Invasive Tracheobronchial Aspergillosis in a Patient with Systemic Lupus Erythematousus-dermatomyositis Overlap Syndrome

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Abstract

A 45-year-old man was referred to our hospital with a 3-month history of dyspnea, polyarthralgia, myalgia and weight loss. He was diagnosed with systemic lupus erythematous/dermatomyositis overlap syndrome with lung involvement, which presented as organizing pneumonia. However, a bronchoscopic examination revealed the presence of multiple plaque-like white lesions with ulcers on the bronchial membrane, located mainly in the central airway. The pathological specimens obtained from bronchoscopy showed numerous filamentous fungal hyphae that were aggressively invading the bronchial walls, suggesting a diagnosis of invasive tracheobronchial aspergillosis. The present case, along with a review of the literature, demonstrates that invasive tracheobronchial aspergillosis can occur in patients who do not appear to be immunosuppressed. This case of aspergillosis should thus be recognized as an extremely rare presentation of an Aspergillus infection.

Key words: Aspergillus fumigatus, dermatomyositis, non-severely immunocompromised patients, systemic lupus erythematosus, invasive tracheobronchial aspergillosis


Introduction

Invasive tracheobronchial aspergillosis is a rare disease that is generally observed in immunocompromised patients with hematological malignancy, hematopoietic stem cell transplantation recipients and solid-organ transplantation recipients. However, we herein present a case of a patient with systemic lupus erythematous/dermatomyositis overlap syndrome who was not on immunosuppressive therapy at the time of diagnosis.

Case Report

A 45-year-old man visited his local hospital with a 3-month history of gradually progressive dyspnea, bilateral thigh pain, polyarthralgia, pyrexia and a weight loss of 10 kg. His medical history was unremarkable; he had been well until the start of his symptoms 3 months earlier. He was a current smoker with a history of 30 pack-years, and worked as an office worker. He reported neither drug use nor dust exposure in his home environment. At his first visit to his local hospital (day 0), a chest X-ray showed infiltration in his right lower lung field (Figure A), and thoracic computed tomography (CT) depicted non-segmental consolidation in the right lower lobe (Figure B). Thus, he was admitted to the hospital with a diagnosis of pneumonia. He was also suspected of having either lung cancer or a collagen vascular disease, so bronchoscopy was performed on day 2. The procedure revealed scattered white-colored plaque-like nodules (Figure C, arrow) on the surface of the bronchial membrane measuring 3 mm in diameter accompanied by ulceration.

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Figure. Chest X-ray shows infiltration in the right lower lung field (A), and thoracic computed tomography shows non-segmental consolidation in the right lower lobe (B). On bronchoscopy, white colored plaque-like nodules were noted (C, arrow) on the surface of the bronchial membrane, measuring 3 mm in diameter, accompanied by ulceration. These lesions were distributed starting from the orifice of the trachea down to the bilateral main bronchi (D). Hematoxylin and Eosin (H&E) staining of the biopsied specimens obtained from the tracheal wall revealed numerous filamentous fungal hyphae that were aggressively invading the bronchial walls (E, F), with the erosion of bronchial epithelial cells (E, black arrow). H&E staining of the transbronchial lung biopsy specimens from the right S8 section demonstrated organizing tissue in the alveolar spaces with abundant neutrophilic infiltration (G), as well as being covered with a metaplastic epithelium (H).

These lesions were observed starting from the orifice of the trachea down to the bilateral main bronchi (Figure D). Hematoxylin and eosin (H & E) staining of the biopsied specimens obtained from these areas revealed the erosion of the bronchial epithelial cells (Figure E, black arrow) as well as numerous filamentous fungal hyphae that were aggressively invading the bronchial walls (Figure E, F). H & E staining of the transbronchial lung biopsy specimens from the right
polymerase chain reaction which showed the presence of Aspergillus fumigatus. Therefore, unstained formalin-fixed and paraffin-embedded tissues were de-paraffinized with xylene so that the DNA could be extracted. These proteins were subjected to nested polymerase chain reaction which showed the presence of Aspergillus species using the following specific primers for Aspergillus spp. as described by Hofman et al. (1): AspNest1 (5’-TCTTGGTTCGCCATCGAT-3’) and AspNest2 (5’-TGA CAAAGCCCCCATACGCT-3’) for the first round and AspNest3 (5’-GAAGAACGCGGAAATGC-3’) and AspNest4 (5’-AACACACAAGCGTGCTTGA-3’) for the second round, respectively, leading to a final PCR product of 146 bp. However, no evidence of lung involvement with the hyphae was recognized. Therefore, the patient was diagnosed with invasive tracheobronchial aspergillosis (ITBA) of the ulcerative type with organizing pneumonia that was induced by an unknown cause.

Five days after starting treatment (day 10) with oral itraconazole and voriconazole for A. fumigatus. His serum value of aspergillus antigen per enzyme-linked immunosorbent assay (ELISA) and β-D-glucan decreased between day 5 (3.0, 33.8 pg/mL) and day 10 (1.9, 18.4 pg/mL), when he was transferred to our hospital. He appeared ill, with a blood pressure of 112/68 mmHg, a temperature of 35.8°C, a respiratory rate of 18/min, a heart rate of 104 beats/min and an oxygen saturation of 92% while on oxygen at 4 L/min via nasal cannula. On physical examination, fine crackles were detected in the lower lung fields bilaterally, and mild proximal muscular weakness (MMT4), the V-neck sign and extensor surfaces of the limbs were also observed. On the other hand, no clinical findings such as Gottron’s sign, the eruption of a heliotrope rash over the face, or Raynaud’s phenomenon were evident. A laboratory examination of the serum showed anemia (Hb: 11.2 g/dL), a low platelet count (9.4×10^9/μL), hypoalbuminemia (1.8 g/dL) and a moderate elevation of muscle enzymes (aspartate aminotransferase: 231 IU/L, creatine kinase: 427 IU/L and aldolase: 28.5 U/L). The marked elevation of serum lactase dehydrogenase (1,690 IU/L), KL-6 (1,482 U/mL) and C-reactive protein (10.6 mg/dL) were also noted. The serum titers for antinuclear antibody (160×) and anti-double-stranded DNA antibody (39.5 IU/mL) were positive. Furthermore, the urinary sediment showed the presence of moderate amounts of protein, abundant red blood cells and granular and waxy casts, thus suggesting glomerulonephritis. He satisfied six of the nine criteria for dermatomyositis (DM) as proposed by the Japan College of Rheumatology (three of the six criteria of the American College of Rheumatology (ACR)), as well as six of the eleven systemic lupus erythematosus (SLE) criteria as proposed by the ACR. He was thus diagnosed with ITBA with SLE/DM overlap syndrome with glomerulonephritis caused by SLE. Although the transbronchial lung biopsy specimens (Figure G, H) showed no apparent evidence of A. fumigatus infection, organizing pneumonia was tentatively considered due to either an A. fumigatus infection or SLE/DM.

Therefore, antifungal therapy with oral voriconazole (400 mg/day) and the intravenous infusion of micafungin (300 mg/day) was continued, and bronchoscopy was repeated on day 17 in our hospital. The procedure demonstrated the complete resolution of the lesions associated with ITBA, with no definite evidence of A. fumigatus infection on either the bronchial washings or TBLB. Thereafter, he was treated intensively with prednisolone (1 mg/kg/day) and cyclosporine (3 mg/kg/day) because his SLE disease activity index (SLEDAI) was very high (score: 25) and he had been diagnosed with co-existing DM. However, his lung lesions deteriorated rapidly over a few days following the second bronchoscopy, and thoracic CT showed a diffuse alveolar damage pattern in both the right middle to lower lobe and the left whole lung. He was therefore intubated on day 21. Despite intensive treatment and the fact that his serum values for β-D-glucan remained negative at day 25, 33 and 40, he died of respiratory failure on day 54, likely due to SLE/DM.

Discussion

Tracheobronchial involvement by Aspergillus has been reported under such names as obstructive bronchial aspergillosis, ulcerative Aspergillus tracheobronchitis and pseudomembranous aspergillosis. ITBA, which refers to both of the latter two forms and is a variant of invasive aspergillosis (2, 3), is a rare clinical entity. Only about 7% of patients with invasive aspergillosis have isolated ITBA in the absence of parenchymal disease (4), and most of the previously reported ITBA cases had underlying diseases, such as solid organ or hematological malignancies (5) or AIDS (6), were post-transplantation (7, 8), or had impaired immunity due to aggressive treatment (corticosteroids and/or immunosuppressants) (9). Ulcerative Aspergillus tracheobronchitis seemed to have a favorable outcome in most lung transplant recipients (3), whereas the present case died of respiratory failure. ITBA is generally limited to the larger airways, and the extension of organisms into surrounding pulmonary parenchyma or blood vessels is rare (10). The present case showed no definite evidence of an A. fumigatus infection in the lung parenchyma on repeated bronchoscopy. How organizing pneumonia is generated in patients with Aspergillus infection unknown, but a few studies of semi-invasive pulmonary aspergillosis have found that organizing pneumonia can develop in areas without hyphae (11). As was seen in the present case, A. fumigatus infection is a leading cause of ITBA, followed by A. flavus, A. niger and A. nidulans (12). The fact that the non-segmental consolidations with ground glass opacities rapidly spread from the right basal lung area to the right middle lobe or left whole lung implies that those
lesions were probably caused by SLE/DM.

It has been reported that the intrinsic immunological aberrations of SLE may play a role in the susceptibility to infections and the alteration of immunological defense mechanisms via impaired cellular immunity or the alteration of phagocytic cells and reduced immunoglobulin production (13). Kim et al. (14) reported that a high SLEDAI score, low complement levels and the presence of anti-double-stranded DNA antibody also increase the risks of infection, especially for *Aspergillus* spp as were found in the present case. They also stated that SLE patients were more susceptible to invasive fungal infection than those with other immunological disorders. However, 11 of the 12 SLE patients in their study had undergone intensive treatment with steroids and/or immunosuppressive drugs (14). At the time of the ITBA diagnosis, the present case had not received any treatment with either steroids or immunosuppressive drugs, which are a risk for *Aspergillus* infection. Bronchoscopic findings of ITBA include a tracheal obstruction with the presence of a yellow-white pseudomembrane and ulcer-like lesions (6, 10). When ulcerative and plaque-like lesions on the bronchial membrane are seen, the differential diagnosis must include cancer as well as viral and fungal infections (15).

To the best of our knowledge, only seven cases, including the present case, have been reported without any evidence of a severe immunosuppressive status (Table), such as solid organ and/or hematological malignancy, post-transplant, AIDS, insulin-dependent diabetes mellitus and steroids and/or immunosuppressive therapy (5, 14, 16-21). Four of the seven reported patients with ITBA were immunocompetent (5, 16, 19), and the others had either SLE/DM, tracheal and bronchial structural abnormalities such as tuberculosis (20) or COPD (21). The male to female ratio of these patients was 5:2, and the mean (±SD) age was 53.1±15 (range, 30 to 75) years. The Aspergillus infection was limited to the larger airways, which might be a characteristic finding on bronchoscopy even in immunocompetent patients, as was recognized in the previous reports involving immunocompromised patients (10). Although the present case died of lung involvement that was likely associated with SLE/DM, two of the seven patients reported in this review died of respiratory failure associated with *Aspergillus* infection. This implies that there is an as yet uncovered and/or a predisposing mechanism for developing invasive pulmonary aspergillosis with ITBA. Although the immunologic mechanisms underlying these processes have not yet been elucidated, physicians should consider the possibility of ITBA when they encounter patients with pseudomembranes, either ulcerative or plaque-like, and obstructive lesions on bronchoscopy, even if the patients do not appear to be immunosuppressed.

The present case indicates that severe immunosuppression is not a necessary condition for the development of ITBA, and that we should consider the possibility of ITBA in any patient with intrathoracic ulcers or plaque-like lesions as seen on bronchoscopy.

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

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**Table. ITBA without Apparent Severe Immunosuppressive Status**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clinical findings</th>
<th>Underlying disease</th>
<th>Location of infection</th>
<th>Therapy</th>
<th>Outcome</th>
<th>Aspergillus spp.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>M</td>
<td>N.A.</td>
<td>None</td>
<td>Right bronchus intermedium</td>
<td>Nebulized AMB</td>
<td>Survived</td>
<td><em>A. fumigatus</em></td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>M</td>
<td>N.A.</td>
<td>None</td>
<td>Right main bronchus and right bronchus intermedium</td>
<td>Nebulized AMB</td>
<td>Survived</td>
<td><em>A. fumigatus</em></td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>M</td>
<td>Cough, hemoptysis breathlessness Fever, non-productive cough, myalgias</td>
<td>None</td>
<td>Trachea</td>
<td>AMB</td>
<td>Survived</td>
<td><em>A. fumigatus</em></td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>M</td>
<td>Wheezing, hypoxemia</td>
<td>COPD</td>
<td>Bronchi and bronchioles</td>
<td>Nebulized AMB</td>
<td>Died</td>
<td>N.A.</td>
<td><em>A. fumigatus</em></td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>F</td>
<td>Productive cough, fever, dyspnea, chest pain</td>
<td>Post-tuberculosis tracheal stenosis</td>
<td>Trachea</td>
<td>AMB</td>
<td>Died</td>
<td>N.A.</td>
<td><em>A. fumigatus</em></td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>F</td>
<td>None</td>
<td>Trachea and both main bronchi</td>
<td>AMB</td>
<td>Died</td>
<td>N.A.</td>
<td><em>A. fumigatus</em></td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>M</td>
<td>Fever, body weight loss, myalgia</td>
<td>SLE, Dermatomyositis</td>
<td>Trachea and main bronchus</td>
<td>Oral VRCZ and MCFG</td>
<td>Died</td>
<td><em>A. fumigatus</em></td>
<td>Present case</td>
</tr>
</tbody>
</table>

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