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Case Report

Tracheal and Endobronchial Mucorales in a Young Liver Transplanted Patient: A Rare Condition

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Abstract

We report here the case of a tracheal and end bronchial infection by the mucormycosis fungi, on a young patient admitted in the ICU for a heatstroke. Several undercurrent pathologies were associated with his condition. Secondary to a multi-organ failure, he received an emergency hepatic transplantation and an immunosuppress or treatment was implemented. Following that, he developed a mucormycosis infection, diagnosed after endotracheal sputum culture and fibro copy. He thus received amphotericin B and isavuconazole in intravenous perfusions and Aerobe, but surgeons decide not to operate because of a too big surgical risk, and a operation considered as impossible to perform Indeed, it is important to know the physiopathology very well and to be able to detect the risk factors to develop this infection to get a chance of a successful outcome. Treatment consist in a combination of an early antifungal treatment, the correction of risk factors, and sometime surgical sanction. However, it is essential to realize that this is correlated with and important morbidity/mortality rate.

Keywords: Amphotericin B; Heatstroke; Immunosuppressor; Liver-transplantation; Mucormycosis; Trachea

Introduction

Mucormycosis is an opportunistic fungal infection that may cause various clinical types of presentation, associated with high morbidity and mortality. It belongs to the zygomycete family, order of Morales, and found in soil and decaying matter [1]. It is an ubiquital fungus, described all around the world. The most frequent species isolated from patients are Apophysomyces (A. variabilis), Cunninghamella (C. bertholletiae), Lichtheimia (L. corymbifera L. raosa), Mucor (M. circinelloides), Rhizopus (R. arrhizus (oryzae) R. microsporus), Rhizomucor (R. pusillus), and Saksenaea (S. vasiformis) [1]. They are common environmental organisms that are normally innocuous for immunocompetent patients. However, it is the third most frequent fungal infection recorded in immunocompromised patients, after aspergilli and candidiasis [2]. Indeed, mucormycosis infection is a relatively frequent complication in patients with risk factors, i.e. especially uncontrolled diabetes mellitus, haematological conditions, organ transplant, renal failure or immunosuppress or medication. Nevertheless, the infection has been observed in healthy patients with trauma with telluric component, burns or skin infections [3]. Clinical presentations are variable, but the tracheal location appears as a rare described condition. Concerning the treatment, it should be implemented as soon as possible, and it is based on the association of antifungal therapy and debunking surgery.

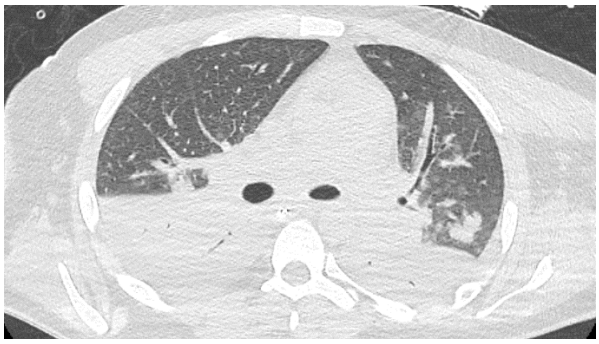

Figure 1: CT thoracic scanner: diffuse infectious bilateral multifocal neuropathy, predominant in the right apex as well as in the lower lobes.

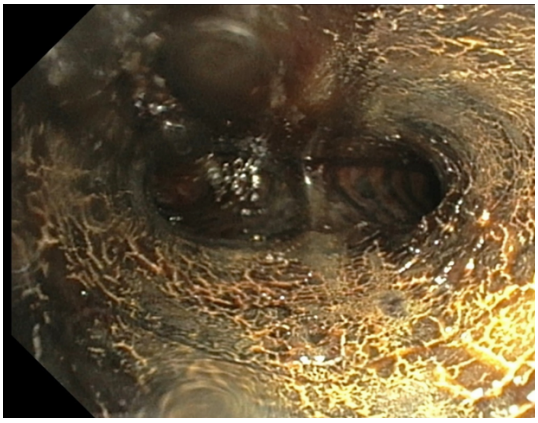

Figure 2: First microscopic examination: blackish deposit extending over the entire tracheal surface up to the emergence of the main bronchi.

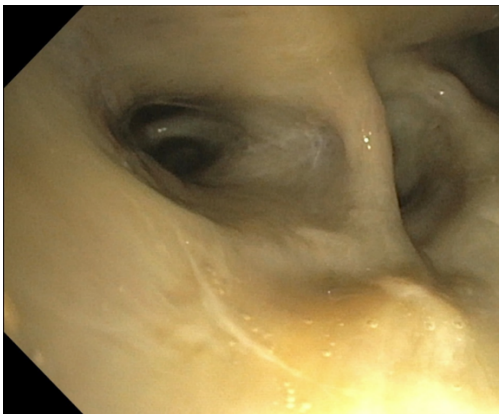

Figure 3: First microscopic examination of the segmental bronchi, which are abnormally whitish with the presence of mycolic filaments.

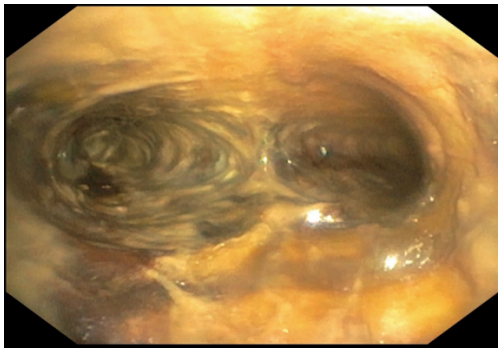

Figure 4: Tracheal microscopic examination seven days after the beginning of antifungal treatment. An improvement of the blackish deposit appearance is noticed.

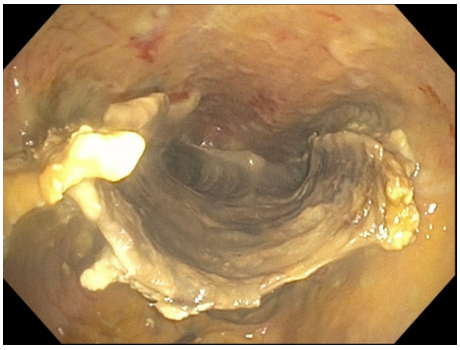

Figure 5: Microscopic examination of the detachment of the entire anterior part of the tracheal mucosa with visualization a pulsatile blood vessel behind the wall.

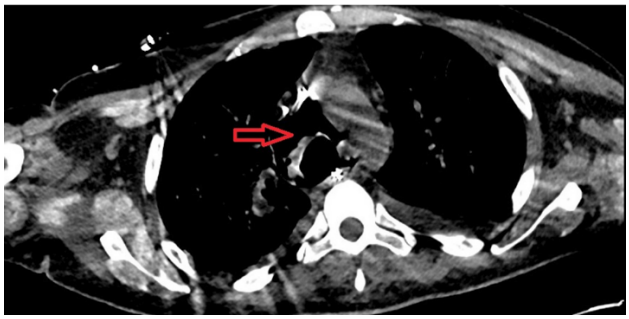

Figure 6: CT Thoracic scanner highlights the complete dehiscence of the anterior wall of the trachea just above the carina, with appearance of pneumomediastinum and pneumopericardium.

Case Report

The patient is a 28 year-old male, without significant comorbidity, who was admitted in the intensive care unit (ICU) for a heatstroke during a football match. He had several seizures on the

field for seven minutes before the arrival of medical rescue and the administration of midazolam. The patient was intubated directly to protect the airway. The suspicion of drug use (amphetamines) was suspected but has never been proved. Following his admission in ICU, the patient quickly developed a multi organs failure, and was transferred in our centre for an emergency liver transplantation, associated with a left hemicolectomy due to an ischemic condition in this area. In this context, the patient was treated by immunosuppress or medication, with administration of Tacrolimus. At first, the therapeutic target dose was 8-10 µg/L before to be revaluated and decreased at 3-4µg/L after fifteen days of treatment. He was also treated with corticosteroids and basiliximab. In total, he therefore benefited from a triple immunosuppressive treatment. Secondary to the heatstroke, he also developed an acute renal failure associated with metabolic acidosis and hyperkalaemia. A continuous vein-venous hemofiltration was thus implemented, which will be continued throughout the duration of his hospitalization. Moreover, he developed a profound circulatory shock, which was treated with high doses of amines (epinephrine, norepinephrine). Other undercurrent pathologies, including an intravascular disseminated coagulation (DIC) (which required multiple blood product transfusions), several skin lesions, and a minimal pneumomediastinum have been reported at the CT thoracic scan. In addition to comorbidities already described above, the patient progressed in a neurological clinical condition close to a minimal conscious state. He was also treated with other antibiotic for multiple pulmonary superinfections. It was decided to realize a tracheostomy because of an estimated duration of mechanical ventilation superior to three weeks. Seven days after admission, and still under mechanical ventilation, the patient developed a pulmonary congestion with right basal rhonchi. The thoracic scanner confirmed an infectious bilateral diffuse neuropathy (Figure 1). A fibro copy was realized, showing a significant blackish deposit all over the trachea up to the carina and in the main bronchus, but with a healthy trachea at the level of the balloon (Figure 2). Besides, bronchi appeared abnormally whiter than usual with mycolic filaments (Figure 3). Finally, the mucosa of bronchioles was strongly hyperaemic. The analyse of samples of endotracheal aspiration and Broncho alveolar lavage showed positive culture for Morales Rhizopus arrhizals (R.oriziae) and the Polymerase Chain Reaction (PCR) was also positive for Morales. The patient was thus treated with antifungal medication such as amphotericin B as a first treatment. Concerning the antifungal therapy, the amphotericin B administered at the dose of 5mg/kg lead to a poor clinical answer after six days of treatment. It was then decided to immediately increase the dose up to 10mg/kg, and associate it with isavuconazole 200mg once a day. We also adjoined amphotericin B in aerosol therapy, on the advice of specialists in fungal infection of Seattle (USA). A surgical debunking was discussed but non performed because of the significant extension of lesions. Indeed, this therapy was considered as too invasive in the global clinical context. Microscopic control realized after six days of treatment showed a suppler blackish cast, even in the upper lobes. (Figure 4). The second endoscopic control, performed two weeks after, showed a detachment of the entire anterior mucosa of the trachea (Figure 5), with visualization of a pulsating vessel trough thinned tissue. Patient remained easy to ventilate despite this endoscopic aspect. A thoracic scanner was carried out and confirmed the complete dehiscence of the anterior tracheal mucosa above the carina, with the occurrence of pneumomediastinum and pneumopericardium (Figure 6). Unfortunately, the patient became destabilized at the respiratory level, shortly after the scanner, leading to his death.

Discussion

The first case of pulmonary mucormycosis was described in 1876, and the end bronchial form was reported in 1959 [4]. Tracheobronchial involvement remains rare, but has been previously reported in the literature [5]. A systematic review from Ruoxi et al. (2018) reported sixty cases of mucormycosis in the tracheobronchial tree. Nevertheless, in all these cases, only ten showed tracheal involvement associated with bronchial lesions [4,6]. In 2022, a study reported two more cases of tracheal involvement of mucormycosis [6]. In conclusion, the tracheal location of the infection appears as a rare described condition. In most cases of fungal affections, underlying conditions predispose the patient to secondary infection. The most common risk factors include diabetes mellitus with or without diabetic ketoacidosis, malnutrition, malignancies (haematological and solid organ tumor), transplant recipients (haematopoietic stem cell and solid organ transplants), renal failure, cirrhosis, Acquired Immunodeficiency Syndrome (AIDS), corticosteroid therapy and neutropenia. However, a significant number of cases have been reported in patients with no underlying disease or risk factors. These patients often suffered of cutaneous mucormycosis after trauma, burns, surgery, use of contaminated dressings and injection [1,3]. The recent COVID-19 pandemic was associated with an increased incidence of mucormycosis including pulmonary mucormycosis [7]. Infection with COVID-19, as well as prolonged treatment with corticosteroids, compromises the immune response and increases the risk of developing opportunistic infections, including those caused by fungi [2]. The main route of infection seems to be through the inhalation of spores from the ambient air, which are then settled on the paranasal sinuses and the lung. Other less encountered routes result from ingestion or direct inoculation through the skin [1]. In case of immunocompromised patients, these innocuous organisms might lead to a devastating and difficult-to-treat opportunistic infection [1]. Several clinical forms of infection could be observed: pulmonary, gastrointestinal, cutaneous, encephalic, and disseminated and rhino cerebral [8].

The last one must be differentiated from allergic fungal sinusitis, which is a non-invasive, local overgrowth on immunocompetent patients [8]. Mucormycosis may also affect the lung parenchyma, the tracheobronchial mucosa or the pleura, could thus be one of the rare causes of black pleural effusion [9]. In our case, the pathway of contamination might be the skin lesions consecutive to the context of contact with the field. It could also be related to the acute renal failure with acidosis and/or the immunosuppressive therapy following the emergency liver transplantation. Histologically, mucormycosis infection is characterized by tissue necrosis due to blood vessel invasion and subsequent thrombosis, which usually follows a rapid progression [10]. Tissue necrosis is pathognomonic of mucormycosis, but the presentation and the diagnostic approach lack sensitivity and specificity [8]. Indeed, we observed this histological finding in our patient, associated with a hyperaemic mucosa and white end bronchial deposits. Other fungal infections, such as Aspergillus or Fusarium, may lead to similar clinical signs. All Morales fungi grow rapidly from three to seven days on most fungal culture media, such as Savoured agar and potato dextrose agar incubated at 25°C to 30°C [8]. For the diagnosis, the most recent recommendations suggest several approaches [10]. Indeed, diagnosis is primarily based on direct examination and culture, both of which are strongly recommended. Direct examination of specimens/samples can be performed using a silver meth enamine stain or fluorescent bleach. Culture could also be really useful because it first allows an accurate identification of the species. A negative culture seems to be related to aggressive treatment of the specimens before plating [10]. In our case, the Morales fungus was isolated and identified from an endotracheal expectoration seven days after the heatstroke. The main problem of these techniques is their lack of sensitivity, knowing that only fifty percent of cases appeared culture-positive [11]. For isolates obtained in culture, molecular identification seems more accurate than morphology [11]. Antifungal susceptibility testing is recommended for better epidemiological knowledge but it is optional recommended for guiding treatment. Histopathology is also strongly recommended. Immunohistochemistry is another possible tool, by using monoclonal antibodies, but must be performed by trained personnel and specialized laboratories [11]. The keys to a successful treatment involve three main aspects: consideration of risk factors and co-morbidities, early and aggressive surgical debridement of infected tissue if possible, and administration of antifungal therapy to control the spread of infection [12]. In this case, we treated the patient with double antifungal intravenous therapy (amphotericin B and isavuconazole), with the adjunction of amphotericin B aerosols. However, it was noticed that these aerosols generated an obstruction of filters of the breathing respiratory circuit. We therefore decided to use the aerosol continuously and change the filter every three hours. Amphotericin B deoxycholate is a very toxic drug, causing cholestasis and renal failure. A monitoring of renal function is therefore crucial [13]. Mucormycosis infections lead to a high mortality rate. The survival rate of patients with mucormycosis without any therapy is estimated at only 3%. A previous review of 929 cases of mucormycosis showed that 96% of patients died with disseminated disease, 85% with gastrointestinal infection, and 76% with pulmonary infection [14]. Another study has shown that patients with limited pulmonary mucormycosis disease tended to have the lowest mortality [15]. Moreover, the mortality rate depends on the site of infection as well as the underlying associated conditions [4]. Patients with symptoms of haemoptysis or dyspnoea would have a high mortality rate in multivariate analysis [4].

Conclusion

Mucormycosis infection appears as a frequent complication in immunocompromised patients. However, the tracheal location remains a rare reported condition. The mortality risk is high, correlated to undercurrent comorbidities of the patient and the route of inoculation. Early diagnosis and aggressive treatment by antifungal therapy and surgery (if feasible) are crucial to expect a favourable issue.

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