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CASE REPORT
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Primary Invasive Aspergillosis of the Larynx in an Immunocompromised Patient: A Case Report

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ABSTRACT

The authors discuss here the case of a 66-year-old man, recently diagnosed with aplastic anemia leading to pancytopenia, who developed a sore throat and dysphonia. Indirect laryngoscopy revealed a supraglottic edema. A cervical CT scan demonstrated right laryngeal mucosal oedema, extending over 6 cm. Diagnosis of primary laryngeal invasive aspergillosis was made based on biopsies performed 10 days after initial symptoms; a secondary pulmonary involvement was discovered on a renewed CT scan. Sequential treatment with amphotericin B followed by voriconazole and then isavuconazole was carried out. The authors performed a second suspension laryngoscopy and discovered extensive pharyngo–laryngo–tracheal necrosis. The authors opted for treatment de-escalation. Autopsy revealed invasive aspergillosis, involving the lungs, heart, liver, thyroid, larynx, and trachea. Laryngeal aspergillosis is rare, mostly arising as an extension of a pulmonary or systemic infection. The authors found only 10 other reported cases of primary laryngeal invasive aspergillosis in an immunocompromised patient; however, this case is the only 1 that became systemic. Laryngeal aspergillosis should be considered in the differential diagnosis of immunocompromised patients presenting with laryngitis-like symptoms. Prophylactic treatment should be initiated promptly upon suspicion. Clinical diagnosis is challenging, and early biopsies will help to identify the fungus rapidly. Any delay in treatment may lead to fatal consequences.

Keywords: aspergillosis, immunocompromised host, larynx

Introduction

The advancements in healthcare resulted in an increasing population of immunocompromised patients who are more susceptible to opportunistic infections. Among these, aspergillosis stands out as a significant contributor to high morbi-mortality rates, affecting vital organs such as the lung, brain, gastrointestinal tract, or kidney. Laryngeal aspergillosis is rare, most of the time arising as an extension of a pulmonary or systemic infection. In this paper, the authors discuss the case of a 66-year-old man suffering from pancytopenia who developed primary invasive aspergillosis of the larynx. The objective is to remind physicians of the importance of recognizing this rare condition, which may be challenging to diagnose, and emphasize that any delay in treatment can lead to fatal consequences.

Case Presentation

A 66-year-old man, recently diagnosed with aplastic anemia leading to pancytopenia, was treated by immunosuppressive therapy including horse antithymocyte globulin, ciclosporine, and methylprednisolone. He also received antifungal prophylaxis with fluconazole. The patient, a former smoker and drinker, had a history of high blood pressure and well-controlled type 2 diabetes.

He developed a sore throat and dysphonia and was subsequently referred to the ENT department, where indirect laryngoscopy revealed an edema of the right arytenoid and aryepiglottic fold, along with right laryngeal hemiparesis. A cervical CT scan demonstrated right laryngeal mucosal oedema,

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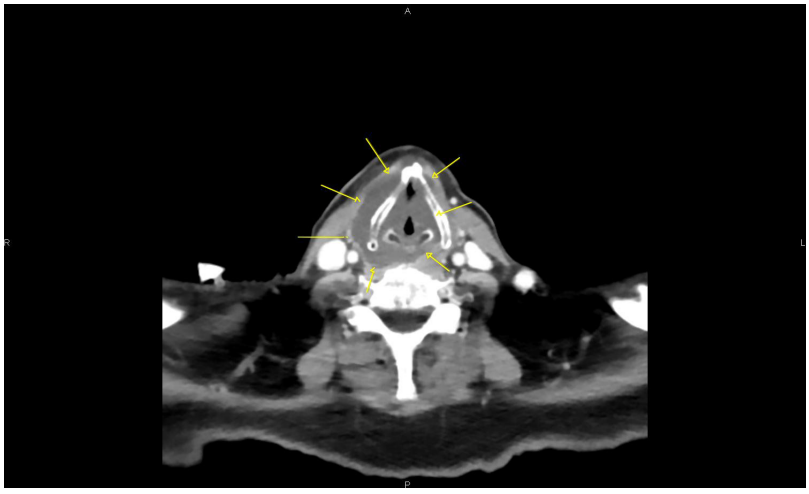

Figure 1. Second neck computed tomography: axial sections.

extending from downstream of the vallecula to the larynx over a length of 6 cm, without evidence of underlying mass or abscess. The chest X-ray was clear.

The patient was being treated with amoxicillin for multi-sensitive *Streptococcus sanguinosis* bacteremia, and an allergic reaction to amoxicillin was thus suspected, leading to a shift in antibiotherapy to moxifloxacin. Vancomycin was added due to a *Staphylococcus haemolyticus* oxacillin-resistant bacteremia, in conjunction with empirical piperacillin/tazobactam. However, despite this change in treatment, the patient's condition worsened with the onset of a stridor. A cervical magnetic resonance imaging revealed an abscess in the right hemilarynx. A diagnosis of bacterial or mycotic infection was raised, and the patient was transferred to this center for further treatment.

Upon his arrival, piperacillin/tazobactam was stopped and cefepime started. The authors conducted a follow-up cervical CT scan, revealing a right paraglottic abscess extending to the supraglottic and subglottic levels. No pleuroparenchymal disease was demonstrated, though the scan did not assess the right lower lobe.

A suspension laryngoscopy with biopsies and bacteriological samples was performed, along with a percutaneous tracheostomy given the patient's respiratory condition. The pathological analysis of the laryngeal biopsies identified a mold compatible with *Aspergillus*. A lung CT scan detected a 4 mm nodule in the apical segment of the right lower lobe. Based on these findings, the authors established a diagnosis of primary invasive laryngeal aspergillosis with secondary pulmonary involvement.

Main points

- Primary invasive aspergillosis of the larynx has a high morbi-mortality in immunocompromised patients. Any delay in treatment may lead to fatal consequences.
- Laryngeal aspergillosis should be considered in the differential diagnosis of immunocompromised patients presenting with laryngitis-like symptoms.
- Clinical diagnosis is challenging, and early biopsies are needed to identify the fungus rapidly.

Treatment initially included amphotericin B and meropenem. Due to renal failure, amphotericin B was replaced with voriconazole, and ultimately switched to isavuconazole following the antibiogram indicating a multi-sensitive *Aspergillus fumigatus* found in endotracheal samples. Although the patient progressively recovered from neutropenia, his laryngeal and pulmonary condition worsened. (Figures 1-3). A second suspension laryngoscopy revealed extensive pharyngo-laryngo-tracheal necrosis (Figure 4). Consequently, the only viable therapeutic option was deemed to be a total pharyngo–laryngectomy. A multidisciplinary meeting was held with the family, who opted for treatment de-escalation. Indeed, despite a third line of antifungal therapy and broad-spectrum antibiotics, the patient showed no signs of clinical improvement. Furthermore, the pancytopenia persisted despite 9 weeks of treatment. Pharyngo–laryngectomy would have been associated with major morbidity and mortality risks. The patient died 2 days after the decision to de-escalate treatment.

The autopsy revealed invasive aspergillosis, involving the lungs, heart, liver, thyroid, larynx, and trachea, accompanied by massive necrosis particularly prominent in the larynx and trachea.

Discussion

Primary invasive laryngeal aspergillosis in an immunocompromised patient is an extremely rare condition and there have been few previous cases reported in the literature (Table 1). Laryngeal aspergillosis typically arises following a pulmonary or systemic infection. *Aspergillus* is an ubiquitous agent colonizing the airways by inhalation.[1] In immunocompromised patients, aspergillosis mostly involves the brain, lungs, gastrointestinal tract, or kidneys.[2] This type of infection tends to be necrotizing, infiltrating, and carries a poor prognosis.[3]

The pathogenesis of primary laryngeal aspergillosis seems to be multifactorial, involving a decrease in the host's defenses and an increased exposure. Suspected potential contributing factors include inhaled corticosteroids, vocal cord abuse,

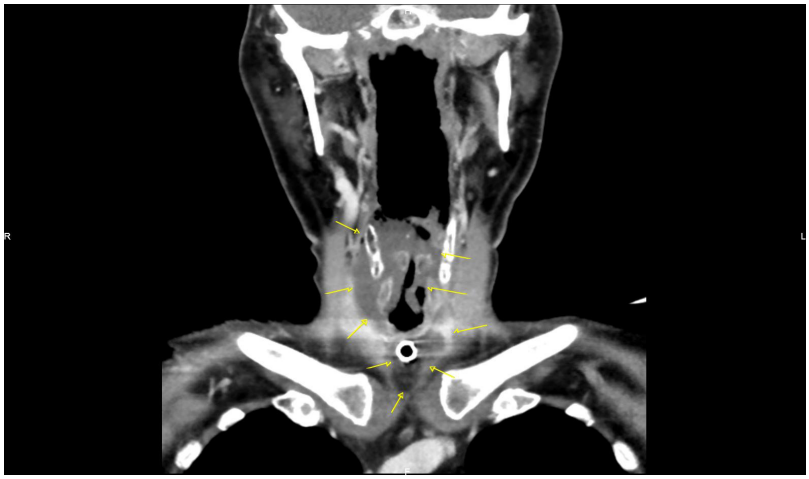

Figure 2. Second neck computed tomography: coronal sections.

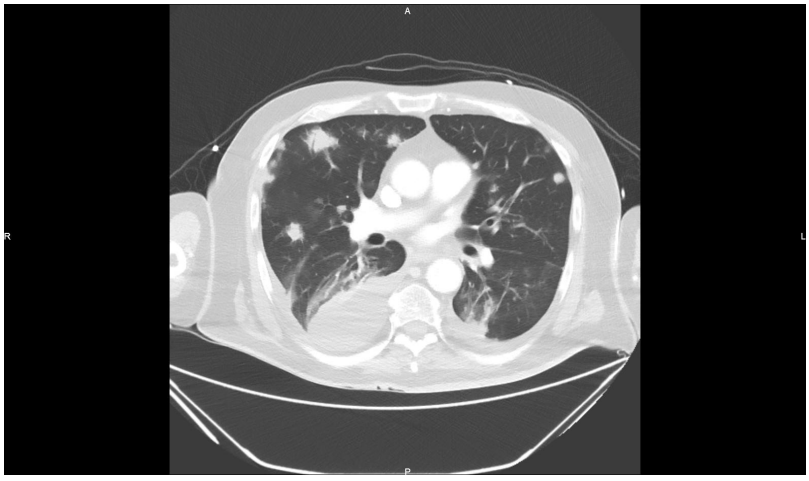

Figure 3. Chest computed tomography: axial sections.

smoking, pharyngo–laryngeal reflux, radiation, and broad-spectrum antibiotics.[4] Immunodeficiency is a predisposing factor of invasive fungal infection.[5] In this case, the patient had no particular risk factor for developing laryngeal aspergillosis, except his past history of smoking. However, pancytopenia consisted of a predisposing condition for developing an invasive infection.

The clinical diagnosis of laryngeal aspergillosis is challenging due to its nonspecific symptoms, which often correspond with those of laryngitis.[5] The patient involved in this study initially presented only with dysphonia and a sore throat.

Clinically, indirect laryngoscopy is similarly aspecific, revealing features like perilaryngeal white plaques, granulation tissue,

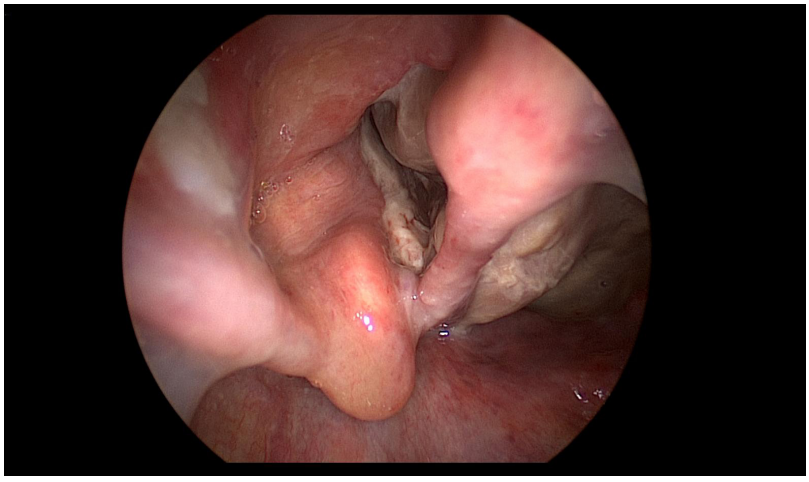

Figure 4. Endoscopic view of the larynx showing complete tissue necrosis.

Table 1. Characteristics of Other Primary Invasive Aspergillosis of the Larynx in an Immunocompromised Patient Documented in the Literature

	Author	Age	Sex	Complaint	Primary Location	Secondary Location	Etiology/ Comorbidity	Treatment	Outcomes
1	Ohashi T.	65	M	Sore throat and dysphagia	Epiglottis	None	Agranulocytosis	AMPH-B, ITCZ	Improved
2	Fairley CK[8]	37	M	Hoarseness	Vocal cord	Yes, pulmonary	HIV	FLCZ, AMPH-B, ITCZ	Fatal outcome
3	Kingdom TT	41	M	Hoarseness	Vocal cord	None	HIV	FLCZ, AMPH-B	Fatal outcome
4	Sriskandabalan P[9]	42	M	Sore throat and tenderness	Epiglottis	Yes, pulmonary	HIV	ITCZ, AMPH-B, L-AMB	Fatal outcome
5	Nagasawa M	19	F	Sore throat and cough	Subglottis	Yes, pulmonary	AA, steroid	FLCZ, AMPH-B, ITCZ	Fatal outcome
6	Athanassiadou F[10]	2	M	Hoarseness	Vocal cord	Yes, pulmonary	ALL, CIN	L-AMB	Improved
7	Williams MS[11]	Young adult	M	Sore throat and cough	Subglottis	None	ALL, CIN	VRCZ	Fatal outcome
8	Swiss T[12]	46	F	Sore throat and dysphonia	Larynx and subglottic	Yes, pulmonary	Myelodysplastic syndrome, LMA	L-AMB, debridement, GM-CSF	Improved
9	Morelli S[13]	53	M	Hoarseness	Vocal cord	None	Felty syndrome, steroids	AMPH-B, L-AMB, ITCZ, GCSF, debridement	Improved
10	Bolivar R[14]	21	F	Hoarseness, sore throat, and mild respiratory distress	Epiglottis	Yes, pulmonary	ALL	AMPH-B	Fatal outcome

AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AMPH-B, amphotericin B; CIN, chemotherapy-induced neutropenia; FLCZ, fluconazole; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HIV, human immunodeficiency virus; ITCZ, itraconazole; L-AMB, liposomalamphotericin B.

ulcerations, erythema, and edema.[5] Differential diagnosis is often difficult, involving other granulomatous diseases of the larynx and malignancies.[6] In this case, the initial examination showed only edema and was misdiagnosed as an allergic reaction.

Definitive diagnosis requires histopathological examination on a biopsy, which shows tissue invasion by hyphae with acute branching patterns, along with hyperkeratosis, slough, and ulceration of the epithelium.[7] However, identifying the specific species is rarely achieved, and the morphologic features are not pathognomonic of *Aspergillus*.[5]

Early treatment is crucial in immunocompromised patients, given the risk of rapid and widespread necrosis and potential hematogenous dissemination. While there are no specific guidelines for the treatment of primary laryngeal invasive aspergillosis, voriconazole is currently considered the drug of choice by the Infectious Diseases Society of America in invasive aspergillosis and should be started as soon as the diagnosis is suspected.[15] Amphotericin B, along with other lipid formulations, and isavuconazole are recommended as alternative therapies due to higher toxicity. Debridement should be considered whenever possible to enhance antifungal action. In this case, prophylactic antifungal therapy consisting of fluconazole was started following immunodepression. Amphotericin B was only started when the diagnosis of invasive aspergillosis was confirmed, 2 weeks after the initial symptoms. It was later switched to voriconazole due to renal failure and ultimately to isavuconazole when the antibiogram revealed a multi-sensitive *Aspergillus fumigatus*. Fungal infection had been suspected as early as the first MRI, at which point initiating antifungal treatment with voriconazole should have been considered. Early debridement had been discussed but deemed too risky given the patient's state and anemia.

Conclusion

Laryngeal aspergillosis should be considered in the differential diagnosis of immunocompromised patients presenting with laryngitis-like symptoms, and prophylactic treatment should be initiated promptly upon suspicion of aspergillosis. Clinical diagnosis is challenging, and early biopsies will help to identify the fungus rapidly. Given the high morbi-mortality in an immunocompromised patient, it is vital to detect it as early as possible, to initiate treatment quickly and thus increase the chances of survival.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no artificial intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of the CHU UCL Namur (Approval no: 83/2023, Date: May 5, 2023).

Informed Consent: The hospital's ethics committee has approved the project with a waiver of consent, given the circumstances surrounding the patient's death, and in order to avoid causing additional pain to the family.

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