Trends in Immunotherapy (2017) Volume 1 Issue 1
doi: 10.24294/ti.v1.i2.49

CASE REPORT

Treatment of a case with anti-MDA5 antibody-positive clinically amyopathic dermatomyositis complicated with stomach cancer and colon cancer

Mana Nishiguchi, Fukumi Furukawa, Takaharu Ikeda*

Department of Dermatology, Wakayama Medical University Graduate School of Medicine, Kimiidera 811-1, Wakayama City, Wakayama, Japan

ABSTRACT

A 74-year-old woman noticed an edematous erythema on the right upper eyelid two months before her first medical examination, and slight fever, arthralgia and edematous erythema on the forearms and palms around the time of the first medical examination. She presented with typical skin lesions of dermatomyositis including Gottron's signs and a heliotrope rash without any abnormal muscle symptoms. An examination by gastrointestinal endoscopy and a computed tomography scan of the chest revealed that she was complicated with stomach cancer (Stage I A), colon cancer (Stage I) and interstitial pneumonia (IP). She was diagnosed with anti-MDA5 antibody-positive clinically amyopathic dermatomyositis (CADM) complicated with two cancers. Because the IP became aggravated, she was treated with corticosteroids at an initial dose of 1 mg/kg/day and immunosuppressive therapies. Tacrolimus was discontinued due to thrombocytopenia, and she also had an allergic reaction to cyclophosphamide. The administration of azathioprine at a dose of 75 mg/day prevented the exacerbation of IP. We were able to taper the dose of corticosteroids, and endoscopic stomach surgery and abdominal rectal surgery was performed. The anti-MDA5 antibody is a characteristic myositis-specific autoantibody associated with CADM and IP, which may cause a poor prognosis. CADM complicated with malignancy occurs less frequently than similarly complicated dermatomyositis and, to the best of our knowledge, this is the first case of CADM complicated with two cancers.

Keywords*: anti-MDA5 antibody; clinically amyopathic dermatomyositis; colon cancer; gastric cancer; interstitial pneumonia*

ARTICLE INFO
Received: May 25, 2017
Accepted: June 29, 2017
Available online: July 10, 2017

***CORRESPONDING AUTHOR**
Takaharu Ikeda, Department of Dermatology, Wakayama Medical University Graduate School of Medicine, Kimiidera 811-1, Wakayama City, Wakayama, 641-0012, Japan; t-ikeda@wakayama-med.ac.jp

CITATION
Nishiguchi M, Furukawa F, Ikeda T. Treatment of a case with anti-MDA5 antibody-positive clinically amyopathic dermatomyositis complicated with stomach cancer and colon cancer. Trends Immunother 2017; 1(1): 89–92.doi: 10.24294/ti.v1.i2.49.

Introduction

Clinically amyopathic dermatomyositis (CADM) presents with skin lesions typical of dermatomyositis (DM) with few or no abnormal muscle symptoms or nor high titers of myogenic enzymes. CADM includes amyopathic dermatomyositis (ADM) and hypomyopathic dermatomyositis[1]. CADM is likely to complicate with rapidly progressive interstitial pneumonia (IP), and DM complicated with malignancy is often resistant to treatment. Interstitial lung lesions and malignancy affect the prognosis of DM. The prognosis and the degree of organ involvement can be predicted by myositis-specific autoantibodies (MSA). In Japan, 10.9%–25.6% of DM patients[2–4] and 53.3%–66.7% of CADM patients[4,5] are positive for the anti-MDA5 antibody. It is one of the MSAs and is associated with IP, which may result in a poor prognosis. Malignancy is observed in 7.6%–32.7% of DM patients[2–4] and in 0–28.6% of anti-MDA5 antibody-positive cases[2,4,5–7]. We report a case of anti-MDA5 antibody-positive CADM complicated with stomach cancer and colon cancer. To the best of our knowledge, a case of anti-MDA5 antibody-positive CADM complicated with two cancers has not previously been reported.

Case report

A 74-year-old woman presented with edematous erythema on the right upper eyelid. Her symptoms were not improved by antibiotic therapy, and she

subsequently developed a slight fever, arthralgia, and edematous erythema on forearms palms and around the nostrils and auricles. She was referred to our department and a physical examination revealed hyperkeratotic rashes on radial index fingers and dorsal elbows, hyperkeratotic erythema of the distal interphalangeal (DIP) joints of her fingers and left knee, and a manual muscle testing (MMT) of 5/5. She did not have flagellate erythema, nail fold bleeding, Raynaud phenomenon, photosensitivity, skin ulcers, myalgia or grasp pain (**Figure 1**). At the initial medical examination, BP129/71 mmHg, HR 96 beat/min, BT 37.1 °C, RR 18 breath/min, and SpO2 96% (room air). Laboratory findings were as follows: WBC 4400 count/μL, Hb 12.5 g/dL, Plt 18.1×10000 count/μL, TP 6.7 g/dL, Alb 3.9 g/dL, CK 40 IU/L, ALD 14.5 U/L, Myoglobin 44.1 ng/mL, GOT 70 IU/L, GPT 67 IU/L, LDH 407 IU/L, Cr 0.54 mg/dL, UN 14 mg/dL, UA 2.0 mg/dL, CRP 0.05 mg/dL, ESR 34 mm/hr, IgG 1206 mg/dL, Ferritin 184 ng/mL, KL-6 476 U/mL, CEA 8.9 ng/mL, ANA<40 times, Anti-SS-A antibody <7.0U/mL, and Anti-ARS antibody 15.4 index (reference range <25.0 index).

She was suffering from sputum, wet cough and dyspnea on exertion but her breathing sounds were normal. A chest X-ray photograph showed bilateral lower peripheral linear opacities and a chest computed tomography (CT) scan showed bilateral middle-lower subpleural linear reticular opacities and consolidations (**Figure 2**).

We performed a skin biopsy from the erythema on her left forearm. Slight hypertrophy of the horny

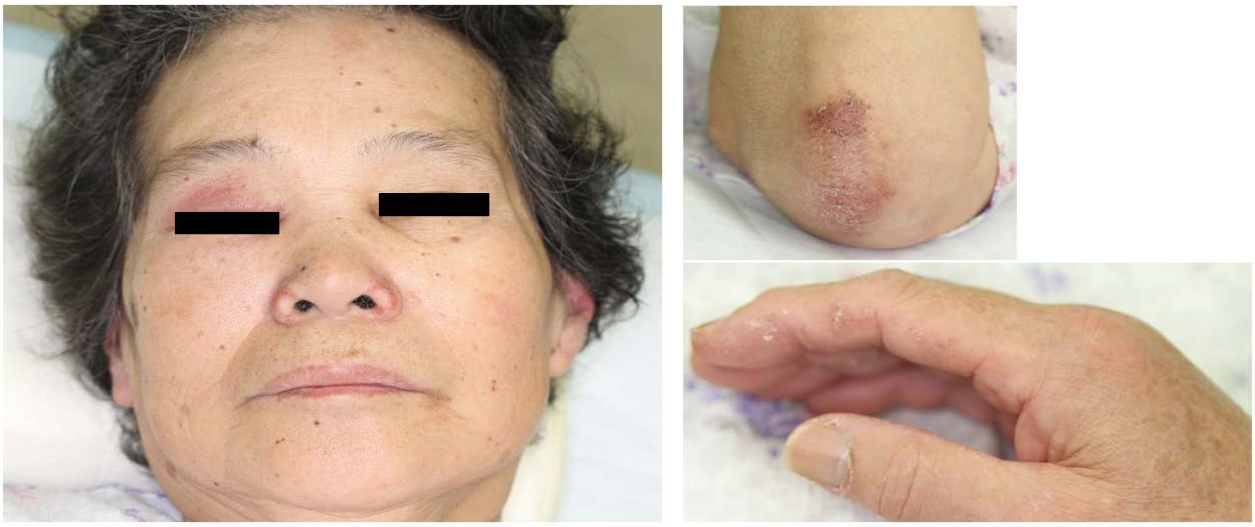

Figure 1. Heliotrope rash, nostril vicinity erythema and auricular erythema were observed on patient's face. She had hyperkeratotic rashes on radial index fingers and dorsal elbows.

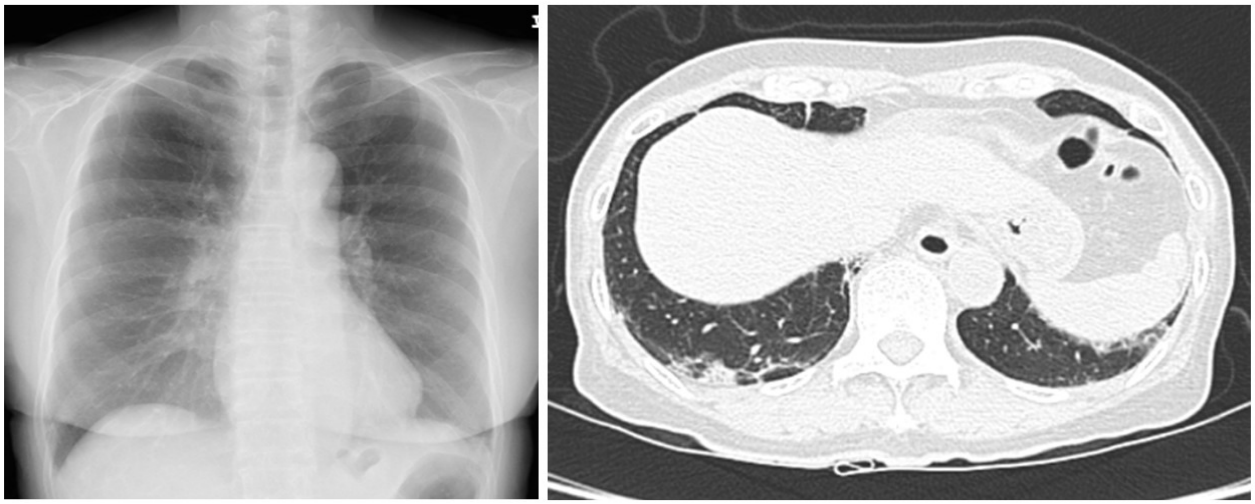

Figure 2. A chest X-ray (left) photograph showing the lower lung peripheral linear shadow. CT scan (right) showed infiltration and linear reticular shadow under the lower lung.

cell layer, lymphocyte infiltration in the upper dermis, edema of the dermis and sparse inflammatory cell infiltration around superficial vessels were seen. Liquid degeneration was not observed. Ga scintigraphy did not show accumulation but an abdominal CT scan showed a tumor in the rectum. Gastrointestinal endoscopy revealed stomach cancer (Stage IA) and colon cancer (Stage I) (**Figure 3**). We diagnosed CADM complicated with two cancers and IP. We planned to treat the malignancy prior to IP because the serum levels of ferritin were slightly elevated and the accumulation in the lung was not observed by Ga scintigraphy. However, the IP became aggravated, so she was administered prednisolones at an initial dose of 1 mg/kg/day and tacrolimus for which the dose was adjusted while referring to blood concentration. The use of tacrolimus subsequently was discontinued due to thrombocytopenia. She was then treated with cyclophosphamide pulse therapy. Erythema on her trunk, deterioration of oxygenation, and high fever appeared after the second and third pulses. We assessed that she had an allergic reaction to cyclophosphamide, so it was also discontinued. The immunosuppressive agent was changed to 75 mg/day of azathioprine, and we tapered the dose of corticosteroids. Endoscopic stomach surgery was carried out after we had tapered to 22.5 mg/day of prednisolone. The pneumonia did not become aggravated but fibrosis remained as sequelae. Later abdominal rectal cancer surgery was carried out. At a later date, we determined that this case was anti-MDA5 antibody-positive. We did not measure other specific autoantibodies because the specific autoantibody usually does not overlap in dermatomyositis. We detected anti-MDA-5 antibody by ELISA[1]. The titer of anti-MDA5 antibody was >150 index (reference range <32 index) before treatment, and it decreased to <5 index after the treatment of malignancy.

Discussion

CADM accounts for 12.8%–37.8% of all DM[2–4,7]. In Japan, the anti-MDA5 antibody, which is one of the MSAs, is observed in 10.9%–25.6% of DM patients[2–4] and 53.3%–66.7% of CADM patients[4,5]. Interstitial lung disease (ILD), high levels of the serum ferritin, skin ulcers, and palmar papules significantly present in anti-MDA5 antibody-positive patients but did not in anti-MDA5 antibody-negative patients[4]. High serum ferritin levels correlated with the disease activity of CADM complicated with rapidly progressing IP[4]. In our case, we estimated that the disease activity of CADM complicated with IP of our case was low because serum ferritin levels were not high, although IP became aggravated later.

The DM and CADM patients with malignancy were older and had a higher incidence of dysphagia, and the incidence of ILD, heliotrope rash, Gottron's sign, periungual erythema, cutaneous necrosis, and flagellate erythema were lower in those with malignancy than those without[2,7]. Although she was elderly, she had generally poor findings which suggested complication with malignancy.

There have been reports of DM complicated with two cancers. Satoh *et al*. reviewed the cases of nine gastric cancer patients and reported that five of them also had colon cancer[8]. However, a case of anti-MDA5 antibody-positive CADM complicated with two cancers has never been reported to the best of our knowledge.

Ikeda N *et al*. and Ikeda S *et al*. reported that IP was present in 36.4%[2] and 45.8%[9] cases of DM. The optimal treatments for IP with DM have not yet been clearly established. High-dose corticosteroids have been used as a standard first-line therapy for IP and it is necessary to use immunosuppressive treatments in combination. Cyclophosphamide pulse therapy is the most common immunosuppressive

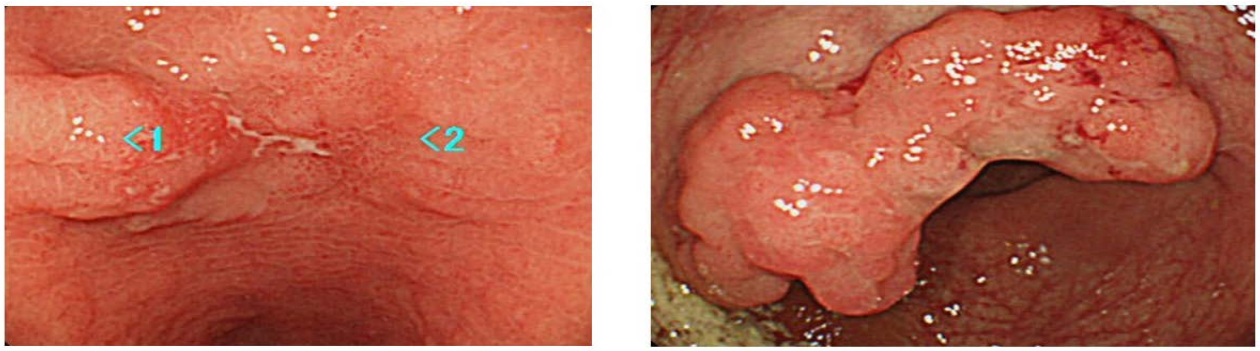

Figure 3. Gastric cancer in the corner of the stomach (left) and a colon cancer in the lower rectum (right)

treatment for IP with DM, and other immunosuppressive agents such as azathioprine and calcineurin inhibitors are also used[10]. Koga T *et al*. reported that 7 out of 17 DM patients with the anti-MDA5 antibody died within six months of the first medical examination[4], and that anti-MDA5 antibody-positive DM was complicated with IP. Ikeda S *et al*. reported in a retrospective study that 6 out of 11 CADM patients with IP received combination therapy[10]. Thus, it is recommended that anti-MDA5 antibody-positive CADM patients with IP are treated with early combination therapy[4].

We decided to choose tacrolimus because the serum levels of ferritin were slightly elevated and the extent of pulmonary disease was limited and the accumulation in the lung was not observed by Ga scintigraphy, although this was a case of CADM complicated with IP. We administered 3 mg/day tacrolimus. However, due to the onset of thrombocytopenia, we changed the treatment with from tacrolimus to cyclophosphamide. Side effects of cyclophosphamide include hemorrhagic cystitis and myelosuppression. In this case, clinical symptoms and images were slightly improved by cyclophosphamide. However, the patient had an erythema-like drug eruption and hypoxemia immediately at the third treatment, so the medication was changed to azathioprine. We were able to taper the dose of corticosteroids. Commonly anti-MDA5 antibody-positive CADM with IP is resistant to treatment, and DM with malignancy usually responds poorly to immunosuppressive therapy[10]. A case of anti-MDA5 antibody-positive CADM complicated with IP and two cancers which could be successfully treated has never been reported to our knowledge. We considered the possible causes of incidental cancer as being unrelated to DM, and the cancers could be treated because IP did not rapidly become aggravated, even though the patient was anti-MDA5 antibody-positive.

Acknowledgments

We thank Prof. Tsuneyo Mimori, Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, for measurement of myositis-specific antibodies.

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of their article.

References

1. 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(4): 626–636. doi: 10.1067/mjd.2002.120621.
2. Ikeda N, Takahashi K, Yamaguchi Y, *et al*. Analysis of dermatomyositis-specific autoantibodies and clinical characteristics in Japanese patients. J Dermatol 2011; 38(10): 973–979. doi: 10.1111/j.1346-8138.2011.01262.x.
3. Hoshino K, Muro Y, Sugiura K, *et al*. Anti-MDA5 and anti-TIF1-gamma antibodies have clinical significance for patients with dermatomyositis. Rheumatology 2010; 49(9): 1726–1733. doi: 10.1093/rheumatology/keq153.
4. Koga T, Fujikawa K, Horai Y, *et al*. The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM. Rheumatology 2012; 51(7): 1278–1284. doi: 10.1093/rheumatology/ker518.
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 2005; 52(5): 1571–1576. doi: 10.1002/art.21023.
6. Labrador-Horrillo M, Martinez MA, Selva-O'Callaghan A, *et al*. Anti-MDA5 antibodies in a large Mediterranean population of adults with dermatomyositis. J Immunol Res 2014; 2014(2014): Article ID 290797. doi: 10.1155/2014/290797.
7. Galimberti F, Li Y, Femandez AP. Clinically amyopathic dermatomyositis: Clinical features, response to medications and malignancy-associated risk factors in a specific tertiary-care-centre cohort. Br J Dermatol 2016; 174(1): 158–164. doi: 10.1111/bjd.14227.
8. Satoh M, Kurihama Y, Nishino Y, *et al*. A case of dermatomyositis coexisting gastric and colon cancer with antibody against the 155/140kDa protein. Japanese J Clin Dermatol 2012; 66(9): 701–705. doi: 10.11477/mf.1412103385.
9. Ikeda S, Arita M, Misaki K, *et al*. Incidence and impact of interstitial lung disease and malignancy in patients with polymyositis, dermatomyositis, and clinically amyopathic dermatomyositis: A retrospective cohort study. SpringerPlus 2015; 4: 240. doi: 10.1186/s40064-015-1013-8.
10. Yokoigawa N, Yamada M, Nakai K, *et al*. A case of gastric cancer with amyopathic dermatomyositis. J Kansai Med University 2013; 64(2013): 1–5. doi: 10.5361/jkmu.64.1.