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Inflammatory Muscle Disease: A New Landscape

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Abstract

Greater accuracy in clinical descriptions combined with advances in muscle histology and immunology have established that inflammatory muscle diseases (IMDs) resemble inflammatory joint diseases in that they constitute a highly heterogeneous group of conditions. The topographic distribution, severity, and tempo of onset vary widely, and the histological findings distinguish at least five different profiles, which may reflect different pathophysiological processes. Most IMDs are connective tissue diseases that can affect multiple organs, among which the most common targets are the skin, joints, and lungs. The extramuscular manifestations may antedate the muscular involvement and should therefore suggest a diagnosis of IMD even in the absence of obvious muscle disease. About 20 different autoantibodies have been identified in patients with IMD. Some are mutually exclusive and associated with specific combinations of clinical manifestations. Following the model of antisynthetase syndrome, about 10 syndromes associated with autoantibodies specific of IMD have been identified. Thus, polymyositis is now emerging as a rare entity that is often mistaken for more recently described patterns of IMD. No consensus exists to date about the classification of IMDs. Nevertheless, the clinical manifestations, autoantibody profile, and muscle histology can be used to distinguish patient subgroups with fairly homogeneous patterns of complications, treatment responses, and outcomes. These subgroups are also characterized by specific genetic and environmental factors. The advances made in the nosology of IMDs have benefited the diagnosis, personalization of treatment strategies, and understanding of pathophysiological mechanisms. They can be expected to assist in the development of specific treatments.

Keywords: Inflammatory muscle disease. Myositis. Dermatomyositis. Necrotizing autoimmune myositis. Inclusion-body myopathies. Inclusion-body myositis.

The skeletal muscle: a common denominator

Involvement of the skeletal muscle is the historical defining criterion for IMD [1]. Typically, myalgia and/or muscle weakness in a symmetrical proximal distribution develop over several weeks. Muscle wasting may occur. Muscle enzyme levels (creatine kinase [CK], aldolase, and transaminases) in blood may be elevated. Creatine kinase elevation has good sensitivity and specificity for the diagnosis of muscle disease [2]. Transaminase elevation may mistakenly suggest liver involvement, which is rare in IMD. The electromyogram (EMG) shows the typical myopathic triad of polyphasic, low amplitude, and short duration motor-unit action potentials, as well as spontaneous fibrillation potentials and positive sharp waves. Magnetic resonance imaging (MRI) may disclose edema and/or fatty infiltration of the skeletal muscles, which may provide information on inflammatory activity and muscle damage [3]. MRI may be useful for guiding the muscle biopsy [4]. The histological features consist of an inflammatory infiltrate and/or muscle fiber necrosis. However, none of these findings is specific of IMD. The diagnosis relies on the combination of muscle abnormalities, extramuscular manifestations, and immunological alterations (Tables 1 and 2).

Distinguishing separate inflammatory muscle diseases: why and how

IMD was long viewed as a single entity called dermatopolymyositis. As with inflammatory joint disease, greater accuracy in clinical descriptions combined with advances in histology and immunology have established that IMDs constitute a heterogeneous group

of conditions whose clinical manifestations, etiological factors, treatment responses, and outcomes vary widely.

Distinctions based on the clinical and histological muscle involvement

The topographic distribution, severity, and tempo of onset vary across IMDs (Table 2). Necrotizing autoimmune myositis (NAIM, see histological definition below) induces muscle alterations at the worst end of the severity spectrum, which translate into severe muscle weakness (<3/5) in about half the patients [5], with a quarter of patients being unable to walk [6]. Muscle wasting is common and the serum CK level often approximates 10 000 IU/L [5], indicating intense muscle fiber necrosis. The full-blown clinical picture develops within 6 months in most patients. The slower onset in the remaining 20% to 30% of patients may mistakenly suggest a genetic muscle disease [7,8]. This difference in development kinetics remains unexplained. The muscle involvement is mild or absent in other IMDs such as amyopathic dermatomyositis. The diagnostic criteria for sporadic inclusion-body myositis (sIBM) include a very slow onset and preferential involvement of the quadriceps and flexors of the wrists and fingers [9]. Demonstration by MRI of this distinctive pattern of distribution may assist in the diagnosis [10].

The histological alterations seen in IMDs have been described in far greater detail than in the past. Abnormalities of the muscle fibers and capillaries, together with the features of the inflammatory infiltrate, are now used to identify distinct histological patterns, which may reflect different pathophysiological processes (Figure 1).

Perifascicular IMD

Historically, pathologic changes in the perifascicular region were associated with dermatomyositis [11]. They have since then been found also in antisynthetase syndromes (AS, see the clinical description below), whose histological features differ somewhat from

those of dermatomyositis [12–14]. In dermatomyositis, the perifascicular fibers are atrophic but rarely necrotic. They express HLA-I and only rarely HLA-II. Deposits of C5b-9 membrane attack complex are found on the capillaries. In AS, in contrast, the perifascicular fibers are necrotic, express both HLA-I and HLA-II, and carry C5b-9 deposits. Capillary deposits of C5b-9 are less common. In 81% of patients, electron microscopy visualizes actin aggregation in the muscle fiber nuclei, a finding that may be highly specific of AS [13]. The pathophysiological significance of these abnormalities has not been elucidated. The underlying mechanism may involve direct cytotoxic effects of interferon type 1 and/or effects of vasculopathy-induced ischemia on the perifascicular region [15].

Necrotizing autoimmune myositis (NAIM)

The predominant abnormality is muscle fiber necrosis and invasion by macrophages [11].. The inflammatory infiltrate is meager or absent. These features may be mistaken for a noninflammatory muscle disease due, for instance, to a toxic agent, endocrine disorder, or genetic abnormality. Immunolabeling studies may show HLA-I expression and C5b-9 deposits on the vessels and muscle fibers [5]. The mechanism causing necrosis may consist in complement activation by antibodies to the muscle fibers [16].

IMD with cytotoxicity

The inflammatory infiltrate is located in the endomysial spaces and invades nonnecrotic muscle fibers that express HLA-I. This histological pattern, previously believed to indicate polymyositis [11], probably indicates early sIBM [17].

Histological inclusion-body myosotis (IBM)

In addition to the histological abnormalities described in the previous paragraph, rimmed vacuoles and protein aggregates in the cytoplasm indicate defective autophagy, which can be confirmed using immunolabeling to detect SMI-31, TDP-43, phosphorylated

tau protein, and ubiquitin [9]. These abnormalities strongly support a role for abnormal protein breakdown in sIBM [18].

Nonspecific inflammatory muscle disease (IMD)

The inflammatory infiltrate exhibits a perimysial and perivascular distribution. None of the features in the above-described patterns is present. These nonspecific abnormalities are common in overlap syndromes, most notably scleromyositis, which combines manifestations of IMD and systemic sclerosis () [19,20]. They probably constitute a histological subgroup whose members remain to be identified.

Distinctions based on the systemic manifestations

The skin lesions of dermatomyositis were the first extramuscular manifestations described in IMDs. Since then, IMDs have emerged as systemic conditions that can involve numerous organs. As shown in Table 3 and Figure 2, the abundance of extramuscular manifestations is usually in inverse proportion to the severity of the muscle involvement. Thus, extramuscular manifestations are generally prominent in dermatomyositis with anti-MDA-5 autoantibodies but absent in NAIM. The extramuscular manifestations may antedate the muscle involvement by several years. They should therefore suggest the diagnosis of IMD even in patients without convincing evidence of muscle disease.

Joint involvement

The joints are among the most common targets of systemic IMD (about 50% of patients). Joint involvement occurs in up to 90% of patients with AS or anti-MDA-5-positive dermatomyositis [21]. The rheumatologist may therefore be the first physician to see patients with IMD and should consider the diagnosis, particularly as an explanation to seronegative peripheral arthritis [22]. Although arthralgia of the small joints is the most common presentation, polyarthritis is not uncommon. Radiographs were classically believed to remain

normal, but osteoarticular abnormalities have now been described and may occur in over one-third of patients with AS [23,24]. Anti-citrullinated peptide antibodies (ACPA) may be detected, suggesting overlap with rheumatoid arthritis. This fact warrants careful attention to the risk of bone and joint damage, whereas the extramuscular manifestations may be less severe [24]. Establishing the diagnosis of IMD is particularly important given that TNFα antagonist therapy may prompt the development or exacerbation of systemic involvement [24].

Thoracic involvement

Most thoracic abnormalities related to IMD have been associated with an increase in mortality. Risk factors have been identified.

Interstitial lung disease (ILD) is present in 20% to 78% of patients with IMD [25]. In most cases, the ILD lesions are nonspecific. However, the other types of ILD (common pneumonitis, bronchiolitis obliterans organizing pneumonia, and diffuse alveolar damage) or mixed computed tomography (CT) patterns are not rare [26]. ILD occurs chiefly in AS, scleromyositis, and anti-MDA-5-positive dermatomyositis, but is uncommon in paraneoplastic IMD. ILD is associated with an increase in overall mortality [27]. Nevertheless, the severity spectrum ranges from asymptomatic disease to acute respiratory distress. Factors known to be associated with adverse outcomes are CT evidence of diffuse alveolar damage [28]; low vital capacity or transfer factor for carbon monoxide [29]; and presence of anti-PL7, anti-PL12 [30], or anti-MDA-5 [31].

Pneumomediastinum is a severe complication associated with skin ulcers, amyopathic dermatomyositis, ILD, and/or presence of anti-MDA-5 antibodies [32,33].

Pulmonary arterial hypertension has been reported in patients with AS [34], scleromyositis [19], and mixed connective tissue disease [35] and can occur in anti-MDA-5-

positive dermatomyositis. Mortality is increased in patients with pulmonary arterial hypertension [34].

The respiratory muscles may be involved. However, ventilatory failure is rare [36] and should suggest another diagnosis such as Pompe disease [37].

Symptomatic cardiac involvement occurs in fewer than 10% of patients with IMD [38]. In contrast, abnormalities in the electrocardiogram or cardiac imaging studies (echocardiography, MRI, scintigraphy) are very common (up to 85% of patients) [39,40]. Although the prognostic significance of asymptomatic cardiac alterations in patients with IMD is unclear, some abnormalities (QTc prolongation, left ventricular diastolic dysfunction) have been associated with increased cardiovascular morbidity and mortality in the general population. Risk factors may include older age, longer disease duration, and presence of autoantibodies [39]. Troponin T is expressed not only by the myocardium, but also by the skeletal muscle. Thus, serum troponin T is elevated in IMD in correlation with the degree of myolysis and independently from any cardiac involvement [41]. Troponin I is specifically expressed by the myocardium. However, whether serum troponin I assays are helpful in IMD is unclear, as levels are not significantly different between patients with IMD and healthy volunteers [39]. In myocarditis due to other causes, the troponin I assay is specific (89%) but lacks sensitivity (34%) [42].

Skin involvement

Recent work has highlighted the heterogeneity of the skin lesions seen in dermatomyositis, which have been associated with syndromes of widely diverging prognosis (as detailed in the section on dermatomyositis).

Hyperkeratosis with cracks over the fingertips and, most prominently, the lateral aspect of the forefinger and middle finger (mechanic's hands) was described first in AS and

subsequently in anti-MDA-5-positive dermatomyositis [43] and anti-PM/Scl scleromyositis [44].

Sclerodactyly is common in AS [30]. Marked sclerosis should suggest overlap with systemic sclerosis, particularly in patients with other skin manifestations of this condition (fingertip ulcers and telangiectasia).

Raynaud's phenomenon is present in about 25% of patients with IMD [45]. This proportion is higher (about 50%) in AS, scleromyositis, and anti-MDA-5-positive dermatomyositis, during which it may be complicated by fingertip ulcers and/or necrosis of the extremities [43,46].

Calcinosis

Calcinosis occurs in about 10% of adults with IMD but is more common in children [47]. Hydroxyapatite crystals deposit in the skin, subcutaneous tissue, fascia, tendons, or skeletal muscle. The lesions may fistulize or cause joint stiffness. Related abnormalities include fingertip ulcers, prolonged disease activity, and the presence of anti-MDA-5, anti-NXP2 [48], or anti-PM/Scl [49] antibodies.

Oropharyngeal and gastrointestinal involvement

Swallowing impairments and dysphagia occur in 20% of cases overall and are more common in sIBM [50], scleromyositis [51], paraneoplastic dermatomyositis [52], and NAIM [53]. Except in the case of sIBM, dysphagia responds to immunomodulators but may require intravenous immunoglobulin therapy [54]. Intestinal pseudoobstruction has been reported [55].

Gastrointestinal vasculitis is rare in adults. An association with primary biliary cirrhosis has been reported in patients with anti-mitochondrial antibodies [56].

Distinctions based on the autoantibody profile

Autoantibodies are found in over 80% of patients with IMD [57]. About 20 different autoantibodies have been identified, and most are highly specific of IMD. Detection kits are commercially available for all these autoantibodies except anti-cN1A (for which a kit is being developed). Nevertheless, testing must often be performed in a specialized medical laboratory.

These specific autoantibodies are mutually exclusive. Each has been associated with a distinctive clinical profile (Table 3). Thus, following the AS model, about ten syndromes associated with autoantibodies specific of IMD have been described. Detecting these autoantibodies may not only assist in the diagnosis of IMD, but also improve the customization of treatment and follow-up strategies. Furthermore, patient follow-up may benefit from the identification of associations linking disease activity to the titers of some autoantibodies ((anti-SRP[58], anti-HMGCR [59], anti-Jo1[60], anti-Mi2, anti-Tif1 gamma[61], and anti-MDA-5[62]).

Distinctions based on etiologies

The etiologies of IMD are unknown. Nevertheless, several constitutional and genetic etiological factors are linked to specific clinical and serological subgroups of IMD.

Immunogenetics

Polymorphisms in *PTN22, UBE2L3*, *CD28*, *TRAF6*, and *STAT4* are associated with IMDs of any type, indicating a role for a common genetic background [63]. Furthermore, distinct HLA haplotypes are associated with each specific autoantibody [64–68], suggesting that immunogenetic factors may contribute to the heterogeneity of IMD. However, the low twin concordance rates [69], high prevalence of the same HLA haplotypes in the general population, and low incidence of IMD support a major influence of environmental factors.

Cancer, dermatomyositis, and necrotizing autoimmune myositis (NAIM)

About 20% of cases of IMD in adults are related to malignancies [70]. Factors positively associated with cancer are older age, male gender, and greater severity of the skin lesions. On the other hand, cancer is less common in patients with joint and/or lung involvement [70].

In dermatomyositis, anti-TIF-1 autoantibodies are associated with presence of a tumor [65], although the association may be weaker when a highly sensitive assay is used [71]. Anti-NXP-2 [71] and anti-SAE [72] antibodies may also be associated with cancer. In keeping with these findings, these three autoantibodies target proteins involved in cell cycle regulation.

In patients with NAIM, the absence of any of the known autoantibodies and, to a lesser degree, the presence of anti-HMGCR are associated with paraneoplastic IMD [73].

Ultraviolet radiation and dermatomyositis

A systematic review suggests that the relative incidence of anti-Mi-2-positive dermatomyositis may be related to ultraviolet radiation exposure [74]. Consistent with this possibility, the Mi-2 antigen is involved in repairing DNA breaks, of which one cause is ultraviolet radiation exposure, which induces Mi-2 overexpression [75].

Antiviral immunity and dermatomyositis

One argument suggesting a role for environmental factors in dermatomyositis is that many patients report a viral infection within a few months before the onset of the disease [76]. Further evidence for a viral factor consists in the presence of a type I interferon signature [77] and overexpression of several receptors involved in innate antiviral immune responses (endosomal toll-like receptors [TLRs], TLR-4, MDA-5, RIG-1) in muscle tissue and/or leukocytes from patients with dermatomyositis [78]. Finally, the dermatomyositis-specific anti-MDA-5 antibodies recognize an antigen involved as a ligand in innate antiviral

immune responses. The prevalence of anti-MDA-5 autoantibodies is associated with the epidemiology of coxsackievirus infections [79].

Statins and necrotizing autoimmune myopathy (NAIM)

A 2010 report describes a subgroup of patients with NAIM characterized by the presence of autoantibodies to the enzyme HMGCoA reductase. A history of statin therapy was found in two-thirds of these patients, a significantly higher proportion than in patients with other types of IMD [6]. In keeping with a causal role for statins, the *HMGCR* gene is expressed by regenerating muscle fibers from affected patients [80] and anti-HMGCoA reductase autoantibodies are not found in statin-exposed patients without evidence of IMD [81].

Smoking and antisynthetase syndrome (AS)

Smoking is associated with the presence of anti-Jo-1 autoantibodies [82], which target histidyl-tRNA synthetase. This enzyme is found in the lung alveoli in a form that is highly sensitive to cleavage by granzyme B [83], whose expression in the lung alveoli is increased by smoking [84]. Smoking may therefore increase Jo-1 cleavage in the lungs, thereby promoting loss of self tolerance in immunogenetically susceptible patients.

Muscle aging, impaired autophagy, autoimmunity, and sporadic inclusion-body myositis (sIBM)

The most common IMD in individuals older than 50 years is sIBM. Several lines of evidence suggest a role in sIBM of impaired autophagy, which in turn is associated with aging [85]. In immunolabeling studies, the protein aggregates found in muscle fibers in sIBM are recognized by antibodies to SMI-31, TDP-43, phosphorylated tau, and ubiquitin, whose presence is a strong diagnostic criterion for sIBM [9]. These proteins are normally broken down by lysosomal enzymes. Similarly, mutations in the autophagy-regulating gene *VCP* produce a muscular phenotype akin to sIBM, and polymorphisms in this gene are

associated with sIBM [86]. Thus, the autoimmune response in sIBM may result from chronic antigen stimulation by nondegraded proteins in patients at risk due to their immunogenetic background [87] and age [88].

Distinctions based on therapeutic response -- optimal personalization of patient care

Treatment responses to immunomodulating agents vary widely in patients with IMD. Several clinical, serological, and/or histological features may help to predict the response, thereby improving treatment personalization from the outset.

Anti-Mi-2-positive dermatomyositis and anti-Jo-1 AS respond well to immunotherapy [30,57,89]. In these diseases, a simple regimen such as a glucocorticoid combined with a disease-modifying antirheumatic drug may be appropriate.

NAIM with anti-SRP or anti-HMGCR antibodies are less sensitive to immunomodulation and may therefore require rescue treatments such as intravenous immunoglobulins (about 50% of patients) or rituximab [5,8,53]. Early treatment is associated with better muscle function recovery [7].

Recent findings in anti-MDA-5-positive dermatomyositis suggest that first-line intensive treatment (combined prednisone, cyclosporine, and cyclophosphamide) may improve survival compared to first-line conventional treatment [90].

In scleromyositis, the response of the muscle diseases varies with the histological pattern. Inflammation predicts a good outcome, whereas other abnormalities are associated with unresponsiveness to treatment [91]. This fact probably deserves consideration when assessing the risk/benefit ratio of glucocorticoid therapy, which is a risk factor for renal crisis in systemic sclerosis [92].

In sIBM, immunomodulating agents have little or no effect and may even increase the risk of death [93].

Newly identified subtypes of inflammatory muscle disease (imd)

The historical entity polymyositis is increasingly being broken up into newly described subtypes of IMD. No consensus about the classification of IMD exists to date. Nevertheless, clinical features, autoantibody profiles, and muscle biopsy findings can be used to identify patient subgroups characterized by fairly homogeneous patterns of complications, treatment responses, and outcomes.

Dermatomyositis

All subtypes share the skin lesions typical for dermatomyositis: photosensitivity; facial rash, which may be accompanied with poikiloderma; more or less linear and scaly macules and/or papules (Gottron's papules) over the extensor surfaces of the hand joints, elbows, and knees; and periungual hyperemia and megacapillaries with cuticle necrosis. Nevertheless, both the detailed features of the skin lesions and the extracutaneous manifestations vary considerably. As described below, several of the autoantibodies specific of dermatomyositis are associated with distinctive clinical patterns and may therefore assist in developing a classification of these diseases.

° ***anti-Mi-2-positive dermatomyositis*** is associated with a rash over light-exposed areas, a low risk of extracutaneous manifestations, a good treatment response, and a good prognosis.

° ***anti-MDA-5-positive dermatomyositis*** is characterized by erythematous, scaly skin lesions (described as the typical dermatomyositis rash combined with mechanic's hands) and by papules with an ivory-colored center and ulcers on the palms of the hands [43] (Figure 3A). There is little or no muscle involvement. In contrast, patients are at risk for rapidly

progressive ILD and pneumomediastinum [32], which increase the mortality rate [94]. A first-line high-intensity treatment strategy may improve the outcome [90]. Patients may also be at risk for calcinosis [48]. Joint involvement is common and may be inaugural, leading to a mistaken diagnosis of rheumatoid arthritis [21].

° ***anti-TIF-1-positive dermatomyositis*** is associated with the classical picture of dermatomyositis. In particular, features include Gottron's papules; a rash, which may be extensive, localized to light-exposed areas, and pruriginous; scaly papules over the palms; psoriasis-like lesions; telangiectatic macules; and punctate follicular erythematous lesions over a leukodermic background (red-on-white lesions). The last two manifestations resemble those seen in subacute cutaneous lupus [95] (Figure 3B). Involvement of the joints and lungs is rare. A concomitant malignancy is common, with the risk being highest in patients with both anti-TIF-1γ and TIF-1α autoantibodies [96].

° ***anti-NXP-2-positive dermatomyositis*** is associated with a well-defined pediatric syndrome of calcinosis (Figure 3C), marked muscle weakness, and a risk of persistent disease activity after 2 years [97]. ILD is rare. In adults, the clinical relevance of anti-NXP-2 autoantibodies is less well understood. In several studies [48,98] and in our experience, the phenotype resembles that seen in children. In other studies, however, no patients had calcinosis [99], ILD was common [100], and/or the risk of a concomitant malignancy was high [71,99]. The reasons for these discrepancies are unclear.

° ***anti-SAE-positive dermatomyositis*** may differ from other dermatomyositis subtypes by an amyopathic disease onset and the presence of dysphagia [101]. In Asian populations, anti-SAE autoantibodies are associated with ILD [102] and cancer [72].

Necrotizing autoimmune myositis (NAIM)

The predominant histological finding by far is muscle fiber necrosis. The inflammatory infiltrate is moderate to absent. The severe muscle involvement contrasts with the low incidence and lesser prominence of extramuscular manifestations. The differential diagnosis may be difficult, most notably with drug-induced necrotizing myositis and muscular dystrophy, particularly when the symptoms set in slowly [7,8] and/or the response to first-line treatment is inadequate, as occurs in many cases [5,53,73].

Three subtypes of NAIM have been identified based on the serological profile.

° ***anti-SRP-positive NAIM*** may be the subtype with the most severe skeletal muscle involvement. Thus, the motor weakness is more severe, muscle wasting and/or dysphagia more common, and the need for aggressive treatments greater than in other NAIM subtypes. Diffuse ILD is present in 20% of patients [5,53,73]. The risk of cardiac involvement suggested by early studies was not confirmed in subsequent work.

° ***anti-HMGCR-positive NAIM*** is associated with a history of statin therapy in about two-thirds of cases[6,8]. A higher risk of cancer of borderline significance compared to the expected incidence was reported recently [73].

° ***seronegative NAIM*** is characterized by an incidence of cancer 8-fold higher than expected [73].

Overlap syndromes

All overlap syndromes are characterized by prominent extramuscular manifestations (but without the rash in dermatomyositis). Overlap syndromes may account for a large proportion of IMDs [89].

Antisynthetase syndrome (AS)

AS is characterized by variable combinations of constitutional symptoms (fever, fatigue, and weight loss), Raynaud's phenomenon, inflammatory joint disease, IMD, ILD,

and skin lesions (mechanic's hands and sclerodactyly) [30]. The picture is often incomplete early in the disease, when there is often a single manifestation such as inflammatory joint disease (1 in 4 patients) or either IMD or ILD (1 in 8 patients). The other features nearly always develop during follow-up. Thus, after a median follow-up of 80 months, only 1 in 10 patients had involvement of a single organ [103].

AS is related to the presence of autoantibodies against aminoacyl-tRNA synthetases, of which the most common target the histidyl-tRNA synthetases (Jo-1) (about 20% of patients with IMD). The other specificities, which are far less common (1% to 5%), target the alanyl (PL-12), threonyl (PL-7), glycyl (EJ), isoleucyl (OJ), asparginyl (KS), tyrosyl-AS (Ha), and phenylalanyl (Zo) tRNA synthetases. The specificity of anti-synthetase autoantibodies may influence the frequency of clinical features and the outcome. Thus, outcomes may be poorer in patients with antibodies to PL7 or PL12, which are associated with a higher frequency of ILD [30].

Scleromyositis

The muscles may be involved in up to 69% of patients with systemic sclerosis [91], and 29% of patients with IMD may have systemic sclerosis [89].

Compared to other patients with systemic sclerosis, those with scleromyositis are more often male and have greater global disease severity with a younger age at onset (44-52 years) and higher frequencies of diffuse skin lesions (40%-63 %), lung disease (24%-62 %), and cardiac involvement (29%), which translate into a higher mortality rate [104–107].

Nevertheless, the serological and histological features should probably also be considered when assessing the prognosis. Among the autoantibodies associated with muscle involvement, anti-Scl70 are among the most common [108] and are associated with diffuse skin lesions, involvement of the heart and lungs, and a higher risk of death [109]. Anti-PM/Scl autoantibodies are associated with less severe disease, a better treatment response,

and better survival [49,110]. Patients with anti-RNP autoantibodies are at risk for pulmonary arterial hypertension, although the prognosis of this condition is better than in other patients [111]. Anti-Ku autoantibodies are associated with lung disease. Their potential link to the prognosis is unclear [112,113]. Anti-RNA Pol III autoantibodies are associated with a higher risk of malignancy [114].

Muscle biopsy features vary widely in systemic sclerosis. No convincing correlations have been reported between serological and histological features [19]. Muscle inflammation may predict a good treatment response [91], whereas fibrosis may indicate a risk of renal crisis [19], particularly in patients taking glucocorticoid therapy [115].

Mixed connective tissue disease

By definition, mixed connective tissue disease is associated with anti-RNP autoantibodies. The diagnostic criteria for systemic sclerosis and/or systemic lupus erythematosus may be met [116]. IMD is present in 20% to 25% of cases and may be associated with a higher frequency of pulmonary arterial hypertension, neurological involvement, and renal involvement [35,117].

Inclusion-body myositis

Correctly diagnosing IBM is of the utmost importance, as immunomodulating agents are not effective and may even increase the risk of death [93]. The diagnosis may be challenging, particularly as autoimmunity is common in sIBM and may manifest as the production of autoantibodies associated with IMD [9]. Autoantibodies to 5'-nucléotidase 1A (cN1A) were found in larger proportions of patients with sIBM (33% to 73%) than of patients with other IMDs. However, anti-cN1A autoantibodies also occur in lupus (14%-20%) and Sjögren's syndrome (23%-36 %) [118].

Does polymyositis exist?

Since it was first described, no associations linking a clinical feature, autoantibody, or histological finding to polymyositis has withstood the test of time. On the contrary, the number of conditions mistakenly diagnosed as polymyositis has increased steadily. It has therefore been suggested that polymyositis is not a disease entity [119] but simply an inflammatory or noninflammatory muscle disease that has not yet been correctly diagnosed. The clinical, MRI, or histological features of many genetic muscle diseases can mimic those of IMD [37] (Tables 1 and 2). The response to glucocorticoid therapy is not a strong diagnostic criterion, as significant benefits of glucocorticoids have been reported in patients with Duchenne muscular dystrophy [120] and IMD can be steroid-resistant.

Conclusion

Although there is no consensus about the classification of IMDs, the available data allow the identification in everyday practice of patient subgroups characterized by fairly homogeneous clinical features, muscle biopsy alterations, autoantibody profiles, etiological factors, and outcomes. As with inflammatory joint diseases, the improved characterization of IMD will benefit the personalization of patient care and may promote the emergence of specific treatments.

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FIGURE LEGENDS

Figure 1: Five histological patterns of inflammatory muscle disease (IMD)

A. **Perifascicular IMD:** The fibers in the perifascicular area are atrophic (asterisk, dermatomyositis) and/or necrotic (AS), express HLA class 1 (dermatomyositis) or 2 (AS), and carry C5b9 deposits (AS). The scant capillaries are dilated and carry C5b9 deposits (which are more common in dermatomyositis). A lymphocytic infiltrate is visible in the perimysium (black arrow) and surrounding the vessels (white arrow).
B. **NAIM:** muscle fiber necrosis is the predominant feature (asterisk), and there is no inflammatory infiltrate. Immunolabeling may demonstrate HLA-I expression and C5b9 deposits on vessels and muscle fibers.
C. **IMD with cytotoxicity:** The inflammatory infiltrate is in the endomysial area (arrow) and invades nonnecrotic muscle fibers (asterisk) demonstrating diffuse HLA-I expression.
D. **Histological inclusion-body myositis:** The lesions are identical to those described above. In addition, the cytoplasm contains rimmed vacuoles (white arrow), eosinophilic inclusions (black arrow), and protein aggregates indicating impaired autophagy, which can be demonstrated by immunolabeling for SMI-31, TDP-43, phosphorylated tau, and ubiquitin.
E. **Nonspecific myositis:** The inflammatory infiltrate is perimysial and/or perivascular (arrow) and the features of the above-described patterns are lacking.

Figure 2: Clinical and serological diversity of inflammatory muscle disease (IMD) The prominence of the extramuscular manifestations is usually in inverse proportion to the

severity of the muscle involvement. The autoantibody profile can be used to identify patient subgroups with globally homogeneous clinical features and outcomes.

Figure 3.

A. Papules with an ivory-colored center at the palm and hyperkeratosis with cracks at the fingers in a female patient with anti-MDA-5-positive dermatomyositis

B. Erythematous, scaly, psoriasis-like lesions of the scalp in a female patient with anti-TIF1γ-positive dermatomyositis

C. Calcinosis of the lumbar region with drainage tracts to the skin in a female patient with anti-NXP-2-positive dermatomyositis

Table 1: Differential diagnosis of inflammatory muscle disease

Lesions	Differential diagnoses
MRI	Trauma: fissure in an adjacent bone, muscle injury, strenuous physical activity
	Denervation: radiculopathy, neuropathy, motor neuron disease
Muscle edema (high signal on T2 images)	Amyloid myopathy
	Genetic muscle diseases: acid maltase deficiency (Pompe disease), myotonic dystrophy type 2, dysferlinopathy, facioscapulohumeral muscular dystrophy
Muscle biopsy	Infectious muscle diseases:
	HIV
Inflammatory lymphoplasmacytic infiltrate	Toxocariasis, trichinosis
	Hematological malignancies:
	Secondary invasion by malignant cells
	Graft-versus-host disease after bone marrow transplantation
	Genetic muscle diseases:
	Dysferlinopathy
	Dystrophin muscular dystrophy (Becker's myopathy)
	Facioscapulohumeral muscular dystrophy
	Mutation in the fukutin-related protein gene *FKRP*
	Laminopathy
	Titinopathy (Udd myopathy)
	Autoinflammatory syndrome (interferonopathy)
Necrosis/regeneration with no inflammatory infiltrate	Toxic myopathy: alcohol, statin, fibrate
	Dysthyroidism
	Genetic muscle disease: dystrophy

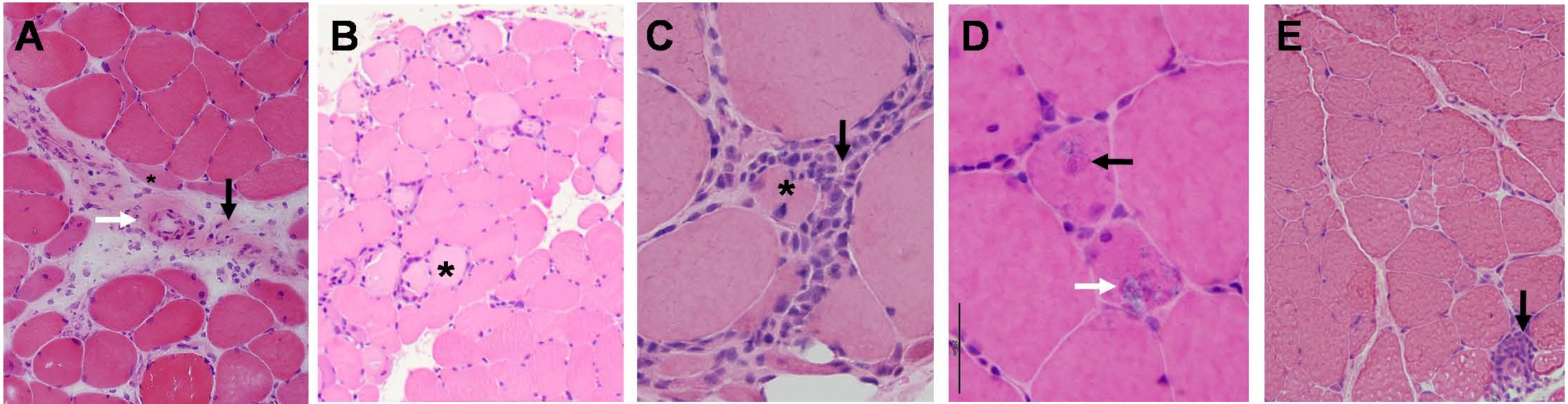
Table 2: Features that distinguish inflammatory muscle diseases (other than inclusion-body myositis) from genetic muscle diseases

	Features suggesting inflammatory muscle disease (other than sIBM)	**Features suggesting genetic muscle disease**
Family history	Autoimmune diseases	Consanguinity, cardiomyopathy, neuromuscular diseases
Age at onset	Any age >2 years	Childhood or early adulthood
Tempo of disease onset	Rapid but may be gradual in NAIM	Slow but may accelerate intermittently
Topographic distribution of affected muscles	Proximal; symmetric, spares the face	Variable; may be asymmetric; may involve the facial, oculomotor, or distal muscles
Muscle trophicity	Generally normal except during NAIM	Selective hypertrophy or amyotrophy
Muscle tone	Normal	Myotony in myotonic dystrophy syndromes
Involvement of the myocardium and/or respiratory muscles	Rare except for myocarditis in scleromyositis	Common
Extramuscular manifestations	Skin, ILD, IR, acrosyndrome	Dysmorphism, central and/or peripheral nervous system, endocrine glands
Creatine kinase level	Usually <5000 IU/L except in NAIM	Often >5000 IU/L
EMG	Fibrillation potentials and positive sharp waves	Myotony (myotonic dystrophy) or concomitant neuropathy
Abnormal MRI signal from muscle	High signal on T2 images	High T1 signal (high T2 signal may be present)
Autoantibodies	Yes	No
Inflammatory infiltrate within muscles	Perimysial and/or perivascular, absent or moderate in NAIM	Absent or endomysial, without invasion of the fibers, which are not necrotic or eosinophilic
HLA class 1	Diffuse expression except in NAIM	Expression absent or focal
C5b-9	Deposits on capillaries, but deposits may occur on muscle fibers in NAIM and ASS	Deposits on fibers
Immunolabeling and/or Western blot for proteins involved in muscular dystrophies	Normal	Diminished
Response to immunomodulating treatment	Usually good, but corticoid resistance may develop	Usually absent, but a moderate improvement is possible

Table 3: Suggested classification for inflammatory muscle diseases in adults

				Risk and features of extramuscular manifestations				
	Muscle histology	Autoantibodies to	Muscle involvement	Cutaneous involvement	Thoracic involvement	Joint involvement	Other involvements	*Excess risk of cancer*
DERMATO-MYOSITIS	**Perifascicular IMD (except anti-MDA-5-positive IMD)**	**Mi-2**	---	DM	Rare	Rare	---	No
		MDA-5	Moderate to absent	DM, MH???, papules on the palms, ulcers	ILD, pneumomedias-tinum	Polyarthralgia /polyarthritis	Fever	No
		NXP-2	Severe	DM, calcinosis	Controversial	Rare	---	Yes
		TIF-1γ	---	DM, extensive, psoriasis-like, red-on-white, lesions	Rare	Rare	---	Yes
		SAE	Dysphagia	DM	ILD (Japanese)	Rare	---	Possibly
NECROTIZING AUTOIMMUNE MYOSITIS	**Muscle fiber necrosis**	**SRP HMGCR Seronégative**	Severe, amyotrophy, dysphagia (SRP>HMGCR)	Absent	Usually absent	Rare	---	HMGCR and sero-negative
ANTISYNTHETASE SYNDROME	**Perifascicular IMD**	**Jo-1, PL7, PL12, EJ,**	(Jo1 > PL7 or PL12)	Mechanic's hands, sclerodactyly	PID (Jo1 < PL7 or PL12), PAH	Polyarthralga/ polyarthritis (Jo1 > PL7 or PL12)	Fever, renal (rare)	No
SCLEROMYOSITIS	**Variable Inflammation inconsistently present**	**Scl70 PM/Scl Ku RNApolII RNP**	Dysphagia	Scleroderma, fingertip ulcers	ILD (Scl70, Ku), myocarditis (Scl70), PAH (RNP)	Polyarthralga/ polyarthritis	Renal	RNApolIII
MIXED CONNECTIVE TISSUE DISEASE	**Perifascicular or nonspecific IMD**	**RNP**	---		ILD, PAH	Polyarthralgia /polyarthritis	Neurological	No
INCLUSION-BODY MYOSITIS	**IMD with cytotoxicity, rimmed vacuoles, and deficient autophagy**	**Mup44**	Slow, asymmetrical, amyotrophy, knee extensors and finger flexors, dysphagia	Absent	Absent	Absent	Associated autoimmune diseases	No

DM, dermatomyositis;ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; IR inflammatory rheumatism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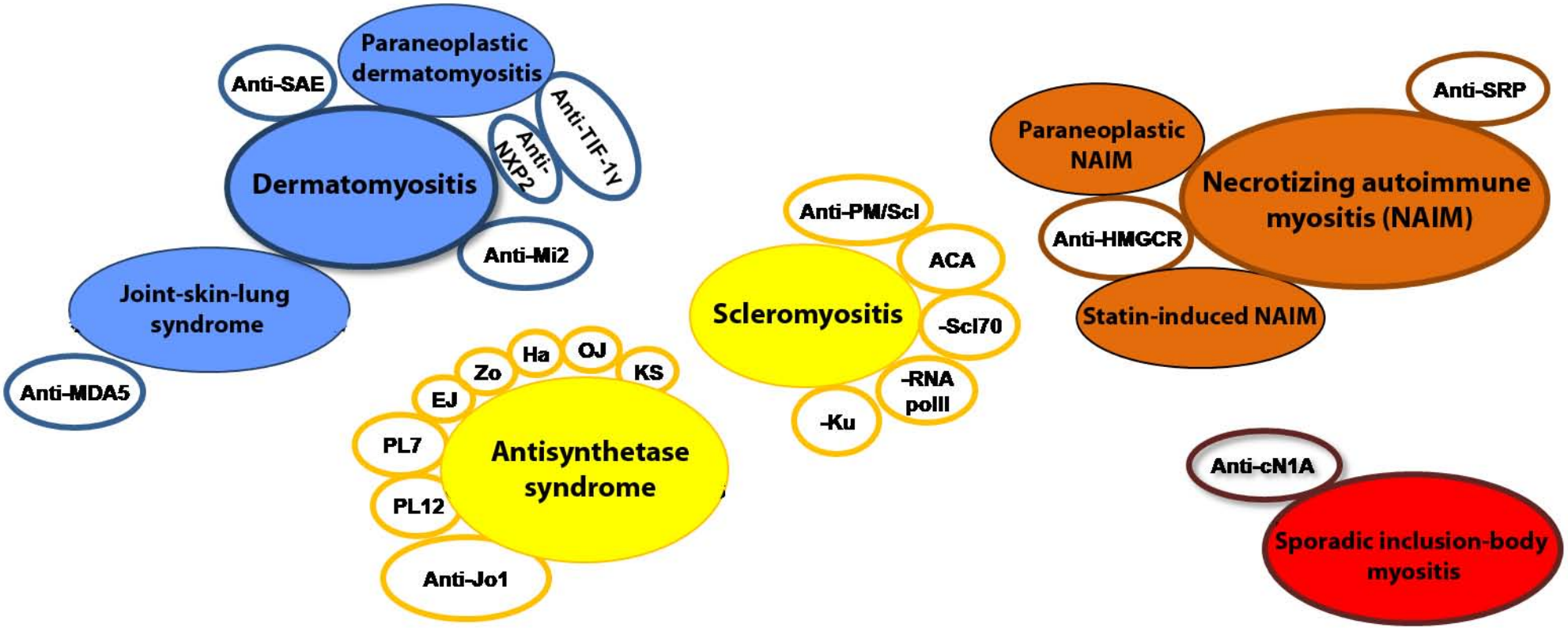
Paraneoplastic dermatomyositis
Anti-SAE
Anti-TIF-1γ
Anti-NXP2
Dermatomyositis
Anti-Mi2
Joint-skin-lung syndrome
Anti-MDA5
Anti-PM/Scl
ACA
Scleromyositis
-Scl70
-RNA polIII
-Ku
Ha
OJ
Zo
KS
EJ
PL7
Antisynthetase syndrome
PL12
Anti-Jo1
Paraneoplastic NAIM
Anti-SRP
Necrotizing autoimmune myositis (NAIM)
Anti-HMGCR
Statin-induced NAIM
Anti-cN1A
Sporadic inclusion-body myositis
Extramuscular involvement
Muscular involvement


A

B

C