Arch Rheumatol 2018;33(3):376-380
doi: 10.5606/ArchRheumatol.2018.6577

CASE REPORT

Histological Findings of Organizing Pneumonia, Based on Transbronchial Lung Biopsy, May Predict Poor Outcome in Polymyositis and Dermatomyositis: Report of Two Autopsied Cases

Hiroshi OIWA[1], Takeshi KONDO[2], Masamoto FUNAKI[3], Toshiaki MORITO[4], Hiroshi YASUI[5], Toru KAMIYA[6]

[1]*Department of Rheumatology, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan*
[2]*Department of Rheumatology, Medical Corporation Jr Hiroshima Hospital, Hiroshima, Japan*
[3]*Department of General Medicine/Center For Medical Education, Nagoya University Hospital, Nagoya, Japan*
[4]*Department of Pathology, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan*
[5]*Department of Pathology, Rakuwakai Otowa Hospital, Kyoto, Japan*
[6]*Department of General Internal Medicine, Rakuwakai Otowa Hospital, Kyoto, Japan*

ABSTRACT

Interstitial lung disease in polymyositis and dermatomyositis is a serious complication, associated with poor prognosis. In this article, we describe two cases with histological findings of organizing pneumonia (OP), based on transbronchial lung biopsy (TBB). One is a 66-year-old female patient with clinically amyopathic dermatomyositis (CADM) with anti-melanoma differentiation-associated gene 5 antibody, and another is a 61-year-old female patient with polymyositis with anti-Jo-1 antibody. Both of our cases rapidly deteriorated to death, and autopsy findings showed diffuse alveolar damage. Our experience indicates that TBB findings of OP may be a poor prognostic factor in CADM and polymyositis, in spite of the profile of myositis-specific antibodies.

Keywords: Clinically amyopathic dermatomyositis; dermatomyositis; diffuse alveolar damage; organizing pneumonia; polymyositis.

Interstitial lung disease (ILD) in polymyositis/dermatomyositis (PM/DM) is associated with poor prognosis. Particularly, patients with clinically amyopathic dermatomyositis (CADM),[1,2] more recently with anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody, often have rapidly progressive ILD (RP-ILD).[3-5] Autopsy findings frequently reveal diffuse alveolar damage (DAD).[6-8] On the other hand, cryptogenic organizing pneumonia (OP) is one of the idiopathic interstitial pneumonias (IIP),[9,10] and presents as acute or subacute IIP.[10] Chest computed tomography (CT) demonstrates patchy and often migratory consolidation, associated with ground-glass opacity. Cryptogenic OP often responds to corticosteroid treatment, leading to a favorable prognosis.[9,11,12]

Secondary OP associated with collagen vascular diseases had a poorer prognosis than cryptogenic OP.[9,13] In this article, we described two cases with CADM and PM with OP findings, based on transbronchial biopsy (TBB) that subsequently developed DAD.

Received: July 12, 2017 ***Accepted:*** November 27, 2017 ***Published online:*** January 15, 2018

Correspondence: Hiroshi Oiwa, MD. Department of Rheumatology, Hiroshima City Hiroshima Citizens Hospital, 730-8518 Hiroshima, Japan.
Tel: +81-82-221-2291 e-mail: hiroshioiwa@aol.com

Citation:
Oiwa H, Kondo T, Funaki M, Morito T, Yasui H, Kamiya T. Histological Findings of Organizing Pneumonia, Based on Transbronchial Lung Biopsy, May Predict Poor Outcome in Polymyositis and Dermatomyositis: Report of Two Autopsied Cases. Arch Rheumatol 2018;33(3):376-380.

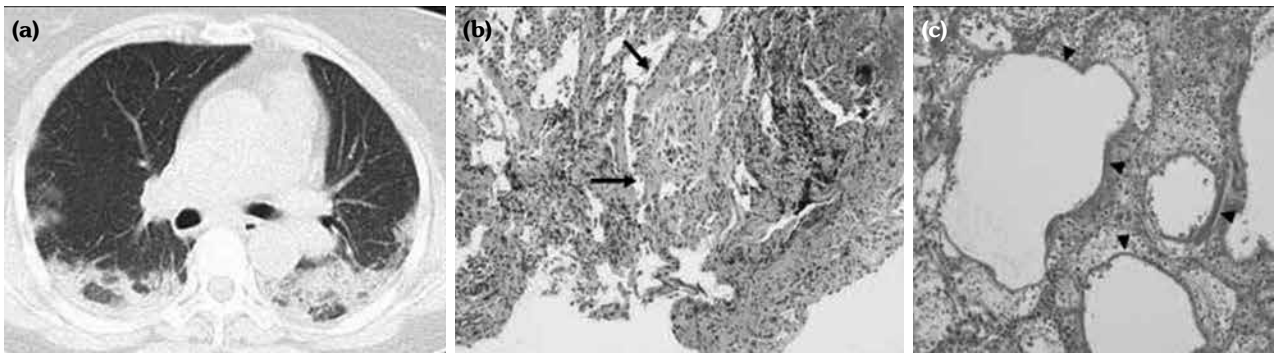

Figure 1. (a) Chest tomography showed consolidations and ground glass opacities in subpleural area. **(b)** Transbronchial biopsy showed polypoid masses of granulation tissue within alveoli, consistent with organizing pneumonia (arrow) (H-E×200). **(c)** Autopsy findings showed infiltration of inflammatory cells and hyaline membranes, consistent with diffuse alveolar damage (arrowhead) (H-E×200).

CASE REPORT

Case 1- A 66-year-old female patient was admitted with a two-week history of dry cough and exertional dyspnea. She also had photosensitivity and rashes on elbows for one year. Medical history included hysterectomy for endometrial cancer 17 years ago. Her oxygen saturation was 93% on room air. There were fine crackles in the lung bases. Manual muscle testing showed normal strength. Erythema was observed on the anterior chest, and the extensor surface of the right elbow (Gottron's sign). On laboratory test, ferritin level was highly elevated at 2110 ng/mL (≤114), while creatine kinase (CK) level was normal. A level of KL-6 (Krebs von den Lungen 6), a serum marker for interstitial pneumonia,[6] was normal. Anti-nuclear antibody and anti-Sjögren's syndrome antigen A (SSA/Ro) antibody were positive at 40-fold dilution (normal, <40-fold dilution) and 12.8 U/mL (<7.0 U/mL), respectively, while anti-aminoacyl transfer ribonucleic acid synthetase (ARS) antibodies were not detected. Chest CT showed consolidation and patchy ground-glass opacities, predominantly in the lower lobes (Figure 1a). T_2-weighted images of magnetic resonance imaging (MRI) of the thighs revealed high-signal lesions in the vastus lateralis muscles, while electromyogram and muscle biopsy showed no signs of myositis. Skin biopsy from the extensor surface of the right elbow revealed massive subepidermal edema and dermal mucinosis with hyperkeratosis, compatible with DM. TBB showed pathological findings of OP (Figure 1b). Then, a diagnosis of CADM with OP was established. Despite treatment with pulse methylprednisolone

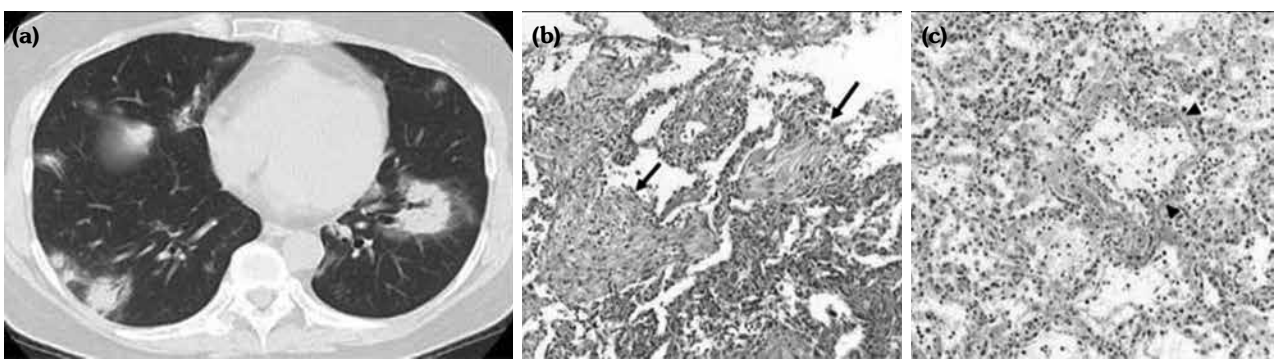

Figure 2. (a) Chest tomography showed multiple nodules and consolidations in subpleural area. **(b)** Transbronchial biopsy showed polypoid fibrotic tissue within alveoli, consistent with organizing pneumonia (arrow) (H-E×200). **(c)** Autopsy findings showed hyaline membranes and inflammation, consistent with diffuse alveolar damage (arrowhead) (H-E×200).

followed by high-dose prednisolone and intravenous cyclophosphamide, her condition deteriorated further. Additional therapy with tacrolimus failed and she subsequently died. Autopsy revealed DAD (Figure 1c). Anti-MDA5 antibody was latterly found in her pre-treatment sera, using immunoprecipitation technique.[14]

Case 2- A 61-year-old female patient was referred for suspected myositis. Eight months previously, she began to have cough and sputum. Three months later, chest CT showed multiple nodules and consolidations in all the lung lobes (Figure 2a), and TBB showed histological findings consistent with OP (Figure 2b). A diagnosis of cryptogenic OP was established, and moderate-dose prednisolone treatment improved her symptoms. A month before admission, she was admitted to the previous hospital for worsening of pneumonia, muscle weakness and elevation of CK (887 U/L). T_2-weighted images of MRI showed high-signal lesions in the gluteus maximus muscles. The result of anti-Jo-1 antibody was positive. After methylprednisolone pulse therapy followed by high-dose prednisolone, she was transferred to our hospital. Medical history included appendicitis in her childhood, and hysterectomy for uterine myoma. Her respiratory rate was 21 per minute and oxygen saturation 93% on room air. There were fine crackles in the lung bases. Manual muscles testing showed 3 out of 5 at all the muscle tested. Laboratory testing showed increased levels of CK (514 U/L; <163) and KL-6 (942U/mL; ≤500). Anti-nuclear antibody and anti-SSA/Ro were negative.

Although we could not plan electromyogram and muscle biopsy for deteriorating course, she was considered to have OP with PM, as previously reported to often precede PM.[15] Despite therapy with tacrolimus, her condition deteriorated. After another course of pulse methylprednisolone, she died of respiratory failure. Autopsy revealed DAD (Figure 2c).

DISCUSSION

In our cases with CADM and PM, TBB showed histological findings of OP. Although the role of TBB in diagnosing OP is limited due to small sample, TBB may be adequate to establish working diagnosis of OP, when clinical and radiological findings are consistent with OP.[16-18] Our cases had histological findings of OP, based on TBB, and subsequently died of DAD. Two possibilities may be considered: *(i)* OP lesions alone at initial presentation that subsequently developed to DAD, *(ii)* coexistence of OP and DAD at initial presentation, in which TBB specimen only included OP lesions. Nevertheless, our experience suggests that TBB findings of OP may predict respiratory deterioration due to DAD in PM and CADM.

After the proposal of CADM,[1,19] an association with RP-ILD gained importance, and thereafter, anti-MDA5 antibody was exclusively discovered in CADM and DM patients.[19-21] A retrospective study showed that 20 (74%) of 27 anti-MDA5 positive patients developed RP-ILD, and nine (33%) subsequently died.[22] Multiple cutaneous ulcers,[23] high titer of the antibody,[24] and ferritin elevation[3,22] have been advocated as poor prognostic factors. Gono et al.[3] reported that all five cases with a ferritin level ≥1,600 subsequently died, as seen in our case (Case 1).

On the other hand, nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia, categorized as chronic fibrosing interstitial pneumonia,[11] is the predominant pattern in anti-ARS antibody-associated IIP.[24,25] However, acute or subacute interstitial pneumonia in anti-ARS positive ILD was also reported in 67%,[5] and even RP-ILD in 5%-18%.[26,27] In an observation of anti-ARS-positive IIP, OP was the second most frequent pattern identified on surgical lung biopsy (52%), after NSIP (67%). Interestingly, OP was found solely in 19%, and concomitantly with NSIP or DAD in 33%.[25] Therefore, the histological findings of OP in Case 2 may also be explained by OP alone or concomitant OP.

Out of 29 previously-reported cases with histological findings of OP with PM/DM/CADM,[17,28,29] mortality was 21%, which was higher than the pooled mortality (6%) in cryptogenic OP.[11] To our knowledge, ours were the first cases with histological findings of OP on TBB, subsequently developing DAD. We propose that TBB findings suggesting OP in PM/DM/CADM may predict poor prognosis, regardless of the profile of myositis-specific antibody.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Gerami P, Schope JM, McDonald L, Walling HW, Sontheimer RD. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis siné myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. J Am Acad Dermatol 2006;54:597-613.
2. Kang EH, Lee EB, Shin KC, Im CH, Chung DH, Han SK, et al. Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis. Rheumatology (Oxford) 2005;44:1282-6.
3. Gono T, Kawaguchi Y, Satoh T, Kuwana M, Katsumata Y, Takagi K, et al. Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford) 2010;49:1713-9.
4. Tanizawa K, Handa T, Nakashima R, Kubo T, Hosono Y, Watanabe K, et al. HRCT features of interstitial lung disease in dermatomyositis with anti-CADM-140 antibody. Respir Med 2011;105:1380-7.
5. Isoda K, Kotani T, Takeuchi T, Kiboshi T, Hata K, Ishida T, et al. Comparison of long-term prognosis and relapse of dermatomyositis complicated with interstitial pneumonia according to autoantibodies: anti-aminoacyl tRNA synthetase antibodies versus anti-melanoma differentiation-associated gene 5 antibody. Rheumatol Int 2017;37:1335-40.
6. Bandoh S, Fujita J, Ohtsuki Y, Ueda Y, Hojo S, Tokuda M, et al. Sequential changes of KL-6 in sera of patients with interstitial pneumonia associated with polymyositis/dermatomyositis. Ann Rheum Dis 2000;59:257-62.
7. Kameda H, Nagasawa H, Ogawa H, Sekiguchi N, Takei H, Tokuhira M, et al. Combination therapy with corticosteroids, cyclosporin A, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. J Rheumatol 2005;32:1719-26.
8. Yoshida N, Kaieda S, Tomozoe K, Tajiri M, Wakasugi D, Okamoto M, et al. An Autopsy Case of Anti-melanoma Differentiation-associated Gene-5 Antibody-positive Clinical Amyopathic Dermatomyositis Complicated by Rapidly Progressive Interstitial Lung Disease. Intern Med 2016;55:1653-9.
9. Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. Bronchiolitis obliterans organizing pneumonia. N Engl J Med 1985;312:152-8.
10. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188:733-48.
11. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;63:1-58.
12. King TE Jr, Mortenson RL. Cryptogenic organizing pneumonitis. The North American experience. Chest 1992;102:8-13.
13. Lohr RH, Boland BJ, Douglas WW, Dockrell DH, Colby TV, Swensen SJ, et al. Organizing pneumonia. Features and prognosis of cryptogenic, secondary, and focal variants. Arch Intern Med 1997;157:1323-9.
14. Nakashima R, Imura Y, Kobayashi S, Yukawa N, Yoshifuji H, Nojima T, et al. The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody. Rheumatology (Oxford) 2010;49:433-40.
15. Oiwa H, Maeda A, Nishisaka T, Yamanishi Y, Yamana S, Takanashi A. A case of polymyositis complicated with organizing pneumonia: case report and literature review. Mod Rheumatol 2004;14:388-93.
16. Bartter T, Irwin RS, Nash G, Balikian JP, Hollingsworth HH. Idiopathic bronchiolitis obliterans organizing pneumonia with peripheral infiltrates on chest roentgenogram. Arch Intern Med 1989;149:273-9.
17. Azzam ZS, Bentur L, Rubin AH, Ben-Izhak O, Alroy G. Bronchiolitis obliterans organizing pneumonia. Diagnosis by transbronchial biopsy. Chest 1993;104:1899-901.
18. Dina R, Sheppard MN. The histological diagnosis of clinically documented cases of cryptogenic organizing pneumonia: diagnostic features in transbronchial biopsies. Histopathology 1993;23:541-5.
19. Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis siné myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J Am Acad Dermatol 2002;46:626-36.
20. Sato S, Hirakata M, Kuwana M, Suwa A, Inada S, Mimori T, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum 2005;52:1571-6.
21. Sato S, Hoshino K, Satoh T, Fujita T, Kawakami Y, Fujita 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;60:2193-200.
22. Gono T, Sato S, Kawaguchi Y, Kuwana M, Hanaoka M, Katsumata Y, et al. Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. Rheumatology (Oxford) 2012;51:1563-70.
23. Cao H, Pan M, Kang Y, Xia Q, Li X, Zhao X, 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 (Hoboken) 2012;64:1602-10.
24. Yousem SA, Gibson K, Kaminski N, Oddis CV, Ascherman DP. The pulmonary histopathologic manifestations of the anti-Jo-1 tRNA synthetase syndrome. Mod Pathol 2010;23:874-80.
25. Chartrand S, Swigris JJ, Peykova L, Chung J, Fischer A. A Multidisciplinary Evaluation Helps Identify the Antisynthetase Syndrome in Patients Presenting as Idiopathic Interstitial Pneumonia. J Rheumatol 2016;43:887-92.
26. Gono T, Kaneko H, Kawaguchi Y, Hanaoka M, Kataoka S, Kuwana M, et al. Cytokine profiles in polymyositis and dermatomyositis complicated by rapidly progressive or chronic interstitial lung disease. Rheumatology (Oxford) 2014;53:2196-203.
27. Chen Z, Cao M, Plana MN, Liang J, Cai H, Kuwana M, et al. Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. Arthritis Care Res (Hoboken) 2013;65:1316-24.
28. Park SH, Kum YS, Kim KC, Choe JY, Park SH, Kim SK. Pneumomediastinum and subcutaneous emphysema secondary to amyopathic dermatomyositis with cryptogenic organizing pneumonia in invasive breast cancer: a case report and review of literature. Rheumatol Int 2009;29:1231-5.
29. Lim JU, Kang HS, Kim YH, Kim TJ. Amyopathic Dermatomyositis Associated with Histopathological Findings of Organizing Pneumonia and Pulmonary Vasculitis. Balkan Med J 2017;34:374-7.