Case Report

Dermatomyositis/Polymyositis and Lung Cancer: Report of Three Cases

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Abstract: **Background:** Although the association between connective tissue disease and malignant neoplasms is well known, the direct causal relationship between the two diseases is not well understood. This study attempted to evaluate the clinical behavior and whether a causal relationship between connective tissue disease and malignant tumor could be documented. **Cases:** We encountered three cases of lung cancer which were associated with connective tissue disease. Case 1 was a 33-year-old woman with dermatomyositis who had been treated by steroids. A right upper and middle lobectomy was performed (pT2N2M0, stageIIIa, adenocarcinoma). Case 2 was a 66-year-old woman who had received maintenance therapy by steroids from age 53 for polymyositis. Squamous cell carcinoma of the right lower lung and stomach cancer were detected. An operation was not carried out because of multiple bone metastasis. Case 3 was a 58-year-old man in whom dermatomyositis, Sjögren's syndrome and Hashimoto disease were diagnosed 6 years previously and had received treatment by steroids. A right upper lobectomy was carried out (pT4N2M0, stageIIIB, adenocarcinoma). **Conclusion:** We describe herein three patients who developed metastasis in the mediastinum, lung and other organs. Being rapidly progressing cancer, the growth and progress of the cancers were very rapid. The etiology and pathogenesis of the association between connective tissue disease and malignancy has not been fully elucidated. Whether the relationships between the malignant tumor and autoimmune disease is related to the immunologic abnormality, we will document our views of the evaluation for malignancy of connective tissue diseases based on the current literature and our cases.

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Key words: Lung cancer, Dermatomyositis, Polymyositis, Sjögren's syndrome, Connective tissue disease

Introduction

Although the association between connective tissue disease and malignant neoplasms is well known, the direct causal relationship between the two diseases is not well understood. We describe herein three patients who developed metastasis earlier in the mediastinum, lung and other organs, followed by dermatomyositis (DM), polymyositis (PM) and two kinds of connective tissue diseases (PM, Sjögren's syndrome (SS) and Hashimoto disease). Our aim is to evaluate the variable clinical behavior and whether a causal relationship between DM/PM, SS and malignant disease could be explained on the basis of these cases.

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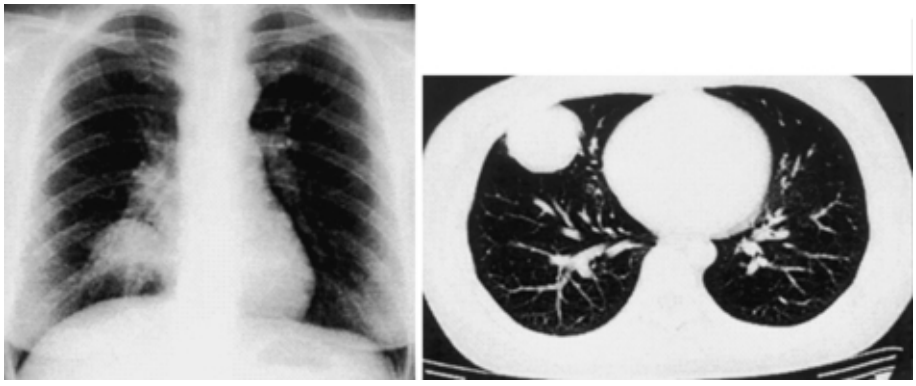
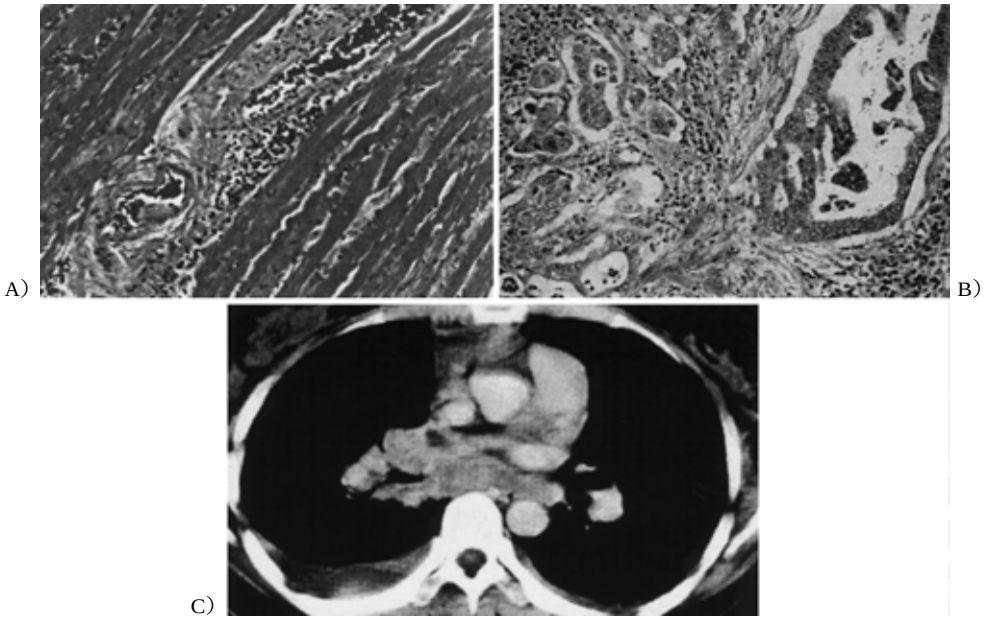
Cases

Case 1. A 33-year-old woman noticed muscle weakness and pain in the bilateral upper and lower limbs and edematous erythema of the face(heliotrope rash). A chest CT showed a mass shadow in the right middle lobe (Fig. 1). The laboratory tests revealed an elevated level of serum CK (2192 IU/l＞13～142), myoglobin (739 ng/ml＞65), GOT (160 IU/l), GPT (64 IU/l), LDH (1197 IU/l＞210～420), CEA (7.1 ng/ml＞5.0) and SLX (390 U/ml＞38). A biopsy obtained from the biceps muscle was compatible with dermatomyositis (Fig. 1A). Good muscular control was achieved following the initiation of a daily dose of 50 mg of prednisone. Transbronchial cytology revealed class III, and the right upper and middle lobectomy (R2a) was

Fig 1. Chest X-ray film and CT scan showing the tumor lesion of the right middle lobe(Case 1)



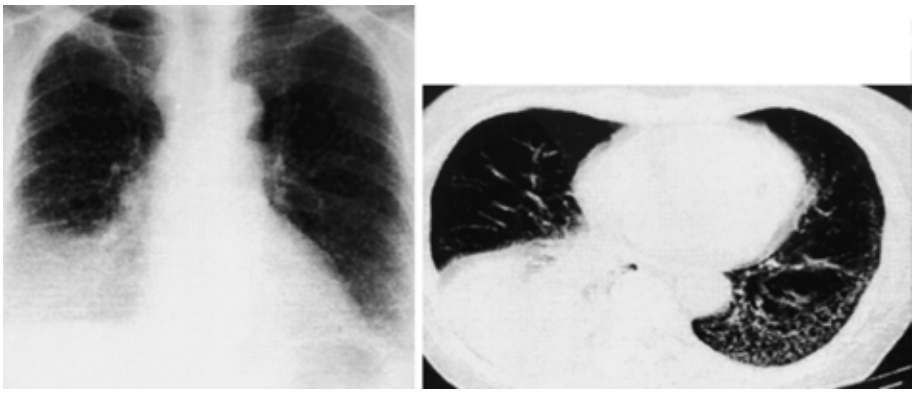
A) Microscopic section of the muscle biopsy specimen reveals perifascicular atrophy with necrotic fibers and perivascular lymphocyte infiltration (Case 1. H & E, ×400).
B) Microscopic section of the right lung tumor shows a moderately differentiated adenocarcinoma (Case 1. H & E, ×200).
C) Chest CT scan one month after operation in case 1 shows a massive mediastinal recurrence.



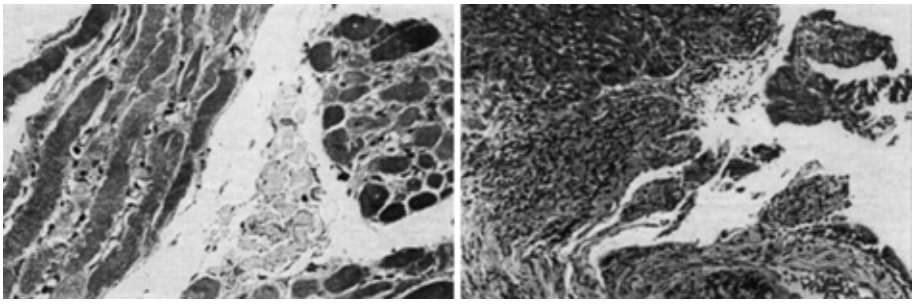
performed (pT2N2M0, moderately differentiated adenocarcinoma, Fig. 1B). In the histology of the resected specimen of the lung, no findings of the interstitial pneumonia could be found. However, a chest CT scan one month after the operation showed a rapid growth of the mediastinal recurrent tumor (Fig. 1C). The patient had been advised to accept treatment with chemotherapy, but she refused. The patient died after two months.

Case 2. A 66-year-old woman had been treated with steroids for PM from the age of 53. The laboratory tests on the first admission revealed elevated levels of serum CK (3745 IU/l), aldorase (128 mu/ml＞0.5～3.1), GOT (326 IU/l), GPT (246 IU/l) and LDH (1200 IU/l). Histologic findings of muscle biopsy showed a typical polymyositis (Fig. 2A). An EMG revealed a myogenic pattern of short duration and low amplitude. Satisfactory control of the muscular symptoms (muscle weakness and pain of the bilateral upper and lower limbs) and the serum levels described above was maintained within the normal range by steroid administration. Thirteen years later, she was admitted to our hospital because of a high grade fever and a mass shadow in the right lower lobe with pleural effusion (Fig. 2). TBLB revealed squamous cell carcinoma of the lung (Fig. 2B). Moreover, the patient noticed an enlarged lymph node of the superior clavicle region on the left side. A search for internal malignancy apart from lung cancer

Fig 2. Chest X-ray film and CT scan showing the atelectasis of right lower lobe and tumor lesion（Case 2）



A）Microscopic section of the muscle biopsy specimen reveals mononuclear inflammatory cell infiltration（Case 2. H & E, ×400）.
B）Microscopic section of the TBLB shows a squamous cell carcinoma（Case 2. H & E, ×200）.

A）  B）

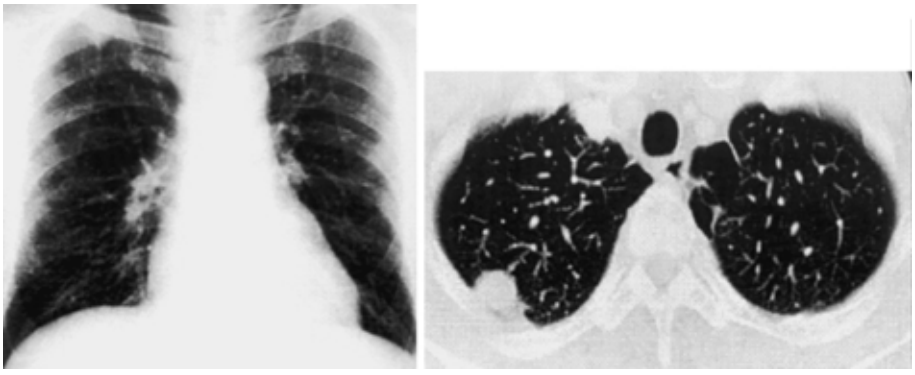
was undertaken and gastric carcinoma（Borrman IV）was detected. The interstitial pneumonia could be observed on the image of a chest CT examination. An operation was not done because of multiple bone metastasis. Two months later the patient died of lymphangitis carcinomatosa.

Case 3. A 58-year-old man had been treated with steroids for two kinds of connective tissue diseases（DM, SS）from the age of 52. The patient had xerostomia, cutaneous erythematous lesions on both hands, the trunk and the upper anterior chest, Gottron's sign and Raynaud's phenomenon of the fingers of the both hands. Histologic findings of a muscle biopsy were compatible with dermatomyositis（Fig. 3A）. Figure 3C shows microscopic findings of a salivary gland biopsy. Regarding the DM, SS and Hashimoto's disease, the symptoms had not shown any progression during treatment by steroids, nor had physical examination revealed any further deterioration. The patient was admitted to our department because of an elevated level of serum CEA and an abnormal shadow on chest CT film（Fig. 3）. A biopsy showed adenocarcinoma of the lung（Fig. 3B）. The laboratory tests are listed in Table 1. A right upper lobectomy was done（pT4N2M0, moderately differentiated adenocarcinoma, T4: class 5 by the small amount of pleural effusion）. In the histologic examination of the resected specimen, findings of interstitial pneumonia could not be recognized. The patient was discharged after chemotherapy. The patient was admitted again six months later because of dyspnea and tachycardia. Chest CT scan showed a large amount of pericardial and pleural effusion. The cytology of effusion in both sides

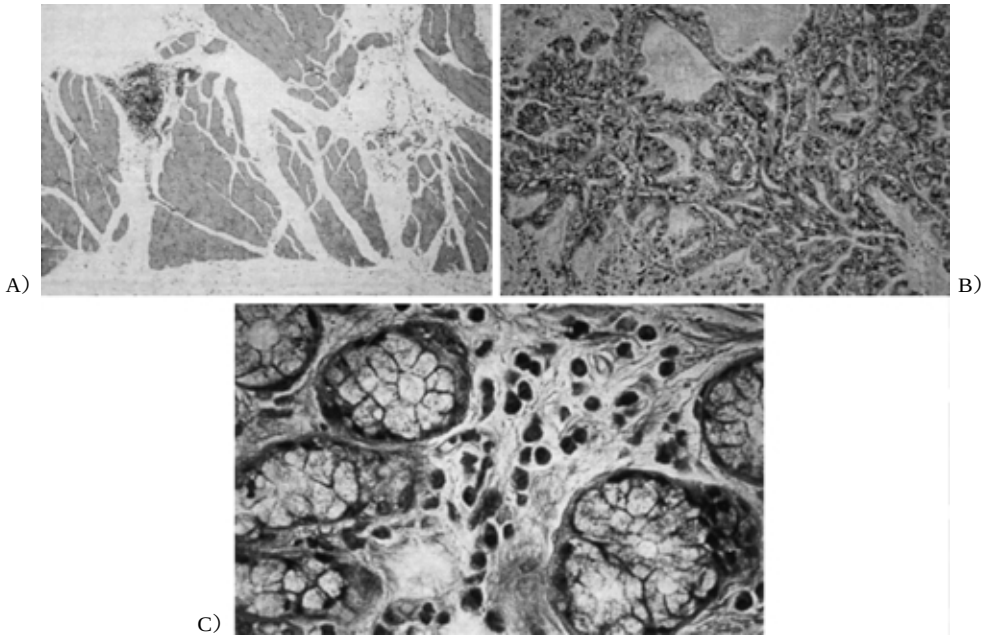
Table 1. Laboratory findings of Case 3

anti SS-A/RO ab	64 ×
anti SS-B/LA ab	negative
anti RNP ab	negative
anti JO-1 ab	negative
ANA	320 ×（speckled type）
RF	32 IU/ml（0-20）
aldorase	4.4 IU/l/37 c（1.7-5.7）
CEA	37.6 ng/ml
γ-globulin	25%（9.0-18.3）
Free T4	0.89 ng/dl（0.72-1.52）
Free T3	3.33 pg/ml（2.29-4.17）
TSH	6.81 μU/ml（0.745-4.667）
ATG	1600 ×（0-100）
AMC	400 ×（0-100）

Fig 3. Chest X-ray film and CT scan showing the tumor of the right upper lobe（Case 3）



A）Microscopic section of the muscle biopsy specimen reveals mononuclear cell infiltration（Case 3. H & E, ×400）.
B）Microscopic section of the right upper lung tumor shows a moderately differentiated adenocarcinoma（Case 3. H & E, ×200）.
C）Microscopic section of the salivary gland biopsy showed an increase of fibrous tissue and infiltration of lymphocytes（Case 3. H & E, ×400）.



revealed classV. The patient died of lymphangitis carcinomatosa one year after the operation.

Discussion

Reports on malignant tumors associated with connective tissue disease, such as dermatomyositis and polymyositis, have been published in great numbers since the first report in which gastric cancer was associated with dermatomyositis by Stertz in 1916[1]. An increase in the incidence of cancer in patients with DM/PM has been reported in many studies[2)~9)], but the direct causal relationship is not uniform. The frequency of cancer in DM/PM and SS is variable, but is estimated to range from 6% to 60% in many groups and the average has been reported as 15～20%[7),15)]. This wide range in incidence probably reflects the heterogeneity of the patient, criteria for diagnosis[10)], overlap forms and so on. The types of malignant tumor seem to roughly parallel those of the general population with carcinomas of the breast, lung and stomach being most common[3),11)]. With regard to the temporal relation of diagnoses of malignant neoplasms and the onset of DM/PM, there are some reports in which the risk of cancer was high during the first five years or within before and after two years or within one year after the onset of DM[5)~7)]. In our present cases, the occurrence time of lung cancer was late, being 6 and 13 years in two cases. A num-

ber of prognostic factors of PM/DM have been reported in the literature. The most acknowledged are the presence of cancer, patient age (＜40 years), type and severity of the myositis and presence of dysphagia.

Other features have been reported as indicators of poor prognosis: sex (female), resistance to treatment, fever, leucocytosis, long delays in initial treatment, extensive cutaneous lesions on the trunk and overlapping forms[5),15)]. The risk of malignancy is increased in patients with DM/PM and SS. Manchul et al[4)] reported that the relative risk of the development of malignant tumor in PM/DM is high. It is known that the frequency in which SS is associated with malignant lymphoma is high. The three present cases were rapidly progressing cancer which invaded and formed metastatic lesions early.

Regarding an association between DM/PM and lung cancer, Lakhanpal et al[5)] reported that of their seven patients with lung cancer, four had polymyositis and three had dermatomyositis, and five of these patients had adenocrcinoma of the lung. The incidence of lung cancer was 7 patients (6.1%) in 115 patients with DM/PM. The indications of operation must be prudently considered, if the severe progressive recurrence appears easily in the postoperative period, as in case 2. This biological behavior has suggested that either the aberrant proliferation of the lymphatic system by the antigen-stimulation of autoimmune disease might affect the progress of the cancer, or that the development of cancer cells is caused by the extreme decrease of cell-mediated immune response due to repeated antigen-stimulation. These possibilities, although uncertain, are of great interest. The etiology and pathogenesis of the association between DM/PM and malignancy has not been fully elucidated. There are some reports suggesting a decreased natural killer cell activity in DM patients[12),13)].The immunologic abnormality, associated with connective tissue disease may be related to oncogene activation, and analysis of microsatellite marker as index may yield interesting results. On the other hand, DM specific autoantigen Mi2β is a part of the NuRD complex (nucleosome remodeling histone deacetylase complex) which affects a cell cycle adjustment, and includes the MTA1 component which is a metastasis-associated factor[14)]. It is also considered that the NuRD complex causes the reorganization of chromatin structure, therefore it seems to have an important role for the development and metastasis of the malignant tumor in the DM patient. At the present time, we have encountered cases of lung cancer and double primary lung cancer which were associated with connective tissue disease. These tumors were advanced cancers, with very rapid metastasis an invasion. A precise analysis of each case is required to determine whether the relationships between the malignant neoplasm and connective tissue disease are related to the factor described above.

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