**Aspergillus Sternomyelitis Developed from Chronic Pulmonary Aspergillosis as a Late Complication to Lobectomy for Lung Cancer**

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Abstract:
Progressive fibroblastic changes in the residual lobes are sometimes observed after lobectomy. *Aspergillus* osteomyelitis is an uncommon infection that rarely occurs sternally. A 70-year-old man who had undergone lobectomy 12 years earlier was admitted to our hospital for chest pain. He was diagnosed with *Aspergillus* sternomyelitis based on sternal bone culture after an ultrasound-guided percutaneous needle biopsy. The fibrosis and right residual lung apex volume loss had gradually progressed over 12 years, and therefore, chronic pulmonary aspergillosis (CPA) with direct invasion sternal from the CPA was considered. *Aspergillus* sternomyelitis can develop from CPA as a late complication of lobectomy.

Key words: *Aspergillus* sternomyelitis, chronic pulmonary aspergillosis, late complication, lobectomy

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Introduction
Progressive fibroblastic changes in the ipsilateral residual lobes are sometimes observed in long-surviving patients after lobectomy for lung cancer (1). In addition, these fibroblastic lungs are infected with various pathogens, including *Aspergillus* (1). Chronic pulmonary aspergillosis (CPA) can develop in residual lungs after lobectomy for lung cancer (2). *Aspergillus* osteomyelitis is an uncommon infection that rarely occurs sternally, especially in immunocompetent patients who have not undergone sternal surgery (3-5).

We herein report a case of *Aspergillus* sternomyelitis that developed from CPA as a late complication of lobectomy for lung cancer.

Case Report
A 70-year-old man was admitted to our institution with a 2-month history of worsening chest pain. Twelve years earlier, he had undergone lobectomy of the right upper lobe for primary lung cancer. A pathological analysis revealed moderately differentiated squamous cell carcinoma. The patient had chronic obstructive pulmonary disease (COPD). A physical examination showed swelling and tenderness of the soft tissue around the sternum and right breast, and laboratory examinations showed high C-reactive protein levels (8.2 mg/L; normal values ≤0.3 mg/L). Computed tomography (CT) showed apical pleural thickening and encapsulated pleural effusion in the apical portion of the right lung (Fig. 1a-c). In addition, destruction of the sternum, disappearance of fatty bone marrow, and swelling of the major pectoral muscle and subcutaneous tissue were observed (Fig. 1c). Furthermore, CT showed emphysema of the lungs and a nodule in the apex of the left lung (Fig. 1d). Positron emission tomography (PET)-CT showed significant inflammation in the right apical pleural thickening and in the sternum and surrounding soft tissues. The left lung nodule also had a high standardized uptake value on PET-CT and was diagnosed as a moderately differentiated squamous cell carcinoma using bronchoscopy. No pathogenic bacteria or fungi were found in sputum culture. A CT-guided percutaneous...
Figure 1. A CT image showing apical pleural thickening and encapsulated pleural effusion in the apical portion of the right lung (red dotted circle) (a-c). In addition, destruction of the sternum, disappearance of fatty bone marrow (triangle), and swelling of the major pectoral muscle and subcutaneous tissue (arrow) are shown (c). A CT image showing emphysema of the lungs and a nodule in the apex of the left lung (yellow dotted circle) (d). CT: computed tomography

needle biopsy was performed for the sternum and surrounding soft tissues. Although yellow pus was aspirated, no malignant cells in the pathological examination and no bacterial growth in the pure culture were observed. Nonbacterial osteomyelitis was suspected; however, bacterial osteomyelitis was not completely ruled out, and treatment with levofloxacin at a dose of 500 mg per day was initiated. Stereotactic body radiation therapy was performed for lung cancer in the apex of the left lung. However, his chest pain worsened.

He was admitted to our hospital two months later for further investigation. At that time, CT showed separation of the manubrium and sternal body, bone erosion of the sternal body, and exacerbated inflammation of the soft tissue surrounding the sternum (Fig. 2). A laboratory examination showed that the serum (1-3)-β-D-glucan (BDG) levels were elevated (63 pg/mL). Because of suspected invasive fungal infections, the patient was administered micafungin. An ultrasound (US)-guided percutaneous needle biopsy was performed again. Then, laboratory examinations revealed positivity for serum galactomannan and Aspergillus antibody using immunoprecipitation. Micafungin was changed to 200 mg of voriconazole twice daily. The sternal bone culture from the US-guided percutaneous needle biopsy showed growth of Aspergillus fumigatus. A retrospective review of follow-up chest X-ray findings obtained over the previous 12 years revealed that the fibrosis and right residual lung apex volume loss had gradually progressed and had sometimes been accompanied by a niveau in progression (Fig. 3). Given these findings, we suspected that CPA had developed in the residual lung, gradually progressed for a long time, and finally resulted in Aspergillus sternomyelitis.

The patient responded well after 4 weeks of treatment.
with voriconazole; therefore, he was discharged and received 150 days of treatment with oral voriconazole. The maintenance dose of oral voriconazole was 200 mg (4 mg/kg) twice daily. The effective trough of voriconazole was controlled within 1-2 μg/mL. The CT findings improved, and there was no recurrence for 2 years after the discontinuation of voriconazole.

**Discussion**

There were two notable clinical findings in this case. First, aspergillosis infection may be involved in progressive fibrobullous changes in the ipsilateral residual lobes after lobectomy for lung cancer. Second, CPA can cause *Aspergillus* sternomyelitis via direct invasion.

Progressive fibrobullous changes in the residual lungs after lobectomy are a late complication that can be accompanied by aspergillosis infection and develop into CPA. Tanaka et al. reported that the incidence rate of progressive fibrobullous changes after lobectomy was 3%, and the rate increased to 5.6% in patients who had survived for ≥5 years (1). Furthermore, they also reported that approximately half of cases of fibrobullous changes were accompanied by infection with agents such as nontuberculous mycobacterium and *Aspergillus* (1). However, pulmonary aspergillosis has been found to be concurrent in patients with lung cancer at various times (6). Tamura et al. reported that 2.3% of patients who undergo lobectomy subsequently develop CPA at 5 years, with the 10-year incidence rate reaching 7.9% (2). COPD and interstitial lung disease are strong risk factors of postoperative CPA (2). In the present case, although the changes in the residual lungs gradually progressed, he did not present with symptoms, and there was no evidence of inflammation, such as elevation in C-reactive protein levels and white blood cells, over the previous 12 years. The change was simply considered to have been caused by fibrobullous changes in the residual lungs after lobectomy. Therefore, we could not assume a fungal infection, and the diagnosis of a fungal infection was overlooked. Thus, CPA was disregarded for a long time and ultimately led to *Aspergillus* sternomyelitis. Since *Aspergillus* infection was not considered and a culture test for fungi was not performed when the CT-guided percutaneous needle biopsy was performed, the diagnoses of CPA and *Aspergillus* sternomyelitis were further delayed. The *Aspergillus* infection may be considered a sequela to COPD, as progressive fibrobullous changes in the ipsilateral residual lobes invaded the air spaces caused by the fibrobullous changes with emphysema re-expansion after the lobectomy. Therefore, careful follow-up involving several examinations, including BDG tests and chest CT in addition to chest X-ray, may be essential for obtaining a diagnosis of CPA in patients after lobectomy.

CPA can cause *Aspergillus* sternomyelitis via direct invasion. *Aspergillus* osteomyelitis can be caused by immunosuppression, trauma, prior thoracic surgery, direct invasion from the lung, and hematogenous dissemination (3). *Aspergillus* osteomyelitis is likely to occur in the vertebra, skull, and ribs, but it rarely occurs in the sternum (3, 4). Extension of lung aspergillosis is a common mechanism of vertebral and costal *Aspergillus* osteomyelitis (3). In particular, *Aspergillus* sternomyelitis usually occurs in patients with immunosuppression, such as those with prolonged neutropenia, solid tumors, and adult immune deficiency syndrome, or in those who are immunocompetent after sternal midline incision and sternal trauma (4). In the present case, the patient had no history of sternal midline incision or sternal trauma, and the degree of his immunosuppression was mild because...
of the recurrence of cancer. Chest CT, which was performed at the diagnosis of *Aspergillus* sternomyelitis, revealed pleural thickening adjacent to the lung foci and a nodule shadow in the lung (Fig. 4). In addition, impaired airway clearance due to fibrobullous changes in the lungs after lobectomy and COPD allowed for the colonization of *Aspergillus* due to fibrobullous changes in the lungs after lobectomy and it was found in the lung (Fig. 4). In addition, impaired airway clearance due to fibrobullous changes in the lungs after lobectomy and COPD allowed for the colonization of *Aspergillus* through the airways, leading to CPA including the right apex. These backgrounds of the patient’s sternum were attributed to the foci being located within the lung rather than at extra-pulmonary sites. Thus, the direct invasion from contiguous pulmonary foci in CPA was the cause of *Aspergillus* sternomyelitis. For patients with *Aspergillus* sternomyelitis, it is important to carefully search for suspected CPA-related changes in the lung.

Regarding the treatment of *Aspergillus* osteomyelitis, surgical intervention, combined with voriconazole where possible, is recommended by the Infectious Diseases Society of America Guidelines for the Diagnosis and Management of Aspergillosis (7). The overall duration of treatment necessary is at least 8 weeks, with >6-month courses frequently necessary. There are no evident advantages to combination antifungal therapy versus therapy with a single agent (3). Regarding the clinical efficacy, target voriconazole trough levels of ≥1.2 μg/mL are recommended (8). Of note, these recommendations are based on reports about vertebral *Aspergillus* osteomyelitis. Data on the treatment of *Aspergillus* sternomyelitis is limited. In the present case, surgical debridement for the sternum was impractical. Thus, treatment with only voriconazole was conducted for six months, and there was no recurrence for two years after the discontinuation of voriconazole.

We encountered a case of *Aspergillus* sternomyelitis that developed from CPA as a late complication of lobectomy for lung cancer. When progressive fibrobullous changes and pleural thickening are observed after lobectomy for lung cancer, the possibility of fungal infection should be considered. Although *Aspergillus* sternomyelitis is an uncommon infection, it can develop from CPA in patients after lobectomy.

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

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