Pulmonary Cryptococcosis with Endobronchial Lesions and Meningitis

Kyuto Odashima¹, Noboru Takayanagi¹, Takashi Ishiguro¹, Yoshihiko Shimizu² and Yutaka Sugita¹

Abstract

A 58-year-old man presented with right chest pain, anorexia, general malaise, and fever. Chest computed tomography showed a mass lesion with right middle lobe atelectasis. The bronchoscopy showed polypoid lesions with a smooth surface in each right middle lobe bronchial lumen. The histopathology revealed the dense accumulation of histiocyte-like cells with foamy cytoplasm under the bronchial epithelium along with yeast-like fungi stained positively with both Alcian blue and Grocott’s stains. Cryptococcus neoformans was cultured from the bronchial washings. We diagnosed the patient with pulmonary cryptococcosis with endobronchial lesions. The fluconazole treatment was changed to liposomal amphotericin-B and flucytosine after the diagnosis of cryptococcal meningitis. The minimum inhibitory concentration of the fungi suggested resistance to fluconazole and flucytosine. The lesion regressed after these treatments.

Key words: pulmonary cryptococcosis, endobronchial polyp, meningitis, drug sensitivity test, minimum inhibitory concentration

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Introduction

Cryptococcus infects humans through the respiratory tract by scattering in the air (1-3). The chest X-rays and computed tomography (CT) scans typically reveal solitary or multiple nodules or infiltrative shadows. We experienced a case of pulmonary cryptococcosis in which a bronchoscopic examination showed polypoid lesions with a smooth surface in the bronchial lumen. Because cases of endobronchial lesions with decreased lung volume or atelectasis are rare (4, 5), we herein report this case and review cases of pulmonary cryptococcosis with endobronchial lesions.

Case Report

A 58-year-old man with diabetes mellitus presented to a local physician with right-sided chest pain, anorexia, and general malaise in February 2010. He was diagnosed as having pneumonia but did not improve. In the first 10 days of March, he developed a fever of 37-38°C, and he presented to our hospital in the latter part of April. He had no previous history to suggest an immunodeficiency disorder, such as the repeated occurrence of pneumonia. His contact history with birds included a house in which approximately 400-500 carrier pigeons were bred that was located about 200 meters away from his home, and he would sometimes visit a friend who raised carrier pigeons. He also raised a ringneck dove (Streptopelia risoria) for 4 years in his thirties. After a chest X-ray showed a right-sided mass lesion (Fig. 1) and chest CT showed both a mass lesion measuring 53 mm in size in the right middle lobe and right hilar lymph nodes clumped with the mass (Fig. 2), he was admitted to our hospital for further evaluation. He was alert and conscious with no meningeal signs and a body temperature of 35.5°C. The respiratory sounds over the lower right lung field were diminished. His white blood cell count was 6,300/mm³ (neutrophils 4,150/mm³, lymphocytes 1,740/mm³, and CD4 lymphocytes 950/mm³), and his C-reactive protein level and serum biochemistries were within the normal

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range. The HIV antibody and labeled antibody to collagen were negative. After his admission, we performed a bronchoscopy, which showed a trifurcated right middle lobe bronchus in which polypoid lesions with a red smooth surface were recognized in each lumen (Fig. 3). A biopsy of the polyps showed the dense accumulation of histiocytes and yeast-like fungi with thick theca that were dyed by the Alcian blue stain but not by Hematoxylin and Eosin staining (Fig. 4). Cryptococcus neoformans was cultured from the bronchial lavage fluid, and thereafter, the serum cryptococcal antigen was measured and was found to be positive at a titer of 1:4,096. We diagnosed this patient as having pulmonary cryptococcosis and began the administration of fluconazole. We also examined his cerebrospinal fluid (CSF), which was colorless and transparent with a protein level of 54.4 mg/dL (serum total protein of 7.4 g/dL) and glucose of 72 mg/dL (serum glucose of 197 mg/dL). Although the CSF pressure was normal, the number of cells was increased at 656/μL (mononuclear cells, 89%); fungi were also present that stained blue by the Alcian blue stain, although C. neoformans was not cultured. Then, on the night of the day after the bronchoscopy, he developed a fever of 38.9°C with headache, and his serum cryptococcal antigen increased to a titer of 1:65,536. We diagnosed him as having cryptococcal meningitis and changed the treatment from fluconazole to liposomal amphotericin B (L-AMB) plus flucytosine (100 mg/kg). Subsequently, the mass lesion on the chest X-ray shrank, and the CSF cell counts decreased; however, it became difficult to continue the L-AMB because it caused renal dysfunction. The minimum inhibitory concentration (MIC) was measured, which suggested resistance to fluconazole and flucytosine (Eiken DP yeast-like fungus; Eiken Chemical Co., Ltd., Tokyo, Japan) (Table 1). Therefore, the L-AMB + flucytosine regimen was changed to voriconazole, and thereafter, he became afebrile and his subjective symptoms also improved. A bronchoscopy was performed that showed that each of the polypoid lesions had uniformly regressed to the periphery while maintaining contact with the airway mucosa (Fig. 5). The patient was discharged, and voriconazole was administered until December 2010, when it was discontinued because the shadow on the chest X-ray had almost disappeared. He has since been followed on an outpatient basis, and there has been no recurrence to date. His serum cryptococcal antigen titer was 1:65,536 until August 2010, but it began to decrease in September 2010, and in May 2012, it finally decreased to 1:64.

Table 1. Minimum Inhibitory Concentration of Antifungal Agents

<table>
<thead>
<tr>
<th>AMPH-B</th>
<th>0.06</th>
<th>ITCZ</th>
<th>0.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FC</td>
<td>16</td>
<td>MCFG</td>
<td>16</td>
</tr>
<tr>
<td>FLCZ</td>
<td>32</td>
<td>VRCZ</td>
<td>0.25</td>
</tr>
<tr>
<td>MCZ</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All units are in mg/L.

The salient features of the present case include the underlying disease of diabetes, the recognition of uniform polyloid lesions in each lumen of the trifurcated bronchus, and the importance of MIC determination in the successful treatment of this patient.

Including the present case, only 14 cases of cryptococcosis with endobronchial lesions have been reported (Table 2) (2-13). In the present case, the uniform polyloid lesions were recognized in each lumen of the trifurcated bronchus, whereas in the 13 previously reported cases, the uniform polyloid lesions projected from the bronchus; and, in many cases, only one lesion was recognized in one bronchus. The locations of the lesions ranged from the trachea to the subsegmental bronchi. In our hospital, a bronchoscopy was performed in 36 of the 45 cases of cryptococcosis, but none of the cases showed bronchoscopic findings similar to those of the present patient (unpublished data). Although endobronchial lesions associated with decreased lung volume or atelectasis are rare, bronchial cryptococcosis should be considered when encountering such cases.

The present case included the underlying disease of diabetes, whereas in the 13 previously reported cases, no underlying diseases were recognized. The correlation of the patient’s immune status with the development of endobronchial cryptococcosis is unknown. Further cases need to be studied.

The mechanism behind the formation of endobronchial lesions has been thought to be by direct extension from the lung parenchymal lesion or direct invasion from the lymph nodes (13). In the present case, the bronchoscopy during antifungal therapy showed that each of the polypoid lesions had uniformly regressed to the periphery while maintaining contact with the airway mucosa, indicating that these lesions were directly contiguous with those located at the periphery of the lung. However, no detailed mechanism could be determined.

Among the 14 previously reported cases, three patients were treated with surgery and the remaining patients with antifungal drugs. No deaths were reported. Five cases, including the present case, were of pulmonary cryptococcosis complicated by cryptococcal meningitis. In the established guidelines (14), the combination therapy of amphotericin B plus flucytosine is recommended for patients with cryptococcosis complicated by meningitis, and L-AMB may be used instead of amphotericin B. We initially treated this patient with fluconazole because he had no obvious symptoms of meningeal irritation and he strongly desired outpatient treatment. After the diagnosis of meningitis from the CSF findings, we changed his treatment to L-AMB and flucytosine. This case suggests the usefulness of performing a routine CSF examination even if the patient is asymptomatic.

Discussion

Figure 4. Transbronchial biopsy specimens. (a) Histopathological examination of the transbronchial biopsy specimens revealed dense accumulation of the histiocytes and yeast-form fungi that did not uptake the Hematoxylin and Eosin (H&E) staining (arrows) (H&E staining, 40×). (b) Histopathological examination showed cryptococci dyed blue (Alcian blue stain, 40×).

Figure 5. Findings from the bronchoscopy performed after 2 months of treatment with voriconazole showed that the polyoid lesion had regressed.
The guidelines recommend maintenance therapy with fluconazole, and voriconazole is cited as the second drug of choice for maintenance therapy (14). This patient was treated with voriconazole because of an elevated MIC to fluconazole (15, 16). The measurement of the MIC for C. neoformans is not a well-established method. However, the rate of treatment failure was reported to be high if the MIC was also high (17). In 25 patients with this disease reported by Aller et al., treatment was unsuccessful in one patient; 4 of 5 patients with a fluconazole MIC of >16 μg/mL expired; and, with the exception of 2 patients who died from other diseases, 18 patients with a fluconazole MIC of ≤8 μg/mL were cured (16). In addition, according to the susceptibility testing using Eiken DP yeast-like fungus, a MIC of >16 μg/mL indicates resistance. Therefore, we concluded that the MIC of 32 μg/mL obtained in the present patient indicated resistance to fluconazole and flucytosine. The measurement of the MIC was useful to discover the elevated MIC of fluconazole and flucytosine in the isolated fungi specimens obtained from this patient.

We herein described a patient with fluconazole-resistant cryptococcosis with endobronchial polypoid lesions. The culture and MIC measurements are necessary to determine an adequate therapeutic regimen. In patients in whom the MIC cannot be measured due to their medical conditions deteriorating during the administration of fluconazole, more cautious follow-up is necessary.

This case was presented previously at the 133rd Japan Society for Respiratory Endoscopy Kanto Branch meeting (July 10, 2010, Tokyo).

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

### Table 2. Reported Cases of Endobronchial Cryptococcosis

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Endobronchial lesion</th>
<th>Chest X-ray or CT findings</th>
<th>Underlying disease</th>
<th>Therapy</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>M</td>
<td>Left lower and upper lobe bronchi</td>
<td>Mass lesion</td>
<td>Left lung collapse</td>
<td>(-)</td>
<td>AMPH-B,5-FC</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>Right upper bronchus</td>
<td>Gelatinous mass</td>
<td>Consolidation of the upper bronchus</td>
<td>(-)</td>
<td>Resection</td>
<td>3</td>
</tr>
<tr>
<td>43</td>
<td>M</td>
<td>Truncus intermedius</td>
<td>White lobulated endobronchial lesion</td>
<td>Right middle and lower lobe collapse</td>
<td>(-)</td>
<td>AMPH-B,5-FC</td>
<td>4</td>
</tr>
<tr>
<td>31</td>
<td>M</td>
<td>Left upper bronchus</td>
<td>Grayish white polypoid lesion</td>
<td>Mass-like shadow and collapse of the left upper lobe</td>
<td>(-)</td>
<td>AMPH-B,5-FC, resection</td>
<td>5</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>Right main bronchus</td>
<td>Large hemorrhagic lesion</td>
<td>Consolidation in the right middle lobe</td>
<td>(-)</td>
<td>AMPH-B,5-FC</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>?</td>
<td>Trachea and major bronchi</td>
<td>White mucosal plaques</td>
<td>Bilateral military infiltrates</td>
<td></td>
<td>AIDS</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>?</td>
<td>Trachea and major bronchi</td>
<td>Cherry red plaques</td>
<td>Large bilateral nodules with cavitation</td>
<td></td>
<td>AIDS</td>
<td>7</td>
</tr>
<tr>
<td>46</td>
<td>M</td>
<td>Left main bronchus</td>
<td>Soft, reddish broad-based lesion</td>
<td>Lingular mass, subcarinal mass</td>
<td>(-)</td>
<td>AMPH-B,5-FC</td>
<td>8</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>Truncus intermedius</td>
<td>Reddish elevated lesion</td>
<td>Multiple nodular shadows</td>
<td>(-)</td>
<td>FL CZ</td>
<td>9</td>
</tr>
<tr>
<td>45</td>
<td>M</td>
<td>Trachea and left bronchi</td>
<td>White plaques</td>
<td>Consolidation including a cavity of the left lower lobe</td>
<td></td>
<td>AIDS</td>
<td>10</td>
</tr>
<tr>
<td>33</td>
<td>M</td>
<td>Left upper bronchus</td>
<td>White polypoid lesion</td>
<td>Mass in the left upper lobe bronchus, left upper lung collapse</td>
<td></td>
<td>Type B viral hepatitis</td>
<td>11</td>
</tr>
<tr>
<td>54</td>
<td>F</td>
<td>Left upper bronchus</td>
<td>Three white elevated lesion</td>
<td>Mass-like shadow</td>
<td></td>
<td>SJogren synd, Sweet synd, PSL</td>
<td>12</td>
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<tr>
<td>64</td>
<td>F</td>
<td>Left posterior basal bronchi</td>
<td>White polypoid lesion</td>
<td>Bilateral airspace consolidation and multiple nodules</td>
<td></td>
<td>RA, PSL 10mg</td>
<td>13</td>
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<tr>
<td>58</td>
<td>M</td>
<td>Right middle bronchus</td>
<td>White polypoid lesion</td>
<td>Mass-like shadow</td>
<td></td>
<td>DM</td>
<td>14</td>
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