Original Article

Two cases of endobronchial aspergilloma with lung cancer: a review the literature of endobronchial aspergilloma with underlying malignant lesions of the lung

Shenghua Jiang, Luning Jiang, Fenglian Shan, Xiulian Zhang, Ming Song

Department of Respiratory Hospital Affiliated to Jining Medical College, Shandong, 272019, China

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Abstract: Endobronchial aspergilloma is a rare disease entity with pulmonary involvement of aspergillus. Few cases of endobronchial aspergilloma associated with malignant lesions have been reported in the literature. We present 2 more cases of endobronchial aspergilloma with underlying lung cancer. And summarize the published literatures to investigate the clinical manifestations, bronchoscopic characters, imaging performances in patients with endobronchial aspergilloma with underlying malignant lesions of the lung. A review of the literature reveals 8 cases of endobronchial aspergilloma with coexisting lung malignant lesions upon presentation. The medical details of the patients including age, sex, clinical symptoms, radiological manifestations bronchoscopic characters, diagnosis and treatment are summarized. Endobronchial aspergilloma is usually incidentally detected in patients with underlying lung disease. With the increasing popularity of flexible bronchoscopy, it is being recognized as a necrotic mass causing bronchial obstruction. We should be paid more attention to prevent misdiagnosis of combined endobronchial aspergilloma and lung malignant diseases.

Keywords: Endobronchial aspergilloma, cancer, tumor, metastases

Introduction

Aspergillus spp. are widespread in the living environment and are the cause of a variety of pulmonary diseases, which have been classified into 4 main groups: saprophytic aspergillosis (aspergilloma), allergic bronchopulmonary aspergillosis (ABPA), semi-invasive aspergillosis (chronic necrotizing pulmonary aspergillosis, CNPA), and invasive pulmonary aspergillosis (IPA) [1, 2]. According to the corresponding different parasitic sites in the thorax, Thoracic aspergilloma are classified into 3 groups: Pulmonary aspergilloma, Pleural aspergilloma and endobronchial aspergilloma [3]. To the best of our knowledge, There are also scattered case reports of endobronchial aspergilloma in the published literatures [4-16]. This is simply the fungus found endobronchially and it may occur with or without pulmonary involvement. We present 2 more cases of endobronchial aspergilloma with lung cancer and herein summarize the published literatures to investigate the clinical manifestations, bronchoscopic characters, imaging performances and treatments in patients with endobronchial aspergilloma combined with lung malignant lesions.

Case No. 1

A 56-year-old female patient was admitted to our hospital due to 2 months history of recurrent hemoptysis and dyspnea. Before that, her general health was always good. NSE was slightly increased (18.28 ng/ml) while CYFRA21-1, CEA as well as SCC were within normal limits. Both G test and GM test were negative. Computed tomography (CT) scan of chest showed a lingular bronchial mass in left lung (Figure 1A). Bronchoscopy examination revealed that the lingular bronchus was almost completely obstructed by a large dark red necrotic lesion (Figure 1B). Pathologic examination of bronchoscopic biopsy specimen showed numerous aspergillus hyphae (Figure 1C). In addition to administration of Voriconazole and caspofun-
gin for systemic anti-aspergillus therapy, bronchoscope interventional treatment was adopted to keep the airway open. The last histopathology showed large amount of aspergillus mycelium along with a few of abnormal cells (Figure 1D). The immunopathology test showed that CD56, TTF-1 and CK were positive, while the CK5/6, P63 and CK7 were negative. The results revealed that the disease was considered to be bronchopulmonary neuroendocrine carcinoma. So after treated by anti-fungal agents conservatively, left upper lobectomy was performed under video-assisted thoracoscopic surgery. The final histologic finding confirmed the diagnosis of bronchopulmonary neuroendocrine carcinoma.

Case No. 2

A 50-year-old woman, complaining of cough and bloody sputum for 1 month, applied to our hospital. There was no history of other illnesses and no reason to suspect that she could be immunocompromised. Computerized tomography (CT) showed a soft tissue mass with obstruction of the right lower lobe (Figure 2A). The serum levels of NSE (20.36 ng/ml), CYFRA21-1 (5.02 ng/ml) were higher, but CEA was normal. Lung cancer was suspected and Bronchoscopy was performed. It revealed a ball shaped mass obstructed Segment of Right Lower Lobe (Figure 2B). The mass was removed with forceps and sent for histopathologic examination which revealed aspergillus hyphae and fungal spores with necrotic material were identified (Figure 2C). Itraconazole was recommended for the treatment of aspergillus. Based on the CT, repeated bronchoscopy and the second pathologic diagnosis was lung adenocarcinoma (Figure 2D). Underwent video-assisted thoracoscopic surgery right lower lobectomy.
were performed, the final histologic finding confirmed the diagnosis of a T2N2M0 adenocarcinoma.

Discussion

The spores or conidia in the air inhaled every day can induce various types of fungal clinical conditions. Depending upon the patient's local and systemic immune status and alterations in host tissues, Aspergillus spp. can cause a wide variety of tracheobronchial and pulmonary manifestations [17]. Including invasive pulmonary aspergillosis (IPA), chronic necrotizing aspergillosis (CNA), allergic broncho pulmonary aspergillosis (ABPA), and aspergilloma. The incidence of pulmonary aspergillus infections has dramatically increased over recent years with increasing numbers of immune-compromised patients, and definitive diagnosis of assisted by. As newer diagnostic methods and techniques applied in the clinical works, new forms of pulmonary aspergillus infections have also been discussed in some articles. Aspergilloma is a fungus ball that develops in a pre-existing cavity within the lung parenchyma. Cavities and cysts are partly filled by growing mycelia and septate hyphae [17]. Other than open state negative and positive cavities in granulomatous infections, in advanced sarcoidosis, and in histoplasmosis, bullae and bronchiectasis may be the site of fungal colonization.

The common sites of aspergillomas are the upper lobe and lower lobe superior segment [18]. It consists of branched, septated hyphae and blood cells [19]. Hemoptysis is the most common clinical symptom with a rate as high as 73% in patients with Pulmonary Aspergilloma [20]. The diagnostic criteria is aspergilloma
Table 1. Endobronchial aspergilloma associated with malignant lesions

<table>
<thead>
<tr>
<th>Report</th>
<th>Age/sex</th>
<th>Clinical presentation</th>
<th>Medical history</th>
<th>CT location</th>
<th>bronchial</th>
<th>Type of cancer histologically</th>
<th>treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No 1 Ham et al., 2006 [9]</td>
<td>70/M</td>
<td>intermittent hemoptysis</td>
<td>Congestive Heart Failure, atrial fibrillation 4 y</td>
<td>multi-lobulated contour and non-enhancing soft tissue mass-like lesion in left upper lobe posterior segment</td>
<td>a whitish and polypoid mass occluding the left upper lobe apicoposterior segment</td>
<td>sarcomatoid carcinoma</td>
<td>Intravenous and oral itraconazole 4 weeks</td>
</tr>
<tr>
<td>Patient No 2 Domenick J [11] 1995</td>
<td>68/F</td>
<td>Acute hypoxemic respiratory failure</td>
<td>COPD/alcoholism</td>
<td>Chest X-ray was essentially clear</td>
<td>a large ovoid carinal mass causing a ball valve obstruction of the right main stem bronchus</td>
<td>Small cell carcinoma by Autopsy</td>
<td>Amphotericin B and bronchoscopic resection</td>
</tr>
<tr>
<td>Patient No 3 Jeong Eun Ma [4] 2011</td>
<td>50/M</td>
<td>Hemoptysis, Cough</td>
<td>smoker</td>
<td>Low-density and lobulating mass in LLL causing obstruction of LLL superior segment</td>
<td>Protruding mass with yellow necrotic material in LLL superior segment</td>
<td>nonsmall-cell lung cancer (NSCLC)</td>
<td>Nothing</td>
</tr>
<tr>
<td>Patient No 4 Jiang</td>
<td>56/F</td>
<td>Hemoptysis, Cough</td>
<td>no</td>
<td>A lingual bronchial mass in left lung</td>
<td>the lingular bronchus was almost completely obstructed by a large dark red necrotic lesion</td>
<td>neuroendocrine carcinoma</td>
<td>Voriconazole and caspofungin bronchoscopic resection</td>
</tr>
<tr>
<td>Patient No 5 Jiang</td>
<td>56/F</td>
<td>blood sputum, cough 1 m</td>
<td>no</td>
<td>A soft tissue mass with obstruction of the right lower lobe</td>
<td>a ball shaped mass obstructed Segment of Right Lower Lobe</td>
<td>adenocarcinoma</td>
<td>Bronchoscopic resection</td>
</tr>
<tr>
<td>Patient No 6 L Ky [16] 2003</td>
<td>61/f</td>
<td>blood sputum, cough 1 m</td>
<td>hepatocellular carcinoma 16 m, recurrence</td>
<td>An elongated contour of well-enhanced mass occupying the lumen of the anterior segmental bronchus of the right upper lobe</td>
<td>An endobronchial mass obstructing the right upper lobar bronchial lumen</td>
<td>hepatocellular carcinoma</td>
<td>Bronchoscopic resection and right upper lobe resection for active bleeding</td>
</tr>
<tr>
<td>Patient No 7 Sethi A [14] 2012</td>
<td>49/M</td>
<td>three weeks of dry cough and occasional hemoptysis</td>
<td>non smoker rectal cancer treated with surgery and chemo-radiation 6 years</td>
<td>LUL mass with adjoining atelectasis</td>
<td>a pearly white lesion in LUL bronchus</td>
<td>Metastatic Adenocarcinoma positive for rectal tumor markers</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Patient No 8 Nilsson JR [15] 2013</td>
<td>56/F</td>
<td>hemoptysis and shortness of breath</td>
<td>None</td>
<td>a left pulmonary infralobar soft tissue mass with an endobronchial component extending into the left lower lobe</td>
<td>a friable, white mass nearly completely obstructing her left lower lobar bronchus.</td>
<td>Carcinoid</td>
<td>a left lower lobectomy after completing a course of voriconazole</td>
</tr>
</tbody>
</table>
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have included a air-crescent sign on CT of the chest, and the mass inside the cavity may change with a change in position; Several rare cases of combined pulmonary aspergilloma in combination with lung cancer have been reported in the literature in recent years [21-26].

Endobronchial aspergilloma is a rare disease entity with pulmonary involvement of aspergillus. Definition of this entity is not well described in the literature and is not usually classified with other pulmonary aspergillosis. It can usually be defined as a non-invasive form of aspergillosis characterized by massive intrabronchial overgrowth of the aspergillus species, mainly aspergillus fumigates, and it may be considered an unusual form of a fungus ball, found inside the bronchus with or without a parenchymal lesion and/or cavity [4]. Few cases of endobronchial aspergilloma associated with malignant lesions have been reported in the literature. To gain more information on the condition, we retrospectively analyzed the clinical data of 8 patients who were pathologically confirmed upon presentation (Table 1).

In our study, there are 8 cases of about aspergilloma combined with lung cancer or tumor. The most common complaint was bloody sputum or mild hemoptysis, pulmonary aspergillosis in patients without immunodeficiency, lesions manifested as an irregular pulmonary nodule on imaging which was suspected to be a lung cancer with no air crescent sign of topical aspergilloma. Common causes of hemoptysis are benign diseases; however, Hemoptysis can also occur in patients with lung cancer more than 50%. The bleeding results from necrosis of a tumor, the rupture of small blood vessels in the area, tumor manipulation during diagnostic fiberoptic bronchoscopy, [27] or a tumor invading one of the pulmonary blood vessels. Massive hemoptysis can sometimes occur due to malignant invasion of central pulmonary vessels by tumors.

In the body of those patients mentioned, the local immune-barrier of intestinal mucosa of the airway has been destroyed caused by cancer. Changes of mucous secretion and similar to a pre-existing cavity due to airway obstruction of lung cancer followed, which benefits the growth of aspergillus. When aspergillus spores are inhaled into the lower airways regularly, the release of an endotoxin and trypsin like proteolytic enzyme from the aspergillus, then wors-

ened hemorrhage occurred. The diagnosis of endobronchial aspergilloma was made primarily based on the presence of an intraluminal mass or necrotic tissue on bronchoscopy and separated fungal hyphae with acute branching angles, characteristic of aspergillus species, on histological examination.

In our study, the chest x-ray revealed abnormalities just like opacity or nodules (except one patient No 2). Chest computerized tomography scan was performed for further evaluation. It usually revealed a soft tissue mass shadow which is compatible with lung cancer or metastatic tumor causing lobar or segmental lung collapse due to obstruction. So clinical application of bronchoscopy examination is the traditional first investigation. The bronchoscopic findings were a whitish to yellow necrotic mass obstructing the bronchus. Ulcerative tracheobronchitis with diffuse mucosal inflammation showed by bronchoscopy in one patient (No 2). So the fiberoptic bronchoscopic finds did not satisfy with clinical imaging. Endobronchial aspergilloma was incidentally found by the operation. The road to the final diagnosis goes hard, only fungal hyphae were observed in the biopsy specimen of the first bronchoscopy, however, the clinical syndrome progresses or improvement is not found, so our patients underwent a second bronchoscopic resection for getting the tumor tissues. The patient (patient No 6) underwent an emergency right upper lobe resection for active bleeding. The other cases were diagnosed by autopsy or post-mortem lung puncture. Intravenous and oral itraconazole Voriconazole or amphotericin B were administered for 6 patients. Pulmonary lobectomy was performed after completing a course of anti-fungal drugs in 3 patients.

There is one patient underwent lobectomy for lung cancer in a study [4]. Aspergilloma occurred unusually with nylon sutures one month after surgery. But there are more reports published and defined as bronchial stump aspergillosis (BSA), Aspergillus infection of bronchial granulation tissue surrounding endobronchial sutures after pulmonary resection, which is another form of tracheobronchial aspergillosis [28-32].

In summary, endobronchial aspergilloma is usually incidentally detected in patients with underlying lung disease. With the increasing
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popularity of flexible bronchoscopy, it is being recognized as a necrotic mass causing bronchial obstruction. Endobronchial aspergilloma also can be life threatening and the condition can delay the proper treatment of the underlying disease just like 8 cases we describe herein. These cases were treatment futility of antifungal, even the size of thoracic lesions on chest image increased, we should be paid more attention to prevent misdiagnosis of combined endobronchial aspergilloma and lung malignant diseases. If combination is confirmed, we also believe that this is another indication for surgical treatment.

Disclosure of conflict of interest
None.

Address correspondence to: Dr. Shenghua Jiang, Department of Respiratory Hospital Affiliated to Jining Medical College, No. 89 Guhai Road, Jining 272019, Shandong, China. Tel: +8605372903069; Fax: +8605372903069; E-mail: jiangyshenghua@163.com

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