Four Cases of Lung Cancer Associated with Idiopathic Interstitial Pneumonia

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Abstract : It is well known that lung cancer develops frequently in patients with idiopathic interstitial pneumonia (IIP) (9.8—22.8%). We investigated 4 patients who developed lung cancer among the 28 patients with IIP (14.3%) who were admitted to our hospital from June 1981 to March 1989. Many reports have pointed out the clinical features of lung cancer associated with IIP as male sex, old age, heavy smoking, and poor prognosis. Our 4 series were agreed with these clinical features. Lung cancer associated with IIP have been often reported to occur in the lower and peripheral regions of the lung, and honeycomb structures are frequently seen. But we found that lung cancer in IIP could actually occur in both the lower and upper regions of the lung and does not occur only in the honeycomb structures. There was no obvious dominance of any histological type among the tumors. If lung cancer is suspected in a patient with IIP, tumor markers are of some value for diagnosis, but are not sensitive enough to be used alone.

Key words : idiopathic interstitial pneumonia, lung cancer, smoking, metaplasia, pathogenesis.

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Introduction

It is well known that lung cancer is common in idiopathic interstitial pneumonia (IIP), and an increase in cases has recently been reported. The percentage of IIP patients developing lung cancer ranges from 9.8 to 22.8% (Ninomiya *et al.*, 1989). In our hospital, 4 cases of lung cancer developed among 28 patients with IIP (14.3%) between June 1981 and March 1989. Some reports have stated that lung cancer in IIP more frequently occurs in the lower lung fields in association with honeycomb-like lung tissue areas. Furthermore, adenocarcinoma and squamous cell carcinoma are reported to be more frequent than small and large cell carcinoma. However, we suggest that the key factor which determines where cancer occurs is not the presence of honeycomb structures but the presence of metaplasia. Metaplasia occurs in any part of the lung, including the upper lung fields. Also, other types of cancer can occur in IIP besides adenocarcinoma and squamous cell carcinoma.

Few reports of this disease have indicated the prognosis following diagnosis at an early stage and active treatment.

We investigated the clinical features, diagnostic methods, histological findings, site of origin of the cancer, and the prognosis.

Patients and Methods

Four cases of IIP with lung cancer were found among 28 patients with IIP who were admitted to our hospital from June 1981. Their clinical data, including sex, age, and smoking habits, is listed in Table 1. The occupations of these patients were recorded to investigate any occupational causes of pulmonary fibrosis. The occupations were public servant, glass-maker, railway worker, and factory worker. We used the Brinkmann Index (BI) to determine the smoking risk in this disease. The BI was also used in the examination of 24 IIP patients without lung cancer. The BIs of the 14 males and 10 females are listed separately to show the influence of sex. The diagnosis of IIP was made according to the criteria of the research group of the Ministry of Health and Welfare on IIP (Homma, 1981). Roentgenography was the method used to diagnose IIP and detect lesions suspected as lung cancers. The X-ray examination results are shown in the Figures.

The diagnostic methods we used for the lung tumors were sputum cytology, brushings collected at bronchoscopy, transbronchial biopsy (TBB), and open lung biopsy. The staging of the tumors was determined by the TNM classification. Pathological examination was performed to determine the histological type of each tumor. We also investigated the changes of tumor marker levels in these patients. The tumor markers used were NSE, SCC, CEA, and CA19-9. The time from tumor diagnosis to death was used to determine the prognosis.

Results

Case 1:

The patient was a 74-year-old male, who was a retired public servant. His BI was 1,800. He was diagnosed as having IIP and lung cancer at the same time. Figure 1 shows multiple nodules and honeycomb changes, which occupied the lower lung fields. The X-ray findings indicate pulmonary fibrosis. In the right lower lung field, there is a dense lesion located in the rS10. This was found to be squamous cell carcinoma.

Case 2:

The patient was a 59-year-old male, glass-maker. His BI was 1,000. He was diagnosed as having IIP in February 1987, and lung cancer was found in March 1988. Figure 2A shows multiple nodules and honeycombing of the lower regions of both lungs. After one year, a lesion was found in the upper part of the left lung, and the honeycomb changes became more apparent (Fig. 2B). Open lung biopsy was performed after the diagnosis could not be made by a bronchoscopy and squamous cell carcinoma was found.

Case 3:

The patient was a 63-year-old male, railway worker. His BI was 1,260. He was di-

Fig. 1. Chest X-ray of Case 1. A 74-year-old male was diagnosed as having IIP and lung cancer (squamous cell carcinoma) at the same time in April 1985.

Fig. 2. Chest X-ray of Case 2. A: Chest X-ray of 59-year-old male having IIP was taken in February 1987. B: Chest X-ray was taken one year later. A dense lesion was found in the upper part of the left lung, which was diagnosed as a squamous cell carcinoma by open lung biopsy.

agnosed as having IIP and lung cancer at the same time. Figure 3 shows pulmonary fibrosis occupying almost 2/3 of both lung fields, with honeycomb changes in the lower parts.

Fig. 3. Chest X-ray of Case 3. A 63-year-old male was diagnosed as having IIP and lung cancer (adeno carcinoma) at the same time in July 1986.

Fig. 4 Chest X-ray of Case 4. A: Chest X-ray of 74-year-old male having IIP was taken in June 1986. B: Chest X-ray was taken two years later. A mass density appeared in the left upper lung field, which was diagnosed as a small cell carcinoma by transbronchial biopsy.

A mass can be seen in the upper right lung field. The tumor was found to be adenocarcinoma and was located in the rB1b through sputum cytology examination and a fiberoptic bronchoscopy.

Table 1. Clinical data of the IIP patients with lung cancer

Case	1	2	3	4
Sex	Male	Male	Male	Male
Age	74	59	63	74
Occupation	Public servant	Glass-maker	Railway worker	Factory worker
BI	1,800	1,000	1,260	1,040
Diagnostic methods	Sputum Bronchofiberscopy	Open lung biopsy	Sputum Bronchofiberscopy	Transbronchial biopsy
Stage	I	I	III	III
Site	rS10	1S3	rS1	1S3
Histological type	Squamous	Squamous	Adeno	Small
Duration *	0	1 year	0	2 years
Survival outcome after tumor diagnosis	Death 20 months	Alive	Death 13 months	Death 2 months
Tumor markers **	N	N	CEA 12.9	NSE 28.7

N=normal, * Duration means the time from the diagnosis of IIP to the diagnosis of cancer,

** Including CEA, SCC, NSE and CA19-9.

Case 4:

The patient was a 74-year-old male, who was a retired factory worker. His BI was 1,040. He was diagnosed as having IIP in February 1986 and as having lung cancer in June 1988. Figure 4A shows multiple fine nodules and lines extending over 2/3 of both lung fields; honeycombing can also be seen in the lower parts. Figure 4B shows that a mass appeared in the left upper lung field and the fibrosis had progressed after two years. A small cell cancer located at the 1S3 was diagnosed by transbronchial biopsy (TBB).

The clinical features of the 4 patients are shown in Table 1. All of them were male, and the mean age was 67 years (range: 59–74). They had no history of exposure to dust.

The mean BI was 1,275 (1,800–1,000). Among the IIP patients without lung cancer, the mean BI was 732 (1,800–0) in males and 109 (550–0) in females (Table 2) (Fig. 5). We excluded the data for females because their BIs were very low. Patients of IIP with lung cancer had significantly more heavy smoking history than those of only IIP ($\chi^2=5.14$, $P<0.05$) (Table 3).

The cancers of 2 cases were diagnosed by both sputum cytology and a fiberoptic bronchoscopy, while the other 2 cases were diagnosed by transbronchial biopsy and open lung biopsy, respectively.

Case 2 underwent partial pneumonectomy. We found a close relationship between interstitial fibrosis, metaplasia, and lung cancer in the resected lung specimen (Fig. 6).

The tumor locations were the rS10, 1S3, rS1, and 1S3 in these 4 cases. Both case 1

Table 2. BI values in the IIP patients without lung cancer

Case	Sex	BI
1	f	0
2	m	350
3	m	900
4	f	550
5	f	0
6	m	600
7	m	300
8	m	1440
9	m	1800
10	m	0
11	m	1200
12	m	1225
13	m	180
14	f	0
15	f	360
16	f	0
17	m	300
18	f	0
19	f	180
20	f	0
21	m	600
22	f	0
23	m	160
24	m	1200

Fig. 5. The BI values for the IIP patients with and without lung cancer.

a : IIP with lung cancer

b : Male IIP patients without lung cancer

c : Female IIP patients

and 2 were stage I, case 3 was stage IIIA, and case 4 was stage III. The histological diagnosis was squamous cell carcinomas, adenocarcinoma, and small cell carcinoma. The

Table 3. Differences in BI values between IIP patients with and without lung cancer

BI	$\geq 1,000$	$< 1,000$	Total	%
IIP-cancer	4	0	4	100
Only IIP	5	9	14	36
Total	9	9	18	50

$\chi^2=5.14$, $P<0.05$.

Fig. 6. The microscopic view of the lung tissue taken from Case 2. A: Squamous metaplasia is seen in some bronchial epithelium. (H. E. original magnification, $\times 200$) B: High power view shows loss of polarity in the whole layer which is considered as "Carcinoma in situ." (H. E. original magnification, $\times 400$) C: The region of hyperplastic change is magnified. (H. E. original magnification, $\times 200$). D: This shows a region of honeycomb structures in the lung. (H. E. original magnification, $\times 40$).

diagnosis of IIP and lung cancer was simultaneous in 2 cases, while in the other 2 cases cancer was found 1 and 2 years after the diagnosis of IIP. Only the patient who underwent pneumonectomy is still alive, with the other 3 patients dying between 2 months and 1.5 years after diagnosis, indicating a poor prognosis (Table 1). Regarding tumor markers, 2 cases showed an increase in CEA (12.9) and NSE (28.7) respectively (Table 1).

Discussion

The high incidence of lung cancer in IIP has increasingly been noticed. According to recent reports in Japan, it ranges from 9.8 to 22.8%; our series fell within this range (14.3%).

It is well known that IIP can cause lung parenchymal damage and produce a honeycomb-like structure. This pathological process is often seen in the peripheral and lower regions of the lung. Diffuse fibrosis of the alveolar wall and interstitial tissues around the terminal bronchi cause alveolar enlargement and thickening of alveolar walls. Narrowing of terminal bronchi can also be seen. These pathological changes produce the honeycomb structure where abnormal epithelial metaplasia can occur. However, we found metaplasia in the upper part of the lung in case 2. Metaplasia was found in the 1S3 near the cancer, but honeycombing was absent. Abnormal epithelial metaplasia without interstitial fibrosis should be held responsible for the occurrence of lung cancer. Metaplasia can occur not only within the honeycomb structure, but also in any part of the lung. This explains why some cancers in IIP occur outside the most prominent regions of honeycombing, which often exist in the lower lung fields. Our finding supports the hypothesis that metaplasia and abnormal hyperplasia cause lung cancer in IIP (Callahan *et al.*, 1952; Fox & Risdon, 1968; Fraire & Greenberg, 1973; Kohno *et al.*, 1983; Meyer & Liebow, 1965; Nozawa *et al.*, 1974; Shimizu, 1985; Tanimura *et al.*, 1987; Turner-Warwick *et al.*, 1980). Our results also agreed with the opinion that carcinoma in IIP is often located in the peripheral region of the lung, which is in accord with the site of abnormal metaplasia.

Some reports have pointed out that the reason for lung cancer developing in elderly patients with IIP may be that their life has been prolonged recently by better medical therapy (Fraire & Greenberg, 1973). Heavy smoking is a definite risk factor. Our results for the BIs in IIP with lung cancer were significantly higher than in IIP without lung cancer ($P < 0.05$) (Table 3), which agreed with many other reports in this field. Smoking may damage the bronchial epithelium and cause metaplasia (Homma, 1981). We suggest that patients with IIP and various risk factors for cancer should be closely followed up to diagnose lung cancer as early as possible.

In the diagnosis of lung cancer, we found cytological examination of the sputum, brushings obtained by bronchofiberscopy, and transbronchial biopsy to be useful. Open lung biopsy is useful if the above methods could not be applicable. If the tumor is found at an early stage and removed, the patient's prognosis can be improved. For example, the cancer in case 2 was found at stage I by open lung biopsy and immediately removed. This patient is still alive.

Many reports have said that squamous cell carcinoma and adenocarcinoma predominate in IIP with lung cancer (Fraire & Greenberg, 1973; Haddad & Massaro, 1968; Nino-miya *et al.*, 1989; Tanimura *et al.*, 1987), but others have disagreed (Fox & Risdon, 1968; Turner-Warwick *et al.*, 1980). We found squamous cell cancer in 2 patients, while adeno-

carcinoma and small cell cancer occurred in 1 case each. However, 4 cases is too few to analyze statistically.

Three of the 4 patients died after a mean survival period of 11.6 months. The diagnosis of IIP and lung cancer was simultaneous in half of our series, and half of the 4 patients were at a late stage according to the TNM classification. Because such tumors are often located peripherally, surgery may be performed in cases detected early and the prognosis may be improved, as in case 2. Thus, early diagnosis is important in such patients.

Tumor markers may give some clues in diagnosing lung cancer in IIP patients, but they seem not to be sensitive enough to be dependable. The IIP patient should still be examined carefully, even though tumor markers are negative.

Conclusion

Recently, the high incidence of lung cancer occurring in IIP has been noted, but its early diagnosis is not easy. If a lesion develops in any part of the lung in an IIP patient, it should be investigated carefully. Also, once the diagnosis of IIP is made, patients should be followed up closely. In order to diagnose cancer at an early stage, a regular X-ray examination is necessary. Sputum cytology and fiberoptic bronchoscopy are useful if there is a suspected cancer. But if a diagnosis cannot be made, open lung biopsy should be considered. The early diagnosis and removal of tumors may improve the prognosis in these patients.

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特発性間質性肺炎に合併した肺癌の 4 例

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要 旨: 特発性間質性肺炎 (IIP) に肺癌が合併しやすいことはよく知られている (9.8—22.8%)。1981 年 6 月から 1989 年 3 月まで当科に入院した IIP 28 例のうち肺癌を合併していたのは 4 例 (14.3%) であった。これまでに IIP に合併した肺癌の特徴として、男性、高齢者、高度喫煙歴を有する患者に多いと言われており、この点では我々の報告と一致していた。発生母地として、気管支の上皮化生が考えられたが、組織型に一定の傾向はなかった。また肺癌発生の部位と蜂巣肺は必ずしも一致していなかった。肺癌早期発見のためには、普段より喀痰細胞診や気管支鏡などの検査が有用であることは言うまでもないが、IIP 合併肺癌を早期に発見するためには必要に応じて開胸肺生検を考慮せねばならないと考えた。また、腫瘍マーカーの測定も、診断に有用であった。

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