Radiological and Pathological Correlation in Anti-MDA5 Antibody-positive Interstitial Lung Disease: Rapidly Progressive Perilobular Opacities and Diffuse Alveolar Damage

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Abstract

We herein present the first case of rapidly progressive interstitial lung disease (RP-ILD) with anti-melanoma differentiation-associated protein 5 (MDA5) antibody evaluated by surgical lung biopsy (SLB). High-resolution CT scan revealed perilobular opacities, which rapidly became thicker and formed consolidation, resulting in remarkable loss of lung volume. Specimens taken from SLB revealed membranous organization with alveolar occlusion, dilation of alveolar ducts, and sacs with collapsed alveoli, which are typical features of diffuse alveolar damage (DAD). Rapidly progressive perilobular opacities may be characteristic of RP-ILD with anti-MDA5 antibody and DAD.

Key words: rapidly-progressive interstitial lung disease, clinically amyopathic dermatomyositis, anti-melanoma differentiation-associated protein 5 antibody, surgical lung biopsy, radiological and pathological correlation, perilobular opacities

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Introduction

Clinically amyopathic dermatomyositis (CADM), a type of dermatomyositis with clinical cutaneous features and subtle or no muscle involvement, occasionally develops into rapidly progressive interstitial lung disease (RP-ILD) with a prevalence of 5-65% (1). Anti-melanoma differentiation-associated protein 5 (MDA5) antibody is a myositis-specific antibody that was identified in 2005 in the sera of patients with CADM (2), although anti-MDA5 antibody is also detected in some ILD patients who have clinical features suggestive of CADM, but do not fully meet the established criteria for CADM (3, 4). Anti-MDA5 antibody is known to be strongly associated with the pathogenesis, disease activity, and an unfavorable prognosis of ILD (5). Although differen-

tiating between specific types of ILD remains challenging and sometimes necessitates surgical lung biopsy (SLB), the aggressive clinical course of anti-MDA5 antibody-positive RP-ILD forces us to reconsider performing biopsies; therefore, the pathological findings remain unclear. We herein report the first case of RP-ILD with anti-MDA5 antibody evaluated by SLB.

Case Report

A 56-year-old man was admitted to our hospital with a 1-week history of fever and fatigue. Antibiotics had been prescribed for suspected bacterial pneumonia 1 week prior to admission to our hospital. Refractory to antibiotics, his symptoms persisted. On admission, physical examination revealed fever (body temperature, 38.0°C), and his oxygen

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Figure 1. A: Chest radiograph on admission reveals reticular shadows in the lower area of both lungs. B: Ground-glass opacities are shown in the subpleural area of both upper lobes on chest CT. C: His chest CT image shows peribular opacities in the subpleural area (arrowheads) of the lower lobes.

saturation by pulse oximetry was 96% on room air; no signs of rash or muscle weakness were observed. Fine crackles were noted in the lower lung fields. Laboratory findings revealed elevated serum levels of Krebs Von den Lungen-6 [685 U/mL (normal, <500 U/mL)] and C-reactive protein [3.31 ng/mL (normal, <0.1 mg/dL)]. Antinuclear antibodies and anti-Jo-1 antibody were not detected. Chest radiography revealed reticular shadows in the lower area of both lungs (Fig. 1A). High-resolution computed tomography (HRCT) scan showed slight ground-glass opacities in the upper lobes (Fig. 1B) and peribular opacities in the lower lobes (Fig. 1C). A pulmonary function test did not suggest a restrictive ventilatory pattern [vital capacity (VC), 3.36 L; % expected VC, 92.6%]. Bronchoalveolar lavage with a recovery rate of 66% from the right middle lobe revealed elevated levels of lymphocytes (25%) and neutrophils (4.5%). On day 26, the ground-glass opacities in the upper lobes observed on admission progressed into peribular opacities on chest CT (Fig. 2A). The area of peribular opacities in the lower lobes observed on admission became consolidation accompanied by a loss of lung volume (Fig. 2B). On day 28 after admission, video-assisted thoracoscopic SLB was performed from the right S3a and S9. Histopathological findings showed acute and organizing diffuse alveolar damage (DAD) without evidence of infection or malignancy (Fig. 3). Some lesions mainly consisted of widespread, poorly aerated

alveoli and intra-alveolar membranous organization, which are typical features of organizing DAD. Other lesions had hallmark features of acute DAD, including hyaline membranes within air spaces and intra-alveolar edema with infiltration by inflammatory cells.

On day 38, Krebs Von den Lungen-6 increased to 1,085 U/mL, and VC remarkably decreased from 3.36 L to 2.07 L (% expected VC, 57%). At that time, periungual erythema and erythema granat appeared on his fingers and toes, and these eruptions evaluated by the dermatologist did not contradict the skin manifestations of dermatomyositis. Although the creatine kinase transiently elevated just after operation, it decreased without any treatment. CADM-associated ILD was suspected according to the skin manifestations and RP-ILD without apparent clinical features of myositis, though the patient did not meet the criteria of CADM. The low-grade fever persisted throughout the hospital stay, and desaturation which persisted after operation rapidly progressed with complaint of dyspnea. On day 40, methyl-prednisolone pulse therapy was initiated; however, respiratory failure progressed. HRCT revealed that the peribular opacities were spreading extensively, forming consolidation with remarkable loss of lung volume (Fig. 2C and D). On day 42, the patient underwent treatment with tacrolimus (3 mg/day), intravenous immunoglobulin, and polymyxin-B direct hemoperfusion for two successive days. Refractory to all treatment,

Figure 2. Radiological course. The HRCT scan just before surgical lung biopsy (SLB) (A, B) and 3 weeks after the SLB (C, D). A: The area of the ground-glass opacity in the upper lobes on admission became peribular opacities (arrowheads). B: The area of the peribular opacities in the lower lobes on admission shows thickening and progression into consolidation (arrowheads) accompanied by loss of lung volume. C: HRCT 3 weeks after the SLB reveals thickening and increased peribular opacities (arrowheads). D: The area of consolidation widely spread in the lower lobes (arrowheads).

Figure 3. Histological findings. High-power views of right S9. A: Membranous organization (arrows) in the alveolar ducts with marked intra-alveolar obliterative fibrosis. (Elastica van Gieson stain, 12x) B: Hyaline membranes, shedding of pneumocytes, and infiltration of inflammatory cells in the alveolar lumina (Hematoxylin and Eosin staining, 12x).

the patient died 2 months after the first consultation. After his death, anti-MDA5 antibody titers were found to be elevated.

Discussion

In this report, we describe the first case of RP-ILD with anti-MDA5 antibody evaluated by SLB. The evaluation of the specimen taken from the SLB revealed acute and organ-

Table. Pathological Findings of CADM Associated ILD with Anti-MDA5 Antibody.

Age / Gender	Specimens and pathological findings	Treatment	Reference	Year
49 F	TBLB: cellular NSIP	mPSL, immunosuppressive therapy, IVIG	6	2008
63 M	Autopsy: DAD	mPSL, IVCY, CyA, PMX	7	2011
9 M	Autopsy: DAD with alveolar hemorrhage	mPSL, IVCY, plasmapheresis	8	2011
77 F	Autopsy: Acute and organizing DAD	mPSL, IVCY, CyA	9	2012
49 M	Autopsy: Exudative and organizing DAD	mPSL, IVCY, CyA	10	2012
Around 60M	TBLB: NSIP	mPSL, IVCY, PMX, sivelestat	11	2013
	Autopsy: Organizing DAD with alveolar hemorrhag			
67 M	TBLB: NSIP	Not described	12	2014
	Autopsy: DAD			
47 F	Autopsy: DAD with alveolar hemorrhage	mPSL, immunosuppressive therapy	13	2014
65 M	SLB: acute and organizing DAD	mPSL, IVCY, CyA, PMX	Our patient	2015

DAD: diffuse alveolar damage, NSIP: nonspecific interstitial pneumonia, TBLB: transbronchial lung biopsy, SLB: surgical lung biopsy, PSL: prednisolone, IVCY: intravenous cyclophosphamide, CyA: Cyclosporin A, IVIG: intravenous high dose immunoglobulin

Figure 4. Radiopathological correlation in right S3a (A, B) and S9 (C, D). A: HRCT shows peribular opacities in right S3a at the time of surgical lung biopsy (SLB). The square indicates the biopsy site. B: A panoramic view of the lung specimen from right S3a shows widespread, poorly aerated alveoli and intra-alveolar organization predominantly involving the subpleural and interlobular septal areas (arrows) (Hematoxylin and Eosin staining, 1×). C: HRCT at the time of the SLB shows consolidation with loss of lung volume in the subpleural area in right S9. The square indicates the biopsy site. D: A lung specimen from S9 demonstrates diffuse collapsed alveoli and membranous organization with fibrosis.

izing DAD in the treatment-naïve phase and clarified the radiopathological correlation. The present case provides two important clinical issues.

First, it is suggested that DAD is the main pathological finding in anti-MDA5 antibody-positive RP-ILD, considering the previous reports and the present case. This is the first case which confirms the pathological findings of RP-

ILD with anti-MDA5 antibody. To date, there are 8 reported cases evaluating the pathological findings of RP-ILD with anti-MDA5 antibody (Table) (6-13). All 8 cases met the criteria of CADM and presented fatal clinical courses, despite intensive therapy. An autopsy was performed in 7 cases, with the pathological examination revealing DAD, similar to the present case. However, 2 out of 7 autopsied cases were

also evaluated with transbronchial lung biopsy (TBLB), with histopathological examination showing nonspecific interstitial pneumonia (NSIP). In the remaining one case evaluated only with TBLB, the NSIP pattern was also observed. Although all specimens obtained by TBLB showed the NSIP pattern, autopsied cases demonstrated the DAD pattern. In the present case, the DAD pattern was also observed in the SLB specimen. We believe that the mechanism underlying the discrepancy in the pathological findings between the TBLB and autopsy could be explained by the sample size (14). In fact, our specimens showed diverse pathological patterns.

Second, perilobular opacity, which rapidly spreads and forms consolidation with remarkable loss of lung volume, is strongly suggestive of RP-ILD with anti-MDA5 antibody and DAD. In general, the typical HRCT findings of ILD with surgically proven DAD pattern include bilateral symmetrical ground-glass opacity with traction bronchiectasis (15-19). However, these features are considerably different from those observed in our case: perilobular opacities were the main radiological findings, which were reported to be the common features in patients with organizing pneumonia (20). In our case, the perilobular opacities became thicker and formed consolidation during the clinical course (Fig. 1C, 2B and D). The area of the perilobular opacities pathologically corresponded to poorly aerated alveoli and intra-alveolar organization with accentuation of the subpleural and interlobular septal areas, which are the features of DAD (Fig. 4A and B). Importantly, perilobular opacities were already present on admission (Fig. 1C), but rapidly spread and formed consolidation (Fig. 2B and D), which pathologically corresponded to membranous organization and fibrosis with the collapse of alveoli (Fig. 4C and D). The present case clearly highlights the pathological change from perilobular opacities to consolidation as mentioned above. Considering the radiological and clinical courses of the case, rapidly progressive perilobular opacities with the loss of lung volume is strongly suggestive of DAD.

Our results provide an important clinical implication; aggressive treatment should be started immediately without SLB in patients with RP-ILD with anti-MDA5 antibody when perilobular opacities are observed. The DAD pattern is pathologically common in lung specimens from acute interstitial pneumonia (AIP), which is known to be a rapidly progressive disease with a poor prognosis. Earlier intervention with intensive immunosuppressive agents was reported to improve the clinical outcome of AIP (21). RP-ILD with anti-MDA5 antibody has pathological findings similar to those of AIP. In addition, similar to AIP, RP-ILD with anti-MDA5 antibody has been reported as a poor prognostic disease with a cumulative 6-month survival rate of approximately 50% (22, 23). Therefore, our pathological findings indicate the necessity of providing early treatment for this disease without SLB in patients with RP-ILD with anti-MDA5 antibody.

In conclusion, we reported the first case of RP-ILD with

anti-MDA5 antibody evaluated by SLB. Chest physicians should be aware that DAD is the main pathological finding and present even in areas of perilobular opacities in RP-ILD with anti-MDA5 antibody. The present case strongly indicates the necessity to immediately initiate aggressive therapy, including steroid pulse therapy and multiple immunosuppressive drugs, when perilobular opacities are observed in RP-ILD.

The authors state that they have no Conflict of Interest (COI).

References

1. Fathi M, Lundberg IE. Interstitial lung disease in polymyositis and dermatomyositis. *Curr Opin Rheumatol* **17**: 701-706, 2005.
2. Ghazi E, Sontheimer RD, Werth VP. The importance of including amyopathic dermatomyositis in the idiopathic inflammatory myositis spectrum. *Clin Exp Rheumatol* **31**: 128-134, 2013.
3. Fischer A, Antoniou KM, Brown KK, et al; ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J* **46**: 976-987, 2015.
4. Labirua A, Lundberg IE. Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. *Curr Opin Rheumatol* **22**: 633-668, 2010.
5. 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* **52**: 1571-1576, 2005.
6. Kumada S, Saito Y, Sogo K, et al. Amyopathic dermatomyositis positive for anti-140kDa polypeptide antibody died from repeated acute flare up of interstitial pneumonia. *Hifuka no Rinsyo (Rinsyo Derma)* **50**: 277-282, 2008 (in Japanese).
7. Kazuma N, Keisuke T, Shigeki N, Mio K, Ryo T, Mari N. Four cases of interstitial pneumonia associated with amyopathic dermatomyositis characterized by the anti-CADM-140 antibody. *Nihon Kokyuki Gakkai Zasshi* **49**: 30-36, 2011 (in Japanese, Abstract in English).
8. Sakurai N, Nagai K, Tsutsumi H, Ichimiya S. Anti-CADM-140 antibody-positive juvenile dermatomyositis with rapidly progressive interstitial lung disease and cardiac involvement. *J Rheumatol* **38**: 963-964, 2011.
9. Morita Y, Kuwagata S, Kato N, et al. 18F-FDG PET/CT useful for the early detection of rapidly progressive fatal interstitial lung disease in dermatomyositis. *Intern Med* **51**: 1613-1618, 2012.
10. Hibino M, Nishiguchi S, Akazawa K, Hikino K, Oe M. A case of rapid progressive interstitial pneumonia with dermatomyositis and atypical cutaneous lesions, characterized by the anti-CADM-140 antibody. *Nihon Kokyuki Gakkai Zasshi (Annals of The Japanese Respiratory Society)* **1**: 27-34, 2012 (in Japanese, Abstract in English).
11. Sakai A, Kita T, Ichikawa Y, Oribe Y, Miyake M, Kasahara K. A case of rapidly progressive interstitial pneumonia with classic dermatomyositis with anti-CADM-140 antibody positive. *Nihon Kokyuki Gakkai Zasshi (Annals of The Japanese Respiratory Society)* **2**: 761-766, 2013 (in Japanese, Abstract in English).
12. Miyake M, Sakai A, Nishijima C, et al. Detection of anti-CADM-140/MDA5 antibodies in patient with classic dermatomyositis developing rapidly progressive interstitial lung disease. *J Dermatol* **41**: 664-665, 2014.
13. Sato K, Morozumi S, Takeuchi Y, Ochiai J, Mabuchi C. A case of dermatomyositis with anti-CADM-140 antibody and alveolar hemorrhage. *Rinsho Shinkeigaku (Clinical Neurology)* **54**: 408-412,

- 2014 (in Japanese, Abstract in English).
14. Churg A, Muller NL. Atlas of interstitial lung disease pathology. In: Pathology with high resolution CT correlations. Lippincott Williams & Wilkins, Wolters Kuwer, 2013.
15. Obadina ET, Torrealba JM, Kanne JP. Acute pulmonary injury: high-resolution CT and histopathological spectrum. *Br J Radiol* **86**: 20120614, 2013.
16. Primack SL, Hartman TE, Ikezoe J, Akira M, Sakatani M, Müller NL. Acute interstitial pneumonia: radiographic and CT findings in nine patients. *Radiology* **188**: 817-820, 1993.
17. Parambil JG, Myers JL, Aubry MC, Ryu JH. Causes and prognosis of diffuse alveolar damage diagnosed on surgical lung biopsy. *Chest* **132**: 50-57, 2007.
18. Ikezoe J, Johkoh T, Kohno N, Takeuchi N, Ichikado K, Nakamura H. High-resolution CT findings of lung disease in patients with polymyositis and dermatomyositis. *J Thorac Imaging* **11**: 250-259, 1996.
19. Akira M, Hara H, Sakatani M. Interstitial lung disease in association with polymyositis-dermatomyositis: long-term follow-up CT evaluation in seven patients. *Radiology* **210**: 333-338, 1999.
20. Ujita M, Renzoni EA, Veeraraghavan S, Wells AU, Hansell DM. Organizing pneumonia: peribular pattern at thin-section CT. *Radiology* **232**: 757-761, 2004.
21. Suh GY, Kang EH, Chung MP, et al. Early intervention can improve clinical outcome of acute interstitial pneumonia. *Chest* **129**: 753-761, 2006.
22. Muro Y, Sugiura K, Hoshio K, Akiyama M, Tamakoshi K. Epidemiologic study of clinically amyopathic dermatomyositis and anti-melanoma differentiation-associated gene 5 antibodies in central Japan. *Arthritis Res Ther* **13**: R214, 2011.
23. Tanizawa K, Handa T, Nakashima R, et al. HRCT features of interstitial lung disease in dermatomyositis with anti-CADM-140 antibody. *Respir Med* **105**: 1380-1387, 2011.