obturator externus
Anterior	Rectus femoris Vastus medialis Vastus intermedius Vastus lateralis Sartorius
Medial	Gracillis Adductor longus Adductor brevis Adductor magnus
Posterior	Semimembranosus Semitendinosus Biceps femoris

Supplementary Table S3. Correlation of the different thigh MRI features among the different clinical groups

	IMNM			IBM(n=153)	PM(n=176)	DM(n=219)	CADM(n=17)	Total(n=666)
	Total (n=101)	HMGCR(n=50)	SRP(n=22)					
	Corr. coeff	Corr. coeff	Corr. coeff	Corr. coeff	Corr. coeff	Corr. coeff	Corr. coeff	Corr. coeff
Atrophy vs. Fatty replac.	0.48***	0.47***	0.54**	0.47***	0.42***	0.45***	0.84***	0.54***
Edema vs. Fatty replac.	0.27**	0.18	0.20	0.40***	0.37***	0.28***	-0.03	0.39***
Edema vs. Atrophy	0.31**	0.23	0.22	0.05	0.37***	0.27***	-0.01	0.33***
Edema vs. Fascial edema	0.31**	0.26	0.48*	0.04	0.38***	0.49***	0.80***	0.30***
Fatty replac. vs. Fascial edema	0.01	0.01	0.06	-0.12	0.02	0.18**	0.19	-0.02
Atrophy vs. Fascial edema	0.03	0.09	-0.02	-0.10	0.12	0.05	0.26	-0.06

* <0.05; ** <0.01; *** <0.001

IMNM: necrotizing myopathy; IBM: inclusion body myositis; PM: polymyositis; DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis
Correlation was calculated using Pearson´s correlation coefficient.

Supplementary Table S2. Difference in the percentage of thigh MRI findings between right and left thighs.

	IMNM			IBM (n=153)	PM (n=176)	DM (n=219)	CADM (n=17)	Total (n=666)
	Total (n=101)	HMGCR (n=50)	SRP (n=22)					
	mean(SD)	mean(SD)	mean(SD)	mean(SD)	mean(SD)	mean(SD)	mean(SD)	mean(SD)
Absolute difference								
Edema	3.4(5.1)	3.0(5.1)	3.4(4.0)	3.8(5.5)	3.3(5.5)	3.2(6.2)	1.2(2.6)	3.3(5.6)
Atrophy	1.8(5.6)	0.8(2.6)	2.5(5.1)	2.5(5.2)***	0.7(2.6)*	0.7(3.7)*	2.0(8.1)	1.3(4.4)
Fatty replacement	2.6(6.0)**	2.3(6.2)	4.5(6.9)	2.1(4.0)*	1.2(3.5)	0.9(2.9)**	0.0(0.0)	1.5(3.9)
Fascial edema	1.6(3.9)	0.9(2.2)**	4.1(6.4)**	1.6(3.6)	1.3(3.6)	2.2(4.7)*	0.8(3.2)	1.7(4.0)
Right minus left side								
Edema	0.8(6.1)	1.0(5.8)	0.3(5.3)	-0.3(6.7)	-0.2(6.4)	0.1(7.0)	0.4(2.9)	0.0(6.5)
Atrophy	0.7(5.8)	0.8(2.6)	1.9(5.4)	-0.2(5.8)	0.1(2.7)	-0.2(3.7)	-2.0(8.1)	-0.0(4.6)
Fatty replacement	-0.0(6.5)	-0.4(6.7)	2.2(7.9)	0.2(4.5)	0.2(3.7)	0.0(3.0)	0.0(0.0)	0.1(4.2)
Fascial edema	-0.3(4.2)	-0.3(2.3)	-1.6(7.4)	0.6(3.8)	0.2(3.8)	0.6(5.2)	0.8(3.2)	0.4(4.4)

* <0.05; ** <0.01; *** <0.001

IMNM: necrotizing myopathy; IBM: inclusion body myositis; PM: polymyositis; DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis

Mean percentage of each major clinical group (IMNM, IBM, PM, DM and CADM) compared with the rest of the sample using Student´s t-test. Anti-HMGCR and anti-SRP patients were compared between them (anti-HMGCR with anti-SRP and vice versa).

Supplementary Table S5. Multivariate analysis of the extent of the different thigh MRI features (percentage of muscles involved) among different clinical subsets using fractional probit regression after excluding patients with possible DM and PM .

	Edema	Atrophy	Fatty replacement	Fascial edema
	dy/dx (95%CI)	dy/dx (95%CI)	dy/dx (95%CI)	dy/dx (95%CI)
Clinical subset (referenced to IMNM)				
IBM	-7.14 [-15.01,0.73]	0.80 [-4.91,6.52]	-0.28 [-7.82,7.26]	1.13 [-4.89,7.14]
PM	-20.22 [-28.09,-12.35]***	-8.65 [-15.28,-2.03]*	-9.54 [-17.37,-1.72]*	0.43 [-4.65,5.51]
DM	-20.64 [-28.47,-12.81]***	-18.90 [-25.40,-12.39]***	-16.30 [-23.62,-8.99]***	10.39 [5.80,14.98]***
CADM	-66.29 [-91.44,-41.15]***	-28.52 [-43.05,-13.98]***	-33.12 [-49.15,-17.09]***	1.87 [-7.27,11.01]
Age at onset (10 years)	0.35 [-1.68,2.38]	2.17 [0.36,3.97]*	1.73 [-0.24,3.69]	-0.80 [-1.79,0.19]
Time from onset to MRI (logarithm of months)	-10.78 [-16.98,-4.57]***	10.93 [5.98,15.89]***	16.89 [11.28,22.49]***	-4.75 [-7.76,-1.73]**
Sex (female)	-10.17 [-15.62,-4.72]***	2.95 [-1.23,7.13]	-9.63 [-14.55,-4.71]***	-3.37 [-6.58,-0.17]*
Race (referenced to white patients)				
Black	2.19 [-6.44,10.82]	-0.22 [-7.26,6.81]	8.01 [0.39,15.62]*	-0.63 [-5.61,4.35]
Other races	1.99 [-6.88,10.87]	4.77 [-1.80,11.34]	2.01 [-6.32,10.34]	-1.05 [-5.60,3.50]

* <0.05; ** <0.01; *** <0.001

dy/dx: Marginal effect (% change of the dependent variable for each 1 point of the predictor variables)

MRI: magnetic resonance imaging; IBM: inclusion body myositis; IMNM: necrotizing myopathy; PM: polymyositis; DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis

Supplementary Table S4. Prevalence of the different features among the different clinical groups

	IMNM			IBM (n=153)	PM (n=176)	DM (n=219)	CADM (n=17)	Total (n=666)
	Total (n=101)	HMGCR (n=50)	SRP (n=22)					
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Gluteal edema	56% (57)***	58% (29)	68% (15)	31% (48)	34% (60)	38% (83)	18% (3)	38% (251)
Lat. rot. edema	40% (40)***	34% (17)*	59% (13)*	13% (20)***	24% (42)	29% (64)	6% (1)	25% (167)
Anterior edema	85% (86)***	82% (41)	95% (21)	94% (144)***	52% (92)***	51% (111)***	18% (3)***	65% (436)
Medial edema	75% (76)***	80% (40)	91% (20)	76% (117)***	47% (83)**	43% (95)***	12% (2)***	56% (373)
Posterior edema	80% (81)***	84% (42)	91% (20)	78% (120)***	48% (84)**	40% (87)***	6% (1)***	56% (373)
Interfascial edema	5% (5)	4% (2)	0%	3% (5)*	7% (13)	10% (21)	18% (3)	7% (47)
Gluteal atrophy	22% (22)***	20% (10)	36% (8)	10% (15)	11% (20)	7% (16)*	0%	11% (73)
Lat. rot. atrophy	43% (43)***	40% (20)*	73% (16)*	25% (38)	19% (33)	8% (18)***	0%*	20% (132)
Anterior atrophy	33% (33)	26% (13)*	50% (11)*	76% (116)***	22% (39)**	10% (21)***	12% (2)	32% (211)
Medial atrophy	36% (36)**	32% (16)*	64% (14)*	45% (69)***	20% (35)	7% (16)***	6% (1)	24% (157)
Posterior atrophy	27% (27)**	24% (12)	41% (9)	32% (49)***	12% (21)*	8% (18)***	0%	17% (115)
Gluteal fatty replacement	54% (55)***	60% (30)	55% (12)	39% (59)	45% (79)	29% (63)***	29% (5)	39% (261)
Lat. rot. fatty replacement	35% (35)***	32% (16)*	59% (13)*	19% (29)	18% (31)	6% (14)***	0%	16% (109)
Anterior fatty replacement	51% (52)	42% (21)*	73% (16)*	88% (134)***	44% (77)	28% (62)***	12% (2)**	49% (327)
Medial fatty replacement	54% (55)*	52% (26)	73% (16)	68% (104)***	43% (75)	24% (53)***	6% (1)**	43% (288)
Posterior fatty replacement	66% (67)**	64% (32)	77% (17)	73% (112)***	50% (88)	36% (79)***	12% (2)***	52% (348)
Gluteal fascial edema	14% (14)	16% (8)	16% (8)	16% (25)	10% (18)	12% (27)	12% (2)	13% (86)
Lat. rot. fascial edema	7% (7)	6% (3)	6% (3)	5% (7)	5% (8)	8% (18)	0%	6% (40)
Anterior fascial edema	21% (21)	12% (6)	12% (6)	13% (20)***	16% (28)**	38% (84)***	12% (2)	23% (155)
Medial fascial edema	13% (13)*	8% (4)	8% (4)	11% (17)***	18% (32)	33% (72)***	24% (4)	21% (138)
Posterior fascial edema	12% (12)**	10% (5)	10% (5)	21% (32)	17% (30)*	38% (83)***	24% (4)	24% (161)

* <0.05; ** <0.01; *** <0.001

IMNM: necrotizing myopathy; IBM: inclusion body myositis; PM: polymyositis; DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis
Prevalence of each major clinical group (IMNM, IBM, PM, DM and CADM) was compared with the rest of the sample. Anti-HMGCR and anti-SRP patients were compared between them (anti-HMGCR with anti-SRP and vice versa). Chi-squared test or Fisher´s exact test were used as appropriate.

Supplementary Table S6: Most relevant muscles and muscle features for each diagnostic group.

Immune mediated necrotizing myositis			Inclussion body myositis			Polymyositis			Dermatomyositis		
	OR	[95%CI]		OR	[95%CI]		OR	[95%CI]		OR	[95%CI]
Adductor brevis edema	3.3	[1.9,5.8]***	Vastus lateralis fatty replacement	8.7	[4.5,16.9]***	Rectus femoris edema	0.5	[0.3,0.7]***	Vastus medialis atrophy	0.3	[0.1,0.5]***
Semitendinosus fascial edema	0.1	[0.0,0.3]***	Vastus medialis atrophy	3.8	[2.0,7.3]***	Rectus femoris fascial edema	0.3	[0.1,0.6]**	Rectus femoris fascial edema	3.7	[1.9,7.1]***
Obturator externus atrophy	4.6	[2.4,8.9]***	Obturator internus edema	0.2	[0.1,0.4]***				Biceps femoris edema	0.2	[0.1,0.3]***
Vastus lateralis fatty replacement	0.3	[0.1,0.5]***	Vastus intermedius edema	3.9	[2.1,7.2]***				Semimembranosus fascial edema	2.9	[1.7,4.8]***
Biceps femoris edema	3.6	[2.0,6.4]***	Gluteus maximus fatty replacement	0.4	[0.2,0.7]***				Vastus medialis fatty replacement	0.4	[0.2,0.6]***
Obturator internus fatty replacement	2.7	[1.3,5.5]**	Adductor brevis edema	0.2	[0.1,0.4]***				Sartorius edema	2.0	[1.2,3.2]**
Gracillis atrophy	0.3	[0.1,0.8]*	Adductor magnus edema	3.0	[1.6,5.6]***						
			Adductor longus atrophy	0.2	[0.1,0.5]***						
			Gracillis atrophy	3.8	[1.6,9.0]**						
			Gracillis fascial edema	0.3	[0.1,0.8]*						

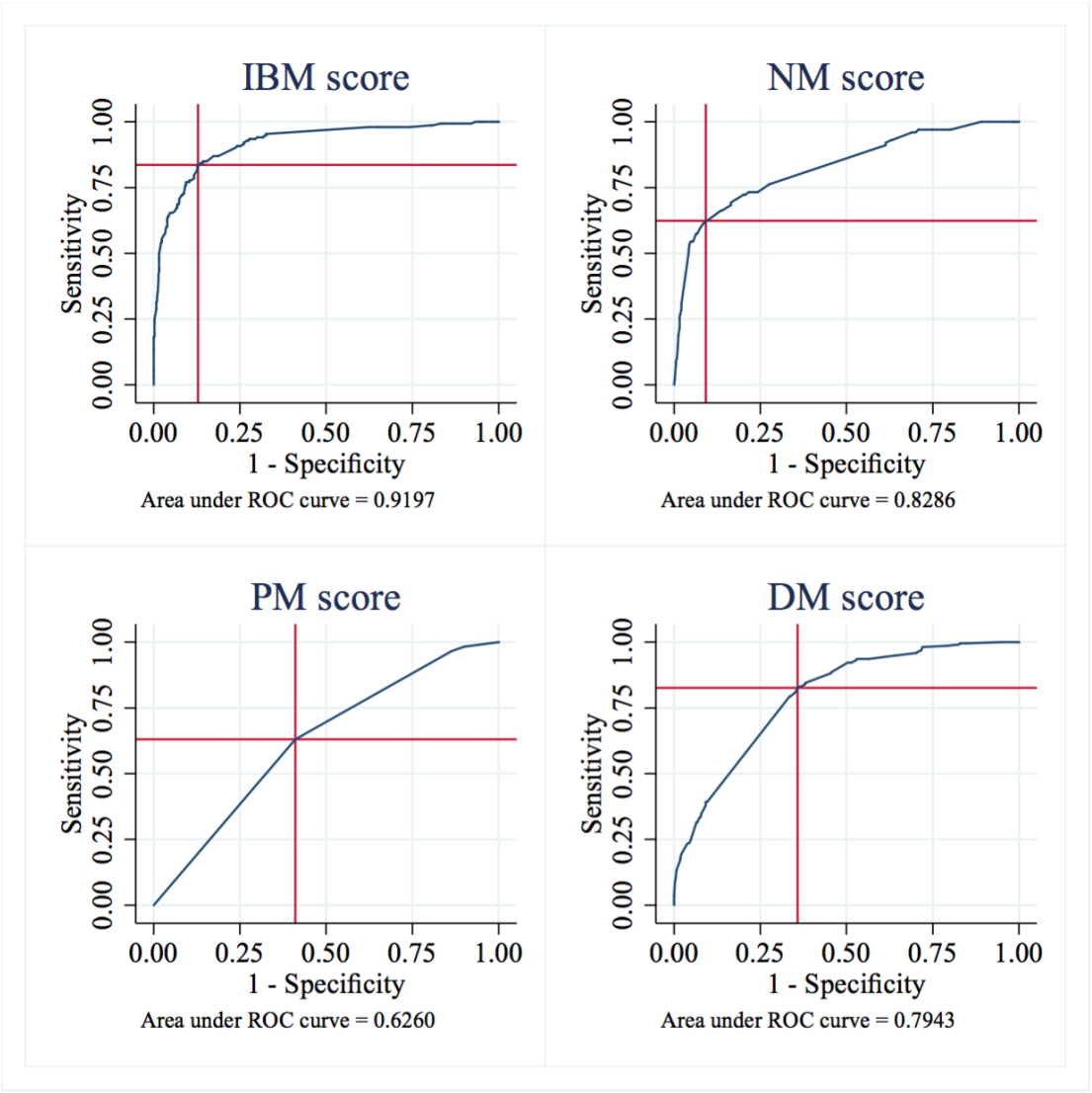
* p<0.05, ** p<0.01, *** p<0.001

Supplementary Table S7: Diagnostic performance of the scoring formulas using the cutoff that maximized Youden´s index.

Score	Formula	AUC(95%CI)	cAUC	Best cutoff	Sensitivity	Specificity	PPV	NPV
IMNM	1/(1+exp(-1.21*E_addbrev + 2.45*F_semit - 1.52*A_obtexternus + 1.33*R_vaslat - 1.27*E_bicfemoris - 1.00*R_obtinternus + 1.20*A_gra + 2.53)	0.83(0.78-0.88)	0.78	0.2	62.4	90.8	54.8	93.1
IBM	1/(1+exp(-2.17*R_vaslat - 1.33*A_vasmedialis + 1.70*E_obtinternus - 1.37*E_vasintermedius + 1.00*R_glutmax + 1.60*E_addbrev - 1.09*E_addmag + 1.65*A_addlon - 1.34*A_gra + 1.14*F_gra + 2.97)	0.92(0.89-0.95)	0.89	0.3	83.7	87.1	66.0	94.7
PM	1/(1+exp(0.74*E_rectfemoris + 1.34*F_rectfemoris + 0.59)	0.63(0.58-0.67)	0.58	0.3	63.1	59.0	35.6	81.6
DM	1/(1+exp(1.30*A_vasmedialis - 1.30*F_rectfemoris + 1.59*E_bicfemoris - 1.05*F_semim + 0.95*R_vasmedialis - 0.67*E_sar + 0.26)	0.79(0.76-0.83)	0.76	0.3	82.6	64.2	53.1	88.3

IMNM: necrotizing myopathy; IBM: inclusion body myositis; PM: polymyositis; DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis

Supplementary Figure S1. Diagnostic utility of the thigh MRI scoring formulas (from Supplementary Table S7) in necrotizing myositis (NM), inclusion body myositis (IBM), polymyositis (PM) and dermatomyositis (DM).*



**Receiver operating characteristic (ROC) curves.*

2. High-resolution manometry in myositis

Casal-Dominguez M, Pinal-Fernandez I, Mego M, et al. High-resolution manometry in patients with idiopathic inflammatory myopathy: Elevated prevalence of esophageal involvement and differences according to autoantibody status and clinical subset. Muscle Nerve 2016.

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HIGH-RESOLUTION MANOMETRY IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY: ELEVATED PREVALENCE OF ESOPHAGEAL INVOLVEMENT AND DIFFERENCES ACCORDING TO AUTOANTIBODY STATUS AND CLINICAL SUBSET

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ABSTRACT: *Introduction:* In this study we assessed high-resolution manometry (HRM) findings in patients with dermatomyositis and polymyositis. *Methods:* From 2008 to 2015, we performed a cross-sectional study of myositis patients. A survey of esophageal symptoms and HRM data were analyzed and compared among different clinical and serologic groups. *Results:* Twenty-four (45%) of the 53 patients included in the study had manometric involvement that was not correlated with any esophageal symptom ($P = 0.8$). Failed waves (34% vs. 0%, $P = 0.004$) and decreased upper esophageal sphincter pressure (50 vs. 70 mm Hg, $P = 0.03$) were more common in polymyositis than in dermatomyositis patients. Jackhammer esophagus was more common in anti–TIF1-γ patients (30% vs. 9%, $P = 0.04$), and lower esophageal sphincter involvement (47% vs. 25%, $P = 0.03$) was more prevalent in patients with the antisynthetase syndrome. *Conclusions:* Esophageal involvement is common in myositis patients, but it correlates poorly with esophageal symptoms. Specific clinical and serologic groups have different manometric features.

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Idiopathic inflammatory myopathies (IIM) are autoimmune systemic diseases characterized by variable skeletal muscle, skin, and lung involvement.[1] Dysphagia has been reported in 32%–84% of IIM patients, mainly as a reflection of the inflammation of the skeletal muscle of the pharynx and the upper third of the esophagus.[2] Interestingly, some investigators have described involvement of the lower part of the esophagus. This part of the gastrointestinal tract is comprised of smooth muscle, which is not the usual target of the inflammatory response in IIM,[3–5] but it is commonly involved in other autoimmune diseases, such as systemic sclerosis.[6]

High-resolution esophageal manometry (HRM) is a new method to assess esophageal motility using a catheter that contains more pressure-recording channels than conventional manometry (between 20 and 36). These channels, spaced at 1-cm intervals, provide higher spatial resolution to detect motor abnormalities limited to a short segment of the esophagus.[7] The normal values for HRM have been well defined in both American and European populations.[8–12] Chicago Classification v3.0, released in 2015, was developed to categorize esophageal motility disorders utilizing HRM.[9]

Although the highest incidence of dysphagia (65%–86%) has been reported in inclusion-body myositis (IBM), 30%–60% of polymyositis (PM) and 18%–20% of dermatomyositis (DM) patients have this manifestation of the disease.[13,14] Although dysphagia in DM and PM responds better to treatment than in IBM,[14] esophageal involvement has been less studied in these 2 diseases.

In this study we examined the HRM findings and the esophageal symptoms among clinical and serologic groups of patients with DM and PM.

METHODS

Patients. From November 2008 to January 2015, a sample of consecutive patients from the Vall d'Hebron Hospital myositis cohort of patients with probable or definite PM or DM according to Bohan and Peter criteria[1] were recruited for this study. Patients with IIM who fulfilled criteria for another defined connective tissue disease were included as myositis overlap syndrome cases, and those with a diagnosis of cancer within 3 years of the diagnosis of myositis were considered cancer-associated myositis (CAM) cases. No patients with sporadic IBM were included in the study. Serologic groups were defined according to the positivity of the

Abbreviations: AS, antisynthetase syndrome; CAM, cancer-associated myositis; CK, creatine kinase; DCI, distal contractile integral; DL, distance contractile latency; DM, dermatomyositis; EGJ, esophagogastric junction; FVC, forced vital capacity; HRM, high-resolution manometry; IBM, inclusion-body myositis; IBP, intrabolus pressure; IIM, idiopathic inflammatory myopathies; ILD, interstitial lung disease; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; PM, polymyositis; Q1, first quartile; Q3, third quartile; UES, upper esophageal sphincter

Key words: autoantibodies; dermatomyositis; dysphagia; esophageal involvement; high-resolution manometry; polymyositis

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different autoantibodies (antisynthetase syndrome, anti–TIF1-γ, anti-PM/Scl, and anti-Ro52).

All patients who participated received an esophageal symptom survey and subsequently underwent HRM (both during the same day). Independent operators who were not aware of the results of the other tests or the patients' clinical characteristics performed and interpreted all examinations. Creatine kinase (CK) and forced vital capacity (FVC) values obtained closest to the time of manometry were collected retrospectively through chart review. FVC values were expressed as percentages that were adjusted according to reference values proposed by Roca[15] for the Mediterranean population. The hospital ethics committee approved the study protocol and patients gave informed consent for all the procedures.

Interstitial lung disease (ILD) was established based on American Thoracic Society criteria using a multidisciplinary approach that combined clinical, radiologic, and pathologic information, as appropriate.[16]

Autoantibody Detection. Myositis-specific and associated autoantibodies were identified by enzyme-linked immunoassay (ELISA) or line immunoassay (Myositis Profile Euroline; Euroimmun, Lübeck, Germany),[17] and were confirmed by RNA or protein immunoprecipitation assay with radiolabeled HeLa cells.[18] Autoantibodies present in $>10\%$ of the patients were considered as a grouping variable for statistical analysis.

Esophageal Symptom Survey. The dysphagia survey included 5 esophageal symptoms: dysphagia for liquids; dysphagia for solids; heartburn; regurgitation; and chest pain. Individual scores for each symptom were obtained according to the following scoring system: 0 = never; 1 = less than once a month; 2 = monthly; 3 = weekly; 4 = daily; and 5 = with every meal or >3 times daily. Individual symptoms were considered clinically significant when the score was ≥ 3, as previously reported.[19]

High-Resolution Manometry. HRM was performed in all patients using a solid-state catheter with 36 circumferential sensors. The sensors were spaced 1 cm apart along the intracorporal part of the catheter assembly (Sierra Scientific Instruments, Inc., Los Angeles, California) (Fig. 1).

Fasting for a minimum of 8 hours was required before the procedure. All drugs that could interfere with esophageal motility were discontinued. The catheter was introduced transnasally with the patient seated, until the most distal recording sensors were correctly placed in the stomach. Once positioned, the catheter was fixed in place by taping it to the nose. Subsequently, the patient adopted the supine position.

The protocol started with the measurements of the basal sphincter pressures after a 30-second period baseline recording. During this time, the patient was requested to breathe normally and not swallow. A minimum of 10 swallows of water (5 ml each) were then indicated, spaced by 30 seconds. The morphology of the peristaltic waves (hypertonic, failed, hypotonic, fragmented, and normal waves), upper (UES) and lower (LES) esophageal sphincter pressures (normal UES pressure: 34–104 mm Hg; normal LES pressure: 15–47 mm Hg), and specific HRM measurements [distal contractile integral (DCI), integrated relaxation pressure (IRP), intrabolus pressure (IBP), and distance contractile latency (DL)] were calculated for each examination using dedicated software (ManoView; Given Imaging, Yoqneam, Israel). To adapt the HRM reports to actual definitions, all examinations were reviewed retrospectively at the end of the study according to the Chicago Classification v3.0. Thus, each HRM was categorized into 1 of the following groups: normal esophageal motility; ineffective esophageal motility; absent contractility; jackhammer esophagus (a disorder characterized by high-amplitude peristaltic contractions in the distal esophagus); esophagogastric junction (EGJ) outflow obstruction; achalasia type I, II, or III; distal esophageal spasm; or fragmented peristalsis.[8]

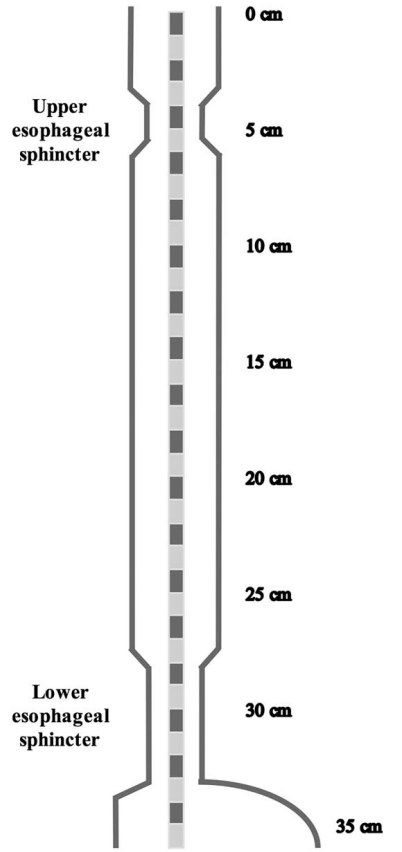

FIGURE 1. Representation of the esophagus with the high-resolution manometry catheter inside. The central scale shows the 36 circumferential sensors placed along the esophagus, spaced by 1 cm.

Statistical Analysis. Dichotomous variables are expressed as percentages and absolute frequencies. Continuous variables are expressed as mean [standard deviation (SD)] or as medians and first and third quartiles (Q1–Q3), as appropriate.

Univariate comparisons between groups were made using the Wilcoxon rank sum test or Student *t*-test for

Table 1. Clinical features and esophageal symptoms by clinical group

	Clinical groups			
	DM ($n = 24$)	PM ($n = 21$)	CAM ($n = 5$)	Total ($n = 53$)
Gender (women)	79% ($n = 19$)	76% ($n = 16$)	80% ($n = 4$)	79% ($n = 42$)
Age at manometry (years)	62.7 (14.3)	53 (16.1)	66.7 (20)	58.3 (16.4)
Time from onset (years)	5.2 (6.4)	5 (4.8)	2.9 (2.7)	5 (5.4)
Maximum CK (IU/L)	600 (300–2,000)*	1,678 (900–3,900)	1,149 (375–2,254)	1,000 (445–3,300)
ILD	46% ($n = 11$)	0% ($n = 0$)	100% ($n = 5$)	47% ($n = 25$)
Autoantibodies				
Anti-Jo1	17% ($n = 4$)	38% ($n = 8$)*	0% ($n = 0$)	23% ($n = 12$)
Anti-PL7	8% ($n = 2$)	0% ($n = 0$)	0% ($n = 0$)	4% ($n = 2$)
Anti-PL12	4% ($n = 1$)	5% ($n = 1$)	0% ($n = 0$)	4% ($n = 2$)
Anti-Mi2	17% ($n = 4$)*	0% ($n = 0$)	0% ($n = 0$)	8% ($n = 4$)
Anti–TIF1-γ	21% ($n = 5$)	10% ($n = 2$)	60% ($n = 3$)*	19% ($n = 10$)
Anti-PM/Scl	13% ($n = 3$)	14% ($n = 3$)	0% ($n = 0$)	15% ($n = 8$)
Anti-Ro52	21% ($n = 5$)	43% ($n = 9$)	40% ($n = 2$)	30% ($n = 16$)
Esophageal symptoms	46% ($n = 11$)	43% ($n = 11$)	80% ($n = 0$)	45% ($n = 24$)
Dysphagia to solids	25% ($n = 6$)	29% ($n = 9$)	40% ($n = 0$)	26% ($n = 14$)
Dysphagia to liquids	8% ($n = 2$)	24% ($n = 6$)	40% ($n = 0$)	17% ($n = 9$)
Pyrosis	8% ($n = 2$)	10% ($n = 6$)	40% ($n = 0$)	11% ($n = 6$)
Regurgitation	17% ($n = 4$)	10% ($n = 8$)	0% ($n = 0$)	11% ($n = 6$)
Painful swallowing	8% ($n = 2$)	0% ($n = 6$)	20% ($n = 0$)	6% ($n = 3$)

Comparisons made between each group (column) and the rest of the sample. Continuous variables are expressed as mean (SD) or as median (Q1–Q3), as appropriate. Qualitative variables are expressed as percent (n). DM, dermatomyositis; PM, polymyositis; CAM, cancer-associated myositis; ILD, interstitial lung disease.

*$P < 0.05$.

continuous variables, and the Fisher exact test or chi-square test for categorical variables. The Pearson coefficient was used to measure correlations between continuous variables. Multiple linear regression was used to explore the association between the FVC and manometric parameters, adjusting for possible confounding variables (age, gender, and autoantibody status).

Statistical analyses were performed using Stata version 13 (StataCorp, Inc., College Station, Texas), following the recommendations of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for reporting results of observational studies.[20] Because this was an exploratory study, a 2-sided $P < 0.05$ without multiple comparison adjustment was considered statistically significant.[21]

RESULTS

Patients. Fifty-three consecutive adult patients were included in the study (79% women; median age at manometry: 60 years): 21 had PM; 24 had DM; 5 had CAM; and 3 had an overlap syndrome. Of these 53 patients, 16 presented with antisynthetase syndrome (AS), 10 were positive for anti–TIF1-γ, 8 for anti-PM/Scl, and 16 for anti-Ro52. Among the 5 patients who had CAM, 3 were positive for anti–TIF1-γ. Among the 3 patients with overlap syndrome, 2 met criteria for systemic sclerosis according to the American College of Rheumatology/European League against Rheumatism collaborative initiative criteria[22] (both positive for anti-PM/Scl), and 1 fulfilled lupus criteria[23] (positive for anti-Ku). No patient had a history of surgery or radiotherapy involving the upper airways or known neurologic, psychiatric, or otorhinolaryngological diseases that may have caused secondary esophageal motility disorders.

Clinical and serologic groups were homogeneous with regard to gender distribution, age at manometry, and time from the onset to manometry. Maximum CK was lower in the DM patients (600 IU/L) than in the remaining patients, and ILD was highly prevalent in the AS (93%) and anti-PM/Scl (88%) groups, yet not detected in any anti–TIF1-γ patient. The median time from manometry to CK assessment was 91 days, and from the manometry to FVC assessment it was 251 days (Tables 1 and 2).

Esophageal Symptoms. Twenty-four (45%) patients had significant esophageal symptoms at the time of the HRM. Dysphagia to solids was the most common symptom (26%, $n = 14$), followed by dysphagia to liquids (17%, $n = 9$) and then pyrosis (11%, $n = 6$). No significant differences were found between the clinical and serologic groups (Tables 1 and 2).

High-Resolution Manometry. *Wave Morphology and High-Resolution Manometry Parameters.* Compared with the rest of the patients, PM patients had an increased percentage of failed waves (46% vs. 16%, $P = 0.006$) and significantly decreased UES pressure (47 vs. 70 mm Hg, $P = 0.04$).

Regarding the different autoantibody groups, anti–TIF1-γ patients had a higher DCI (2,848 vs. 1,144 mm Hg/cm·s, $P = 0.05$) and IBP (23 vs. 18 mm Hg, $P = 0.05$) and more fragmented waves

Table 2. Clinical features and esophageal symptoms by serologic group

	Serologic groups				
	AS ($n = 16$)	Anti–TIF1-γ ($n = 10$)	Anti-PM/Scl ($n = 8$)	Anti-Ro52 ($n = 16$)	Total ($n = 53$)
Gender (women)	69% ($n = 11$)	100% ($n = 10$)	75% ($n = 6$)	63% ($n = 10$)	79% ($n = 42$)
Age at manometry (years)	51.9 (13.5)	58.7 (22.4)	50.1 (17.3)	57.8 (15)	58.3 (16.4)
Time from onset (years)	4 (7.9)	3.2 (2.6)	4.9 (4.3)	4 (4)	5 (5.4)
Maximum CK (IU/L)	1,489 (636–4,185)	1,000 (479–2,174)	1,346 (729–2,048)	1,346 (729–2,048)	1,000 (445–3,300)
ILD	94% ($n = 15$)***	0% ($n = 0$)**	88% ($n = 7$)*	56% ($n = 9$)	47% ($n = 25$)
Autoantibodies					
Anti-Jo1	75% ($n = 12$)***	0% ($n = 0$)	0% ($n = 0$)	38% ($n = 6$)	23% ($n = 12$)
Anti-PL7	13% ($n = 2$)	0% ($n = 0$)	0% ($n = 0$)	6% ($n = 1$)	4% ($n = 2$)
Anti-PL12	13% ($n = 2$)	0% ($n = 0$)	0% ($n = 0$)	6% ($n = 1$)	4% ($n = 2$)
Anti-Mi2	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	8% ($n = 4$)
Anti–TIF1-γ	0% ($n = 0$)*	—	13% ($n = 1$)	13% ($n = 2$)	19% ($n = 10$)
Anti-PM/Scl	0% ($n = 0$)	10% ($n = 1$)	—	13% ($n = 2$)	15% ($n = 8$)
Anti-Ro52	50% ($n = 8$)	20% ($n = 2$)	25% ($n = 2$)	—	30% ($n = 16$)
Esophageal symptoms	38% ($n = 6$)	70% ($n = 7$)	38% ($n = 3$)	56% ($n = 9$)	45% ($n = 24$)
Dysphagia to solids	25% ($n = 4$)	50% ($n = 5$)	25% ($n = 2$)	38% ($n = 6$)	26% ($n = 14$)
Dysphagia to liquids	19% ($n = 3$)	20% ($n = 2$)	25% ($n = 2$)	25% ($n = 4$)	17% ($n = 9$)
Pyrosis	6% ($n = 1$)	20% ($n = 2$)	0% ($n = 0$)	6% ($n = 1$)	11% ($n = 6$)
Regurgitation	19% ($n = 3$)	0% ($n = 0$)	13% ($n = 1$)	25% ($n = 4$)	11% ($n = 6$)
Painful swallowing	0% ($n = 0$)	20% ($n = 2$)	13% ($n = 1$)	0% ($n = 0$)	6% ($n = 3$)

Comparisons made between each group (column) and the rest of the sample. Continuous variables are expressed as mean (SD) or as median (Q1–Q3), as appropriate. Qualitative variables are expressed as percent (n). AS, antisynthetase syndrome; ILD, interstitial lung disease.

*P < 0.05.

**P < 0.01.

***P < 0.001.

(2.2%, $P = 0.002$) than the rest of the sample. Moreover, AS patients had decreased LES pressure (17 vs. 23 mm Hg, $P = 0.04$) and an increased percentage of low LES pressure values (44% vs. 16%, $P = 0.04$) (Tables 3 and 4).

Chicago v3.0 Classification. HRM showed an esophageal disorder in half of the patients in our sample, the most common being ineffective esophageal motility (17%, $n = 9$), absent contractility (17%, $n = 9$), and jackhammer esophagus (9%, $n = 5$). Significantly fewer patients with PM had a normal HRM compared to those with DM (38% vs. 71%, $P = 0.05$), and jackhammer esophagus was significantly more frequent in the anti–TIF1-γ patients than in the rest of the sample (30% vs. 5%, $P = 0.04$) (Tables 3 and 4).

Association between Manometric Findings and Esophageal Symptoms. Esophageal symptoms were not significantly associated with manometric pattern. Indeed, 48% of the patients with normal manometry had symptoms, but just 42% of those with a pathologic HRM had significant esophageal manifestations ($P = 0.8$).

Association between Esophageal Involvement and Creatine Kinase. Median CK was not correlated with any manometric parameter and was not increased significantly in patients with esophageal symptoms or with any Chicago v3.0 diagnosis.

Association between Esophageal Involvement and Interstitial Lung Disease. Independent of their age, gender, or autoantibody status, patients with regurgitation had lower FVC than patients without regurgitation (58% vs. 79%, $P = 0.04$), and upper esophageal pressure was weakly to moderately associated with FVC ($R = 0.4$, $P = 0.04$).

DISCUSSION

In this study, using HRM we have demonstrated that patients with IIM have a high prevalence of esophageal involvement, which is more common in PM than in DM. We also found that manometric involvement is poorly correlated with the esophageal symptoms and that specific autoantibody groups have characteristic manometric features with a higher prevalence of jackhammer esophagus in anti–TIF1-γ patients and LES involvement in the AS patients. Finally, we found an association between esophageal involvement and ILD severity.

Esophageal smooth muscle involvement in IIM was proposed long ago. In fact, in the 1960s, Donoghue *et al.* reported that 45% of DM patients had generalized esophageal muscular defects that resembled esophageal involvement in systemic sclerosis. Moreover, they noted that the upper esophageal skeletal muscle weakness, which is

Table 3. Manometric features, wave morphology, and Chicago Classification v3.0 by clinical group

	Clinical groups			
	DM ($n = 24$)	PM ($n = 21$)	CAM ($n = 5$)	Total ($n = 53$)
DCI (mm Hg/cm·s)	1,428 (959–2,660)	775 (0–1,798)	3,874 (892–4,767)	1,311 (370–2,900)
IRP (mm Hg)	10 (6.5–12)	8 (5–12)	6 (5–12)	10 (5–12)
DL (s)	6 (5–7)	5 (0–6)	7 (5–7)	6 (5–7)
IBP (mm Hg)	19 (15–25)	19 (15–22)	19 (15–27)	19 (15–22.5)
Wave morphology [mean %]				
Hypertonic	2.5 (7.2)	4.8 (12.9)	13.4 (30)	4.9 (13.6)
Failed	16.2 (28.7)	45.9 (42)**	22 (43.8)	27.8 (37.7)
Hypotonic	14.5 (22.2)	3.8 (11.5)*	4 (8.9)	9.4 (18)
Fragmented	0.4 (2)	0.5 (2.2)	0 (0)	0.4 (1.9)
Normal	66.4 (35)	45.1 (38.4)	60.6 (43.7)	57.5 (37.3)
Pharyngeal pressure (mm Hg)	11.5 (9–17.5)	14 (9–17)	14 (9–15)	12 (9–17)
UES pressure (mm Hg)	71 (39–93.5)	47 (26–65)*	70 (32–72)	62 (36–82)
LES pressure (mm Hg)	23 (15.5–35)	20 (13–29)	20 (18–22)	22 (16–35)
High UES pressure (%)	12.5% ($n = 3$)	0% ($n = 0$)	44.7% ($n = 2.2$)	7.5% ($n = 4$)
Low UES pressure (%)	12.5% ($n = 3$)	33.3% ($n = 7$)	54.8% ($n = 2.7$)	22.6% ($n = 12$)
High LES pressure (%)	4.2% ($n = 1$)	9.5% ($n = 2$)	44.7% ($n = 2.2$)	9.4% ($n = 5$)
Low LES pressure (%)	25% ($n = 6$)	33.3% ($n = 7$)	0% ($n = 0$)	24.5% ($n = 13$)
Chicago Classification v3.0				
Normal esophageal motility	70.8% ($n = 17$)*	38.1% ($n = 8$)*	54.8% ($n = 2.7$)	54.7% ($n = 29$)
Ineffective esophageal motility	12.5% ($n = 3$)	23.8% ($n = 5$)	0% ($n = 0$)	17% ($n = 9$)
Absent contractility	8.3% ($n = 2$)	28.6% ($n = 6$)	44.7% ($n = 2.2$)	17% ($n = 9$)
Jackhammer esophagus	8.3% ($n = 2$)	4.8% ($n = 1$)	44.7% ($n = 2.2$)	9.4% ($n = 5$)
EGJ outflow obstruction	0% ($n = 0$)	4.8% ($n = 1$)	0% ($n = 0$)	1.9% ($n = 1$)
Achalasia type I, II, or III	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)
Distal esophageal spasm	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)
Fragmented peristalsis	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)

Comparisons made between each group (column) and the rest of the sample. Continuous variables are expressed as mean (SD) or as median (Q1–Q3), as appropriate. Qualitative variables are expressed as percent (n). DM, dermatomyositis; PM, polymyositis; CAM, cancer-associated myositis; DCI, distal contractile integral; IRP, integrated relaxation pressure; IBP, intrabolus pressure; DL, distance contractile latency; UES, upper esophageal sphincter; LES, lower esophageal sphincter; EGJ, esophagogastric junction.

*$P < 0.05$.
**$P < 0.01$.

usually obvious clinically, may obscure symptoms of dysphagia arising from the rest of the esophagus.[3] Since that original study, among the main advances in myositis has been the discovery of autoantibodies associated with characteristic clinical[24] and histopathologic features.[25] In the present study, in addition to reproducing most of the results of earlier studies,[3,4] we could define specific manometric features for some serologic subgroups in myositis.

Antisynthetase syndrome is a clinic–serologic disease characterized by the presence of autoantibodies against 1 of the aminoacyl-tRNA synthetases.[26] We found decreased LES pressure and a higher proportion of hypotonic LES in the AS cohort, suggesting that, in this syndrome, the autoimmune reaction may affect smooth muscle of the esophageal body and LES, as it occurs in other autoimmune diseases, such as systemic sclerosis.[27]

Interestingly, we could not detect manometric LES involvement in patients positive for anti-PM/Scl, which is an autoantibody also associated with scleroderma-like features. As pointed out in what follows, the analysis of this specific group of patients was probably underpowered, considering that we studied 16 patients with the AS and just 8 positive for anti-PM/Scl.

Another relevant autoantibody important in inflammatory myopathy is anti–TIF1-γ, which is strongly correlated with cancer.[28] In our study, it was found to be associated with a higher DCI (a parameter used to measure the distal esophageal contraction), a higher IBP (used to measure the pressure of the liquid bolus into the esophagus), and jackhammer esophagus. Even if the etiology of jackhammer esophagus is still largely unknown, the association with anti–TIF1-γ is intriguing and, if confirmed, would suggest either a common pathophysiology or that the inflammatory phenomenon is triggering the esophageal disease. This last theory would be supported by reports suggesting that the trigger of jackhammer esophagus may be local irritation caused by gastroesophageal reflux.[29]

High-resolution manometry is the "gold standard" for evaluation of motility disorders of the body and LES of the esophagus, but its usefulness for evaluating the pharynx and UES is more limited due to the complex anatomy and movement of this part of the esophagus. Although the Chicago

Table 4. Manometric features, wave morphology, and Chicago Classification v3.0 by serologic group

	Serologic groups				
	AS ($n = 16$)	Anti–TIF1-γ ($n = 10$)	Anti-PM/Scl ($n = 8$)	Anti-Ro52 ($n = 16$)	Total ($n = 53$)
DCI (mm Hg/cm/s)	1,052 (311–1,517.5)	2,847.5 (892–6,197)*	1,206.5 (536–2,804)	1,206.5 (536–2,804)	1,311 (370–2,900)
IRP (mm Hg)	7 (3–11)	11 (6–12)	10 (7.5–12.5)	10 (7.5–12.5)	10 (5–12)
DL (s)	6 (5–6.5)	6.5 (6–7)	5.5 (2.5–6)	5.5 (2.5–6)	6 (5–7)
IBP (mm Hg)	16 (13–22)	22.5 (19–27)*	19.5 (14.5–21.5)	19.5 (14.5–21.5)	19 (15–22.5)
Wave morphology [mean %]					
Hypertonic	1.3 (5)	13.7 (24.7)	12.7 (0)	0.6 (2.5)	4.9 (13.6)
Failed	31.9 (37.2)	13 (31.3)	41.6 (0)	37.9 (38.2)	27.8 (37.7)
Hypotonic	12.9 (22.3)	2 (6.3)	3.2 (0)	6.1 (13.6)	9.4 (18)
Fragmented	0 (0)	2.2 (4.4)**	3.5 (0)	0.6 (2.5)	0.4 (1.9)
Normal	53.9 (38)	69.3 (33.1)	39.7 (33)	54.8 (35.6)	57.5 (37.3)
Pharyngeal pressure (mm Hg)	12 (8.5–20)	13.5 (11–14)	11.5 (8.5–16)	11.5 (8.5–16)	12 (9–17)
UES pressure (mm Hg)	68 (50–87.5)	38.5 (32–94)	45 (20.5–83)	45 (20.5–83)	62 (36–82)
LES pressure (mm Hg)	17 (11.5–30.5)*	22.5 (18–41)	28.5 (16–39)	28.5 (16–39)	22 (16–35)
High UES pressure (%)	6.3% ($n = 1$)	10% ($n = 1$)	0% ($n = 0$)	6.3% ($n = 1$)	7.5% ($n = 4$)
Low UES pressure (%)	18.8% ($n = 3$)	30% ($n = 3$)	37.5% ($n = 3$)	37.5% ($n = 6$)	22.6% ($n = 12$)
High LES pressure (%)	0% ($n = 0$)	20% ($n = 2$)	12.5% ($n = 1$)	0% ($n = 0$)	9.4% ($n = 5$)
Low LES pressure (%)	43.8% ($n = 7$)*	20% ($n = 2$)	25% ($n = 2$)	25% ($n = 4$)	24.5% ($n = 13$)
Chicago Classification v3.0					
Normal esophageal motility	62.5% ($n = 10$)	60% ($n = 6$)	62.5% ($n = 5$)	62.5% ($n = 10$)	54.7% ($n = 29$)
Ineffective esophageal motility	18.8% ($n = 3$)	0% ($n = 0$)	12.5% ($n = 1$)	18.8% ($n = 3$)	17% ($n = 9$)
Absent contractility	18.8% ($n = 3$)	10% ($n = 1$)	12.5% ($n = 1$)	18.8% ($n = 3$)	17% ($n = 9$)
Jackhammer esophagus	0% ($n = 0$)	30% ($n = 3$)*	12.5% ($n = 1$)	0% ($n = 0$)	9.4% ($n = 5$)
EGJ outflow obstruction	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	1.9% ($n = 1$)
Achalasia type I, II, or III	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)
Distal esophageal spasm	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)
Fragmented peristalsis	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)

Comparisons made between each group (column) and the rest of the sample. Continuous variables expressed as mean (SD) or as median (Q1–Q3), as appropriate. Qualitative variables are expressed as percent (n). AS, antisynthetase syndrome; DCI, distal contractile integral; IRP, integrated relaxation pressure; IBP, intrabolus pressure; DL, distance contractile latency; UES, upper esophageal sphincter; LES, lower esophageal sphincter; EGJ, esophagogastric junction.

*$P < 0.05$.

**$P < 0.01$.

Classification v3.0 does not consider this region, there is evidence suggesting that HRM may be more trustworthy than videofluoroscopic swallow study or X-ray–based analysis of swallowing.[30,31] Our results identified significant involvement of the pharynx and UES region, as expected, because this part of the esophagus with skeletal muscle is known to be susceptible to involvement in the myositis inflammatory process. Moreover, in our experience, life-threatening dysphagia due to pharyngeal or UES weakness is a rare phenomenon in myositis (around 1.5% of the patients of our cohort) and, in the only patient included in the study with this extremely severe form of dysphagia, the HRM showed severely decreased pharyngeal and UES pressure.

Interestingly, we identified an association between esophageal involvement and ILD. Specifically, patients with regurgitation showed lower FVC than patients without it, and UES pressure was directly associated with FVC, independent of the autoantibody group. The cross-sectional design of our study could not demonstrate causality, and thus it is equally plausible that regurgitation may induce ILD or, on the contrary, that ILD increases the likelihood of regurgitation.

If regurgitation was a contributing factor to ILD, anti-reflux medication may be considered as an adjuvant therapy for ILD. In support of this finding, chronic microaspiration has been recently associated with the genesis of ILD in systemic sclerosis,[32] and, as discussed earlier, some myositis groups (such as the AS group) showed evidence of systemic sclerosis-like lower esophageal involvement.

Alternatively, the severity of ILD may lead to an increase in intrathoracic pressure and exacerbate gastroesophageal reflux. In any case, given the high prevalence of functional esophageal disorders associated with IIM and the poor correlation between the symptoms and manometric involvement, it is reasonable to suggest a need for screening DM and PM patients for functional esophageal disorders. This screening could lead to early treatment, thus avoiding harmful secondary effects such as Barret

esophagus or esophageal neoplasms. This would be especially true for patients with polymyositis due to the higher risk of esophageal involvement we found in our study, and those with the AS, because of the higher rate of LES dysfunction.

Our study must be regarded as exploratory and with a number of limitations. First, even if the number of patients included was rather high considering the rarity of the disease, some analyses may still have been underpowered. Second, as mentioned previously, the cross-sectional nature of the study cannot demonstrate causality, and the heterogeneity of the patients may have induced bias even after statistical adjustment. Third, we could review the HRM retrospectively to adapt it to actual definitions[9] but the esophageal symptom survey could not be adapted to the modern instrumentation that was unavailable at the start of the study.[33] Finally, in some cases, there was a significant amount of time between laboratory data collection and pulmonary function tests and the date of manometry, which may explain why there was no significant association between the manometric parameters and CK. However, there was no potential bias regarding the time between the HRM and the esophageal symptoms survey, because both were performed at the same time.

In conclusion, inflammatory myopathies have significant esophageal involvement that correlates poorly with esophageal symptoms. In addition, we found an association between esophageal involvement and ILD severity and characteristic manometric features in specific autoantibody groups.

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3. Cohort study of the antisynthetase syndrome

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Original article

A longitudinal cohort study of the anti-synthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies

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Abstract

Objective. The aim was to study the prevalence, rate of appearance and severity of clinical features in patients with different anti-synthetase syndrome (ASyS) autoantibodies.

Methods. All Johns Hopkins Myositis Longitudinal Cohort subjects positive for any ASyS autoantibodies were included. Clinical information, including symptoms, signs, strength, creatine kinase concentrations and pulmonary function tests, were prospectively collected. The standardized mortality and cancer rates and the rate of appearance and intensity of the different organ manifestations were assessed using univariate and multivariate analysis and compared between ASyS autoantibodies.

Results. One hundred and twenty-four (73.4%) patients were positive for anti-Jo1, 23 (13.6%) for anti-PL12, 16 for anti-PL7 (9.5%) and 3 (1.8%) for anti-EJ or anti-OJ, respectively. The mean length of follow-up was 4.1 years. Anti-PL12 was more frequent in black subjects. Anti-PL12 and anti-PL7 were associated with more prevalent and severe lung involvement, often without muscle involvement. Anti-Jo1 displayed more severe muscle involvement compared with anti-PL12 patients. Concurrent anti-Ro52 was more prevalent in anti-Jo1 patients and was associated with earlier development of mechanic's hands, DM-specific skin findings and arthritis. Independent of ASyS antibody status, black patients demonstrated more severe lung involvement than white patients. There was no significant increase in mortality or cancer risk in ASyS patients compared with the general US population.

Conclusion. Different ASyS autoantibodies are associated with phenotypically distinct subgroups within the ASyS spectrum. Anti-PL7 and anti-PL12 are characterized by more severe lung involvement, whereas anti-Jo1 is associated with more severe muscle involvement. Black race is a major prognostic factor associated with lung disease severity.

Key words: myositis, anti-synthetase syndrome, dermatomyositis, polymyositis, cohort study, prognostic factors, anti-Ro52, anti-synthetase antibodies

CLINICAL SCIENCE

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Rheumatology key messages

- Different anti-synthetase autoantibodies are associated with phenotypically distinct subgroups within the anti-synthetase spectrum.
- Anti-PL7 and anti-PL12 syndromes are characterized by more severe interstitial lung disease.
- Black race is a major prognostic factor associated with lung disease severity.

Introduction

The anti-synthetase syndrome (ASyS) is a complex autoimmune disorder characterized by the presence of autoantibodies against one of the aminoacyl-transfer (t)RNA synthetases. It is a clinical syndrome including variable expression of myositis, interstitial lung disease (ILD), polyarthritis, mechanic's hands, RP and/or fever.

Anti-Jo1, directed against the histidyl-tRNA synthetase protein, is the most common of the anti-synthetase antibodies [1]. Other aminoacyl-tRNA synthetases targeted by autoantibodies and associated with the ASyS include anti-PL7 [2], anti-PL12 [3], anti-OJ [4], anti-EJ [4], anti-KS [5], anti-Zo [6] and anti-Ha [7].

The type of ASyS autoantibody and the co-positivity with anti-Ro52 have been proposed to be major prognostic indicators predicting the manifestations and severity of ASyS. Thus, it has been suggested that anti-Jo1 patients have more prevalent muscle involvement, whereas patients with anti-PL7 and anti-PL12 are more likely to have ILD and gastrointestinal complications [8–10]. In addition, anti-Ro52 has been associated with a higher cancer risk and more severe muscle and joint involvement [11].

Two large cohort studies [8, 12] have compared the clinical features of anti-Jo1 patients with other ASyS autoantibodies, finding evidence that non-anti-Jo1 patients, particularly anti-PL7 and anti-PL12, were more likely to have isolated lung involvement and increased mortality. Moreover, two recent large multicentre cohort studies have analysed the natural history of anti-Jo1 ASyS [13, 14], clarifying the dynamic nature of ASyS manifestations over time, the heterogeneity in clinical features of the syndrome and the tendency to chronicity of ASyS ILD.

In this large single-centre study using an equivalently sized but independent cohort of patients from the Johns Hopkins Myositis Center cohort, we compare the different ASyS autoantibodies in terms of survival, cancer rate, clinical features at the onset of the disease and their rate of appearance. Moreover, we assess the role of anti-Ro52 as a disease modifier and study the severity of the lung, muscle and joint involvement over time.

Methods

Study population and autoantibody testing

Patients enrolled in the Johns Hopkins Myositis Center Longitudinal Cohort study between 2003 and 2016 were included if tested positive for an anti-synthetase autoantibody.The initial sera from all patients was screened for anti-Jo1, anti-PL7, anti-PL12, anti-EJ, anti-OJ and anti-Ro52 autoantibodies by ELISA, line blotting (Euroline Myositis Profile 4; Euroimmun), by immunoprecipitation at the Oklahoma Medical Research Foundation and/or using Quest Diagnostics myositis panels.

At each visit, arm abduction and hip flexion strength were evaluated by the examining physician using the Medical Research Council scale. This scale was transformed to Kendall's 0–10 scale for analysis purposes as previously described [15]. Serial strength measurements for each patient were made by the same physician. For the purposes of analyses, right- and left-side measurements for arm and hip strength were combined and the average was used for the calculations (possible range 0–10). Serum creatine kinase (CK) concentrations were included for analysis if obtained within 6 weeks of the date when strength testing was performed. Myositis-specific skin involvement, symptoms of oesophageal involvement and ASyS-associated clinical features (e.g. mechanic's hands, RP, arthritis, fever) were documented both retrospectively at the onset of the disease and prospectively at each visit. ILD was defined through a multidisciplinary approach as suggested by the American Thoracic Society [16]. Pulmonary function testing included spirometry, lung volumes measured by helium dilution and diffusing capacity by single-breath carbon monoxide based on American Thoracic Society criteria [17]. This study was approved by the Johns Hopkins Institutional Review Board; written informed consent was obtained from each participant.

Statistical analysis

Dichotomous variables were expressed as percentages and absolute frequencies, and continuous features were reported as means and SD. Pairwise comparisons for categorical variables between groups were made using the χ^2 test or Fisher's exact test, as appropriate. Student's *t*-test was used to compare continuous variables among groups. CK, a highly positively skewed variable, was expressed as the median, first and third quartile for descriptive purposes and transformed through a base-10 logarithm for regression analysis.

Indirect standardization was used to compare the number of cases of cancer that we observed in our sample during the 3 years before or after the onset of the disease [18] with the number one would expect in the general population with the same age and sex distribution. Cancer incidence by age and sex groups was taken from the 2008–2012 United States Cancer Statistics registry. The observed and expected numbers of cases were compared using the standardized incidence ratio (observed/expected cases of cancer) and its 95% CI. The number of years at risk for cancer was allocated to the correct age interval. In the event a patient had

cancer, died or had <3 years of follow-up after disease onset, the number of years at risk for that patient would end at the occurrence of the event.

Patients who died were identified using Johns Hopkins medical record system and the March 2014 version of the USA Death Master File. Mortality incidence by age and sex groups was also compared with the general population using indirect standardization based on the 1999–2014 Compressed Mortality File. The number of years at risk from the disease onset to the date of death or to March 2014 was allocated to the correct age interval. The observed and expected numbers of cases were compared using the standardized mortality ratio (observed/expected deaths) and its 95% CI.

To account for the different number of visits per patient, the evolution of the pulmonary function tests, the CK concentrations and the muscle strength were studied using multilevel linear regression models with random slopes and random intercepts. The mean of hip flexor and arm abductor strength (range 0–10) was used as the strength outcome for regression analysis.

Locally weighted regression was applied to analyse graphically the evolution of the strength, CK concentrations and the pulmonary function tests. The Kaplan–Meier estimator and Cox regression were used to study the hazard to develop each one of the different clinical features over time and to compare cancer and mortality among autoantibody groups.

The influence of non-modifiable risk factors (sex, race, length of illness and age at the onset of the first symptoms), the CS dose and the administration of IVIG, rituximab, MTX, AZA and MMF were used as adjusting covariates. Other treatments administered to <10% of the cohort were not included in the analysis.

All statistical analyses were performed using Stata/MP 14.1. To account for the number of statistical tests performed, a two-sided P-value of $\leqslant 0.001$ was considered statistically significant for the univariate analysis, whereas 0.05 was considered significant for the multivariate analysis.

Results

Patients

From the 2042 patients enrolled in the Myositis Centre Longitudinal Cohort Study, 1198 (59%) were tested for anti-synthetase antibodies and 169 of these were positive (14.1%). One hundred and twenty-four (73.4%) individuals were positive for anti-Jo1, 23 (13.6%) for anti-PL12, 16 for anti-PL7 (9.5%) and 3 (1.8%) for anti-EJ and anti-OJ, respectively (supplementary Fig. S1, available at *Rheumatology* Online). We analysed a total of 1458 visits, with a mean (S.D.) of 8.6 (6.7) visits per patient and a mean (S.D.) follow-up time of 4.1 (3.4 years). Considering the small sample size of anti-EJ and anti-OJ, they were not included for further subgroup analysis.

Of the ASyS patients, 73% were females, 32% were black, and the mean (S.D.) age at onset was 47.4 (13.5 years). Anti-PL12 autoantibodies were found more frequently in black patients. Anti-Jo1 was more common in white patients and was more frequently associated with anti-Ro52 autoantibodies. No differences were detected in the age at onset or sex distribution among autoantibody groups. CSs and AZA were the two drugs most commonly used in these patients, followed by MTX, MMF and IVIG (Table 1).

Clinical features: univariate analysis

The clinical features of these patients both at the onset and during their follow-up are shown in Table 2. In brief, exclusive, clinically apparent lung involvement at the onset of the disease was common in anti-PL12 and anti-PL7 patients (anti-PL12 65% and anti-PL7 56% *vs* anti-Jo1 26%), whereas sole muscle involvement was more common in anti-Jo1 patients (anti-Jo1 26% *vs* anti-PL12 0% and anti-PL7 12%). During the course of follow-up, most patients experienced both muscle and lung involvement (>60% in all groups). However, anti-PL12 and anti-PL7 patients trended towards having lung involvement without ever experiencing muscle involvement (anti-PL12 30% and anti-PL7 19% *vs* anti-Jo1 10%), and anti-Jo1 patients trended towards exclusive muscle involvement (anti-Jo1 26% *vs* anti-PL12 4% and anti-PL7 0%; Table 2).

The severity of weakness was not significantly different depending on sex, race, age at onset or anti-Ro52 status (Table 3). However, at the first visit, patients with anti-Jo1 showed a trend towards being weaker (mean hip flexor strength 8.3) than anti-PL12 and anti-PL7 patients (both mean hip flexor strength >9.4). The CK concentrations of anti-PL12 patients were significantly lower than the rest (median CK concentration 78 IU/L, $P < 0.001$).

Autoantibody status and race seemed to be the most important prognostic factors associated with ILD severity. Thus, anti-PL12 patients showed the most severe ILD phenotype [percentage forced vital capacity (%FVC) = 57%, percentage diffusing capacity for carbon monoxide (%DLCO) = 55%] and anti-Jo1 patients the mildest (%FVC = 71%, %DLCO = 67%). Anti-PL7 patients presented intermediate ILD severity (%FVC = 61%, %DLCO = 53%). Black patients showed strikingly more severe ILD (>15% lower FVC and DLCO, all $P < 0.001$) than the rest of the patients (Fig. 1A and B; supplementary Fig. S2, available at *Rheumatology* Online). The severity of ILD was not significantly different depending on sex, age at onset or anti-Ro52 status (Table 3).

Strength and ILD evolution: multivariate analysis

We performed a mixed effect regression analysis to assess the effect of the race and autoantibody status on the severity of weakness and ILD independent of possible confounding variables (age at onset, sex, time from the onset and immunosuppressant treatments). This analysis confirmed that patients with anti-PL12 autoantibodies showed lower CK concentrations and more severe ILD (lower FVC and DLCO) compared with patients with anti-Jo1 ASyS (all $P < 0.05$). Moreover, patients with anti-PL7 showed lower DLCO than anti-Jo1 patients

Table 1 General features of anti-synthetase patients

	Anti-Jo1 (n = 124)	Anti-PL12 (n = 23)	Anti-PL7 (n = 16)	Anti-EJ (n = 3)	Anti-OJ (n = 3)	Total (n = 169)
Age of onset, mean (s.d.), years	46.6 (13.5)	47.5 (14.9)	49.2 (12.1)	54.1 (7.6)	63.6 (6.7)*	47.4 (13.5)
Number of visits, mean (s.d.)	8.0 (6.6)*	12.3 (6.2)**	9.1 (6.3)	10.3 (4.5)	5.7 (4.0)	8.7 (6.6)
Length of follow-up, mean (s.d.), years	4.1 (3.3)	4.8 (3.9)	3.3 (3.3)	4.1 (1.7)	2.1 (1.2)	4.1 (3.4)
Sex, female, % (n)	73 (91)	83 (19)	69 (11)	33 (1)	33 (1)	73 (123)
Race, % (n)						
White	**71 (88)*****	**17 (4)*****	44 (7)	33 (1)	67 (2)	60 (102)
Black	**23 (28)*****	**70 (16)*****	50 (8)	33 (1)	33 (1)	32 (54)
Other races	6 (8)	13 (3)	6 (1)	33 (1)	0 (0)	8 (13)
Cancer-associated myositis, % (n)	2 (2)	9 (2)	6 (1)	0 (0)	0 (0)	3 (5)
Mortality, % (n)	6 (7)	13 (3)	19 (3)	0 (0)	0 (0)	8 (13)
Anti-Ro52, % (n)	**74 (92)*****	43 (10)*	44 (7)	67 (2)	0 (0)*	66 (111)
Treatments, % (n)						
CSs	92 (114)	100 (23)	100 (16)	100 (3)	33 (1)*	93 (157)
AZA	52 (64)	61 (14)	50 (8)	67 (2)	33 (1)	53 (89)
MTX	37 (46)**	17 (4)	12 (2)	0 (0)	0 (0)	31 (52)
MMF	34 (42)*	48 (11)	62 (10)*	67 (2)	33 (1)	39 (66)
IVIG	33 (41)	35 (8)	19 (3)	33 (1)	33 (1)	32 (54)
Rituximab	22 (27)	22 (5)	25 (4)	0 (0)	0 (0)	21 (36)

Dichotomous variables are expressed as a percentage (number of patients), whereas the age at onset is expressed as the mean (s.d.). Bivariate comparisons of continuous variables were made using Student's *t*-test, whereas bivariate comparisons of dichotomous variables were made using either the χ^2 test or Fisher's exact test, as appropriate. Bold values are statistically significant. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

(−14%, $P < 0.05$) and a trend towards lower FVC (−4%, $P > 0.05$). Consistent with the univariate study, black patients showed strikingly more severe ILD (18% lower FVC, $P < 0.001$; 12% lower DLCO, $P < 0.01$) than white patients, with no interaction detected between the autoantibody status and the race (all $P > 0.05$).

This analysis also showed that independent of the autoantibody status (and the rest of the confounding variables), CK concentrations tended to decrease over time ($\beta = 0.04$ IU/l/year, $P < 0.001$) and the %FVC tended to increase in a barely clinically relevant manner ($\beta = 0.89$%/year, $P < 0.01$), whereas the strength and DLCO remained stable over time (Table 4).

Independent of autoantibody status, race, sex, time from the onset, age at onset or treatments, CK concentrations were highly associated with the strength ($\beta = -0.66$, 95% CI: −0.87, −0.45; $P < 0.001$). Thus, a 10-fold decrease of the CK was estimated to be associated with a corresponding increase of 0.7 points of strength. The logarithm of CK concentrations continued to decrease linearly even after patients had reached maximal proximal muscle strength, which happened at ∼1 year of follow-up (Fig. 1C). Finally, anti-Ro52 autoantibodies were not associated with the severity of the weakness or ILD (all $P > 0.05$).

Rate of development of clinical manifestations

Independent of the race, sex and age at onset, anti-Ro52 was associated with earlier development of arthritis [hazard ratio (HR) = 2.0; 95% CI: 1.1, 3.8; P = 0.03], mechanic's hands (HR = 2.0; 95% CI: 1.1, 3.7; P = 0.03) and DM-specific skin signs (HR = 2.0; 95% CI: 1.1, 3.6; P = 0.02; supplementary Fig. S3, available at *Rheumatology* Online).

Both anti-PL12 (HR = 4.0, 95% CI: 1.5, 10.4) and anti-PL7 patients (HR = 4.2, 95% CI: 1.8, 11.1) developed symptoms of gastro-oesophageal reflux disease at a higher rate than anti-Jo1 patients (both $P < 0.004$; supplementary Fig. S4, available at *Rheumatology* Online).

Additional signs and symptoms associated with the ASyS showed no difference in the rate of development over time among the different autoantibody groups.

Mortality and cancer risk

Thirteen patients with ASyS died during the follow-up (seven anti-Jo1 and three anti-PL12 and anti-PL7, respectively). Five patients (two anti-Jo1 and one anti-PL12 and anti-PL7) were diagnosed with cancer (all adenocarcinomas: two colon, two breast and one lung, respectively) within 3 years of the onset of the disease. Compared with the general population, no increase in mortality or cancer was observed either in the whole cohort or when analysing each autoantibody group separately (Fig. 2). Also, independent of age, sex, race and age at onset, no autoantibody group showed a significant increase in mortality or cancer compared with the rest (all $P < 0.05$). Anti-Ro52 was not significantly associated with increased cancer (standardized incidence ratio 0.7, 95% CI: 0.09, 2.6) or mortality (standardized mortality ratio 1.4, 95% CI: 0.5, 3.0).

Table 2 Symptoms and signs of the patients with anti-synthetase syndrome

	Anti-Jo1 (n = 124)		Anti-PL12 (n = 23)		Anti-PL7 (n = 16)		Total (n = 169)	
	Onset	Cumulative	Onset	Cumulative	Onset	Cumulative	Onset	Cumulative
Simplified clinical groups[a]								
Lung and muscle involvement	35 (43)*	60 (74)	9 (2)*	65 (15)	31 (5)	81 (13)	30 (51)	62 (105)
Muscle involvement	26 (32)*	26 (32)**	0 (0)**	4 (1)*	12 (2)	0 (0)*	21 (36)	20 (34)
Lung involvement	**26 (32)*****	10 (13)*	**65 (15)*****	30 (7)*	56 (9)*	19 (3)	34 (57)	14 (24)
Exclusive joint involvement	10 (13)	3 (4)	22 (5)	0 (0)	0 (0)	0 (0)	11 (18)	2 (4)
No muscle, joint or lung involvement	3 (4)	1 (1)	4 (1)	0 (0)	0 (0)	0 (0)	4 (7)	1 (2)
Signs and symptoms								
Dyspnoea	52 (65)	63 (78)**	65 (15)	87 (20)*	75 (12)	94 (15)*	56 (94)	69 (117)
Cough	23 (29)	**38 (47)*****	39 (9)	70 (16)*	44 (7)	69 (11)	27 (46)	46 (78)
Muscle weakness	**60 (75)*****	85 (106)	**9 (2)*****	70 (16)	44 (7)	81 (13)	51 (87)	82 (139)
Arthritis	21 (26)	55 (68)*	17 (4)	52 (12)	12 (2)	25 (4)*	19 (32)	50 (84)
DM-specific skin involvement[b]	14 (17)	58 (72)	17 (4)	70 (16)	19 (3)	56 (9)	15 (25)	59 (100)
Raynaud's phenomenon	15 (19)	40 (49)*	4 (1)	17 (4)	19 (3)	31 (5)	14 (23)	35 (59)
Mechanic's hands	10 (13)	51 (63)	0 (0)	57 (13)	25 (4)	56 (9)	11 (18)	53 (89)
Dysphagia	10 (12)	21 (26)	9 (2)	30 (7)	12 (2)	19 (3)	9 (16)	22 (37)
Gastro-oesophageal reflux disease	11 (14)	**24 (30)*****	30 (7)*	61 (14)**	6 (1)	56 (9)*	14 (23)	33 (55)
Fever	10 (13)	19 (23)	17 (4)	39 (9)*	0 (0)	6 (1)	10 (17)	20 (33)
Calcinosis	3 (4)	11 (14)*	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	8 (14)

Values are given as a percentage (number of patients). Bold values are statistically significant. Bivariate comparisons of dichotomous variables were made between each category and the rest of the sample using either the χ^2 test or Fisher's exact test, as appropriate. [a]Muscle and lung involvement groups were categorized disregarding the status of joint involvement, whereas joint involvement excluded lung or muscle involvement. [b]DM-specific skin involvement includes heliotrope rash, Gottron sign or papules. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

Discussion

Our findings confirm the hypothesis that different ASyS autoantibodies have clinically distinct phenotypes. Both anti-PL7 and anti-PL12 are associated with more prevalent and severe ILD, whereas anti-Jo1 was associated with more intense muscle involvement than anti-PL12. Moreover, independent of the autoantibody status, black race was a major prognostic factor for ILD severity. Anti-Ro52 was detected more frequently with anti-Jo1 and was associated with earlier development of arthritis, mechanic's hands and DM-specific skin findings.

Muscle involvement is one of the most characteristic features of the ASyS. However, its severity is milder compared with other types of myositis (e.g. anti-SRP- or anti-HMGCR-associated myositis) [19, 20]. After 1 year of follow-up, most of the patients recovered near-full proximal muscle strength no matter what combination of treatments was used (Fig. 1). This would suggest a conservative immunosuppressant schedule (e.g. CSs plus MTX or AZA) as the treatment of choice in ASyS myositis when not accompanied by lung disease. The CK continued to decrease after the strength had reached near-full strength (ceiling effect), suggesting that CK has a broader dynamic range as a marker of muscle injury than the strength as measured using the standard Medical Research Council scale. By using this surrogate marker, we detected milder muscle involvement in anti-PL12 myositis compared with anti-Jo1. Considering the low price, high availability and objectivity of the CK determination, our data suggest that the logarithm of the CK could be a good surrogate marker for muscle disease activity in ASyS patients.

We show that patients with anti-PL7 and, to an even greater degree, anti-PL12 have more severe lung involvement than those with anti-Jo-1. Nonetheless, regardless of the autoantibody status, the tendency in ASyS is towards stability in lung function with treatment over time, as previously suggested [13]. This course indicates that lung inflammation with irreversible damage may occur very early after the onset of the disease. If this were to be confirmed, it would suggest that early aggressive therapy in new-onset ILD might improve the long-term outcome.

The increase in the rate of gastro-oesophageal reflux disease detected in anti-PL7 and anti-PL12 patients is concordant with the increase in gastrointestinal manifestations suggested by Marie *et al*. [9]. However, this could be either secondary to an increase in the intrathoracic pressure swings attributable to ILD or to lower oesophageal involvement, which was suggested to be common in myositis patients but never demonstrated in a definite manner [21, 22].

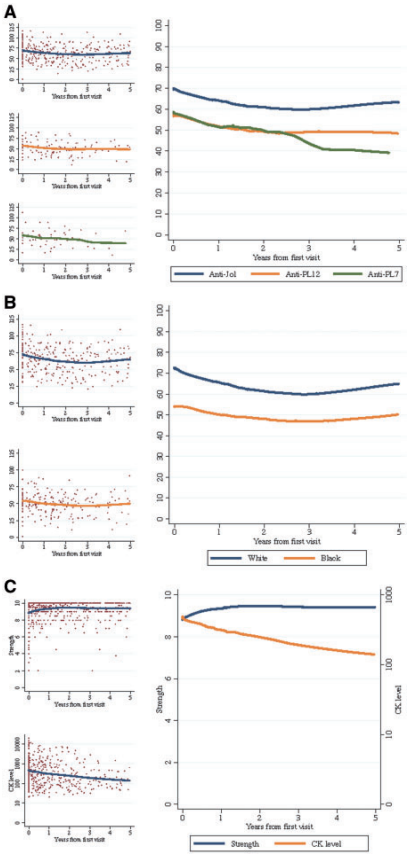
The mortality in our cohort was strikingly lower compared with previous studies. For example, Trallero-Araguás *et al.*

Table 3 Univariate analysis of muscle and lung involvement in patients with the anti-synthetase syndrome

	Anti-Jo1 Mean (S.D.)	Anti-PL12 Mean (S.D.)	Anti-PL7 Mean (S.D.)	Sex			Race			Age of onset		Anti-Ro52			Total (95% CI)
				Female	P-value	Male	White	P-value	Black	Corr. coeff	P-value	No	P-value	Yes	
Hip flexors															
Hip flexor strength at first visit	8.3 (2.2)*	9.4 (0.9)	9.7 (0.7)	8.6	0.5	8.3	8.3	0.07	9.1	0.0	1.0	8.8	0.3	8.4	8.5 (8.1, 8.9)
Follow-up hip flexor strength	9.0 (1.4)	9.3 (0.8)	9.5 (0.6)	9.0	0.02	9.6	9.1	0.8	9.2	0.0	0.8	9.2	0.7	9.1	9.1 (8.9, 9.3)
Hip flexor strength at last visit	9.1 (1.5)	9.3 (1.1)	9.6 (0.7)	9.0	0.05	9.6	9.0	0.6	9.2	−0.0	0.8	9.1	0.9	9.2	9.1 (8.9, 9.4)
Arm abductors															
Arm abductor strength at first visit	8.9 (1.7)	9.5 (0.9)	9.6 (0.7)	9.1	0.8	9.0	9.0	0.7	9.2	−0.1	0.1	9.1	0.8	9.0	9.0 (8.7, 9.3)
Follow-up arm abductor strength	9.4 (1.1)	9.4 (0.9)	9.7 (0.4)	9.3	0.02	9.8	9.5	0.8	9.4	0.1	0.5	9.5	0.4	9.4	9.4 (9.2, 9.6)
Arm abductor strength at last visit	9.4 (1.0)	9.5 (1.0)	9.8 (0.4)	9.3	0.08	9.7	9.4	1.0	9.4	0.1	0.6	9.7	0.2	9.3	9.4 (9.2, 9.6)
CK concentration [median (Q1–Q3)]															
CK at first visit	498 (150–1606)	**78 (46–242)*****	508 (424–762)	377	0.1	498	410	0.7	448	−0.2	0.06	404	0.7	461	428 (274, 634)
Follow-up CK	205 (99–863)	90 (54–204)*	285 (79–938)	149	0.06	254	192	0.4	176	−0.2	0.03	176	0.5	189	190 (138, 238)
Maximal CK	647 (178–2330)*	123 (50–531)**	634 (264–1597)	474	0.1	809	469	0.2	857	−0.2	0.02	430	0.1	647	518 (396, 778)
%FVC															
FVC at first visit	68.1 (19.1)*	51.2 (16.9)**	60.7 (17.2)	62.9	0.2	69.3	**71.4**	**<0.001**	**54.3**	0.2	0.09	65.1	0.9	64.3	64.6 (60.6, 68.6)
Follow-up FVC	71.4 (19.5)**	57.2 (14.3)**	61.3 (22.8)	66.7	0.4	70.3	**77.0**	**<0.001**	**55.2**	0.2	0.05	67.7	1.0	67.6	67.7 (63.8, 71.5)
FVC at last visit	76.6 (17.1)**	58.1 (17.1)**	66.1 (13.6)	69.9	0.3	75.5	**80.6**	**<0.001**	**59.4**	0.3	0.05	69.2	0.4	73.8	72.0 (66.8, 77.1)
%DLCO															
DLCO at first visit	70.0 (24.3)**	54.8 (16.6)*	56.5 (25.5)	65.1	0.7	67.5	**71.9**	**<0.001**	**54.3**	0.0	0.7	61.4	0.2	68.6	65.7 (60.8, 70.7)
Follow-up DLCO	**67.4 (23.7)****	54.5 (17.5)	53.1 (19.1)	62.5	0.9	62.9	**68.8**	**<0.001**	**53.2**	0.1	0.5	59.2	0.2	65.0	62.6 (58.2, 67.1)
DLCO at last visit	62.6 (20.2)	55.1 (12.7)	47.4 (19.3)	61.0	0.5	56.9	61.9	0.3	56.3	0.1	0.6	56.4	0.4	61.4	59.4 (54.1, 64.7)

Strength and FVC values are expressed as the mean (S.D.) and CK as the median [quartile 1–quartile 3 (Q1–Q3)]. Bivariate comparisons were made using Student's *t*-test for the strength and the Wilcoxon rank-sum test for CK. Pearson's *r* was used to calculate the correlation coefficient for strength and Spearman's ρ for the CK. Follow-up strength was defined as the mean strength of all the visits, excluding the first one. Bold values are statistically significant. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$. CK: creatine kinase; DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity.

FIG. 1 Longitudinal evolution of percentage predicted diffusing capacity for carbon monoxide, strength and creatine kinase concentrations



Trends were calculated using locally weighted scatterplot smoothing. (**A**) Percentage predicted DLCO by autoantibody status. (**B**) Percentage predicted DLCO by race. (**C**) Strength and CK concentrations. CK: creatine kinase; DLCO: diffusing capacity for carbon monoxide.

[13] reported 5 and 10 year survival rates of 88 and 75% in anti-Jo1 patients, whereas ours were 97 and 89%. The definition of the onset of the disease (at first symptoms instead of at diagnosis), a younger population of patients and the different origin of the patients (Rheumatology [14], Internal Medicine [13] or a Multidisciplinary Clinic in our study) might explain these differences. Non-Jo1 anti-synthetase patients [12] and myositis patients with ILD [23] have been associated with higher mortality rates. We did not find significant differences in mortality between autoantibody groups, possibly because of our limited sample size or the high survival rates.

The rate of cancer was not significantly higher in this cohort than in the general population. Although some reports have associated ASyS with cancer [9, 11], those studies were not adjusted for age and sex. Further studies have refuted this observation, suggesting that ASyS is not associated with cancer [24]. Our data support the absence of association for anti-Jo1 and might suggest that cancer screening could be more limited in these patients.

Anti-Ro52 is associated with many autoimmune diseases, but it is especially prevalent in anti-Jo1 patients [11, 25]. In the present study, we confirm that the association is stronger for anti-Jo1 (74%) than for anti-PL12 (43%) or anti-PL7 (44%). Anti-Ro52 does not appear to portend worse lung involvement in ASyS but is associated with earlier development of arthritis, mechanic's hands and DM-specific skin findings.

Finally, we found a striking increase in the severity of the ILD in black compared with white patients and confirmed an association between the race and the type of ASyS autoantibody [26]. The severity of the lung involvement in black patients does not seem to be attributable to the higher prevalence of anti-PL12 in this group of patients, because both factors were independent predictors of the ILD severity without any detectable interaction between them. Thus, this would suggest that: (i) there is a mechanistic link between race and anti-PL12 autoantibodies; and (ii) both the race and the autoantibody status act as independent modifiers of the disease severity.

The present study has several limitations. First, most of the conclusions of this study are based on signs and symptoms that were recorded prospectively from the start of the study in 2003. Consequently, we could not include activity and damage tools or comprehensive arthritis scoring systems that were not available when the study started. Second, as this is a reference centre for myositis, it is possible that the most severe patients of the spectrum were selected; however, comparing our data with similar cohort studies it seems that the severity of our patients was similar or even lower than in previous studies [13, 14]. Finally, the increased ILD severity that we detected in black patients might be partly explained by socio-economic factors that we could not take into account. However, these socio-economic factors would presumably also have led to increased muscle weakness, and we could not detect this.

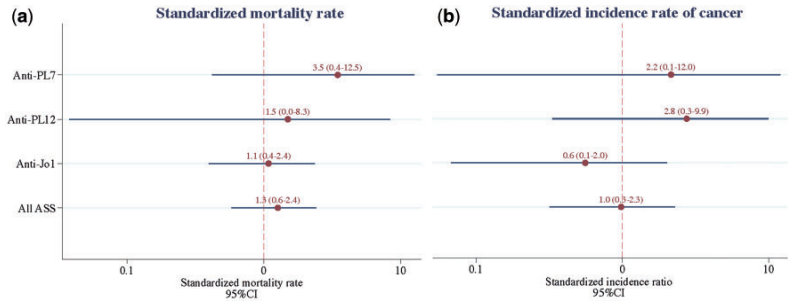
These limitations notwithstanding, this is the largest ASyS cohort study conducted longitudinally in a single centre and provides valuable information suggesting that the different anti-synthetase autoantibodies define different diseases within the ASyS spectrum. Thus, anti-PL7 and anti-PL12 syndromes are characterized by more severe ILD, whereas anti-Jo1 patients show more severe muscle involvement. Black race was identified as a major

Table 4 Multivariate longitudinal analysis of muscle and lung involvement in patients with the anti-synthetase syndrome

	Mean strength Coefficient (95% CI)	CK concentration (logarithmic scale) Coefficient (95% CI)	%FVC Coefficient (95% CI)	%DLCO Coefficient (95%CI)
Autoantibody (compared with anti-Jo1)				
Anti-PL12	0.28 (−0.27, 0.82)	**−0.42 (−0.71, −0.14)****	**−9.70 (−17.56, −1.84)***	**−10.47 (−19.71, −1.24)***
Anti-PL7	0.32 (−0.25, 0.89)	0.03 (−0.27, 0.33)	−3.92 (−13.63, 5.80)	**−13.95 (−25.42, −2.48)***
Time from onset to visit (1 year)	0.02 (−0.01, 0.06)	**−0.04 (−0.07, −0.02)*****	**0.89 (0.28,1.51)****	−0.09 (−0.49, 0.31)
Age of onset (each 10 years)	−0.05 (−0.18, 0.09)	**−0.09 (−0.17, −0.02)***	0.59 (−1.61, 2.80)	−2.15 (−4.76, 0.46)
Female *vs* male	−0.12 (−0.51, 0.28)	−0.12 (−0.33, 0.10)	−4.73 (−11.00, 1.54)	2.04 (−5.18, 9.26)
Black *vs* white	0.04 (−0.36, 0.45)	0.08 (−0.13, 0.29)	**−17.53 (−23.87, −11.18)*****	**−11.73 (−19.13, −4.32)****

Multilevel regression with random slopes and random intercepts. Multivariate analysis was adjusted by time from onset, age at onset, sex, race and immunosuppressant drugs (CS dose and treatment with IVIGs, rituximab, MMF, MTX or AZA). Bold values are statistically significant. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$.

Fig. 2 Standard mortality and cancer incidence rates



prognostic factor associated with the severity of the ASyS ILD.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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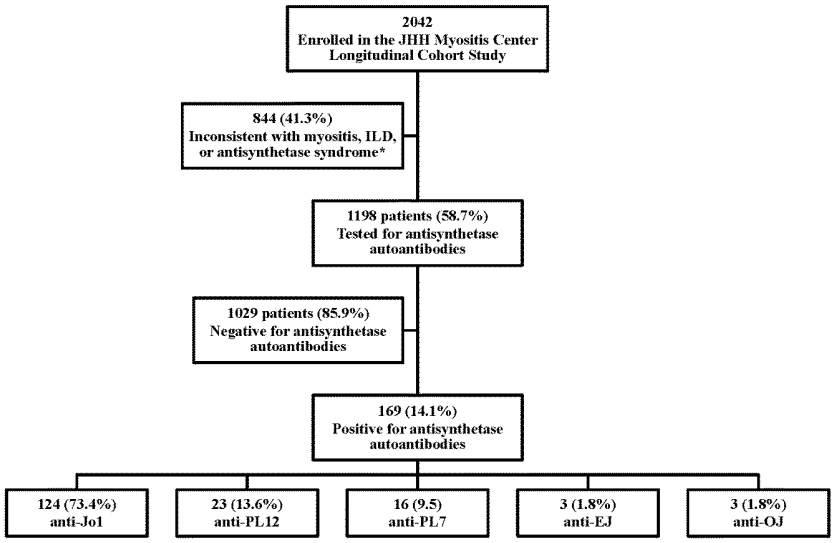
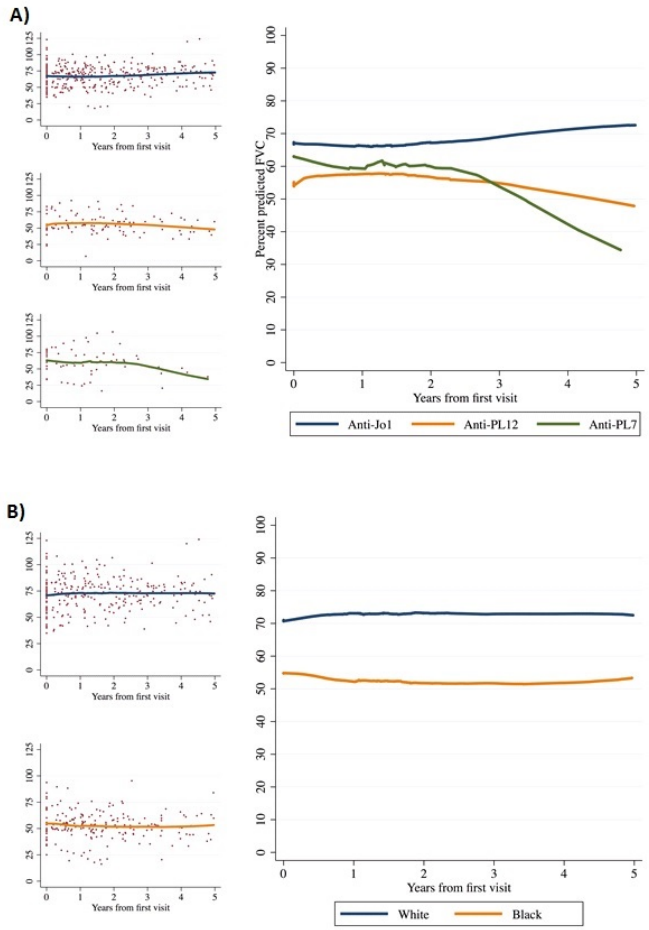
SUPPLEMENTARY DATA

Supplementary figure S1. Patient flow chart



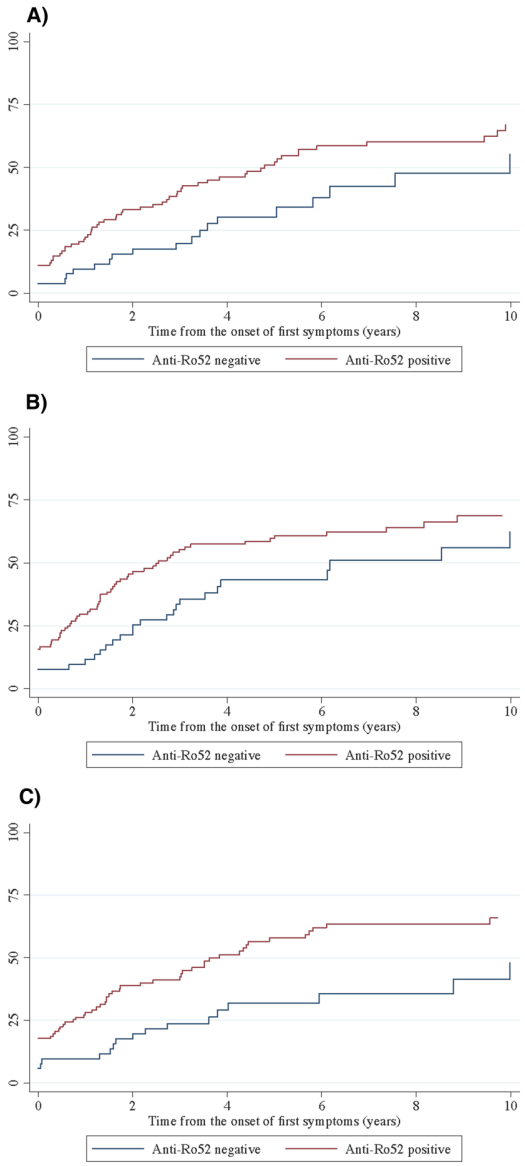
*The Myositis Center Longitudinal Cohort Study includes myositis confounders (e.g. self—limited muscle pain, transient creatinine kinase elevation, congenital muscle dystrophies…) that are routinely not tested for myositis autoantibodies.

Supplementary figure S2. Longitudinal evolution of FVC percent predicted[a]



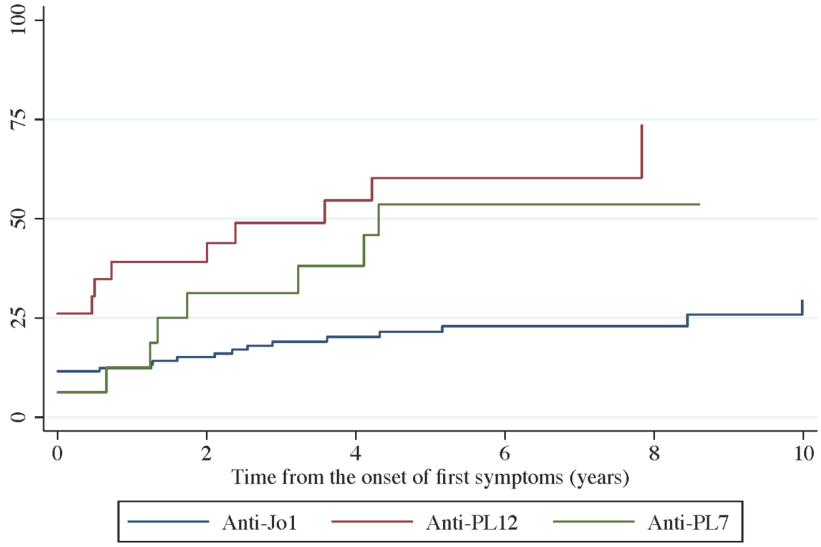
A) Percent predicted FVC by autoantibodies. B) Percent predicted FVC by race. [a]Trends were calculated using locally weighted scatterplot smoothing (LOWESS).

Supplementary figure S3. Rate or development of clinical features depending on anti-Ro52 status



A) Cumulative prevalence of Mechanics hands. B) Cumulative presence of Skin involvement. C) Cumulative presence of Arthritis.

Supplementary figure S4. Rate of development of gastroesophageal reflux disease depending on the type of antisynthetase antibody



Cumulative prevalence of Gastroesophageal reflux disease

IV. DISCUSSION

1. General discussion

As previously discussed in this thesis, IMs are a complex syndromic group of disorders including several distinct diseases with radically different clinical features, prognosis and response to treatment.

Since the Bohan and Peter IMs classification was published, several scientific advances have revolutionized our understanding of myositis. These include the discovery of the MSA and the association of IMs with certain types of HLA. However, doctors and scientists are still struggling to find the most efficient strategy to diagnose, manage and predict the prognosis of these patients.

This thesis has been conducted based on the hypotheses:

-A systematic analysis of retrospective data using magnetic resonance imaging (MRI) of the muscles could provide clear data about the diagnostic and prognostic utility of these technique and help us understand the evolution of IM.

-Using high resolution manometry (HRM) to analyze esophageal involvement could shed a light on the pathophysiology of this process in patients with IM, and help to assess the necessity of treating this type of manifestation in patients with myositis.

-An IM classification based on autoantibodies may be useful to assess the prognosis of patients with IM

Here, we have conducted three different studies, each one designed to investigate one or more of the above-mentioned hypotheses. These studies will be discussed separately in the following pages.

2. Thigh magnetic resonance imaging in immune-mediated necrotizing myositis

IMNM represents about 19% of all the IM[468]. It is more common in the adult population and causes severe weakness and dramatic rise in the CK levels[85,469]. The muscle biopsy in IMNM is defined by 1) scattered necrotic fibers, 2) scant inflammatory infiltrate consisting predominantly of macrophages, and 3) deposits of complement on capillaries and non-necrotic cells[470].

Until recently, the IMNM was not distinguished from PM, given the absence of rash. However, recent evidence shows that it should be recognized as a distinct form of myositis. There are two types of autoantibodies associated with the IMNM, those recognizing the signal recognition particle (SRP) and those which bind to 3-hydroxymethyl-3-glutaryl coenzyme A reductase (HMGCR). Patients with this autoantibody, especially, those with anti-SRP, are usually refractory to immunosuppressive treatment[470].

The thigh magnetic resonance imaging in the inflammatory myopathies

Several researchers have used muscle MRI to characterize muscle abnormalities in PM, DM, IBM [353,471-474] and anti-SRP patients[475], but none of them has analyzed the pattern of muscle involvement in patients with IMNM.

In the first paper presented in this thesis, we analyzed the thigh magnetic resonance imaging (tMRI) features in a large cohort of patients with IM, comparing IMNM with other IM subsets. We also compared the tMRI features of anti-SRP-positive IMNM patients with those who had autoantibodies recognizing HMGCR.

As MRI is a non-invasive technique that recognizes changes in soft tissues, it is the optimal study to examine muscles in IM[351,476-478]. Based on the different relaxation

times of the tissues (T1: longitudinal relaxation time and T2: transverse relaxation time) after being exposed to a magnetic field which is then disrupted by an external radiofrequency energy, diverse tissues can be identified and their pathogenic features detected. In muscle, the STIR sequence is able to eliminate the fat signal allowing a clearer interpretation of muscle edema[478,479].

tMRI patterns in IM

In our study, we demonstrate that patients with IMNM have more widespread muscle edema, atrophy and fatty replacement compared with those with PM and DM. This fact is independent of the age at the disease onset, sex, race and duration of the illness. A characteristic pattern of muscle involvement in patients with IMNM was also found in our analysis. Atrophy and fatty replacement more commonly occurred in the lateral rotators, glutei, medial and posterior compartments compared to the other IM subgroups. We have also found that patients with anti-SRP autoantibody have more extensive edema, atrophy and fatty replacement in the lateral rotator group, more atrophy and fatty replacement in the anterior compartment and more atrophy in the anterior compartment compared with anti-HMGCR positive patients. In other words, patients with antibodies against the signal recognition particle show evidence of more severe muscle involvement. These data reinforce the idea that autoantibodies define different groups and may be more useful than the clinical groups as prognosis factors in IM patients.

Apart from the abovementioned features in the MRI of those with IMNM, we found some patterns of muscle involvement that are characteristic of other IM subsets. For example, CADM showed the least extensive tMRI muscle involvement. Fascial edema was the most characteristic tMRI finding in patients with DM. Consistent with the results of other studies[343,344,475], patients with IBM had more involvement of the anterior

compartment, with an increased prevalence of fatty replacement of the vastus lateralis and atrophy of the vastus medialis compared with other myositis subgroups. However, in our study, edema, fatty replacement and atrophy also affected the posterior and medial compartment in IBM patients considerably more than the other of types of myositis. Patients with PM have been reported to show posterior thigh involvement[344], diffuse muscle edema with no subcutaneous edema[480] and mild fatty infiltration[344,475]. However, in our study, PM patients showed no defined pattern of involvement for any of the tMRI features compared with the rest of myositis patients.

We also identified some characteristics that apply to all forms of IM. Fatty replacement was found to occur relatively early in all forms of IM, occurring first 1-2 years after the onset of the disease, then spreading to other muscle groups. Based on this observation, we hypothesize that starting immunosuppressant drugs earlier and at higher doses, may limit or avoid the spread of muscle damage in IM patients with PM, DM and IMNM.

tMRI to diagnose IM subgroups

According to previous reports, MRI is a sensitive tool that shows abnormal findings in around 90% of patients with PM and DM[481]. Compared with the muscle biopsy it has been described to be more sensitive for detecting disease activity[344]. The specificity of this complementary exam has been reported to be 80-88%[344,480,482], and the positive predictive value (97%), similar to that of the biopsy (100%). However, MRI has been shown to have a better negative predictive value than the muscle biopsy (64% vs 38%)[483].

In our study, we determined the usefulness of the patterns of muscle involvement by MRI for the diagnosis of the different IM subsets. Dion et al. found IBM patients to have atrophy and fatty infiltration in the anterior compartment[344]. However, PM patients

in their study showed a global thigh or posterior thigh involvement and isolated inflammation. Based on these findings, they suggested that MRI is helpful to differentiate PM and IBM[344]. Another study proposed the utility of MRI-pattern recognition for the diagnosis of IBM, finding that the involvement of the quadriceps and the distal sartorius muscles is a useful sign to diagnose IBM[345]. After analyzing our data, we found that, the positive predictive value of the logistic regression formulas that we used to diagnose PM, DM and IMNM based on the tMRI pattern was suboptimal. However, a formula for IBM had a positive predictive value at >60%. In contrast, the negative predictive value of these formulas in IBM (94.7%) and IMNM (93.1%) were excellent and very good in DM (88.3%). In summary, these models had only modest positive predictive values for identifying myositis subsets but very good negative predictive values to rule out the presence of IM. We found that MRI models for PM performed especially poorly, which is consistent with the PM category including an especially heterogeneous population of patients.

This study has a number of limitations. First, we were not able to perform longitudinal studies on individual subjects because the majority of the patients had only one muscle MRI available. Despite this, we used statistical methods to model the extent of muscle MRI involvement according to the duration of the disease in different IM subsets. Second, our study only used data about whether a particular feature (e.g. edema) was present or absent in a particular muscle. Although the tMRI protocol included semiquantitative assessment of individual muscles for each radiologic feature (three levels of extent for all tMRI features), we considered that the reproducibility of our findings would increase and the methodology would be simplified by analyzing the presence or absence of each tMRI feature. Thus, we analyzed, in addition to the pattern of muscle involvement, the spread of this involvement to additional muscles over time,

but we did not analyze the severity or extent of each muscle feature within a given muscle. Third, only about 50% of the patients (666 out of 1312 patients) had an available tMRI performed at Hopkins. The patient consent, scheduling issues, and the availability of a recent tMRI performed in a hospital other than Hopkins may have led to the lack of a tMRI. Nonetheless, the proportion of patients of each clinical group with a tMRI was similar (IMNM: 55.5%; IBM: 57.1%; PM: 51.2%; DM: 46.3%; CADM: 37.8%). Despite these limitations, given our large sample size and the robust set of features analyzed, it is unlikely that a selection bias would have influenced the results in our study. Finally, interobserver reproducibility was not formally assessed but a standardized set of definitions developed and agreed upon by the two participating radiologists in consensus so as to minimize this.

These limitations notwithstanding, this study demonstrates the extensive muscle involvement present in patients with IMNM compared with other IM subtypes. IMNM patients also showed a characteristic pattern of muscle abnormalities involving glutei and hip rotators. On the other hand, patients with DM had the most widespread fascial muscle involvement. Our analysis also revealed that fatty replacement and atrophy occur early after the onset of the disease in myositis patients. Finally, we demonstrated that anti-SRP autoantibody positive patients had more severe muscle involvement compared with anti-HMGCR positive IM.

3. High-resolution manometry in myositis

Disorders affecting the esophagus are known to be a major cause of morbidity and mortality in PM and DM patients due their potential to cause life threatening complications like recurrent aspiration pneumonia[484-486]. According to the literature, patients affected with IM and dysphagia have a 1-year mortality rate of 31%[487].

In the second study of this thesis, we examined the HRM findings and the esophageal symptoms among clinical and serological groups of patients with DM and PM.

According to the literature, the prevalence of dysphagia caused by oropharyngeal and esophageal impairment in IM patients is between 32 and 84%[151,284,488,489]. It can appear as the first symptom of IM or later on[490]. Moreover, it can precede weakness of the extremities or be present as a sole symptom[212,487,491]. Patients usually complain more about swallowing problems with solid food (71-96%)[216,217,492], but around 50% of them have problems with liquids[216]. Heartburn/gastroesophageal reflux disease has been reported in 33-46%[284-286,488,493] of patients with IM, being the third most prevalent esophageal symptom after dysphagia to solids and swallowing problems with liquid. Other swallowing issues than can occur in IM patients are nasal regurgitation[284], coughing while eating[217,285,493] and odynophagia[490,493]. Consistent with the literature, in our study, 45% of the patients had significant esophageal symptoms. Dysphagia to solids was the most common symptom (26%), followed by dysphagia to liquids (17%), and heartburn (11%).

From all clinical subtypes of IM, IBM patients have been reported to be the most affected by dysphagia (65-68%). However, PM (30-60%) and DM (18-20%) can develop the symptoms as well[487,494]. In PM and DM, dysphagia is more frequent in the acute phase of the disease[495] and patients with ASyS who are positive for anti-Jo1 antibody have been

reported to show more common esophageal impairment[493]. In our study, no patients with sporadic inclusion body myositis were included and only patients with PM, DM, CAM, and overlap syndromes were analyzed. Serological groups were defined according to the positivity of the different autoantibodies (ASyS, anti-TIF1γ, anti-PM/Scl, anti-Ro52). In terms of symptoms of dysphagia, no significant differences were found between the clinical or serological groups that we analyzed.

The involvement of the skeletal muscle of the pharynx and upper esophagus has been reported to be the leading cause of dysphagia in IM patients[12,215]. But the involvement of the distal esophagus has been scarcely studied. Some authors have reported involvement of the esophageal smooth muscle in IM dysphagia and other swallowing problems. In 1960, Donoghue et al described that 45% of DM patients had generalized esophageal muscular defects that resembled systemic sclerosis esophageal involvement with diminished or absence of peristalsis on the X-ray barium swallowing test and loss of esophageal motility on the manometry. Some of their patients had localized dysphagia in the pharyngeal region but also a generalized esophageal involvement including the lower third[283]. Another group described a delayed gastric emptying in patients with PM and DM, concluding that this was due to involvement of the smooth muscle of the upper gastrointestinal tract[286].

Several other studies have demonstrated the involvement of the esophageal smooth muscle in patients with myositis using different techniques. Cine-esophagogram has shown lower esophageal abnormalities like abnormal peristalsis and dysmotility[488]. In the X-ray barium swallowing test some authors reported loss of peristalsis in the lower esophagus[283] and dilation in its distal part[284]. Finally, conventional esophageal manometry exams have demonstrated reflux, diminished lower esophageal sphincter

(LES) pressure, impaired non-peristaltic and low amplitude simultaneous contractions in the distal esophagus in IM patients[284,488].

In our study, we reproduce most of the results of earlier studies[283,284] finding also specific manometric features for some serologic myositis subgroups. In this study, we show using HRM that patients with IIM have a high prevalence of esophageal involvement, which is more common in PM than in DM. In patients with ASyS we detected decreased LES pressure and a higher proportion of patients with hypotonic LES, suggesting that, in this syndrome, the autoimmune reaction may affect the smooth muscle of esophagus and LES, as it occurs for instance in systemic sclerosis[496]. Interestingly, we could not detect manometric LES involvement in anti-PM-Scl-positive patients, which is an autoantibody also associated with SSc-like features. Another relevant autoantibody important in inflammatory myopathy and that is also associated with malignancy is anti-TIF1γ [67]. In our study, anti-TIF1γ was associated with a higher DCI (a parameter used to measure the distal esophageal contraction), a higher IBP (used to measure the pressure of the liquid bolus into the esophagus), and with jackhammer esophagus. The association of jackhammer esophagus with anti-TIF1γ is interesting. It would suggest a common trigger of the muscle and esophageal disorders or that the esophageal hyperexcitability is triggered by the inflammatory phenomenon. This last theory has been supported by other reports[497].

Although the HRM is the gold standard for evaluating the motility disorders of the esophageal body and the LES, there is conflicting evidence regarding its use to evaluate the pharynx and UES. However, there is evidence that this technique could be more reliable than the videofluoroscopic swallow study or X-ray-based analysis of swallowing[498,499]. In our study, we found a significant involvement of the pharynx region and the UES confirming the reliability of the technique to detect such skeletal muscle

involvement. The HRM of the only patient that presented with life-threatening dysphagia, showed severely decreased pharyngeal and UES pressure. However, in our experience, this is a rare phenomenon in myositis (around 1.5% of the patients of our cohort).

It has been reported that patients with dysphagia may have less ILD that those without it[500]. Interestingly, we have found a significant association between the presence of esophageal involvement and the severity of the ILD. A lower FVC was found in patients that presented with regurgitation and the pressure of the UES was directly associated with the FVC independent of the autoantibody group, even if this could be also explained by diaphragmatic weakness.

If regurgitation followed by aspiration was a contributing factor to ILD, anti-reflux medication may be considered as an adjuvant therapy for ILD. Interestingly, regurgitation with chronic microaspiration has been recently associated with the genesis of ILD in systemic sclerosis[501] and, as it has been previously discussed, some myositis groups (such as the ASyS group) show evidence of systemic sclerosis-like lower esophageal involvement.

An alternative explanation for the association of ILD and regurgitation is that ILD increases the likelihood of regurgitation by increasing the intrathoracic pressure. However, the cross-sectional design of our study could not demonstrate causality.

In any case, as the prevalence of esophageal disorders in those with IM is high. Given the correlation between symptoms and manometric results is low, it would be reasonable to suggest the utility of screening DM and PM patients for functional esophageal disorders. This screening would allow starting treatment early to avoid Barret´s esophagus or esophageal neoplasms due to gastric acid reflux in these patients.

The association of dysphagia with CK levels has been reported and the screening of CK levels is recommended in new cases of pharyngeal dysphagia of uncertain etiology

due to their high predictive value[502]. On the contrary, in our study, median CK was not correlated with any manometric parameter and was not significantly increased in patients with esophageal symptoms or with any Chicago v3.0 diagnosis.

This study has several limitations. First, even if the number of patients included was rather high considering the rarity of the disease, some analysis could still have been underpowered. Second, it is not possible to demonstrate causality due to the cross-sectional nature of the study. Moreover, the heterogeneity of the patients could have induced bias even after statistical adjustment. Third, although we could review the HRM retrospectively to adapt it to actual definitions[356], the esophageal symptom survey could not be adapted to modern instruments that were not available at the start of the study[503]. Finally, some exams like the laboratory values and pulmonary function tests were performed, in some patients, long before or after the date of the manometry. The lack of association between CK levels and the manometric parameters could be explained by this fact. However, there was no possible bias regarding the time between the HRM and the esophageal symptoms survey, because both examinations were performed at the same time.

In conclusion, esophageal involvement in IM is significant and correlates poorly with esophageal symptoms. Additionally, we found a significant association between esophageal involvement and ILD severity and characteristic manometric features in specific autoantibody groups.

4. Cohort study of the antisynthetase syndrome

As it was explained before, ASyS is a disease characterized by antisynthetase autoantibodies and clinical characteristics including myositis, arthritis, ILD, fever, RP and mechanic's hands[42].

Several authors have suggested the existence of different phenotypes among ASyS patients depending on the autoantibody group[40,43,504-507]. The third study presented in this thesis is the first longitudinal cohort study analyzing the evolution of clinical features in ASyS patients with anti-PL12 and anti-PL7 compared to those with anti-Jo1. Our findings support the hypothesis that different AS autoantibodies have clinically distinct phenotypes.

Lung and muscle involvement

It has been previously reported that muscle and lung involvement at the onset and during the course of the disease is different across the different ASyS autoantibodies. Thus, lung involvement has been found to be more frequent in anti-PL7 and anti-PL12 than in anti-Jo 1 positive patients[30,44]. The opposite has been reported regarding muscle involvement, with more common muscle involvement in patients with anti-Jo1 positive autoantibodies than in the other two autoantibody groups[508]. However, there are several studies stating that the most frequent manifestation in patients with anti-PL7 positive is myositis[509,510]. In our study, we found that at the onset of the disease, patients with anti-Jo1 positive autoantibody had more muscle involvement than anti-PL7 and anti-PL12 positive patients. On the contrary, patients with anti-PL12 and anti-PL7 had more lung involvement at the onset of the disease that those positive for anti-Jo1 autoantibodies.

ILD in ASyS can be the initial symptom as well as the only manifestation of the disease[511]. In our study, 30% of the anti-PL12 positive patients as well as 19% of the anti-

PL7 and 10% of the anti-Jo1 positive patients presented lung involvement with no muscle signs or symptoms. On the other hand, 26% of patients with anti-Jo1 positive autoantibodies but just 4% anti-PL12 positive patients developed isolated muscle disease without pulmonary involvement.

Analyzing the intensity of ILD, we found that it was more severe in patients with anti-PL12 antibodies, followed by those positive for anti-PL7. Patients with anti-Jo1 autoantibodies presented with the mildest forms of ILD. With treatment, ILD evolution in all the autoantibodies of our cohort tended towards stability, as it was previously reported for anti-Jo1 patients[512]. This non-progressive course of the ILD, suggests that lung inflammation with irreversible damage most often occurs early after the onset at the disease. If this were to be confirmed, it would suggest early aggressive therapy in new-onset ILD might improve long-term outcomes and emphasizes the importance of developing procedures in clinical practice to differentiate in an accurate manner active from chronic lung disease in order to avoid treating residual non-reversible ILD.

With regard to race, black patients had more severe ILD than patients of other races, independent of the auto-antibody status. So, we can conclude that both the ASyS autoantibody status and the race are important factors associated with ILD severity in ASyS patients.

With regard to the weakness severity, it was not significantly different depending on sex, race or age at onset. However, the CK levels of anti-PL12 patients were significantly lower than those from patients positive for anti-PL7 or anti-Jo1 autoantibodies.

Gastrointestinal involvement

Marie et al. suggested that anti-PL7/PL12 positive patients had more common gastrointestinal manifestations than those with anti-Jo1 auto-antibodies[43]. In our study, we confirmed this result by finding an increased rate of gastroesophageal reflux in anti-PL7 and anti-PL12 patients compared with anti-Jo1. Of note, this finding may be due to an increase in the intrathoracic pressure caused by ILD or to a higher rate of lower esophageal involvement, which has been suggested to be common in myositis patients but never demonstrated in a definite manner until now (see second study)[216,217].

Mortality and cancer

The survival rate of patients positive for anti-Jo1 autoantibodies has been reported to be 90%[508,512] at 5 years and 75%[508,512] at 10 years from the diagnosis of the disease. Trallero-Araguas et al. reported a standardized mortality ratio (SMR) of 4.03 (2.79-5.64, CI 95%) for anti-Jo1 positive patients[512]. The survival rate in our study was 97% and 89% at 5 and 10 years respectively with a SMR of 1.1 (0.4-2.4, CI 95%) for anti-Jo1 positive patients. Thus, the mortality in our cohort was strikingly lower compared with previous studies. Moreover, we did not find significant differences in mortality between the different AS autoantibody groups (anti-Jo1, anti-PL7 and anti-PL12 positive patients).

We found that the cancer rate in ASyS patients, was not significantly higher in our cohort than in the general population. This is consistent with some studies that have suggested that ASyS is not associated with cancer[307]. Despite this, data is still conflicting and some observational studies have report a positive association between ASyS and neoplasm[43,45].

Association with anti-Ro52

Anti-SS-A (Ro52/Ro60) is found in patients with several autoimmune diseases like Sjögren's syndrome, SSc, myositis and SLE. But this autoantibody is especially prevalent in anti-Jo1 patients[45,132]. In this study, we confirm that the association with anti-Ro52 is stronger for anti-Jo1 (74%) than for anti-PL12 (43%) or anti-PL7 (44%). There have been conflicting reports associating the presence of anti-Ro52 autoantibodies with the severity of the pulmonary involvement, but in our study we could not find differences in the strength or the severity of ILD depending on anti-Ro52 status in our cohort of patients[513,514]. Similarly, we did not find differences in muscle strength between these with and without anto-Ro52 auto-antibodies.

Johnson et al. reported that non-Jo1 ASA positive participants were more likely to be African-American than Caucasian as compared to the anti-Jo1 positive patients ($p = 0.01$)[515]. This association was confirmed in our study, finding a striking increase in the severity of the ILD in black patients compared with other races. The severity of the lung involvement in black patients did not seem to be due to the higher prevalence of anti-PL12 in this group of patients, since both factors were independent predictors of the ILD severity without any detectable interaction between them. Rather, our findings suggest that there is a mechanistic link between race and anti-PL12 autoantibodies and also that both the race and the autoantibody status act as independent modifiers of the disease severity.

There are certain limitations in this study. First, signs and symptoms were recorded prospectively from the start of the study in 2003 and most of the conclusions are based on those signs and symptoms. Thus, most modern comprehensive arthritis scoring systems or activity and damage tools could not be included. Second, since this is a reference center for myositis, it is possible that the most severe patients of the spectrum

were selected, however, comparing our data with similar cohort studies it seems that the severity of our patients was similar or even lower than in previous studies[512,516]. Finally, the socioeconomic factors like lower treatment compliance or late start of treatment, may explain the increased ILD severity in black patients. However, these socioeconomic factors would have also presumably lead to increased muscle weakness and we could not detect this.

Despite these limitations, this is the largest longitudinal ASyS cohort study conducted in a single center and suggests that different diseases within the ASyS spectrum are defined by the different antisynthetase autoantibodies. Thus, anti-Jo1 patients present with more severe muscle involvement and anti-PL7 and anti-PL12 syndromes are characterized by more severe ILD. Black race was identified as a major prognostic factor associated with severity of the ASyS-ILD in patients with all three ASyS autoantibodies studied.

V. CONCLUSIONS

First, I am going to expose the conclusions of each one of the three studies that compose this thesis, and after that, the general conclusions of the dissertation.

1. Conclusions of the different studies

Study 1

Thigh muscle MRI in immune-mediated necrotizing myopathy: extensive edema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity.

-Different clinical and serological IM groups present different characteristic patterns of muscle involvement in t-MRI

-IMNM is characterized by more widespread muscle involvement compared with DM or PM patients.

-Muscle involvement in IMNM patients is more severe in anti-SRP-positive patients than in those with anti-HMGCR autoantibodies.

-An early therapeutic intervention is necessary in IM patients, due to the early fatty replacement that spreads to additional muscle groups more quickly during the early phases of the disease.

Study 2

High-resolution manometry in patients with idiopathic inflammatory myopathy: elevated prevalence of esophageal involvement and differences according to autoantibody status. and clinical subset

-Specific clinical and serologic groups have different manometric features.

-Although esophageal involvement is common in patients with IM, its correlation with esophageal symptoms is poor.

Study 3

A longitudinal cohort study of the antisynthetase syndrome: Increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies.

-Different ASyS autoantibodies are associated with phenotypically distinct subgroups within the ASyS spectrum.

-Among patients with ASyS, those that are positive for anti-PL7 and anti-PL12 autoantibodies are characterized by more severe lung involvement while anti-Jo1 is associated with more severe muscle involvement.

-In ASyS, the black race is a major prognostic factor associated with lung disease severity.

2. General conclusions

-Different clinical and serological IM groups present with different characteristic patterns of muscle and esophageal involvement as assessed in t-MRI and HRM, respectively.

-IMNM, and specially patients with anti-SRP autoantibodies, present with more severe muscle involvement than the other IM subsets.

-t-MRI patterns are specific, but not sensitive to distinguish the different IM subsets.

-An early therapeutic intervention is necessary in IM patients, due to the early fatty replacement that spreads to additional muscle groups more quickly during the early phases of the disease.

-Esophageal involvement is common in IM patients, but it correlates poorly with esophageal symptoms.

-ASyS autoantibodies as well as race are useful prognosis markers in ASyS patients

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