

Clinical Features of Pulmonary Sarcoidosis Complicated by Lung Cancer

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Abstract

Objective For lung cancer complicated with sarcoidosis, there are no exact features that indicate whether lymphadenopathy is metastatic. This makes the validity of surgery uncertain for clinicians. The aim of this study was to clarify the clinical features of pulmonary sarcoidosis complicated by lung cancer, especially from the viewpoint of evaluating lymphadenopathy.

Methods We retrospectively reviewed medical records from 2004 to 2013 at our institution, and 18 patients who were diagnosed with sarcoidosis and lung cancer were thus found to be eligible. We investigated the relationship between the clinical and pathological findings of their swollen lymph nodes.

Results Of 18 patients, 11 conducted surgery, and the postoperative pathological evaluation of swollen lymph nodes was done in 8 of the patients. Postoperative N factor in all these patients was 0, even though lymphatic metastasis had been suspected preoperatively because of the unbalanced distribution of lymphadenopathy or the accumulation of fluorodeoxyglucose.

Conclusion In patients with lung cancer complicated by sarcoidosis, the clinical assessment of the state of lymphadenopathy is difficult to make. However, as many of them tend to be benign, we suggest that surgical resection should be considered for a complete cure in the absence of any remote metastasis.

Key words: carcinoma, granuloma, lymphatic metastasis, sarcoidosis

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Introduction

Sarcoidosis is a systemic disease characterized by granuloma formation and it can occur in any organ (1). It remains controversial as to whether lung cancer is present more frequently in patients with sarcoidosis (2-4), but we do sometimes encounter such cases. However, few studies have reviewed more than 10 cases of lung cancer complicated by sarcoidosis, and only a few case reports have been published (5). In these studies, clinicians had difficulty in deciding the clinical stage of lung cancer, primarily because of the problems encountered in evaluating the state of lymphadenopathy. This is an important theme for judging the validity of surgery. The aim of this study was to clarify the frequency and clinical features of lymphatic metastasis in patients with lung cancer complicated by sarcoidosis.

Materials and Methods

Eighteen patients diagnosed with lung cancer at our institution from 2004 to 2013, who had a past medical history of sarcoidosis, were eligible. The diagnosis of sarcoidosis was made according to the criteria defined in the 2006 guidelines of the Japan Society of Sarcoidosis and Other Granulomatous Disorders (6), and sex, age, smoking history, and diagnostic procedure were assessed. Regarding lung cancer, the period of occurrence after the diagnosis of sarcoidosis, pathological type, distribution of lymphadenopathy, and treatment were assessed. In patients who had undergone surgical resection, the relationship between the clinical findings, such as the distribution of lymphadenopathy or the accumulation of fluorodeoxyglucose (FDG), and the pathological findings were reviewed. The study protocol was approved by the Ethics Committee of Jichi Medical University

Table 1. Characteristics of Patients with Sarcoidosis.

Patient's characteristics	n=18
Sex (M/F)	9/9
Mean age at diagnosis of sarcoidosis	61.9 (26-77)
Smoking status	
Never	7 (39%)
Current or former	11 (61%)
Diagnostic procedure of sarcoidosis	
Clinically	4 (22%)
Pathologically	14 (78%)
Observation period* (years)	7.9 (0-32)
Pathological type of lung cancer	
Adenocarcinoma	9 (50%)
Squamous cell carcinoma	6 (33%)
Small cell carcinoma	2 (11%)
Others [†]	1 (6%)
Distribution of lymphadenopathy	
BHL	1 (6%)
BHL+mediastinum	5 (28%)
UHL	1 (6%)
Mediastinum	6 (33%)
UHL+mediastinum	2 (11%)
No swelling	3 (17%)
Treatment of lung cancer	
Surgical resection	11 (61%)
Chemotherapy	5 (28%)
Best supportive care	2 (11%)

*Observation period means time from diagnosis of sarcoidosis to lung cancer.

[†]Others mean poorly differentiated adenocarcinoma and squamous cell carcinoma.

M: male, F: female, BHL: bilateral hilar lymphadenopathy, UHL: unilateral hilar lymphadenopathy

(approval number, A15-013).

Results

The characteristics of the patients are shown in Table 1. Half of all patients were male and the mean age of the patients diagnosed with sarcoidosis was 61.9 years. Four patients were clinically diagnosed and 14 were pathologically diagnosed. The diagnosis of sarcoidosis either preceded or coincided with lung cancer in all of them, and the mean observation period was 7.9 years. The breakdown of the pathological types was as follows: adenocarcinoma in 9 patients (50%), squamous cell carcinoma in 6 (33%), small cell carcinoma in 2 (11%), and others in 1 (6%). Bilateral hilar lymphadenopathy (BHL) was observed in 6 patients (33%), which is often seen in lymph node sarcoidosis. In contrast, 1 patient (6%) showed isolated unilateral hilar lymphadenopathy (UHL), 6 (33%) showed only mediastinum lymphadenopathy, and 2 (11%) showed both UHL and mediastinum lymphadenopathy. No lymphadenopathy was seen in 3 patients (17%). Surgical resection for lung cancer was carried out in 11 patients. Among them, one had previously undergone surgery at another institution. Table 2 shows the char-

acteristics of the remaining 10 patients who underwent surgery at our institution. As no lymphadenopathy was seen in 1 patient and lymphadenectomy was not performed in another patient, a postoperative pathological evaluation of the regional lymph nodes was carried out in 8 patients. The shorter diameter of these lymph nodes was more than 1 cm and they met the size criteria for speculative malignancy (7). Atypical distribution of lymph nodes for sarcoidosis, such as only mediastinal or UHL, was seen in 4 patients. Preoperative FDG-positron emission tomography (PET) was also conducted in 4 patients, who all showed a significant accumulation of FDG. However, all N factor of these 8 patients were postoperatively proven to be 0.

Discussion

In our study, a postoperative pathological evaluation of lymphadenopathy that was suggestive of lymphatic metastasis was done in 8 patients. We speculated that metastasis was present from the lymph node distribution that was atypical for sarcoidosis. Criado et al. reported that isolated UHL was seen in <5% of sarcoidosis cases and that an exclusive enlargement of the mediastinal lymph nodes was even less common (8). From such a viewpoint, unilateral or only mediastinal distribution appeared as metastatic rather than sarcoidosis. However, the lymphadenopathy of 4 patients who showed such an atypical distribution were all postoperatively proven to be benign. Hence, atypical distribution does not suggest lymph node metastasis. FDG-PET was preoperatively conducted in 4 patients. Although a significant FDG accumulation was seen in these 4 patients, postoperative pathological evaluations showed no malignancy in these lymph nodes. Teirstein et al. reported that the standardized uptake value (SUV) obtained using FDG-PET in sarcoidosis patients ranged from 2.0 to 15.8 in the lymph nodes and lung fields (9). Therefore, we could not demonstrate the usefulness of FDG-PET for distinguishing between benign and malignant lymphadenopathy in sarcoidosis patients. Recently, L-[3-¹⁸F]- α -methyltyrosine (FMT)-PET was reported to be useful for distinguishing malignant lymphadenopathy from lymph node sarcoidosis (10), but it can only be performed at a small number of institutions. The chronological size change of lymph nodes seen in lung cancer is sometimes useful for evaluation. However, CT is not regularly performed because of the nature of pulmonary sarcoidosis, which usually remains stable without any noticeable progression. This makes the comparison over time difficult. Accordingly, an evaluation of the state of lymphadenopathy is difficult if the information is limited to radiographic findings, such as the distribution on CT scans or FDG accumulation.

We must emphasize that the postoperative N factor was 0 in all 8 patients with lymphadenopathy. There have previously been a small number of case reports regarding surgery for lung cancer complicated by sarcoidosis, and Mimura et al. summarized them in 2011 (5). Among the 24 cases of

Table 2. Patient Characteristics at Surgical Resection.

ID	Origin site	Primary site	Lymphadenopathy	Accumulation of FDG	Pathological staging
1	Ad	R, S ²	Mediastinum		pT1N0M0 (IA)
2	Ad	R, S ⁹	BHL+mediastinum		pT2N0M0 (IB)
3	Ad	R, S ⁵	No swelling		pT1N0M0 (IA)
4	Sq	L, S ¹⁺²	BHL+mediastinum		Unknown*
5	Sq	R, S ⁸	Mediastinum		pT1N0M0 (IIA)
6	Sq	R, S ⁸	BHL+mediastinum		pT1N0M0 (IA)
7	Sq	R, S ¹⁰	UHL+mediastinum	5.62	pT2N0M0 (IB)
8	Ad	L, S ⁴⁻⁵	Mediastinum	Accumulated [†]	pT1N0M0 (IA)
9	Ad	R, S ¹⁰	BHL+mediastinum	Accumulated [†]	pT2bN0M0 (IIA)
10	Ad	L, S ¹⁺²	BHL+mediastinum	7.97	pT2aN0M0 (IB)

BHL suggestive of lymph node sarcoidosis was only seen in 5 of 10 patients. Significant accumulation of FDG were seen in 4 patients. However, postoperative staging of lung cancer was all N=0 except for one case in which lymphadenectomy was not carried out.

*Surgical resection was not carried out to avoid invasive surgery.

[†]Exact SUV was not known but accumulation was reported to be significant.

FDG: fluorodeoxyglucose, BHL: bilateral hilar lymphadenopathy, UHL: unilateral hilar lymphadenopathy, SUV: standardized uptake value

Table 3. Simultaneously Diagnosed Cases.

ID	pStage	Distribution of lymphadenopathy	Serum ACE (IU/L)	Extrapulmonary lesions of sarcoidosis
8	T1aN0M0	Mediastinum	18.1	No lesion
9	T2bN0M0	BHL+Mediastinum	16.2	Eye
10	T2bN0M1	BHL+Mediastinum	16.7	Eye

These cases were diagnosed as lung cancer and sarcoidosis simultaneously.

ACE: angiotensin converting enzyme, BHL: bilateral hilar lymphadenopathy, UHL: unilateral hilar lymphadenopathy

sarcoidosis with lung cancer and contralateral hilar lymphadenopathy, the postoperative N factors were 0, 1, and 2 in 18 cases, 1 case, and 3 cases, respectively, suggesting that lymphadenopathy in patients with lung cancer tends to be benign when complicated by sarcoidosis. We speculate that sarcoid granuloma in the regional lymph nodes might suppress lymphatic metastasis from the primary lesion of lung cancer, and it is accompanied by a good surgical outcome. Therefore, surgery might be recommended for a complete resection of carcinoma, even if lymphadenopathy is present, but with no metastasis. Recently, endobronchial

ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA) has been widely used for diagnosing lymph node lesions, and the diagnosis rate is reported to be high. As for lymph node metastasis from lung cancer, the diagnostic accuracy was 98.0% using EBUS-TBNA, which was higher than that achieved using CT (60.8%) or FDG-PET (72.5%) (11). In a previous study regarding lymph node sarcoidosis, EBUS-TBNA also achieved a high diagnostic accuracy rate of 91.4% (12). Hence, it is also important to carry out preoperative pathological evaluations as far as possible to avoid missing an opportunity to perform complete

resection.

In the postoperative cases, a simultaneous diagnosis of sarcoidosis and lung cancer was reached in 3 cases. In these cases, distinguishing between sarcoidosis and a tumor-related sarcoid reaction is important. To date, there is no standard that clearly distinguishes these states. However, uveitis suggestive of an eye lesion of sarcoidosis was present in 2 cases and another case showed a symmetrical distribution of mediastinum lymphadenopathy in spite of the tiny size of the primary cancer (Table 3). These findings suggest the systemic inflammatory changes of sarcoidosis rather than a local sarcoid reaction, even though the serum angiotensin converting enzyme (ACE) levels were not high.

There are some limitations associated with our study in regard to its retrospective design and the small number of patients. A pathological evaluation of the lymph nodes was possible in only 8 patients; and all had visited the respiratory center of a single university hospital in Tochigi Prefecture. However, this is the first study to analyze the clinical characteristics of this lesion using a similar-sized patient population. A greater number of cases is thus needed in the future.

Conclusions

In conclusion, the clinical evaluation of lymphadenopathy in lung cancer complicated by sarcoidosis is generally not sufficient to achieve an accurate diagnosis. Regarding the high frequency of benign lesions in such cases, we suggest including a pathological evaluation and considering surgical resection to obtain a complete cure in the absence of any distant metastasis.

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

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