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CASE REPORT

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Systemic sclerosis and pseudomesotheliomatous adenocarcinoma of the lung

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Abstract A 55-year-old man, diagnosed with systemic sclerosis (SSc) for 20 years, was admitted to our hospital for exertional dyspnea and pleural effusion. Computed tomography scan and cytological findings of the pleural fluid suggested malignant mesothelioma. In the postmortem examination, the tumor was pathologically diagnosed as pseudomesotheliomatous adenocarcinoma (PMA) of the lung, classified into pleomorphic carcinoma with adenocarcinoma component according to the new World Health Organization guidelines. This is the first case report of SSc with PMA.

Key words Mesothelioma · Neoplasm · Pleomorphic carcinoma · Pseudomesotheliomatous adenocarcinoma (PMA) · Systemic sclerosis (SSc)

Introduction

Epidemiological data have suggested possible implication of systemic sclerosis (SSc) in development of malignancies.[1–5] Of them, lung cancer based on pulmonary fibrosis is the most frequently noted.[1,2,4] Here we report a case of SSc complicated with pseudomesotheliomatous adenocarcinoma (PMA), which originates from the lung tissue and shows indistinguishable clinical, radiological, and macroscopic features from malignant pleural mesothelioma. About 100 cases of PMA have been documented since Harwood et al. first reported it, but none of them have been diagnosed as SSc.[6–20]

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Case report

A 55-year-old Japanese man, who had been diagnosed with SSc because of Raynaud's phenomenon, systemic skin sclerosis, pulmonary fibrosis, and chronic pericarditis for 20 years, was admitted to our hospital due to progressive exertional dyspnea in September 2002. He had smoked a pack of cigarettes a day for 36 years, but had no history of asbestos exposure. He had been treated with prednisolone, D-penicillamine, and beraprost until admission since he first visited our hospital in July 1991. Physical examination showed remarkable tabescence (height 167 cm, weight 44.2 kg) and diffuse type scleroderma. Sclerodactylia in the patient is shown in Fig. 1. Pulse and respiratory rates were 110/min and 37/min, respectively. Respiratory sounds were reduced on the right lung field, and fine crackles were audible on the left. Blood gas analysis in ambient air revealed pH 7.471, pCO_2 29.9 torr, pO_2 61.8 torr, and SaO_2 93.3%. Laboratory data revealed positive antinuclear antibody (ANA; ×640, speckled pattern) and anti-ribonucleoprotein (RNP) antibody, and increased serum KL-6 level (2610 U/ml). While chest computed tomography (CT) scan had shown diffuse pulmonary fibrosis and emphysema without pleural changes in February 2002 (Fig. 2A,B), the follow-up examination on admission demonstrated right unilateral pleural effusion with pleural thickness, pericardial effusion, and multiple mediastinal lymphadenopathy in addition to lung lesions (Fig. 2C,D). Cytological examination of the pleural fluid showed Class V cells suggesting malignant mesothelioma with severe atypia, though cytological examination of pericardial effusion was negative. Serum levels of

carcinoembryonic antigen (CEA) and cytokeratin 19 fragments (CYFRA) increased to 9.8 ng/ml and 170 ng/ml, respectively, while positive CEA (53.6 ng/ml) and no elevation of hyaluronic acid were found in the pleural effusion. Because of impaired cardiopulmonary functions, further examinations including pleural biopsy were suspended. He was supportively treated until he died of insufficient venous return and respiratory failure due to uncontrollable pleural effusion in November 2002 (Fig. 2E,F).

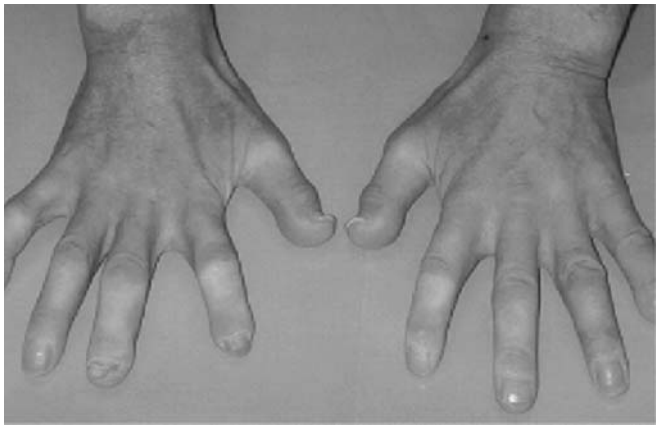

Fig. 1. Sclerodactyly observed in the patient's digits. Nail absorption and shortness of fingertips are shown in the right second and third digits

The postmortem examination was performed with the informed consent of next of kin. Besides massive effusion in the bilateral thoracic cavities, diffuse pleural thickness was found over almost the entire surface of the right lung (Fig. 3). In the lung, subpleural bulla, fibrosis, and moderate medial hypertrophy of the small-sized pulmonary arteries were also discovered as pathological findings of systemic sclerosis. Microscopic examinations demonstrated that the thickened pleura consisted of anaplastic tissue (Fig. 4A,B). In addition, a small mass of 8 mm diameter was found in the subpleural region of the right S2. The lesion showed ductal structure with mucin production, suggestive of adenocarcinoma (Fig. 4A,C). Interestingly, immunohistochemistry revealed distinct immunoreactivity between two components. The anaplastic elements were positive for MOC-31, but negative for CEA, calretinin, and WT1, whereas the adenocarcinomatous elements were positive for CEA and MOC-31, and negative for calretinin and WT1 (Fig. 4D). These findings suggest that the tumor originated in the lung tissue rather than the mesothelium. Besides the right lung,

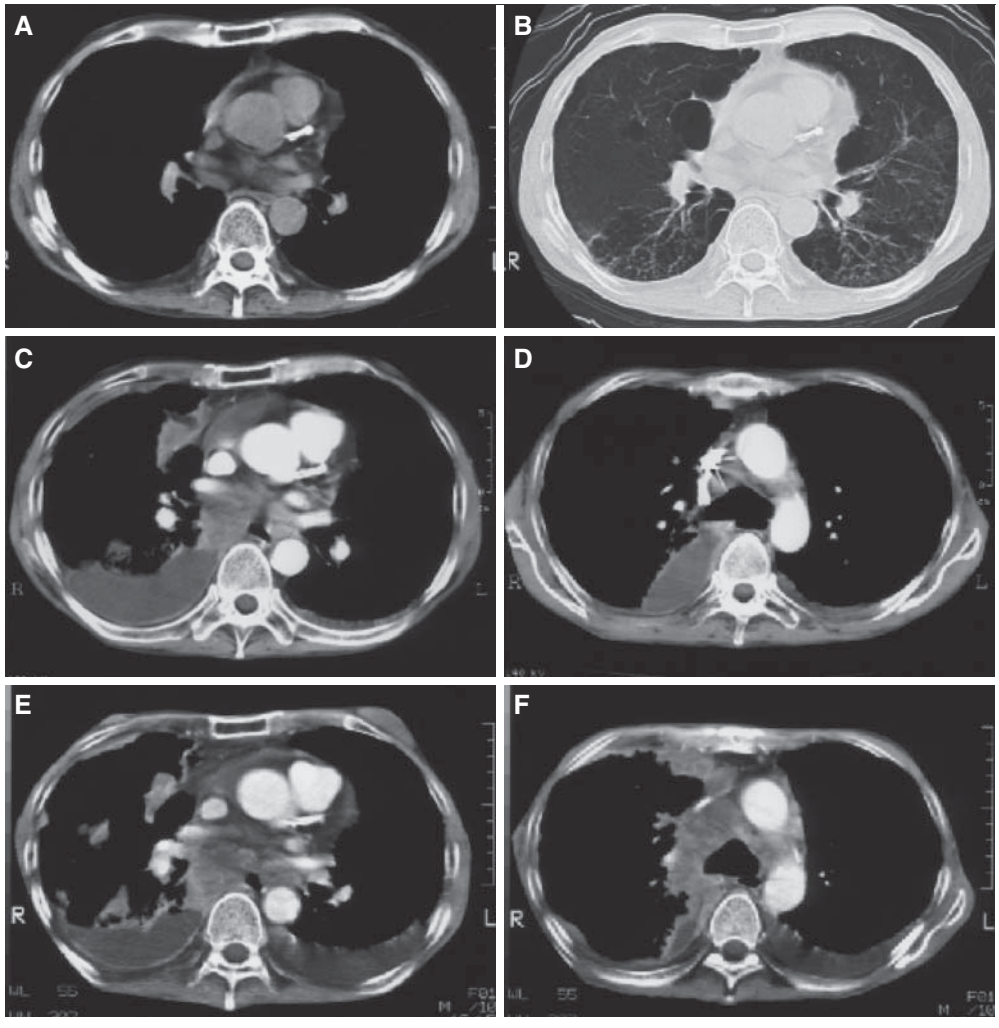

Fig. 2A–F. Chest computed tomography scan images. **A,B** The images (February 2002) show pulmonary fibrosis and emphysema without pleural effusion. **C,D** The images (September 2002) show right unilateral pleural effusion, lymphadenopathy of the mediastinum, and thickness of the right pleura. **E,F** The images just before death (November 2002) show bilateral pleural effusion, and enlargement of lymphadenopathy of the mediastinum and of thickness of the right pleura

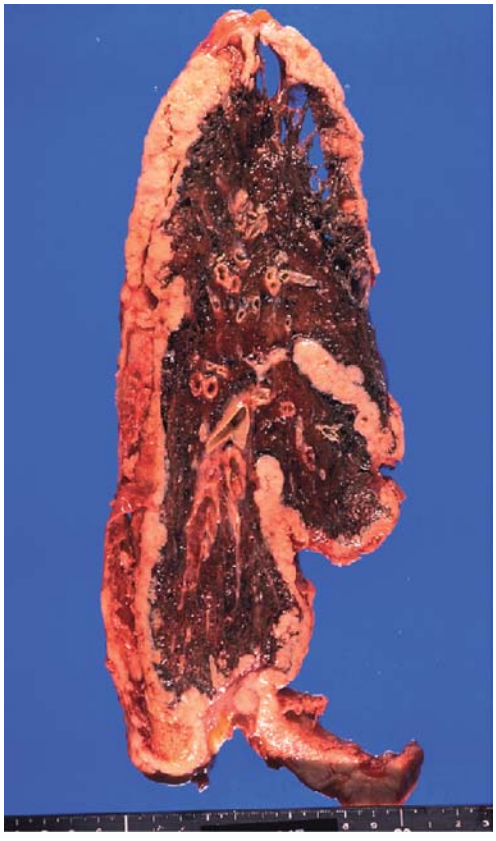

Fig. 3. A sagittal section of the right lung shows mild to moderate thickening of the pleura over almost its entire surface

the tumor directly invaded the trachea and pericardium, and metastasized into the left lung, adrenal glands, and cervical, mediastinal, and abdominal lymph nodes.

Discussion

We here present the case of an SSc patient complicated with PMA of the lung, which is a prototype of peripheral lung cancer invading along the pleura. The clinical and radiological features are indistinguishable from those of malignant mesothelioma.[7,10,11,15,17,18] It is also sometimes difficult to make the pathological diagnosis because of lack of typical ductal or tubular structures. However, immunohistochemical examination is helpful in determining the origin of tumor cells.[3,7,10,15,18] In the present case, radiological and cytological findings had strongly suggested malignant mesothelioma, though tumor markers rather suggested ademocarcinoma. Postmortem examination revealed that the tumor contained an adenomatous component having a ductal structure with mucin production, which was positive for CEA and TTF1, suggesting that the tumor originated in the lung tissue.

The patient did not have a history of asbestos exposure, which increases the risk of mesothelioma. He was, however, a heavy smoker, as were most patients with PMA in previous reports.[7,10,11,15,17,18]

It is controversial whether SSc is one of the predisposing conditions leading to neoplasms. There are several studies

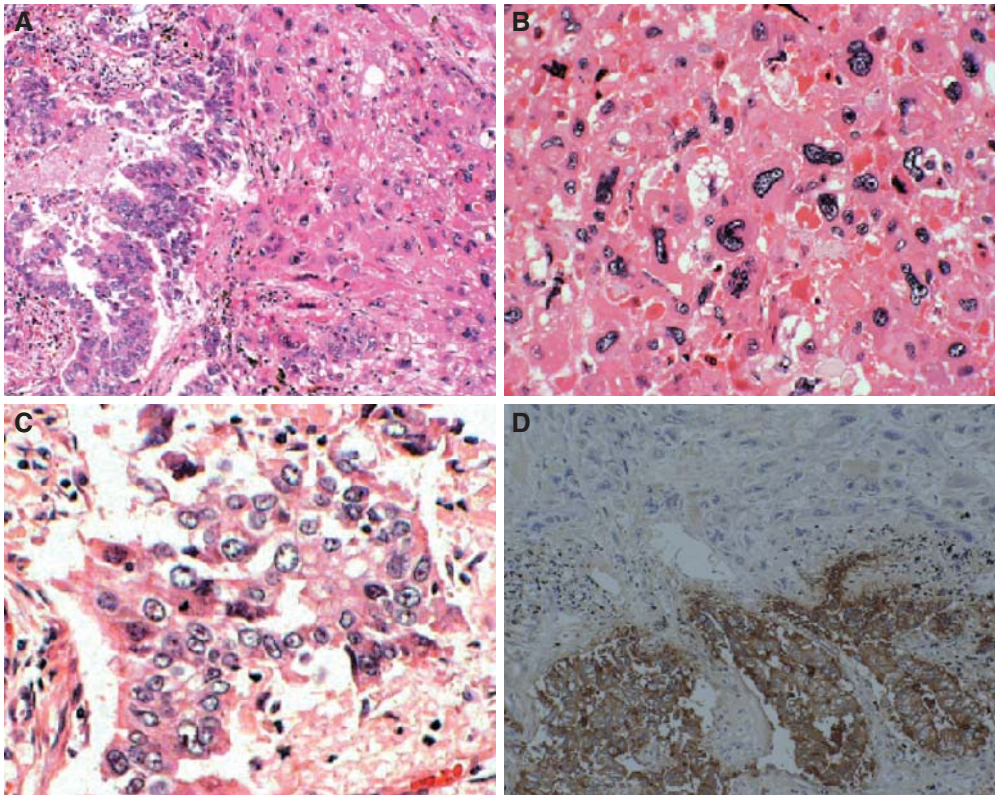

Fig. 4A–D. Microscopic appearance of the tumor. **A** Microscopic appearance showed a mixture of adenocarcinomatous (*left part of the panel*) and anaplastic (*right part of the panel*) components in the tumor (H&E stain, ×100). **B** A high-power view of the anaplastic component shows a cluster of anaplastic cells. **C** A high-power view of the adenocarcinomatous component shows adenomatous cells composed of a ductal structure. **D** Immunohistochemical analysis shows that CEA is positive in the adenocarcinomatous component (*lower part of the panel*), but not in the anaplastic component (*upper part of the panel*). Immunohistochemical staining

showing that SSc is associated with increased risk of cancer, especially lung cancer.[1–5] Standardized incidence ratios (SIRs) for all cancers calculated in these studies ranged from 1.5 to 2.1, whereas those for lung cancer were from 4.9 to 8.3.[2–4] Coexistence of lung cancer might be related to pulmonary fibrosis, which is another predisposing factor to lung cancer, irrespective of etiology.[21] On the other hand, a population-based cohort study showed no association of SSc with susceptibility to cancer except liver cancer.[22] Positive autoantibody to topoisomerase I (Scl-70) had been suggested to increase the risk for malignancy in SSc patients,[23] though recent studies failed to reproduce this finding.[22,24] Otherwise, no association has been found between the disease-related autoantibodies, including anti-U1 RNP antibody, and malignancy in patients with SSc.[22]

In this patient, smoking may be one of the most important risk factors for PMA as well as other histological types of lung cancer. No coexistence of this rare tumor with collagen diseases including SSc, rheumatoid arthritis, and Sjögren's syndrome has ever been shown. Regarding immunological disorders, at least two patients have been reported as having PMA with human immunodeficiency virus infection.[17] Immunological abnormalities in SSc might be implicated in the oncogenesis of this tumor.

In conclusion, we report an SSc patient complicated with a rare type of lung tumor, PMA. In addition to smoking, fibrotic lesions and immune abnormalities of SSc may contribute to the development of PMA as local and systemic predisposing factors, respectively. Finally, we would like to mention that this tumor is categorized into pleomorphic carcinoma according to the new World Health Organization classification.[25]

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