The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody

Ran Nakashima1, Yoshitaka Imura1, Shio Kobayashi1, Naoichiro Yukawa1, Hajime Yoshifuji1, Takaki Nojima1, Daisuke Kawabata1, Koichiro Ohmura1, Takashi Usui1, Takao Fujii1, Katsuya Okawa2 and Tsuneyo Mimori1

Abstract

Objectives. Various autoantibodies are detected in the sera of PM/DM patients. Some of them are specific to PM/DM patients and closely associated with clinical manifestations of the diseases. Recently, the anti-CADM-140 antibody was reported to be found specifically in clinically amyopathic DM (C-ADM) patients and to be associated with acute interstitial lung disease (ILD). We assessed the clinical significance of the anti-CADM-140 antibody and then investigated the autoantigen recognized by the anti-CADM-140 antibody.

Methods. Autoantibodies were screened in 192 patients with various CTDs and 21 healthy controls using immunoprecipitation with [35S]methionine-labelled HeLa cells. Immunoabsorbent column chromatography was used to purify an autoantigen that was subsequently subjected to peptide mass fingerprinting.

Results. The anti-CADM-140 antibody was revealed to be specific to DM. Most of the anti-CADM-140-positive patients were C-ADM although some of them showed apparent myositis. The anti-CADM-140-positive patients frequently showed hyperferritinaemia and acute progressive ILD with poor prognosis. The anti-CADM-140 antibody was shown to recognize IFN induced with helicase C domain protein 1 (IFIH1), also known as the melanoma differentiation-associated gene 5 (MDA5), which is one of the RIG-I-like receptors and plays a role in innate immune responses.

Conclusion. The anti-CADM-140 antibody was a marker of DM and intractable ILD and recognized IFIH1/MDA5, which is involved in innate immunity. These findings may give a new insight into the pathogenesis of DM.

Key words: Anti-CADM-140 antibody, Amyopathic dermatomyositis, Interferon induced with helicase C domain protein 1, Interstitial lung disease, Ferritin, Innate immunity, Virus.

Introduction

Idiopathic inflammatory myositis (IIM), including PM/DM, are systemic inflammatory disorders that involve the skin, lungs and muscle. A number of autoantibodies can be detected in PM/DM patient sera, some of which are specific to PM/DM [known as myositis-specific autoantibodies (MSAs)] or the myositis overlap syndrome [known as myositis-associated autoantibodies (MAAs)]. Moreover, these autoantibodies are closely associated with clinical manifestations of PM/DM, such as symptoms, complications, reactivity to therapy and prognosis [1].

IIM are categorized heterogeneously as many different classification subsets have been proposed. Among these subgroups, the disorder that shows the typical skin manifestations of DM but has no or little evidence of clinical myositis is defined as clinically amyopathic DM (C-ADM) [2]. Until recently it was thought that MSAs...
could not be detected in patients with C-ADM and this appeared to be a characteristic feature. In 2005, however, Sato et al. [3] reported the identification of a specific autoantibody in C-ADM patients. They screened the sera of 314 patients and controls by [35S]methionine-labelled protein immunoprecipitation (IPP) and immunoblotting techniques using K562 cells, and 8 of 15 patients with C-ADM immunoprecipitated a 140-kDa protein. This newly identified autoantibody was named as the anti-CADM-140 antibody. Japanese patients with C-ADM frequently develop acute progressive interstitial lung disease (ILD) and have poor prognosis. Thus, this antibody may be useful as a specific serological marker for a subset of DM and acute ILD [3].

We have characterized the antibody by screening 213 patients and compared the clinical features of DM patients that were anti-CADM-140 positive with those that were anti-CADM-140 negative. Moreover, we identified the antigen recognized by the anti-CADM-140 antibody as IFN induced with helicase C domain protein 1 (IFIH1).

**Patients, materials and methods**

**Patients**

Serum samples were obtained from 192 Japanese adult patients with CTDs and related disorders who were followed up at Kyoto University Hospital, and 21 healthy volunteers. Patients’ diagnoses included PM (n = 47), DM (n = 37) [C-ADM (n = 15)], IBM (n = 2), SSc (n = 10), RA (n = 17), overlap syndrome/MCTD (n = 16), UCTD (n = 7), SS (n = 3), PMR (n = 3), vasculitis syndrome (n = 4), ILD (n = 23) and hypothyroidism (n = 2). We diagnosed patients with C-ADM to see if they had the characteristic skin rash of DM, but there were no or little clinical muscle symptoms and their serum creatine kinase (CK) levels were <300 IU/l. The presence of MSAs and MAAs was determined by ELISA (SRL, Tokyo, Japan) and RNA-IPP assays. Sera from all patients were collected at their first visits and most of them were within 3 months after the onset of the diseases.

The patients were diagnosed as having ILD according to the results of chest radiography, chest CT and pulmonary function tests. Rapidly progressive ILD was defined as those who had progressive dyspnea, hypoxiaemia and interstitial lesions on the chest radiography or CT within a few months from the onset of respiratory symptoms.

All patients and healthy volunteers provided informed consent in accordance with the Declaration of Helsinki, before collecting samples. This study was approved by the Medical Ethics Committee of Kyoto University Graduate School of Medicine.

**Statistical analyses**

Statistical analyses were performed using Stat View version 5.0 software (SAS Institute Inc., Cary, NC, USA). Differences between the anti-CADM-140-positive and -negative patients with DM were examined using the Fisher’s exact test except for age differences, which were tested using a Student’s t-test.

**IPP**

IPP was performed using extracts of HeLa cells as previously described [4]. Ten microlitres of sera were mixed with 2 mg of protein A Sepharose™ CL-4B (GE Healthcare, Uppsala, Sweden) in 500 μl of IPP buffer [10 mM Tris–HCl at pH 8.0, 500 mM NaCl, 0.1% Nonidet P-40 (NP-40)] and incubated on the rotator for 2 h at 4 °C. The IgG-coated Sepharose was washed four times in 500 μl of IPP buffer, and resuspended in 400 μl of IPP buffer for polypeptide studies or NET-2 buffer (50 mM Tris–HCl at pH 7.5, 150 mM NaCl, 0.05% NP-40) for analysis of RNA.

For the polypeptide studies, 2 × 10⁷ HeLa cells in 100 ml of methionine-free minimal essential medium were labelled with 18.5 MBq of [35S]methionine (Perkin Elmer, Waltham, MA, USA) overnight at 37 °C. Cells were then pelleted by centrifugation before resuspension in 2 ml of IPP buffer and sonication using a Misonix microson (Misonix, Farmingdale, NY, USA) three times for 40 s. The soluble supernatant was recovered by centrifugation (10 000 g for 20 min). Antibody-coated Sepharose beads were mixed with 100 μl of [35S]methionine-labelled HeLa cell extracts (derived from 1 × 10⁸ cells), and rotated at 4 °C for 2 h. After four washes, the Sepharose beads were resuspended in the SDS sample buffer, and the polypeptides were fractionated by 6.5% SDS–PAGE and detected by autoradiography. For RNA studies, RNA-IPP was performed as previously described [5].

**Immunoblotting**

Immunoblotting analysis was performed using cytoplasmic or nuclear extracts in a modification of the procedure described by Towbin et al. [6]. Cytoplasmic or nuclear extracts were prepared in a modification of the procedure described by Lerner et al. [7]. HeLa cells (1 × 10⁶) were resuspended in a hypotonic buffer (10 mM Tris–HCl, pH 7.5, 1.5 mM MgCl₂, 10 mM KCl, 0.5 mM dithiothreitol) containing a protease inhibitor cocktail (Promega, WI, USA), and homogenized using a Dounce tissue homogenizer (20 strokes) on ice. The cell homogenates were loaded on a 30% sucrose solution and centrifuged at 25 000 g for 20 min at 4 °C. The supernatant was used as the cytoplasmic extract and the pellet was used as the nuclear extract after sonication.

**Imunoabsorbent column chromatography**

IgG was purified from 12 ml of patient serum containing anti-CADM-140 using an IgG purification kit [ImmunoPure (G) IgG purification kit, Pierce, Rockford, IL, USA]. The purified IgG (10 mg/g of gel) was coupled with cyanogen bromide-activated Sepharose 4B beads (GE Healthcare) according to the manufacturer’s instructions. The IgG-Sepharose 4B beads (20 ml of gel matrix) were then poured into a glass column (BIO RAD, Hercules, CA, USA) and the cytoplasmic extracts of 6 × 10⁶ HeLa cells were circulated through the column at 4 °C overnight using
a peristaltic pump. The column was then washed with 200 ml of Tris-buffered saline (TBS) (10 mM Tris–HCl, 150 mM NaCl, pH 7.5) containing 0.1% NP-40. The antigen bound to the column was eluted step-wise with 1 M NaCl, 1 M MgCl₂ and finally 3 M MgCl₂ (adjusted to pH 7.0 with Tris base). The eluates were dialyzed against TBS containing 0.05% NP-40, concentrated to ~0.5 mg/ml using an Amicon Centriprep concentrator (Millipore, Billerica, MA, USA) and subjected to electrophoresis to analyse antigens.

To confirm the presence of IFIH1, 10 μg of eluted protein was immunoblotted using rabbit anti-human melanoma differentiation-associated gene 5 (IFIH1/MDA5) polyclonal antibody (Life Span Biosciences, Seattle, WA, USA) and alkaline phosphatase-labelled donkey anti-rabbit IgG (H + L) conjugates [Anti-ACTIVE Qualified (Promega)] secondary antibody, before development by chemiluminescence.

Identification of protein by peptide mass fingerprinting
Mass spectrometric identification of proteins was performed as previously described [8]. Briefly, after SDS-PAGE, proteins were visualized by silver staining and excised separately, followed by in-gel digestion with trypsin (Promega) in a buffer containing 50 mM ammonium bicarbonate (pH 8.0) and 2% acetonitrile overnight at 37°C. Molecular mass analyses of tryptic peptides were performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS) using an Ultraflex TOF/TOF (Bruker Daltonics, Billerica, MA, USA). Proteins were identified by comparison between the molecular weights determined by MALDI-TOF/MS and theoretical peptide masses from the proteins registered in NCBInr.

Expression and identification of IFIH1
A partial 5' region and 3' region (spanning IFIH1 nucleotides 220–1830 and 1747–3310, respectively) of IFIH1 cDNA [9] were prepared from the total RNA of HeLa cells. Reverse transcription and PCR reactions were performed in a single tube using SuperScript™ one-step RT-PCR (Invitrogen, CA, USA) with gene-specific primers under the conditions specified by the manufacturer. The integrity of the cDNA sequence was confirmed by sequencing. The 5' and 3' regions of IFIH1 cDNA were cloned into the pcDNA™6.2/V5/GW vector using directional TOPO (Invitrogen, CA, USA) cloning reactions. The partial N-terminal and C-terminal polyepitides of IFIH1 were expressed in an in vitro transcription/translation system (STP3, Novagen, Darmstadt, Germany) using the method recommended by the manufacturer. The reactivity of the anti-CADM-140 antibody against in vitro translated IFIH1 polypeptides was examined by IPP.

Results
Screening for anti-CADM-140-positive patients
Using IPP with [³⁵S]methionine-labelled HeLa cells, we screened 192 patients with various CTDs (including 47 with PM and 37 with DM) and 21 healthy controls (HCs) by IPP. Sera from 13 patients immunoprecipitated the same 135-kDa protein (Fig. 1). We also performed immunoblot analysis using fractionated HeLa cells and confirmed that the 135-kDa protein was directly recognized by the autoantibodies in the sera of these patients and that the protein was cytoplasmic (Fig. 2).

To confirm whether the anti-p135 antibody detected using HeLa cells was identical to the anti-CADM-140 antibody, which was identified by Sato et al. using [³⁵S]methionine-labelled K562 cell extracts, IPP using HeLa cells was performed and showed that the protein precipitated by the anti-p135 antibody migrated to the same position as that of the anti-CADM-140 antibody in the reference serum (kind gift of Dr Sato, Keio University), confirming that the anti-p135 was identical to the anti-CADM-140 antibody (data not shown).

Clinical and laboratory features of patients with the anti-CADM-140 antibody
We assessed the clinical profiles of 13 patients presenting with the anti-CADM-140 antibody (Table 1). Two patients had typical DM and 11 had C-ADM. The anti-CADM-140 antibody was not identified in any of the sera from patients with other diseases or HCs. Furthermore, none of the anti-CADM-140-positive sera was revealed to have other MSAs or MAAs. Nine (62%) patients had fever >38°C,
whereas 12 patients (92%) had ILD; 7 developed acute progressive ILD, of which 6 died of respiratory failure. We compared the clinical findings of the anti-CADM-140-positive patients with those of the anti-CADM-140-negative DM patients (Table 2). The anti-CADM-140-positive patients had less muscle weakness and/or lower CK levels than the anti-CADM-140-negative patients (46 vs 83%; \( P = 0.028 \) and 38 vs 87%; \( P = 0.006 \), respectively). Interestingly, the serum ferritin concentrations in 11 patients were already elevated within 1 month of their admission with significantly high frequency in comparison with the anti-CADM-negative DM patients (85 vs 33%; \( P = 0.005 \)). Moreover, the worse the ILD of the anti-CADM-140-positive patients became, the higher their serum ferritin concentrations were (supplementary figure 1, available as supplementary data at Rheumatology online). The maximum level of ferritin in the seven anti-CADM-140-positive patients exceeded 1000 ng/ml, and one of them exceeded 10,000 ng/ml (Table 1). With one exception, all patients showed abnormalities in their levels of hepatobiliary enzymes (not only transaminases but also \( \gamma \)-glutamyl transpeptidase and alkaline phosphatase), which worsened in accordance with ILD and ferritin levels (data not shown). The frequency of acute, progressive ILD was higher in the anti-CADM-140-positive patients than in the anti-CADM-140-negative DM patients (54 vs 4%; \( P = 0.001 \)), which was also the case for the overall frequency of ILD (92 vs 54%; \( P = 0.027 \)). Life prognosis was poorer in the anti-CADM-140-positive patients than in the anti-CADM-140-negative DM patients, and about half of them died within 6 months from the onset of the disease (46 vs 8%; \( P = 0.013 \)) (supplementary figure 2, available as supplementary data at Rheumatology online). An internal malignancy was found in only one of the anti-CADM-140-positive patients (8%) and disease activity of the patient was not affected even after the neoplasm (malignant colon polyp) was successfully removed. Thus, the anti-CADM-140 antibody appeared to be specific in DM, especially in C-ADM, and patients with this antibody frequently developed life-threatening acute progressive ILD.

Identification of the autoantigen recognized by the anti-CADM-140 antibody

Because the amount of antigen was too small to be detected using IPP and silver staining, we tried to purify the target antigen using immunoaffinity chromatography. The proteins in each eluate from the charged anti-CADM-140 IgG affinity column are shown in Fig. 3A. To determine which polypeptide is specifically recognized by the anti-CADM-140 antibody, we employed immunoblot using the

<table>
<thead>
<tr>
<th>TABLE 1 Clinical manifestations of 13 patients with the anti-CADM-140 antibody</th>
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<tbody>
<tr>
<td><strong>No.</strong></td>
</tr>
<tr>
<td>Age at onset/sexa</td>
</tr>
<tr>
<td>Gottron</td>
</tr>
<tr>
<td>Heliotrope</td>
</tr>
<tr>
<td>Maximal CK value, IU/l</td>
</tr>
<tr>
<td>Maximal ferritin, ng/ml</td>
</tr>
<tr>
<td>EMG</td>
</tr>
<tr>
<td>RP</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Intersitial pneumonia</td>
</tr>
<tr>
<td>Prognosis</td>
</tr>
<tr>
<td>MSA/MAA</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
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</table>

Fever up means >38°C. Bold emphasis indicates significant values. aAge in years. ND: not done; M: male; F: female.
same sera from which IgG was purified to use for immunoadfinity chromatography (Fig. 3B). The ~135-kDa polypeptide in the 3 M MgCl₂ eluate reacted with the anti-CADM-140-positive serum. We also confirmed that the 135-kDa polypeptide in the 3 M MgCl₂ eluate reacted with other anti-CADM-140-positive sera but not with the anti-CADM-140-negative sera (Fig. 3C). When the band corresponding to the 135-kDa polypeptide was cut out and subjected to peptide mass fingerprinting, it was identified as either IFIH1 (Fig. 4) or splicing factor 3B subunit 3. A polyclonal antibody against human IFIH1 reacted with the 135-kDa polypeptide in the 3 M MgCl₂ eluate (Fig. 3C), suggesting that the 135-kDa protein was IFIH1.

Confirmation of IFIH1 as the CADM-140 antigen

To confirm that the anti-CADM-140 antibody specifically recognized IFIH1, two recombinant human IFIH1 proteins, N-terminal half (536 amino acids) and C-terminal half (518 amino acids), were prepared using an in vitro transcription/translation system. Both polypeptides were labelled with [³⁵S]methionine and immunoprecipitated using the sera of the anti-CADM-140-positive patients, but were not recognized by sera with other autoantibodies or HCs (Fig. 5: C-terminal polypeptide, data of N-terminal polypeptide are not shown.). Thus, we confirmed that IFIH1 was the antigen recognized by the anti-CADM-140 antibody.

Discussion

In these studies, we confirmed that the anti-CADM-140 antibody was specific for DM, especially C-ADM, and closely associated with acute progressive ILD with poor prognosis. In this study all the anti-CADM-140-positive patients had DM, the majority of which were C-ADM, and only two cases had DM with evident myositis (muscle weakness and elevated CK levels), although Sato et al. [3] reported that all of the anti-CADM-140 positive patients were C-ADM. As for sensitivity, the anti-CADM-140 antibody was found in 35% of all DM and 73% of C-ADM patients. Among the 13 anti-CADM-140-positive patients, 7 (54%) developed acute progressive ILD and 6 died within 6 months of disease onset. Such high frequency of intractable acute progressive ILD is consistent with the report of Sato et al. [3]. Thus, the anti-CADM-140 may be also the marker of intractable ILD in ADM.

The incidence of acute ILD in association with C-ADM is frequent in Asia, including Japan, Korea and China [10–13]. By contrast, C-ADM patients seem to have a much better prognosis in North America and Europe [14, 15]. Gerami et al. [16] carried out a systematic review of adult-onset C-ADM in a total of 291 cases reported from over 19 countries. In their review, 15% of the patients with C-ADM or pre-myopathic DM (the term of their definition) developed ILD and only 6% of them died of ILD.

The increased incidence of malignancy in PM/DM patients has been reported in most studies [17–19]. In our study, malignancy occurred in only one (8%) anti-CADM-140-positive patient, whereas it occurred in four (16%) of antibody-negative DM patients. In addition, the clinical course of C-ADM of this patient did not correlate with the concomitant malignant disease. Thus, the presence of the anti-CADM-140 antibody does not seem to be associated with malignancy.

In this study, we demonstrated that the target of the anti-CADM-140 was IFIH1. However, when we prepared this manuscript, Sato et al. [20] also reported that IFIH1/MDA5 was identified as the autoantigen of anti-CADM-140 by screening a HeLa cell-derived cDNA expression library using a phage expression system. IFIH1, also known as MDA5, is one of the RIG-I-like receptors (RLRs), which are involved in the recognition of viral RNAs and play an important role in innate immune

<table>
<thead>
<tr>
<th>Feature</th>
<th>x-CADM-140(+), n = 13</th>
<th>x-CADM-140(−), n = 24</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, mean (s.d.), years</td>
<td>57.3 (9.4)</td>
<td>61.3 (11.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>No. of males/no. of females</td>
<td>3/13</td>
<td>8/16</td>
<td>0.47</td>
</tr>
<tr>
<td>Gottron’s sign, %</td>
<td>92</td>
<td>75</td>
<td>0.38</td>
</tr>
<tr>
<td>Heliotrope rash, %</td>
<td>15</td>
<td>58</td>
<td>0.017</td>
</tr>
<tr>
<td>Muscle weakness, %</td>
<td>46</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Elevation of CK, %†</td>
<td>38</td>
<td>87</td>
<td>0.028</td>
</tr>
<tr>
<td>Elevation of serum ferritin concentration, %</td>
<td>85</td>
<td>33</td>
<td>0.005</td>
</tr>
<tr>
<td>RP, %</td>
<td>8</td>
<td>25</td>
<td>0.38</td>
</tr>
<tr>
<td>Arthritis, %</td>
<td>69</td>
<td>38</td>
<td>0.09</td>
</tr>
<tr>
<td>Malignancy, %</td>
<td>8</td>
<td>17</td>
<td>0.64</td>
</tr>
<tr>
<td>ILD, %</td>
<td>92</td>
<td>54</td>
<td>0.027</td>
</tr>
<tr>
<td>Rapidly progressive ILD, %</td>
<td>54</td>
<td>4</td>
<td>0.001</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>46</td>
<td>8</td>
<td>0.013</td>
</tr>
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</table>

Bold indicates significant values. *CK ≥ 300.
responses. RIG-I and IFIH1/MDA5 are able to interact with the viral RNA and mediate signalling pathways leading to the transcription of the type I IFN and inflammatory cytokines [21, 22]. Because RLRs are highly homologous, Sato et al. [20] evaluated cross-reactivity of the anti-CADM-140 antibody with other RLRs, RIG-I and LGP-2, performing immunoblot using recombinant RLRs, and they revealed all nine anti-CADM-140-positive sera reacted only with recombinant IFIH1, not with recombinant RIG-I or recombinant LGP-2. Then they suggested IFIH1 was specifically recognized by the anti-CADM-140 antibody.

Finding IFIH1 as the autoantigen specifically recognized by one of DM-specific autoantibodies, the anti-CADM-140 antibody, strikingly interested us because many reports have suggested the possible association...
between myositis and viral infections, in particular the Coxsackie virus belonging to the picornaviruses that are targeted by IFIH1. In fact, a high prevalence of the Coxsackie B virus antibodies was found in patients with juvenile DM [23]. Several studies have been carried out searching for viral genomes in the muscle tissue of PM/DM patients, but current data are controversial [24–30]. Despite many reports suggesting an association between infection and myositis, there is no report that shows an association between infection and C-ADM. The discovery of the autoantibody to IFIH1 may give new insights into the aetio-pathogenesis of C-ADM and ILD. Self-tolerance might be broken when IFIH1 interacts with certain viral RNA and generates cryptic epitopes, or when the elevated IFN-β levels upregulate IFIH1 [9], which may lead to overexpression and release from damaged cells.

Not only infection but also the genetic background of the host is essential for the development of the disease and the production of autoantibodies in autoimmune myositis. In animal models of virus-induced muscle inflammation, immune responses are heterogeneous among different strains of mice [31, 32]. There is a report suggesting that the HLA class II antigens correlate to the presence of ILD and MSAs/MAAs in adult-onset myositis [33]. Therefore, the ethnical differences in the frequency of ILD accompanied with C-ADM may be explained by the influence of both genetic and environmental factors on autoimmune phenomena.

In general, hyperferritinaemia is associated with inflammation, infections and malignancies. There are many reports evaluating hyperferritinaemia in patients with autoimmune diseases [34–36]. The highest ferritin levels in autoimmune disorders are typically seen in patients with the macrophage activation syndrome (MAS) often associated with Still’s disease. Ramanan and Baildam [35] suggested that the MAS was a secondary haemophagocytic lymphohistiocytosis (HLH) disorder. In addition, Allen et al. [37] suggested that very high levels of ferritin, >10,000 μg/l, were particularly suggestive of HLH and that HLH might be underdiagnosed in those with high ferritin levels and an illness of unknown cause. In our study, the anti-CADM-140-positive patients frequently showed hyperferritinaemia even before the ILD was exacerbated and, in some cases, the concentration of ferritin elevated to an extremely high level in accordance with their disease activity. These facts may suggest that macrophage activation plays some role in the pathophysiology of ILD with C-ADM.

In summary, patients with DM, especially C-ADM, often develop rapidly progressive ILD, and detecting the anti-CADM-140 antibody in the early stage of the disease is very useful in letting us predict the patients’ clinical course and survival. In this regard, the use of ELISA for detecting the anti-CADM-140 antibody, which was established by Sato et al. [20], gives us much convenience and benefit in daily practice.

To increase our understanding of the pathophysiology of acute ILD accompanied with C-ADM and to develop more effective therapy, we need to investigate whether the IFIH1 and anti-IFIH1 antibody have pathogenic roles in the C-ADM with ILD.

Rheumatology key messages

- The anti-CADM-140 antibody is specific to DM with acute ILD.
- The anti-CADM-140 antibody identifies IFIH1.
- Dysregulated immune response triggered by innate immunity may play a role in the pathophysiology of C-ADM.

Acknowledgement

We thank Dr Shinji Sato from the Keio University School of Medicine for performing IPPs and confirming that the anti-p135 antibody is identical to the anti-CADM-140 antibody.

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Supplementary data

Supplementary data are available at Rheumatology Online.

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