

Letter to the Editor

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Anti-EJ, anti-MDA5 double-positive chronic clinically amyopathic dermatomyositis: a case report

Key message

- Clinical interpretation of coexisting anti-ARS and anti-MDA5 antibodies must be made carefully.

Anti-aminoacyl-tRNA synthetase (ARS) and anti-melanoma differentiation-associated gene 5 (MDA5) antibodies are known to be myositis-specific autoantibodies (MSAs). These antibodies are closely associated with interstitial lung disease (ILD) [1, 2]. These MSAs are, in general, mutually exclusive; therefore, coexistence of these antibodies is rare.

In 2016, a 53-year-old Japanese woman was admitted to our department with a dry cough and dyspnoea, worsening over 2 months. She had been diagnosed with clinically amyopathic DM associated with ILD in 2001. Initially, she had heliotrope rash, facial erythema, Gottron papules with some shallow ulcers, mechanic's hands and periungual erythema. Skin biopsy from the Gottron papule showed interface dermatitis. She had RP but no arthritis. Although muscle pain or weakness was not present, there was a slight elevation of creatine kinase (range of 200–250 U/l) on the blood test and myogenic changes on electromyographic examination in biceps and tibialis anterior (muscle MRI and biopsy were not performed). Initial treatment with prednisolone 30 mg/day (0.8 mg/kg/day) and ciclosporin improved the skin lesions and ILD. She later experienced three episodes of ILD flare-up (in 2002, 2005 and 2007), but increasing prednisolone from maintenance dose of 7–8 mg/day to 30–55 mg/day (0.8–1.0 mg/kg/day) in combination with either ciclosporin or i.v. CYC therapy (500 mg/m² monthly) was successful in inducing remission of ILD each time. The disease was well controlled with prednisolone ~7–8 mg/day and tacrolimus 4 mg/day for 8 years. Anti-glycyl-tRNA synthetase (anti-EJ) antibody was detected by RNA immunoprecipitation in 2001 and 2005.

On admission in 2016, the patient showed heliotrope rash, Gottron papules and mechanic's hands. Muscle weakness and pain were not present. Lung auscultation identified considerable fine crackles bilaterally. Laboratory tests included creatine kinase (71 U/l), lactate dehydrogenase (411 U/l) and CRP (2.1 mg/dl). Investigations for respiratory infection were negative, including sputum specimen culture [1–3], β -D-glucan assay, *Aspergillus* galactomannan assay and IFN- γ release assay for tuberculosis (QuantiFERON-TB). Chest CT showed newly developed peripheral random ground-

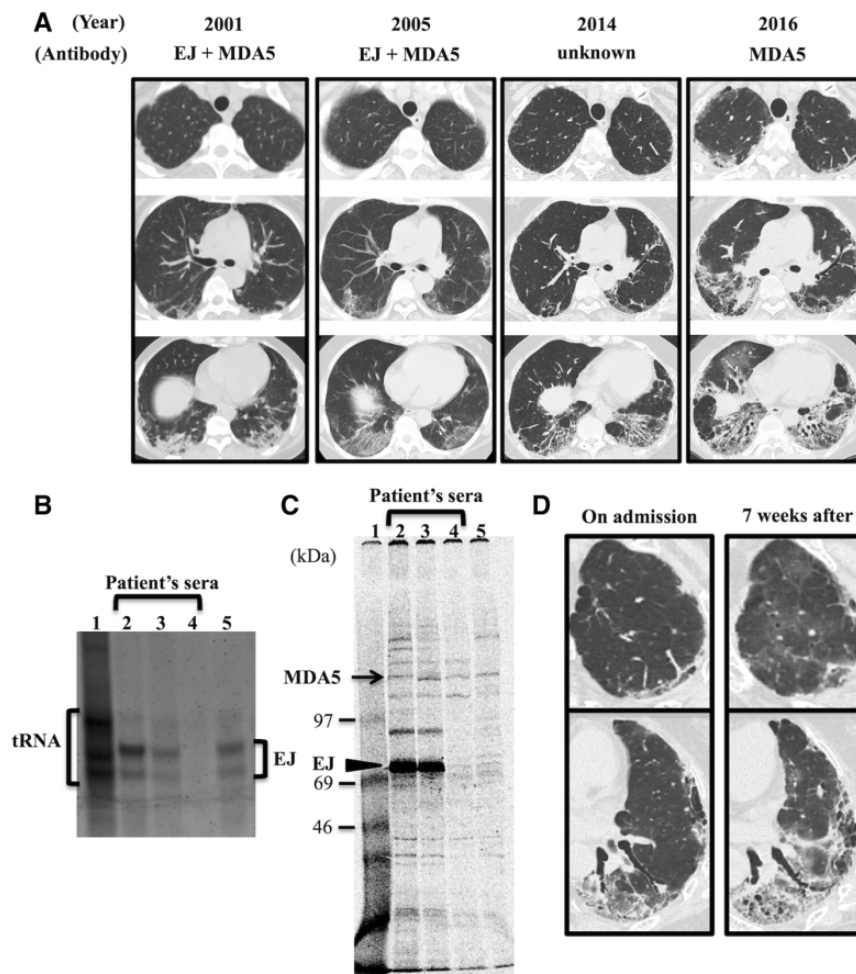
glass attenuation (GGA), marked reticulation, traction bronchiectasis and volume loss in the lower lung field bilaterally (Fig. 1A).

Although anti-EJ antibody had been detected twice previously, RNA immunoprecipitation on admission was negative (Fig. 1B). Anti-MDA5 antibody was detected by ELISA and confirmed by protein immunoprecipitation. We retrospectively screened frozen sera from 2001 and 2005, identifying anti-MDA5 antibody in both samples by ELISA and protein immunoprecipitation (Fig. 1C). We realized that anti-EJ and anti-MDA5 antibodies had coexisted from the onset of disease, but that anti-EJ antibody became negative during the clinical course.

Acute exacerbation of ILD related to clinically amyopathic DM with anti-MDA5 antibody was diagnosed, and we therefore treated our patient with intensive combined immunosuppressive therapy of high-dose prednisolone, tacrolimus and biweekly i.v. CYC therapy. However, her respiratory status deteriorated, and high-flow nasal cannula oxygen therapy was introduced 7 weeks after admission. Follow-up chest CT at the time showed newly developed random GGA (Fig. 1D). Plasmapheresis was then introduced. Subsequent chest CT showed no remarkable deterioration. Plasmapheresis was performed once every 2–3 days, and up to seven times in total, but discontinued when catheter-related infection was suspected. The patient's respiratory condition stabilized, and high-flow nasal cannula oxygen therapy was successfully withdrawn.

Coexistence of anti-ARS and anti-MDA5 antibodies is rare, because MSAs are, in general, mutually exclusive [3]. Only one report has described a case of DM with both anti-ARS (anti-PL-7) and anti-MDA5 antibodies [4]. To the best of our knowledge, ours is the second case with both anti-ARS (anti-EJ) and anti-MDA5 antibodies, but is also unique in that the antibody profile and clinical phenotype changed during the long clinical course.

Clinical features of ILD with anti-ARS antibody (ARS-ILD) or anti-MDA5 antibody (MDA5-ILD) have been well reported. Patients with ARS-ILD respond well to glucocorticoid therapy but suffer from more frequent recurrence than anti-ARS-negative patients [1, 5]. ARS-ILD chest CT is characterized by reticulation, GGA and traction bronchiectasis, which are predominantly distributed in the lower lobe, peripheral and/or peribronchovascular areas. Progression of fibrosis and volume loss of the lower lobe are often observed during a long clinical course [1, 2]. MDA5-ILD is distinguished by rapidly progressive ILD and poor short-term prognosis, especially among Asian populations, and therefore often requires intensive combined immunosuppressive therapy from the outset [5, 6]. Chest CT of MDA5-ILD is reportedly characterized by lower consolidation or a random GGA pattern and absence of intralobular reticular opacities and traction bronchiectasis [7].

Fig. 1 Chest CT images and immunoprecipitation analysis

(A) Chest CT images from 2001 (disease onset), 2005 (second flare-up), 2014 (clinically stable period) and 2016 (on admission). **(B)** RNA immunoprecipitation assay with patient sera. Lane 1, total RNA; lane 2, serum from 2001; lane 3, serum from 2005; lane 4, serum from 2016; lane 5, positive control serum for anti-EJ antibody. **(C)** Immunoprecipitation of polypeptides with patient sera. Lane 1, molecular marker; lane 2, serum from 2001; lane 3, serum from 2005; lane 4, serum from 2016; lane 5, positive control serum for anti-MDA5 antibody; arrow, anti-MDA5 antibody (140 kDa); arrowhead, anti-EJ antibody (75 kDa). **(D)** Chest CT images on admission and 7 weeks later. EJ: glycyl-tRNA synthetase; MDA5: melanoma differentiation-associated gene 5.

In our case, the initial chest CT findings were characterized by lower peripheral reticulation and GGA. The ILD responded well to initial glucocorticoid therapy, but there were several relapses over the following 15 years, along with gradually progressive traction bronchiectasis and volume loss of the lower lobes. The clinical findings and disease course appear to match ARS-ILD. In contrast, 15 years after the onset of disease, acute exacerbation of ILD showed a rapidly progressive course with newly developed random GGA, which is more compatible with MDA5-ILD. Moreover, resistance to high-dose prednisolone and immunosuppressant at this time showed features of MDA5-ILD. Unlike the previous report, which concluded that the clinical course and

chest CT findings of ILD showed combined features of ARS-ILD and MDA5-ILD simultaneously, our patient showed features of ARS-ILD for most of the clinical course, but later gained features of MDA5-ILD when acute exacerbation occurred and anti-ARS antibody was negative.

When anti-ARS and anti-MDA5 antibodies coexist, clinicians are confronted with a problem regarding clinical interpretation because these conditions show significantly different clinical features and require a different intensity of treatment. Whether the clinical course presents as ARS-ILD, MDA5-ILD or a combination is unclear, and thus clinical decisions should be made carefully.

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