Clinical characteristics and treatment outcome of *Candida* tracheobronchitis

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Abstract

Although *Candida* species can cause invasive fungal diseases, such as disseminated infection and pneumonia, they rarely cause tracheobronchitis, which is often fatal. To identify the clinical characteristics of *Candida* tracheobronchitis, we retrospectively evaluated 8 patients who had pathologically proven *Candida* tracheobronchitis. Their median age was 64 (range: 51–70) years and 5 were females. Three patients had solid cancers and 5 had hematological malignancies. We classified tracheobronchitis into localized and diffuse types. Of the 8 patients, 5 had localized and 3 had diffuse tracheobronchitis. While all patients with diffuse tracheobronchitis had predisposing risk factors for invasive fungal disease, such as prolonged corticosteroid use, recent use of nucleoside analogues, or recent neutropenia (<500/m3), only 2 of the 5 with localized tracheobronchitis had predisposing risk factors. Four of the 5 patients with localized tracheobronchitis had loco-regional bronchial mucosal damage (e.g., radiation or photodynamic therapy). Although all 8 patients ultimately died, some improved with or without antifungal treatment. Two of the 5 patients (1 with localized and the other with diffuse tracheobronchitis) who received antifungal agents improved after treatment, and 1 patient with localized tracheobronchitis who did not receive antifungal treatment improved spontaneously. Two of the 3 patients with diffuse tracheobronchitis did not respond to antifungal treatment.

*Candida* tracheobronchitis can present as both localized and diffuse types. While the former was influenced more by loco-regional mucosal damage, the latter was influenced more by the patient’s immune status. The treatment outcomes were especially poor in patients with diffuse tracheobronchitis.

**Abbreviations:** CT = computed tomography, IFD = invasive fungal diseases, TEVAR = thoracic endovascular aortic repair.

**Keywords:** bronchial disease, *Candida*, invasive fungal disease

1. **Introduction**

The mortality rate is higher in critically ill patients with nosocomial fungal infection than in those without it.1 Although the incidence of fungal tracheobronchitis is lower than that of other invasive fungal diseases (IFD), it can progress rapidly and cause airway obstruction, leading to respiratory failure and death.2,3 Common etiologies of invasive fungal tracheobronchitis are *Aspergillus*, *Coccidioides*, *Cryptococcus*, and *Zygomycota*...
We retrospectively reviewed the medical records of 196 patients diagnosed with any type of pulmonary IFD between January 1995 and May 2015 at Samsung Medical Center, a referral hospital, in Seoul, South Korea. All cases were confirmed histologically by bronchial or lung biopsies. After excluding 185 patients who were diagnosed with a fungal infection other than Candida spp., we found 11 patients who were diagnosed with invasive candidiasis. We followed the guidelines of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group for invasive fungal infection diagnosis. Tracheobronchitis was defined as an endobronchial nodule, mass, pseudomembrane, or eschar in the trachea, or a bronchus revealed by bronchoscopy.

Table 1

| Patient No. | Sex/Age | Underlying disease | Host factors predisposing to IFD | Previous lobar treatment | Morphological classification of tracheobronchitis | Antifungal treatment | Improvement of Candida tracheobronchitis | Survival time (days) after diagnosis of tracheobronchitis | Cause of death |
|-------------|---------|-------------------|-------------------------------|--------------------------|-----------------------------------------------|---------------------|----------------------------------------|-----------------------------------------------|---------------|
| 1           | F/63    | Tracheal ACC      | No                            | Parenteral chemotherapy   | Localized                                     | Yes                 | No                                | 9 ACC                                           |               |
| 2           | M/70    | NSCLC             | No                            | Chemoradiation            | Localized                                     | No                  | Yes                                | 1130 NSCLC                                      |               |
| 3           | M/70    | DLBCL             | No                            | Radiation therapy of thoracic vertebra | Localized                                     | Yes                 | No                                | 52 Pneumonia                                     |               |
| 4           | F/51    | MM                | Corticosteroid                | Endobronchial brachytherapy | Localized                                     | No                  | Yes                                | 35 MM                                           |               |
| 5           | F/59    | AML               | Corticosteroid                | Endobronchial photodynamic therapy | Localized                                     | Yes                 | Yes                                | 111 AML                                         |               |
| 6           | M/65    | Burkitt’s lymphoma| Neutropenia & nucleoside analogue | Neutropenia               | Diffuse                                        | No                  | Yes                                | 4 Neutropenia                                    |               |
| 7           | F/67    | Burkitt’s lymphoma| Neutropenia                   | Diffuse                   | No                                             | Yes                 | Yes                                | 203 AML                                         |               |
| 8           | M/65    | AML               | Neutropenia & nucleoside analogue | Diffuse                   | No                                             | Yes                 | Yes                                | 203 AML                                         |               |

ACC = adeno-oid cystic carcinoma, AML = acute myeloid leukemia, DLBCL = diffuse large B cell lymphoma, IFD = invasive fungal disease, MM = multiple myeloma, NSCLC = non-small cell lung cancer.
time of Candida tracheobronchitis diagnosis. However, 3 of the 5 patients with localized tracheobronchitis had no known host factors for IFD (Table 1). Figures 1 and 2 show the bronchoscopic and pathological findings.

Of the 5 patients with localized tracheobronchitis, 3 did not receive antifungal treatment because the attending physicians did not consider the localized Candida infection to be serious. Despite the lack of antifungal treatment, the Candida tracheobronchitis
improved spontaneously in 1 patient (patient no. 2), who survived for more than 3 years after the initial diagnosis of Candida tracheobronchitis. Of the 2 patients who received antifungal treatment, 1 improved (patient no. 5).

Of 3 patients with diffuse Candida tracheobronchitis who received antifungal treatment, 1 improved, but all ultimately died after 3, 4, and 203 days due to pneumonia-associated septic shock, airway obstruction caused by Candida tracheobronchitis, and progression of underlying lymphoma, respectively. One patient with diffuse tracheobronchitis and another with localized tracheobronchitis improved after antifungal treatment, but ultimately died from their underlying malignant diseases.

4. Discussion

Here, we present the results of a retrospective study of the clinical manifestations and natural course of Candida tracheobronchitis. To our knowledge, this is the first study to comprehensively describe the 2 types of Candida tracheobronchitis. Whereas localized Candida tracheobronchitis was associated with loco-regional mucosal damage rather than immunosuppression, diffuse Candida tracheobronchitis was mainly associated with immunosuppressive conditions, particularly neutropenia.

Among immunocompromised patients, those with IFD had a poor prognosis regardless of the site of infection. However, few studies have focused on fungal tracheobronchitis caused by Candida spp. Compared with invasive tracheobronchitis caused by Aspergillus spp., Candida tracheobronchitis is not well-recognized because most reports describing this entity are principally concerned with other fungal diseases.

Although a few studies have reported Candida tracheobronchitis, they included small numbers of cases and did not fully describe the presentation or clinical course of Candida tracheobronchitis. In addition, previous studies did not clearly demonstrate tissue invasion by Candida spp., which is crucial for diagnosing tracheobronchitis. In our study, we assessed the clinical presentation and course of both the localized and diffuse types of (pathologically confirmed) Candida tracheobronchitis.

As shown by our results, the development of localized tracheobronchitis is associated with local mucosal damage. In 1 case report, localized Candida tracheobronchitis occurred several days after thoracic endovascular aortic repair (TEVAR). The patient did not have predisposing factors for systemic IFD; loco-regional ischemic damage to the airway mucosa appeared to be the cause of the tracheobronchitis, consistent with our finding that loco-regional damage may be a risk factor for this condition. In that case, localized tracheobronchitis occurred as a result of ischemic changes in the airway mucosa caused by a reduction in bronchial artery blood flow due to graft placement during TEVAR. Other studies reported Candida tracheobronchitis at the anastomosis site in lung transplant patients. We also found that local mucosal injuries caused by endobronchial brachytherapy, photodynamic therapy, and radiation therapy can contribute to Candida tracheobronchitis.

Other studies reported cases of Candida tracheobronchitis not associated with local mucosal damage. Our study, and several previous ones, showed that diffuse Candida tracheobronchitis can occur in immunocompromised patients. Previous studies also showed that immunocompromised patients, including those with neutropenia, poorly controlled diabetes mellitus, and heavy alcohol consumption, can suffer from IFD caused by Candida spp. We summarize the reported cases of Candida tracheobronchitis in Table 2.

It is generally considered that the presence of Candida spp. in lower respiratory tract samples is not indicative of severe infection or associated with treatment outcomes. However, recent studies have shown that Candida spp. can cause lower respiratory IFD, such as Candida pneumonia. However, Candida tracheobronchitis is rarely reported and not well recognized. Although rare, our study, and previous ones, clearly showed that Candida infection can manifest as tracheobronchitis, similar to other fungal infections. Our results indicate that clinicians should be aware that loco-regional mucosal damage and a severely compromised immune system can predispose patients to localized and diffuse Candida tracheobronchitis, respectively, and that the prognosis of this disease is poor (especially for diffuse Candida tracheobronchitis).

This study had several limitations. First, it used a retrospective, single-center design. Second, the number of cases analyzed was small because of the rarity of the disease. Further studies with more patients are needed. However, our study was the first to comprehensively assess pathologically proven Candida tracheobronchitis, in terms of its presentation, histopathology, treatment, and natural course.

5. Conclusions

Candida tracheobronchitis can present in localized and diffuse forms. The former is mainly associated with loco-regional mucosal damage, while the latter is more dependent on the

| Table 2 | Reported cases of Candida tracheobronchitis. |
|--------|---------------------------------------------|
| Study  | Number of cases | Diagnostic method | Form of tracheobronchitis | Suspected predisposing factor |
| Spear, 1976 | 1 | EBBx | Diffuse | Broad-spectrum antibiotics |
| Clarke, 1991 | 2 | EBBx (1 case) Autopsy (1 case) | Diffuse | Metastatic cancer (1 case) Unknown (1 case) |
| Nurem, 2002 | 2 | EBBx | Localized | Lung transplantation |
| Khan, 2010 | 1 | EBBx | Diffuse | Fulminant hepatic failure |
| Schaeffer, 2009 | 12 | EBBx (4 cases) BAL (8 cases) | NA | Lung transplantation |
| Lin, 2017 | 2 | EBBx and/or BAL | NA | NA |
| Tanaka, 2017 | 1 | BAL | Diffuse | Uncontrolled DM |
| Takaki, 2018 | 1 | EBBx | Localized | Ischemia after TEVAR |

BBB = bronchoalveolar lavage, DM = diabetes mellitus, EBBx = endobronchial biopsy, NA = not available, TEVAR = thoracic endovascular aortic repair.
patient’s immune status. The treatment outcomes were especially poor in patients with diffuse tracheobronchitis.

**Author contributions**

HG and BY were the major contributors to the writing of the manuscript. They also analyzed and interpreted the data on invasive fungal tracheobronchitis and contributed equally to this work. TL performed the histological examinations of bronchial tissue and contributed to the writing of the manuscript. MYK performed the radiological review of the cases. HC and HY helped with the writing and substantively revised the manuscript. HK, OJK, and SJC reviewed the manuscript and provided medical advice. HL designed the study and served as the principal investigator and corresponding author. All authors read and approved the final manuscript.

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