COMMENTARY

Amyopathic Dermatomyositis, with anti-MDA5 antibody-associated RP- ILD.

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Commentary

Clinically amyopathic form (CADM), a subset of dermatomyositis (DM) is characterized by classical cutaneous lesions that may progress without myopathy (Sontheimer criteria).[1] For more than three decades, anti-Jo-I autoantibody (histidyl transfer RNA (tRNA) synthetase) has been well established as one of the classic markers for polymyositis/dermatomyositis (PM/DM).[2] Myositis specific antibodies (MSAs) are new autoantibodies discovered in 70% of patients with idiopathic inflammatory myositis (IIM).[3] MSAs are found to be associated with distinct clinical phenotypes and prognosticate the underlying conditions. Anti-aminoacyl transfer RNA (tRNA) synthetases (ARS) have clinical significance in a small number of patients with idiopathic interstitial lung disease (ILD).[4] Other autoantibodies are equally important. However, the presence of anti-melanoma differentiation-associated gene 5 (MDA5) antibody had changed the clinical scenario in patients with DM for the last decades among other MSAs. Many case series or reports revealed that anti-MDA5 antibody was frequently detected in 50 -73% of patients with CADM and associated with rapidly progressive ILD (RP-ILD).[5,6,7,8] A study by Li *et al* had shown that the anti-MDA5 antibody is an important diagnostic biomarker for CADM as well as an unfavourable prognostic factor in the presence of RP-ILD.[9]

Cutaneous lesions in CADM and subacute cutaneous lupus erythematosus (SCLE) are clinically and histologically similar. The diagnosis depends on the detection of specific autoantibodies. Anti-SSA has been identified in SCLE whereas in CADM, the MDA5 antibody is almost exclusively present.[10] The coexistence is rare. Delay in treatment may result in adverse outcomes in patients with MDA5 antibody complicated by ILD.

Interstitial lung disease (ILD) which is synonymously described as pulmonary fibrosis, has a diverse spectrum of aetiologies with a varied clinical course.[11,12] ILD significantly contributes to a high morbidity and mortality. In recent years, ILD has been more comprehensively and elaboratively described to reach a consensus on standardization in image reporting. It is of utmost importance and crucial to identify the underlying aetiology of ILD. In autoimmune disease, ILD has been well recognized to be a complication of systemic sclerosis and rheumatoid arthritis.[13,14] High resolution computed tomography (HRCT) of the lungs provides ancillary evidence assisting a clinical diagnosis of ILD. ILD in DM occurs in 5-30% of patients, with nonspecific interstitial pneumonia (NSIP) as the main histopathologic finding.[15,16,17] Other findings such as diffuse alveolar damage (DAD), bronchiolitis obliterans organizing pneumonia (BOOP), cellular interstitial pneumonia (not otherwise specified), and usual interstitial pneumonia (UIP) were uncommon in previous studies.[18,19] However, lung biopsy can be deferred with an accurate imaging report and confirmed clinical diagnosis.

The availability of MSA tests is relatively new in some developing countries. Quantitative measurement is important in assessing the progress of a patient with DM/CADM especially with MDA5-ILD but it remains an expensive test. Hence, qualitative measurement of MSAs and good clinical acumen, vigilance and assessment of a patient with CADM with MDA5 antibody-associated RP-ILD remains the standard of care in developing countries.

Many such complex cases were managed based on clinical judgment and literature review before the MSA test became available. Although it is qualitative, a more accurate diagnosis could be made. Detailed imaging reports will further facilitate early diagnosis and management of the disease.

There is no standard treatment for MDA5 antibody-associated RP-ILD cases. Various regimes have been used in previous cases with

differing outcomes. The gold standard is still corticosteroid although the combination with other immunosuppressants such as cyclophosphamide, hydroxychloroquine, cyclosporine, mycophenolate, tacrolimus, immunoglobulin, and rituximab including plasma exchange had been used and advocated in severe or refractory cases. [20] Most cases presented late which resulted in a poor response to the treatment regimes. Individual response to such treatments may also vary. Inevitably, pharmacological failure led to respiratory failure which eventually resulted in death despite intensive management including mechanical ventilatory support.

Factors that may influence the treatment outcome are possible genetic predisposition as the prevalence of CADM with MDA5 antibody-associated RP-ILD is higher in Asian countries, and identification of the underlying aetiologies and the progress of pulmonary imaging changes i.e. ground-glass opacities, traction bronchiectasis, and fibrosis. [21,22] Early detection of MDA5 antibody is of paramount importance in identifying patients who are at a higher risk of developing RP-ILD. An extensive literature review by Mehta *et al* had highlighted the heterogeneity in the spectrum of clinical phenotype, ethnicity variability, and genetic predisposition with the hypothetical etiopathogenesis.[20] Teamwork between the rheumatologist, pulmonologist, and radiologist will effectively deliver the proper management.
More research is needed to define the genetics and epidemiology for understanding the pathogenesis of MDA5 antibody-associated RP-ILD. As the prevalence estimates could not be equated with defined treatment needs, such studies should determine the unmet needs for diagnostic MSA assays and imaging services by taking into consideration severity, disability, morbidity and mortality attributable to the condition.

References

1. Euwer RL, Sontheimer RD. Amyopathic dermatomyositis (dermatomyositis sine myositis) Presentation of six new cases and review of the literature. J Am Acad Dermatol. 1991; 24:959–66.
2. Nishikai M, Reichlin M. Heterogeneity of precipitating antibodies in polymyositis and dermatomyositis. Characterization of the Jo-1 antibody system. Arthritis Rheum. 1980; 23:881–888.
3. Fujimoto M, Watanabe R, Ishitsuka Y, et al. Recent advances in dermatomyositis-specific autoantibodies. Curr Opin Rheumatol. 2016 Nov;28(6):636-644
4. Nakashima R, Imura Y, Hosono Y, et al. The multicentre study of a new assay for simultaneous detection of multiple anti-aminoacyl-tRNA synthetases in myositis and interstitial pneumonia. TPLoS One. 2014; 9(1): e85062.
5. Ortiz-Santamaria V, Babot A, Ferrer C. Anti-MDA5-positive dermatomyositis: an emerging entity with a variable clinical presentation. Scand J Rheumatol. 2017; 46:509–11. DOI: 10.1080/03009742.2017.1340512
6. Sato S, Hoshino K, Satoh T, et al. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. Arthritis Rheum. 2009; 60:2193–2200.
7. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kD polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum. 2005; 52:1571–1576.
8. Cao H, Pan M, Kang Y, et al. Clinical manifestations of dermatomyositis and clinically amyopathic dermatomyositis patients with positive expression of anti-melanoma differentiation-associated gene 5 antibody. Arthritis Care Res. 2012; 64:1602–10. DOI: 10.1002/acr.21728
9. Li L, Wang Q, Yang F, et al. Anti-MDA5 antibody as a potential diagnostic and prognostic biomarker in patients with dermatomyositis. Oncotarget. 2017(Apr); 18;8(16):26552-26564. DOI: 10.18632/oncotarget.15716.
10. Cuesta-Mateos C, Colom-Fernández B, Portero-Sainz I, et al. Autoantibodies against TIF-1-γ and CADM-140 in Spanish patients with clinically amyopathic dermatomyositis (CADM): clinical significance and diagnostic utility. J Eur Acad Dermatol Venereol. 2015(Mar);29(3):482-9. doi: 10.1111/jdv.12591.
11. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. N Engl J Med 2020; 383:958-968. DOI: 10.1056/NEJMra2005230
12. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. N Engl J Med 2018; 378:1811-1823. DOI:10.1056/NEJMra1705751
13. Clarke J. European consensus reached on interstitial lung disease in SSc. Nat Rev Rheumatol 2020; 16:127. Doi.org/10.1038/s41584-020-0379-3
14. Wells AU, Denton CP. Interstitial lung disease in connective tissue disease-mechanisms and management. Nat Rev Rheumatol 2014; 10:728-739. Doi.org/10.1038/nrrheum.2014.149

15. Schwarz MI. Pulmonary and cardiac manifestations of polymyositis-dermatomyositis. J Thorac Imaging. 1992 Mar;7(2):46-54. DOI: 10.1097/00005382-199203000-00006.
16. Ikezoe J, Johkoh T, Kohno N, et al. High-resolution CT findings of lung disease in patients with polymyositis and dermatomyositis. J Thorac Imaging. 1996 Fall;11(4):250-9..
17. Douglas WW, Tazelaar HD, Hartman TE, et al. Polymyositis-dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med. 2001 Oct 1; 164(7):1182-5.
18. Ikezoe J, Johkoh T, Kohno N, et al. High-resolution CT findings of lung disease in patients with polymyositis and dermatomyositis. Thorac Imaging. 1996 Fall; 11(4):250-9.
19. Nicholson AG, Colby TV, du Bois RM, et al. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med. 2000 Dec; 162(6):2213-7.
20. Mehta, P., Machado, P.M. & Gupta, L. Understanding and managing anti-MDA 5 dermatomyositis, including potential COVID-19 mimicry. Rheumatol Int (2021). doi.org/10.1007/s00296-021-04819-1
21. Betteridge Z, Tansley S, Shaddick G et al (2019) Frequency, mutual exclusivity, and clinical associations of myositis autoantibodies in a combined European cohort of idiopathic inflammatory myopathy patients. J Autoimmun 101:48–55.
22. Sato S, Murakami A, Kuwajima A, et al (2016) Clinical utility of an enzyme-linked immunosorbent assay for detecting anti-melanoma differentiation-associated gene 5 autoantibodies. PLoS ONE 11: e0154285.