A Case of Unresolving Pneumonia

Sawako Kaku Hosokawa, MD,1 Shuhei Yamamoto, MD,2 Yuki Kataoka, MD, MPH,1,3 and Taro Shimizu, MD, MBA, MPH,4

1 Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center
2 Department of General Medicine, Hyogo Prefectural Amagasaki General Medical Center
3 Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical Center
4 Division of General Internal Medicine, Tokyo Joto Hospital, Tokyo, Japan

A 33-year-old woman was transferred to our hospital for an unresolving pneumonia, who initially presented with dyspnea. Initially antibiotic therapy was started under the suspicion of community-acquired pneumonia, however, her respiratory status worsened at the previous hospital. Computed tomography (CT) on presentation showed peripheral ground glass opacities in both sides of the upper lobe. Also despite additional prednisolone therapy, her respiratory status worsened.

On admission to our hospital, physical examination showed Gottorón’s sign in her right elbow. From the nature of the rash, the absence of myositis symptoms and rapid respiratory worsening, we suspected clinically amyopathic dermatomyositis (CADM). After the triple drug therapy, her respiratory status improved.

Keywords: dyspnea, interstitial lung disease, periungual erythema, CADM

Case Presentation
A 33-year-old Japanese woman was referred to our hospital because of progressive dyspnea. Three months before admission to our hospital, she noticed weight loss. A month before the admission, she complained of general malaise and low-grade fever. She visited a hospital. Her oxygen saturation was under 90%. The findings of chest X-ray and computed tomography (CT) of the chest were bilateral infiltration shadows. She was diagnosed as having community-acquired pneumonia. She was admitted and treated with meropenem and clindamycin. One day later, her respiratory status had not improved despite the treatment. The next day, azithromycin and micafungin were added, however, they did not give any improvement. She was then transferred to our hospital on the 2nd hospital day for further evaluation and treatment.

At the time of admission, her major symptoms were low-grade fever, malaise, weight loss, anorexia, dyspnea, and dry cough. She denied chills, headache,

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lymph node swelling, sputum, palpitations, edema, or arthralgia. Past medical history included endometriosis that was well controlled without medication, and her menstrual cycle tended to be prolonged. She had no significant family history. She did not smoke or drink alcohol. She had no known allergies. She denied any exposures to sick persons including those with tuberculosis, farm or domestic animals and birds, and mosquito or tick bites, and she had not travelled recently. Last year she moved to a newly-built condominium. She denied sexual history.

Dyspnea is defined as an abnormally uncomfortable awareness of breathing, commonly seen in the primary care setting; its intensity is quantified by establishing the amount of physical exertion necessary to produce the sensation. In a setting of a one-month history of dyspnea which is refractory to antibiotics with chest X-ray infiltration shadows, there are multiple possibilities to note cardiovascular disease (such as chronic pulmonary embolism, infective endocarditis, congestive heart failure), infections (such as mycobacterium infection, pneumocystis pneumonia), drug induced pneumonia and autoimmune diseases (such as chronic hypersensitivity pneumonitis, chronic eosinophilic pneumonia, interstitial lung disease (ILD) related to connective tissue disease, vasculitis, sarcoidosis), neoplasms (lymphoma, primary and metastatic lung cancer), and Idiopathic interstitial pneumonia (i.e., IIPs) such as idiopathic pulmonary fibrosis, asbestosis), and may be present before detection of changes on radiological examination. Otherwise, given other nonspecific physical examination findings above lowers the possibility of cardiovascular disease, connective tissue disease, and vasculitis. There were no manifestations indicative of collagen diseases, such as arthritis or eruptions, at that time. The periungual erythema was not considered as a specific symptom associated with connective tissue diseases at the time through a discussion with a dermatologist, and she was treated with difluprednate.

Laboratory data are shown in Table 1. The white blood cell count was 8,800/μL. Serum creatinine kinase was normal. Ferritin was 360 ng/mL. The serum lactate dehydrogenase (LDH) level was elevated [360 IU/L; normal range, 119–229 IU/L]. CRP was 1.3 mg/dL. Serum KL-6 was elevated [667 U/mL; normal < 500 U/mL]. Antinuclear antibody (ANA) was positive at 1:80 with both perinuclear and cytoplasmic.
patterns. Anti-double strand deoxyribonucleic acid antibody was negative (normal < 20 IU/mL), and anti-Jo-1 antibody and other autoantibodies to specific antigens were all negative.

The chest radiograph on admission revealed bilateral reticular shadows adjacent to the pleura (Figure 1A). Chest CT (Figure 1B and Figure 1C) showed randomized peripheral ground glass opacities and consolidation of both lower lungs.

Table 1. Laboratory data

<table>
<thead>
<tr>
<th>CBC</th>
<th>8800 /µL</th>
</tr>
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<tbody>
<tr>
<td>Neutrophil</td>
<td>83.6 %</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>3.3 %</td>
</tr>
<tr>
<td>Basophil</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>6.3 %</td>
</tr>
<tr>
<td>Monocyte</td>
<td>6.3 %</td>
</tr>
<tr>
<td>RBC</td>
<td>385 × 10^6 /µL</td>
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<tr>
<td>Ht</td>
<td>33.1 %</td>
</tr>
<tr>
<td>Hb</td>
<td>10.5 g/dl</td>
</tr>
<tr>
<td>MCV</td>
<td>90.0 Fl</td>
</tr>
<tr>
<td>MCH</td>
<td>32.0 Pg</td>
</tr>
<tr>
<td>Plt</td>
<td>28.2 × 10^4 /µL</td>
</tr>
<tr>
<td>T-Bil</td>
<td>0.3 Mg/dl</td>
</tr>
<tr>
<td>AST</td>
<td>55 IU/L</td>
</tr>
<tr>
<td>ALT</td>
<td>38 IU/L</td>
</tr>
<tr>
<td>ALP</td>
<td>247 IU/L</td>
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<tr>
<td>γ-GTP</td>
<td>0.3 IU/L</td>
</tr>
<tr>
<td>TP</td>
<td>7.7 g/dl</td>
</tr>
<tr>
<td>Alb</td>
<td>2.5 g/dl</td>
</tr>
<tr>
<td>LDH</td>
<td>360 IU/L</td>
</tr>
<tr>
<td>CRP</td>
<td>1.3 mg/dl</td>
</tr>
<tr>
<td>Na</td>
<td>140 mEq/L</td>
</tr>
<tr>
<td>K</td>
<td>3.1 mEq/L</td>
</tr>
<tr>
<td>Cl</td>
<td>110 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>8.4 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.32 mg/dl</td>
</tr>
<tr>
<td>Blood Suger</td>
<td>93 mg/dl</td>
</tr>
<tr>
<td>Ferritin</td>
<td>360 IU/L</td>
</tr>
</tbody>
</table>

Cryptococcus antigen (—)
β-D glucan 6.0 ng/ml
Procalcitonin 0.122 pg/ml
Cytomegalovirus antigen (—)
Tuberculosis Interferon-Gamma Release Assays
HTLV-1 antibody (—)
HIV 1/2 antibody (—)
Legionella urinary antigen assay (—)

IgG 1715 mg/dl
IgA 425 mg/dl
IgM 225 mg/dl
RF 10 IU/ml
MMP-3 41.3 ng/ml
ANA 80
dsDNA 2.0 IU/ml
c-ANCA (—)
p-ANCA (—)

Anti RNP antibody (—)
Anti Sm antibody (—)
Anti Scl-70 antibody (—)
Anti Jo-1 antibody (—)
Anti ARS antibody (—)
Anti mitochondria antibody (—)

Laboratory data did not show eosinophilia or renal dysfunction. Random peripheral ground glass opacities and consolidation appeared in both lower peripheral lungs, which suggested an organizing pneumonia pattern. Based on the CT pattern, tuberculosis, pneumocystis pneumonia, pulmonary edema, and sarcoidosis were less likely. The relative and absolute cell counts findings in bronchoalveolar lavage (BAL) fluid is sometimes useful in a variety of ILD.3

Continued.
Pathological finding from transbronchial lung biopsy (TBLB) also has the possibility as auxiliary diagnosis. So we performed bronchoscopy and got the BAL fluid and Transbronchial lung biopsy. BAL fluid showed 67% macrophages, 17% lymphocyte, 15% neutrophil, and 1% eosinophil. CD4/CD8 ratio was 1.5 and Grocott staining did not show *Pneumocystis jirovecii*. Transbronchial lung biopsy indicated atypical interstitial pneumonia, but it did not show any other specific findings. Cryptogenic organizing pneumonia was suspected from the history, CT, and the pathological findings. Prednisolone (40 mg/day) was started, and her clinical symptoms improved in a week. She complained less dyspnea and oxygenation was improved slightly. However, her respiratory status gradually worsened again 3 weeks after the beginning of the treatment, and she finally required 15 L/min of oxygen. At 3 weeks after the admission, CT showed worsening of the interstitial shadow. From the progressive ILD which is resistant for antibiotics and steroid therapy, we discussed the possibility of ILD associated with collagen disease. Dermatomyositis sometimes causes rapidly progressive ILD. We tried to check dermatological examination again. Physical examination showed newly observed swelling of bilateral upper eyelids (Figure 2A). Painful periungual erythema was observed in all fingers (Figure 2B). A scaly erythematous eruption at the right elbow was found, which was highly suggestive of Gottron’s papule (Figure 2C).

The eyelid swelling without pruritus suggests a heliotrope rash. The scaly erythematous eruption at the right elbow is often seen in dermatomyositis.

Since the patient developed acute progressive respiratory failure with ILD, dermatological manifestations of dermatomyositis without muscle symptoms and a normal muscle enzyme level, clinically amyopathic dermatomyositis (CADM) was suspected.

CADM is characterized by cutaneous manifestations of classical DM occurring for 6 months or longer with no clinical evidence of proximal muscle weakness. Although the duration was less than 6 months, it was decided to start treatment for CADM because of the patient’s severe respiratory status. The anti-MDA5 (CADM-140) antibody is considered to be useful as a specific serological marker for
Combination therapy with 50 mg oral prednisolone (1 mg/kg/day), 200 mg/day cyclosporine A, and cyclophosphamide every two weeks was started. Her oxygen saturation improved immediately within a week. After a week, she needed only 5 L/min of oxygen. Her clinical condition and the skin lesions also improved gradually. Every two-week 750 mg/body cyclophosphamide therapy was given a total of 8 times, and prednisolone was gradually tapered in parallel. Her respiratory status finally improved so that oxygen therapy was not necessary, and she was discharged on the 139th hospital day.

**Discussion**

This was a case of a 33-year-old woman with rapidly progressive dyspnea caused by ILD with periungual erythema that turned out to be CADM.

To diagnose classical dermatomyositis (CDM), the Bohan and Peter Criteria are frequently used. This set of classification criteria consists of the occurrence of typical rash of dermatomyositis and at least three of the other four individual features: symmetric proximal muscle weakness, muscle biopsy evidence of myositis, or increased serum skeletal muscle enzymes, and characteristic electromyographic pattern.

CADM is described as cutaneous manifestations of classical DM occurring for 6 months or longer without clinical evidence of proximal muscle weakness. It consists of two subtypes, amyopathic DM (ADM) and hypomyopathic dermatomyositis (HDM). Patients who have no muscle symptoms and who do not meet the criteria of CDM are classified as ADM. There are several sets of classification criteria. According to Gerami’s definition of terms, ADM is a subset of DM characterized by biopsy-confirmed hallmark cutaneous manifestations of CDM occurring for 6 months or longer, with no clinical evidence of proximal muscle weakness, no serum muscle enzyme abnormalities, no electrophysiology abnormalities, or no radiologic abnormalities; HDM differs from ADM in that, although these patients do not exhibit any clinical evidence of muscle weakness, they may have subclinical evidences of muscle involvement on laboratory, electrophysiology, and/or radiologic evaluation. CADM encompasses both the amyopathic and hypomyopathic DM groups and predominant clinical problem of CADM is protracted skin disease.

The prevalence of CADM within the DM population is not clear. In the only small retrospective population-based study, 21% of DM patients had CADM. A typical clinical picture of ILD in DM is mild, chronic, and non-progressive course with immunosuppressive treatment, while rapidly progressive ILD may occur in some cases. The proportion of rapidly progressive ILD secondary to CADM is unknown. In Asia, the prevalence of rapidly progressive ILD in CADM may be higher than in other countries and that may be related to increased mortality, despite a lack of direct comparisons. According to a study in Japan, DM patients with normal CPK levels showed poor prognosis since they developed corticosteroid-resistant ILD.

The prognosis of ILD in CADM patients also varies with type of antibodies. Anti-aminoacyl transfer RNA
synthetase (ARS) antibody is a major myositis-specific autoantibody and is useful for the diagnosis of polymyositis and dermatomyositis (PM/DM). ILD has common pulmonary manifestations in patients who are anti-ARS antibody-positive and it has a good response to steroid therapy. On the other hand, anti-melanoma differentiation-associated gene 5 (MDA5) antibody (anti-CADM-140 antibody) is also one of the myositis-specific autoantibodies and is associated with a fatal outcome due to acute progressive ILD. Anti-MDA5 antibody is relatively specific, seen in 40–70% of CADM cases, while its presence is relatively uncommon (0–10%) in classic DM, and it is useful for the early diagnosis of ILD with DM. Hyperferritinemia is a factor that can be used to predict disease severity and prognosis for anti-MDA5 antibody-positive patients, especially when the ferritin level is over 1600 ng/mL. The predominant patterns in the chest CT findings of anti-MDA5 antibody-positive cases were lower consolidation or ground-glass attenuation (GGA) pattern (50.0%) and random GGA pattern (33.3%). They were also well characterized by the absence of intralobular reticular opacities.

The best therapy for CADM has not yet been established, but early combined immunosuppressive therapy with high-dose prednisolone (PSL) and intravenous pulse cyclophosphamide every 3–4 weeks has been pointed out to be more effective than high-dose PSL and one immunosuppressive agent. It is important to diagnose CADM in its early stage because of its poor prognosis. However, in the present case, the underestimation of the importance of the periungual erythema and the late appearance of Gottron’s papules delayed the diagnosis. There have been few studies of the nail changes of PM/DM, hence the diagnostic value of periungual erythema in the setting of CADM is unclear. According to a case-control study in Turkey, splinter hemorrhages and capillary loops in the proximal nail fold in fingernails are significantly frequent in PM/DM patients, but the prevalence of periungual erythema remains obscure. However, periungual erythema had a high specificity for systemic lupus erythematosus in this study, and there were no cases in the control group without connective tissue disease with periungual erythema. Thus, periungual erythema should be considered as a meaningful sign.

From the other reports, heliotrope erythema, Gottron’s papules, and periungual erythema were the most frequent skin lesions; 15% of patients with dermatomyositis show atypical skin lesions. In anti-MDA5-positive cases, it is characteristic to have skin ulceration, tender palmar papules, or both. Typical areas of skin ulceration include lateral nail folds and elbows. In some cases, erythema is also shown on the upper eyelids, fingers and elbows. Patients also had an increased risk of oral soreness and/or ulceration, hand swelling, arthritis/arthritis, and diffuse hair loss.

**Conclusion**

This case was a challenging example in diagnosing CADM that progressive respiratory failure with ILD and periungual erythema might be a clue for the diagnosis. Whenever acute or subacute ILD is found, it is pivotal to examine carefully for skin changes and if those exist, consider CADM with positive anti-CADM-140 antibody.

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**References**


