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REVIEW ARTICLE

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Myositis an evolving spectrum of disease

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ABSTRACT

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of disorders characterized, as common feature, by inflammation of skeletal muscle and muscle weakness. Traditionally, IIMs have been subclassified in into polymyositis, dermatomyositis and inclusion body myositis, but this subclassification has several limitations, because clinical features as well as treatment response vary within the three IIM subgroups. In the last years several novel autoantibodies in patients with IIMs have been identified. These autoantibodies can be myositis-specific autoantibodies (MSAs) or myositis-associated autoantibodies (MAAs) and they may lead to a new approach to the classification of IIMs. This novel approach could help to subdivide patients in more homogeneous groups because, it is very rare that a patient has more than one MSAs positivity and each autoantibody is frequently associated with specific clinical features. Moreover, MSAs can help to identify subsets of IIMs also without muscular symptoms, like patients in which skin manifestations, arthritis or interstitial lung disease represent the main clinical feature. Additionally, as some autoantibodies may be associated to markedly severe manifestations, such as cancer or rapidly progressive interstitial lung disease, they can also provide a prognostic stratification of the patients.

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Myositis; idiopathic inflammatory myopathies; autoantibodies; clinical phenotype

1. Introduction

The idiopathic inflammatory myopathies (IIM) or collectively named myositis constitute a heterogenous group of disorders that, based on different clinical and histopathological features, for decades have been sub grouped into polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM) [1]. These are rare disorders and treatment response is often disappointing leaving many patients with persisting muscle weakness, functional impairment and low health related quality of life [2,3]. Thus, there is an unmet need for new treatment modalities. To develop new therapies, we need to improve knowledge of pathophysiology of myositis including molecular mechanisms in early phase of disease as well as in chronic established disease. Clinical features as well as treatment response vary between the three IIM subgroups, polymyositis, dermatomyositis and IBM, therefore it is likely that different molecular pathways predominate between these subgroups. Furthermore, even within these subgroups we see different clinical manifestations and various prognosis suggesting that even within these traditional subgroups of IIM the molecular mechanisms may not be the same. On the other hand, there are similarities such as muscle biopsy features, that may be similar in patients classified as PM and IBM and also in patients classified as DM and PM, emphasizing the limitation of subclassifying patients into these three major subgroups of IIM as has also been discussed elsewhere [4]. Additional subgroups have been proposed such as unspecific myositis [5] and clinic-serologically defined myositis [6]. Overall, the classifications used for these subgroups so far have required a significant myopathy with clinical manifestations of muscle weakness as well as signs of inflammation in muscle tissue.

An interesting observation over the last decade is the high number of cases diagnosed with IIM having extramuscular manifestations such as skin rash, interstitial lung disease (ILD) or arthritis, where the extramuscular manifestation is the predominating symptom and where muscle symptoms are absent, such as in amyopathic dermatomyositis. Furthermore, there are patients where the extramuscular features are the presenting manifestations [7]. To identify these cases early as being part of the myositis disease spectrum an increased awareness of the broader phenotype of IIM is essential. A move forward in this direction was the development of the

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2017 EULAR/ACR classification criteria for adult and juvenile onset idiopathic inflammatory myopathies. These criteria classify patients as IIM and subgroups based on a probability score and by using these criteria a patient can be classified as having IIM without any signs of myopathy but with typical skin rash of DM, amyopathic DM [8]. To improve our understanding of the pathophysiology of myositis we need to rethink the IIM as a broad spectrum of disease.

One important scientific achievement, that has had a major influence in our observation of the changing spectrum of the IIMs, is the identification of several new autoantibodies that are present in patients with IIM. These autoantibodies can be divided into myositis specific autoantibodies (MSA) that are mainly found in patients with IIM and myositis associated antibodies (MAA) that can also be detected in patients with other autoimmune diseases like systemic lupus erythematosus (SLE) or Sjögren's syndrome [9]. The new MSAs have been discovered by the use of immunoprecipitation (IP) in clinically well-defined patient cohorts. Immunoprecipitation is an extremely valuable method to detect new antigen specificities but it is a tedious and costly method that limits its use in clinical practice. Over the last years line blot assays and ELISAs have been developed that enable testing of sera in clinical routine [10–12]. The sensitivity and specificity of these tests for several of the antigen specificities are still unknown and there is a strong need to validate these autoantibody tests. This could and should be done in an international collaboration.

2. Serological and clinical phenotypes of IIM

The myositis specific autoantibodies (MSAs) are not only helpful in the diagnosis of IIM in relation to other disorders but are also helpful to identify clinical subgroups of IIM as the MSAs are also closely associated with distinct clinical phenotypes as reported already with identification of the first MSAs [13]. There is also an emerging data to suggest that the histopathology features of muscle biopsies may be more closely associated with the MSA phenotypes than the previously used subgrouping of IIM into PM, DM and IBM.

The first identified MSAs were anti-Jo1, anti-Mi-2 and anti-SRP [13]. There are now more than 15 MSAs, some more common like anti-Jo1 and some very rare. There are also ethnic differences in prevalence of MSAs, and the clinical phenotype associated with a specific MSA may vary between different ethnic groups [9]. Thus, international collaborations are critical in research to develop further understanding on the role of these autoantibodies as a tool in diagnostics and in research to understand if they have a role in pathogenesis.

3. Anti-tRNA synthetase autoantibodies

The MSAs can be subdivided into groups in their relation to clinical phenotypes. Of the MSAs the autoantibodies that target the tRNA synthetases are the most frequent and called anti-tRNA synthetase autoantibodies, of which anti-histidyl-tRNA synthetase antibodies (anti-Jo1) are the most common, present in up to 20%–30% of patients with IIM. The anti-tRNA synthetase autoantibodies are associated with a distinct clinical phenotype called antisynthetase syndrome (ASS) where myositis is one clinical manifestations and other manifestations are interstitial lung disease (ILD), arthritis, Raynaud's phenomenon and a skin rash named mechanic's hands as first described by Dr L. Love [13]. There are now eight identified anti-tRNA synthetase autoantibodies targeting different tRNA synthetases (anti-Jo1, anti-PL7, anti-PL12, anti-EJ, anti-OJ, anti-Ha, anti-Zo and anti-KS; Table 1) [9]. Importantly, an extramuscular manifestation can be the presenting symptom and can even predominate the clinical phenotype of ASS, and some patients do not experience muscle weakness or develop laboratory signs of a myopathy [14]. In a Spanish cohort 148 of patients with ASS 32.4% presented with ILD, 26.9% with myositis, 17.9% with arthritis and 22.8% with ILD and myositis [7]. Over the years even under immunosuppressive treatment 81.8% had developed ILD and 67.6% had developed ILD and myositis.

Although they are all associated with the clinical ASS, the predominating features of the ASS vary between these anti-tRNA synthetase autoantibodies. Patients with anti-Jo1 antibodies have a high frequency of myositis and ILD [7,14]. Whereas patients with anti-PL12 and PL7 have a high frequency of ILD. Anti-PL7 antibodies have also been associated with pericarditis [15]. Anti-EJ antibodies are associated with higher prevalence of ILD with frequent relapses, skin rash and lower frequency of arthritis/arthralgias [16,17]. Patient with anti-Jo1 and PL-7 have also been reported to have a higher incidence of arterial pulmonary hypertension compared to controls [18–20], even if more recent data did not confirm these observations (Table 1) [21].

The tRNA antisynthetase autoantibodies target enzymes that facilitate binding of a tRNA to a specific amino acid to form peptides. How and why these intracellular enzymes that are important in the protein synthesis become autoantigens is not known, nor is it known if they have a role in pathogenesis of IIM or constitute an epiphenomenon. The antisynthetase autoantibodies are associated with different HLA-DR type, suggesting that they have a role

Table 1. Antisynthetase autoantibodies and clinical characteristics.

Antibody	Target tRNA synthetase	Prevalence	ILD	PAH	Myositis	Arthritis	Fever	Mechanic's hand	Raynaud phenomenon	Dysphagia	Pericarditis	Ref
Anti-Jo1	Hystidyl-	20–30	++++	++	++++	+++	+	++	+	−/+	−/+	[16,21,46,49,67]
Anti-PL7	Threonyl-	5–12	++++	+	++++	+++	++	++	++	+	++	[15,16,21,49,67]
Anti-PL12	Alanyl-	5–17	++++	++	+++	++	++	++	++	+	+	[16,21,47,67]
Anti-EJ	Glycyl-	1–10	++	−	++	+	++	++	+	+	+/−	[16,21,67]
Anti-OJ	Isoleucyl-	1–5	++++	−	+	+	+	++	+	N.A.	N.A.	[21,67]
Anti-KS	Asparaginyl-	1–5	++++	N.A.	+	++	+	+	++	N.A.	N.A.	[67]

Legend: −, no correlation; −/+ <5%; +, 5%–25%; ++, 26%–50%; +++, 51%–75%; ++++, >75%.
ILD: interstitial lung disease; PAH: pulmonary artery hypertension; N.A.: not available.

in immune activation of patients with these antibodies [22]. Little information is available about other risk factors than HLA-DR type. However, in one study smoking was found to be a risk factor for anti-Jo1 antibodies among patients with myositis, which may suggest that lung exposure to toxins or infections may contribute to the pathogenesis of this subgroup of IIM: there was also an association between smoking and HLA-DR B1*03 and anti-Jo1 antibodies which may indicate a gene environment interaction but more research is needed to confirm this hypothesis [23]. There is no internationally agreed upon classification of ASS. The most often used to classify a patient as having ASS to date is presence of one clinical manifestations of ASS together with one antisynthetase autoantibody [24]. For future research there is a need for internationally agreed upon classification criteria for ASS and such an effort is planned in an international collaboration under the ACR-EULAR umbrella.

4. Autoantibodies in patients with skin rash – Dermatomyositis

The first identified MSA to be associated with skin rash typical of dermatomyositis was the anti-Mi2 antibody (Table 2) [13]. Anti-Mi2 antibodies are typically associated with rash in sun-exposed areas such as heliotrope rash, V-sign and shawl-sign as well as Gottron's sign and cuticular overgrowth [13]. In longitudinal studies this subgroup of patients with IIM has been reported to have a good prognosis [13,25].

Anti-TIF1 gamma antibodies, present in 13%–31% of patients with DM [26–28], are associated with some typical skin rashes of DM: palmar hyperkeratotic papules, psoriasis-like lesions, hypopigmented and telangiectatic patches, and with muscle weakness (Table 2). Importantly anti-TIF1 gamma antibodies are in adult patients with DM associated with a risk of malignancies as discussed below.

Anti-NXP2 antibodies are associated with peripheral edema, calcinosis, milder skin lesions (relative to dermatomyositis associated with other autoantibodies), and a low frequency of Gottron's sign [29]. Adult patients with anti-NXP2 antibodies usually have muscle weakness.

Anti-melanoma differentiation-associated protein 5 (MDA5) antibodies are associated with ulcerations over the interphalangeal joints, palmar erythematous macules and papules over the interphalangeal joint creases, and palmar and fingertip mottled erythema [30,31]. Patients with anti-MDA5 often present with no or mild muscle weakness, so called amyopathic or hypomyopathic DM [32].

Table 2. Clinical associations between autoantibodies associated with skin rash in patients with IIM.

Antibody	Prevalence in IIM	Heliotrope rash	Gatton's sign/papules	V-sign	Periungual changes	Skin ulcers	Myositis	ILD	Cancer	References
Mi-2	9.3–35	+++	++++	++++	++++	−	++++	−/+	−/+	[30,65,68–70]
Tif1-gamma	3.5–20.9	+++	++++	++++	++	−/+	+++	−/+	++++	[26,27,30]
MDA5	7	+++	+++	+++	+++	+++	++	+++	−/+	[30,31,71]
SAE	1.2–4.1 (4–10 JDM)	++	++++	++	++	−	++++	−	−	[9,65,72]
NXP2	1.2–17.2 (23–25 JDM)	+++	+	+++	+++	+	++++	−	++	[29,65,73,74]

Legend: −, no correlation; −/+, <5%; +, 5%–25%; ++, 26%–50%; +++, 51%–75%; ++++, >75%.
ILD: interstitial lung disease; JDM: juvenile dermatomyositis.

Anti-SAE autoantibodies are antibodies targeting Anti-SUMO-activating enzyme (SAE). Anti-SAE antibodies are often associated with an initial presentation of amyopathic dermatomyositis, sometimes with quite severe rash, and a subsequent progression to IIM with a high incidence of severe dysphagia [33].

Antisynthetase antibodies are associated with mechanic's hands as described above.

5. Autoantibodies associated with amyopathic dermatomyositis

The term clinically amyopathic dermatomyositis, for patients with typical skin rash of DM but without clinical signs of muscle weakness was suggested by Dr. Euwer and Sontheimer in 1993 [34]. These individuals are defined by cutaneous manifestations of classical dermatomyositis that occur for 6 months or longer with no clinical evidence of proximal muscle weakness and no serum muscle enzyme abnormalities [34]. The term amyopathic dermatomyositis also encompasses patients with clinically mild myopathy, called hypomyopathic DM [35]. The skin rash in patients with amyopathic dermatomyositis is not different from classical DM. It is not pathognomonic and may resemble skin rash seen in patients with psoriasis, eczema, and multicentric reticulo-histiocytosis. Therefore in patients with skin rash suggesting DM but without clinical signs of myositis a skin biopsy is recommended to rule out other skin disorders [36].

Amyopathic DM is associated with anti-melanoma differentiation-associated protein 5 (MDA5) antibodies [37]. Also, adult patients with the less prevalent anti-small ubiquitine-like modifier enzyme (SAE) antibodies may present with amyopathic dermatomyositis but may then develop clinical signs of myopathy with muscle weakness and sometimes with severe dysphagia [38,39].

Patients with amyopathic dermatomyositis may develop other organ manifestations such as malignancies and ILD. In particular patients with anti-MDA5 antibodies with clinically amyopathic DM have a high risk to develop ILD, as discussed below.

6. Autoantibodies associated with cancer

That adult patients with IIM have an over risk for malignancies, in particular patients with DM, has been well known since 1916 [40]. Up to ∼20% of patients with DM have a malignancy [41]. The risk of having a malignancy in patients with DM is highest within 3 years from DM diagnosis, suggesting that DM in these cases could be a paramalignant phenomenon [41]. This form of dermatomyositis is often called cancer associated DM. The association between cancer and the other myositis subgroups is less clear. In clinical practice the association between malignancy and DM implicates a screen for malignancies in adult patients with new onset DM and during follow-up, in particular, if patients are not responding to immunosuppressive treatment. There are currently no international guidelines how to perform cancer screening in patients with myositis.

Until recent years there has been no biomarker to flag for myositis associated cancer. A break through recently is the discovery of two MSAs that are associated with an increased risk of malignancies in adult patients with IIM. Both these MSAs are associated with DM skin rash and malignancy, anti-TIF1 gamma also known as E3 ubiquitin-protein ligase TRIM33 and anti-NXP2 also known as antibodies against MORC family CW-type zinc finger protein 3 [42]. Anti-TIF1 gamma antibodies are the more prevalent in adult cases of these two antibodies. The frequency of TIF1 gamma in cancer associated DM is up to 78% and the positive and negative predictive value for cancer in patients with anti-TIF1 gamma antibodies were 6.29 and 0.25 in a meta-analysis [28]. Interestingly, the anti-TIF1 gamma antibodies are only seen in patients with DM and these antibodies are mainly associated with cancer detected within three years of DM diagnosis [42,43]. The TIF1-gamma antibodies may be present before cancer diagnosis and may disappear with successful treatment of cancer [44]. More information is needed about the longitudinal development of anti-TIF1 gamma antibodies and to understand if the antibodies have a role in the pathogenesis of DM and cancer.

The anti-NXP2 antibodies are also associated with cancer and DM but they are less prevalent than anti-TIF1 gamma antibodies [9,42].

7. Autoantibodies with ILD

As described above, interstitial lung disease (ILD) is frequently seen in patients with IIM. The overall frequency of ILD in patients with PM and DM was up to 78% when patients were screened regularly for ILD [45]. In patients with certain MSAs or myositis associated antibodies, ILD may be even more frequent. Thus, in patients with anti-Jo1 antibodies ILD was reported in up to 76% [46], and in relation to other antisynthetase autoantibodies ILD was found in 90% of patients with anti-PL12 [47], 77% in patients with PL7 [15]. The remaining anti-synthetase antibodies are rare and epidemiological data are scarce, but ILD can be present with all anti-synthetase autoantibodies (Table 1) [16].

The frequency if ILD in patients with anti-MDA5 antibodies is high. In a Japanese study 93% of patients with anti-MDA5-antibodies had ILD. In the same cohort 77% of patients who had clinical amyopathic DM had ILD [30].

The pattern of ILD seems to vary between anti-synthetase associated ILD and ILD associated with anti-MDA5 antibodies in that ILD in patients with anti-synthetase antibodies is often of the non-specific interstitial pneumonia (NSIP) or Usual interstitial pneumonia (UIP) type, which are usually slowly progressive. Contrary, the ILD in patients with anti-MDA5 antibodies is often of the phenotype of rapidly progressive ILD with high risk of mortality [48].

Anti-PM-Scl, one of the myositis associated antibodies is also associated with an increased risk of ILD [49,50].

Anti-Ro antibodies, another myositis associated antibody is often found together with anti-Jo1 antibodies. The combination of anti-Jo1 and anti-Ro antibodies seems to be a risk factor of a more aggressive ILD with a poor prognosis compared to ILD in patients with only one of these antibodies [51].

8. Autoantibodies associated with necrotizing myopathy

Two of the myositis specific autoantibodies are associated with a so called necrotizing myopathy, anti-signal recognition peptide (SRP) and anti-hydroxymethylglutaryl coenzyme A reductase (HMGCR) antibodies [52–54]. Necrotizing myopathy is characterized by muscle weakness, high serum levels of muscle enzymes such as CK and by presence of necrotic muscle fibers in muscle biopsies. Inflammatory infiltrates often characteristic of an inflammatory myopathy are often scarce or not detected. Necrotizing myopathy can also be found in individuals with cancer or in patients with some muscle dystrophies. The discovery that necrotizing myopathy can be associated with autoantibodies have led to the hypothesis that these antibodies could have a role in the pathogenesis of necrotizing myopathy and this has even been suggested in naming of this entities of IIM as immune mediated necrotizing myopathy (IMNM) [55]. Some recently published experimental data supports that anti-SRP and anti-HMGCR antibodies may have an effect on proliferation and differentiation of myotubes but evidence is still lacking that these antibodies cause muscle fiber necrosis [56].

9. A muscle specific autoantibody, anti-FHL1 antibody

All the above discussed autoantibodies that are mainly present in patients with IIM target ubiquitously expressed antigens, present in all cell types and do not explain why muscle cells become target of the immune system. This was the background for a study which started by screening a muscle cDNA library with sera from patients with IIIM to identify muscle specific autoantibodies. Through a serial of experiments FHL1 was identified as a muscle specific antigen that was targeted by autoantibodies in patients with IIM [57]. This autoantibody was rarely found in other systemic rheumatic diseases and not in neuromuscular disorders suggesting this antibody to be myositis specific. Furthermore, anti-FHL1 antibodies were associated with a severe myopathy, often with clinical muscle atrophy and pronounced histopathological changes with accumulation of fat and connective tissue in muscle biopsies [57]. Patients with anti-FHL1 antibodies also had a worse prognosis with progressive muscle weakness despite immunosuppressive treatment compared to patients with IIM who were anti-FHL1 negative. Whether the anti-FHL1 antibodies are involved in the pathogenesis or are a consequence of disease still needs to be determined [58]. The antiFHL1 antibodies are not yet available for commercial testing.

10. Autoantibodies associated with IBM

An antibody, anti-cytosolic 5′-nucleotidase 1 A (CN1a) was detected primarily in patients with IBM and not in patients with PM or DM and was considered to be specific for IBM [59]. However, later this antibody was also detected in patients with SLE and Sjögren's syndrome thus this antibody could be determined a myositis associated antibody [60]. Patients with IBM and anti-C1Na were found to have similar prognosis compared to antibodies negative patients [61].

11. Autoantibodies in juvenile dermatomyositis

In JDM different MSA and MAA have been detected. Anti-TIF1 gamma is the most common autoantibody detectable in 18%–25% of JDM and was associated with a more severe skin involvement with ulceration and greater muscle weakness [62,63]. Anti-NXP2 (present in 15% of patients) was associated with severe muscle weakness and skin calcinosis [64,65]. Contrasting data about the prevalence of ILD and the rapidly progressive ILD in anti-MDA5 positive Juvenile DM [62,65] has been reported [66]. Other autoantibodies are uncommon in patients with juvenile myositis.

12. Conclusions

Myositis specific autoantibodies are associated with distinct clinical phenotypes, and are helpful in the diagnosis as well as sub-diagnosis of patients with IIM. Although the different autoantibodies are associated with distinct clinical phenotypes, little information is available on the effects of MSAs on treatment response and prognosis. This is an important area of research that needs to be performed in international collaborations that include large enough cohorts of patients to permit subgrouping according to autoantibody profiles and clinical manifestations and with longitudinal data. Moreover, in patients with IIM overall ~50% have detectable autoantibodies [9]. The explanation for the antibody negative cases could be that novel autoantibodies are still to be detected, or that other molecular mechanisms than involvement of the specific immune system may predominate in the antibody negative subgroup. Naturally, if so, this will be important to determine as treatment response may differ depending on molecular pathogenesis.

The recognized changing of clinical phenotypes of patients within the myositis disease spectrum has consequences in several ways one being that patients may initially present in other clinics than those usually take care of patients with IIM; rheumatology, dermatology or neurology clinics, but may also present in pulmonary disease clinics or early arthritis clinics. Thus, an increasing awareness of these patients with autoimmune systemic disease is needed to avoid delay in diagnosis and treatment that may have a negative impact on prognosis.

Disclosure statement

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