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Idiopathic inflammatory myopathies: A non-systematic review

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Abstract

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune diseases that primarily affect the muscles and skin but may also involve other organs, including the lungs, heart, and joints. They are rare compared to other autoimmune inflammatory rheumatic diseases. There have been changes in their classification criteria with the recognition that numerous autoantibodies play a role in disease pathogenesis. IIMs are currently classified into five main types: Dermatomyositis, polymyositis, overlap syndromes and antisynthetase syndrome, immune-mediated necrotizing myopathy, and inclusion body myositis. Autoantibodies implicated in IIMs are categorized as myositis-specific antibodies (MSA) or myositis-associated antibodies. Each MSA is associated with specific clinical and pathological features. Identifying these antibodies during diagnosis is valuable for both the treatment and prognostic assessment. For example, anti-Mi2 positivity is associated with milder disease courses and favorable treatment responses. Anti-MDA5 positivity is closely associated with rapidly progressive interstitial lung disease. In contrast, anti-TIF1-γ and anti-NXP2 antibodies are important risk factors for the development of malignancy. Early diagnosis and treatment are crucial for disease control. Most patients respond well to corticosteroids, while methotrexate or azathioprine are commonly used as corticosteroid-sparing drugs. If necessary, more potent immunosuppressive, biological agents, and intravenous immunoglobulin can be used. In this review, we summarized the recent advances in the understanding and management of IIMs over the last 10 years.

Keywords: Idiopathic inflammatory myopathies; Interstitial lung disease; Myositis-specific antibodies; Antisynthetase syndrome; Myositis-associated autoantibodies

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1. Introduction

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of systemic, autoimmune diseases that primarily affect the muscles but can also involve multiple organs. Although classically characterized by muscle inflammation, certain forms of IIM spare the skeletal muscles. These amyopathic or hypomyopathic forms are still considered IIM because of their common serologic features and etiopathogenesis.

Furthermore, patients with IIM may present to a variety of medical specialties, including neurology, rheumatology, dermatology, and pulmonology, making a comprehensive case description challenging. Given these reasons, it has been proposed that the term IIM does not fully reflect the characteristics of these diseases. Alternative terms such as "systemic autoimmune myopathies," "myositis spectrum disorder," and "autoimmune myositis" have been suggested. However, they are not yet widely used in the literature.[1,2]

In recent years, research interest in IIMs has increased. Some of the significant advances include the identification of new myositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs), refinement of classification systems, better understanding of disease pathogenesis, and the development of immunosuppressive drugs and targeted therapies. The discovery of numerous new autoantibodies has been particularly instrumental in elucidating disease mechanisms and guiding new treatments.[3] In this article, we review recent progress in the understanding of IIMs and discuss key clinical entities that may mimic or overlap with these conditions, in light of developments over the past decade.

2. Methods

This review is a non-systematic review that adopts a structured literature search to summarize recent developments in understanding IIMs. Studies were selected if they were categorized as clinical trials, randomized controlled trials, reviews, or systematic reviews, conducted within the last 10 years, and had full-text versions available online in English. We conducted a PubMed search covering the time period from January 1, 2015, to early February 2025. The following terms were used as keywords: "myositis" (881 results), "idiopathic inflammatory myopathies" (923 results), and "antisynthetase syndrome" (56 results).

After screening abstracts and titles and excluding articles that addressed overlapping or duplicate topics, a total of 75 articles were included for review. In addition, 21 key articles from earlier years were included, resulting in a total of 96 articles analyzed. For etiology, epidemiology, and immunopathogenesis, the available articles were deemed sufficient, and no additional screening was performed.

In addition to the introduction and methods sections, this review is structured into several main parts. These include an overview of the epidemiology of IIMs, followed by a section on their brief history and classification. The etiopathogenesis of IIMs is then discussed, along with detailed descriptions of the clinical subtypes, including dermatomyositis (DM), polymyositis (PM), overlap myositis, antisynthetase syndrome (ASS), and inclusion body myositis (IBM). The review also covers other myositis types encountered in clinical practice, such as statin-related myotoxicity (SRM), cancer-associated myositis (CAM), and immune checkpoint inhibitor (ICI)-induced myositis. Subsequent sections cover the diagnosis of IIMs, emphasizing laboratory testing and the roles of MSAs and MAAs, followed by treatment approaches, prognosis, and conclusion.

3. Epidemiology of idiopathic inflammatory myopathy

IIMs are rare diseases that can be seen all over the world. Although different figures have been reported for the incidence and prevalence of IIMs across countries, the overall incidence is estimated at 0.2–2.0 new cases/100,000 people/year, and the prevalence is 2–25 IIM cases/100,000 people. Thus, IIMs are considerably less common compared to rheumatoid arthritis, spondylarthritis, or even giant cell arteritis. However, they are regularly encountered in rheumatology clinics and can lead to high morbidity and mortality if sufficient precautions are not taken.[1,4,5]

4. Brief history and classification of idiopathic inflammatory myopathy

Historically, PM was the general term encompassing various forms of inflammatory myopathies. However, over time, the nomenclature has changed as a result of developments and a better understanding of these conditions.[6,7] It has become clear that these conditions are not from a single disease but represent a heterogeneous group of diseases, although they share common features, such as muscle involvement, skin manifestations, and lung complications.

In the second half of the 18th century, several authors published some of the earliest detailed descriptions of patients exhibiting muscle disease accompanied by characteristic skin lesions. These initial cases were typically characterized by muscle pain, muscle weakness, eyelid discoloration, and pulmonary involvement, and were later recognized as DM.[6,7]

During the early 20th century, similar cases were reported under various names, including poikiloderma vascularis atrophicans, myositis universalis acuta, PM, and pseudotrichinosis. Over time, the association between myositis and malignancy, as well as the distinct entity of juvenile DM, was also established.[6,7]

Pioneering publications in 1975 proposed five major criteria for the diagnosis of PM and DM, incorporating clinical, laboratory, histopathologic, and neurophysiologic features. These frameworks clearly distinguished DM from PM and identified important subtypes of these diseases,

including neoplasia-associated myositis, juvenile or childhood myositis (predominantly juvenile DM, JDM), and overlap syndromes involving other autoimmune connective tissue diseases (CTDs).[6,7]

Between 1976 and 1985, several MSAs and ASSs were described, and rapid and significant progress was made in understanding the classification, underlying mechanisms, autoantibodies, and treatment approaches of IIMs.[1,8] In 1991, sporadic IBM was defined, and diagnostic criteria for IBM were published. Later, in 2004, the European Neuromuscular Center defined the concepts of immune-mediated necrotizing myositis (IMNM) and non-specific myositis. The majority of patients with IMNM were positive for anti-3-hydroxy-3-methylglutaryl-CoA reductase (anti-HMGCR) autoantibodies—often associated with prior statin exposure in adult patients—or anti-signal recognition particle (anti-SRP) autoantibodies. Finally, in 2017, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) jointly published new classification criteria for adult and juvenile IIMs and their subgroups.[1,6,9]

Since the Bohan and Peter period, there has been a shift toward classifying myositis according to clinical, serological, and histopathological features. Today, classification is based on clinical, laboratory, and histopathological features, as well as the presence of specific antibodies that reflect underlying pathogenic mechanisms. Accordingly, IIMs are recognized under five main groups: (i) DM, (ii) PM, (iii) ASS, (iv) IMNM, and (v) IBM.

The most important milestone in the field of myositis is the discovery of MSAs, which can be helpful in diagnosis and have prognostic significance due to their association with organ involvement. The first identified MSA, anti-Mi2 antibody, was discovered in 1976, followed over the next few years by the identification of anti-Jo1 and anti-SRP antibodies, as well as several non-Jo-1 antisynthetase antibodies. The discovery of MSAs has also shed light on the pathogenesis of IIMs.

Each MSA is typically associated with a characteristic clinical phenotype. For example, anti-Mi-2 positivity is associated with myositis, featuring heliotrope rash, shawl sign, and Gottron's papules, usually accompanied by sparse lung involvement. In contrast, antisynthetase antibodies, most notably anti-Jo-1, are closely associated with interstitial lung disease (ILD) and are defining features of the ASSs, which also include Raynaud's phenomenon, mechanic's hands, and arthritis. Similarly, the presence of autoantibodies recognizing small ubiquitin-like modifier activating enzyme or melanoma differentiation-associated gene antibodies (anti-MDA5) is characterized by rapidly progressive ILD (RP-ILD). Anti-transcriptional intermediary factor 1 gamma (anti-TIF1-γ) antibodies, on the other hand, are closely associated with the development of malignancy.[8,10,11] The discovery of MSAs and their influences on clinical presentation and prognosis have provided a new perspective on the classification of IIMs, although developments in this area are still ongoing.

Usually, only one MSA is detected in a patient. Rarely, multiple MSAs are found together. The most recognized example is the association between anti-MDA5 and ASS antibodies, associated with a more favorable disease course.[12] Two other MSAs reported more recently, anti-cell division cycle and apoptosis regulator protein 1 (anti-CCAR1) and anti-Sp4, appear to reduce the risk of cancer in patients with anti-TIF1-γ.[3]

Today, 16 MSAs are identified, and this number will increase over time. Efforts to classify IIMs based on MSA positivity have emerged. However, autoantibodies have not yet been fully integrated into the classification system, and around 30% of IIM cases remain seronegative,[8,10,11] underscoring the need for continued research to identify additional autoantibodies and refine disease categorization. The identified MSAs and their characteristic clinical associations are summarized in Table 1.

In addition to MSAs, patients with IIMs may have MAAs—autoantibodies that are also present in other autoimmune disorders, such as systemic lupus erythematosus (SLE), systemic sclerosis, or Sjögren syndrome (SjS).[13] These antibodies generally developed against nuclear or cytoplasmic antigens and include anti-SjS-related antigen A (anti-Ro), anti-SjS-related antigen B, anti-PM/Scl, anti-Ku, anti-U1 small nuclear ribonucleoprotein, anti-mitochondrial antibody, anti-cytosolic 5'-nucleotidase 1A (anti-cN1A), and anti-nuclear pore complex. The presence of each is associated with different clinical courses. For example, anti-Ro positivity can be detected in various autoimmune diseases, especially in SjS, and can cause non-specific myositis. Moreover, the presence of its subunit anti-Ro52 in the absence of anti-Ro60, together with ASSs, can increase the risk of ILD and cause drug resistance for ILD.[14-22] Similarly, anti-PM/Scl and anti-Ku are also associated with an increased risk of ILD. Anti-cN1A are reported in more than 50% of patients with IBM; however, they have also been detected in other CTDs, notably SLE and SjS, but are not associated with IBM.[13,15] Conversely, anti-TIF1-γ positivity significantly increases the risk of cancer but appears to be a risk-reducing factor for ILD.[16-19] Anti-mitochondrial autoantibodies, while characteristic markers of primary biliary cirrhosis, can also coexist with other autoimmune disorders, including systemic sclerosis, SjS, rheumatoid arthritis, and IIMs. In such cases, anti-mitochondrial positivity has been associated with granulomatous myositis, chronic

Table 1. Myositis-specific antibodies and their associated clinical features

Antibody	Targeted antigen	Frequency (%)	Typical clinical features
Anti-Mi-2	Nucleosome-remodeling deacetylase complex	10–21	Classical DM: Periorbital edema, heliotrope rash, Gottron's papules, Gottron sign, shawl sign, V sign, cuticular overgrowth, low ILD and malignancy, myositis, good prognosis, and good response to treatment
Anti-MDA5	Melanoma differentiation-associated protein-5	15–20	DM, CADM, RP-ILD, subcutaneous emphysema, fever, polyarthritis, vasculopathy, soft erythematous papules and skin ulcerations in nail folds and on extensor surfaces of joints, pharyngeal and laryngeal involvement, and alopecia
Anti-T1F1-γ	Transcriptional intermediary factor 1-γ	10–15	DM, significantly increased risk of malignancy (at least 78% of all cancer-related diagnoses among DM patients), severe and widespread skin involvement, oval palatal patch, lateral hip rash (Holster sign), and muscle enzymes vary and can therefore be classified as CADM in addition to classical DM In contrast to ASS or anti-MDA5-associated myositis, the prevalence of Raynaud phenomenon, arthritis, and ILD, especially RP-ILD, is relatively low
Anti-NXP2	Nuclear matrix protein 2	1–5	DM, significantly increased risk of malignancy, distal and proximal muscle involvement, muscle atrophy, edematous myositis, DM sine dermatitis; polyarthritis, dysphagia, severe calcinosis, joint contractures, and intestinal vasculitis It is more common among juvenile DM cases (20%)
Anti-SAE	Small ubiquitin-like modifier activating enzyme	1	DM, dysphagia, late elevation of muscle enzymes increased ILD risk (in Asians, not in Europeans), and increased risk of malignancy Often initially presents as CADM and then progresses to develop myositis with a higher frequency of systemic features, including dysphagia, which is seen in 30–78% of patients who show anti-SAE positivity
Anti-SRP	Signal recognition particle	5	Acute progression, severe muscle symptoms, cardiac involvement, absence of cancer, and absence of rash
Anti-HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase	-	Statin exposure, less ILD, and absence of rash
Antisynthetase antibodies	tRNA synthetase	-	Raynaud phenomenon, arthritis, fever, mechanic's hand, myositis, rash (inconstant), and ILD (may be the first or unique presentation)
Anti-cN1A	Cytosolic 5'-nucleotidase 1A	-	Associated with IBM (52% of IBM cases) and poorly responsive to conventional immunotherapies
Anti-Sp4/ anti-CCAR1	Sp4/cell division cycle and apoptosis regulator protein 1 (CCAR1)	-	These antibodies have been reported to coexist with anti-TIF1-γ. Anti-Sp4 coexists in approximately 40% of patients with anti-TIF1-γ-positive DM. These antibodies reduce the risk of cancer in anti-TIF1-γ-positive patients to a level similar to that in the general population

Note: Data acquired from previous studies.[3,11,18-22]
Abbreviations: DM: Dermatomyositis; CADM: Clinically amyopathic dermatomyositis; IBM: Inclusion body myositis; ILD: Interstitial lung disease; RP-ILD: Rapidly progressive interstitial lung disease.

disease course, muscle atrophy, and cardiopulmonary involvement, independent of primary biliary cirrhosis.[3,15,17]

5. Etiopathogenesis of idiopathic inflammatory myopathy

The pathogenic mechanisms of IIMs are complex and not yet fully understood. However, as with many autoimmune diseases, it is thought that IIMs begin in genetically predisposed individuals after exposure to certain environmental triggers. Infectious agents, ultraviolet radiation, smoking, environmental pollutants, drugs, and chemicals are the main implicated risk factors.[10]

Infection risk factors have been suggested in the etiology of IIMs for several reasons. For example, seasonal variations have been observed in disease onset.[23] The anti-MDA-positive IIM subgroup is reported more frequently during winter months,[24] whereas anti-SRP-associated myositis is more common in autumn, and ASSs are more common in spring.[10] These seasonal patterns suggest that environmental factors, especially infections prevalent during specific times of the year, may trigger the onset of IIMs.

Viruses are the most commonly implicated infectious agents. Parvovirus B19, Coxsackie B virus, enteroviruses, human T-cell lymphotropic virus type 1 (HTLV-1), and HIV are the most commonly encountered viruses. Antibodies against Coxsackie B virus and HTLV-1 are more frequently detected in IIM patients than in healthy

individuals. In particular, Coxsackie B virus antibodies are more prevalent in juvenile IIMs, and this virus can induce IIMs experimentally, supporting its potential role in the pathogenesis of IIMs.[10]

Multiple mechanisms have been proposed for the pathogenesis of inflammatory myopathies triggered by infectious agents. Viruses can alter the structure or conformation of host proteins, breaking immune tolerance and rendering self-proteins immunogenic. For example, viruses use tRNA synthetase enzymes for replication; the presentation of these enzymes together with viral proteins may lead to immune recognition and generation of antisynthetase antibodies, leading to the development of ASS. Other proposed mechanisms include molecular mimicry and autoreactive B-cell activation.[10,25]

In addition to infections, many chemicals and drugs have been identified as risk factors for myositis. Notably, statins, ICIs, and corticosteroids can cause varying degrees of muscle damage. The most typical example is SRM. Statins inhibit HMGCR and are widely used to lower cholesterol levels. Due to their widespread use, side effects and negative effects on the muscles are common, although severe side effects remain rare.

6. Clinical subtypes of idiopathic inflammatory myopathy

While IIMs are a heterogeneous group of diseases, they share some common features, but clinical and prognostic features may vary depending on the presence of different autoantibodies.

A more homogeneous classification of IIMs can be achieved through the use of MSAs. While current evidence is insufficient to support a fully antibody-based classification, ongoing advances suggest its potential in the near future.[9,18-20]

In general, proximal muscles are affected in IIMs. Patients typically report difficulty climbing stairs and rising from a seated position. In addition, many of them are accompanied by characteristic cutaneous manifestations, including purplish redness on the eyelids, edema, erythematous rashes over the extensor surfaces of the joints (Gottron's papules), rashes over the shoulders and back of the neck (shawl sign), poikilodermatous rashes with hypo- and hyperpigmented lesions, wounds that cause a dirty appearance on the fingertips (mechanic's hand), Raynaud's phenomenon, and lung involvement (e.g., ILD). Lung involvement is common and carries significant prognostic implications, and often leads to dyspnea. Mechanic's hand, Raynaud's phenomenon, and lung involvement frequently coexisted with ASS. In addition, dysphagia may occur due to the involvement of the striated muscles of the proximal esophagus, and in some cases can be severe.[19,20]

6.1. DM

In the EuroMyositis registry, which consists of 3,067 cases from 11 countries, the most common type of IIM was DM (31%), followed by PM (27%), ASS (17%), and CTD-related myositis (12%). However, it is thought that a significant portion of PM cases are not pure PM but rather represent DM. Overall, 70% of patients are women, and disease onset most often occurs in the 40s and 50s.[26]

Patients with DM usually present with progressive proximal muscle weakness and characteristic skin manifestations developing over several weeks or months. They typically report difficulty climbing and descending stairs and standing from a seated position. On examination, muscle strength is decreased, and muscle enzyme levels are increased in more than 90% of cases, usually by 10–50-fold above normal; increases exceeding 100-fold are rare. In some cases, muscle creatine kinase (CK) levels remain normal or only slightly elevated for at least 6 months, a condition termed clinically amyopathic DM (CADM).[13] In addition, the presence of anti-MDA5 is closely related to CADM.[27]

Characteristic skin manifestations of DM include heliotrope rash, periorbital edema, facial erythema affecting nasolabial sulcus, Gottron's papules on the upper extremities, shawl sign, poikilodermatous rash, subcutaneous calcifications, arthritis, mechanic's hand, and Raynaud phenomenon. Dysphagia occurs in approximately 43% of DM cases, ILD in 21%, and cancer in up to 20%.[28] The risk of cancer is significantly increased in the presence of anti-TIF1-γ and anti-nuclear matrix protein 2 (anti-NXP2) antibodies. These patients require follow-up for malignancy, as anti-NXP2 positivity is also associated with calcinosis.[13,19,29-31]

MSAs are detected in up to 70% of DM cases, and different MSAs are associated with distinct clinical presentations. Anti-Mi2 is characteristic of classical DM, often indicating a favorable prognosis and good response to therapy. Anti-NXP2 is associated with cancer, distal and proximal muscle involvement, dysphagia, and calcinosis.[13,19] Anti-MDA5 positivity is linked to CADM, severe skin ulcerations, and RP-ILD.[19,32] Pharyngeal and laryngeal involvement is also common in patients positive for anti-MDA5 and anti-Ro52.[3] In patients positive for anti-small ubiquitin-like modifier activating enzyme (anti-SAE), muscle enzyme elevations may initially be delayed, leading to a CADM-like presentation; muscle weakness and enzyme elevation often develop months later. Dysphagia

may develop in up to 78% of such patients. Although ILD is uncommon in European series, it has been found more frequently in Japanese cohorts.[8,11,30,33-35]

6.2. PM

According to the EuroMyositis registry, PM cases constitute 27% of all IIM cases.[23,24] However, as explained earlier, this proportion is probably an overestimate. The age of onset and female-to-male ratio in PM are similar to those of DM. Clinically, PM patients also present with progressive proximal muscle weakness, and many features seen in DM can also be observed in PM cases, although to a lesser extent. In contrast, cutaneous manifestations, which are present in nearly 100% of DM cases, are almost 0% in PM cases. While muscle involvement is observed in 98% of cases, periungual erythema (6%), Raynaud phenomenon, mechanic's hand (8%), and subcutaneous calcification (1%) are uncommon. In addition, ILD is detected in 17% of cases, malignancy in 8%, and dysphagia in 35%. CK levels may increase to up to 50-fold above normal.[20,26,28]

6.3. ASS

Following the first reported antibody against histidyl tRNA synthetase (also known as anti-Jo-1), nine other anti-tRNA synthetase antibodies have been identified to date. These antibodies belong to the MSA class and are collectively associated with a characteristic clinical phenotype known as ASS. These antibodies include anti-Jo-1, anti-PL-7 (threonyl), anti-PL-12 (alanyl), anti-EJ (glycyl), anti-OJ (isoleucyl), anti-KS (asparaginyl), anti-Ha (tyrosyl), and anti-Zo (phenylalanyl) tRNA synthetase antibodies. Of these, anti-Jo-1 is the most common antibody, found in 15–25% of DM patients, whereas the others are usually found in 0–7% of cases.[3,8,13,21,25,30,34,36] The fact that only anti-Jo-1 was taken into account in the 2017 EULAR/ACR classification criteria is a shortcoming of these criteria.[4,37,38]

ASS is a serologic subtype of IIM characterized by the presence of antisynthetase antibodies and the development of DM or PM, symmetric non-erosive arthritis or arthralgia, ILD, mechanic's hand, fever, Raynaud phenomenon, and shawl or V signs. Less common features include photosensitive dermatitis, cutaneous vasculitis, calcinosis cutis, periungual telangiectasia, sclerodactyly, renal involvement, pulmonary hypertension, and cardiac involvement.

Although there are many common features typical of ASSs, some features may be more prominent in certain antibodies. For example, anti-Jo-1, anti-EJ, and anti-PL-7 are more closely associated with myositis, whereas anti-PL-7-positive DM patients tend to have milder myositis characterized by lower CK levels compared to anti-Jo-1-positive cases.[11,30,39,40] ILD may develop in up to two-thirds of patients with ASS and may occasionally develop without Raynaud phenomenon or myositis, both of which are otherwise typical features of the syndrome.[41,42] According to the EuroMyositis registry, 69% of ASS patients are women, and disease onset most often begins in the 40s and 50s, such as classical DM.[26] Table 2 summarizes ASS antibodies and their clinical presentations.

6.4. Immune-mediated necrotizing myopathy

Another major form of myotoxicity associated with statin therapy is IMNM, classified as SRM6, and should be considered a true autoimmune myopathy. This type of autoimmune myopathy is rare, occurring in 2–3/100,000 patients exposed to statins. It is typically characterized by the presence of anti-HMGCR, directed against the enzyme that catalyzes the rate-limiting step in cholesterol synthesis. Fewer cases of IMNM are characterized by anti-SRP; this group of patients is not related to statin exposure.[43-45] In the EuroMyositis registry, all cases of statin-associated IMNM (SRM6) or statin-related myopathy with anti-HMGCR were reclassified as IMNM, while SRM0–SRM5 cases were excluded from this classification. This reclassification is considered appropriate given the distinct histopathological and serological features of IMNM.[26]

Seronegative IMNM is still not fully understood today. However, available data suggest that seronegative IMNM carries a higher risk of cancer and a poorer prognosis than seropositive cases. For example, Allenbach *et al.*[45] found

Table 2. Antisynthetase antibodies and their clinical subtypes

Autoantigen	tRNA synthetase	Prevalence in adult IIM (%)	Discriminative features
Jo-1	Histidyl	25–30	ILD, arthritis, fever, mechanic's hands
PL-7	Threonyl	3–4	Severe ILD, myositis
PI-12	Alanyl	3–4	Severe ILD, less myositis, less skin rash
EJ	Glyceryl	<2	ILD, myositis
KS	Asparaginyl	<2	Amyopathic or mild myositis
OJ	Isoleucyl, lysyl	<2	ILD, malignancy
Zo	Phenylalanyl	<2	Less myositis
Ha	Tyrosyl	<2	Less myositis
Ly	Cysteinyl	<2	Recently detected autoantibodies
VRS	Valyl	<2	Recently detected autoantibodies

Note: Table modified from Wang and McHugh.[3]
Abbreviation: ILD: Interstitial lung disease.

that 15 of 115 IMNM cases were seronegative, with a cancer incidence of 28.6% in the seronegative group, compared to 17.3% in the anti-HMGCR-positive group and 8.1% in the anti-SRP-positive group.

Clinically, affected patients often present with progressive proximal muscle weakness involving the upper and lower limb girdles, serum CK levels rise to 10–100 times the upper limit of normal (ULN; 2,000–20,000 IU/L), and myopathic changes (detected through electromyography). Muscle biopsy, if performed, is usually characterized by necrotic and regenerating muscle fibers with sparse inflammation, mostly composed of macrophages.[26]

6.5. IBM

IBM is a sporadic muscle disease that usually affects people over 50 years of age and is unusual before the age of 40. The disease predominantly affects men. The prevalence of IBM in inflammatory myopathies is reported to be 8% according to the EuroMyositis registry.[24] Serum CK levels can be elevated up to 10 times the ULN. IBM is a type of IIM characterized by both clinical and pathological heterogeneity, a slowly progressive course, and frequent diagnostic delay due to overlap with other neuromuscular disorders common in elderly individuals.[46-48]

IBM is often confused with PM due to the absence of skin manifestations. The disease typically begins with distal muscle weakness, affecting wrist extension, forearm movement, and fine motor activity of the hands, together with quadriceps involvement. As a result, it can mimic compressive neuropathies of the wrist, elbow, or lumbar radiculopathy due to the involvement of finger flexors, knee extensors, and ankle dorsiflexors. Patients experience difficulty with wrist extension and fist formation. Unlike other IIM subtypes, IBM can also affect the facial and axial muscles, leading to head drop and *camptocormia*. Dysphagia is detected in more than half of patients. This condition is slowly progressive and does not respond to immunosuppressive therapy, leading to significant disability, especially from falls and grip weakness.[49,50] Because of its insidious course and absence of typical IIM features, IBM can be mistaken for hereditary myopathies or neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. IBM should also be considered in men over 50 years of age who present with slowly progressive weakness of the finger flexors and knee extensors with moderately elevated CK levels.

Apart from anti-cN1A, which can be present in up to 52% of IBM cases, the absence of other typical IIM-specific antibodies supports the diagnosis.[22,50,51] However, it should be noted that anti-cN1A may also occur in SjS and SLE without IBM.[15] Histopathologically, IBM muscle biopsies in early disease show a predominance of cluster of differentiation (CD)8^+ T-cells, similar to PM. Diagnostic differentiation relies on cytochrome oxidase, p62, and congophilic amyloid staining, as well as the presence of vacuoles, which are hallmarks distinguishing IBM from PM.[47,50,52]

6.6. Overlap myositis

Due to the increasing recognition of IIMs detected in the course of CTDs, overlap myositis is now an established concept. The CTDs most commonly associated with myositis include progressive systemic sclerosis, SLE, SjS, rheumatoid arthritis, and mixed CTD. The prevalence of overlap myositis in inflammatory myopathies is reported to be 12% according to the EuroMyositis registry.[26] Although SLE myositis is predominantly inflammatory, fibrosing myositis may entail a different presentation and outcome in progressive systemic sclerosis. On the other hand, progressive systemic sclerosis is the most common CTD associated with inflammatory myopathies, but there is still no consensus on whether this manifestation is a true overlap or rather a complication associated with systemic sclerosis.[3,15,53]

7. SRM

Statins, a class of drugs that inhibit the HMGCR enzyme, are widely used in the treatment of cardiovascular diseases. However, a well-known side effect of these drugs is myotoxicity. While most cases of SRM can be controlled without discontinuing statins, in rare instances, they can lead to necrotizing myopathy.[54-56]

The terminology used to describe SRM is not yet standardized. Terms such as myalgia, myopathy, and myositis are often used, but SRM can be broadly applied to encompass the spectrum of statin-induced muscle disorders.

Most SRM cases occur within the first 12 weeks of statin exposure, and many patients recover completely or nearly completely after discontinuation of the drug. However, some may recover incompletely or not at all (Table 3). It has been reported that statin-related PM developed after a median of 26 months in patients under stable statin monotherapy. However, it should be noted that SRM may occur at any time following an increase in statin dosage or the addition of another myotoxic drug, and that autoimmune myositis may develop even up to 3 years after exposure.[56]

Several risk factors have been suggested for the development of SRM. It is classically known that patients taking statins with fibrates, such as fenofibrate and

Table 3. General features of statin-related myotoxicity and suggestions

Class	Prevalence	Key distinguishing clinical/laboratory features	Suggestions
SRM0	15–26%	Asymptomatic, CK elevation (<4 times the ULN)	Statins are not usually discontinued
SRM1	0.3–33% (190/100,000 patients/year)	Tolerable myalgia, no CK elevation	If patients can tolerate mild muscle pain, statins are not usually discontinued
SRM2	0.2–2/1,000	Intolerable myalgia, CK elevation (1–3 times the ULN)	If the drug is stopped, full recovery occurs
SRM3	5/100,000 patients/year	Myopathy, muscle symptoms may or may not present, CK elevation (4–10 times the ULN)	If the drug is stopped, full recovery occurs
SRM4	0.11%	Severe myopathy, muscle symptoms, CK elevation (10–50 times the ULN)	Complete recovery after cessation of statin
SRM5	0.1–8.4/100,000 patients/year	Rhabdomyolysis, CK elevation (10 times the ULN) and renal findings (pigment nephropathy with brown urine due to myoglobinuria, and renal failure due to acute tubular necrosis), or CK elevation (50 times the ULN)	Statins must be discontinued and, in most cases, avoided in the future for safety reasons; muscle biopsy is not generally indicated; complete recovery after cessation of statins
SRM6	~2/1 million patients/year	Autoimmune-mediated necrotizing myositis, HMGCR antibodies, HMGCR expression in muscle biopsy	Discontinue statins, incomplete or no recovery after cessation of statins

Note: Adopted from Alfirevic A, *et al.*[57]
Abbreviations: CK: Creatine kinase; HMGCR: 3-Hydroxy-3-methylglutaryl-CoA reductase; SRM: Statin-related myotoxicity; ULN: Upper limit of normal.

gemfibrozil, are at increased risk of statin myopathy, especially rhabdomyolysis. Among fibrates, the risk of rhabdomyolysis was reported to be higher for gemfibrozil than for fenofibrate (8.7 and 4.5/million prescriptions, respectively).[56] Other recognized risk factors include a preceding history of increased CK levels, advanced age (>80 years), low creatinine clearance (<60%), high-dose statin therapy, and major surgery (the American Heart Association recommends temporary cessation of statins before major surgery).

Numerous drug interactions can further increase the risk of SRM. These include CYP3A4 inhibitors (e.g., diltiazem, verapamil, clarithromycin, telithromycin, erythromycin, itraconazole, cyclosporine, protease inhibitors [such as ritonavir, indinavir, and saquinavir], amiodarone, and fusidic acid), CYP2C9 inhibitors affecting fluvastatin metabolism (e.g., omeprazole and fluconazole), and OATP1B1 inhibitors affecting statin hepatic uptake (e.g., gemfibrozil). Consumption of grapefruit juice (>200 mL daily) can also increase serum levels of simvastatin, atorvastatin, and lovastatin. Additional factors such as infections, family history of myopathy, predominant neuromuscular disease, hypothyroidism, or strenuous exercise may increase the risk of SRM. Therefore, patients with these risk factors should be carefully evaluated before starting statin therapy. In addition, genetic factors may increase the risk of SRM for some, if not all, statins. A common single-nucleotide polymorphism in the *SLCO1B1* gene has been associated with a higher risk of SRM in patients treated with simvastatin, although it is unclear whether this increased risk also applies to other statins.[19,54,56]

Patients who develop SRM may present with a variety of symptoms, including fatigue, muscle pain, muscle weakness, muscle tenderness, and cramps. These symptoms tend to be predominant in the proximal muscles symmetrically but may also cause widespread muscle entrapment. They can worsen with vigorous exercise or following the introduction of another muscle-acting drug.[56]

On the other hand, SRM does not present in a homogeneous structure. It can range from mild CK elevation to severe rhabdomyolysis or IMNM. Alfirevic *et al.*[57] classified SRM into SRM0–SRM6 based on clinical and prognostic features. While SRM0 is characterized by mild CK elevation, IMNM occurs in SRM6. The frequency of SRM decreases from mild to severe, with SRM6 being the rarest form that leads to autoimmune necrotizing myopathy. The general features of these categories are summarized in Table 3.[56] Some authors have proposed a simplified classification: rhabdomyolysis, myalgia, mild hyperCKemia, self-limiting toxic statin myopathy, and the recently described IMNM.[19] It is also essential to exclude other potential causes of myopathy, such as hereditary disorders or hypothyroidism.

The most common form of SRM is statin-induced myalgia, in which CK elevation is generally below 5 times the ULN (<1000 IU/L), corresponding to SRM0 and SRM1. This condition causes only myalgia or mild hyperCKemia. In these cases, if there is no muscle weakness and the CK level is below 10 times the ULN, statin treatment can be continued under close monitoring. CK levels should be re-evaluated periodically, and if they remain stable or decline, treatment can be continued.

Especially in patients at high cardiovascular risk, such as those with severe atherosclerotic cardiovascular disease, it would be appropriate to continue treatment. If necessary, the statin dose can be reduced or switched to a different statin molecule. In refractory cases, a switch can be made with antihyperlipidemic drugs that act with different mechanisms. After statin discontinuation, patients should be monitored clinically with serial assessments of muscle strength and CK levels. Improvement in clinical findings and CK levels indicates recovery. However, if symptoms persist beyond 2 weeks after discontinuation, muscle biopsy and anti-HMGCR screening should be considered. If the patient is clinically stable, biopsy can be postponed, but testing for anti-HMGCR remains essential. Anti-HMGCR positivity supports a diagnosis of IMNM, warranting the consideration of immunosuppressive treatments.[54-56]

The decision to reintroduce statins in SRM3 patients is controversial. For those with high cardiovascular risk, clinicians may consider reinitiating therapy using a different statin, a lower dose, or an alternate-day schedule, accompanied by strict monitoring of clinical status and serum CK levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which act through different mechanisms, can also be considered, although clinical experience in these patients remains limited.[55]

When statin administration is associated with serious complications such as rhabdomyolysis (SRM5; CK > 50× ULN, myoglobinuria, and renal failure due to acute tubular necrosis), statins should be discontinued and permanently avoided. If such patients are at high cardiovascular risk, the use of other, recently approved, effective drugs, such as PCSK9 inhibitors, is recommended. Clinicians should also consider the possibility of non-pharmaceutical statin exposure, as certain foods naturally contain statin-like compounds.[56]

The diagnosis of SRM is based on a combination of drug history, clinical presentation, and laboratory tests, with muscle biopsy reserved for selected cases. Routine CK measurement is not recommended for all patients on statins for the diagnosis of SRM, but should be performed for symptomatic patients. The relationship between CK elevation and statin exposure can be established using patients' past electronic records.

A CK elevation more than 4 times the ULN warrants evaluation for potential SRM. If the patient's cardiovascular risk is taken into account and the clinical condition is stable, statin therapy can be continued without changing. When CK levels exceed 10 times the ULN, renal function and myoglobinuria should be evaluated; the presence of renal impairment is indicative of rhabdomyolysis. In addition to CK, measurement of alanine aminotransferase, lactate dehydrogenase, urine myoglobin levels (when clinically indicated), and renal function tests may be useful.[54-56]

In patients with suspected autoimmune myopathy, anti-HMGCR testing and muscle biopsy should be considered. In the meantime, other causes that may cause CK elevation should not be ignored.[56]

8. CAM

Adults with DM have a malignancy risk of up to 25%, especially within the first 3–5 years from the onset of the disease. CAM is a term used to describe patients who develop both cancer and inflammatory myopathy within 3 years. Although not common, a parallel clinical course is observed—myositis improves when the cancer is treated and reappears upon cancer recurrence. It has been suggested that CAM is a paraneoplastic syndrome in which shared tumor and regenerative muscle antigens trigger antitumor immunity.[57-60]

The most commonly associated malignancies are ovarian, breast, colorectal, and nasopharynx cancers (in Asians), melanoma, and non-Hodgkin lymphoma.[29,45] Although myositis may develop in the course of any cancer type, CAM is most frequently reported in ovarian cancer. Among the types of IIM, DM and seronegative IMNM are most frequently associated with cancer, while IBM and ASS are rarely cancer-associated. The malignancy risk is highest in patients positive for anti-TIF1-γ or anti-NXP2. In particular, the risk of cancer is increased 27-fold in anti-TIF1-γ-positive patients, and approximately 70% of DM patients with cancers are anti-TIF1-γ-positive.[55] Two other MSAs more recently reported are anti-CCAR1 and anti-Sp4. They appear to reduce cancer risk among patients with anti-TIF1-γ positivity.[3] Other antibody subgroups, such as anti-SAE1, anti-Mi2, anti-MDA5 (in DM), and anti-HMGCR (in IMNM), are associated with an intermediate increase in cancer risk.[2]

Patients with IIM generally require comprehensive annual cancer screening, especially during the first 3 years after disease onset. Routine cancer screening is not necessary in juvenile-onset IIM. Cancer risk should be considered in all adult patients with IIM, and screening should be considered especially in those with the following risk factors: Age >40 years at disease onset; male sex; dysphagia, cutaneous necrosis, resistance to immunosuppressive therapy, rapid disease onset, anti-TIF1-γ positivity; anti-NXP2 positivity, and absence of identifiable MSA.[2,61-63]

Management of CAM is similar to that of non-CAM. However, caution should be exercised regarding the interaction between chemotherapeutics and treatments

for myositis. ILD is rare in CAM cases and generally non-problematic; however, myositis can be resistant to treatment, although it can also improve with cancer treatment. Notably, recurrence of myositis may be a signal of cancer relapse.[57,59]

9. ICI-induced myositis

ICIs provide significant clinical benefits in the treatment of a wide range of tumors, including melanoma, non-small cell lung cancer, and renal cell carcinoma. ICI receptors, such as programmed cell death 1 (PD-1), PD ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), are highly expressed on cancer cells, allowing them to evade immune surveillance and continue proliferating. ICIs promote sustained, non-specific T-cell activation and increased antitumor response, enabling favorable outcomes in refractory or disseminated cancers.[62]

However, as the use of ICIs has expanded, it is not surprising that they are also associated with an increasing number of side effects. Monotherapy with anti-PD-1/PD-L1 antibodies or the anti-CTLA-4 antibody ipilimumab may cause significant side effects in more than 20% of cases, while this probability increases to more than 50% with the combination of these drugs.[64] Along with numerous autoimmune side effects, ICI-induced neuromuscular side effects have also become part of our daily practice. The main presentations are musculoskeletal pain, myositis, polymyalgia rheumatica-like syndromes, and ocular myositis. Although these neuromuscular side effects are less common than other autoimmune phenomena and most are mild, they warrant clinical attention. Arthralgia and myalgia are the most frequent rheumatic manifestations. Myalgia occurs in 4–5% of patients receiving anti-PD-1 monotherapy, whereas severe side effects are reported in <1%.[62]

A study by Liewluck *et al.*[65] examined 654 patients receiving PD-1 inhibitors (pembrolizumab, n = 389; nivolumab, n = 264; both drugs, n = 1) and identified 5 patients (0.7%; all receiving pembrolizumab) who developed ICI-associated myopathies—2 with necrotizing myopathies, 1 with early DM, and 2 with non-specific myopathies. Notably, lung and skin cancers, the diseases for which these drugs are most commonly used, are also the most common malignancies associated with ICI-related myositis.[66]

On the other hand, myositis can also occur as a reactivation of previous paraneoplastic PM or DM, or as CAM. These situations can cause difficulties in differential diagnosis. Key clinical clues that aid in differentiation are outlined below.

As with IIM patients, the first complaint of patients with ICI-related myositis is usually proximal upper and lower extremity weakness, often accompanied by myalgia and fatigue. However, oculomotor and bulbar symptoms, such as ophthalmoplegia, diplopia, ptosis, dysphagia, dysarthria, and dysphonia, can be seen in up to 25% of patients and are useful in differential diagnosis, as they are extremely rare in IIM cases. In addition to dysphagia, diaphragmatic involvement is rarely reported.[66] ICI-induced myositis typically presents within the first 2 months after initiation of ICI therapy, but can occasionally present as early as 5 days or as late as 19 weeks after therapy. The disease generally progresses rapidly over days to weeks.

Compared with IIMs, such as DM and PM, ICI-induced myositis has a more sudden onset of symptoms, and no fluctuation in symptoms or fatigue has been reported. It is necessary to note that ICI-induced myositis resembles myasthenia gravis in that the shoulder–limb–girdle distribution is prominent and the oculomotor symptoms are often present. While MAAs are present in up to 70% of classical IIM cases, they are positive in only 29% of ICI-related myositis cases.[64] Rarely, myositis may be associated with other autoimmune manifestations. It should be noted that ICI-associated myositis has a particularly high mortality rate when associated with myocarditis and myasthenia gravis. Mortality is also increased in cases triggered by combination ICI therapy, such as nivolumab plus ipilimumab therapy.[66]

In the presence of cardiovascular symptoms, including dyspnea, palpitations, chest pain, or syncope, clinicians should be alert to a potential concurrent myocarditis. The Common Terminology Criteria for Adverse Events, recommended by the National Institutes of Health and the National Cancer Institute, grades immune-related adverse events resulting from cancer treatment into five groups according to their severity: Grades 1 and 2 indicate mild or moderate weakness, Grade 3 indicates severe weakness, Grade 4 indicates life-threatening consequences, and Grade 5 indicates treatment-related death. Table 4 summarizes ICI-related adverse events and treatment approaches.[66-68]

Treatment of ICI-related myositis depends on clinical symptoms and presentation, and requires teamwork involving neurology, rheumatology, and oncology. The basis of treatment is based on short-term corticosteroid therapy, with the addition of immunosuppressive agents if necessary. Starting treatment early increases the chance of success.

The most important question here is whether ICI treatment should be stopped or continued. This decision should be based on the severity of rheumatic immunologically related adverse events, the extent of immunosuppressive regimen required, tumor response

Table 4. Immune checkpoint inhibitor-related adverse events and treatment approaches

Grade	Clinical features	Treatment
Grade 1	Mild pain	Start with prednisolone 0.5–1 mg/kg/d and monitor response. If there is a good response, reduce the dose and continue with the lowest dose.
Grade 2	Moderate pain associated with weakness, limiting age-appropriate activities of daily life	If there is an inadequate response, proceed as for Grades 3–4.
Grade 3	Pain associated with severe weakness, limiting age-appropriate activities of daily life	Start with intravenous methyl prednisolone 1 g for 5 d. Monitor the response. If there is a good response, reduce the dose to 1.5 mg/kg/d and continue with the lowest dose. If there no response to this treatment, treat as Grade 4.
Grade 4	Life-threatening implications	Sufficient response, plasmapheresis, intravenous immunoglobulin (0.4 g/kg/d for 5 d). In the presence of life-threatening consequences, immunotherapy must be discontinued.
Grade 5	Treatment-related death	-

Notes: Data from Sundarrajan *et al.*[66], National Cancer Institute[67], and Kostine *et al.*[68]

and duration, and future oncology treatment plan. Ideally, the decision should be made jointly by oncology and rheumatology teams, with input from other specialties as needed, and in consultation with the patient.

Myositis can be a serious condition. In such cases, discontinuation of immunotherapy should not be considered as the first option; rather, the decision should be guided by clinical severity. In the presence of life-threatening symptoms, including bulbar symptoms (e.g., dysphagia, dysarthria, and dysphonia), dyspnea, and myocarditis, immunotherapy must be discontinued, and high-dose glucocorticoids, intravenous immunoglobulin (IVIG), and/or plasma exchange should be considered.[66,68,69]

Pre-existing autoimmune rheumatic and/or systemic disease should not preclude the use of cancer immunotherapy. A detailed medical history and thorough clinical examination are required before initiating ICI therapy, though prior screening for autoantibodies associated with inflammatory rheumatic diseases is not mandatory.[68]

10. Diagnosis of idiopathic inflammatory myopathy

10.1. Clinical features

The diagnosis of IIMs is based on the characteristic clinical features, increased muscle enzymes, autoantibody positivity, and the presence of diagnostic features on muscle imaging and biopsy. In patients with progressively increasing proximal muscle weakness and consequent difficulty in climbing hills/stairs or standing from a seated position, we should consider investigating muscle diseases. On physical examination, findings such as erythema affecting the nasolabial sulci (which are spared in lupus), periorbital edema with heliotrope rash, and Gottron's papules represent hallmark dermatologic signs and are often the first diagnostic clues.[1,18,19,47,70]

While proceeding through the diagnostic process, medications that may cause weakness, increased muscle enzymes, systemic diseases that may affect the heart and lungs, CTDs, sarcoidosis, hypothyroidism, and infections such as Lyme disease and HIV infection should be excluded. A drug history of statins or ICIs and the presence of underlying CTDs are important features for diagnosis and differential diagnosis. For SRM, it should also be considered that statin exposure may occur through certain foods containing statin-like compounds.[56] In addition, Raynaud phenomenon, mechanic's hand, and ILD associated with progressive dyspnea are also important clues in the diagnosis of IIMs. It should not be forgotten that muscle weakness may not be prominent in some patients, and skin manifestations may not always be present in diseases such as PM and IBM. Furthermore, MSAs and MAAs should be evaluated to identify potential overlap syndromes with CTDs.

In addition to detailed medical history and physical examination, laboratory tests are essential for diagnosis and differential diagnosis. General blood tests, acute-phase reactants, muscle enzymes (e.g., CK, transaminases, lactate dehydrogenase, and aldolase), chest X-ray, and tests for other potential diseases, including metabolic and infectious diseases that may cause muscle weakness, are needed. Multidisciplinary collaboration involving rheumatology, neurology, cardiology, and pulmonology is strongly recommended. MAAs and MSAs are studied as a wide panel. A detailed history of the patient is taken in terms of potential malignancy, and additional examinations, such as upper and lower endoscopic gastrointestinal examinations, gynecological examination, mammography, and prostate examination, are performed according to the patient's age and sex.[1,18,19,47,70]

The risk of ILD increases in some special cases. Zhang *et al.*[16] proposed a risk prediction model based on the evaluation of seven factors for ILD, including age, respiratory symptoms, ASS, anti-MDA5, anti-TIF1-γ, serum KL-6, and B-line number on lung ultrasound. While anti-TIF1-γ positivity acts as a protective factor, the others stand out as factors that increase the risk of

ILD. These individuals require closer follow-up for ILD. In addition, the presence of pleural effusion, observed in 17.7% of cases, is also a factor that increases the risk of RP-ILD and mortality rate.[71] If there are antibodies, such as anti-TIF1-γ, anti-NXP2, and other factors that increase the risk of malignancy, more stringent malignancy screening is required, including positron emission tomography and endoscopic gastrointestinal screening every 6 months, especially during the first 2 years after diagnosis.[61,72]

10.2. Laboratory

The other step in the diagnostic process is the evaluation of laboratory findings. Non-specific elevation of acute-phase reactants and anemia of chronic disease may be detected. Serum CK levels are usually elevated 5–50 times the ULN in individuals with PM. This elevation parallels the number and extent of necrotic muscle fibers. In contrast, CK levels may remain within the normal range in many genetic and metabolic myopathies without necrosis. Marked elevations exceeding 100 times the ULN are rare.

Serum CK levels can be used in conjunction with a careful physical examination to monitor myositis activity. Under effective treatment, serum CK levels usually return to normal within 6–10 weeks. However, in cases of chronic or late-stage PM, serum CK levels may be within normal limits despite ongoing disease activity. On the other hand, CK levels are usually minimally elevated or normal in patients with IBM, and within reference ranges in patients with corticosteroid-induced myopathy.[54,73] Serum aldolase levels generally increase in parallel with CK activity, although isolated aldolase elevation may be detected in very early stages or in special cases.[74] Anti-nuclear antibody positivity may also be observed. Nevertheless, a broad-spectrum MSA panel study remains the most important laboratory investigation. Detailed information for MSAs is summarized in Table 1.

10.3. EULAR/ACR 2017 classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups

Following the Bohan and Peter criteria, various diagnostic and classification criteria have been published. Most recently, the EULAR/ACR joint classification criteria were introduced. Although these criteria can be used to obtain a standard patient profile in scientific studies and provide an idea in daily practice, they are not suitable for making a patient diagnosis. In addition, they have several disadvantages, such as insufficient emphasis on autoantibodies (e.g., MSAs) and inadequate recognition of certain IIM subgroups. Therefore, new classification and diagnostic criteria that incorporate autoantibody profiles more comprehensively are needed.

The EULAR/ACR classification criteria were derived based on data from 976 IIM patients (74% adults, 26% children) and 624 non-IIM patients with disorders mimicking IIMs (82% adults, 18% children). These criteria classify patients as having definite, probable, or non-IIM, based on weighted scores and calculated probability using the following variables:

- Age of onset: 18–39 years or ≥40 years for adults
- Muscle weakness: Upper proximal, lower proximal, neck flexors, and lower proximal are weaker than the distal muscles
- Skin manifestations: Heliotrope rash; Gottron's papule; Gottron sign
- Other clinical manifestations: Dysphagia or esophageal dysmotility
- Laboratory measurements
- Muscle biopsy: Patients with pathognomonic dermatomyositis rashes (heliotrope rash, Gottron's papules, or Gottron sign) are correctly classified according to EULAR/ACR classification criteria without the need for muscle biopsy. A muscle biopsy is recommended for patients without these skin manifestations. Skin biopsy is recommended for DM patients without muscle involvement. The biopsy must be evaluated by an experienced pathologist.

Each item is assigned a weighted score (0–20.8), corresponding to a calculated probability of having IIM (0–100%). A probability ≥55% corresponds to a score of ≥5.5 (≥6.7 with muscle biopsy) and defines "probable IIM," offering optimal sensitivity/specificity of 87%/82% (without biopsies) and 93%/88% (with biopsies). A probability ≥90% corresponds to a score of ≥7.5 (≥8.7 with muscle biopsy) and defines "definite IIM." A probability between 50% and 55% indicates "possible IIM." A probability <50% corresponds to a score of <5.3 (<6.5 with muscle biopsy) and excludes IIM.[4] These calculations are available online (https://www.imm.ki.se/biostatistics/calculators/iim).

10.4. Imaging in idiopathic inflammatory myopathy diagnosis

Although imaging methods in IIM diagnosis are not represented in diagnostic and classification criteria, they can provide useful information in clinical practice. It is possible to document muscle inflammation and destruction that develop during the course of IIMs using various imaging methods.

Direct X-ray does not provide sufficient information for IIMs, but it can be helpful if there is subcutaneous calcification. Ultrasonography is an imaging method that has become increasingly popular in recent years. However, more evidence is needed.[75,76] Muscle magnetic resonance

imaging (MRI) has been used for many years, but is not included in the EULAR/ACR criteria. It can provide several clinically relevant benefits, such as diagnosis and exclusion. Absence of increased T2 signal activity can help rule out active myositis. It can also be used to determine the biopsy area to identify the activity of inflammation in the muscle. In addition, signal hyperintensity on T2-weighted or short tau inversion recovery (STIR) sequences correlates with clinical and laboratory indicators of disease activity. Moreover, MRI enables the examination of muscles, fascia, and skin.

A 1.5-Tesla MRI is generally sufficient for detecting muscle inflammation; 3-Tesla MRI has not shown superior diagnostic accuracy and may even increase artifact formation. T1- and T2-STIR for routine pelvic and thigh muscle analyses are sufficient. Whole-body MRI is not required in most cases, though it may be useful in some cases:

- IBM: to evaluate anterior and distal muscle involvement of the thigh and forearm.
- CADM: to identify subclinical muscle inflammation.
- Concurrent malignancy assessment: as a supplementary tool for cancer screening.

Contrast administration is not required for routine muscle MRI. Patients should avoid intense exercise before the MRI examination, as it may lead to false positives. Following effective therapy, MRI abnormalities are expected to improve within 1–2 months and resolve by the 3rd month after therapy.[76,77]

11. Idiopathic inflammatory myopathy therapy

Immunosuppressives are used in the treatment of IIMs. However, there is no universal standard treatment that is effective for all subtypes. In general, Sun protection, local corticosteroids, hydroxychloroquine, and calcineurin inhibitors (CNIs) are effective in the treatment of skin manifestations. Importantly, the response of skin lesions may not be parallel to myositis treatment. In some patients, skin manifestations may recur despite successful control of myositis. In such cases, more intensive immunosuppressives may be required.[78,79]

Systemic corticosteroids are effective in improving both skin and muscle symptoms, but corticosteroid-sparing drugs are needed due to side effects that may occur with long-term use. There are various options among these drugs, such as azathioprine (AZA), methotrexate (MTX), mycophenolate, CNIs, IVIG, rituximab (RTX), and, more recently, Janus kinase inhibitors (JAKI), which are classified as targeted synthetic disease-modifying antirheumatic drugs.

Among these, AZA and MTX are often the first options. AZA, MTX, mycophenolate, and CNIs are often used in similar indications, namely skin, lung, and muscle involvement. Cyclosporine has been studied more extensively in myositis, whereas tacrolimus is promising for ILD management. Leflunomide is also effective in muscle and skin involvement. On the other hand, IVIG, RTX, and JAKI can be used in cases resistant to these treatments.[69,78-92] IVIG has been used for many years in the treatment of IIM. It can be used in combination with conventional agents for resistant myositis. Its therapeutic effect typically begins after 1–3 months. IVIG treatment is particularly effective in myositis-associated dysphagia. It can be used as the first-line treatment in severe myositis or dysphagia. However, because patients with IIMs already have an increased baseline risk of thromboembolism, precautions must be taken during IVIG therapy.[68,88]

Meanwhile, RTX therapy is a favorable treatment modality, especially for ILD. It generally has fewer side effects than those used in other diseases, such as rheumatoid arthritis and lupus, and may even respond to treatment at lower doses than the standard regimen (500 mg + 500 mg RTX regimen; 2 weeks apart) in IIM patients. It can be given in combination with drugs such as MTX.[79,80] JAKIs may be useful in the treatment of muscle, skin, and joint symptoms. Caution should be exercised in terms of infection and thrombotic events, especially in elderly patients.[80]

Interleukin-6 receptor blockers, tocilizumab and abatacept, have been investigated for DM. Anti-HMGC-positive and anti-SRP-positive IMNM refractory to standard treatment achieved clinically significant responses in 63% of cases. Patients with high basal serum IL-6, muscle *IL6* mRNA, or $CD56^+$ muscle fiber percentage are more likely to respond.[93] In the presence of ILD, tofacitinib, tacrolimus, and RTX have shown positive results. Meanwhile, in the presence of progressive fibrosis, antifibrotic agents may be useful.[80,86]

Combination therapy involving IVIG, RTX, MTX, or AZA is commonly used in resistant cases. Before starting immunosuppressive treatment, screening for infections such as hepatitis and HIV, and obtaining a baseline chest X-ray are recommended. In addition, attention should be paid to whether the patient has been vaccinated against pneumococcus.[68,88]

12. Prognosis

The prognosis of IIMs is closely related to multiple factors, including patient age, disease severity, extent of organ involvement (such as the heart or lungs), presence of concomitant diseases (such as cancer), autoantibody

profile, and the IIM type. Early diagnosis and treatment are also a factor that positively affects prognosis. Overall, the 10-year survival rate for IIMs has been reported as 67%. Cancer, lung and heart complications, and infections are the main causes of mortality.[92] Anti-Mi-2 positivity, a marker for classic DM, is associated with favorable treatment response and better prognosis, whereas anti-SRP positivity, a sign of IMNM, is linked to treatment resistance and poorer prognosis. Similarly, anti-MDA5 positivity is also a risk factor for the development of RP-ILD, significantly affecting prognosis. Interestingly, the presence of ASS in anti-MDA5-positive patients seems to have a positive effect on prognosis.[12,94-96] In contrast, anti-Ro52 positivity in the absence of anti-Ro60 in ASS cases has been reported as a poor prognostic sign for the development of ILD.[15]

13. Conclusion

In conclusion, IIMs are a heterogeneous group of diseases that share many common clinicopathological features, with DM being the most frequently detected form. The classification of IIMs is currently based on clinical presentation, pathological findings, and serological profiles. The discovery of new antibodies continues to refine our understanding of disease pathogenesis and is expected to reshape classification criteria in the future. Treatment decisions are determined according to patient age, comorbidities, organ involvement, and the specific antibody profile detected. Notably, anti-TIF1-γ and anti-NXP2 are recognized as significant risk factors for malignancy. Early diagnosis and treatment of patients remain crucial determinants of prognosis in patients with IIM.

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