

Myositis Specific Autoantibodies: A Clinical Perspective

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Abstract: Dermatomyositis (DM) is an idiopathic inflammatory condition characterized by myositis and variable skin manifestation. The existence of myositis specific autoantibodies usually manifests with varying degrees of skin or muscle inflammations. The condition has a well-established association with most clinical phenotypes, and these autoantibodies are useful in informing the diagnosis, management and prognosis of the disease. DM-specific autoantibodies include anti-MDA5, anti-NXP2, anti-SAE, anti-Mi-2, anti-ARS, anti-TIF1-gamma. Anti-Mi-2 antibodies are widely associated with DM cases that exhibit mainly cutaneous symptoms, such as cuticular overgrowths, Gottron's papules while being less susceptible to complications like interstitial lung disease or malignancy. The most distinct clinical features of patients with anti-SAE antibodies are their high prevalence of dysphagia and cutaneous manifestations that antecede the development of myopathies. In addition, DM patients with positive anti-PL-7 antibodies tend to have milder myositis characterized by low levels of creatine kinase as compared to patients with positive anti-Jo-1 antibodies. The anti-NXP2 antibodies are associated with transcriptional regulation and production of various proteins targeted by other DM antibodies, while anti-TIF1- γ facilitates the transcription of deoxyribonucleic acids and regulates the growth and subsequent differentiation of body cells by controlling the signaling of TGF- β . The present review targets DM specific autoantibodies, considering their association, significance, and clinical presentation

Keywords: dermatomyositis, specific autoantibodies, clinical presentation

Introduction

Dermatomyositis (DM) is an idiopathic inflammatory condition characterized by chronic inflammation of the skin and muscle. Muscle involvement usually manifests in the form of symmetrical proximal muscle weakness, with or without myalgias. A skin rash usually appears before or during muscle weakness and its manifestations can be quite variable, affecting the skin around the eyes (heliotrope rash), or over the knuckles (Gottron's papules) which are hallmark signs of DM. Some patients have less common (V-sign, and shawl sign, holster sign and cuticular overgrowth) and nonspecific (periungual telangiectasias, calcinosis, poikiloderma and vesiculobullous lesions) skin manifestations.¹⁻⁶ Besides, the most common complications of DM are interstitial lung disorders and malignancy.

Serologic as well as clinical traits of DM tend to vary between populations as well as individuals who are affected. This variation largely depends on immunogenetic traits and apparently due to possible environmental triggers.⁷ There is distinctness in terms of immune mechanisms and anatomic focus of injury in the

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muscle tissue in DM. There are two other major immune mediated myopathies which comprise of immune mediated necrotizing myopathy (IMNM) an inclusion body myositis (IBM). Clinical findings along with certain serological markers are shared between IMNM and DM whereas, IBM and IMNM are found to have histopathologic findings with regards to biopsy of muscle which distinguishes it from DM.

Similar to other connective tissue disorders, a peculiar immunological characteristic exhibited by DM is the existence of autoantibodies, which tend to target various nuclear and cellular body components.⁸ These antibodies are significant as their presence suspected in patients with DM and used for a diagnostic, prognostic, or therapeutic approach in DM, as shown in Table 1. Some myositis-specific autoantibodies (MSAs) are differentiable, as they tend to be exclusively present in patients with idiopathic inflammatory diseases. DM-specific autoantibodies include anti-MDA5, anti-NXP2, anti-SAE, anti-TIF1-gamma, anti-ARS, anti-Mi-2 and SRP. These antibodies manifest with varying degrees of skin or muscle inflammations and have a close correlation with most clinical phenotypes.^{9–15} The present review targets DM specific autoantibody, considering their association, significance, and clinical presentation.

Table 1 Summarize the Myositis Specific Auto Antibodies and Their Clinical Perspective

Antibodies	Characteristic Clinical Spectrum
Anti-Mi-2 Antibodies	Cutaneous symptoms Good response to treatments Less susceptible to ILD or cancer
Anti-SAE Antibodies	Cutaneous manifestations Dysphagia
Anti-MDA5 Antibodies	Cutaneous manifestations ILD Risk
Anti-NXP-2 Antibodies	Calcinosis Malignancy Risk
Anti-TIF1-Gamma Antibodies	Malignancy Risk
Anti-ARS Antibodies	Types: Jo-1 PL-7 PL-12 OJ EJ KS Ha Zo

Anti-Mi-2 Antibodies

Autoantibodies targeting the nuclear antigen of Mi-2 is common in both adult and juvenile DM patients¹⁰ While these antibodies are disease-specific and tend to be indiscriminate with regards to age the frequency of anti-Mi-2 antibodies in adolescents is 5 to 10%, which is lower than adults suffering from the disease.¹⁰ Anti-Mi-2 antibodies are widely associated with DM cases that exhibit mainly cutaneous symptoms, such as cuticular overgrowths, Gottron's papules, Shawl and Heliotrope rashes. Clinically, patients with anti-Mi-2 positive antibodies tend to have mild tissue inflammations and respond well to treatments.¹⁶ Additionally, these patients are less susceptible to complications like interstitial lung disease (ILD) or malignancy. Therefore, DM with anti-Mi-2 antibodies is bound to have a relatively favourable prognosis. Studies in the past reported a strong association between anti-Mi-2 and DM with frequency up to 31% and high positive predictive value for such disease subset. For instance, the study by Yang et al (2017) reported that application of immunodiffusion and immunoprecipitation techniques for detection of DM reveals the existence of anti-Mi2 antibodies. In contrast, a study by Femia et al (2013) indicates that the use of enzyme-linked immunosorbent assay to test for these antibodies could illustrate varying distributions of DM which revealed that only fifty-six per cent of anti-Mi-2-positive patients had the disease while the others suffered from other idiopathic inflammatory myositis.¹⁰ While other, analyses conducted using gold standard immunoprecipitation assay indicate that anti-Mi-2 antibodies are exclusively found in DM patients, representing one of the MSAs.¹ UV-radiation from the sun encourages the amelioration of Mi-2 proteins in human keratinocytes, a factor that further highlights the potentiality of DM amongst individuals through the regulation of myoblast differentiation.¹⁷ These findings warrant a careful interpretation of using different anti-Mi-2 antibody detection methods.

Anti-SAE Antibodies (Anti-Small Ubiquitin-Like Modifier Activating Enzyme)

In 2007 anti-SAE (Anti-small ubiquitin-like modifier activating enzyme) antibodies were discovered by Betteridge and his colleagues in serum obtained from DM patients.^{18–20} Over the years, anti-SAE autoantibodies continue to be exclusively detected with at least 8.4% of DM patients.²¹

The most distinct clinical features of patients with these antibodies are a high prevalence of dysphagia and cutaneous manifestations that antecede the development of myopathies.¹⁸ Since it usually takes at least three months for myositis to set in after the initial development of cutaneous symptoms, patients that test positive for anti-SAE antibodies are usually diagnosed with clinically amyopathic dermatomyositis (CADM) following which they receive a DM re-diagnosis after the advent of muscle weaknesses. These antibodies also facilitate post-translational modifications and play a vital role in binding other proteins¹⁸.

The corresponding autoantigen is a minute ubiquitin kind of modifier which is said to trigger the enzyme. Such an antibody is particular to DM and is found to occur within 6–8 per cent of cases of DM in European groups. In contrast, the frequency is found to be quite low amongst Asian groups and have been recorded to range between 1.5–3 per cent of the adult patients with DM. Patients who are anti-SAE positive frequently emerge as CADM at the outset and later the advance to develop myositis with a superior frequency of systemic features. This is inclusive of dysphagia that occurs amongst 30–78 per cent of patients who are anti-SAE positive. Within European groups, anti-SAE does not seem to have any association with ILD however, it was quite common amongst Asian groups. According to Fujimoto et al²² have suggested that ILD of patients with positive anti-SAE within a Japanese group were generally quite mild and found to respond well to therapy. Such variations within the phenotype and frequency of patients might be linked with ethnicity.

Anti-ARS Antibodies (Autoantibodies Against Aminoacyl-tRNA Synthetases)

Shinji Sato and colleagues described some patients with positive Anti-Jo-1, with the former being the most prevalent of all the eight anti-ARS antibodies that have been detected till date.⁹ Interestingly, it is still quite difficult to identify more than one anti-ARS antibody within a serum from a single patient. As an outcome, these antibodies tend to be associated with similar clinical characteristics. These features are jointly known as “anti-synthetase syndromes” and are defined by myositis that is typically characterized by Raynaud’s phenomenon, interstitial lung disease (ILD), arthritis and mechanics hand.^{9,23,24}

Anti-ARS synthetase is those enzymes that are known to catalyse the bonding between amino acids to consistent transfer of RNAs to create aminoacyl-tRNAs, in a manner that is largely dependent on energies. As per evidence, around eight diverse RNAs have been recognized as auto-antigens of Myositis specific auto-antibodies (MSAs) and this is inclusive of anti-Jo-1 (histidyl-tRNA synthetase),²⁵ anti-PL-7 (threonyl), anti-PL-12 (alanyl), anti-EJ (glycyl), anti-OJ (isoleucyl), anti-KS (asparaginy), anti-Ha (tyrosyl) and anti-Zo (phenylalanyl) tRNA synthetase antibodies. Out of these, anti-Jo-1 is an antibody that is most commonly found amongst 15–25 per cent of DM patients, whereas all other anti-ARSs are generally found amongst 0–7 per cent of the cases.⁹

One of the most characteristic patterns of anti-ARS induced DM is a non-specific ILD. While anti-ARS syndromes might have similar clinical symptoms, differences are also likely to be observed depending on the type of anti-ARS antibodies that are prevalent amongst patients. Anti-Jo-1, anti-EJ, and anti-PL-7 antibodies have been proven to be closely related to myositis. In specific, DM patients with anti-PL-7 antibodies tend to have milder myositis characterized by low levels of creatine kinase as compared to patients with positive anti-Jo-1 antibodies.⁹

Anti-NXP-2 Antibodies

A new autoantibody was detected and duly, named as anti-MJ by Oddis and his colleagues in 1997, and subsequently in 2007 Targoff and fellow researchers renamed it to anti-NXP-2 autoantibodies.²⁶ Anti-NXP-2 antibodies have been well defined amongst juvenile DM²⁷ than in adults with a prevalence rate of 20%,²⁶ and usually associated with severe calcinosis, muscle atrophy, polyarthritis, joint contractures, and intestinal vasculitis.^{28,29} However, amongst adult DM patients with myositis, anti-NXP-s are detected in only 1%¹² of cases with a possible link between anti-MJ antibodies and a higher risk of malignancy indicating a poor prognosis.^{29,30} In studies conducted among adult DM patients, it has been suggested that these antibodies were associated with transcriptional regulation and the production of various proteins that are later targeted by other DM antibodies²⁸

A relation between anti-NXP2 and a substantial compromise with regards to functional status been suggested by Espada et al³¹ which was characterized with atrophy and contractures in the muscle within a pediatric group in Argentina. There were two other groups that were independent within the regions of the UK and France which

indicated that anti-NXP2 was linked with a chronic subset of juvenile DM and developed a muscular disease which was extremely severe and had a low rate of remission.

Anti-MDA5 Antibodies (Anti-Melanoma Differentiation-Associated Gene 5)

Anti-MDA5 antibodies were first detected by Sato and colleague in serum obtained from Japanese clinically amyopathic dermatomyositis (CADM) patients.³² Initially, anti-MDA5 was reported as a particular autoantibody for CADM and termed as anti-CADM-140 during 2005. Later, the target autoantigen was recognized as gene 5 linked with melanoma differentiation (MDA5). It is also widely known as interferon-induced with helicase C domain protein 1 (IFIH1). MDA5 is said to be a receptor that is akin to cytoplasmic retinoic acid-inducible gene-I (RIG-I) which on recognizing viral RNAs prompts type 1 interferon and other inflammatory cytokines to be expressed. Anti-MDA5 is an auto-antibody particular to DM and has been found amongst 20–50 per cent of Asian adult patients with DM (this is inclusive of CADM) and is linked with a comparatively lower level of creatine kinase (CK), superior frequency of ILD (90–95 per cent), particularly rapidly advancing ILD (50–80 per cent) and poor prognosis owing to respiratory failure.

The positivity for anti-MDA5 antibodies can be detected in approximately 7% to as much as 60% of all cases of DM.^{33,34} Previous studies found that anti-MDA-5 antibodies were associated with a rapidly progressive interstitial lung disease (RP-ILD), a life-threatening condition characterized by poor prognosis and resistance to immunosuppressive therapy.^{32,35,36} Patients with these antibodies also present characteristic clinical features such as vasculopathy, soft erythematous papules, and skin ulcerations in nail folds and over joints' extensor surfaces.³² According to the study by Sato et al (2013), patients with cutaneous ulcers and anti-MDA5 antibodies also have higher frequencies of fever and polyarthritis³³.

Anti-TIF1-Gamma Antibodies

Anti-transcriptional intermediary factor 1- γ (TIF1- γ) antibody is one of the most frequently detected MSAs in both juvenile and adult DM patients. Anti-TIF1- γ , is also known as TRIM33, Ret-fused gene 7 and PTC 7 and ectodermin, plays an important role in the facilitation of deoxyribonucleic acid transcription and controls TGF- β

signaling, which suppresses cell growth.^{37–39} The most distinct clinical feature of anti-TIF-1 γ autoantibodies is their higher risk to malignancy, a factor that makes them account for at least 78% of all cancer-related diagnosis among DM patients.⁴⁰ Patients with these antibodies also tend to exhibit severe and extensive skin symptoms with a heightened frequency of DM skin lesions like Heliotrope rashes and Gottron's papules. However, the variances in the severity of myopathies allow for anti-TIF-1 γ autoantibodies to be detected in both CADM and classic DM. Unlike in anti-ARS or anti-MDA5 antibodies, the prevalence of Raynaud's phenomena, arthritis, and ILD are relatively low, particularly RP-ILD.⁴¹

Conclusion

In summary, myositis specific autoantibodies define the various phenotypes that exist within the broad clinical spectrums of various idiopathic inflammatory syndromes by being actively involved in skin and muscle damages and subsequent disease management. The early detection of these antibodies is crucial as it can aid in the prediction of a patient's clinical course and prognosis.

Disclosure

The author reports no conflicts of interest in this work.

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