Lung Cancer Arising in Association with Middle Lobe Syndrome

AKIRA YAMASAKI, KATSUYUKI TOMITA, HIROKI CHIKUMI, TOSHIYUKI TATSUKAWA, YASUSHI SHIGEOKA, MASAKI NAKAMOTO, KIYOSHI HASHIMOTO, YASUYUKI HASEGAWA and EIJII SHIMIZU

Division of Internal Medicine and Molecular Therapeutics, Department of Multidisciplinary Internal Medicine, Faculty of Medicine, Tottori University, Tottori Prefecture, 683-8503, Japan

Abstract. Middle lobe syndrome, caused mainly by benign inflammatory diseases, such as chronic bronchitis and bronchiectasis, is manifested clinically as a chronic cough with sputum production. The prognosis associated with this syndrome is considered good in most cases which are caused by chronic inflammatory diseases. A patient who developed lung cancer in the course of long-term treatment for right middle lobe syndrome is described. A 63-year-old woman was admitted to our hospital with complaints of right iliac bone pain. She had been treated for chronic bronchitis and bronchiectasis associated with middle lobe syndrome for 16 years before admission. Work-up of a lung adenocarcinoma originating from the right middle lobe disclosed bone metastasis to the ilium. Tumorigenesis in association with middle lobe syndrome has not yet been reported, but this first reported case suggests the need to be alert to the possibility.

Middle lobe syndrome was first defined, by Graham and colleagues, as middle lobe atelectasis resulting from bronchial compression by mediastinal lymph node enlargement caused by respiratory infectious diseases (1). Since the twelve cases reported by Graham et al., many other investigators have reported cases as a result of the change in definition of the syndrome suggested by Graham.

Middle lobe syndrome can be categorized into one of two types: one obstructive and the other non-obstructive (2). In the obstructive type lung cancer is among the major causes, while in the non-obstructive type inflammatory diseases, such as chronic bronchitis or bronchiectasis, predominate. The prognosis of non-obstructive middle lobe syndrome is generally good (3), and tumorigenesis in this type of middle lobe syndrome has not been reported. Here, the first occurrence of lung cancer in association with right middle lobe syndrome, previously treated as chronic bronchitis and bronchiectasis for 16 years, is reported.

Case Report

A 63-year-old woman was admitted to our hospital because of right buttock pain. A radiograph of the right ilium showed osteosclerotic changes, while a bone scintigram showed abnormally high uptake. A bone biopsy was performed and pathological examination of a specimen from the lesion showed metastatic adenocarcinoma.

The patient had been treated with various expectorants for chronic bronchitis and bronchiectasis over a period of 16 years. The chest radiograph showed collapse of the right middle lobe at her first hospital evaluation. During the 16-year course, no significant change from that initial chest radiograph had been evident (Figure 1A to D). Fiberoptic bronchoscopy at the first evaluation disclosed bone metastasis to the right middle lobe bronchus. Neither bronchial fluid after saline lavage nor brushings from the right middle lobe bronchus contained cytologically evident malignant cells. The patient was thus diagnosed with non-obstructive middle lobe syndrome.

Since no significant change from the initial findings was evident in the chest radiographs obtained over 16 years, investigations of the source of the bone metastasis by abdominal computed tomography, as well as fiberoptic endoscopy of the upper and lower gastrointestinal tract, were carried out. As none of these investigations disclosed a malignant tumor, fiberoptic bronchoscopy was performed. Small bronchial polyps were found at the carina and in the right main bronchus. No obvious tumor or obstruction was found in the accessible portion of the right middle lobe bronchus (Figure 2), but cytological examination of bronchial lavage from the right middle lobe bronchus showed adenocarcinoma. Histologically, the bronchial polyps proved to be endobronchial metastatic adenocarcinoma.
The patient was ultimately diagnosed with primary lung adenocarcinoma arising in the setting of right middle lobe syndrome. After radiotherapy to the metastatic bone lesion, systemic chemotherapy with docetaxel (60 mg/m²) was complicated by severe neutropenia and liver dysfunction. The chemotherapy agent was changed to gemcitabine (1000 mg/m²). After three courses of systemic chemotherapy, multiple metastases appeared in lumbar and thoracic vertebrae. Administration of bisphosphonates relieved pain from the bone metastases, but the patient’s general condition gradually worsened as progressive metastasis involved multiple organs. The patient died of respiratory failure 1 year after diagnosis adenocarcinoma of the lung had been made.

At autopsy, the right middle lobe was found to have been replaced by cancer (Figure 3) and metastases were demonstrated in multiple organs, including the lung, liver and adrenal glands. The cancer was a mucin-producing adenocarcinoma. No lesions with potential to metastasize to multiple organs were found except in the right middle lobe.

Discussion

Several respiratory diseases are known to cause middle lobe syndrome (4-7). The obstructive type of the syndrome often results from lung cancer involving the middle lobe or lingular lobe bronchus, causing atelectasis of the peripheral part of the lobe or lingula. On the other hand, non-specific inflammation...
Figure 2. Bronchoscopic findings in the right middle lobe bronchus. No obstructive tumor was observed.

Figure 3. Gross appearance of the right lung cut sagittally at autopsy. The entire right middle lobe had been replaced by lung cancer.
and bronchiectasis are major causes of the non-obstructive type of this syndrome (2). Our patient was treated for bronchiectasis and chronic bronchitis, showing typical middle lobe syndrome in radiographs presented 16 years previously when no obstructive lesion had been found at bronchoscopy. The case, therefore, may be the first where lung cancer had arisen from non-obstructive middle lobe syndrome.

The prevalence of middle lobe syndrome was 0.17% in 30,358 individuals surveyed by chest radiographic screening over a period of 2 years (8); accordingly this syndrome is not rare. Wagner and colleagues reviewed 933 patients with middle lobe syndrome and found a malignant tumor to be the cause in 22% (4). Thorough examination including bronchoscopy should, therefore, be carried out for specific diagnosis in patients with middle lobe syndrome.

Bronchoscopy was performed in the course of our patient’s first diagnostic assessment, but no malignant tumor had been found. Bross et al. suggested that even a slight suspicion of malignant tumor as a cause of middle lobe syndrome could be an absolute indication for surgical resection, even with no other evidence of cancer (9). However, our patient only had a chronic cough with sputum production and repeated follow-up chest radiographs showed essentially no interval change.

The possibility could not be excluded that the adenocarcinoma might have existed in the middle lobe for 16 years or more. Some lung adenocarcinomas progress very slowly, with 10- to 20-year clinical histories (10-12). Masumoto et al. noted that mucin-producing adenocarcinomas might progress more slowly than other adenocarcinomas of the lung (10) and our patient’s tumor was of this type. Even so, bronchoscopy at initial presentation showed neither an obstructive mass nor malignant cells.

Malkinson et al. found that chronic inflammation enhanced the risk of lung cancer in a mouse model (13). In our case, chronic inflammation had persisted for at least 16 years. De Boeck et al. reported the outcomes of a 10-year follow-up of middle lobe syndrome in childhood when no malignant tumors had been observed (14). However, the long-term prognosis of middle lobe syndrome in adulthood has not been fully studied and follow-up study of an adequate number of cases is needed.

In conclusion, our case may be the first reported of lung adenocarcinoma to have arisen in right middle lobe syndrome. Careful follow-up, using computed tomography and bronchoscopy, should aid in the diagnosis of such carcinomas.

References