Case Report

Aspergillus Laryngotracheobronchitis in a Child with Primary Immunodeficiency

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ABSTRACT

Laryngotracheobronchitis (LTB) is a common disease in the pediatric population, and it is rarely caused by a fungal infection. Acute respiratory failure caused by fungal LTB mainly occurs in immunocompromised patients, and early diagnosis is closely associated with morbidity and mortality. However, an appropriate diagnosis is challenging for pediatricians because symptoms and signs of LTB caused by *Aspergillus* spp. are nonspecific. Here, we report a case of progressive respiratory failure caused by pseudomembranous LTB in a child with a suspicion of primary immunodeficiency and highlight the importance of an early investigation, especially in immunocompromised patients.

Keywords: Invasive pulmonary aspergillosis; *Aspergillus fumigatus*; Immunocompromised host

INTRODUCTION

Laryngotracheobronchitis (LTB), commonly known as croup, is usually caused by the parainfluenza virus and mainly affects children between the ages of 3 months and 5 years.¹⁾ LTB can typically be diagnosed without a specific examination based on a cough.¹⁾ However, LTB can also be caused by fungi in rare cases, mainly in immunocompromised conditions such as prolonged neutropenia, hemato-oncologic malignancies, and treatment with immunosuppressants, including corticosteroid.²⁻⁴⁾ Here, we report a rare case of “atypical croup” and progressive respiratory failure caused by pseudomembranous tracheobronchial aspergillosis in a child with primary immunodeficiency disease (PID).

CASE

The patient was a 19-month-old boy born after a full-term normal delivery with a birth weight of 3.6 kg (50th percentile). At the age of 5 months, he was referred to our hospital with suspicion of PID based on recurrent eczema, skin infection, and failure to thrive after birth. From birth, atopic dermatitis with eczema on scalp, face, and trunk was presented, and combined with fever and skin infection (**Fig. 1**). Moreover, weight gain was poor, and at the age of 5 months,

Author Contributions

Conceptualization: Lee S, Park JD; Data curation: Lee S, Kim YS, Park JD; Formal analysis: Lee S, Park JD; Investigation: Lee S; Writing - original draft: Moon SY; Writing - review & editing: Kim YS, Park JD, Choi YH.

Fig. 1. Atopic dermatitis on trunk had a waxing and waning clinical course from birth.

the patient's height (62.5 cm) and body weight (5.8 kg) were less than 3 percentile. Several immunologic work-ups and genetic tests were performed (**Table 1**), and the results showed hypogammaglobulinemia and decreased cluster of differentiation CD4/CD8 ratio. Although a specific PID was not identified, the patient was suspected of combined immunodeficiency based on clinical manifestations and immunological results. Since the age of 5 months, the patient was kept on prednisolone (<0.5 mg/kg/day) to control eczema and non-infectious etiologies of fever. Monthly intravenous immunoglobulin (400 mg/kg) was also administered. Additionally, oral fluconazole was administered from 6 months to 12 months of age due to recurrent oral thrush and *Candida albicans* infection on the skin accompanying eczema. Cytomegalovirus (CMV) antigenemia was identified, and fundus examination showed CMV retinitis at the age of 8 months; treated by administration of intravenous ganciclovir and continuation of valganciclovir.

Table 1. Laboratory tests performed to diagnose specific primary immunodeficiency in the patient at the age of 5 months

Laboratory tests	Patient	Reference range for age (5 months) ^{5,6)}
Complete blood count		
White blood cells	6,400/mm ³	5,500–18,000/mm ³
Absolute lymphocyte count	1,708/mm ³	1,400–22,000/mm ³
Absolute neutrophil count	2,611/mm ³	500–9,500/mm ³
Hemoglobin	10.7 g/dL	10.1–14.5 g/dL
Hematocrit	34.0%	33–42%
Platelet	241×10 ³ /μL	206–445×10 ³ /μL
Ig		
IgG	212 mg/dL	172–1,069 mg/dL
IgA	<1 mg/dL	4.4–84 mg/dL
IgM	10 mg/dL	33–126 mg/dL
IgE	3 IU/mL	0–230 IU/mL
Lymphocyte-subset		
CD19	57/mL, 3%	775–2,238/mL
CD3	1,033/mL, 60%	2,284–4,776/mL
CD4	44/mL, 3%	1,523–3,472/mL
CD8	1,007/mL, 59%	524–1,583/mL
CD16/CD56	629/mL, 37%	230–801/mL
CD4/CD8	0.044	1.48–3.77

Genetic testing for primary immunodeficiency: all were negative

BTK, *RAG 1*, *RAG 2*, *PI3KCD*, *ADA*, *CD40LG*, *CD 45*, *CYBB*, *DCLRE1C*, *FOXP3*, *IKBKG*, *IL2RG*, *IL7R*, *IRF8*, *TACI*, *TNFR13B*, *ZAP70*, *WAS*, *SPINK5*.

Abbreviations: Ig, immunoglobulin; CD, cluster of differentiation.

At 17 months, the patient underwent ileostomy due to necrotizing enterocolitis and was discharged without acute complication. Two months later, the patient was admitted for ileostomy reversal. During the surgical treatment, previous medications, including prednisolone (0.5 mg/kg/day), were continued. When the patient was intubated under general anesthesia, an anesthesiologist evaluated the airway as Cormack's grade 1, and there were no problems for intubation, and no evidence of fungal infection, such as oral thrush. After extubation, he was transferred to the ward without any acute complication, including respiratory symptoms. On day 12 of hospitalization, he developed fever, sputum, cough, and stridor. Chest X-ray and laboratory tests were normal. Human parainfluenza virus 2 was positive in a respiratory viral polymerase chain reaction (RV PCR), but it was controversial to interpret the results because the patient consistently showed positive results by RV PCR for the same virus since the age of 6 months. Nevertheless, based on suspicion of typical croup, intravenous dexamethasone (0.3 mg/kg/day) was administered along with inhaled epinephrine for 2 days. However, on day 16 of hospitalization, stridor with desaturation and hypercapnia were aggravated despite high-flow nasal cannula application and the patient was transferred to the pediatric intensive care unit where mechanical ventilation (MV) was initiated. Chest X-ray at arrival was unchanged, and laboratory tests, including inflammatory markers, were not notable (leukocyte count: 4,390/mm³ [neutrophil 29.1%, lymphocyte 63.6%]; hemoglobin: 8.2 mg/dL; platelet count: 275,000/dL; C-reactive protein: 0.75 mg/dL; procalcitonin: 0.096 ng/mL). The dose of intravenous dexamethasone was increased (0.25 mg/kg every 6 hours). Three days later, he was no longer dependent on MV and was extubated.

Over the following 2 days, the patient's condition deteriorated again with respiratory distress accompanying stridor, biphasic wheezing, and suprasternal/subcostal retraction, and he was reintubated. Because he showed atypical course of croup, high-dose dexamethasone used for 5 days was stopped, and the airway was evaluated using rigid bronchoscopy on day 24. Whitish plaques were observed from the glottis to the trachea, and fungal infection was suspected (**Fig. 2**); thus, caspofungin (70 mg/m² every 24 hours) was promptly started. Three days later, the fungal pathogen was identified as *Aspergillus fumigatus* (**Fig. 3**), and the antifungal agent was changed to a combination of intravenous voriconazole (9 mg/kg every 12 hours) and inhaled amphotericin B liposomal (2.5 mg/kg every 12 hours). Because *A. fumigatus* was only identified at the pathology specimen of larynx and was not isolated from tracheal aspirate culture, the antifungal susceptibility testing was not performed. Chest computed tomography (CT) showed diffuse enhancing wall thickening with multifocal luminal narrowing in the trachea and bronchi (**Fig. 4A-C**).

One week after diagnosis, due to drug-induced neutropenia, ganciclovir was changed to foscarnet, and a granulocyte colony-stimulating factor was infused. Fiberoptic bronchoscopy was performed five more times at the bedside to remove pseudomembranes and improve airway obstruction. However, from day 63 of hospitalization, the condition further deteriorated with severe respiratory acidosis (pH 7.1, pCO₂ 93 mmHg). Donor granulocyte infusions were administered to improve the qualitative deficiency of circulatory granulocytes, along with various attempts to decrease airway resistance and ultimately reduce ventilator pressure, such as heliox instead of nitrogen in MV and inhaled bronchodilators. Nevertheless, there was no clinical improvement, and follow-up chest CT showed an aggravated state of diffuse peribronchial consolidations with multiple air cysts (**Fig. 4D-F**). Additionally, the physical removal of pseudomembrane in the airway was no longer effective in improving ventilation due to bleeding caused by detachment. On day 102 of hospitalization, the patient died of progressive obstructive respiratory failure.

Fig. 2. Rigid bronchoscopic findings at the time of diagnosis of *Aspergillus* laryngotracheobronchitis (day 24 of hospitalization) according to the level of airway: (A) larynx, (B) upper trachea, (C) mid-trachea, and (D) carina. The airway was patent, but the entire mucosa was covered with whitish patches.

This case was certified as exempt by the Institutional Review Board (IRB) (IRB No. H-2002-093-1103) and informed consent was waived.

Fig. 3. Pathologic findings of the bronchial mucosa obtained using bronchoscopy (hematoxylin and eosin stain, magnification 20×). Numerous fungal hyphae and spores were observed, and *Aspergillus fumigatus* was ultimately confirmed.

Fig. 4. (A-C) Chest CT was performed at the time of diagnosis of *Aspergillus* laryngotracheobronchitis. CT showed diffuse enhancing wall thickening with multifocal luminal narrowing in the tracheobronchial trees and collapsed left upper lung. (D-F) Chest CT on day 83 of hospitalization presented aggravated peribronchial consolidation with ground glass opacity and developed multiple small cysts that are visible in the left lung. Abbreviations: CT, computed tomography.

DISCUSSION

An *Aspergillus*-related airway infection is an unusual form of invasive pulmonary aspergillosis (IPA), accounting for only 6.9% of cases.⁷⁾ Among these, *Aspergillus* LTB, as a form of *Aspergillus* tracheobronchitis (AT), with additional involvement of the larynx, is extremely rare, with only four cases reported to date.^{2,8,10)} A recent literature review indicated that approximately 30–50% of adults with AT initially present with productive cough, dyspnea, and fever, while 20% are asymptomatic; on radiologic examination, 50% of patients show normal findings.³⁾ Therefore, since typical symptoms or signs of AT are unclear, diagnosis and treatment are often delayed, which may contribute to a poor prognosis. Additionally, because *Aspergillus* LTB can progress without noticeable laboratory and radiologic results, it is a challenge for pediatricians to suspect fungal LTB, given the more common viral cause. Therefore, suspicion of atypical LTB itself is the first step toward appropriate treatment in a child at risk of AT.

The main predisposing factors for AT in adults are similar to those for other forms of IPA,⁷⁾ including an immunocompromised state, which is secondary to treatment or a disease such as a lung/hematopoietic transplantation and solid organ/hematologic malignancy.^{3,4,7)} This seems to be similar for pediatric patients.^{2,9)} To the best of our knowledge, this is the first case of *Aspergillus* LTB in a child suffering from PID. The innate immune response to invasive *Aspergillus* infection plays a critical role in the recognition and elimination of the fungus from the pulmonary system,¹²⁾ especially by phagocytic cells like neutrophils and macrophages. Therefore, invasive fungal infection is more common in case of chronic granulomatous disease, which is characterized by phagocytic immune deficits, than in other PID.¹³⁾ In this

case, the specific PID was not identified, but laboratory tests showed a normal neutrophil count and phagocytic function that was considered tolerable as there were no severe bacterial infections leading to life-threatening conditions before admission. Consequently, we suspect that other predisposing factors, in addition to PID, contributed to the occurrence of *Aspergillus* LTB in this case.

Long-term corticosteroid therapy is a well-known risk factor for AT in both immunocompetent and immunocompromised patients.³⁾ Approximately 80% of patients with AT were reported to be receiving corticosteroids at the time of presentation.³⁾ Corticosteroids are widely used for various purposes, including inflammation reduction, even in patients with PID.¹⁴⁾ However, corticosteroids can impair neutrophil function in response to *Aspergillus* infection by suppression of neutrophil-induced hyphal damage and respiratory burst in response to opsonized and non-opsonized hyphae.¹⁵⁾ This effect is considered to be dose- and time-dependent. In this case, the patient was treated with corticosteroid from the age of 5 months. Therefore, life-long exposure to corticosteroids, despite their low doses, is a potential contributor to *Aspergillus* LTB in the present case, in addition to PID. Moreover, after respiratory symptoms were aggravated, we used dexamethasone, a strong-potency corticosteroid for 5 days based on suspicion of a typical croup caused by a viral infection. Thus, the LTB may have been accelerated due to the delay in discontinuation of corticosteroids with a strong potency, since the initial working diagnosis was croup. This case study suggests that corticosteroids should be very cautiously used under an empirical diagnosis of viral croup in young children with conditions favorable to fungal infection.

With the correct diagnosis of AT, prompt administration of antifungal agents such as amphotericin B or voriconazole is the most effective treatment,^{3,4)} along with several supportive treatments. To relieve airway obstruction immediately, fungal materials are physically removed by bronchoscopy, especially in cases of a pseudomembranous type of *Aspergillus*.^{7,11)} In our experience, this procedure was helpful early in the diagnosis but was useless in the late phase because the pseudomembranes became thick and stuck firmly along the airway. Granulocyte colony-stimulating factor can also be used to stimulate neutrophil production and enhance phagocytic activity against fungi since a fall in the absolute quantity of neutrophils is strongly associated with a high mortality rate in AT.⁴⁾ On the other hand, granulocyte transfusion can reinforce circulating granulocytes for patients with AT.^{4,16)} In the present case, all of these treatments were applied but were not sufficient to improve the outcome. Indeed, there is only low-grade evidence of such supportive treatment with no indication of improved outcomes. Nevertheless, various interventions could be attempted in cases refractory to conventional therapy.

Therefore, timely diagnosis and treatment are crucial for a better outcome of invasive aspergillosis in immunocompromised children, but early diagnosis of IPA based on clinical manifestations is still challenging due to atypical clinical manifestations.¹⁷⁾ In addition to clinical suspicion of IPA, a combination of radiology findings and microbiologic tests is recommended for early diagnosis. Despite highly heterogeneous findings, chest CT scan showed better discrimination than X-rays, especially in the early stages of IPA.¹⁷⁾ *A. fumigatus* serology test such as galactomannan assay is also helpful for early diagnosis.¹⁷⁾ However, as seen in our case, for identification of LTB or AT, flexible or rigid bronchoscopy is the first of choice over any other tests. Thus, bronchoscopy should be performed immediately for an accurate diagnosis, but the clinical status such as hypoxemia and bleeding should be considered.¹⁸⁾

In conclusion, because it is difficult to distinguish atypical croup caused by atypical pathogens like *Aspergillus*, LTB may be misdiagnosed as a typical croup based on symptoms and laboratory findings. Pediatricians should be aware of the possibility of fungal infection as a cause of respiratory failure in high-risk patients, and early intervention should be considered for timely diagnosis and management.

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요약

소아에서 후두기관지염이 진균에 의해 발생하는 경우는 매우 드물고 주로 선행 요인이 있는 환자에 보고된다. 또한, *Aspergillus* 감염에 의한 후두기관지염은 초기에 무증상이거나 가슴 X선 사진에서 특이점이 없는 경우가 많아 조기 진단이 어렵다. 저자는 피부증상과 비감염성 발열을 조절하기 위해 장기간 저용량 스테로이드를 사용했던 복용력이 있는 일차성 면역 결핍 질환이 의심되는 환자에서 점진적인 호흡 부전을 보였고 가막성 아르페르길루스증 (Pseudomembranous aspergillosis)에 의한 후두기관지염으로 밝혀진 사례를 보고하여 *Aspergillus* 후두기관지염의 고위험 환자군에서 조기 진단을 통한 치료의 중요성을 알리고자 한다.