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ORIGINAL ARTICLE

The Prevalence and clinical characteristics of primary Sjogren's syndrome patients with lung cancer: An analysis of ten cases in China and literature review

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Abstract

Background: A retrospective analysis of clinical data from primary Sjogren's syndrome (pSS) patients with lung cancer was conducted in order to guide further clinical work.

Methods: From January 1993 to December 2010, 10 pSS patients with lung cancer were hospitalized at the Peking Union Medical College Hospital. One hundred and three pSS patients were recruited as the controls. Patients' clinical data was retrospectively analyzed.

Result: The incidence rate of lung cancer in pSS patients was 0.477%. The duration from diagnosis of pSS to lung cancer in the 10 patients was 0.92~42 years. The pSS patients with lung cancer were significantly older than those without lung cancer (60.8 ± 8.9 vs. 44.9 ± 12.1, $P < 0.001$). Eight of the pSS patients with lung cancer (80%) were female nonsmokers; five pSS patients with lung cancer (50%) had lung involvement, exhibiting diffuse parenchymal lung disease. Adenocarcinoma was the most common pathological type of lung cancer (90%). Tumor node metastasis staging of lung cancer included: four cases of Ib (40%), one case of IIIb (10%), four cases of IV (40%) and one case undetermined (10%).

Conclusion: The incidence rate of lung cancer in pSS patients was higher with respect to the normal population. Physicians should closely observe lung cancer incidence during the pSS follow-up period. Adenocarcinoma was the most frequently seen lung cancer pathology in pSS patients. Clinical stages and individualized treatment for pSS patients with lung cancer should be carefully determined.

Introduction

The incidence rate of malignancy is high for patients with systematic connective tissue disease (CTD). Lung cancer is one of common malignancies.[1] High incidence rates of lung cancer have been reported in patients with scleroderma, rheumatoid arthritis, and dermatomyositis.[2] CTD is one of the independent risk factors of lung cancer. The mechanisms involved in the development of cancer in CTD patients are still poorly understood. There are several possible pathogenic mechanisms, including: abnormal autoimmunity of CTD patients, long-term oral immunosuppressant treatment resulting in a secondary onset of immunosuppression, and CTD lung involvement resulting in interstitial lung disease. Sjogren's syndrome is a chronic, slowly progressive autoimmune disease, characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia and dry eyes. Approximately one-third of patients present with systemic manifestations. The incidence rate of malignant tumor in primary Sjogren's syndrome (pSS) patients is higher than in the normal population; the incidence rate of lymphoma is 15.57~37.46 times higher than in the normal population. Solid malignant tumors, such as cervical and colon cancers, have been reported in the literature;[3,4] however, there are few reports on pSS patients with lung cancer. pSS patients with lung cancer are rare, with a lower incidence rate than other CTDs[1,2] of 0.15%[5]~1.79%.[4]

Table 1 Clinical characteristics of pSS with lung cancer and pSS patient groups

Variable	pSS with lung cancer group	pSS group	*P* † *value*
Female: male	8:2	20:1	0.226
Age (year)	60.8 ± 8.9	44.9 ± 12.1	<0.001‡
Organ involvement			
Xerostomia	100%	79.5%	0.247
Keratoconjunctivitis sicca	100%	58.0%	0.024
Hematologic involvement	30%	52.6%	0.306
Liver function abnormality	20%	19.4%	1.00
Diffuse parenchymal lung disease	50%	60.0%	0.772

†*P*-value in χ^2 test. ‡*P*-value in Student's *t*-test. pSS, Primary Sjogren's syndrome.

From January 1993 to December 2010, 10 pSS patients with lung cancer were hospitalized at the Peking Union Medical College Hospital (PUMCH), the largest number of pSS patients with lung cancer reported. This retrospective study analyzes the related clinical characteristics of pSS patients with lung cancer using clinical data of the patients admitted to our hospital and summarizing the cases of pSS patients with lung cancer reported in the literature, in order to guide further clinical work.

Patients and methods

From January 1993 to December 2010, 2096 cases of pSS patients were hospitalized at PUMCH; 10 of these were pSS patients with lung cancer. pSS patients admitted to PUMCH in 2010 with a pathological exam of the lip area tissue supporting a diagnosis of pSS, were randomly selected as the control group. Therefore, 103 pSS patients were recruited as the control.

Primary Sjogren's syndrome patients fulfilled the international classification criteria (2002) for pSS.[6] The diagnosis of lung cancer was based on pathological confirmation, and histologic types of lung cancer were classified according to the World Health Organization histologic classification formulated in 2004. The staging of lung cancer was based on the 2009 International Association for the Study of Lung Cancer Tumor Node Metastasis (TNM) Staging Manual.[7]

Clinical data of the pSS patients with lung cancer were retrospectively analyzed. Medical records were reviewed for the following clinical factors: age, gender, smoking status, clinical symptoms, the duration from diagnosis of pSS to lung cancer, histologic type and staging of lung cancer, and treatment for lung cancer. The terms "Primary Sjogren's syndrome" and "malignancy" were searched in PubMed, and further collated by lung cancer cases. The following factors were retrospectively analyzed: the incidence rate of lung cancer, the age at which a patient developed lung cancer, smoking history, the duration from diagnosis of pSS to lung cancer, lung involvement existing in pSS, and histologic type and staging of lung cancer.

The SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) was used for data processing and analysis. Continuous variables (mean ± standard deviation) were determined using the nonparametric test. Categorical variables were determined using the Pearson chi-squared test (using the continuity corrected chi-squared when the minimum expected count was less than 5 and using Fisher's exact test when the minimum expected count was less than 1). The Student's *t* test was used for continuous data in all tests. *P* values less than 0.05 were considered significant.

Results

The incidence rate of lung cancer for pSS patients was 0.477%. Clinical characteristics of the pSS with lung cancer and pSS groups are shown in Table 1. The duration from diagnosis of pSS to lung cancer of the 10 patients was 0.92~42 years. Organ involvement in pSS patients with lung cancer included: xerostomia (10 cases, 100%); keratoconjunctivitis sicca (10 cases, 100%); lung involvement (5 cases, 50%, exhibiting diffuse parenchymal lung disease); joint involvement (3 cases, 30%); liver function abnormality (2 cases, 20%); and hematologic involvement (3 cases, 30%). Five pSS patients with lung cancer (50%) received immunosuppressor treatment, three (30%) received glucocorticoid treatment (0.5 mg/kg/d equivalent dose of prednisone), one was administered CTX at the same time, one received tripterygium glycosides, and one received anethol trithione. Among the 103 controls, 79.5% had xerostomia; 58.0% presented with keratoconjunctivitis sicca; 52.6% had hematologic involvement; 19.4% had liver function abnormality; and 60.0% had diffuse parenchymal lung disease.

The age at onset of lung cancer was 60.8 ± 8.9 years (48~76 years). The pSS patients with lung cancer were significantly older than those who did not develop lung cancer (60.8 ± 8.9 vs. 44.9 ± 12.1, $P < 0.001$). Only two male lung cancer patients had a smoking history; none of the female lung cancer patients had a smoking history. The symptoms of lung cancer included: cough (6 cases, 60%), productive cough (4 cases, 40%), chest pain (1 cases, 10%), and weight loss (4 cases,

Table 2 Clinical features of the 10 pSS patients with lung cancer

No.	Gender	Age (year)	Smoking History	pSS lung involvement	Surrounding type	Pathological classification	Staging	Treatment
1	M	48	Y	Y	Y	Adenocarcinoma	UK	Withdrew
2	F	63	N	N	Y	Adenocarcinoma	Ib	Surgical +chemotherapy
3	F	76	N	N	N	SCLC	IV	Chemotherapy
4	F	52	N	Y	N	Adenocarcinoma	Ib	Surgical +chemotherapy
5	F	55	N	N	Y	Adenocarcinoma	Ib	Surgical
6	F	72	N	N	Y	Adenocarcinoma	IV	Targeted therapy
7	F	56	N	Y	Y	Adenocarcinoma	Ib	Surgical +chemotherapy
8	M	62	Y	Y	N	Adenocarcinoma	IIIb	Withdrew
9	F	57	N	N	N	Adenocarcinoma	IV	Chemotherapy
10	F	67	N	Y	N	Adenocarcinoma	IV	Targeted therapy

Primary Sjogren's syndrome; SCLC, small cell lung cancer.

40%); 90% of the patients suffered from at least one of these symptoms. In pSS patients with lung cancer, computed tomography (CT) findings of lung cancer lesions manifested as a consolidation-like mass in six patients (60%), a nodule in three patients (30%), ground-glass opacities (GGO) in two patients (20%), tracheal stenosis in one patient (10%), and lymph node enlargement in six patients (60%). Tumor lesions were classified into central and peripheral types according to CT images; there were five central type (50%) and five peripheral type lesions (50%).

In our study, the most common histology type of lung cancer was adenocarcinoma (9 cases, 90%), followed by small cell lung cancer (SCLC) (1 case, 10%). TNM Staging of lung cancer included: four cases of Ib (40%), one case of IIIb (10%), four cases of IV (40%) (all 4 patients were suspected of lung metastasis because chest imagery suggested multiple nodules and ground-glass opacities in the lung, but there was no extrapulmonary metastasis in 3 patients), and one with an undetermined stage. Two patients received targeted therapy; four received surgical therapy (3 of them received chemotherapy at the same time); two patients received only chemotherapy; and two patients withdrew from treatment because of severe pulmonary symptoms caused by pSS lung involvement. The results of diagnosis and treatment of the 10 patients are shown in Table 2.

A literature Summary is shown in Table 3.

Discussion

The incidence rate of lung cancer reported in this paper is 0.477%, similar to previous studies.[3,5] This study confirms that patients with pSS have an increased risk of developing lung cancer. Only two of the 10 cases were male smokers, while the other eight patients were female nonsmokers, thus, not high-risk groups of lung cancer. Likewise, there were five female cases (71.4%) reported in the literature. For pSS patients with lung cancer, females were more frequently seen, which was interrelated with a high incidence of pSS in females. Our study revealed that the duration from diagnosis of pSS to lung cancer was as long as 0.92~42 years. Fifty percent of patients received immunosuppressant therapy. Meanwhile, the pSS patients with lung cancer were significantly older than those who did not develop lung cancer (60.8 ± 8.9 vs. 44.9 ± 12.1, $P < 0.001$). pSS disease and

Table 3 Clinical features of pSS patients with lung cancer reported in literatures

	Study	n	Incidence rate	Gender	Age (year)	pSS course of disease (year)	Smoking History	Lung lymphatic infiltration	Pathological classification
1	Takabatake *et al*.[8]	1		F	78	2	N	Y	Adenocarcinoma
2	Touma *et al*.[9]	1		F	69	7	N		UK
3	Uji *et al*.[10]	1		F	69	3		Y	Adenocarcinoma
4	Nishimura *et al*.[11]	1		M	72				SCLC
5	N Engl J[12]	1		M	68		Y		Squamous carcinoma
6	Lazarus *et al*.[4]	2	1.79%	F	57	4			Adenocarcinoma
				F	82	8			UK
7	Theander *et al*.[3]	4	0.79%						
8	Zhang *et al*.[5]	2	0.15%						

Primary Sjogren's syndrome; SCLC, small cell lung cancer.

immunosuppressant application might be associated with lung cancer.

We found that symptoms including cough (6 cases, 60%), productive cough (4 cases, 40%), chest pain (1 cases, 10%), and weight loss (4 cases, 40%), were more common in pSS patients with lung cancer. Our study suggested that physicians should pay attention to these symptoms during follow-up of pSS patients. Chest CT scanning could show direct signs of lung cancer; therefore it is important for the diagnosis and assessment of lung cancer in pSS patients. Close attention should be paid to radiological manifestations of lung cancer in pSS patients, such as consolidation-like masses, nodules, GGOs, and lymph node enlargement. For pSS patients with lung involvement, an annual follow up of chest high resolution (HR)CT is recommended, not only to evaluate lung involvement, but also for malignancy screening (lung cancer or lymphoma). However, an annual follow up of chest HRCT or X-ray is not recommended for pSS patients without lung involvement. Chest CT should be performed if any new respiratory symptoms exist.

In our study, adenocarcinoma was the most common pathological type of lung cancer (90%) in pSS patients. Likewise, within the known five pathological results reported in the literature, three were adenocarcinoma. This suggests that the incidence rate of adenocarcinoma is high in pSS patients; however, the mechanism is not clear. As to the clinical staging of lung cancer, four patients were in stage Ib. Because pSS patients must have chest imaging routinely re-examined, lung cancer lesions can be detected early, which is of great value for early diagnosis of lung cancer. Four of the patients were in IV stage and were suspected of lung metastasis as their chest image suggested multiple nodule and ground glass opacities in the lung; extrapulmonary metastasis was found in one patient. Because chest imaging of pSS lung involvement has various manifestations, such as ground-glass, consolidative, reticular, and nodular opacities, and cyst lesions,[13] further pathological diagnosis is required to determine whether the nodule lesions within the lung are lung cancer metastasis or pSS lung involvement. The subsequent results may affect lung cancer staging. In this study, an upper right and a lower right small nodule were found in case 7. Intraoperative pathological findings suggested that the upper right lung nodule was lung cancer and the lower right lung nodule was fiber tissue with hyaline degeneration. Consequently, the pathological TNM staging was stage Ib. Therefore, in pSS patients with lung cancer, if there are other single nodules within the lung but no metastasis outside the lung, further confirmation of the pathological diagnosis of the nodule within the lung is recommended, in order to diagnose the correct lung cancer clinical staging and provide relevant treatment. It an be difficult to identify multiple nodules for pathological diagnosis; three patients in this study with multiple nodules but without extrapulmonary metastasis were judged to be stage IV and were given systemic anti-cancer treatment.

Treatments for pSS patients with lung cancer should be carefully determined. Patients 1 and 8 withdrew from treatment because of the severe pulmonary symptoms of diffuse parenchymal lung disease. Previous studies have reported that surgical procedure chemotherapy and epidermal growth factor receptor-tyrosine kinase inhibitors induced an exacerbation of pulmonary fibrosis. Hematologic involvement and liver function abnormality, the major organ involvements of pSS, can hinder anti-tumor treatment. Fortunately, in our study, there were eight patients without severe organ dysfunction who received effective anti-tumor treatment, and four of these patients were treated with immunosuppressors.

CTD lung involvement might be one of the reasons for the high incidence of lung cancer. Lung involvement is common in pSS patients. There are various histological patterns of pSS lung involvement, such as nonspecific interstitial pneumonia, organizing pneumonia, noncaseating granulomas, lymphocytic interstitial pneumonia, lymphocyte alveolitis, and chronic, follicular, and constrictive bronchiolitis.[13] In this study, 50% of patients had combined pSS lung involvement, which is the manifestation of diffuse parenchymal lung disease. However, we did not investigate the pathological characteristics of pSS-associated diffuse parenchymal lung disease. In the literature there were two patients reported to have suffered from lymphocyte alveolitis manifestation. Because of bronchia and lung tissue involvement in pSS patients, the factors of long-term repeat chronic inflammation and inflammatory repair, lymphocyte infiltration, and local immune environment turbulence might be correlated with the onset of lung cancer.

These were some limitations to our study. First, the pSS patients in our study were inpatients, most of whom had serious complications. Because complete clinical data of outpatients with pSS at PUMCH could not be collected, outpatients could not be included in the control groups. Second, the cancer treatments for pSS patients were not the same, and conclusions on the best therapeutic schedule could not be made. Third, because of the small research sample and the lack of a large lung cancer patient control group, we could not determine any difference between the prognosis of pSS patients with lung cancer and lung cancer patients. Finally, we did not identify the histological patterns of pSS lung involvement, which might help us to understand lung cancer onset in pSS.

Conclusion

The incidence of pSS lung cancer is higher than in the normal population. Most patients were female nonsmokers and adenocarcinoma was the most common pathological type of lung cancer. Physicians should closely observe lung cancer

incidence during the pSS follow-up period. Lung cancer related symptoms should be focused upon and chest CT scanning is important for the diagnosis and assessment of lung cancer in pSS patients. Clinical stages and individualized treatments for pSS patients with lung cancer should be carefully determined.

Disclosure

No authors report any conflict of interest.

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