A Rare Combination of Dermatomyositis, Interstitial Pneumonia, and Lung Cancer in a Patient Treated with Immunosuppressive Therapy and Chemotherapy

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Abstract:
We herein report the rare case of co-occurring dermatomyositis (DM), interstitial pneumonia (IP), and lung cancer in a 59-year-old man. Computed tomography (CT) and positron emission tomography-CT showed the presence of a left lung tumor with IP, which was diagnosed as lung adenocarcinoma by a CT-guided tumor biopsy. We diagnosed DM based on the presence of myalgia, Gottron’s papules, and anti-aminoacyl-tRNA synthetase antibody positivity in the patient. Co-occurrence of the above-mentioned three diseases is rare, and acute exacerbation of IP is a major cause of death in such cases. These patients can be treated with immunosuppressive therapy followed by chemotherapy.

Key words: dermatomyositis, interstitial pneumonia, lung cancer

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Introduction
The occurrence of malignant tumors is a well-known complication in dermatomyositis (DM). The reported rate of occurrence of malignant tumors in patients with DM is 15-30% (1, 2). A major complication of DM is interstitial pneumonia (IP). The management of IP is very important because this may be a prognostic factor in patients with DM. However, there are notably few cases of patients who have malignant tumors with DM and IP (2, 3). We herein report an extremely rare case of co-occurring DM, IP, and lung cancer.

Case Report
A 59-year-old man had felt pain in his left arm since July 2016, dyspnea on exertion, and swelling of the finger joints since September 2016. He consulted our hospital in October 2016. On a physical examination, we noted Gottron’s papules and erythema in the joints of his extremities, myalgia in his left forearm, and arthralgia in his left shoulder, left elbow, both side of the hand joints and finger joints, and knees. Radiographs of these joints did not show destruction of the bones. The decline in his muscle strength was not remarkable. A blood analysis (Table) showed elevated levels of Krebs von den Lungen-6 (KL-6), which is a serum marker for IP, as well as some tumor markers (carcinoembryonic antigen: CEA, and cytokeratin subunit 19 fragment: CYFRA 21-1). The level of creatine kinase (CK) was in the normal range; however, inflammatory changes, such as the elevation of the white blood cell (WBC) count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), were noted.

On computed tomography (CT), the tumor diameter was 8 cm, and the tumor was observed on the apex of the left lung with IP. It was suspected that the lesion had invaded the mediastinum and the left brachial plexus. We also observed two nodules with ring enhancement in the brainstem and the left temporal lobe on magnetic resonance imaging (MRI); these nodules were clinically diagnosed as metastatic brain tumors. Positron emission tomography (PET)-CT
showed an accumulation in the left lung tumor (maximum standardized uptake or SUVmax of 6.5) and in the ipsilateral and contralateral mediastinal lymph nodes (SUV max 2.9) (Fig. 1). These findings strongly indicated the presence of a malignant lung tumor.

Gamma knife therapy was performed for the brain metastases, followed by the intravenous infusion of dexamethasone. We performed a CT-guided biopsy for the left lung tumor and diagnosed it as lung adenocarcinoma (cT4N3M1b, stage IV, per the 7th edition of the Tumor-Node-Metastasis classification). We diagnosed DM based on the typical physical findings, including the presence of Gottron’s papules (although the skin biopsy from the finger joint showed only hyperkeratosis), myalgia on the upper arms, arthralgia without destruction of the bones, and findings such as inflammatory reactions and elevation of CK levels on blood analyses after the initial analysis. On additional blood examinations, staining was negative for the anti-histidyl-tRNA synthetase antibody (anti-Jo-1 antibody) but positive for the anti-aminoacyl-tRNA synthetase antibody (anti-ARS antibody) while the anti-histidyl-tRNA synthetase antibody (anti-Jo-1 antibody) showed negative results. The disease activity of DM was also high.

We inferred that the IP was progressing based on the exacerbation of dyspnea, the findings of CT (Fig. 2A and B), and the increased levels of KL-6 from 865 pg/mL to 1,273 pg/mL. In addition, the CK level, which had been in the normal range at the first blood analysis, was elevated to 332 U/L. The muscular symptoms and the swelling of the finger joints did not show any remarkable changes, but we inferred that the disease activity of DM was also high.

We initiated treatment for IP using steroid pulse therapy followed by the administration of oral prednisolone and cyclosporine. These treatments resulted in improvements in the physical symptoms, oxygen saturation, and the findings on CT (Fig. 2C). The level of CK was also normalized. We therefore believed that the disease statuses of IP and DM were stable.

In January 2017, we initiated chemotherapy for the lung adenocarcinoma with carboplatin (CBDCA, at a dose of area under the concentration-time curve 5, on day 1) and paclitaxel (PTX, at a dose of 80 mg/m², on days 1, 8, 15) every 4 weeks. The clinical course is shown in Fig. 3. The patient experienced grade 3 anemia, which needed to be treated with blood transfusions, and grade 1 dizziness, which may have been caused by neurotoxicity of the treatment with PTX. After three cycles, the target lesion was classified as stable disease (SD) on CT (Fig. 4A and B). In this case, we were able to perform chemotherapy by maintaining a stable disease status for IP. The patient has been alive for a total of six months at this point.

**Discussion**

This case includes some important findings. First, this case showed a combination of DM, IP, and lung cancer. It is well-known that DMs often coexist with IPs or malignant tumors and that malignant tumors are unlikely to occur in cases of DM with IP (2, 3). A previous report showed that the rate of occurrence of such a combination of DM, IP, and lung cancer was only 0.47% (3 of 635 cases of DM), and only 10 cases in total have been reported in Japan in the past 25 years (3). In addition, the incidence of malignant tumors in cases that are positive for anti-ARS antibody has not been reported. The anti-ARS antibody is strongly related to IP (4, 5) and is a clinical feature of DM that is unlikely to coexist with malignant tumors (2). We can therefore infer that the incidence of malignant tumors is likely low in cases of DM that are positive for the anti-ARS antibody. To our knowledge, this is the first report of a patient with a combination of DM positive for the anti-ARS antibody, IP, and lung cancer.

**Table. Initial Blood Analysis.**

<table>
<thead>
<tr>
<th>WBC</th>
<th>10,800/μL</th>
<th>TP</th>
<th>6.5 g/dL</th>
<th>ANA</th>
<th>&lt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neu</td>
<td>88.0 %</td>
<td>Alb</td>
<td>2.8 g/dL</td>
<td>PR3-ANCA</td>
<td>&lt;1.0 U/mL</td>
</tr>
<tr>
<td>RBC</td>
<td>403×10^6/μL</td>
<td>UA</td>
<td>3.6 mg/dL</td>
<td>MPO-ANCA</td>
<td>&lt;1.0 U/mL</td>
</tr>
<tr>
<td>Hb</td>
<td>11.9 g/dL</td>
<td>CRP</td>
<td>2.81 mg/dL</td>
<td>ARS</td>
<td>137 U/mL</td>
</tr>
<tr>
<td>Pht</td>
<td>28.8×10^4/μL</td>
<td>ESR(1hr)</td>
<td>52 mm/hr</td>
<td>Jo-1 (-)</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>36 U/L</td>
<td>CK</td>
<td>121 U/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>29 U/L</td>
<td>KL-6</td>
<td>865 pg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>400 U/L</td>
<td>CEA</td>
<td>11.3 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>17.0 mg/dL</td>
<td>CYFRA21-1</td>
<td>16.5 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cre</td>
<td>0.61 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>139 mEq/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>4.2 mEq/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>103 mEq/L</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Increased levels of WBC count, CRP, ESR, and LDH were observed. Levels of tumor markers such as CEA, CYFRA 21-1, and KL-6 were also elevated. With regard to autoantibodies, the ARS antibody tested positive while the anti-histidyl-tRNA synthetase antibody (anti-Jo-1 antibody) showed negative results.

lung cancer.

Second, we controlled the disease status of both IP and lung cancer in a patient by appropriate treatments. Usually, the prognosis of a cancer patient depends on the status of the malignant tumor. However, it is notable that the major cause of death in cases with a combination of these diseases (DM, IP, and lung cancer) is the exacerbation of IP, and the prognoses of such patients are very poor after the diagnoses of the above-mentioned diseases. A previous report showed that the cause of death in six of eight patients with these disease combinations was the exacerbation of IP, and their prognosis was one to nine months (3). This means that anticancer chemotherapy does not favorably control IP with DM, even though patients may have paraneoplastic syndrome. It might be better to prioritize the treatment of IP over the other diseases if the IP disease activity is assessed to be high.

Predictive factors for the occurrence of malignancies in patients with DM have been discussed in some previous studies (6-8). These studies listed male gender, old age, dysphagia, cutaneous necrosis, and elevated ESR as risk factors for the occurrence of malignancies. The present case of DM was observed in an elderly man who showed inflammatory changes and an elevated ESR level on the initial blood analysis. These clinical features might influence the coexistence of DM and lung cancer despite the occurrence of IP, the representative clinical factor that reduces the risk of malignancy.

**Figure 1.** Initial images of computed tomography (CT), positron emission tomography (PET) -CT, and head contrast-enhanced magnetic resonance imaging (MRI). A, B: The lesion was detected at the apex of the left lung, was about 8 cm in diameter, and suspected to invade the mediastinum and the left brachial plexus. C: Interstitial shadows were detected in both lungs. D: PET-CT scans showed accumulations on the left lung tumor with a maximum standardized uptake value of 6.5. E: Two nodules with ring enhancements were detected in the pons and left temporal lobe.

**Figure 2.** Computed tomography (CT) images of the transitional stages of interstitial pneumonia (IP) showed that, compared to the initial CT (A) findings, the interstitial shadow worsened after about 2 weeks (B). We immediately initiated 2 cycles of steroid pulse therapy followed by oral prednisolone and cyclosporine. Following this, the interstitial shadow improved (C).
Anti-ARS antibody positivity is an important finding with respect to mapping out the course of treatment. Anti-ARS antibodies include some myositis-specific antibodies. Of these, the most common is the anti Jo-1 antibody; the rate of positivity of this antibody in cases of polymyositis (PM) or DM is 10-30%, while that of others is <5%. The positive rate of anti-ARS antibody in cases of PM or DM is reported to be 30.8% (77 of 250 cases), and 89.4% of anti-ARS antibody-positive patients experienced complications of interstitial lung disease (ILD) (9). Interestingly, this antibody was detected in 10.7% of patients with idiopathic IP (18 of 168 cases) (9). The response of ILD to corticosteroids was significantly better in anti-ARS antibody-positive patients than in anti-ARS antibody-negative patients (9, 10). However, ILD recurred more frequently in anti-ARS antibody-positive patients (10, 11); therefore, this antibody is useful for predicting the treatment response and clinical course of ILD (11). Consistent with previous reports, in the present case, IP showed a good response to immunosuppressive therapy. We have maintained the administration of the prednisolone and cyclosporine in the patient to prevent the re-exacerbation of IP.

We must also consider the influence of immunosuppressive therapies on malignancies. Some previous studies have reported the possible association of malignant tumors and cyclosporine treatment; cyclosporine induces the increased expression of transforming growth factor (TGF)β and vascular endothelial growth factor (VEGF), which contribute to tumor invasion, metastases, and angiogenesis (12, 13) and may be involved in the development of virus-associated
lymphoma and the increased expression of interleukin (IL)-6, which induces B-cell activation (14). In addition, cyclosporine may cause a decline in immunity in cancer by suppression of the T-cell function due to the inhibition of the IL-2 gene activation, which is known to influence T-cell proliferation (14). Immunosuppressive therapies are key treatments for the control of IP and DM in co-existent cases, such as the patient reported in the present study. However, we should bear in mind that immunosuppressive therapies may influence the disease status of malignant tumors. The standard chemotherapy regimen for patients with non-small cell lung cancers (NSCLCs) who have IP has not yet been established. Several treatments have been suggested, such as CBDDCA plus weekly PTX (15, 16) and CBDDCA plus S-1 (tegafur/gimeracil/oteracil) (17). In this case, we utilized chemotherapy with CBDDCA and weekly doses of PTX were able to treat IP effectively during chemotherapy. There might be two reasons for this: (1) we prioritized immunosuppressive therapy for IP, and (2) the utilization of a suitable chemotherapy regimen, which was less likely to worsen the IP. Chemotherapy regimens with a low potential for interstitial lung injury may be used for the treatment of cancer with IP (18).

**Conclusion**

We encountered a rare case of the combination of DM, IP, and lung cancer in a patient who received treatment for both IP and lung cancer. For both of these diseases, we were able to control the disease status adequately. It has been reported that the prognoses of these cases with a combination of these diseases are usually poor, and the main cause of deaths in these cases is the exacerbation of IP. Thus, it might be better to prioritize the treatment of IP if the disease activity of IP is assessed to be high. It is also important to choose suitable chemotherapy regimens with low possibilities of interstitial lung injury for NSCLC with IP.

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

**References**