Role of Myositis Autoantibodies in Management and Prognosis

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Key Points to Remember

- Anti-TIF1-γ, anti-NXP2, and the absence of MSA/MAA are predictive of concomitant malignancy in adults.
- Anti-synthetase and anti-MDA5 antibodies are associated with a high risk for ILD. Anti-MDA5-associated ILD tends to be treatment-refractory requiring intensive immunosuppression, while anti-ARS-associated ILD may be more responsive to immunosuppression including glucocorticoids and rituximab.
- Immune-mediated necrotizing myopathy, particularly in anti-SRP-positive patients, is associated with treatment-refractory disease and warrants aggressive therapy, while anti-Jo-1 and anti-Mi-2 antibodies are associated with a favorable response to rituximab.

Introduction

The muscular and extramuscular manifestations of the various subsets of idiopathic inflammatory myopathy (IIM) include cutaneous, gastrointestinal, pulmonary, cardiac, musculoskeletal, and vascular features. Therefore, disease subsetting or phenotyping is of vital importance for the appropriate management of myositis, particularly interstitial lung disease (ILD) and malignancy, as these complications are the leading causes of death in myositis patients [1]. Myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) are powerful predictive and prognostic tools regarding future clinical manifestations, treatment response, and prognosis when assessing patients and developing a management plan. Figure 19.1 incorporates autoantibody assessment in a proposed algorithm for the diagnosis and treatment of polymyositis (PM) and dermatomyositis (DM) patients.

Malignancy Survey

There is a well-known association of cancer with DM (and to a lesser extent PM) in up to 20% of cases [2, 3] with the diagnosis frequently being made within 1 year before or after the diagnosis of myositis [4]. Therefore, malignancy screening is essential at the time of a myositis diagnosis and

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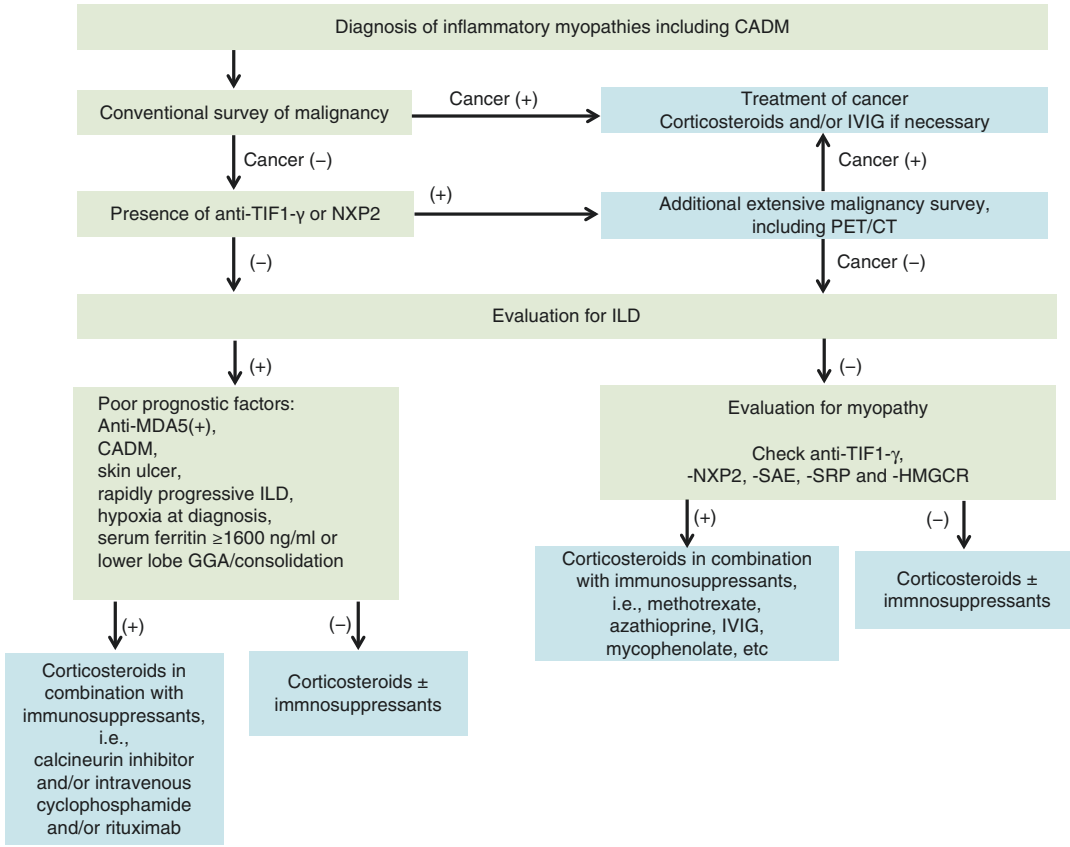

Fig. 19.1 A proposed algorithm for the management of PM/DM patients considering the MSA profile. MSAs myositis-specific autoantibodies, CADM clinically amyopathic DM, PET positron emission tomography, CT computed tomography, ILD interstitial lung disease, GGA ground-glass attenuation

the contribution of autoantibody testing is critical in stratifying the malignancy risk. In this regard, the presence of anti-TIF1-γ autoantibody or the absence of other MSAs/MAAs, including anti-Jo-1, anti-PM-Scl, anti-U1RNP, anti-U3RNP, and anti-Ku, at the time of myositis diagnosis indicates a high risk of cancer-associated myositis (CAM) [5]. In fact, this combination had a 94% sensitivity and 99% negative predictive value for the diagnosis of CAM, although the specificity and positive predictive value were only 45% and 9%, respectively for a CAM diagnosis. A meta-analysis of 312 patients with DM revealed that the sensitivity and specificity of anti-TIF1-γ antibody for the diagnosis of concomitant cancer were 78% and 89%, respectively [6], while other MSAs, most importantly anti-NXP2, and perhaps anti-SAE and anti-HMGCR positivity were also associated (to a much lesser degree) with malignancy in adult PM and DM patients [3, 5, 7–10] (Fig. 19.2). Even with anti-TIF1-γ positivity, patients over age 45 are most at risk for malignancy, as juvenile and younger adult DM patients may not be at risk for cancer. Nevertheless, clinicians should conduct an extensive malignancy survey with a diagnosis of DM and anti-TIF1-γ antibody or anti-NXP2 positivity, but the degree of cancer screening in DM patients negative for these autoantibodies remains a matter of debate. An extensive malignancy screen should include age-appropriate cancer screening; comprehensive blood tests including cancer markers; CT scans of the chest, abdomen, and pelvis; and, perhaps, a whole-body PET-CT scan in selected cases. Screening for malignancies in low-risk patients (without these high-risk antibodies) should be

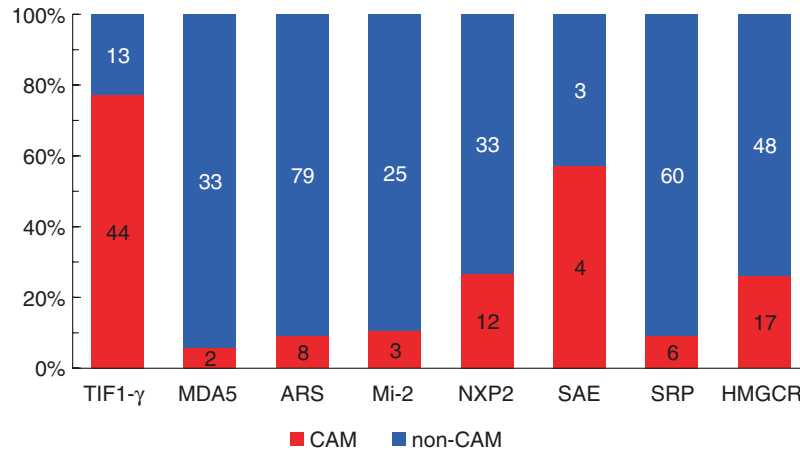

Fig. 19.2 Prevalence of concomitant malignancy in patients with PM/DM, stratified by MSAs [3, 5, 7–10]. MSA myositis-specific autoantibody, CAM cancer-associated myositis

guided by clinical suspicion and the prevalence of individual cancers in specific ethnic groups or the country of origin. Age-appropriate screening and noninvasive tests (e.g., fecal occult blood, gynecological evaluation, prostatic-specific antigen) should be considered in all patients.

High risk for malignancy: anti-TIF1-γ, anti-NXP2, absence of an MSA/MAA.

High-risk patients should undergo extensive cancer screening and close follow-up.

Risk Stratification and Treatment of Interstitial Lung Disease

The frequency of ILD in patients with IIM is highly variable, ranging from 10% to 90%, depending on the autoantibody spectrum [11]. Moreover, the clinical course and treatment response of ILD are variable as some patients may have mild ILD responsive to glucocorticoids alone, while others may have rapidly progressive ILD (RP-ILD) resistant to intensive immunosuppressive regimens, leading to death due to respiratory failure. Clinical diagnoses are somewhat useful in predicting 5-year overall survival rates in patients with ILD: 82% in patients with PM, 71% in those with classic DM, and 59% in those with CADM [12]. However, MSAs provide much more useful information regarding frequency, severity, and treatment response in ILD. Figure 19.3 summarizes the frequency of ILD in patients with individual MSAs [8, 10, 13–15]. Anti-synthetase autoantibodies and anti-MDA5 are strongly linked to the presence of ILD, with a frequency approaching 90% and 50%, respectively, in the western literature. Anti-MDA5 is associated with an even higher risk in Asian countries. Although Caucasian patients with anti-SAE have a lower risk of ILD than Asian populations, the number of patients examined are too small to be confident of this association [10, 16]. The 5-year overall survival rates in patients with anti-synthetase antibodies were much better than those with anti-MDA5 (96% versus 67%) [12], as anti-MDA5 is strongly associated with RP-ILD, as shown in Fig. 19.4 [17–19]. Even though anti-MDA5 is clearly associated with CADM, its presence has a worse prognosis due to RP-ILD rather than the CADM clinical subset itself [20, 21]. Other risk factors for poor ILD outcomes in patients with PM/DM include skin ulcers, rapidly progressive deterioration of pulmonary function, hypoxia at diagnosis, hyperferritinemia, and ground-glass attenuation/consolidation in the lower lobe of the lung by high-resolution computed tomography (HRCT)

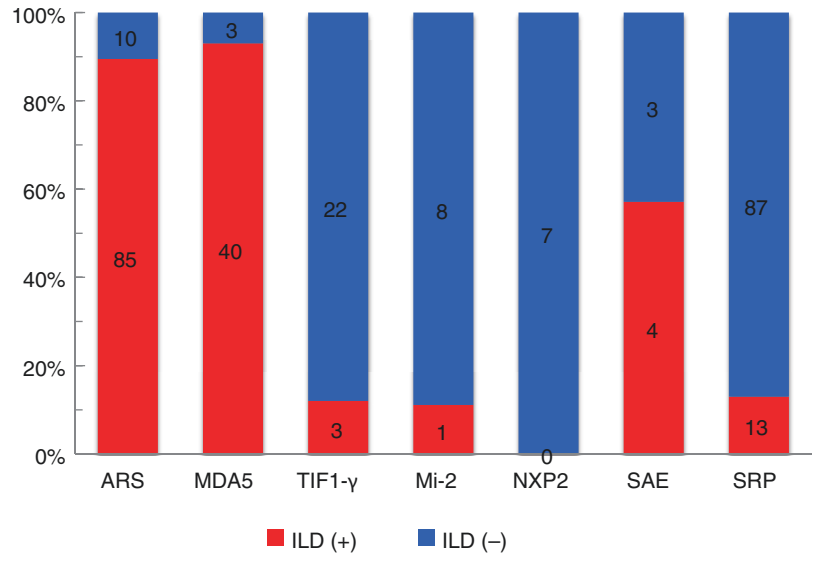

Fig. 19.3 Prevalence of ILD in patients with PM/DM stratified by MSAs [8, 10, 13–15]. ILD interstitial lung disease, MSA myositis-specific autoantibody

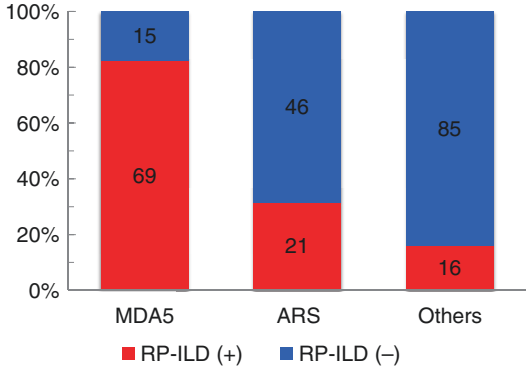

Fig. 19.4 Prevalence of RP-ILD in patients with PM/DM stratified by MSAs [17–19]. RP-ILD rapidly progressive interstitial lung disease, MSA myositis-specific autoantibody

[12, 22, 23]. Patients with an MSA associated with a high risk of ILD should undergo high-resolution CT scanning of the chest even in the absence of overt pulmonary symptoms and should be monitored for future development of ILD. In patients with an established diagnosis of ILD, one should initiate early and aggressive immunosuppressive treatment in the setting of

Anti-synthetase and anti-MDA5 autoantibodies have the highest risk of ILD.

Anti-MDA5-associated ILD is most often rapidly progressive.

anti-MDA5 positivity or other risk factors for ILD progression.

Although most studies demonstrate the need for intensive immunosuppressive treatment, there is no clear evidence that one particular regimen is superior to another. High-dose glucocorticoids, in combination with immunosuppressive agents including calcineurin inhibitors, intravenous cyclophosphamide pulse therapy, and rituximab, are used in anti-MDA5-positive patients with a high risk for developing RP-ILD [24, 25]. For such patients, it is important to initiate intensive immunosuppressive regimens as early as possible. On the other hand, the short-term response to treatment with high-dose glucocorticoids is often favorable in patients with anti-synthetase autoantibodies, although ILD recurrence frequently occurs during steroid tapering necessitating additional immunosuppressive agents. In synthetase-positive patients, the choice of an immunosuppressive agent depends on severity, but rituximab is emerging as a frequently used agent [26, 27].

Anti-synthetase-associated ILD may be more responsive to immunosuppression including glucocorticoids and rituximab.

Anti-MDA5-associated ILD tends to be treatment refractory requiring intensive immunosuppression.

Refractory Myopathy

The severity of skeletal muscle involvement is quite variable, ranging from no apparent clinical myopathy (i.e., CADM) to severe disability. In some studies, DM patients with anti-TIF1-γ, anti-NXP2, and anti-SAE antibodies have more extensive myopathy (including dysphagia and severe muscle weakness) compared with subjects with an anti-synthetase, anti-MDA5, or anti-Mi-2 antibody [28–30]. Anti-SRP and anti-HMGCR are associated with immune-mediated necrotizing myopathy, which is often resistant to conventional immunosuppressive treatment [31]. In contrast, anti-synthetase, anti-U1RNP, anti-PM/Scl, or anti-Ku antibodies predict favorable responses to the treatment of myositis. Patients positive for MSAs linked to treatment resistance should receive glucocorticoids combined with any one of several immunosuppressive drugs, such as azathioprine, methotrexate, intravenous immunoglobulin, and rituximab (Fig. 19.1) [32–35]. Reports show that the therapeutic response to rituximab is more favorable in patients who are autoantibody positive, particularly those with anti-Jo-1 or anti-Mi-2, than in those with no MAA [26].

Immune-mediated necrotizing myopathy (particularly anti-SRP) is associated with treatment-refractory disease and should be managed aggressively, while anti-Jo-1 and anti-Mi-2 autoantibodies are associated with a favorable response to rituximab.

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