Early clinical diagnosis of synchronous multiple primary lung cancer

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Abstract. The diagnosis of synchronous multiple primary lung cancer (SMPLC) remains a formidable challenge. The aim of the present study was to identify useful clues for the clinical diagnosis of SMPLC, in particular for the early stages. The medical records of 10 patients diagnosed with SMPLC with different histological types were analyzed retrospectively. Chest computed tomography (CT) findings showed two pulmonary lesions in all patients. The two lesions displayed malignant characteristics of primary lung cancer. The levels of a number of tumor markers, including carcinoembryonic antigen, neuron-specific enolase, cytokeratin fragment 21-1, squamous cell carcinoma and CA125 increased in 2 patients. Auxiliary examinations of other physical sites in these patients did not show signs of neoplasm metastasis. Two tumors were separately staged and appropriate treatment was carried out based on the revised stage, which provided more benefits for SMPLC patients. The diagnosis of SMPLC might be delayed or mistaken owing to its similarity to neoplasm metastasis. A high index of awareness is required for the early diagnosis of this disease. The malignant characteristics of primary lung cancer in various lesions may be valuable clues for the diagnosis of SMPLC. Alterations in the levels of tumor markers may be a poor diagnostic tool for the detection of SMPLC. Separate biopsies for different pulmonary masses should be performed for clinical staging as soon as possible and reasonable treatment based on the stage should also be selected.

Introduction

Patients with lung cancer have an increased danger of developing a second tumor in the lung. Synchronous multiple primary lung cancer (SMPLC) is characterized by the presence of the second tumor concurrently. The incidence of SMPLC has been variably reported as being between 1 and 16% (1). However, the exact incidence is not easily evaluated due to the difficulty in distinguishing SMPLC from a single pulmonary neoplasm with intrapulmonary metastases or pulmonary metastases originating from primary cancers in different organs.

The diagnostic criteria of SMPLC proposed by Martini and Melamed is as follows (2): i) lesions occur in different lobes or in different segments of the same lobe, ii) lesions originate respectively from different kinds of carcinoma *in situ* and show different histological types, and iii) no metastasis is detected in the lymphatic systems and other organs. Nevertheless, not all patients can be stratified in accordance to the above standards.

To date, there is no universal agreement regarding which methods should be followed in the diagnosis of SMPLC cases. Therefore, the aim of the present study was to identify useful clues used for the diagnosis or prognosis of SMPLC through the retrospective study of 10 cases with SMPLC.

Patients and methods

Between January 2000 and December 2010, out of 2,991 patients diagnosed with lung cancer in our clinic (Chinese PLA General Hospital), 10 patients were diagnosed as having SMPLC with different histological categories by three radiologists. The diagnosis of SMPLC was based on the combination of clinical presentations, radiological findings and biopsy following pulmonary lobectomy, bronchoscopy or percutaneous puncture.

The ethics board in our hospital made the decision that there was no need to gain informed consent from the patients since this was a retrospective investigation.

The patients underwent chest radioscopy and abdominal ultrasonography. A total of 8 patients underwent brain magnetic resonance imaging (MRI) and radionuclide bone scanning. Two patients underwent systemic positron emission computed tomography/computed tomography (PET/CT) scan. We retrospectively analyzed these cases through reviewing the patient medical records, radiological findings, pathological changes, treatment strategy and survival time following diagnosis.

Results

The patients included in this study were 8 males and 2 females. Their mean age was 64.3 (range, 48-78 years). A total of 8 male

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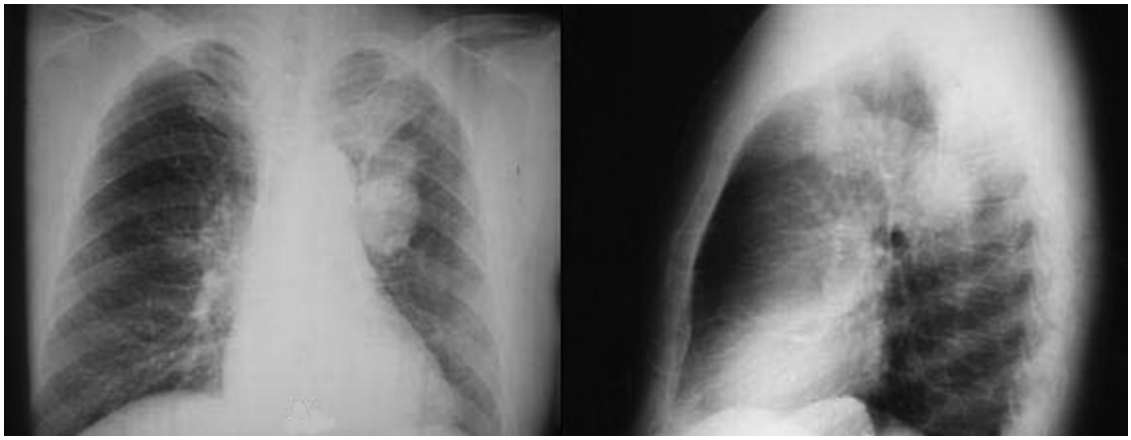

Figure 1. Chest radiograph demonstrating 2 similar zone masses located on the 2 segments of the left upper lobe in patient 3.

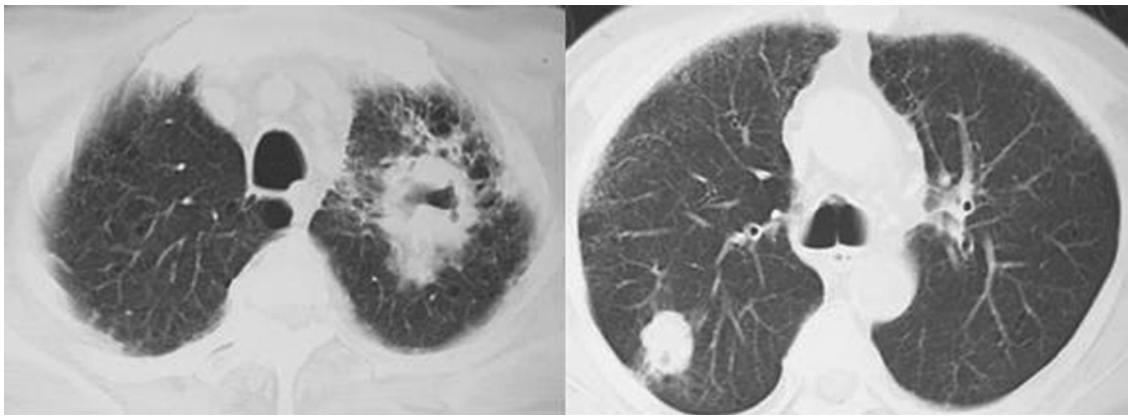

Figure 2. Chest CT demonstrated 2 masses located on the bilateral upper lung in patient 4. CT, computer tomography.

patients were smokers, whose average smoking history was 44 years [4 pack-years (range, 15-80 pack-years)]. The detailed information is listed in Table I.

Chest CT findings demonstrated two pulmonary lesions arising in different sites in patients. The two pulmonary lesions occurred in the bilateral lung in 3 patients, in different lobes of the unilateral lung in 6 patients, as well as the same lobe of the unilateral lung in 1 patient. The sizes of lesions were similar in 7 cases. All these lesions displayed malignant characteristics of primary lung cancer, including an irregular margin, spicule formation, abnormal lung lobulation, irregular cavity, signs of bronchiole inflation and signs of pleural indentation. In addition, chest CT findings revealed no lymphadenectasis other than for 1 patient. Admission chest radiograph demonstrated that 2 similar tumor masses were located in 2 segments of the left upper lobe of patient 3 (Fig. 1). One mass (3x3x2 cm) in the anterior segment of the left upper lobe displayed malignant characteristics, such as spicule formation and pleural indentation, and the other mass (5x4x3 cm) in the posterior segment of the left upper lobe displayed malignant characteristics, such as spicule formation and bronchiole inflation. Chest CT showed no lymphadenectasis in the hilum of the lung and the mediastinum. In case 4, one mass (4.5x3.2x2 cm) was located in the left upper lobe with an irregular cavity, and honeycomb-like changes were found surrounding the mass. The other mass (2x1.5x1 cm), located in the right upper lobe, displayed signs of pleural indentation (Fig. 2). There was no lymphadenectasis observed in the chest CT.

The levels of a number of tumor markers increased in 2 patients. In patient 5, the levels of the tumor markers were as follows: neuron-specific enolase (NSE) 79.26 ng/ml, cytokeratin fragment 21-1 (CYFRA21-1) 7.98 ng/ml and squamous cell carcinoma (SCC) 4.3 ng/ml. In patient 4, the results were as follows: carcinoembryonic antigen (CEA) 13.04 ng/ml, NSE 51.02 ng/ml and SCC 12.80 ng/ml.

The combined results obtained from abdominal ultrasonography, brain MRI, radionuclide bone scanning and PET/CT scanning showed no metastatic lesions in these patients. Pathological examination on the biopsy specimens from bronchoscopy, percutaneous puncture or pneumonectomy confirmed that 2 lesions showed different histological properties. On the basis of the pathological changes, chest CT findings and the results of the tumor marker test, their preliminary clinical diagnoses of primary lung cancer staged IIIB or IV with intrapulmonary metastasis were revised as SMPLC staged I, II and IIIA. According to the revised clinical stage, a reasonable treatment strategy was drawn. A total of 7 patients were treated with pulmonary resection, regional and mediastinal lymphadenectomy. Following the treatment, 6 patients lived longer than 1 year, out of which 3 patients lived longer than 3 years.

Table I. Clinical characteristics of 10 patients with SMPLC.

No.	Age/ gender	Smoking (pack-years)	Number of lesions	Tumor size (cm)	Primary TNM stage	Pathology	Revised TNM stage	Location of lesions	Treatment plans	Survival (months)
1	73/M	50	2	4.5x4.5x3 0.5x0.5x0.3	T4N0M0	SQ LA	T2aN0M0 T1aN0M0	Rt upper lobe Rt middle lobe	Lobectomy + segmentectomy + chemoradiation	19 50
2	48/M	40	2	4x3x3 1.4x1.3x1	T4N0M0	LA AD	T2aN0M0 T1aN0M0	Lt lower lobe Lt upper lobe	Pneumonectomy + chemo-radiation	50
3	67/M	60	2	5x4x3 3x3x2	T3N0M0	SM SQ	LD T1bN0M0	Rt upper lobe Rt upper lobe	Pneumonectomy + chemo-radiation	45
4	76/M	40	2	4.5x3.2x2 2x1.5x1	T2aN0M1a	SQ SM	T2aN0M0 LD	Lt upper lobe Rt lower lobe	Chemoradiation	14
5	58/M	15	2	3.5x2x2 2x1.3x1	T2aN0M1a	SQ SM	T2aN1M0 LD	Rt upper lobe Lt upper lobe	Chemoradiation	4
6	55/F	0	2	2.8x2x2 1.6x1.6x1.5	T4N0M0	AD BAC	T1bN0M0 T1aN0M0	Lt upper lobe Lt lower lobe	Lobectomy + segmentectomy	64
7	59/M	80	2	2.3x2.1x1.5 1.6x1.5x1.5	T1aN0M1a	AD BAC	T1aN0M0 T1aN0M0	Rt lower lobe Lt lower lobe	Lobectomy + lobectomy	6
8	65/M	40	2	3x2x2 1.5x1.4x1.4	T4N0M0	AD BAC	T1aN0M0 T1aN0M0	Rt lower lobe Rt upper lobe	Lobectomy + segmentectomy	26
9	78/M	30	2	3.5x2.5x2 2.8x1.9x1.2	T4N0M0	AD BAC	T1bN0M0 T1aN0M0	Rt upper lobe Rt lower lobe	Chemoradiation	17
10	64/F	0	2	12x8.5x3 3x3x2	T4N0M0	BAC AD	T3N0M0 T1bN0M0	Lt upper lobe Lt lower lobe	Pneumonectomy + chemo-radiation	14

AD, adenocarcinoma; SM, small cell carcinoma; LA, large cell carcinoma; SQ, squamous cell carcinoma; BAC, bronchioloalveolar carcinoma; LD, limited deadline; M, male; F, female; Rt right; Lt, left; SMPLC, synchronous multiple primary lung cancer; TNM, tumor-node-metastasis classification.

Another patient remains alive. The remaining 3 patients did not undergo surgery owing to poor heart and pulmonary functions, and instead were treated with chemoradiation. Following the chemoradiation treatment, 2 patients lived longer than 1 year, while the other lived less than 1 year.

Discussion

When 2 or more primary tumors are contemporaneously detected in different pulmonary sites, they are termed as SMPLC. According to the results from the present study, SMPLC presents apparent preponderance in smokers. These results are consistent with those from a previous report that the intensity and duration of smoking was associated with the occurrence of SMPLC (3). The incidence of SMPLC has been reported to range from 0.7 to 20% in all patients with lung cancer in previous studies (4-10), and to increase with the progression of diagnostic techniques in recent years. A possible cause for this variability is that the discrimination of multiple primary lung cancers from intrapulmonary metastasis is very difficult. In this study, out of 2,991 patients diagnosed with lung cancer, only 10 were diagnosed as SMPLC. This incidence was lower than other reported data, which suggested that SMPLC patients might be overlooked. Thus, a high index of awareness of this disease is required for early diagnosis.

Iconography findings of all 10 patients in this study shared some common characteristics: i) two pulmonary lesions arised in different sites of lung, ii) the sizes of lesions were similar, iii) the lesions displayed malignant characteristics of primary lung cancer without signs of lymphadenectasis in the hilum of the lung and the mediastinum, and iv) no extensive metastatic lesions were detected. All the above characteristics are considered to be potential clues for the early diagnosis of SMPLC.

Tumor markers have been extensively investigated in lung cancer. The most extensively studied tumor markers for non-small cell lung cancer are CEA, SCC and cytokeratins [CYFRA, tissue polypeptide antigen (TPA) and tissue polypeptide-specific antigen (TPS)]. NSE was considered to be the representative tumor marker for small cell lung cancer (SCLC). None of these markers are ideal (11-18). In this study, the levels of these tumor markers simultaneously increased in 2 patients, which indicates poor performance of these tumor markers in the diagnosis of SMPLC.

The staging of lung cancer is crucial for the evaluation and prognosis of the disease, exchanging information among clinicians and researchers, and providing a guidance for the most appropriate treatment strategy (19-22). In the present study, the 2 tumors in SMPLC patients were separately staged. Based on the different stages of the 2 tumors, corresponding surgery was thus performed, which proved to be more beneficial for the patients. Thus, separate biopsies for different pulmonary masses should be performed as soon as possible in suspected SMPLC patients.

In conclusion, the diagnosis of SMPLC might be delayed or mistaken as lung cancer with intrapulmonary metastasis. A high index of awareness is required for the early diagnosis of this disease. The malignant characteristics of primary lung cancer in different lesions might be valuable clues for the diagnosis of SMPLC. Alterations in the levels of tumor markers may be a poor diagnostic tool for the detection of SMPLC. A separate staging of different tumors in SMPLC patients should be beneficial. Therefore, separate biopsies for various pulmonary masses should be performed for clinical staging as soon as possible, and reasonable treatments based on this staging should also be selected.

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