Research progress on amyopathic dermatomyositis associated with interstitial lung disease

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To the Editor: Clinically amyopathic dermatomyositis (CADM) is a rare sub-type of dermatomyositis (DM) which includes amyopathic dermatomyositis (ADM) and hypomyopathic dermatomyositis (HDM). ADM is characterized by the presenting of classic DM signs for 6 months or longer without any muscle abnormality.

Interstitial lung diseases (ILDs) refer to a group of disorders that primarily involve the pulmonary parenchyma. Though its definite classification has not been determined in the most recent guidelines, a unique subset of ILD, rapidly progressive ILD (RP-ILD) can be identified on a clinical setting according to its rapid disease onset and progression rate. Interestingly, patients with ADM are often combined with ILD and it has been known RP-ILD is more common in the ADM subset. Unfortunately, the pathogenesis of ADM-ILD is currently under-studied thus no specific clinical strategies have been established. However, due to the discovery of important marker as anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab), a better understanding of the disease pathogenesis is expected in near future. In this study, we reviewed current understanding of the pathogenesis, clinical manifestations, and clinical managements of the disease and provide insight into future study directions.

The pathogenesis of ADM-ILD has yet remained to be elucidated and the clinical management is mainly empirical. There are reports suggested correlation between the activation of immune system and the onset of ADM-ILD. More specifically, one crucial player that might participate in the pathogenesis of ADM-ILD is anti-MDA5 Ab.[1] MDA5 is involved in the interferon signaling pathway and functions as a virus sensor by recognizing double stranded RNA (dsRNA) pattern receptor and participating in the autoimmunity with the molecular mimicry paradigm. It has been known that anti-MDA5 Ab is present in a portion of patients with ADM-ILD and the titer often correlates with the disease stages.

It is important to point out that the expression of anti-MDA5 Ab is not restricted to the ADM subsets but can also be observed in other DM subsets. Since not all patients with CADM expressing anti-MDA5, it seems like the concept of CADM is not as important as the presence of anti-MDA5 Ab in determining the clinical treatment.

Recent studies have pointed out the importance of anti-MDA5 Ab to the pathogenesis of ADM-ILD and the presence of this autoimmune antibody is now generally accepted as a risk factor for the development of potentially fatal ILD in patients with DM, especially those with the CADM sub-phenotype. It has been speculated that the anti-MDA5 Ab induced the autoimmunity after virus infection and participate in the pathogenesis of ADM-ILD. Unfortunately, due to the lack of animal model and *in vitro* experiments, the exact contribution of anti-MDA5 Ab needs to be further examined. However, the identification of close correlation between anti-MDA5 Ab and ADM-ILD is truly exciting and can provide insight into future studies.

The clinical manifestation of ADM is heterogeneous, thus provides a diagnostic challenge for doctors. Almost all patients with ADM present at least one characteristic skin lesions. More importantly, patients with ADM demonstrate no or at least sub-clinical muscle disease. Patients with ADM that complicated with ILD often present the classic ILD symptoms such as shortness of breath, dry cough, and weight loss.

The diagnosis of ADM-ILD relies heavily on chest high-resolution computed tomography (CT). The CT scans for ADM-ILD are consistent with the classic ILD which present as widespread ground-glass opacities with subpleural patchy consolidation with reticulations and traction bronchiectasis. Consolidation is mainly observed in acute/sub-acute ILD-ADM, while the presence of traction bronchiectasis is more common in chronic disease.

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Interestingly, the patients with positive anti-MDA5 often progress rapidly on CT scan and often associate with mediastinal emphysema, subcutaneous emphysema, and pneumothorax.

Pulmonary function tests, especially forced vital capacity, carbon monoxide diffusing capacity, and the partial pressure of oxygen in blood gas examination of patients with ADM with ILD is lower than those without ILD. Meanwhile, the serum lactate dehydrogenase and krebs von den lungen-6 levels are often increased. It has been estimated that 8% to 12% of the patients with ADM correlate with internal malignance thus different tumor markers may be seen at the tumor work-up. In addition, inflammatory marks as ferritin and cytokines like interleukin-6 (IL-6) can be elevated and often indicate a poor prognosis.

ADM is diagnosed in patients with typical cutaneous disease with no evidence of muscle weakness and in whom serum muscle enzyme levels are repeatedly normal over a 2-year period in the absence of the use of disease-modifying therapies, such as corticosteroids, immunosuppressive agents, or both for 2 months or longer. The diagnosis of ADM-ILD is made when patients with ADM present newly on-set ILD that suggested by classic high-resolution CT and lung function tests.

Current clinical management of ADM-ILD is mainly empirical and the efficacy of different treatments has not been well evaluated on large population. Thus, the optimal treatment program for the disease has not been established.

Immunosuppressive therapy and glucocorticoid pulse therapy are two classic strategies for ADM-ILD that often prove successful. Specifically, immunosuppressants such as cyclophosphamide, gamma globulin, and methotrexate are often combined with glucocorticoid. Calcineurin inhibitors are also very important for the treatment of ADM-ILD and should be considered as an alternative. It has been known that adding pirfenidone to the regimen can increase the survival rate of patients with ADM-ILD compared to those who only accepted the conventional treatments. In addition, plasma exchange and hemoperfusion have also been proven effective in clinic and may be considered when traditional therapy is impropriate.[2,3]

In our clinical practice, the combination of immunosuppressive therapy and glucocorticoid pulse therapy is considered when patients with ADM complicated with rapidly progressive ILD. For those who do not respond well, the addition of pirfenidone can often improve the prognosis. It is not difficult to imagine that using immunosuppressive regents and glucocorticoid will be inevitably accompanied by an increased risk of serious and life-threatening infections. However, due to the rapid progressive nature of the disease, the early use of the combination therapy outweighs the risk. Giving the situation of patients with ADM-ILD complicated with severe infection, pirfenidone, plasma exchange, and hemoperfusion should be considered to substitute the combination therapy.

Though most cases present with rapid progress symptoms, the prognosis of ADM-ILD varies. Followings are the factors that have been shown to indicate the prognosis of ADM-ILD. Though the merits of these factors in predicting the outcome of ADM-ILD are appreciated, future studies are needed to establish a comprehensive scoring system that can shed light upon on choosing the right treatment strategy.

1. *Anti-MDA5 antibody*. As introduced above, RP-ILD is more likely to occur on patients with ADM that positive for the anti-MDA5 Ab, and these patients are more likely to develop RP-ILD with symptoms of progressive dyspnea and hypoxemia and often present with poor prognosis than those who are negative for this autoantibody.
2. *Serum ferritin*. High serum ferritin (SF) has been shown to be an important indicator of poor prognosis of ADM-ILD. The exact contribution of SF to the disease pathogenesis has not been well studied, but there are clinical case reports suggested that the high level SF often indicate a lower response rate to the treatment and a faster deterioration rate. Similar to the anti-MDA5 Ab, the amount of SF can be increased as the patients show no improvement to treatment thus may be useful in monitoring the efficiency of current therapy.[4]
3. *Pneumomediastinum*. Clinical studies also revealed that the presence of pneumomediastinum (PNM) often indicates a poor prognosis of ADM-ILD. It is believed that PNM is a refractory respiratory complication and tended to occur in patients with ADM who are positive for anti-MDA5 Ab and DM patients with low creatine kinase levels. Le Goff *et al*[5] retrospectively collected a multi-center series of dermatomyositis and polymyositis (PM) cases complicated by PNM and found that 52% were ADM and 25% died within 1 month after the onset of PNM, which further suggest that the occurrence of PNM in patients with ADM often indicates poor prognosis.
4. *Other indicators*. As introduced earlier, patients with ADM-ILD often co-exist with internal malignance. The elevation of tumor markers in patients with ADM-ILD may suggest the existence of correlated cancer and indicates a more complicated case. Besides the prognostic factors introduced earlier, the elevation of non-specific infection markers and liver enzymes also predicts a worse prognosis.[6] These laboratory findings could provide valuable predictive information of patients with ADM-ILD. In addition, some non-specific changes of cytokine levels might also indicate the status of ADM-ILD and can be useful in predicting prognosis.[7] For instance, the increasing of interferon-β, interleukin (IL)-6, and A disintegrin and metalloprotease (ADAM)-17 has been associated with disease activity and severity. Besides all the cytokines introduced earlier, emerging studies suggest the importance of cytokines such as anti-transcription intermediary factor-1β, IL-8, IL-10, and IL-18 in participating the pathogenesis and predicting the prognosis of ADM-ILD.

In summary, ADM is a rare disease that can progress rapidly once complicated with ILD. The clinical manifestations of ADM-ILD are diverse and can be easily misdiagnosed. However, by identifying the characteristic skin lesions and high-resolution CT images, correct diagnosing ADM-ILD is not difficult. Due to the lack of

animal model and bench research, the pathogenesis of ADM-ILD is currently understudied. Here we summarized several proposed mechanisms. Among these different mechanisms, we found the anti-ADM5 antibody is particularly important. It may not only participate in the pathogenesis by affecting the autoimmunity, but also determine the severity of the disease. However, future studies are needed to further explore this possibility. Next, we introduced the present treatment strategies of ADM-ILD. All patients with ADM-ILD should be given combined immunosuppressants and glucocorticoid if it was allowed. For people do not response well to or intolerant with this treatment, other choices like pirfenidone, plasma exchange, and hemoperfusion should be considered. Last but not the least, we summarized different prognosis factors of ADM-ILD that may not only be used as an indicator of the prognosis but also can evaluate the efficacy of the current treatment. By reviewing the related studies and sharing our thoughts and experience of treating ADM-ILD, we wish we can help clinicians better understand this rare but lethal disease and shed light upon its future studies.

Conflicts of interest

None.

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