Review Article

Narrative review of autoantibodies in idiopathic inflammatory myopathies

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Objective: To discuss the characteristics of autoantigens, detection methods and roles of myositis associated autoantibodies (MAAs) and myositis specific autoantibodies (MSAs), as well as the clinical features of disease subgroups defined by MAAs/MSAs.

Background: Autoantibodies in patients with idiopathic inflammatory myopathies (IIMs) are conventionally divided into MAAs and MSAs. MAAs usually refer to autoantibodies which are also available in systematic autoimmune diseases (anti-PM/SCL, anti-Ku, anti-Ro52 and anti-U1RNP antibodies). MSAs refer to autoantibodies which were distinctive for IIM (anti-Mi-2, anti-MDA5, anti-TIF1gammma, anti-NXP2, anti-SAE, anti-synthetase, anti-SRP, anti-HMGCR and anti-cN1A antibodies). The discovery and identification of novel autoantigens is a long and complicated process, which brought light in immunopathogenesis of IIMs. Detection methods of MAAs/MSAs mainly consist of monospecific methods [immunoprecipitation, enzyme-linked immune sorbent assay (ELISA) and indirect immunofluorescence] and multispecific methods [line immunoassay (LIA), dot immunoassay (DIA) and addressable laser bead assay (ALBIA)]. Patients with different MAAs/MSAs have different clinical features and require different clinical management.

Methods: The search engine PubMed (https://www.ncbi.nlm.nih.gov/pmc/) was used to research the keywords “autoantibodies”, “idiopathic inflammatory myopathies”, “detection methods” and “clinical features”. A narrative review was conducted to literature findings from 1975 to 2020.

Conclusions: Development and validation of efficient detection methods of MAAs and MSAs help clinicians for diagnosis, classification and management of IIMs. The exploration of clinical features associated with different autoantibodies that facilitate the creation of diagnostic and classification guidelines and further clinical decision-making is of high value.

Keywords: Idiopathic inflammatory myopathies (IIMs); myositis associated autoantibodies (MAAs); myositis specific autoantibodies (MSAs); detection methods; clinical features

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Introduction

The idiopathic inflammatory myopathies (IIMs) consist of several subgroups, including overlap myositis, dermatomyositis (DM), anti-synthetase syndrome (ASS), immune-mediated necrotizing myopathy (IMNM) and inclusion body myositis (IBM). The diagnosis of IIMs requires careful assessment of clinical symptoms, elevated creatine kinase level, muscle magnetic resonance imaging (MRI) changes, electromyography findings, skeletal muscle biopsy results and analysis of myositis associated autoantibodies (MAAs) and myositis specific autoantibodies (MSAs). An integrated clinical-serologic approach for

identifying subgroups of IIMs may be warranted (1).

MAAs are usually found in patients with overlap syndrome and less specific for IIMs. But MAAs are useful biomarker for diagnosis of IIMs and for subsequent identification of related connective tissue diseases (CTDs). MAAs mainly includes anti-PM/SCL antibodies, anti-Ku antibodies, anti-Ro52 antibodies and anti-U1RNP antibodies. MSAs are specific for IIM and each antibody correlates a distinct phenotype of IIMs with few exception (1) including DM (anti-Mi-2, anti-MDA5, anti-TIF1gammma, anti-NXP2 and anti-SAE antibodies), ASS (anti-EJ, OJ, Jo1, PL7, PL12, Ha and Zo antibodies), IMNM (anti-SRP and anti-HMGCR antibodies) and IBM (anti-cN1A antibodies) (2,3). Generally, one patient rarely generates two or more MSAs simultaneously (*Table 1*).

The discovery and knowledge of MAAs and MSAs took decades (*Figure 1*). Anti-Mi-2 antibodies, the first one of defined MSAs, were detected in a DM patient in 1976 (4). Since then, more than 20 kinds of autoantigens and corresponding MAAs/MSAs have been observed (*Figure 2*). The correlation of presence and titer of autoantibodies with clinical features has been discovered. Testing for MAAs and MSAs plays a more and more important role in diagnosis, classification and management of IIMs (5). We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-475/rc).

Methods

The search engine PubMed (https://www.ncbi.nlm.nih.gov/pmc/) was used to research the keywords "autoantibodies", "idiopathic inflammatory myopathies", "detection methods" and "clinical features". A narrative review was conducted to review findings of published literatures in English from 1975 to 2020 including case reports, case series, cohort studies, experiment studies and so on.

Detection of MAAs/MSAs

Multiple methods have been found to test autoantibodies (*Figure 3*). Immunoprecipitation, enzyme-linked immune sorbent assay (ELISA) and indirect immunofluorescence are usually considered as monospecific methods. Immunoprecipitation is widely used for detection of autoantibodies. Autoantigens from human cell lysis bind to autoantibodies from patients' serum. Then protein A/G beads binds to Fc segment of autoantibodies. Thus, antigen-antibody-protein A/G beads complex is formed. Specific antigens are extracted after centrifugation and identified by SDS-PAGE, immunoblotting or mass spectrum. Generally, immunoprecipitation is regarded as the gold-standard (6) for detecting autoantibodies because of its high sensitivity and specificity (7,8). However, immunoprecipitation is not able to distinguish antigens with similar molecular weight (9). Operation of immunoprecipitation is tedious and time-consuming and high-quality operation is needed in order to get accurate results. It is not efficient for clinical diagnostic laboratories in needing of high throughput tests.

ELISA is also widely used in diagnostic laboratories. Autoantigens are coated in a plate and bind to a specific autoantibody from patients' serum. The titer is measured by absorption photometry. It is simple to use and has high sensitivity. However, the kinds of recombinant antigens for autoantibodies testing are limited and the coating procedure can introduce loss of epitopes (10). Besides, cross-reactivity exists between some autoantibodies as a result of homologous peptide fragment, leading to decrease in specificity (11).

Indirect immunofluorescence is commonly used in antinuclear antibodies detection but is not a routine method for MSAs detection. Autoantigens existing in cultured cells or tissue slices bind to autoantibodies from patients' serum. Then fluorescent anti-human immunoglobulin reagent binds to Fc segment of autoantibodies. Each kind of autoantibodies has a specific immunofluorescent pattern which requires experienced reading (7,8). Additionally, cell-line based assay is rarely used for MAAs/MSAs detection. Only one credible cell-line based assay method for detection of autoantibodies against cytosolic 50-nucleotidase 1A (cN1A) by using COS7 cell line was reported (12).

Line immunoassay (LIA), dot immunoassay (DIA) and addressable laser bead assay (ALBIA) are multispecific assay methods and are generally used in clinical diagnostic laboratories. These methods provide semi-quantitative information and are convenient for larger-sized samples. For LIA and DIA, the autoantigens are coated on the stripes as bands or dots. Each band or dot is coated with a different kind of autoantigen. This coating procedure can reduce the sensitivity because of loss of epitopes (13). Autoantigens bind to autoantibodies from patients' serum and anti-human immunoglobulin reagent conjugated to an enzyme bind to the Fc segment of autoantibodies. Conversion of substrates reacting with enzymes makes antigen-antibody complex visible. The color intensities of the bands or dots can be assessed by software automatically and provide

Table 1 Characteristics of common MAAs/MSAs in IIMs

Autoantibodies	Common detection methods	Autoantigen location	Main function of autoantigen	Clinical characteristics
MAAs in overlap myositis				
Anti-PM-SCL	Immunoprecipitation, ELISA, immune lines	Nucleus	Cellular RNA processing	PM, overlap myositis with scleroderma, oesophageal involvement
Anti-Ku	Immunoprecipitation, ELISA, immune lines	Nucleus	Transcription regulation and DNA repair	PM, DM, overlap myositis with scleroderma, scleroderma, Sjögren syndrome and SLE
Anti-Ro52	Immunoprecipitation, ELISA, immune lines	Nucleus, cytoplasm	Cell cycle and Ubl conjugation pathway	ASS with anti-Jo1 autoantibodies, overlap myositis with SLE and scleroderma
MSAs in ASS				
Anti-Jo1 (histidyl)	Immunoprecipitation, immune lines, indirect immunofluorescence	Cytoplasm	Loading the amino acid with its tRNA	High prevalence of muscle disease, ILD
Anti-PL7 (threonyl)				More associated with ILD, severe muscle weakness, DM rashes
Anti-PL12 (alanyl)				More associated with ILD and DM rashes
Anti-EJ (glycyl)				DM rashes, more severe muscle weakness, ILD
Anti-OJ (isoleucyl)				Rare in ASS, less severe muscle disease, ILD
MSAs in DM				
Anti-Mi-2	Immunoprecipitation, ELISA, immune lines, indirect immunofluorescence	Nucleus	Remodeling of chromatin	Associated with typical DM rashes
Anti-MDA5	Immunoprecipitation, ELISA, immune lines	Nucleus and cytoplasm	Sensing virus infection and activation of antiviral responses	Various skin disease and associated with CADM, RP-ILD
Anti-NXP-2	Immunoprecipitation, ELISA, immune lines	Nucleus	Transcription regulation and interaction with TP53	Subcutaneous calcinosis and edema, severe muscle disease, high risk of malignancy
Anti-TIF1-γ	Immunoprecipitation, ELISA, immune lines	Nucleus	Transcriptional regulation and participate ubiquitin proteasome pathway.	Skin disease with photoexposed pattern, high risk of malignancy
Anti-SAE	Immunoprecipitation, ELISA, immune lines	Nucleus	Protein sumoylation	High frequency of dysphagia, skin involvement prior to muscle disease

Table 1 (*continued*)

Table 1 (*continued*)

Autoantibodies	Common detection methods	Autoantigen location	Main function of autoantigen	Clinical characteristics
MSAs in IMNM				
Anti-SRP	Immunoprecipitation, ELISA, immune lines	Endoplasmic reticulum and cytoplasm	Targeting proteins to the rough endoplasmic reticulum membrane	Severe muscle weakness, poor response to treatment, mimic muscle dystrophy
Anti-HMGCR	Immunoprecipitation, ELISA, ALBIA, indirect immunofluorescence	Endoplasmic reticulum	Rate-limiting enzyme in cholesterol biosynthesis	With or without statin exposure; severe muscle weakness, poor response to treatment, mimic muscle dystrophy
Autoantibodies in IBM				
Anti-cN1A	Immunoprecipitation, cell line based assay	Cytoplasm	Dephosphorylates deoxyribonucleotides	Associated with IBM, other CTDs and juvenile myositis

MAAs, myositis associated autoantibodies; MSAs, myositis specific autoantibodies; IIMs, idiopathic inflammatory myopathies; ELISA, enzyme-linked immune sorbent assay; PM, polymyositis; DM, dermatomyositis; SLE, systemic lupus erythematosus; ASS, anti-synthetase syndrome; ILD, interstitial lung disease; CADM, clinically amyopathic dermatomyositis; RP-ILD, rapidly progressive interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; ALBIA, addressable laser bead assay; IBM, inclusion body myositis; CTDs, connective tissue diseases.

titer information. Results with low positive intensity must be interpreted prudently because it can exist in non-IIM patients with other autoimmune rheumatic diseases (13).

ALBIA is also commonly used for multispecific assay of antibodies (14). Autoantigens are coated on fluorescent beads and are incubated with patients' serum. Each bead carries a unique internal fluorescent signature and is coated with a single autoantigen. The mixture of beads are able to test multiple antibodies. The fluorescent signal intensities are assessed by flow cytometry and provide quantitative information. Fully automatic operation is available which is suitable for high-throughput screening though the testing platform and reagents can be high-cost. Commercial kits are usually made for LIA/DIA and ALBIA which are suitable for medium to large-size samples from diagnostic laboratories.

However, LIA/DIA and ELISAs are poorly applicable to detect anti-OJ autoantibodies, leading to high false negative rate. It stems from the fact that "anti-OJ antibodies" is actually "anti-OJ complex autoantibodies". Immunoprecipitation must be performed if anti-OJ syndrome is highly suspected with negative testing results by ELISA/LIA/DIA (15).

Recently, new methods such as particle-based assay are used for testing MSAs/MAAs (16) in order to strike a balance between accuracy and efficiency. The newly developed kit must be validated by immunoprecipitation and larger patient cohort is required (17).

Autoantigens to MAAs/MSAs

Autoantigens are closely associated with clinical subtypes of myositis (*Table 1*). Autoantigens of DM including Mi-2, NXP-2, MDA5, SAE and TIF-1 are nucleoproteins. DM patients with autoantibodies with these autoantigens share similar manifestations including typical skin lesion, interstitial lung diseases (ILDs) and muscle involvement and similar pathological changes including peripheral atrophy and obvious microangiopathy. Autoantigens of ASS are aminoacyl-tRNA synthetase in cytoplasm. Patients with ASS show similar clinical characteristics to DM but the myopathology shows necrotizing myopathy with slight microvessel damage, which makes ASS a distinct subtype of myositis. Autoantigens of IMNM including SRP and HMGCR which locate and function in endoplasmic reticulum. Patients with IMNM show severe muscle damage with necrotizing myopathy changes and show little extramuscular involvements, which makes it distinct from

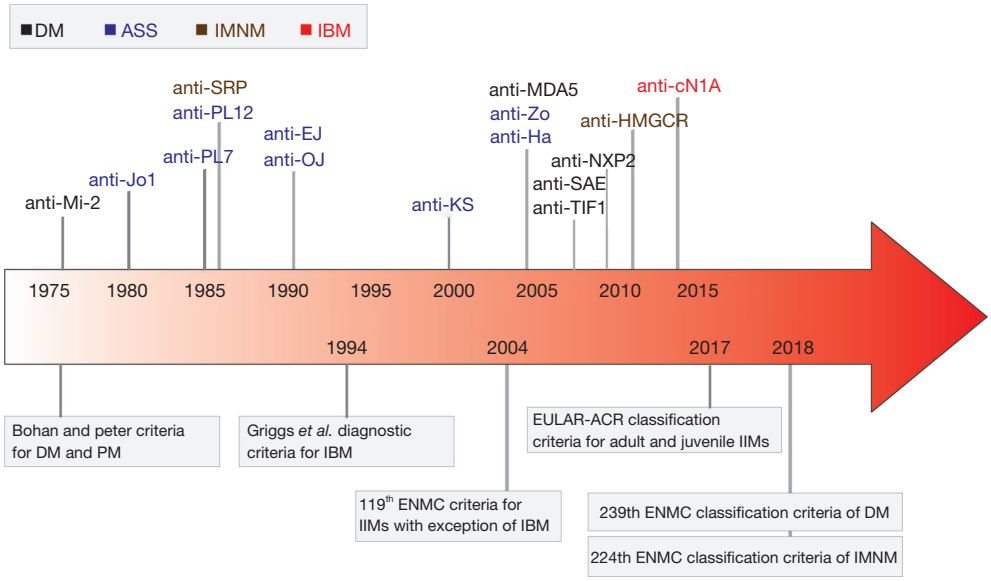

Figure 1 Timeline of discovery of MSAs and main diagnostic or classification criteria for IIMs. DM, dermatomyositis; PM, polymyositis; ASS, anti-synthetase syndrome; IMNM, immune-mediated necrotizing myopathy; IBM, inclusion body myositis; ENMC, the European Neuromuscular Centre; EULAR-ACR, the European League Against Rheumatism and the American College of Rheumatology; IIMs, idiopathic inflammatory myopathies; MSAs, myositis specific autoantibodies.

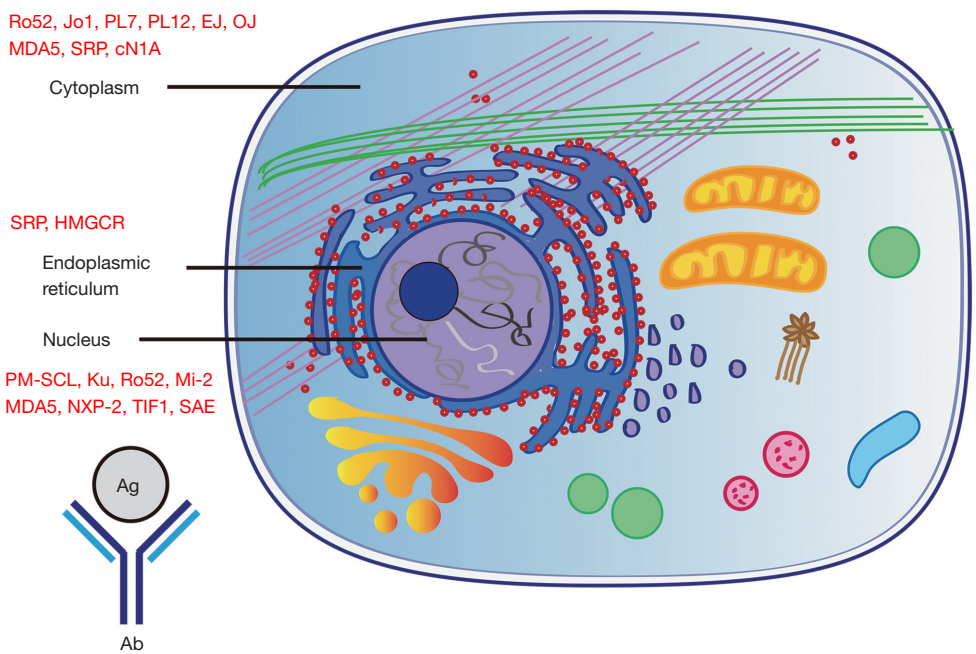

Figure 2 Distribution of autoantigens in human cells.

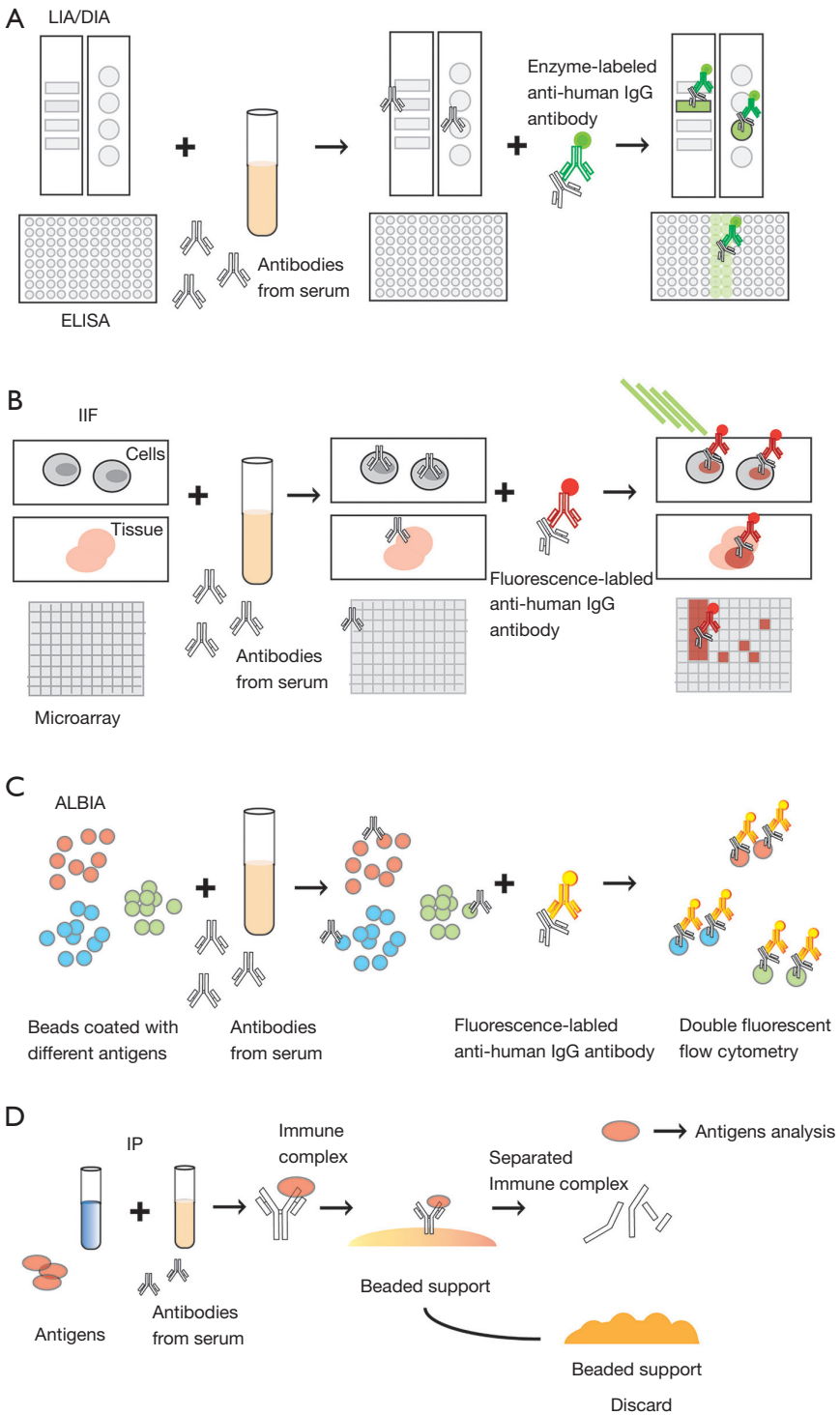

Figure 3 Mechanisms of different testing methods. (A) LIA/DIA and ELISA. (B) Indirect immune fluorescence and microarrays. (C) ALBIA. (D) Immunoprecipitation. LIA, line immunoassay; DIA, dot immunoassay; ELISA, enzyme-linked immune sorbent assay; ALBIA, addressable laser bead assay.

ASS and DM.

In addition, the functions of each autoantigen may contribute to unique clinical features of patients with certain autoantibodies. Most autoantigens have a wide distribution and are critical to cell functions. The reason why some organs are affected in IIM while others are not is not yet clear. The autoantigens might function falsely and disturb the biological process in which they participate. For example, transcription intermediary factor 1-alpha (TIF1-α) involves in the regulation of cell proliferation and apoptosis by ubiquitylation and by negatively regulating p53 levels (18). Transcription intermediary factor 1-gamma (TIF1-γ) acts as an E3 ubiquitin-protein ligase and also has a role in cell proliferation (19). Both of TIF1-α and TIF1-γ involve in crucial procedures in carcinogenesis. The coexistence of anti-TIF1-α and anti-TIF1-γ autoantibodies were reported to be correlated with a higher prevalence of malignancy (20).

Recently, some new autoantibodies have been shown to be associated with IIMs. Some anti-endothelial cell antibodies which bind to heat shock cognate 71KD protein and other chaperone proteins were identified in juvenile DM (21). The results provide new insights that anti-endothelial cell antibodies may contribute to vasculopathy of juvenile DM directly. Autoantibodies against PUF60, which locates in nucleus and plays a role in apoptosis, are associated with anti-TIF1 autoantibodies, clinically amyopathic DM (CADM) and skin ulcerations (22). Autoantibodies against eukaryotic initiation factor 3, a cytoplasmic complex of proteins, were found in polymyositis and showed correlation of good prognosis and response to treatment (23). Although it is increasingly difficult to find new specific autoantibodies, the discovery of new autoantibodies will bring light to studies of mechanisms of IIM.

Roles of autoantibodies in myositis

The roles of autoantibodies in the pathogenesis of myositis are not clear. There is no evidence to prove that autoantibodies associated with overlap syndrome, DM and ASS participate in the damage of muscle directly. However, the titer of autoantibodies in these disease might correlate with disease activity (24) and treatments response (25). On the contrary, anti-SRP antibodies and anti-HMGCR antibodies introduced muscle atrophy and impaired muscle regeneration (26) and participate in damage of muscle with activation of classical complement pathway (27). Anti-HMGCR antibodies titers correlated with creatine kinase levels and muscle strength, indicating a possible role in pathogenesis (28).

MAAs/MSAs in diagnostic criteria of IIMs

In 2004, the 119th ENMC international workshop included MSAs detected in serum into "other laboratory criteria" for the first time while the MAAs was not mentioned (29). The criteria emphasized the significance of autoantibodies, but the associations between autoantibodies and clinical characteristics of each disease were not completely understood. Additionally, some important MSAs, such as anti-HMGCR antibodies, had not been discovered yet. In the 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile IIMs and their major subgroups, only anti-Jo1 antibodies were included due to low frequency of other antibodies documented (30). In 2017, Suzuki *et al.* (2) put forward an integrated diagnostic project of IIMs which proposed that diagnosis of IIMs should emphasize both muscle pathology and MSAs detection in addition to clinical features. To *et al.* (31) also thought that the introduction of MSAs brought better performance of myositis classification criteria because MSAs usually correlate with distinct phenotypes of IIMs. As the significance of MSAs in classification and management of IIMs has been demonstrated by multiple researches, the inclusion of MSAs by diagnostic criteria should be put on the agenda. Besides, as MAAs have been found to be associated with clinical conditions such as comorbidity and prognosis, clinical suggestions should be included in the criteria as well (32,33).

MAAs/MSAs in IIMs

MAAs in overlap myositis

Overlap myositis refers to myositis combined with other types of CTDs, which might be the largest subtype within IIMs in adult patients. Anti-PM-SCL antibodies were detected in 4–12% patient with overlap syndrome in total (32) and less common in juvenile patients (34). Muscle weakness was present at onset in only 37% of anti-PM-SCL positive patients while 93% finally developed weakness during follow-up (35). PM and scleroderma overlap syndrome is most commonly associated with anti-PM-SCL autoantibodies (36). We found skin changes can be various and easily ignored, which need careful examination (37). Marie *et al.* (38) reported that ILD was frequent (60%) and

oesophageal involvement occurred as a severe complication in anti-PM-SCL autoantibodies. Long-term outcome of PM/DM patients with anti-PM-SCL autoantibodies showed remission in 10% of patients and deterioration in 20% patients which suggested anti-PM-SCL autoantibodies as a poor prognostic marker. Anti-PM-SCL antibodies should be tested when patients have progressive muscle weakness along with oesophageal involvement even if MSAs tests are negative.

Anti-Ku autoantibodies was found in 1–2% DM, 1–3% PM, and 9–19% overlap syndrome (32). Common clinical features of anti-Ku positive patients with IIMs included myalgia (91%), proximal muscle weakness (89%), and dysphagia (36%). Rare symptoms such as camptocormia were also found in anti-Ku positive patients (39,40). The anti-Ku associated overlap syndrome includes a wide range of CTDs including scleroderma, Sjögren syndrome and systemic lupus erythematosus (SLE) (41). ILD was corticosteroid-resistant (75%) and was more frequent in patients with IIMs (82%) than without (10.5%) (41).

Anti-Ro/SSA antibodies, including anti-Ro60 and anti-Ro52 autoantibodies, are another common antibodies in overlap syndrome, which was most common in Sjogren's syndrome (42), and also found in SLE and scleroderma (42,43). Anti-Ro52 autoantibodies were also common in Jo1 positive patients, who had more severe IIMs and joint involvement, symptomatic ILD and cancer and lower survival rate (44). We retrospectively categorized 1,509 suspected myositis patients and found anti-Ro52 antibodies were most common, especially accompanied by presence of antisynthetase antibodies (unpublished data).

Besides, high concentration of anti-Ro52 autoantibodies also predicted acute progressive ILD and resistance to immunosuppressant treatment in anti-Jo1 positive ASS (45). In juvenile patients with myositis, anti-Ro52 autoantibodies were associated with ILD and more severe disease (46).

Histopathological changes of overlap myositis varied and sometimes non-specific. Primary inflammation was a prominent myopathological feature (67%) in anti-PM-SCL positive IIMs patients (47). Myofiber necrosis and regeneration were found in 78% anti-Ku positive patients (48). Patterns of muscle MRI of overlap myositis with different MAAs remained unknown.

MSAs in ASS

ASS is a disease consistent of all or some clinical manifestations of ILD, Raynaud's phenomenon, mechanics hands, arthritis, fever, cutaneous rash and IIMs. A meta-analysis of 27 studies (3,487 patients) reported that the most common antibodies of ASS were anti-Jo1 autoantibodies (9–24%). Other autoantibodies included PL7 (1–8%), PL12 (1–5%), EJ (0–3%), OJ (0–3%) and KS (0–3%) (32).

Anti-EJ, anti-PL12 and anti-PL7 autoantibodies were associated with DM skin disease involvement (49). Anti-Jo1 autoantibodies were more associated with muscle disease while anti-PL7 and PL12 autoantibodies were more associated with ILD (40,41), which were confirmed by another longitudinal cohort study (50). We found recurrent fever was common in our patients with anti-EJ antibodies and muscle damage. The mortality was thus higher in patients with anti-PL7 and PL12 autoantibodies due to presence of ILD. Another study found that patients with anti-EJ and anti-PL7 autoantibodies were more likely to present with ILD and then develop IIMs, and often developed more severe muscle weakness compared with anti-PL12, anti-OJ or anti-KS autoantibodies (49).

Myofiber necrosis or regeneration was the major histopathological change of ASS (65–75%) (48,51). Nearly half necrosis was found in perifascicular regions in patients with anti-aminoacyl-tRNA synthetases autoantibodies, especially in patients with anti-Jo1 autoantibodies (75.8%) (52). Diffused myofiber necrosis and regeneration was occasionally observed in ASS patients with anti-OJ (10%), anti-PL7 (4%) and anti-Jo1 (2%) autoantibodies (53). Endomysial fibrosis was rare (17%) compared with other kinds of IIMs (48). Ubiquitous sarcoplasmic MHC-I expression was generally observed while MHC-II expression was mainly observed in perifascicular myofibers. C5b-9 deposition was specifically observed on sarcolemma of non-necrotic fibers in perifascicular regions rather than capillaries (54).

A cross-sectional study of thigh muscle MRI changes in ASS showed that muscle edema was pronouncedly observed in anterior groups while fatty replacement was dominantly observed in posterior groups. Anti-Jo1 positive patients showed higher muscle edema score, total edema score, total damage score and total MRI score compared with anti-Jo1 negative patients (55).

MSAs in DM

DM patients usually have skin rashes and muscle weakness, and some have ILDs, arthropathy and other rheumatic symptoms. DM is also clinically heterogeneous among and within each subgroup with different autoantibodies. Some

subgroups had unique skin changes. Anti-SAE positive patients commonly (75%) had distinctive diffuse dark-red or pigment-like skin rashes in a Chinese cohort (56). Anti TIF1-γ autoantibodies were associated with more extensive skin lesions which had a striking photoexposed pattern (54%), including significantly higher frequencies of scalp rash, facial rash, V-neck rash, and back rash. Novel cutaneous features also included palmar hyperkeratotic papules, psoriasiform lesions and unique hypopigmented and telangiectatic ("red on white") patches (57). Anti-MDA5 autoantibodies were found to be associated with characteristic cutaneous manifestations of hand swelling, arthritis, skin ulceration, palmar papules, mechanics hands, panniculitis, alopecia and oral ulcers (58). Subcutaneous tissue was also involved in anti-NXP-2 positive patients including subcutaneous edema (59) and subcutaneous calcinosis which occurred early and disseminated rapidly (58).

Muscle weakness always affects the proximal of limbs in DM. Patients with anti-NXP-2 autoantibodies usually had severe muscle weakness in proximal and distal of limbs, as well as in the neck. Dysphagia was common in anti-NXP-2 positive patients (60) as well as anti-SAE positive patients (61). On the contrary, anti-MDA5 autoantibodies were associated with CADM or slight muscle weakness (58). It was noteworthy that patients with anti-SAE autoantibodies commonly developed skin disease a few months prior to the onset of muscle weakness. Diagnosis of CADM should be made carefully in anti-SAE positive patients (61,62).

ILD was significantly associated with anti-MDA5 autoantibodies (58,63,64). Researches from both Asia (65-67) and Western countries (68,69) demonstrated that anti-MDA5 autoantibodies were also associated with rapidly progressive ILD, which is a predictor of poor outcome. Forty-six percent of patients died of respiratory failure within 6 months of disease onset (70).

Anti-SAE, anti-TIF1 and anti-NXP-2 autoantibodies were all associated with malignancy in IIMs (71,72). Patients with anti-TIF1-γ autoantibodies had a malignant rate of 48% (73) while had a malignant rate of 73% together with anti-TIF1-α autoantibodies (20). Recent studies demonstrated that anti-TIF1-γ autoantibodies were not associated with solid tumor nor paraneoplasmic rheumatic syndrome, making it a specific marker for cancer-associated DM (74). Patients with anti-NXP-2 autoantibodies also had an increased risk of malignancy, especially in patients above 60 years old (75). The types of malignancy varied significantly and included both solid and hematological malignancies (59,76).

Perifascicular atrophy and C5b-9 deposition on capillaries are characteristic histopathological changes in DM. The frequency of perifascicular atrophy varied between DM with different MSAs, including 67% in anti-Mi-2 positive patients, 64% in anti-TIF1-γ positive patients, 65% in anti-NXP-2 positive patients and 40% in anti-MDA5 positive patients. Mitochondrial dysfunction was another characteristic change in DM which was common in anti-TIF1-γ and anti-MDA5 positive patients (47). Muscle ischemic changes was common in juvenile anti-NXP-2 positive patients and indicated a severe subtype (77).

Muscle, fascial and subcutaneous edema were typical MRI changes in DM. In a study combined with muscle MRI and histopathology findings, significant association was found between inflammatory infiltrate and both muscle and fascial edema. Besides, muscle edema was found to be associated with pouched-out vacuoles (78). Differences of MRI changes between patients with different MSAs remain unknown.

MSAs in IMNM

Skeletal muscle involvement is principal in IMNM, barely accompanied with extramuscular manifestations and usually with poor recovery (79). Anti-SRP and anti-HMGCR autoantibodies are crucial for the diagnosis and the prognosis (80,81). Muscle atrophy and refractory to immunotherapy made it difficult to distinguish anti-SRP positive or anti-HMGCR positive IMNM from muscular dystrophy (5,82).

IMNM with anti-SRP autoantibodies present generally in adults and rarely in children (83), and was associated with severe muscle weakness, a high level of creatine kinase and requirement of aggressive treatment. Younger onset was associated with more severe weakness whether patients had improved strength after treatment of immunosuppression or not. Most of them had ongoing disease activity demonstrated by elevated creatine kinase levels (82). Anti-SRP autoantibody titers correlated with improvement of muscle strength after treatment, indicating it a helpful marker for monitoring of disease (84).

Although anti-HMGCR autoantibodies were firstly found in statin-associated autoimmune myopathy, not all anti-HMGCR positive patients with IMNM had a history of exposure to statins (85). In addition, anti-HMGCR autoantibodies were absent in severe self-limited statin-related myopathy (86), strengthening the association with IMNM (81). Anti-HMGCR positive IMNM was

occasionally observed in children and often resembled limb-girdle muscular dystrophy (81). Juvenile patients could have extremely high creatine kinase levels, severe disease and poor response to treatment (87,88). Anti-HMGCR autoantibody titers were associated with creatine kinase levels and muscle strength improvement after treatment, suggesting it a marker for disease activity (89).

The main histopathological changes of anti-SRP and anti-HMGCR positive IMNM were myofiber necrosis and regeneration while extent of myofiber necrosis and regeneration was higher in anti-SRP positive patients than in anti-HMGCR positive patients. Sarcolemmal deposition of C5b-9 was also prominent in both anti-SRP and anti-HMGCR positive patients. In addition, C1q and immunoglobulin G deposition were found close to sarcolemma. Inflammatory infiltrate was common and CD68 positive cells were most abundant (27). In chronic cases, marked endomysial fibrosis was observed which was hard to distinguish from muscle atrophy (81,90).

MRI changes of IMNM include higher proportion of muscle edema, fatty replacement and atrophy while fascial and subcutaneous were less involved. Lateral rotator and gluteal muscular groups were most affected. Anti-SRP positive patients had more muscle atrophy and fatty replacement than anti-HMGCR positive patients, indicating more severe muscle involvement (91). Additionally, anti-SRP positive patients with striking fatty replacement were refractory to therapy, suggesting MRI a good method for monitoring treatment response (92).

Autoantibodies in IBM

Patients with IBM have finger flexor and quadriceps weakness and are easily to be misdiagnosed as chronic PM and receive multiple immunotherapy. Thus, the discovery of autoantibodies against cytosolic 5'-nucleotidase 1A (cN1A or NT5C1A) brought insights into the immunopathogenic mechanisms of IBM (93). Anti-cN1A autoantibodies were detected in 30–50% of patients with IBM (94), who were more likely to be older than age 60 years at disease onset (95). Lilleker *et al.* (96) have reported that anti-cN1A positive patients had a higher adjusted mortality risk compared with anti-cN1A negative patients indicating it a prognostic marker. Nevertheless, anti-cN1A autoantibodies were also found in other autoimmune diseases such as Sjögren syndrome and SLE (97). Besides, Yeker *et al.* (98) found anti-cN1A autoantibodies were present in 27% children with juvenile myositis and juvenile idiopathic arthritis compared with 12% in healthy children. These results make it controversial whether anti-cN1A autoantibodies are specific for IBM.

Endomysial inflammatory infiltrates and rimmed vacuoles were typical histopathological changes of IBM. Increased expression LC3, TDP-43 and p62 were observed in the vacuoles. Mitochondrial deficiency in NADH staining and in cytochrome oxidase staining was also commonly observed (99). Muscle edema and fatty replacement were observed in MRI of IBM patients and the anterior group of thighs were more involved. The severity of disease in MRI increased from proximal to distal muscles (99).

Conclusions

The presence of MAAs or MSAs in patients aid clinicians to make more precise diagnosis, classification and management of IIMs. Thus, detection methods of MAAs/MSAs should be properly chosen and the results should be prudently interpreted. Further studies of roles of autoantibodies and autoantigens in immunopathogenesis will provide insights into immunotherapy and prediction of prognosis.

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Footnote

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