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INTEGRATED STUDY MASTER'S FINAL THESIS

The Importance of Myositis-Specific Autoantibodies (MSA) in Diagnosing Inflammatory Myopathies and Identifying Disease Subtypes. Literature Review

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ABBREVIATIONS

IIM · idiopathic inflammatory myopathies

MSA/MSAs · myositis-specific autoantibody/autoantibodies

MAA/MAAs · myositis-associated autoantibody/autoantibodies

DM · dermatomyositis

PM · polymyositis

IMNM · immune-mediated necrotizing myopathy

ASS · antisynthetase syndrome

IBM · inclusion body myositis

OM · overlap myositis

CADM · clinically amyopathic dermatomyositis

JDM · juvenile dermatomyositis

ILD · interstitial lung disease

RP-ILD · rapidly progressive interstitial lung disease

EMG · electromyography

MRI · magnetic resonance imaging

EULAR· European Alliance of Associations for Rheumatology

ACR · American College of Rheumatology

tRNA · transfer RNA

cN1A · cytoplasmic 5′-nucleotidase 1A

CCAR1 · cell cycle and apoptosis regulator protein 1

EJ · glycyl-transfer ribonucleic acid synthetase

FHL1 · four-and-a-half LIM domain protein 1

Ha/YRS · tyrosyl-transfer ribonucleic acid synthetase

HMGCR · 3-hydroxy-3-methylglutaryl-coenzyme A reductase

Jo-1 · histidyl-transfer ribonucleic acid synthetase

KS · asparaginyl-transfer ribonucleic acid synthetase

Ly · lysyl-transfer ribonucleic acid synthetase

MDA5 · melanoma differentiation-associated protein 5

Mi-2 · nucleosome remodelling deacetylase complex

NXP2 · nuclear matrix protein 2

OJ · isoleucyl-transfer ribonucleic acid synthetase

PL-7 · threonyl-transfer ribonucleic acid synthetase

PL-12 · alanyl-transfer ribonucleic acid synthetase

SAE · small ubiquitin-like modifier activating enzyme
Sp4 · specificity protein 4
SRP · signal recognition particle
TIF1-γ · transcription intermediary factor 1 gamma
TIF2 · transcription intermediary factor 2
VRS · valyl-transfer ribonucleic acid synthetase
Zo · phenylalanyl-transfer ribonucleic acid synthetase.

SUMMARY

ENGLISH SUMMARY

Idiopathic inflammatory myopathies are rare and heterogeneous autoimmune diseases characterized by chronic inflammation and progressive muscle weakness. In addition to muscular involvement, these diseases frequently affect other organ systems, including the skin, lungs, and joints. This heterogeneity contributes to the significant clinical complexity of the disease. Idiopathic inflammatory myopathies present challenges in diagnosis, classification, and management, and there is a need for improved understanding of the disease subtypes.

This thesis aimed to evaluate the role of myositis-specific autoantibodies in the diagnosis of idiopathic inflammatory myopathies and to determine their value in identifying distinct disease subtypes. To achieve this, the history and classification of idiopathic inflammatory myopathies were examined. The role of myositis-specific autoantibodies in current diagnostic approaches and their association with distinct clinical phenotypes were reviewed.

A literature-based approach was used to analyse current studies on established myositis-specific autoantibodies and their clinical associations. Relevant literature was identified through database searches and critical evaluations of the research findings.

The results demonstrate that individual myositis-specific autoantibodies are strongly associated with specific clinical features and disease outcomes. Anti-MDA5 is associated with clinically amyopathic dermatomyositis and rapidly progressive interstitial lung disease, representing a severe disease phenotype. Anti-NXP2 antibodies are associated with calcinosis in juvenile patients and malignancy in adult patients. In contrast, anti-Mi2 is highly specific to dermatomyositis and is associated with a favourable prognosis and good response to treatment. Anti-TIF1-γ is associated

with malignancy in adult patients, while presenting different clinical features in juvenile patients. Anti-Jo-1 is the most common myositis-specific autoantibody present in antisynthetase syndrome. Next to anti-Jo-1 many other myositis-specific autoantibodies exist for antisynthetase syndrome, which associate with interstitial lung disease, but are a lot less common. Immune-mediated necrotizing myopathy is another subtype of idiopathic inflammatory myopathies that presents with two antibodies: anti-SRP and anti-HMGCR.

Despite these diagnostic advances, some limitations remain. Myositis-specific autoantibodies are not entirely disease-specific. Variability in the laboratory testing methods can affect accuracy. A significant proportion of patients remain seronegative, suggesting that additional autoantibodies must be identified. Clinical presentation can vary within subgroups, and findings across studies are not always consistent.

In conclusion, myositis-specific autoantibodies play a central role in improving the understanding, diagnosis, classification, and management of idiopathic inflammatory myopathies. However, their interpretation requires integration with clinical findings, and further research is needed to refine the classification systems and improve patient management.

LITHUANIAN SUMMARY

Idiopatinės uždegiminės miopatijos - tai retos ir heterogeniškos autoimuninės ligos, kurioms yra būdingas lėtinis raumenų uždegimas bei progresuojantis silpnumas. Be raumeninio audinio, šios ligos dažnai pažeidžia ir kitus organus ar audinius, įskaitant odą, plaučius ir sąnarius. Šis heterogeniškumas lemia šių ligų klinikinį kompleksiškumą. Dėl šios priežasties idiopatinės uždegiminės miopatijos kelia daug iššūkių jas diagnozuojant, klasifikuojant bei gydant, todėl yra būtinas geresnis šios ligų grupės ir jos potipių supratimas.

Šio darbo tikslas buvo įvertinti miozitui specifinių autoantikūnų reikšmę diagnozuojant idiopatines uždegimines miopatijas ir nustatyti jų vertę identifikuojant skirtingus ligos potipius. Siekiant šio tikslo, buvo nagrinėjama idiopatinių uždegiminių miopatijų istorija ir klasifikacija. Taip pat buvo apžvelgta miozitui specifinių autoantikūnų vaidmuo šiuolaikiniuose diagnostikos metoduose ir jų sąsaja su skirtingais ligos klinikiniais fenotipais.

Buvo taikytas literatūros analizės metodas, nagrinėjant šiuolaikinius tyrimus apie žinomus miozitui specifinius autoantikūnus ir jų klinikines sąsajas. Tinkama literatūra buvo atrinkta atliekant paiešką duomenų bazėse ir kritiškai vertinant mokslinių tyrimų rezultatus.

Rezultatai parodė, kad atskiri miozitui specifiniai autoantikūnai yra glaudžiai susiję su tam tikrais ligos klinikiniais požymiais ir jos eiga. Anti-MDA5 yra siejamas su amiopatiniu dermatomiozitu, greitai progresuojančia intersticine plaučių liga ir sunkia ligos formą. Nustatytas ryšys tarp anti-NXP2 antikūnų ir kalcinozės vaikų populiacijoje bei piktybinių navikų suaugusiųjų populiacijoje. Tuo tarpu anti-Mi-2 yra labai specifinis dermatomiozitui ir siejamas su palankia prognoze bei geru atsaku į gydymą. Anti-TIF1-γ siejamas su piktybiniais navikais suaugusiems pacientams, tačiau vaikų populiacijoje pasireiškia kitokiais klinikiniais požymiais. Anti-Jo-1 yra dažniausias miozitui specifinis autoantikūnas, nustatomas antisintetazės sindromo atveju. Be anti-Jo-1, šiam sindromui būdingi ir kiti autoantikūnai, kurie siejami su intersticine plaučių liga, tačiau jie pasitaiko daug rečiau. Imuninės kilmės nekrotizuojanti miopatija yra dar vienas idiopatinių uždegiminių miopatijų potipis, kuriam būdingi du pagrindiniai autoantikūnai: anti-SRP ir anti-HMGCR.

Nepaisant pažangos ieškanti naujų diagnostikos metodų, yra ir tam tikrų trūkumų. Miozitui specifiniai autoantikūnai nėra visiškai specifiški ligai. Laboratorinių tyrimų atlikimo metodikų skirtumai gali turėti įtakos diagnostiniam tikslumui. Reikšminga dalis pacientų išlieka seronegatyvūs, o tai rodo, kad dar yra neidentifikuotų autoantikūnų. Klinikinė ligos išraiška gali skirtis net ir tose pačiose pogrupiuose, o skirtingų mokslinių tyrimų rezultatai ne visada sutampa.

Apibendrinant galima teigti, kad miozitui specifiniai autoantikūnai atlieka svarbų vaidmenį gerinant supratimą apie idiopatines uždegimines miopatijas, jų diagnostiką, klasifikaciją ir gydymą. Tačiau jų interpretacija turi būti derinama su klinikiniais duomenimis, o tolesni tyrimai yra būtini siekiant tobulinti klasifikavimo sistemas ir gerinti pacientų priežiūrą.

KEYWORDS

Myositis ·Idiopathic inflammatory myopathies · Myositis-specific autoantibodies · Diagnosis · Clinical phenotype · Disease subtype

1. INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are rare and heterogeneous systemic autoimmune diseases (1,2). The key clinical features of IIM are chronic muscle inflammation and progressive muscle weakness (2,3). In addition to skeletal muscle involvement, these conditions frequently affect other organ systems, including the skin, lungs, and joints (1). This heterogeneity contributes to the clinical complexity and overall disease burden of IIM (1,2). Clinicians face significant challenges in accurately diagnosing IIM and its subtypes, which is essential for appropriate patient management (1,2). Although rare, IIM is associated with considerable morbidity and mortality (4,5).

Historically, classification has been based on clinical and histopathological features (6). Early classification systems primarily distinguished between dermatomyositis (DM) and polymyositis (PM), and later also inclusion body myositis (IBM) (6–10). With advances in research, new subtypes have emerged, first according to clinical features and histopathological changes, and later with autoimmunological research, highlighting the limitations of traditional classification approaches (6). This broader spectrum entails distinct disease entities, including immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome (ASS), and overlap myositis (OM) (2). These subgroups differ in clinical features, level of presentation, organ involvement, prognosis, and treatment response (2,6).

The identification of myositis-specific autoantibodies (MSAs) has significantly advanced the understanding of IIM and is key to modern IIM disease classification (2). Autoantibodies are detected in up to 60-80% of patients, and MSAs are largely mutually exclusive and strongly associated with specific clinical phenotypes (2,11,12). These associations make MSAs powerful tools for supporting diagnosis, refining classification, anticipating complications such as interstitial lung disease (ILD) or cancer, and guiding monitoring and management strategies (11,13,14). Their discovery led to a shift from clinical and histopathological classification systems to integrated approaches that combine clinical, serological, and pathological features (6,15). This has improved the recognition of distinct disease subsets and supported more individualized patient assessments (2,6).

Despite these developments, several limitations remain. The interpretation of autoantibody testing is complicated because assay technologies differ in sensitivity, specificity, and standardization; however, they are routinely used in practice (11). Current classification systems incorporate only a

limited number of MSAs and do not reflect the widespread subtypes of IIM (6,7). Despite their clinical value, approximately one-third of patients with IIM remain seronegative for known MSAs (16). This suggests that additional autoantibodies remain to be identified and that current classification systems need to evolve further (2,13).

These considerations demonstrate the need for a better understanding of the role of MSAs in IIM. In this context, the aim of this study was to evaluate the role of MSAs in the diagnosis of IIM and to determine their value in identifying distinct disease subtypes. To achieve this aim, the thesis first provides an overview of IIM subtypes and MSAs, as well as myositis-associated autoantibodies (MAAs). This is followed by an overview of the historical development of IIM classification and the discovery of MSAs. The associations between individual autoantibodies and specific clinical phenotypes were then explored. The diagnostic and prognostic value of these autoantibodies across different disease subgroups was then assessed. This thesis discusses the limitations of current autoantibody testing and its implications for disease classification and clinical interpretation.

2. METHODOLOGY

This thesis was conducted as an extended (narrative) literature review to evaluate the role of MSAs in the diagnosis of IIM and to identify distinct clinical disease subtypes. A narrative method was chosen to allow a comprehensive synthesis of diverse clinical, serological, and phenotypic data reported in different study designs.

A systematic search was conducted in the biomedical database PubMed to identify relevant literature published between January 2020 and 2025. The search strategy combined the following keywords: (“myositis-specific autoantibodies” OR “MSA”) AND (“inflammatory myopathies” OR “idiopathic inflammatory myopathies” OR “dermatomyositis” OR “polymyositis” OR “antisynthetase syndrome”) AND (“diagnosis” OR “classification” OR “subtype” OR “prognosis”). Filters were applied to limit articles published in English and to specific study types, including systematic reviews, clinical trials, cohort studies, and clinical guidelines. This search strategy yielded 75 records.

The titles and abstracts of all identified studies were screened for their relevance. This was followed by a full-text evaluation of the suitable articles. Studies were included if they focused on MSAs in the context of IIM and provided clinically relevant information regarding diagnosis, classification, or disease phenotypes. Studies showing clear associations between specific MSA and disease subtypes or distinct clinical manifestations were preferred. Articles that did not directly address

MSAs or lacked clinical relevance were excluded unless they were required to support essential background knowledge. From the identified studies, 32 were included in the final analysis following screening and application of the inclusion criteria. Some papers published prior to 2020 were included if they contained background information or were original studies published on the historical context. Examples include the development of classification systems, such as the EULAR/ACR classification criteria published in 2017 by Lundberg et al (7). In addition to systematic database searches, artificial intelligence tools (ChatGPT, OpenAI, ConsensusAI) were used to support the identification of relevant literature on specific topics. All sources identified in this manner were critically evaluated and included only if they met the predefined criteria for relevance and scientific quality.

The extracted data were organized into a literature matrix using Microsoft Excel software. This allowed for a structured comparison of the study's characteristics. This included the study type, investigated IIM subtype, associated autoantibodies, main findings, and reported implications for diagnosis, prognosis, and treatment of IIM. The literature matrix additionally includes relevance scores and identified limitations. Some selected excluded literature was also documented in the literature matrix, particularly where the relevance score was borderline for inclusion.

Data from the selected studies were qualitatively synthesized, with particular emphasis on the relationship between MSAs and subtypes, including DM, IMNM, and ASS. The findings were organized by disease subgroups and stratified according to the MSAs. To address the relevance of identifying and diagnosing IIM, this thesis includes a section on the history of classification criteria.

No formal quantitative or meta-analyses were performed because of the heterogeneity of the included studies. Consequently, this work represents a narrative review rather than a systematic review. The limitations of this approach include potential selection bias related to narrative reviews and the absence of a formal quality assessment of the included studies. Nevertheless, the methodology used in this thesis allows for a clinically meaningful integration of current evidence and supports the aim of showing the important role of MSAs in diagnosing IIM and identifying its disease subtype.

Artificial intelligence tools (ChatGPT and Paperpal) were used to support grammar and language editing throughout the thesis, as well as to translate the summary into Lithuanian. All the content was reviewed and approved by the author.

3. RESULTS

3.1. OVERVIEW OF IDIOPATHIC INFLAMMATORY MYOPATHIES AND THEIR SUBTYPES

IIM represents a heterogeneous group of autoimmune diseases primarily characterized by chronic inflammation of the skeletal muscle, leading to progressive muscle weakness and varying degrees of extramuscular involvement (1,5). In addition to muscular symptoms, IIM frequently involves other organ systems, including the skin, lungs, and joints, reflecting its systemic nature (1). Patients typically present with symmetrical proximal muscle weakness, resulting in difficulties with activities such as climbing stairs, rising from a seated position, or lifting objects, and may also experience myalgia, fatigue, and other constitutional symptoms (1,5). The range of symptoms and extra-muscular manifestations pose challenges in diagnosis (5). IIM is a rare disease with an incidence rate of 0.2-2 cases per 100.000 person (4,5). Although IIM is uncommon, it significantly affects patient mortality and morbidity (4,5). Consequently, there is an urgent need for new strategies and interventions to improve clinical outcomes in these patients (5). The classification of IIM varies across studies, reflecting the differences between traditional clinical classifications and more recent serological approaches (6). Historically, IIM has been classified into PM and DM based on clinical presentations and histopathological findings (6). Contemporary classification systems increasingly incorporate MSAs and distinct clinical phenotypes (2,6). Consequently, certain subtypes, such as overlap myositis, are inconsistently defined or incorporated into broader categories, including antisynthetase syndrome (11). This variability highlights the evolving nature of IIM classification and the need for integrated approaches that combine clinical, serological, and pathological features (2,3).

Based on the current clinical and serological understanding, the major IIM subtypes can be categorized as follows: **Dermatomyositis** (DM) is an autoimmune myopathy characterized by proximal muscle weakness and distinctive cutaneous manifestations, such as heliotrope rash, Gottron´s papules, shawl sign and V sign (1,13,17). Usually, myopathy develops within 6 months of skin changes (1). Patients exhibit dominant systemic complications, including ILD and an increased risk of malignancy (1,2). Numerous MSAs have been identified in DM, and each MSA exhibits distinct characteristics, such as anti-TIF1-γ and its correlation with malignancy. Less than 20% of patients present with clinically amyopathic DM (CADM), a subtype of DM (1). CADM presents with characteristic skin findings but minimal or no clinically apparent muscle involvement, frequently associated with anti-MDA5 (1,2).

Juvenile dermatomyositis (JDM) is the most common inflammatory myopathy in children and presents with proximal muscle weakness and characteristic cutaneous manifestations similar to those of adult DM (2,18). In contrast to adult DM, JDM is less frequently associated with malignancy but is more commonly complicated by calcinosis (2,18). Distinct MSA profiles have been observed, with anti-TIF1-γ and anti-NXP2 being the most prevalent, each associated with specific clinical phenotypes (2,13).

Polymyositis (PM), historically defined as an inflammatory myopathy affecting skeletal muscle without skin involvement, now considered a diagnosis of exclusion (2,17,18). Advances in serological and histopathological classification have shown that many cases previously diagnosed as PM can be reassigned to more specific subtypes, such as DM, ASS, or IMNM (17,18). In a cohort study by Sun et al., 129 patients were initially classified as having PM according to the 2017 EULAR/ACR criteria; however, after re-evaluation, only six patients (1.1% of the total cohort) fulfilled the strict criteria for PM, with the majority being reclassified into other IIM subtypes based on autoantibody profiles and pathological findings (19).

Immune-Mediated Necrotizing Myopathy (IMNM) is a distinctive subtype characterized by severe proximal muscle weakness/atrophy, increased muscle enzyme levels, and prominent muscle fiber necrosis with minimal inflammatory infiltrates on biopsy (1,5). It is commonly associated with anti-SRP or anti-HMGCR antibodies and may be linked to statin exposure or autoimmune mechanisms (5,17). Cases of IMNM have been documented in association with connective tissue disease, malignancy, and viral infections, including hepatitis C and human immunodeficiency virus (1). Cardiorespiratory complications have been found in all subtypes of IMNM, with abnormalities such as diastolic dysfunction on echocardiography, changes on electrocardiography, and respiratory muscle weakness evident in lung function tests (1). It is also known as necrotizing autoimmune myopathy (1).

Inclusion Body Myositis (IBM) is a myopathy with both inflammatory and degenerative features, typically affecting older individuals, with a male predominance, and showing limited response to immunosuppressive therapy (1,5). It is the most common acquired myopathy in individuals over 50 years of age, although it is often misdiagnosed (1). It is characterized by a slowly progressive course with a distinctive pattern of muscle involvement, including asymmetrical muscle weakness, particularly weakness of the quadriceps and long-finger flexors (1). Approximately 70% of patients have dysphagia, disease progression may lead to foot drop, and respiratory muscles may weaken (1).

Antisynthetase Syndrome (ASS) is defined by the presence of anti-aminoacyl-transfer RNA synthetase antibodies, most commonly associated with anti-Jo-1 antibodies, characterized by myositis, ILD, nonerosive arthritis, Raynaud`s phenomenon, fever, and mechanic`s hands (hyperkeratosis and fissuring of the palmar skin) (1,2,17). In addition to anti-Jo-1 antibodies, other MSAs have been identified: anti-PL7, anti-PL12, anti-OJ, anti-EJ, anti-Zo, anti-KS, and anti-Ha/YRS (17).

Overlap Myositis (OM) refers to myositis occurring in association with other connective tissue diseases, characterized by mixed clinical and serological features, often involving MAAs (2,13). Other connective tissue diseases include systemic lupus erythematosus, scleroderma, rheumatoid arthritis, and mixed connective tissue disease (1).

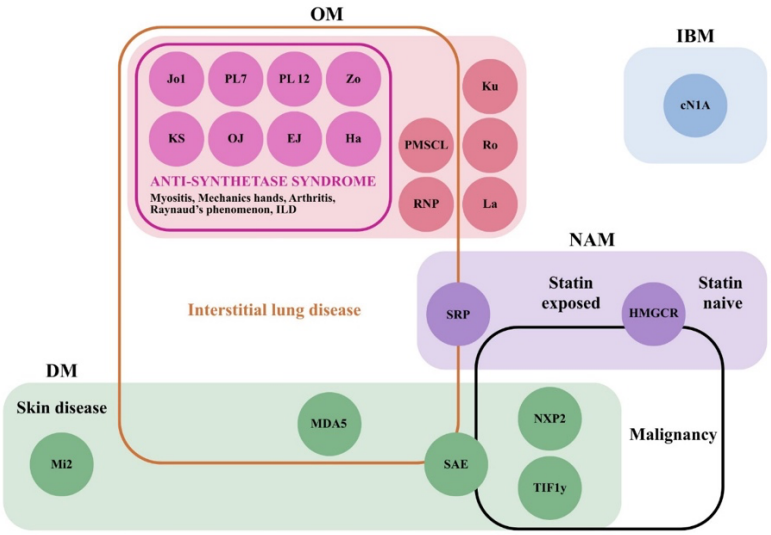

Fig. 1. Myositis-specific autoantibodies and associated disease subtypes. Adapted from Ashton et al. (1). *Abbreviations: DM, dermatomyositis; cN1A, cytoplasmic 5'-nucleotidase 1A; EJ, glycyl-transfer ribonucleic acid synthetase; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IBM, inclusion body myositis; Jo-1, histidyl-transfer ribonucleic acid synthetase; KS, asparaginyl-transfer ribonucleic acid synthetase; MDA5, melanoma differentiation-associated protein 5; NAM, necrotizing autoimmune myopathy; NXP2, nuclear matrix protein 2; OJ, isoleucyl-transfer ribonucleic acid synthetase; OM, overlap myositis; PL-7, threonyl-transfer ribonucleic acid synthetase; PL-12, alanyl-transfer ribonucleic acid synthetase; PM-Scl, polymyositis/scleroderma overlap antigen; RNP, ribonucleoprotein; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; TIF1γ, transcription intermediary factor 1 gamma; YRS/Ha, tyrosyl-transfer ribonucleic acid synthetase; Zo, phenylalanyl-transfer ribonucleic acid synthetase; ILD, interstitial lung disease.*

The heterogeneity and complexity of IIM and MSAs pose significant challenges to their classification. This complexity is illustrated in Figure 1. Understanding the historical development of these classification systems is essential for the role of MSA in the diagnosis and identification of disease subtypes.

3.2. CLASSIFICATION CRITERIA IN THE HISTORY OF IDIOPATHIC INFLAMMATORY MYOPATHIES

Classification and classification criteria are necessary in everyday practice to correctly diagnose patients. Classification is the link between research and clinical applications. It is crucial to find universal agreements in the era of international collaborations to advance research, especially for rare autoimmune diseases (20). The classification of IIM is difficult because of the heterogeneous nature of the disease group, which is characterized by numerous clinical, histopathological, serological, and genetic findings (2,10). The rare systemic autoimmune disease group cannot be diagnosed using a single laboratory, clinical, imaging, or diagnostic test (6). Historically the first set of classification criteria was found in 1975 by Dr. Anthony Bohan and Dr. James B. Peter (8,9,20). Since then, various classification criteria have been developed (14,21–28) . The most recent being the 2017 European Alliance of Associations for Rheumatology (EULAR) / American College of Rheumatology (ACR) Classification Criteria for adult and juvenile IIM by Lundberg et al. (7). Since then, the application use, sensitivity, and specificity of the 2017 EULAR/ACR criteria have been investigated (15,29). The following section explores the historical developments that have led to current efforts to establish new criteria, including MSAs.

3.2.1. HISTORY 1975- 2017

The first classification criteria for IIM, the so-called Bohan and Peter criteria, were published in 1975 based on a single-institution case series (6,8,9). This early widely used criterion differentiated between DM and PM for the first time (20). The criteria included five items: 1. Pattern of Muscle Weakness, 2. Typical muscle biopsy findings, 3. Elevated muscle enzyme levels, 4. Characteristic Electromyography (EMG) abnormalities, and in the matter of DM, 5. Heliotrope rash, Gottron´s sign, and papules (6,20). The Bohan and Peter criteria classify IIM into “definite,” “probable,” and “possible” based on the number of criteria met. A “definite” requires four out of five criteria (including a rash for DM), “probable” requires three out of five, and “possible” requires two out of five criteria for diagnosis (20). This historical milestone in the classification criteria is outdated. It includes only two subtypes - DM and PM- , but does not recognize other described subtypes of IIM, such as CADM (6,8,9). It has been criticized for including non-specific features of myositis, such as

EMG abnormalities (20). As the criteria were derived from a single-centre case series, they did not fully represent the broader IIM population (6,20). Furthermore, the absence of an appropriate control group limits the ability to distinguish IIM from other neuromuscular disorders with similar clinical features (20). However, subsequent studies published from 1977 to 1993 demonstrated that the criteria effectively differentiated DM and PM from systemic lupus erythematosus and systemic sclerosis, with sensitivities ranging from 74-100% (6).

Shortly after the publication of the Bohan and Peter criteria, IBM was identified as a subtype of myositis resistant to glucocorticosteroid treatment with specific histopathological changes, which were included in the Dalakas criteria in 1991 (21). Other researchers have described MSAs for the first time, along with histopathological changes (20). Seven MSA-targeting cytoplasmic ribonucleoproteins have been identified, including anti-Mi-2, anti-SRP, and multiple anti-aminoacyl-tRNA synthetase antibodies, such as anti-Jo-1, PL-7, PL-12, EJ, and OJ (20). These findings revealed that autoantibodies are associated with distinct clinical phenotypes in IIM. In 1991, Love et al. introduced new classification criteria for IIM based on these findings following a cross-sectional study of 212 patients with IIM (22). Their study demonstrated that unique clinical features, genetic associations, and prognostic profiles correlated with individual MSA subtypes (22). This contributed to a better understanding of IIM and its disease subtypes, including ASS or anti-Mi-2 phenotype DM (22). Furthermore, it emphasized that these disease subtypes presented with specific clinical features and differed in terms of diagnosis, prognosis, and management (20). This contributed to a more refined understanding of IIM subtypes and emphasized that these represent distinct clinical entities with implications for diagnosis, prognosis, and management (12).

Following a multicenter retrospective study with questionnaires and chart reviews, Tanimoto et al. proposed an alternative set of diagnostic criteria for PM and DM in 1995 (23). These criteria included nine diagnostic variables in addition to the five from the Bohan and Peter criteria (8,9,23). The four additional criteria were: “ 1) muscle pain on grasping or spontaneous muscle pain; (2) non-destructive arthritis or arthralgias; (3) signs of systemic inflammation—fever, elevated C-reactive protein, or erythrocyte sedimentation rate; and (4) the presence of anti-Jo1 antibody” (23). However, except for the last aspect, the presence of anti-Jo-1 antibodies, these new variables are rather nonspecific and could occur in other autoimmune diseases. Although it is notable for including MSA for the first time in its criteria, the Tanimoto criteria do not recognize any additional subtypes beyond DM and PM (23).

In 1997, Targoff et al. proposed modifications to the Bohan and Peter criteria to improve diagnostic specificity by including a new variable: newly discovered MSAs (anti-Mi2, SRP, and ASS autoantibodies) (24). Furthermore, Magnetic Resonance Imaging (MRI) of muscle inflammation was added as a substitute option for muscle weakness or elevated muscle enzyme levels (24). Similar to the Bohan–Peter criteria, patients are categorized as having "definite," "probable," or "possible" IIM based on whether they meet four, three, or two criteria, respectively (24). There have been notable improvements over the Bohan–Peter criteria; however, the Targoff criteria have been criticized for being based on expert opinion rather than empirical data (6).

As a consequence of recognizing IBM as a distinct clinical entity, Griggs et al. published diagnostic criteria in 1995, which classified patients into "definite" and "possible" categories based on their histopathological changes (25). Three muscle biopsy features were required to be present for "definite" cases: "1) mononuclear cell invasion of nonnecrotic muscle fibers; 2) vacuoles in muscle fibers, and 3) intracellular amyloid deposits or 15–18 nm tubulofilaments in muscle fibers" (25). If only the first finding was present, a "possible" IBM diagnosis could be made if other clinical and laboratory features were observed (25). Clinical findings included a disease duration of longer than six months, an age of onset >30 years, and/or distal muscle weakness (25). Laboratory results would show increased serum creatine kinase levels and EMG findings that align with IIM (25). A critique of the low sensitivity of the Griggs criteria was found, as vacuoles are required for a "definite" diagnosis (6). Similar to the Targoff criteria, the Griggs criteria are based on expert opinions and not empirical data (25). Despite this, the Griggs criteria were the first classification in the history of IBM and a step towards more subtypes than DM and PM (6).

Since the early 2000s, the understanding and classification of IIM have evolved rapidly, resulting in new subtypes due to the emergence of further MSAs and increasing attention to histopathological changes and/or clinical findings (20). For example, patients who presented with characteristic skin manifestations of DM without the clinical appearance of muscle involvement were, for some time, classified as having ADM, and were included in the revised Dalakas diagnostic criteria from 2003 (20,26). However, Sontheimer wrote in 2002 an editorial proposing further differentiation between ADM and hypomyopathic DM, another subtype that had arisen (27). Researchers have found that some subtypes, such as IBM, were sometimes misclassified due to a lack of histopathological understanding in previous classifications (20).

In response to these challenges, in 2004, the European Neuromuscular Centre, an international workshop with interdisciplinary expert opinions, on behalf of the Muscle Study Group, published

new classification criteria with comprehensive inclusion and exclusion criteria (30). These criteria incorporate clinical features, laboratory findings, muscle imaging, and histopathological assessment to define several distinct IIM subtypes (30). The inclusion criteria included clinical findings, increased muscle enzymes, other findings such as MSA in the serum, EMG abnormalities, MRI showing inflammatory lesions, and muscle biopsy findings of perifascicular atrophy and endomysial infiltration (30). The exclusion criteria were ocular weakness, isolated dysarthria, and evidence of toxic myopathies or IBM (30). IIM subtypes include DM, PM, and IBM, but also CAMD, IMNM, and non-specific myositis (30). The role of MSAs in the diagnosis and classification of IIM has been strengthened through the European Neuromuscular Classification Centre (6,20). Histology-based classification systems were also introduced during this period, which better reflected the underlying pathogenesis of IIM (20). However, purely histopathological approaches, such as Pestronk's classification from 2011, have limitations and low sensitivity because biopsy findings may change or overlap with subtypes over the course of the disease (20,31).

In the early 2000s, research excelled, and numerous MSAs were identified and studied, such as three new anti-aminoacyl tRNA synthetases (asparaginyl (KS), tyrosyl (HA), and phenylalanyl (Zo)), anti-melanoma differentiation antigen 5 (anti-MDA5), anti-small ubiquitin-like modifier activating enzyme (anti-SAE), anti-transcriptional intermediary factor 1 (anti-TIF1), anti-antinuclear matrix protein (anti-NXP-2), and anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (anti-HMGCR) (20). Many MSAs are associated with characteristic clinical phenotypes and disease courses (20). For example, anti-TIF1γ is strongly correlated with cancer-associated DM, and anti-HMGCR is a marker of IMNM associated with statin use (20). These antibody associations have been used to develop clinical-serological classification approaches that combine clinical manifestations with MSAs profiles (20).

In 2005, Troyanov et al. introduced such a classification system, which additionally emphasized the importance of overlap features such as arthritis, ILD, and Raynaud's phenomenon, and divided patients into four main subsets: OM, pure DM, pure PM, and cancer-associated myositis (28). OM was the most frequent subgroup and was characterized by the presence of antisynthetase antibodies or other overlap features; DM included a DM rash and/or positivity for anti-Mi2, and PM referred to patients without overlap features or MSA (28). In 2016, Benveniste et al. proposed a classification system that integrated clinical and pathological findings, which divided patients into four subtypes (IBM, OM, IMNM, and DM) that were further subdivided by their MSA status (14). Although this classification system, which resembles the Troyanov classification system, represents

a positive step in the history of IIM, it primarily relies on expert opinion and needs further validation; these approaches remain largely based on expert opinion and require further validation (14,20).

3.2.2. THE 2017 EULAR/ACR CLASSIFICATION CRITERIA

The debate regarding the challenges in accurately identifying IIM patients and their subtypes has persisted for decades (2,6). To address these issues, a comprehensive international multidisciplinary effort led to the creation of the 2017 EULAR/ACR Classification Criteria for both adult and juvenile IIM (6,7,20). This group consisted of international IIM experts in the fields of adult and paediatric rheumatologists, dermatologists, neurologists, epidemiologists, and biostatisticians (7). Their aim was to create a classification criterion for adult and juvenile IIM (7). Specifically, a criteria that would differentiate IIM from similar conditions and organize IIM subtypes using a minimum of clinical and easily accessible laboratory characteristics (7). A statistical model incorporating 16 weighted variables from six categories differentiated IIM from non-IIM patients, leading to a probability score that classifies patients as having "possible," "probable, " and "definite" IIM (7). Furthermore, this model allows differentiation between major subgroups: DM, PM, ADM, IBM, and JDM (7). Figure 2 illustrates the pathway for subgroups according to the 2017 EULAR/ACR Classification criteria (7).

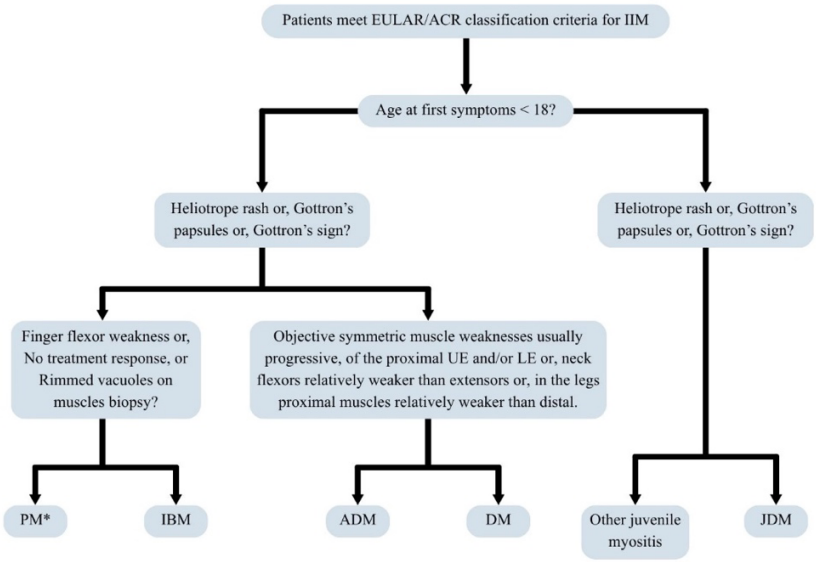

Fig. 2. Flowchart of subgroups of idiopathic inflammatory myopathies according to the 2017 EULAR/ACR classification criteria. Adapted from Lundberg et al. (7). *Abbreviations: IIM, idiopathic inflammatory myopathies; DM, dermatomyositis; ADM, amyopathic dermatomyositis; JDM, juvenile dermatomyositis; PM, polymyositis; IBM, inclusion body myositis; UE, upper extremity; LE, lower extremity.*

The model was developed using data from 976 IIM patients and 624 non-IIM controls from 47 centres worldwide (7). The data included clinical manifestations, laboratory examinations, autoantibody status (anti-Jo-1), and muscle biopsy results (7). The non-IIM controls were patients with diseases that could mimic IIM, such as systemic inflammatory diseases, muscular dystrophies, motor neuropathies, neuromuscular disorders, dermatological diseases, and various other types of myopathies (7). An internal validation process was conducted, and the criteria demonstrated high diagnostic performance, with a sensitivity ranging from 80-100% and specificity above 90% in various studies (6,20). Compared with earlier classification systems, the EULAR/ACR criteria have comparable or improved accuracy (6). It is now a widely used criterion in clinical practice and research (29). However, limitations remain, including the underrepresentation of rare disease subtypes, exclusion of modalities such as MRI, and the fact that it took 10 years to assemble enough patients, during which new MSAs appeared (7,32). Despite the growing recognition of a broad spectrum of MSAs associated with clinical phenotypes, the incorporation of only a single myositis-specific autoantibody, anti-Jo-1, limits this classification criterion (29). Consequently, significant MSAs subgroups are not represented in these widely used classification systems. This limitation reduces diagnostic sensitivity in certain patient populations, leading to poorer prognoses and treatment outcomes for these populations (29,32). Thus, a shift towards an MSA-based classification criterion is imminent. Glaubitz et al. described that recent studies have demonstrated that incorporating additional MSAs and diagnostic tools, such as muscle MRI and positron emission tomography-computed tomography, can greatly enhance diagnostic sensitivity and accuracy (6). They also highlighted that significant advances have been made in understanding IIM since the 2017 EULAR/ACR classification criteria, including the identification of new subgroups (6). Casal-Dominguez et al. described that although the 2017 EULAR/ACR classification criteria correctly identified 91% of patients with positive MSAs as IIM, it misclassified subgroups (15).

Furthermore, testing for MSAs in clinical practice and laboratories has become easily accessible and is now part of the standard clinical routine practice (11,33). With the rapid discovery of new MSAs and their distinct clinical phenotypes, there is a pressing need for a revised and updated classification system(34).

3.3. MYOSITIS SPECIFIC AUTOANTIBODIES AND MYOSITIS ASSOCIATED ANTIBODIES

The identification of MSAs has transformed the understanding, diagnosis, and classification of IIM, as they are present in over 50-70% of patients with IIM (2). The identification of these autoantibodies has demonstrated that IIM comprises a heterogenous group of disorders, rather than a single disease entity, with individual autoantibodies being associated with distinct phenotypes and disease courses (6,13,17). This is illustrated in Figure 1. MSAs represent a major advancement in the understanding, classification, diagnosis, prognosis, and treatment of IIM. Their identification in patients with IIM is correlated with specific patterns of organ involvement, including muscle, skin, and pulmonary manifestations or cancer-related disease courses (13,17). Thus, MSAs not only improve diagnostic accuracy in disease subgroups (2,17,35). They also play a significant role in ensuring appropriate patient management and treatment (2,17,35). However, despite their diagnostic value, MSAs may also be detected in other autoimmune conditions and are not entirely disease-specific (36–38). However, their interpretation is further complicated by the limited specificity of commonly used immunodetection methods (36). A retrospective study of 270 patients using multiplex immunodot assays found that some patients with positive results did not have IIM but instead presented with other autoimmune diseases or isolated ILD (36). Consequently, immunodot findings should always be interpreted in the context of clinical presentation (2,36). Similarly, Loarce-Martos et al. reported that only approximately half of the detected MSAs and MAAs identified by immunoassays were clinically relevant (39). False-positive results occur with low antibody signal intensity and the absence of supporting clinical features (39). These findings further emphasize that autoantibody results should always be interpreted together with the clinical context and never in isolation (39).

In addition to MSA, a second group of autoantibodies, MAA, has been described. Both groups target a range of cellular components, including the nuclear and cytoplasmic components (2). While MSA are relatively specific for IIM, MAA often occur together with other autoantibodies and are not specific to IIM (2). They are also found in other autoimmune rheumatic diseases and are frequently associated with overlap syndrome (13). These autoantibodies are frequently associated with extramuscular manifestations, such as ILD, arthritis, and Raynaud's phenomenon, and may suggest a more complex clinical phenotype that involves features of multiple connective tissue diseases (13,17). MAA frequently overlap with each other or with MSAs; however, MSAs are nearly exclusively found in patients with IIM, with only a small percentage overlapping with multiple MSAs or MAA (2). In practice, MAA do not aid in the diagnosis of IIM; rather, they help distinguish between inflammatory and non-autoimmune myopathies (2). The variety and an

overview of MSAs are shown in the following table, as described in the review by Allameen et al. (2025) (2):

Table 1: Overview of myositis-specific autoantibodies

Autoantibody	Target antigen	Main clinical associations and associated phenotype
Myositis-specific autoantibodies		
Anti-Jo1	Histidyl-tRNA synthetase	ASS, ILD
Anti-Ha/YRS	Tyrosyl-tRNA synthetase	ASS, ILD
Anti-Zo	Phenylalanyl-tRNA synthetase	ASS, ILD
Anti-EJ	Glycyl-tRNA synthetase	ASS, ILD
Anti-PL7	Threonyl-tRNA synthetase	ASS, ILD
Anti-PL12	Alanyl-tRNA synthetase	ASS, ILD
Anti-OJ	Components of the multi-enzyme synthetase complex	ASS, ILD
Anti-KS	Asparaginyl-tRNA synthetase	ASS, ILD, arthritis
Anti-Ly	Cysteinyl-tRNA synthetase	Unknown
Anti-MDA5	Melanoma differentiation-associated protein 5	Severe skin manifestations (ulcerations), RP-ILD, inflammatory arthritis and arthralgia
Anti-TIF1	Transcriptional intermediary factor 1	Severe skin manifestations, mild muscular symptoms, dysphagia, malignancy
Anti-NXP2	Nuclear matrix protein 2	Calcinosis, muscle involvement, gastrointestinal symptoms, malignancy
Anti-Mi2	Nucleosome remodelling deacetylase complex	Classical cutaneous dermatomyositis, severe muscle involvement
Anti-SAE	Small ubiquitin-like modifier-activating enzyme	Classical cutaneous dermatomyositis, mild muscular symptoms, dysphagia, ILD, malignancy
Anti-SRP	Signal recognition particle	Severe muscle involvement, including dysphagia and cardiac involvement
Anti-HMGCR	3-hydroxy-3-methylglutaryl coenzyme A reductase	Severe muscle involvement

Overview of MSAs, their target antigens, main clinical associations, and associated phenotypes adapted from Allameen et al. (2). *Abbreviations: ASS, antisynthetase syndrome; HMGCR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; ILD, interstitial lung disease; MDA5, melanoma differentiation-associated protein 5; NXP2, nuclear matrix protein 2; RP-ILD, rapidly progressive interstitial lung disease; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle, TIF1, transcriptional intermediary factor 1*

In their 2025 review, Allameen et al. classified MSAs according to their clinical relevance and association with major subgroups of IIM (2). These include autoantibodies in DM, ASS, and IMNM (2). As these categories cover the majority of current MSAs, the following section adopts a similar structure. Although an increasing number of novel autoantibodies have been identified in IIM, their routine application remains limited (37). This is due to their low prevalence, limited assay availability, and reduced positive values (37). Consequently, the present literature review focuses on currently well-established and routinely used MSAs. Less common or emerging autoantibodies were not discussed in detail. Furthermore, approximately 30-40% of patients remain seronegative using current autoantibody panels (12,37,40). This suggests that additional, yet unidentified autoantibodies contribute to disease heterogeneity and incomplete disease classification (37). The progressive discovery of MSAs over time, as illustrated in Fig. 3, reflects this ongoing expansion of knowledge. This dynamic evolution suggests that further autoantibodies remain to be identified, refining future classification systems (2,12,13).

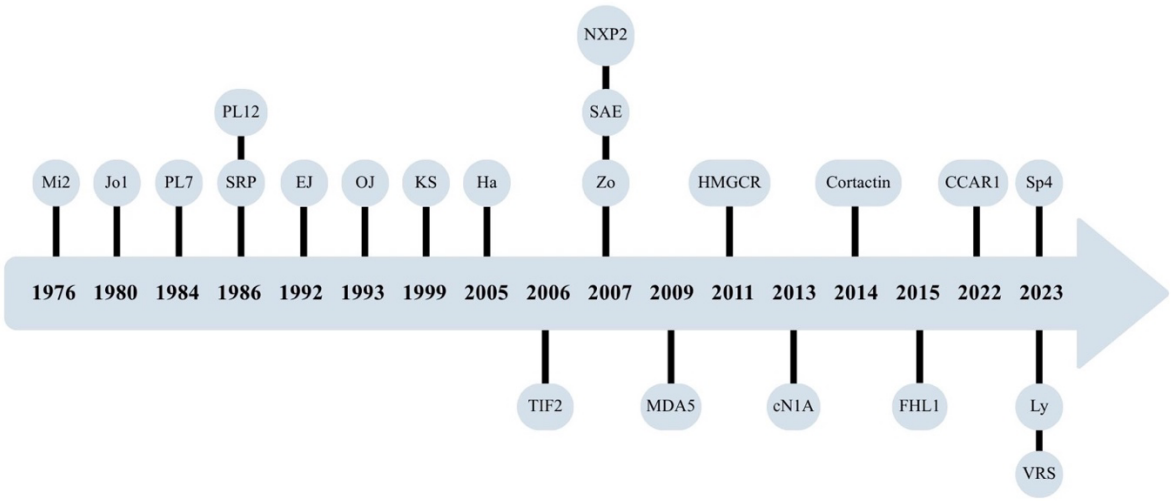

Fig. 3. Timeline of myositis autoantibody discovery. Adapted from Wang et al. (35). The figure illustrates the chronological identification of major myositis-specific and-associated autoantibodies. *Abbreviations: cN1A, cytoplasmic 5'-nucleotidase 1A; CCAR1, cell cycle and apoptosis regulator protein 1; EJ, glycyl-transfer ribonucleic acid synthetase; FHL1, four-and-a-half LIM domain protein 1; Ha, tyrosyl-transfer ribonucleic acid synthetase; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; Jo-1, histidyl-transfer ribonucleic acid synthetase; KS, asparaginyl-transfer ribonucleic acid synthetase; Ly, lysyl-transfer ribonucleic acid synthetase; MDA5, melanoma differentiation-associated protein 5; Mi-2, nucleosome remodelling deacetylase complex; NXP2, nuclear matrix protein 2; OJ, isoleucyl-transfer ribonucleic acid synthetase; PL-7, threonyl-transfer ribonucleic acid synthetase; PL-12, alanyl-transfer ribonucleic acid synthetase; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; Sp4, specificity protein 4; TIF2, transcription intermediary factor 2; VRS, valyl-transfer ribonucleic acid synthetase; Zo, phenylalanyl-transfer ribonucleic acid synthetase.*

3.4. AUTOANTIBODIES IN DERMATOMYOSITIS

Dermatomyositis is characterized by unique skin features and is frequently associated with muscle inflammation. Cutaneous manifestations may include a "periorbital heliotrope (blue-purple) rash with edema, erythematous rash on the face, anterior chest ('V sign'), back and shoulders ('Shawl sign') or the lateral aspect of the thighs ('Holster sign'), and violaceous papules or plaques or erythema located on the dorsal part of the metacarpophalangeal or interphalangeal joints ('Gottron papules' or 'Gottron's sign')" (2). These signs are shown in Figure 4.

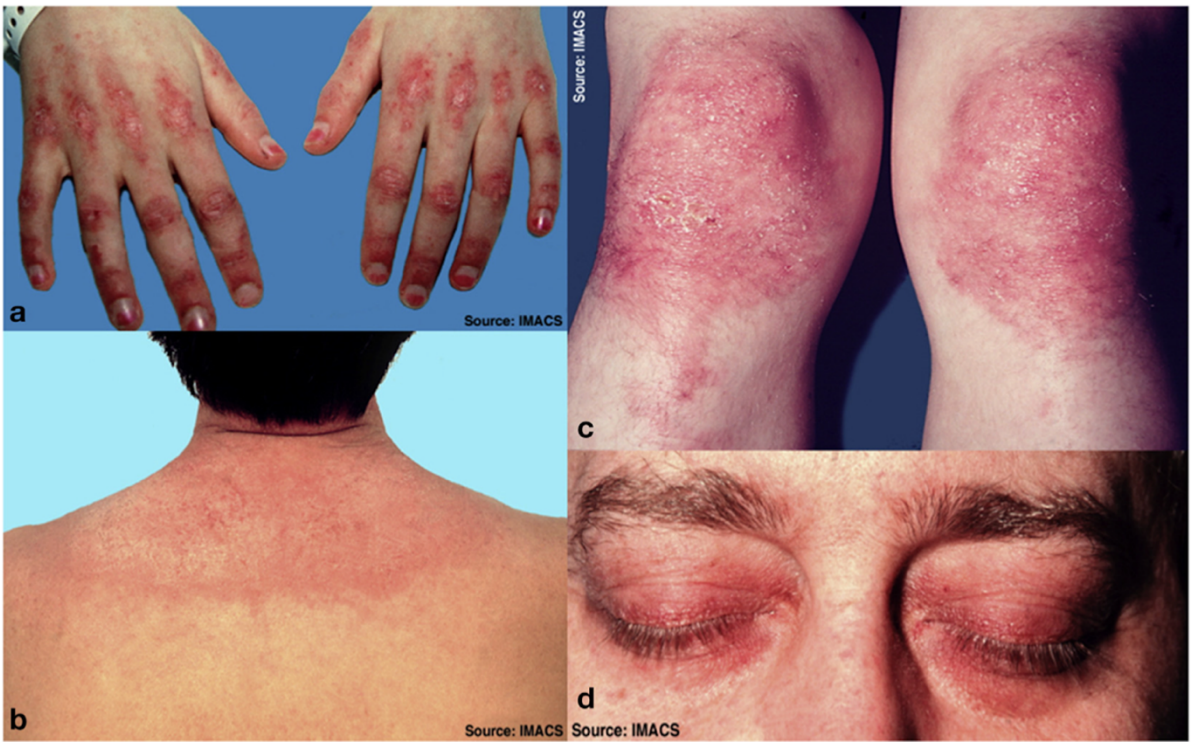

Fig. 4. Typical cutaneous manifestations of dermatomyositis. (a) Gottron's papules; (b) shawl sign; (c) Gottron's sign; (d) heliotrope rash. Adapted from Parker et al. (41), with the image source IMACS.

However, not all skin features appear in every patient with DM, and their disease may present with different clinical phenotypes related to the MSAs found. There are important clinical and serological differences between adult- and juvenile-onset DM. Although MSAs are present in approximately 60% of patients in both populations, their distribution varies considerably (2,17). Juvenile DM is most commonly associated with anti-TIF1- γ and anti-NXP2 autoantibodies, but is much less frequently associated with malignancy in compared with the adult DM (2,13). In contrast, antibodies such as anti-MDA5 occur less frequently, whereas anti-Mi-2 and anti-SAE antibodies are comparatively uncommon(2,13). This section analyses the different autoantibodies found in patients with DM, as well as their clinical importance and correlation with disease symptoms and outcomes.

Most patients with DM are seropositive for at least one of the following MSA:

- Anti-MDA5 (anti-melanoma differentiation associated gene 5)
- Anti-Mi-2
- Anti-TIF1 (anti-transcriptional intermediary factor 1)
- Anti-NXP2 (anti-nuclear matrix protein 2)
- Anti-SAE (anti-small ubiquitin-like modifier activating enzyme)

3.4.1. Anti-MDA5

Anti-MDA5 autoantibodies are among the most clinically significant MSA, as they are strongly associated with distinct clinical phenotypes of DM (2,13). These autoantibodies target the helicase domains of the MDA5 cytoplasmic protein, which is involved in innate immune responses against viruses and were first discovered in 2005 in a Japanese cohort (2,17). In addition to its central role in innate immune signalling, MDA5 plays a role in the induction of type I interferon responses (2). The involvement of this pathway is thought to contribute to the characteristic vasculopathic and systemic manifestations observed in anti-MDA5-positive patients (2).

Epidemiological studies have shown geographic variability in the presence of anti-MDA5 antibodies in patients with DM. In Europe, MDA5-associated DM prevalence rates represent less than 2% of adult-onset IIM, whereas in Asia, they range from 7-60% (2). In juvenile DM, prevalence rates have been reported as 6-13% in European cohorts and up to 28% in Asian cohorts (2). Similarly, cohort studies have shown that anti-MDA5 antibodies occur in approximately 10–48% of adult DM cases in East Asia, compared with substantially lower frequencies of 6–13% in US cohorts (17).

Clinically, anti-MDA5 is strongly associated with CADM or hypomyopathic DM, in which muscle involvement is minimal or even absent despite significant systemic disease (2,13). This feature distinguishes anti-MDA5 from other MSAs, which are typically associated with prominent muscle weakness (13). These patients often present with the typical skin features of DM, but more so with characteristic ulcerative lesions and palmar papules, which reflect underlying vasculopathy and are less commonly seen in other DM subtypes (2,13). These specific cutaneous manifestations are seldom found in other cases of DM and may not be recognized by general physicians, leading to delayed diagnosis (2). One of the most clinically significant aspects of anti-MDA5-positive DM is its strong association with ILD, especially rapidly progressive ILD (RP-ILD) (2). The severity of

lung involvement highlights the importance of early identification of this antibody for the timely initiation of aggressive therapy (2).

Skin ulcerations and anti-MDA5 positivity are hallmarks of a close correlation with ILD/RP-ILD(2). RP-ILD refers to a severe form of ILD characterized by rapid deterioration of respiratory function and radiological progression within a short period, typically within weeks to months of symptom onset, which constitutes a major determinant of morbidity and a mortality rate of up to 50% in this patient group (13,17). Anti-Ro52 MAA are present in up to 75% of patients with MDA5-DM, and their combination indicates high rates of RP-ILD and mortality (2).

Regional differences in IDL and RP-ILD have also been observed in patients with DM. Studies have found that in East Asian populations, 82-100% of patients with anti-MDA5 DM develop ILD, and RP-ILD occurs in 39-100% of these cases (2). In contrast, patients from Europe, North America, and Brazil have reported lower frequencies, with 38-73% of patients developing ILD and 20-57% developing RP-ILD (2). These differences are clinically relevant not only for the correct diagnosis but also for the treatment and prognosis of the disease. These studies show that East Asian cohorts are more frequently characterized by severe, rapidly progressive lung disease that is often refractory to immunosuppressive therapy and associated with high mortality (17). One study showed that mortality due to respiratory failure occurred in up to 45% of anti-MDA5-postive patients within six months of diagnosis, highlighting the poor prognosis of this phenotype (17).

Recent cohort studies have improved our understanding of the prognostic factors of anti-MDA5-positiv DM with ILD (42,43). A large multicenter cohort study by Wu et al. demonstrated that baseline lung function, as measured by forced vital capacity, was a strong predictor of short-term mortality (43). Patients with preserved lung function had significantly lower mortality rates, in contrast to patients with reduced lung function, who had markedly worse outcomes (43). Patients who were unable to perform the pulmonary function test due to severe disease had the highest mortality, reaching up to 86-97% within six months (43). In addition to physiological markers, immunological markers can be used for prognosis in anti-MDA5 positive patients (42). A large cohort study of 190 patients by Xu et al. showed that higher levels of anti-MDA5 IgG1 and IgG3 subclasses were significantly associated with mortality in patients with DM-ILD (42). An anti-MDA5 IgG1 titer of >13U/ml was identified as an independent risk factor for death (42). Similarly, patients with elevated IgG1 levels exhibit more severe disease features and poorer survival outcomes (42). Together, these two studies demonstrate that both clinical and immunological factors can be used as predictors of prognosis in anti-MDA5 positive patients (42,43). However,

despite these findings, inconsistencies remain in the literature regarding the correlation between seropositivity for anti-MDA5 antibodies and ILD, as highlighted by Allameen et al. (2). These discrepancies may reflect differences in study populations and methodologies, and further research is needed to establish more consistent prognostic markers (2).

In addition to cutaneous features and pulmonary involvement, anti-MDA5-positive patients may display systemic inflammatory features such as fever, inflammatory arthritis, and/or arthralgia (2). Elevated ferritin levels are often found as a specific laboratory feature in these patients, which is associated with disease severity and correlates with worse outcomes, especially in ILD (2). Patients also exhibit liver enzyme abnormalities without a correlating elevation in muscle enzymes (2,13). Furthermore, anti-MDA5 frequently coexists with anti-Ro52 antibodies (MAA), and this combination has been linked to an increased risk of severe ILD and mortality (2). The clinical phenotype of anti-MDA5 DM is so heterogeneous that it can be further subdivided into different predominant manifestations, including ILD-dominant disease, dermato-rheumatological presentations, and vasculopathic forms with severe skin involvement (2). These variations further highlight the complexity of this antibody-defined subset and the need for individualized clinical assessments (2).

From a diagnostic perspective, anti-MDA5 antibodies are particularly valuable for identifying patients with CADM who may otherwise be underdiagnosed using traditional classification systems that emphasize muscle weakness as the key feature. Therefore, their detection supports a shift toward serology-based classification and early disease recognition in idiopathic inflammatory myopathies (2,17). Overall, anti-MDA5 autoantibodies illustrate the evolving role of MSAs in IIM. They defined a clinically distinct and high-risk subgroup of DM characterized by vasculopathic skin lesions, minimal muscle involvement, and a strong association with life-threatening ILD (2,13). Anti-MDA5 identification is essential for disease classification, early diagnosis, prognostic assessment, and correct patient management, particularly in relation to interstitial lung disease (2,13,17).

3.4.2. Anti-Mi-2

Anti-Mi-2 autoantibodies are among the earliest identified MSA and are strongly associated with DM, especially the classic form (2,13). The prevalence of anti-Mi-2 antibodies varies across populations but is generally lower than that of several other DM autoantibodies, with numbers ranging from 11-59% in adult and 4-10% in juvenile DM patients (17). Satoh et al. described that

the prevalence of anti-Mi-2 varies within countries, possibly depending on the correlation between ultraviolet radiation and production of anti-Mi-2 antibodies (13). This suggests that genetic and environmental factors play a role in the production of anti-Mi-2; however, further research is needed (13).

These autoantibodies target components of the nucleosome deacetylase complex, which plays a role in the regulation of gene transcription. Mi-2 is essential for epidermal remodelling; therefore, patients with anti-Mi-2 positivity typically present with prominent skin manifestations, which may facilitate early recognition of the condition (2,13). These skin features include heliotrope rash, Gottron's papules, shawl sign, and V-sign. These patients may present with symptoms of arthritis, joint pain, and Raynaud's phenomenon (2). Next to these typical cutaneous manifestations, signs of severe muscle involvement is present characterized by pronounced muscle weakness and increased creatine levels (2,13,17). However, the severity of muscle disease is often moderate and responds well to treatments (13). This group of patients exhibit much fewer severe extra muscular complications such as ILD, calcinosis or malignancy compared to other MSAs subgroups, such as anti-MDA5 (2,13,17). Thus, DM with anti-Mi-2 positivity is generally considered a mild subtype of DM with a favourable disease course and good prognosis. Additionally, patients tend to respond well to conventional treatment, which consists of glucocorticoid steroid therapy (2). These factors result in anti-Mi-2-positive DM being considered a relatively benign phenotype within the spectrum of IIM (2). Nevertheless, variability exists, and careful clinical evaluation remains necessary (2).

The presence of anti-Mi-2 antibodies has long been considered a marker of classic DM and remains an important tool in clinical practice (13). In addition to diagnostic implications, where anti-Mi-2 shows high specificity for DM, this autoantibody is also an indicator of disease severity. The levels of anti-Mi-2 antibodies correlate directly with muscle strength and creatine kinase levels, reflecting the disease severity (2). Thus highlighting the importance of MSA in refining disease classification and guiding clinical management.(2,13,17). In summary, anti-Mi-2 autoantibodies define a subgroup of DM characterized by classic skin manifestations, good response to therapy, and favourable prognosis, with an important role in diagnostic and prognostic purposes (2,13).

3.4.3. Anti-TIF1- γ

Anti-transcription intermediary factor 1 gamma autoantibodies are among the most clinically significant MSAs associated with DM, particularly because of their strong association with cancer in adult patients, with malignancy found in up to 50% of anti-TIF1- γ patients (2,13). These

autoantibodies target nuclear proteins belonging to the transcription intermediary factor (TIF1) family, which includes TIF1-α, TIF1-β, TIF1-γ, and TIF1- δ (17). They target a group of proteins, including the120-kDa, 140-kDa protein and 155-kDA protein, involved in transcriptional regulation, chromatin remodelling, and cellular differentiation, including those related to tumor suppression (2,13,17). Anti-TIF1 autoantibodies are strongly associated with DM and define a clinically important subgroup with distinct features (2). The pathophysiological link between anti-TIF1 and malignancy is thought to involve immune responses directed against tumor antigens that cross-react with skin and muscle tissues (2). Mutations or altered expression of TIF1 proteins in tumors may trigger autoantibody production, leading to the development of DM as a paraneoplastic phenomenon (2). This mechanism highlights the interplay between autoimmunity and cancer in this subgroup of patients (2).

Among these, TIF1- γ has been identified as the primary antibody in DM (2). The clinical phenotype of anti-TIF1- γ patients differs between adult- and juvenile-onset DM, highlighting important age-related differences in disease presentation (2). In adult patients, anti-TIF1- γ seropositivity is strongly associated with malignancy-associated DM, with a significantly elevated risk of underlying cancer compared to other myositis subtypes (2). This association makes anti-TIF1- γ one of the most important serological markers for identifying patients requiring comprehensive malignancy screening and surveillance in patients with DM. This association is further supported by multiple cohort studies demonstrating that anti-TIF1- γ antibodies define DM with a markedly increased risk of malignancy (44–46). In a Japanese cohort of 77 patients, 19 anti-TIF1- γ- positive patients were more likely to have internal malignancies, as well as clinical features such as dysphagia and characteristic skin manifestations (44). Motegi et al. found that male sex and dysphagia were associated with an increased risk of malignancy in anti-TIF1- γ- positive patients, whereas ILD occurs less frequently, highlighting a distinct cancer-associated disease phenotype (44). Similar findings were reported in a Chinese monocentric retrospective study, including 134patients with adult-onset DMs (45). Anti-TIF1- γ- positivity (together with anti-Mi2) is associated with malignancy, and these autoantibodies have been incorporated into a multivariable logistic model with good sensitivity and specificity for detecting malignancy-associated DM (45). Furthermore, a Greek cohort study demonstrated a significantly higher cancer prevalence and reduced overall survival in anti-TIF1- γ- positive patients compared to antibody-negative individuals (46). Together, these findings confirm anti-TIF1- γ as a robust biomarker for malignancy-associated DM and suggest that additional factors, such as age, sex, and dysphagia, may further refine individual cancer risk stratification (44–46).

In contrast, in juvenile DM, anti-TIF1- γ antibodies are not strongly linked to malignancy but are associated with characteristic skin manifestations, including ulceration, calcinosis, and lipodystrophy (2). Anti-TIF1 autoantibodies are the most common MSA identified in juvenile-onset IIM, predominantly in children diagnosed at a younger age (2).

Clinically, patients with anti-TIF1-γ antibodies, particularly in the paediatric population, frequently exhibit pronounced and often severe cutaneous manifestations (2). These include DM features such as heliotrope rash and Gottron`s papules, as well as more extensive skin involvement, including widespread erythema, photodistributed rashes, ulcerations, calcinosis, and lipodystrophy (2,13,17). Additionally, atypical skin manifestations, such as hyperkeratotic papules and psoriasis-like lesions, (2,13,17). Muscle involvement varies and may range from mild to moderate weakness, but is often less severe than in other MSA subgroups; however, patients may frequently experience severe dysphagia (5,8,9). Aside from the strong association with malignancy, patients have a lower risk of many systemic manifestations or other typical DM manifestations, such as Raynaud's phenomenon(5,8). Unlike anti-MDA5 antibodies, anti-TIF- γ positivity is not associated with severe ILD, further emphasizing the heterogeneity of DM subtypes defined by different autoantibodies (9).

Overall, anti-TIF1-γ autoantibodies define a clinically important subgroup of DM characterized by typical skin features and a strong association with malignancy in adult patients, while presenting different phenotypes in juvenile disease (8,9). This highlights the importance of MSAs in refining disease classification and guiding diagnostic evaluation, prognostic assessment, and cancer screening strategies (5,8).

3.4.4. Anti-NXP2

Anti-NXP2 autoantibodies, also known as anti-MJ, are MSAs primarily associated with DM and define a clinically distinct subgroup within IIM (5,8,9). Nuclear matrix protein 2 (NXP2), also known as MORC3, is a nuclear protein involved in transcriptional regulation, RNA metabolism, and maintenance of nuclear architecture, and has also been implicated in tumor suppressor pathways (2,13). The identification of anti-NXP2 antibodies has contributed significantly to the shift towards autoantibody-defined subgroups of IIM (6).

Anti-NXP2 was initially described in juvenile DM and remains particularly relevant in paediatric diseases (13). Several cohort studies have demonstrated a relatively high prevalence in juvenile patients, with reported frequencies of approximately 23-25% (13). In juvenile DM, anti-NXP2 is

strongly associated with a severe disease phenotype, including muscle atrophy, joint contractures, functional impairment, and calcinosis (13). Calcinosis is a major source of morbidity in juvenile diseases and has been consistently linked to anti-NXP2 seropositivity (13,17). Calcinosis appears more frequently in juvenile populations and is a distinctive characteristic of anti-NXP2 positive patients (17). Their exhibition reflects a more severe and potentially refractory disease course (2). These findings highlight the prognostic importance of anti-NXP2 antibodies in identifying high-risk paediatric patients who may require closer monitoring and more aggressive treatment strategies (2).

A key clinical characteristic of patients with anti-NXP2 DM is prominent muscle involvement (2). Patients with severe muscle myopathy present with proximal and distal muscle weakness, dysphagia, and dysphonia (2,17). Subcutaneous edema and myalgia have also been reported as characteristic features (17). Notably, cutaneous manifestations are minor or even absent compared to other DM subgroups, and pathognomonic rash may be absent, which can hinder diagnosis if classical skin findings are key items for diagnostic criteria (2). Anti-NXP2 is associated with significant extramuscular complications. Severe gastrointestinal involvement has been described, including vasculopathy, intestinal smooth muscle necrosis, and serosal calcinosis (2). Some patients also present with polyarthritis. These features support the concept that anti-NXP2 identifies a systemic disease phenotype rather than a purely muscular disorder (2).

In adult populations, anti-NXP2 positivity has been linked to an increased risk of malignancy (2,13). Several studies report anti-NXP2 positive adult patients develop cancer, with an estimated of approximately 31-38% (17). This association highlights the importance of cancer screening in this subgroup. In contrast, no association has been found between malignancy in juvenile patients, suggesting different pathogenic mechanisms between paediatric and adult diseases (2).

Overall, anti-NXP2 autoantibodies define a clinically important subgroup of DM characterized by severe muscle involvement, calcinosis, and systemic complications. In children, anti-NXPE2 is strongly associated with calcinosis and functional impairment, whereas in adults it is additionally linked to malignancy risk (2,13,17). The integration of anti-NXP2 into modern classification frameworks supports the shift toward a serology-based classification system for IIM, improving not only diagnosis but also prognosis (6,7).

3.4.5. Anti-SAE

Anti-SAE autoantibodies are MSAs associated with DM and represent a relatively rare but clinically distinct subgroup of IIM (2,13). These autoantibodies target the small ubiquitin-like modifier activating enzyme (SAE), which plays a central role in post-translational protein modification, cellular signalling, and transcriptional regulation (13).

Anti-SAE-positive DM is associated with characteristic cutaneous manifestations, with muscle involvement often developing later in the disease course (13). These cutaneous features, which are often extensive, include classical findings such as heliotrope rash, Gottron's papules, and photodistributed rashes (13). Characteristic skin findings and subclinical muscle weakness may lead to a diagnosis of CADM (17). Over time, however, patients frequently develop progressive proximal muscle weakness, which tends to be mild, and dysphagia often occurs (2,13). A correlation between ILD and an increased risk of malignancy has been found (2).

From a diagnostic perspective, anti-SAE autoantibodies are particularly useful in identifying patients who first present with isolated or predominant cutaneous disease before the onset of muscle involvement (18). This is particularly important because a correlation between anti-SAE positivity and malignancy exists, and early cancer screening is advised (2). This finding supports the concept of a serology-based classification system. These patients generally have a good prognosis, despite challenges in managing extensive skin findings, resulting in multiple medication changes (2,17). The clinical heterogeneity of DM can be further illustrated by comparing the phenotypic features associated with the individual MSAs (Table 2).

Table 2: Myositis-specific autoantibodies in dermatomyositis and their clinical characteristics

Autoantibody	Frequency	Muscle involvement	Skin manifestation	Extra muscular features	Prognosis / Clinical course
Anti-MDA5	Variable (low in Europe, higher in Asia; ~6–48%)	Minimal or absent (CADM/ hypomyopathic)	Ulcerations, palmar, papules, typical DM rash	Strong association with ILD, especially RP-ILD; fever, arthritis, elevated ferritin	High mortality risk due to RP-ILD; severe disease phenotype
Anti-Mi-2	~11–59% adults; 4–10% juvenile	Prominent but moderate; good response to treatment	Classic DM features (heliotrope rash, Gottron's papules, shawl sign, V-sign)	Rare severe extramuscular involvement	Favourable prognosis; good response to steroids

Continued Table 2: Myositis-specific autoantibodies in dermatomyositis and their clinical characteristics

Anti-TIF1-γ	Common in DM; most common in juvenile DM	Mild to moderate	Severe skin involvement, ulceration, calcinosis, lipodystrophy, psoriasis-like lesions	Strong malignancy association in adults; dysphagia; less ILD	Malignancy-associated DM in adults; different phenotype in juvenile DM
Anti-NXP2	~23–25% juvenile DM	Severe muscle involvement (proximal + distal), dysphagia, dysphonia	Often mild or absent	Calcinosis (JDM),GI involvement, edema, polyarthritis	Severe disease in children; malignancy association in adults
Anti-SAE	Rare	Initially minimal; muscle involvement develops later	Prominent early skin manifestations	Dysphagia, systemic features	Delayed muscle involvement; variable course

Clinical characteristics of dermatomyositis-associated autoantibodies compiled by the author based on Allameen et al. (2), Betteridge et al. (12), Duremala et al. (5), Halilu et al. (17), Motegi et al. (44), Satoh et al. (13), Syrmou et al. (46), Tang et al. (45), and Vaezi et al. (47). *Abbreviations: DM, dermatomyositis; CADM, JDM, juvenile dermatomyositis; clinically amyopathic dermatomyositis; ILD, interstitial lung disease; RP-ILD, rapidly progressive interstitial lung disease.*

3.5. AUTOANTIBODIES IN IMMUNE-MEDIATED NECROTIZING MYOPATHY

IMNM represents a distinct, rare and well-defined subgroup within the spectrum of IIM, characterized by severe proximal muscle weakness, markedly elevated creatine kinase levels, and the histopathological hallmark of prominent muscle fiber necrosis with minimal inflammatory cell infiltration on muscle biopsy (2,13,17). In contrast to other IIM, in which inflammatory infiltrates play a key role in muscle damage, IMNM is differentiated by a predominantly necrotic process (17). This suggests a different underlying pathophysiological mechanism with minimal inflammation, possibly reflecting to a humoral immune response (3,47,48). The identification of MSAs, especially the discovery of anti-HMGCR antibodies in 2009, has reshaped our understanding of IMNM (17). This disease is now largely classified into distinct subgroups depending on the presence of specific autoantibodies, namely, anti-SRP and anti-HMGCR (2,3). Each is associated with unique clinical, pathological, and prognostic features (47). Anti-HMGCR can be further classified into statin-associated or statin-naïve forms, and some patients present with IMNM and seronegativity for these two associated MSAs (5,7). Among these, anti-SRP autoantibodies define a well-characterized and clinically significant subgroup, which will be discussed first.

3.5.1. Anti-SRP

The signal recognition protein (SRP) is a cytoplasmic ribonuclear protein responsible for the translocation of synthesized proteins across the endoplasmic reticulum and was first described in 1986 as a novel autoantibody in patients with PM (13,17). Anti-SRP autoantibodies are strongly associated with IMNM and define a subgroup characterized by severe muscle involvement (2,3). Severe necrotizing myopathy leads to impaired and progressive muscle weakness (17). Marked elevation of creatine kinase, possibly ten times the upper limit of normal, is a hallmark feature, as is minimal inflammatory infiltration on biopsy, with prominent necrosis (17,47). Patients exhibit fewer skin findings; however, they have an increased risk of esophageal dysmotility and respiratory muscle involvement (5,17). Anti-SRP myopathy associates with ILD and cardiac involvement, such as rhythm or conduction abnormalities and cardiac insufficiency (2,5). This also differentiates this group from anti-HMGCR-positive patients, in whom mostly skeletal muscles are affected (2). These patients experience a high disease burden and have limited or absent responses to glucocorticoid therapy (2,17). This poor response to immunotherapy, and hence an increase in mortality, in combination with debilitating myopathy, indicates a poor prognosis (47). Research has indicated that anti-SRP titres correlate with creatine kinase enzyme levels, suggesting their potential use for monitoring disease activity; however, further research is required (17). Anti-SRP IMNM developing in paediatric and younger patients is linked to a more aggressive disease course (2). In a longitudinal study of 37 anti-SRP-positive IMNM patients from the Johns Hopkins Myositis Cohort (380 visits), Pinal-Fernández et al. (2017) found that younger age at onset was associated with more severe muscle weakness over time (49). They found that only approximately 50% of patients achieved near-full or full strength after four years of immunosuppressive treatment, rituximab appeared effective in 13 of 17 treated patients, and anti-SRP-positive patients were significantly weaker than anti-HMGCR-positive patients, supporting anti-SRP as a marker of a more severe IMNM subtype (49).

Overall, anti-SRP autoantibodies define a clinically severe and prognostically unfavourable subtype of IMNM, characterized by rapidly progressive muscle weakness, high disease burden, and limited response to conventional immunosuppressive therapy, emphasizing their importance in disease classification and clinical management (2,17). In addition to anti-SRP, anti-HMGCR autoantibodies define a major subgroup of IMNM and will be discussed next.

3.5.2. Anti-HMGCR

3-hydroxy-3-methyglutaryl coenzyme A reductase (HMGCR) is a glycoprotein that plays an important role in cholesterol biosynthesis, where HMG-CoA is converted to mevalonic acid(2,17). The anti-HMGCR specifically recognize the intracellular C-terminal region of the enzyme and are strongly associated with IMNM (2). HMGCR is inhibited by statins, as it's their main side of action, and therefore statin use is a, even if rare, risk factor for developing anti-HMGCR positive IMNM (2,5). Although statin exposure is a known risk factor, patients may develop this disease without prior statin use, suggesting additional roles for genetic and environmental factors (2). A strong genetic association has been identified with the HLA-DRB1*11:01 haplotype, suggesting that genetic predisposition plays an important role in disease susceptibility (2). Epidemiological observations further suggest that additional factors may influence disease development, as patients from Asian cohorts with anti-HMGCR-positive IMNM have been reported to have lower rates of statin exposure than those from Europe and North America (2). Nevertheless, most patients have a history of statin exposure and are middle-aged or older adults (47). It has been proposed that statin exposure may lead to increased expression or structural changes of HMGCR, which, in genetically susceptible individuals, could contribute to loss of immune tolerance and thus autoantibody production (2). Clinically, anti-HMGCR-positive IMNM patients present with proximal muscle weakness and elevated creatine kinase levels, similar to anti-SRP-positive disease (2,17). However, the onset of muscle weakness may be more insidious (17). Extramuscular manifestations are generally uncommon in adult-onset disease, although skin findings have been reported, particularly in juvenile cases (2). The association between anti-HMGCR autoantibodies and malignancy remains unclear, with conflicting results reported in the literature (2).

Common histopathological findings for both subtypes include widespread necrosis, infiltration by macrophages, and limited lymphocytic inflammation (3,47). However, anti-HMGCR regenerating fibers are more prevalent than anti-SRP myopathy (47,48). This indicates a quicker recovery of the muscle tissue in anti-HMGCR. Patients show variable responses to steroid therapy, and in some cases, alternative treatment strategies are considered, although relapse is frequently observed during steroid tapering (17). Refraction to steroids appears to be more common in younger patients and those without prior statin exposure (17).

In addition to its diagnostic value, anti-HMGCR autoantibody levels have been shown to correlate with disease activity (17). Antibody titres correspond directly to creatine kinase levels and tend to decrease with clinical improvement, supporting their role as biomarkers for disease monitoring (17). In Yang et al. (2024), anti-HMGCR IgM-positive IMNM patients were younger, had more neck

weakness, higher disease activity, and more often followed a polycyclic or refractory disease course, with minimal early remissions, compared with IgM-negative patients (50).

Overall, anti-HMGCR autoantibodies define a clinically important subgroup of IMNM characterized by a variable disease course, association with statin exposure, and potential utility as a marker of disease activity (2,17). This further emphasizes the importance of MSAs in diagnosis, classification, and disease monitoring.

3.6. AUTOANTIBODIES IN ANTISYNTHETASE SYNDROME

ASS represents a distinct clinical entity within IIM, characterized by the presence of autoantibodies targeting aminoacyl-transfer RNA (tRNA) synthetases, as well as characteristic clinical findings(2). Aminoacyl-tRNA synthetases are cytoplasmic enzymes responsible for catalysing the attachment of specific amino acids to their corresponding transfer RNA during protein synthesis (2,17). They participate in immune regulation and cellular signalling, which may explain their ability to act as autoantigens in autoimmune diseases such as ASS (51). These antisynthetase antibodies are among the most common MSAs, detected in approximately 35–40% of patients with IIM; however, they are rarely found in IIM in children (2,52). Typical clinical features include muscle inflammation, inflammatory arthritis, ILD, Raynaud's phenomenon, mechanic's hand, or persistent and unexplained fever (53). Clinical manifestations may develop at different times in ASS, making diagnosis and differentiation from other IIM subgroups difficult (2,17). In some patients, ILD may be the initial presenting feature, preceding the onset of muscle, joint, or cutaneous findings (2).

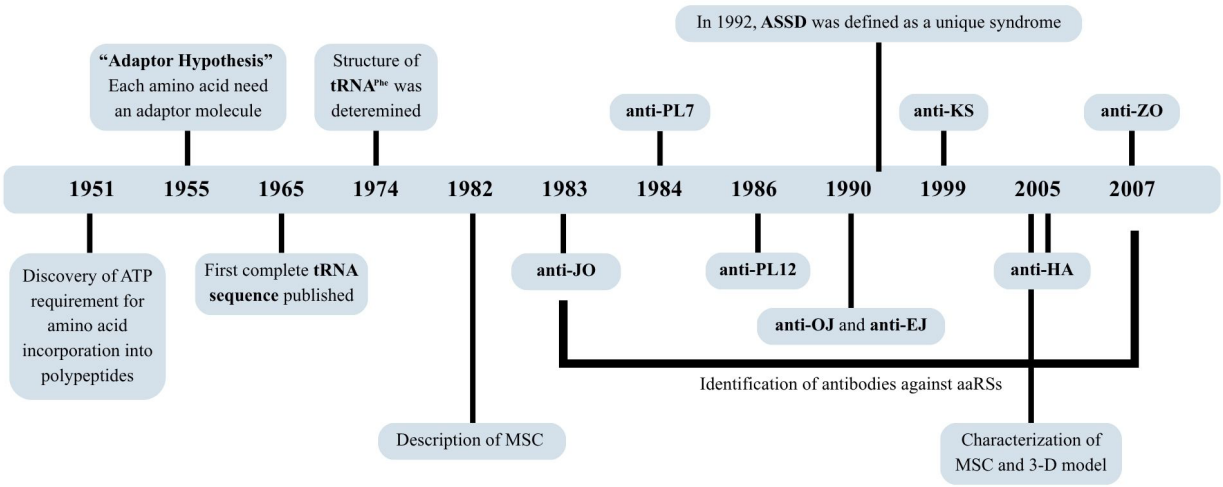

Fig. 5. Timeline of the discovery of antisynthetase antibodies. Adapted from Galindo-Feria et al. (51). *Abbreviations: aaRSs, aminoacyl-transfer ribonucleic acid synthetases; anti-EJ, anti-glycyl-transfer ribonucleic acid synthetase; anti-Ha, anti-tyrosyl-transfer ribonucleic acid synthetase; anti-Jo-1, anti-histidyl-transfer ribonucleic acid synthetase; anti-KS, anti-asparaginyl-transfer ribonucleic acid synthetase; anti-OJ, anti-isoleucyl-transfer ribonucleic acid synthetase; anti-PL-7, anti-threonyl-transfer ribonucleic acid synthetase; anti-PL-12, anti-alanyl-transfer ribonucleic acid synthetase; anti-Zo, anti-phenylalanyl-transfer ribonucleic acid synthetase; ASSD, antisynthetase syndrome disease; ATP, adenosine triphosphate; MSC, multi-enzyme synthetase complex; tRNA, transfer ribonucleic acid.*

A range of antisynthetase autoantibodies has been identified over the years (Figure 5)., including anti-Jo 1 (anti-histidyl-tRNA synthetase), anti-PL7 (anti-threonyl-tRNA synthetase), anti-PL12 (anti-alanyl-tRNA synthetase), anti-EJ (anti-glycyl-tRNA synthetase), anti-OJ (anti-isoleucyl-tRNA synthetase), anti-KS (anti-asparaginyl-tRNA synthetase), anti-Zo (anti-phenylalanyl-tRNA synthetase) and anti-Ha/Yrs (anti-tyrosyl-tRNA synthetase), where specific antibodies associate with distinct clinical features and disease patterns (2,5,17). Novel autoantibodies have been discovered in recent years, such as autoantibodies against cysteinyl-tRNA; however, their clinical relevance needs to be further investigated (51). For this discussion, autoantibodies found in ASS were categorized into anti-Jo-1 and non-anti-jo-1 subgroups. Anti-Jo-1 autoantibodies represent the most prevalent and well-studied subgroup and are addressed first. Other antisynthetase autoantibodies occur at substantially lower frequencies and will be addressed together in the Non-anti-Jo-1 section (51).

3.6.1. Anti-Jo-1

Among antisynthetase antibodies, anti-Jo-1 is the most common, well-known, and best-characterized subtype. Anti-Jo-1 autoantibodies were the first MSA to be identified in 1980 (Figures 3 and 5), marking the initial discovery of MSAs in IIM (13). The inclusion of anti-Jo-1 also marked the first incorporation of MSAs into the IIM classification criteria (6). Early studies demonstrated its strong disease specificity and association with a distinct phenotype, later named antisynthetase syndrome (13). This distinct phenotype is characterized by the presence of myositis, ILD, arthritis, mechanic´s hands, fever and Raynaud`s phenomenon (1,13,17,51). ILD is a central and frequently occurring manifestation and is considered a hallmark of this MSA (17). ILD frequencies are reported in approximately 70-95% of patients with anti-Jo-1 positive ASS in IIM (1,17). In these cases, ILD may present with preceding muscle involvement as a presenting symptom (17). However, in many cases, ILD and myositis develop simultaneously, and only a small proportion of patients have muscle inflammation preceding pulmonary involvement (1,17). The clinical presentation of ILD may range from incidental findings to subacute or rapidly progressive diseases (17). In patients with ASS, ILD is the primary cause of mortality and morbidity, often dominating their clinical course (51). ILD with positivity for anti-synthetase autoantibodies has been reported to respond better to steroid therapy than ILD without MSAs for ASS (17).

In addition to pulmonary involvement, anti-Jo-1 positivity is linked to its unique clinical presentation of a higher frequency of myositis, inflammatory arthritis, mechanic´s hands and Raynaud´s phenomenon (1,13). Raynaud´s phenomenon is often an early clinical feature that may precede the onset of myositis (17). Anti-Jo-1 antibody levels have been reported to correlate modestly with creatine kinase levels and disease activity in the muscles and joints, suggesting a potential role in monitoring the disease course and treatment (17).

Overall, anti-Jo-1 autoantibodies defined the most common and best characterized subgroup of ASS and exemplify the role of MSAs is identifying clinically distinct subtypes with characteristic patterns of organ involvement (2,13,17).

3.6.2. Non-Anti-Jo-1

Non-anti-Jo-1antisynthetase antibodies include anti-PL7, anti-PL12, anti-EJ, anti-OJ, anti-KS, anti-Zo, anti-HA/Yrs, each of which occurs less frequently, with individual prevalence generally ranging from approximately from 0.5-6% among patients with IIM (1,13,17). Despite sharing a common association with antisynthetase syndrome, these antibodies have some minor differences in clinical

presentation and disease course compared to anti-Jo-1- positive patients and represent a heterogeneous disease group (13).

A prominent feature of non-anti-Jo-1 antisynthetase antibodies is their strong association with ILD (2,5). In particular, anti-PL7,anti-PL12, anti-OJ, anti-EJ and especially anti-KS are frequently linked to early-onset and more severe ILD, which is associated with poorer prognosis than compared to anti-Jo-1-positive disease (2,17,52). Similar to anti-Jo-1, ILD represents the most common cause of death in these patients (17). A retrospective cohort study by Wang et al. demonstrated that anti-EJ-positive patients presented more frequently with ILD than other autoantibody groups (52). Research suggests that in some non-anti-Jo-1 antibodies, such as anti-PL7, anti-PL12, and anti-KS, muscle involvement is much milder, even in the presence of ILD (2,13). Anti-PL12 is additionally associated with features overlapping with systemic sclerosis, including esophageal involvement and pulmonary hypertension, further highlighting its systemic nature (1,17).

In contrast to the prominent pulmonary phenotype, muscle involvement in non-anti-jo-1-positive patients is often less pronounced. Studies have shown that patients with anti-PL7 and anti-PL12 antibodies tend to exhibit milder muscle disease and lower recurrence rates than anti-Jo-1-positive patients (13). However, certain antibodies, including anti-PL7, anti-EJ, and anti-OJ, have been associated with more prominent myopathic features in some cohorts, indicating variability within this subgroup and contradictory reports (17). Anti-OJ antibodies are associated with severe myositis and ILD as primary manifestation (2). Anti-OJ positive patient tend to have less arthritis and respond better to steroid therapy (2,5,17) .

Additional systemic and extramuscular manifestations further contribute to the heterogeneity of the non-anti-Jo-1 antisynthetase syndrome. Cutaneous manifestations, although not always resembling classical DM rashes, are more frequently observed in patients with anti-EJ, anti-PL7, and anti-PL12 antibodies (17). Anti-PL7 has also been associated with Gottron´s sign and DM-like features in certain patient subtypes (5). In addition, the rarity of certain antibodies, such as anti-Zo and anti-Ha/Yrs, has limited the ability to clearly define their clinical phenotypes, with current knowledge based on case reports (17).

Overall, non-anti-Jo-1 antisynthetase autoantibodies are a subgroup of ASS with the typical clinical features of the IIM subtype; however, they have heterogeneous differences among themselves. These patients present with predominantly severe and often early ILD, often milder myopathy, and

diverse systemic features (2,13,17). This further implicates the importance of antibody-specific classification in identifying clinically distinct disease subtypes and guiding diagnostic and prognostic evaluations.

Table 3: Myositis-specific autoantibodies in antisynthetase syndrome and their clinical characteristics

Autoantibody	Frequency in IIM	Muscle involvement	Interstitial Lung Disease (ILD)	Other clinical features	Prognosis / Clinical course
Anti-Jo-1	Most common, 10-20%	Prominent myositis	Very common (70–95%); may precede muscle disease or occur simultaneously	Arthritis, mechanic's hands, Raynaud's phenomenon, fever	ILD major driver of morbidity and mortality; responds better to steroid therapy
Anti-PL7	~0.5–6%	Often milder; lower recurrence	Early onset, often severe ILD	Gottron's sign, DM-like features	Associated with poorer prognosis due to severe ILD
Anti-PL12	~0.5–6%	Often mild or absent	Strong association; may be isolated ILD	Systemic sclerosis -like features, esophageal involvement, pulmonary hypertension	Severe ILD; worse outcomes compared to Jo-1
Anti-EJ	~0.5–6%	Variable; sometimes more prominent	Frequently associated ILD	More frequent cutaneous manifestations	Variable clinical course
Anti-OJ	~0.5–6%	Can be severe	ILD as primary manifestation	Less frequent arthritis	Responds better to steroids
Anti-KS	~0.5–6%	Mild	Strong association with severe ILD	—	Associated with poor prognosis
Anti-Zo / Anti-HA (Yrs)	Rare	Not defined	Not defined	Limited data (case reports)	Clinical phenotype unclear

Clinical characteristics of antisynthetase syndrome associated autoantibodies based on the data compiled by the author based on Ashton et al. (1), Allameen et al. (2), Betteridge et al. (12), Duremala et al. (5), Galindo-Feria et al. (51) Satoh et al. (13), and Wang et al. (52).

Abbreviations: ILD – interstitial lung disease; DM – dermatomyositis.

4. CONCLUSION

This thesis shows that myositis-specific autoantibodies have changed the understanding and classification of idiopathic inflammatory myopathies. Idiopathic inflammatory myopathies are a group of syndromes often defined by autoantibody profiles (2,15). Myositis-specific autoantibodies link serology with clinical features and help define meaningful subgroups in a very heterogeneous disease (2).

Several myositis-specific autoantibodies are associated with specific clinical features. Anti-MDA5 is strongly associated with clinically amyopathic dermatomyositis and rapidly progressive interstitial lung disease (42,43). This represents one of the most severe phenotypes and requires early recognition to ensure the best possible outcome for patients (2,43). This is particularly important in patients with clinical amyopathic dermatomyositis, where muscle symptoms may be minimal and misleading to clinicians (2,13). Studies have also shown that both clinical and immunological factors can predict the prognosis in anti-MDA5 positive patients (34,42). This demonstrates that myositis-specific autoantibodies are not merely diagnostic markers but also provide clinically important information that directly influences patient management (17,35).

Many myositis-specific autoantibodies further highlight the clinical value of serological classifications (1,2). Anti-Mi-2 shows high specificity for dermatomyositis and is also linked to disease severity, where antibody levels correlate with muscle strength and creatine kinase levels (2,13). Anti-TIF-γ seropositive patients define a subgroup with typical dermatomyositis cutaneous features and strong association with malignancy in adults (2,13,44). This underlines the importance in cancer screening in adults, while they present a different phenotype in juvenile disease (1,2,13,44). Anti-NXP2 further demonstrates the differences between adult and juvenile diseases. Initially described in juvenile dermatomyositis, it associates with severe disease course and calcinosis, leading to a major source of morbidity (2,13,17). In contrast, in adult patients, Anti-NXP2 myositis-specific autoantibody correlate with an increased risk of malignancy (2,17). The absence of similar association in juvenile patients in these two autoantibodies suggests differences in underlying pathogenesis between paediatric and adult disease (1,2,13,17). Correspondingly, results differ between various studies across the field of idiopathic inflammatory myopathies, which may reflect differences in study population and methods, but also the complex clinical heterogeneity and not fully understood underlying pathogenic mechanisms of idiopathic inflammatory myopathies (2).

Similarly, in immune-mediated necrotizing myopathy, anti-SRP and anti-HMGCR identify clinically distinct subgroups with differences in disease severity and treatment response (48–50). Anti-SRP antibody positivity is associated with severe disease and poor treatment response, whereas anti-HMGCR antibodies define a subgroup often linked to statin exposure with a different disease course (48–50). Within antisynthetase syndrome, variability between individual antibodies further reflects the complexity of the disease (5,13). Overall, these findings show that idiopathic inflammatory myopathies are highly heterogeneous. Even within the same subtype or myositis-specific autoantibody group, patients can present differently (2,5,13,17). This makes the disease spectrum complex and reflects the presence of conflicting results across studies (2). This variability highlights the need for cautious interpretation of the serological findings.

The evolution of classification systems further reflects this shift in focus. Early criteria, such as those proposed by Bohan and Peter, relied on clinical and histopathological features and did not account for disease heterogeneity (6,8,9). Although the 2017 European Alliance of Associations for Rheumatology/American College of Rheumatology classification criteria improved diagnostic accuracy, their limited incorporation of autoantibodies restricts their ability to fully capture disease subtypes (7,15). These developments reflect the historical progression from purely clinical classification systems to integrated serological approaches. The evidence presented in this thesis supports the need for updated classification systems that integrate clinical, serological, and pathological data.

Despite recent advances, with many myositis-specific autoantibodies identified, important limitations remain. Myositis-specific autoantibodies are not entirely disease-specific and may be detected in other autoimmune conditions, complicating their interpretation (36,39). Additionally, variability in immunoassays can lead to false results, emphasizing that serological findings must always be interpreted in a clinical context (36). Furthermore, approximately 30-40% of patients with idiopathic inflammatory myopathy remain seronegative, indicating that additional autoantibodies remain to be discovered (2,13). These unidentified autoantibodies may contribute to the current incomplete diagnostic framework and disease heterogeneity (2,13).

A limitation of this study is its focus on selected idiopathic inflammatory myopathy subtypes, including dermatomyositis, immune-mediated necrotizing myopathy, and antisynthetase syndrome. Other subtypes, such as inclusion body myositis and overlap myositis, were not explored in depth, although they represent clinically relevant entities within the idiopathic inflammatory myopathy spectrum. In addition, myositis-associated autoantibodies were only briefly discussed, although they

are important for understanding the concept of autoantibodies in autoimmune diseases and their overlap with idiopathic inflammatory myopathy.

In conclusion, myositis-specific autoantibodies are essential for the modern understanding of idiopathic inflammatory myopathies. They allow the identification of clinically distinct subgroups with important diagnostic, prognostic, and therapeutic implications. However, their limitations demonstrate the need for integrated diagnostic approaches and further research.

5. RECOMMENDATIONS

Based on these findings, several practical recommendations can be made. First, testing for myositis-specific autoantibodies should be included in the routine diagnostic work-up of patients with suspected idiopathic inflammatory myopathies. The detection of antibodies associated with, such as anti-MDA5 or anti-TIF—γ, should prompt further investigation, including targeted screening for interstitial lung disease or malignancy. Second, autoantibody results should be interpreted in the clinical context, as current testing methods are limited by their sensitivity and specificity. Therefore, reliance on serological results alone may lead to misclassification. Third, clinicians should be aware of the heterogeneity of idiopathic inflammatory myopathies. Even within the same disease subgroup, patients may present differently. Finally, further research is needed to identify novel autoantibodies, improve the standardization of diagnostic assays, and refine classification criteria to better reflect the complexity of idiopathic inflammatory myopathies and support more precise and individualized patient care.

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