Abstract

A 51-year-old woman developed small cell lung cancer (SCLC). She was a non-smoker and had interstitial pneumonia associated with systemic sclerosis (SSc). Sixteen additional cases obtained from the literature describing patients with SCLC associated with SSc are reviewed. The majority of patients were women with underlying interstitial pneumonia. In 3 patients who were non-smokers, interstitial pneumonia was complicated and cancer had developed in the peripheral lung field but not in the central lung field. Since SCLC is very rare in non-smokers, these findings suggest a positive association between SCLC and interstitial pneumonia associated with SSc.

Key words: small cell lung cancer, systemic sclerosis, non-smoker, fibrosis, interstitial pneumonia

Introduction

Although an association between systemic sclerosis (SSc) and malignancy has been an area of debate, Abu-Shakra et al reported that the frequency of cancer is increased in patients with SSc and the most frequent types were cancers of the lung and breast (1). Yang et al reviewed 96 reported cases of SSc associated with lung cancers and demonstrated that the most common type of lung cancer reported among patients with SSc is adenocarcinoma or bronchioloalveolar cell carcinoma (BAC) (2). Other authors have also reported an extraordinarily high frequency of BAC in patients with SSc (3, 4). Small cell lung cancer (SCLC) occurring in patients with SSc appears to be very rare. Therefore, few studies discuss the association of the clinical features of SCLC and SSc (5).

Here, we report a case of a female non-smoker who had SCLC associated with SSc. In addition, we reviewed the literature to demonstrate the clinical features of SCLC associated with SSc.

Case Report

A 51-year-old woman who had been diagnosed with SSc 15 years previously, was admitted to our hospital for further investigation of a mass shadow in the left lung. She was an office-worker and had never smoked. She had interstitial pneumonia associated with SSc and a routine chest CT scan the previous year did not reveal a mass shadow. She has been treated with prednisolone 5 mg/day, and was never treated with any immnosuppressive drugs which can cause interstitial pneumonia or can promote secondary tumorigenesis. She had slight dyspnea on effort due to interstitial pneumonia. She showed characteristic features of systemic sclerosis, a sharp pinched nose, thin lips, tight, shiny, and atrophic skin, and swollen fingers. On auscultation, there were numerous fine crackles throughout both lung fields, more prominent on the left and back.

Laboratory tests were as follows; leucocytes 4,100/µl, LDH 398 U/l, and CRP 0.05 mg/dl. Pro-GRP, CEA, SCC, and SLX were within a normal range. NSE (13.2 ng/ml) was slightly elevated. KL-6 (1,580 U/ml) was significantly increased. Results of other routine hematologic and biochemical tests were not significant. In lung function tests, %VC was 83.9%, and FEV1.0% was 75.2%. Chest X-ray showed interstitial shadows and a coin lesion in the left lower lung field (Fig. 1A arrow). CT scans revealed ground-glass shadows, traction bronchiectasis, irregularity of peribronchovascular bundle, but no honeycomb changes (Fig. 1B). A mass shadow with irregular edges was surrounded by ground-glass shadows in the peripheral area of the left lower lobe, and came in contact with pleura. Subtracheal lymph nodes were swollen. There was no evidence of distant metastasis.

The specimen obtained from CT-guided tumor biopsy revealed SCLC (Fig. 2). Radiation pneumonitis is a common toxicity after radiation therapy, and it has been reported that...
underlying pulmonary fibrosis is a significant risk factor of treatment-related death caused by radiation therapy (6). In addition, in several clinical studies which include radiation therapy as a treatment modality, patients with interstitial pneumonia were excluded irrelevant to the grade of fibrosis (7, 8). In the present case, although the clinical stage of cancer was limited disease, radiation therapy was not performed due to the existence of interstitial pneumonia. She was given chemotherapy with carboplatin and etoposide. The effect of chemotherapy was a partial response. In the 3 months following chemotherapy, the patient has been well and recurrence has not been observed.

**Literature review**

Patients with SCLC associated with SSc were collected through literature review; seventeen reported cases including the present case are listed in Table 1 (1, 5, 9–18). There were 11 women and 4 men, with a median age of 58.8. Five patients were smokers, 5 were non-smokers, and 7 were unknown smoking status. Interstitial pneumonia was described in 9 cases.

We paid attention to the location of tumor. SCLCs which developed in smoking patients were usually located in the central airway. However, it is noteworthy that SCLC associated with SSc developed in the peripheral lung field in all 3 patients who were non-smokers and had interstitial pneumonia (cases 4, 6, and the present case).

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**Figure 1.** Chest X-ray and CT findings on admission. A; Chest radiograph shows interstitial shadows bilaterally and a mass shadow (arrow) in the left lower lung field. B; Chest CT scan shows ground-glass, traction bronchiectasis, irregularity of peribronchovascular bundle, but no honeycomb changes. A mass shadow with irregular edges is surrounded by interstitial shadows in the peripheral area of left lower lobe.

**Figure 2.** Histology of specimen obtained from CT-guided biopsy shows small cell carcinoma (Papanicolaou stain, ×100).
Table 1. Reported Cases of Small Cell Lung Cancer with Systemic Sclerosis

<table>
<thead>
<tr>
<th>Case (ref.)</th>
<th>Author</th>
<th>Year</th>
<th>Age &amp; Sex</th>
<th>Smoking history</th>
<th>Interstitial pneumonia</th>
<th>Central or Peripheral</th>
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<tbody>
<tr>
<td>1 (9)</td>
<td>Hale</td>
<td>1944</td>
<td>61 M</td>
<td>ND</td>
<td>ND</td>
<td>Peripheral</td>
</tr>
<tr>
<td>2 (10)</td>
<td>Richards</td>
<td>1958</td>
<td>65 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Central</td>
</tr>
<tr>
<td>3 (11)</td>
<td>Ashba</td>
<td>1965</td>
<td>30 F</td>
<td>ND</td>
<td>Yes</td>
<td>Central</td>
</tr>
<tr>
<td>4 (12)</td>
<td>Haqqani</td>
<td>1973</td>
<td>55 F</td>
<td>No</td>
<td>Yes</td>
<td>Peripheral</td>
</tr>
<tr>
<td>5 (13)</td>
<td>Monti</td>
<td>1973</td>
<td>74 F</td>
<td>ND</td>
<td>Yes</td>
<td>Peripheral</td>
</tr>
<tr>
<td>6 (14)</td>
<td>Trotta</td>
<td>1982</td>
<td>54 F</td>
<td>No</td>
<td>Yes</td>
<td>Peripheral</td>
</tr>
<tr>
<td>7 (15)</td>
<td>Roumm</td>
<td>1985</td>
<td>57 M</td>
<td>Yes</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>8 (16)</td>
<td>Sarma</td>
<td>1985</td>
<td>64 M</td>
<td>ND</td>
<td>ND</td>
<td>Central</td>
</tr>
<tr>
<td>9 (5)</td>
<td>Winkelmann</td>
<td>1988</td>
<td>52 F</td>
<td>No</td>
<td>ND</td>
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<td>10 (5)</td>
<td>Winkelmann</td>
<td>1988</td>
<td>58 F</td>
<td>Yes</td>
<td>ND</td>
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<td>11 (5)</td>
<td>Winkelmann</td>
<td>1988</td>
<td>69 F</td>
<td>Yes</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>12 (5)</td>
<td>Winkelmann</td>
<td>1988</td>
<td>69 F</td>
<td>Yes</td>
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<td>ND</td>
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<tr>
<td>13 (5)</td>
<td>Winkelmann</td>
<td>1988</td>
<td>53 F</td>
<td>No</td>
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<td>14 (1)</td>
<td>Abu-Shakra</td>
<td>1993</td>
<td>ND</td>
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<td>15 (17)</td>
<td>Rosenthal</td>
<td>1995</td>
<td>ND</td>
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<td>16 (18)</td>
<td>Katsura</td>
<td>2000</td>
<td>69 F</td>
<td>ND</td>
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<td>Central</td>
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<td>Present case</td>
<td>Kanaji</td>
<td>2005</td>
<td>51 F</td>
<td>No</td>
<td>Yes</td>
<td>Peripheral</td>
</tr>
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</table>

ND: Not described.

Discussion

Interstitial pneumonia is the most common pathological finding in the SSc lung. It is found in 74–90% of autopsied cases (2). In many cases, the patients had suffered from SSc with interstitial pneumonia for many years and lung malignancy developed as a terminal event. A number of studies have provided evidence of an increased association between lung cancer and pulmonary fibrosis (19). It has been speculated that the pulmonary fibrosis, which preceded the cancer in most cases, predisposes the lung to subsequent malignant transformation (1). Most lung cancers associated with interstitial pneumonia develop in the peripheral lung field. Peters-Golden et al have reported that 3 cases of lung cancer were observed among 71 patients with SSc during a follow-up period for a mean of 5 years. Although all 3 patients had interstitial pneumonia, no association between cancer development and smoking was described (20).

Takeuchi et al have reported that patients with idiopathic interstitial pneumonia (IIP) and lung cancer were generally heavy smokers, and 90.0% of cancers are located in peripheral lung fields (21). Interestingly, it has been reported that areas of atypical epithelial proliferation occurred in the terminal airspaces in eight patients with idiopathic pulmonary fibrosis (IPF), and in 3 of these patients, cancer developed within areas of advanced fibrosis (22). Hironaka et al have reported that squamous metaplasia in the honeycombed areas occurred more frequently in patients with IPF [usual interstitial pneumonia pattern (UIP) on histology] with lung carcinoma than in UIP without lung carcinoma (23). They also suggested that the quantitative predominance of squamous metaplasia might reflect a constitutional susceptibility of patients with UIP to develop lung carcinoma.

The pathological classification of interstitial pneumonia associated with SSc should be considered. It has been reported that the pathological classification of about half of the patients with interstitial pneumonia associated with SSc are non-specific interstitial pneumonia (NSIP), and the remaining half are UIP (24). Since there are no honeycombed areas in NSIP, the above-mentioned scenarios may not always apply to patients with SSc.

Another mechanism of tumorigenesis in patients with SSc is through the effects of cytokines and growth factors. Cytokines and growth factors, such as fibronectin, platelet-derived growth factor, alveolar macrophage-derived growth factor, and insulin-like growth factor-1, promote the inflammation, destruction, and subsequent fibrosis of lung parenchyma with its permanent disorganization (25). In the case of tumorigenesis, cytokines such as transforming growth factor-β (TGF-β) may be mitogenic and cause excess cellular division resulting in transformation (26). Considerable evidence is accumulating for T-cell activation in SSc, both in the peripheral blood and at tissue sites (27). At tissue sites, infiltrating mononuclear cells produce platelet-derived growth factor and TGF-β. In addition, a longstanding immunological imbalance noted in patients with SSc and poor removal of pollutant carcinogens via blocked lymphatic channels by the fibrotic tissue may predispose cancer development (28). The problem of whether or not immunological imbalance and cytokines induce SCLC in patients with SSc should be evaluated in future studies.

In summary, although the exact mechanism of the development of SCLC with SSc remains unclear, the occurrence of SCLC in non-smokers with SSc should be kept in mind.
References