Refractory Dermatomyositis Complicated with Myelodysplastic Syndrome

Takashi Nakanishi, Hideyuki Horikoshi, Yasuyoshi Kusanagi, Takeshi Yamamura, Reiko Takahashi, Fumihiko Kimura and Kenji Itoh

Abstract

We herein describe a case of refractory dermatomyositis (DM) complicated with myelodysplastic syndrome (MDS). Despite intensive immunosuppressive therapies, the activity of myositis, skin ulcers, and interstitial pneumonia did not improve. The patient ultimately died following the progression of interstitial pneumonia. There are few reports of DM accompanying MDS to date, and any association in the pathogenesis between the two is still unclear. However, underlying MDS may have the potential to influence the therapeutic response of DM.

Key words: dermatomyositis, immunosuppressive therapy, myelodysplastic syndrome

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Introduction

Dermatomyositis (DM) is a chronic, systemic autoimmune inflammatory disorder primarily affecting the proximal muscles and skin. It is often complicated with interstitial pneumonia. The association between DM and various types of malignancies has been well documented and the associated risk markedly varies, ranging from 13 to 42% (1). With regard to the hematological malignancy, non-Hodgkin’s lymphoma was reported to be significantly associated with DM (2); however, the relationship between DM and other hematological malignancies is not well understood.

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by refractory anemia and the susceptibility to acute myelogenous leukemia. The patients with MDS frequently experience autoimmune inflammatory manifestations, such as skin vasculitis, arthritis, polymyalgia, myositis, Sjögren’s syndrome, relapsing polychondritis, systemic lupus erythematosus (SLE) and polymyalgia rheumatica, whereas there have been only a few reports of MDS accompanying DM (3, 4).

In this report, we describe the case of a patient with DM associated with MDS, which was resistant to intensive immunosuppressive therapies. In addition, we provide a review of the literature.

Case Report

A 66-year-old Japanese woman was referred to and admitted to our hospital in November, 2011 due to a 7-month history of progressive erythematous papules with ulcerations and a 5-month history of non-specific interstitial pneumonia (NSIP) diagnosed by a lung biopsy. She presented with skin involvement, such as Gottron’s papules, indicative of erythema, with scaling over the extensor surfaces of the metacarpophalangeal and interphalangeal joints; a shawl sign (another symptom of erythema) over the upper back, posterior neck, and shoulders; and a V-neck sign indicating confluent macular erythema over the lower anterior neck and upper anterior chest. Ulcers were visible at the pressure points, such as the shoulders, elbows, knees and hips (Fig. 1). Fine, bilateral crackles were noted in the lower lung fields. Moreover, manual muscle testing revealed muscle weakness in the right deltoid muscle. A hematological examination revealed a normal white blood cell count of 7,900/mm³ with 90.9% segmented neutrophils, 5.7% monocytes, and 3.4% lymphocytes. The patient had anemia with a red blood cell count of 3.12x10⁸/mm³, a hemoglobin level of 9.3 g/dL, a hematocrit level of 27.9%, a decreased reticulo-
cytopenia of 4.6×10^4/μL, and a platelet count of 17.4×10^4/mm^3. Blood chemistry tests showed an elevated lactate dehydrogenase level of 502 IU/L and an aldolase level of 10.2 IU/L, although the creatine kinase level was not elevated (67 IU/L). Krebs von den Lungen-6 (KL-6) was also elevated at a level of 976 U/mL. In the serological tests, neither antinuclear antibody (ANA) nor anti-Jo-1 antibody was detected. A computed tomography (CT) scan of the chest demonstrated a reticular and linear shadow in the lower dorsal side of the lungs (Fig. 2a); however, a graphical progression was not seen in comparison with the CT scan taken five months previously. Electromyography showed a myogenic change in the right deltoid and right iliopsoas muscles upon examination. Furthermore, the pathology results from a skin biopsy were consistent with a skin lesion of DM. Given this, the patient was diagnosed with DM and a complication of interstitial pneumonia. Screening examinations for cancer, including a systemic contrast-enhanced CT scan and gastrointestinal endoscopy, were performed and indicated no signs of solid cancers to the extent that we could examine.

A daily administration of 40 mg of oral prednisolone was initiated to treat the active skin lesion and muscle weakness. Initially, her skin and muscle symptoms gradually improved, although the anemia continued to worsen. However, no blast or dysplastic cells were seen in the peripheral blood, and an examination of the bone marrow revealed hypoplasia, a nucleated cell count of 2.41×10^4/mm^3, a megakaryocyte count of 6/mm^3, and dysplasia with 1.2% blasts, including more than 10% of hyposegmented mature neutrophils (pseudo-Pelger abnormality), more than 10% of hypogranular neutrophils, more than 10% of erythroblasts with megaloblastoid changes, and a few erythroblasts with multinuclearity or budding (Fig. 3). No abnormal variation of the karyotype was observed. According to these findings, a diagnosis of MDS was made, which was subclassified as refractory cytopenia with multilineage dysplasia (RCMD) according to the 2008 World Health Organization (WHO) classification. The risk of MDS was classified as intermediate grade I and intermediate, according to the International Prognostic Scoring System and WHO adapted Prognostic Scoring System.
Figure 3. May-Giemsa stained bone marrow cells (400× magnification). The bone marrow aspirate smear shows (a) hyposegmented mature neutrophils, (b) dysgranular neutrophils, (c) erythroblasts with megaloblastoid change and (d) erythroblasts with multinuclearity change.

Discussion

We herein reported a case of refractory DM complicated with MDS. The association between DM and various types of malignancies has been well documented (1, 2). In the hematological malignancy, non-Hodgkin’s lymphoma was found to be significantly associated with DM with a standardized incidence ratio of 3.6 [95% confidence interval (95% CI): 1.2-11.1] (2). However, the association between DM and other hematological malignancies has not been well described. Marie et al. reported that out of 32 patients diagnosed with DM/polymyositis (PM) complicated with hematological malignancies, only three had MDS (5). They also reviewed a further 115 cases of patients diagnosed with DM/PM associated with hematological malignancies from the literature and identified three cases of DM/PM associated with MDS. In addition, we carefully reviewed the literature and found only four case reports of patients diagnosed with DM/PM associated with MDS (6-9) (Table). Conversely, a previous report of 2,471 MDS patients in the United States revealed that MDS was not associated with an increased risk of DM/PM as compared with 42,886 population-based controls matched for both age and gender (odds ratio: 0.46; 95% CI: 0.11-1.90) (3). Nevertheless, the prevalence of MDS among the patients with DM is estimated to be very rare.

The question is whether the previously reported cases of DM with MDS are coincidental or if any relationship in their pathogenesis exists. The patients with MDS frequently respectively. Given this, supportive care with red blood cell transfusion for the MDS was provided.

Approximately 10 days after admission, the condition of her skin ulcers continued to worsen. Moreover, dysphagia and dysarthria, which were considered to be part of the symptoms of muscle weakness, also worsened. Furthermore, NSIP flared up with aspiration pneumonia (Fig. 2b). The serum level of KL-6 rose to 3,366 IU/mL. The (1, 3) beta-D-glucan test was lower than the cutoff value throughout the clinical course under the prophylactic administration of sulfamethoxazole/trimethoprim. It was unlikely that pneumonia was caused by a fungal or Pneumocystis jirovecii infection. The administration of intravenous pulse methylprednisolone at 1 g/day for 3 days followed by two courses of intravenous cyclophosphamide at 500 mg/body every two weeks proved to be ineffective. In the very late stage of the condition, 5 mg/kg of ganciclovir twice daily was administrated due to a positive test for cytomegalovirus pp65 antigen. The patient ultimately died due to respiratory failure 53 days after her admission (Fig. 4).
Table. Reported Cases of DM/PM Associated with MDS.

<table>
<thead>
<tr>
<th></th>
<th>Ref. 6</th>
<th>Ref. 7</th>
<th>Ref. 8</th>
<th>Ref. 9</th>
<th>Present case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/sex</td>
<td>49/F</td>
<td>60/M</td>
<td>51/M</td>
<td>66/M</td>
<td>66/F</td>
</tr>
<tr>
<td>Subset of myositis</td>
<td>PM</td>
<td>PM</td>
<td>RAEB (FAB)</td>
<td>RA (WHO)</td>
<td>RAEB (FAB)</td>
</tr>
<tr>
<td>Time of diagnosis of MDS</td>
<td>simultaneously with PM</td>
<td>simultaneously with PM</td>
<td>3 months before DM</td>
<td>8 months after DM</td>
<td>1 month after DM</td>
</tr>
<tr>
<td>Classification of MDS</td>
<td>RAEB (FAB)</td>
<td>RA (WHO)</td>
<td>MDS-U (FAB)</td>
<td>RCMD (WHO)</td>
<td>RCMD (WHO)</td>
</tr>
<tr>
<td>Joint involvement</td>
<td>absent</td>
<td>absent</td>
<td>absent</td>
<td>absent</td>
<td>absent</td>
</tr>
<tr>
<td>Interstitial pneumonia (IP)</td>
<td>absent</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Anti-Jo1 antibody</td>
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<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Treatment</td>
<td>PSL 80mg/day</td>
<td>PSL 60mg/day</td>
<td>mPSL pulse</td>
<td>PSL 60mg/day</td>
<td>PSL 60mg/day</td>
</tr>
<tr>
<td>Anti-MDA5 antibody</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Prognosis</td>
<td>died of sepsis</td>
<td>alive</td>
<td>alive</td>
<td>alive</td>
<td>died of IP</td>
</tr>
</tbody>
</table>


Ref. 6 did not describe the data (Table). These characteristics were similar to those shown in a previous study of PM/DM patients complicated with hematological malignancy (5). Although the prevalence of DM complicated with MDS is not frequent, the similar characteristics between the reported cases suggest that both the pathogenesis of MDS and DM are associated through a common mechanism. We did not examine the presence of anti-Melanoma differentiation-associated gene 5 (MDA5) antibody.


have a variety of immunological abnormalities, such as serological autoimmune responses (e.g., ANA, rheumatoid factor, hypergammaglobulinemia, a direct Coombs’ test, and lupus anticoagulant), and autoimmune symptoms, specifically rheumatoid arthritis, Sjögren’s syndrome, SLE, polymyalgia rheumatica, autoimmune hemolytic anemia, chronic rheumatic heart disease, polyarteritis nodosa, discoid lupus erythematosus, and pernicious anemia (3, 4, 10). There have additionally been an increasing number of reports of MDS with the cytogenetic abnormality of trisomy 8 complicated with refractory intestinal Behçet’s disease (11). The present case and the previously reported cases of DM/PM complicated with MDS typically demonstrate similar clinical characteristics, such as a relatively old age, a lack of joint involvement or interstitial pneumonia, and negative test results for anti-Jo1 antibody (ref. 6 did not describe the data) (Table). These characteristics were similar to those shown in a previous study of PM/DM patients complicated with hematological malignancy (5). Although the prevalence of DM complicated with MDS is not frequent, the similar characteristics between the reported cases suggest that both the pathogenesis of MDS and DM are associated through a common mechanism. We did not examine the presence of anti-melanoma differentiation-associated gene 5 (MDA5) antibody or anti-aminocacyl tRNA synthetase (ARS) antibody in the present case. More than 90% DM patients with anti-MDA5 antibody or anti-ARS antibodies develop interstitial lung disease (ILD). Particularly, anti-MDA5 antibody posi-
tive patients showed a 20-fold higher risk of having rapidly progressive-ILD (RP-ILD) than patients negative for anti-MDA5 antibody (12). The typical anti-MDA5 antibody positive DM patients are categorized into “clinically amyopathic DM” (CADM) and are much less likely to be associated with malignancy (13). The typical ILD associated with the anti-ARS antibody positive DM patient is chronic progressive and characteristically shows a good response to steroid therapy. The clinical presentation of the present case significantly differed from that of anti-MDA5 antibody positive or anti-ARS antibody positive DM patients.

Moreover, the present case and three out of the four previously reported cases were refractory to steroid therapy. In most cases of cancer-related autoimmune phenomena, an effective treatment for cancer is likely to lead to an improvement in the paraneoplastic autoimmune conditions (14). However, the present case (and all the reported cases described in Table) did not meet the criteria for the treatment for MDS. One case showed an improvement of MDS after the administration of high-dose prednisolone in combination with methotrexate (8). In the other cases, immunosuppressive therapies for PM/DM led to neither an improvement nor an exacerbation of MDS. Despite a lack of consensus on how to treat the underlying MDS complicated with DM or other autoimmune diseases, three case reports mentioned that cord blood stem cell transplantation resolved the symptoms of Behçet’s disease complicated with MDS (15-17). Furthermore, three MDS case reports showed that the administration of 5-azacytidine for the treatment of MDS also ameliorated the accompanying autoimmune symptoms (18). Another case report of SLE complicated with MDS showed a clinical improvement in SLE with negative results for ANAs and a significant decrease in the CD4+FoxP3+ regulatory T cell count after the administration of 5-azacytidine for the treatment of MDS (19). According to the therapeutic guideline for treating MDS, the present case was not applicable for therapy with intensive treatments for MDS, such as stem cell transplantation or the administration of 5-azacytidine. Despite this, we may have considered these treatments for MDS to actively treat the resistant condition against immunosuppressive therapies for DM.

In conclusion, we herein reported a case of refractory DM associated with MDS. It is a very rare complication; however, a probable association in the pathogenesis may exist as it does for other malignancy-related autoimmune conditions, such as myositis. Given this, further investigation is necessary to establish the effective therapeutic strategy for this particular disease condition.

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

References


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