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Editorial

Ethnic Differences in Development of Interstitial Lung Disease Associated with Anti-CADM-140/MDA5 Antibody Positive Amyopathic Dermatomyositis

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Editorial

Polymyositis and Dermatomyositis (PM-DM) are forms of idiopathic inflammatory myositis. DM is identified by muscle weakness accompanied by a characteristic rash, whereas PM is defined as a myopathy without the skin rash seen in DM. When a patient has the typical DM rash but no or little muscle weakness, the clinical diagnosis is Amyopathic DM (ADM) [1]. Interstitial Lung Disease (ILD) in PM-DM is recognized as a serious complication and a major cause of death in this disease [2]. Especially the patients with ADM sometimes develop rapidly progressive ILD, which is often resistant to intensive therapy with high dose corticosteroids and immunosuppressive agents and results in fatal respiratory failure [3]. Rapidly progressive ILD in ADM has been reported predominantly in Asia such as Japan and Korea suggesting racial differences in the manifestation of the disease [4,5].

About 30 percent of patients with DM-PM have myositis-associated autoantibodies with clinical findings of the relatively acute disease onset, constitutional symptoms, Raynaud's phenomenon, mechanic's hands, arthritis, and ILD. Three major categories of myositis-specific autoantibodies are anti-aminoacyl-tRNA synthetase antibodies, anti-SRP antibodies, and anti-Mi-2 antibodies. In addition to them, an autoantibody associated with ADM was identified and termed anti-CADM-140 antibody [6]. It is called anti-CADM-140/MDA5 antibody at present, because the antibody recognizes an antigen of an RNA helicase encoded by Melanoma Differentiation-Associated Gene 5 (MDA5) [7]. MDA5 functions as a pattern recognition receptor and typically recognizes dsRNA over 2000nts in length. After recognizing the RNA of internalized viruses, cytoplasmic pattern recognition receptors mediate production of type-1 Interferons (IFNs) and antiviral immune responses. A recent study showed that gain-of-function mutations in *IFIH1*, the human counterpart of MDA5, lead to upregulated type-1 IFN responses [8]. Individuals with these mutations exhibit phenotypes consistent with autoimmune diseases, including Aicardi-Goutières syndrome and systemic lupus erythematosus.

In the patients with the anti-CADM-140/MDA5 antibody, there seems to be ethnic variations in disease phenotypes and distribution of classic DM and ADM. Several reports from Japan demonstrated that the anti-CADM-140/MDA5 antibody titers are correlated with disease activity and predicted the course of ILD associated with ADM (Table 1) [9-12]. Whereas, reports from non-Japanese populations show differences infrequencies of DM and ADM and in clinical findings (Table 2). In 64 Chinese patients with PM-DM, anti-CADM-140/MDA5 antibodies were strongly associated with rapidly progressive ILD, however, a meta-analysis demonstrated a significantly higher frequency of ADM in Japanese than in non-Japanese patients [13]. In a cohort of patients with ADM in the US, anti-CADM-140/MDA5 antibody was frequently found in patients with severe vasculopathy affecting the skin with increased risk of ILD [14]. In another US cohort, 11 of 160 patients with DM (6.9 percent) had the antibodies [15]. Nine of the 11 patients presented with a symmetric inflammatory polyarthritis and the majority of these patients also had overt clinical myopathy and ILD. In a large series of Spanish patients with DM, the association of the anti-CADM-140/MDA5 antibodies with rapidly progressive ILD was also confirmed [16]. Although an analysis of sera from 76 consecutive adult Italian

Table 1: Representative reports of anti-CADM-140/MDA5 antibody positive ADM-ILD from Japan.

Authors	Publication Year	Case n	Major Fingings	Reference
Sato et al.	2005	42	discovery of an autoantigen recognizinga polypeptide of ~140 kd those with anti-CADM-140 antibodies had more rapidly progressive ILD	[6]
Sato et al.	2009	294	identification of an RNA helicase encoded by MDA5 as the CADM-140 antigen ELISA using MDA5 as the antigen showed 85% sensitivity and 100% specificity	[7]
Muro et al.	2012	11	anti-CADM-140/MDA5 antibodies could monitor disease activity in ADM-ILD	[9]
Koga et al.	2012	79	anti-CADM-140/MDA5 antibody titer predicts the prognosis of ADM-ILD	[10]
Gono et al.	2012	27	anti-CADM-140/MDA5 antibody titer, ferritin, and IL-18 are useful for the evaluation of the response to treatment of ADM-ILD	[11]
Sato et al.	2013	14	anti-CADM-140/MDA5 antibody titer correlates with disease activity and predicts disease outcome in patients with ADM-ILD	[12]
Takada et al.	2015	14	CX3CL1 may be involved in the pathogenesis of ADM-ILD with anti-CADM-140/MDA5 antibody	[19]

Abbreviations: ADM: Amyopathic Dermatomyositis; ILD: Interstitial Lung Disease; MDA5: Melanoma Differentiation-Associated Gene 5

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Table 2: Representative reports of anti-CADM-140/MDA5 antibody positive ADM-ILD from Western countries.

Authors	Publication Year	Case n	Major Fingings	Reference
Hall et al.	2013	160	MDA5 antibodies are found in DM with a symmetric polyarthritis Most anti-MDA5-positive patients had overt clinical myopathy and ILD	[15]
Labrador-Horrillo et al.	2014	117	anti-MDA5 antibodies are associated with ILD	[16]
Ceribelli et al.	2014	76	anti-MDA5 positive cases were affected by ADM with typical skin disease rapidly progressive ILD was only one of five cases	[17]
Narang et al.	2015	152	anti-MDA5 antibodies are associated with cutaneous ulcer association of cutaneous ulcers with ILD depends upon anti-MDA5 antibodies	[14]

Abbreviations: ADM: Amyopathic Dermatomyositis; MDA5: Melanoma Differentiation-Associated Gene 5; DM: Dermatomyositis; ILD: Interstitial Lung Disease

patients with PM-DM demonstrated that the antibody positive cases were affected by ADM with typical skin disease, rapidly progressive ILD was only one of five cases [17].

Since MDA5 plays a role in the recognition and innate immune signaling against viruses, a possible association is suggested between virus infection and the development of ADM with anti-CADM-140/MDA5 antibodies. Sun et al. reported that the mRNA expressions of IFN-regulated genes, *IRF7* and *MxA*, and plasma IFN-α protein were up-regulated in peripheral blood from the patients with ADM, which suggests that dysregulation of the type 1 IFN system may be implicated in ADM pathogenesis [18]. The latest study suggested that CX3CL1 might be involved in the development of anti-CADM-140/MDA5 antibody positive ADM-ILD [19]. The authors measured the antibody titers using an enzyme-linked immunosorbent assay and serum cytokine/Growth Factor (GF) protein concentrations using Multiplex Suspension Array (Merck Millipore) before treatment. Relationship analyses between the antibody titers and each cytokine/GF protein concentrations revealed high Spearman's rank correlation coefficients in CX3CL1 and TGFα ($r = 0.8897$ and $r = 0.7110$, respectively. The cell-bound CX3CL1 promotes strong adhesion of leukocytes to activated endothelial cells, whereas soluble CX3CL1 potently chemo attracts T cells and monocytes [20-22]. Suzuki et al. reported that serum CX3CL1 level could be a surrogate marker of disease activity in PM-DM [23]. Further study of serum cytokine/GF proteins with more patients in other populations will be needed to investigate the etiologies for ADM with anti-CADM-140/MDA5 antibodies.

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