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Tracheal, laryngeal and pulmonary mucormycosis followed by organizing pneumonia in a patient with Adult Onset Still's Disease

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ABSTRACT

We report a case of tracheal, laryngeal and pulmonary mucormycosis in a patient receiving immunosuppressive medication for an autoinflammatory fever syndrome. Mucormycosis was confirmed by histopathology from tracheal specimens and molecular evidence of Lichtheimia.

A surgical approach was not possible because of the multifocal disease pattern and the extent of tracheal involvement. The patient was successfully treated with liposomal amphotericin B followed by posaconazole maintenance therapy. After 9 months, recurrent pulmonary mucormycosis was suspected but emerged as organizing pneumonia without evidence of active fungal infection.

1. Introduction

Invasive mucormycosis (formerly known as zygomycosis) is an often fatal opportunistic infection caused by fungi belonging to the ubiquitous order Mucorales. Underlying conditions include hematologic malignancies, immunosuppressive pharmacotherapy, diabetes and trauma. Pulmonary disease, caused by inhalation of asexual spores, is among the most common manifestations and is associated with high mortality, reaching up to 56% [1]. Tracheal and laryngeal mucormycosis have rarely been described and can lead to local complications, such as airway obstruction and cartilage damage [2–4]. Clinical guidelines for the diagnosis and management of mucormycosis were published in 2014. Diagnosis is usually based on direct microscopy of clinical specimens, histopathology and culture. The reversal of predisposing factors and surgical debridement in addition to liposomal amphotericin B are recommended as first-line therapies, and posaconazole is recommended for salvage treatment [5].

2. Case

A 74-year-old male was referred after ineffective antibacterial therapy for pneumonia. He had a 12-year-history of glucocorticoid use for an autoinflammatory fever syndrome classified as Adult Onset Sill´s Disease (AOSD). He had received prednisolone pulse therapy at 0.6 mg/kg/d for 7 days (d − 72 to day − 66) and was on 5 mg/day at admission (day − 8). There had been molecular evidence of respiratory infection with Influenza H1N1/09 infection (day − 60), which had not been treated specifically. Empiric antibiotic treatment regimens had included cefuroxime, clarithromycin and levofloxacin. The patient presented a slightly reduced general condition with persistent cough, hemoptysis, chest pain, hoarseness and weight loss (5 kg in 2 months). He was afebrile, had no dyspnea and there were no rales or wheezes on lung auscultation. Blood pressure was 125/75 mmHg, heart rate was 100/min and respiratory rate was 18/min.

The blood C-reactive peptide (CRP) level was > 400 mg/L in the absence of leucocytosis and procalcitonin elevation. There was no serologic evidence of invasive aspergillosis. Blood gas analysis was unremarkable at admission and during the hospital course. Selected laboratory parameters are shown in Table 1. Chest radiography (day − 8) demonstrated infiltrates in the left upper and lower lobe (Fig. 1**A**). Contrast-enhanced computed tomography (CT) at day − 7 revealed left upper lobe consolidation, small cavitary lesions in the right upper lobe

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Table 1
Selected laboratory test results before and during antifungal treatment. Liver enzymes and blood gas analysis were unremarkable at all times and are not reported. Renal function deteriorates with liposomal amphotericin B administration (day + 21), resulting in renal failure at day + 42 with concomitant bacterial infection. Posaconazole maintenance therapy was started at day + 62.

Selected parameter and unit	day − 3	Day + 20	Day + 42	Day + 62	Day + 124
Leukocytes $\times 10^9$/L	4.64	3.95	7.88	4.06	7.59
Segmented Granulocytes %	35		81	54	
Lymphocytes %	46		14	29	
Monocytes %	13		3	8	
Eosinophils %	5		1	9	
Hemoglobin mmol/L	6.4	5.0	5.9	4.9	7.0
C-reactive protein (CRP) mg/L	446	130	622	179	< 3
Procalcitonin µg/L	0.09		1.49	0.2	
Creatinine µmol/L	105	166	501	177	115
GFR (CKD-EPI) ml/min/1.73^{2}m	60	35	10	32	54
Aspergillus-Ag (galacto-mannan)	Negative				
Aspergillus antibody titer (indirect hemagglutinin test)	1: < 80				

and irregularities of the posterior tracheal wall (Fig. 1**B**). The corresponding finding on tracheobronchoscopy (Fig. 2**A-C**) was a necrotic alteration comprising the lower two-thirds of the pars membranacea. A whitish plaque was noted on the left vocal cord and an ulcerating lesion was found at the ostium of the left S3 bronchus (day − 7). Histopathology from tracheal tissue samples provided evidence of necrotizing inflammation and invasion of non-septate fungal hyphae with wide-angled branching (Fig. 3**A-C**), prompting the diagnosis of mucormycosis. Microscopy and culture from transbronchial lung biopsies and bronchoalveolar lavage (BAL) fluid remained non-diagnostic. Molecular methods were not available at day 0. Semi-nested polymerase chain reaction (PCR) was carried out on formalin-fixed paraffin-embedded tissue specimens from the trachea, when genus identification was sought months later. 18s-ribosomal DNA of *Lichtheimia* was detected (PCR protocol according to [6], day + 208). Due to a lack of sequence specificity, identification of the species was not possible.

After the patient had received empirical antifungal therapy (voriconazol 2 × 250 mg/day) between day − 21 and day − 14, targeted therapy was started with liposomal amphotericin B at a dose of 3 mg/kg/day (day 0). A surgical approach did not seem appropriate because of the multifocal disease pattern and the extent of tracheal disease. At day + 20, dose reduction became necessary due to an increased serum creatinine level and hypokalemia. Improvement of the radiologic and endoscopic findings was noted, but at day + 42, bacterial infection with evidence of *Enterobacter cloacae* in respiratory specimens and acute renal failure had developed (Table 1).

These complications were successfully managed, including the administration of piperacillin/tazobactam, while no antifungal therapy was applied between day + 42 and day + 62. Oral posaconazole (300 mg once daily) was established as an antifungal maintenance therapy at day + 63. Eight weeks later (day + 124), the patient presented in good a condition. His symptoms had resolved and laboratory findings were unremarkable except for a mild elevation of serum creatinine. Radiological findings had improved substantially (Fig. 4**a, b**). Endoscopy showed remission of the tracheal (Fig. 4**c**), laryngeal and endobronchial alterations. As no significant adverse drug reactions had occurred, antifungal therapy was continued. A maintenance dose of 4 mg prednisolone was considered necessary by the patient´s rheumatologist.

The patient was followed up with chest radiography, laboratory tests and bronchoscopy every two months. At day + 306, the patient was hospitalized with increasing dyspnea and treated with piperacillin/tazobactam for suspected pneumonia before being referred to our hospital again. Imaging at day + 316 and day + 321 showed progressive bilateral pulmonary consolidations, predominantly in the right upper lobe (Figs. 5**a,** 6**a**). Tracheobronchoscopy was unremarkable. BAL and transbronchial lung biopsy depicted no causative organism. Histology revealed intra-alveolar granulation tissue consistent with organizing pneumonia (OP). Antifungal therapy was terminated at day + 321 and the patient was started on prednisolone (beginning at 0.5 mg/kg prednisolone per day), which led to a gradual remission of the consolidations (Fig. 6**a-c**). At the last follow-up 8 months later (day + 522) the patient was well and there were no signs of recurrent fungal infection, but he still required steroids for control of his autoinflammatory disease.

3. Discussion

The presented case illustrates a variety of manifestations of mucormycosis in the respiratory system. Diagnosis was delayed because bronchoscopy was not conducted in a timely manner. However, medical management with liposomal amphotericin B and posaconazole led to a favorable outcome. In contrast, in six of seven other previously reported cases of tracheal mucormycosis, endoscopic debridement [4] or surgical debridement and/or resection [2,3,7–9] were performed in addition to conventional or liposomal amphotericin B. Five of these six

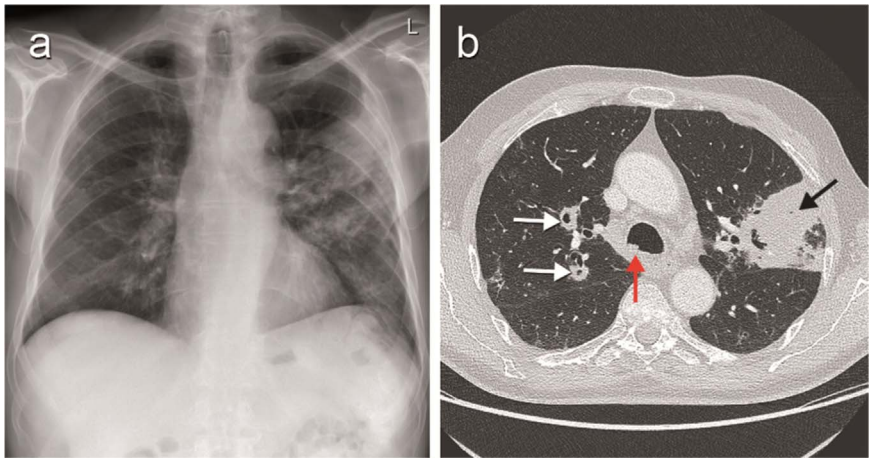

Fig. 1. a: Chest radiograph showing opacities in the left upper lobe, lingula and lower lobe. **b:** Contrast-enhanced computed tomography of the chest showing left upper lobe consolidation (segment 2, black arrow), right upper lobe cavities within foci of consolidation, measuring up to 1.5 cm in diameter (white arrows), and irregularities of the posterior tracheal wall (red arrow).

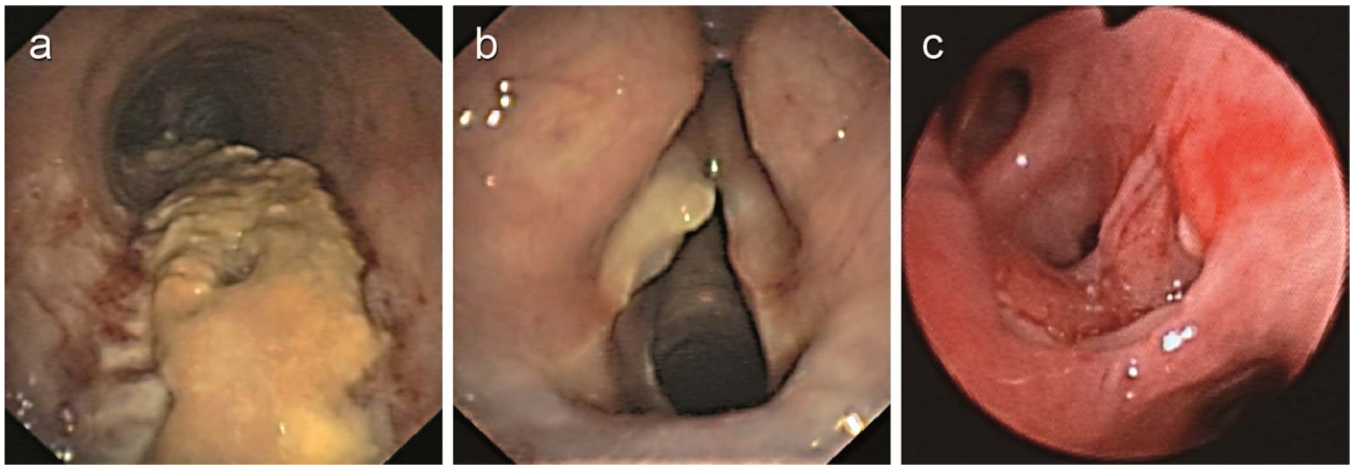

Fig. 2. a: Tracheobronchoscopy demonstrating an endotracheal necrotic mass and mucosal erythema, reaching the carina. **b** Fibrinous plaque on the left vocal cord and minor accordant alteration of the right vocal cord. **c:** Ulcerating lesion at the ostium of the left S3 bronchus, surrounded by vulnerable and hemorrhagic mucosa.

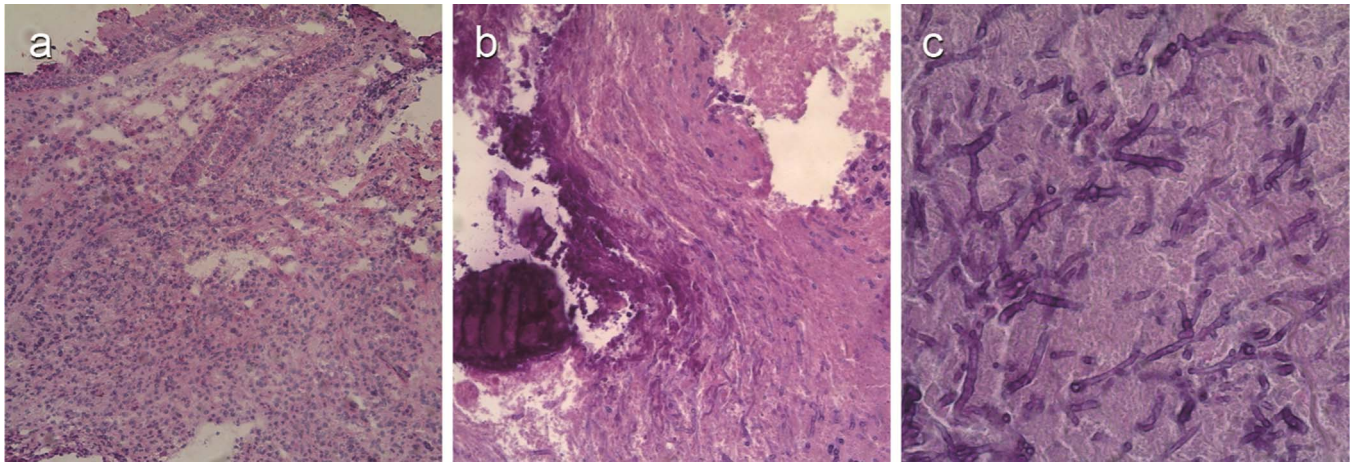

Fig. 3. a: Tracheal mucosa with inflammatory cell infiltration (carina, Hematoxylin-Eosin stain, frozen Section, 100×). **b**: Necrosis, regressive calcifications (deep purple) and fungal hyphae (trachea, hematoxylin-eosin stain, 100×). **c**: Fungal hyphae with few or no septae, 10–25 μm in width, featuring irregular and wide-angled branching (Trachea, periodic acid-Schiff stain, 200×).

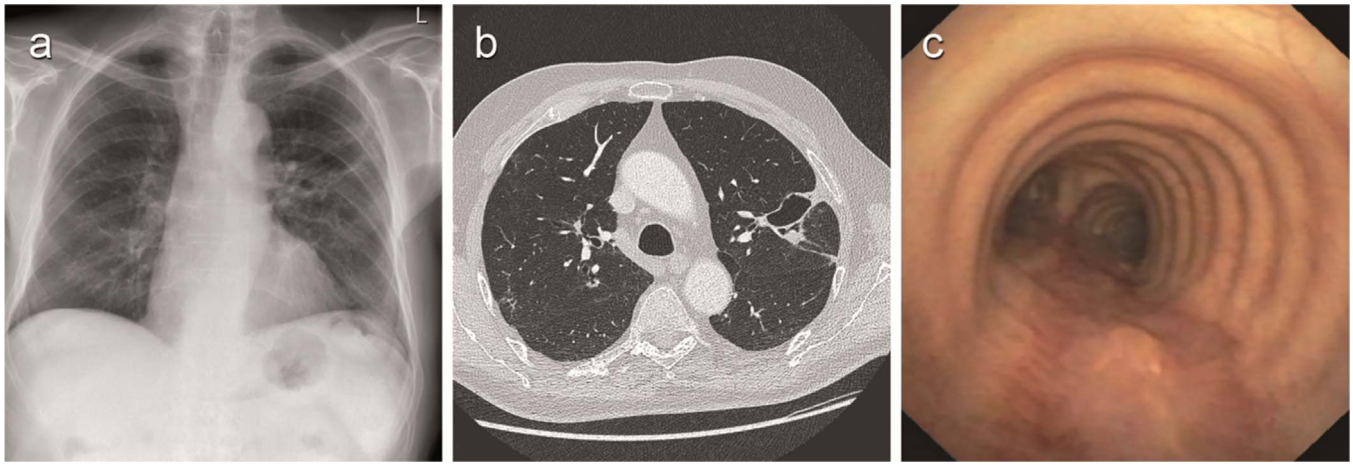

Fig. 4. a: Chest radiograph showing response to antifungal treatment at day + 124. **b:** Contrast-enhanced computed tomography of the chest demonstrating subtotal resolution of the left upper lobe consolidation with adjacent pneumatocele (day + 125). **c:** Tracheobronchoscopy showing considerable improvement with a residual, solid, circumscribed mucosal elevation (day + 126).

patients survived, but two of them retained a tracheostomy after 4 months and 9 months, respectively [8,9]. Only one patient developed a fulminant disease course and died before any surgical intervention could be attempted [10].

Although in the presented case the pathogen could not be isolated from peripheral lung biopsies or BAL fluid, proof of tracheal mucormycosis strongly suggested pulmonary involvement. Considering the abnormal computertomographic findings and the relative frequency of

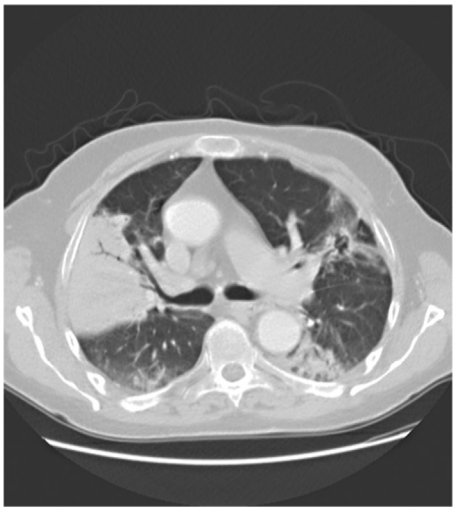

Fig. 5. a: Contrast-enhanced computed tomography of the chest showing bilateral consolidations with predominant subpleural distribution, most extensive in the right upper lobe, with air bronchogram (day + 321).

pulmonary mucormycosis, a CT-guided lung biopsy was considered dispensable.

Whereas immunosuppressive medication is a recognized risk factor for fungal infection, the role of the precedent influenza H1N1 infection is uncertain. Invasive fungal disease has been linked to H1N1 infection by some authors [11–13] and H1N1 pneumonia preceded a case of tracheal mucormycosis reported by Mohindra and co-authors [8].

The clinical presentation of pulmonary and respiratory tract mucormycosis is non-specific. Cough, fever, hemoptysis and dyspnea are the most common symptoms, but in a recent retrospective study including 35 patients, 11% were asymptomatic [14]. Radiological features in pulmonary mucormycosis are also non-specific and numerous findings have been described, including consolidation, cavitations, nodular infiltrates, ground glass opacities, the reversed halo sign and pleural effusion [14,15]. In a literature review describing endoscopic findings in pulmonary mucormycosis, endobronchial lesions occurred in 34 of 35 patients. Bronchial stenosis and obstruction, erythema, exsudates and fungating or polypoid mass were the most common findings, however; ulceration, tracheitis and plaques were also found [15].

Histopathologic examination of affected tissue samples is the most important procedure for diagnosing mucomycosis. Mucorales possess broad, wide-angled hyphae with few or no septae. These distinct morphologic features facilitate discrimination from other molds, primarily aspergillus. This differentiation is of particular importance, because voriconazole and echinocandins are not effective against Mucorales. Angioinvasion and necrosis are characteristic histopathological patterns. Culturing allows genus and species identification and drug susceptibility testing, but its sensitivity is not optimal. In cases with positive cultures, *Rhizopus* species, *Mucor* species and *Lichtheimia species* were the most commonly identified genera in a European registry study. *Lichtheimia* species (commonly *L. corymbifera* and *L. ramosa*) accounted for 19% of all mucormycoses [1]. PCR targeting the 18S-ribosomal DNA of Mucorales has higher sensitivity than cultures [16] but no assays are commercially available. Genus and species identification usually does not guide therapeutic management at this time, but helps to enhance epidemiological knowledge.

Whereas the use of polyenes, such as Amphotericin B, is often limited by severe adverse drug effects, azoles usually have acceptable toxicity profiles. In the presented case, despite precautious dosing (3 mg/kg instead of 5 mg/kg), liposomal Amphotericin B had to be discontinued after 6 weeks. Between day + 42 and day + 62, no antifungal treatment was given due to bacterial infection and acute renal failure. Posaconazole maintenance therapy was well tolerated for 9 months. No adverse events were reported and there was no indication of liver injury. No prospective studies have been undertaken to investigate optimal treatment duration and risk of recurrence in mucormycosis. According to current clinical guidelines, antifungal treatment should be sustained until a complete response is confirmed on imaging and a permanent reversal of predisposing factors is achieved [5]. However, adequately timing the withdrawal of antifungal therapy is challenging and remains a highly individualized decision.

Organizing pneumonia (OP) is defined pathologically by the presence of granulation tissue in distal air spaces, containing fibrin exsudates, loose collagen and fibroblasts. It reflects a non-specific inflammatory process resulting from different types of lung injury. OP is most commonly associated with infection, connective tissue disorders, vasculitis or drugs [17]. Fungal pathogens that have been reported in this context are Cryptococcus neoformans, Pneumocystis jiroveci and Aspergillus [17–20]. Organizing pneumonia has also been described as a form of lung involvement in patients with AOSD [21]. As it is not possible to differentiate between organizing pneumonia and active infection on diagnostic imaging, careful histological clarification is essential [22]. Steroid therapy is the treatment of choice and, as seen in this case, the excellent response can confirm the diagnosis clinically.

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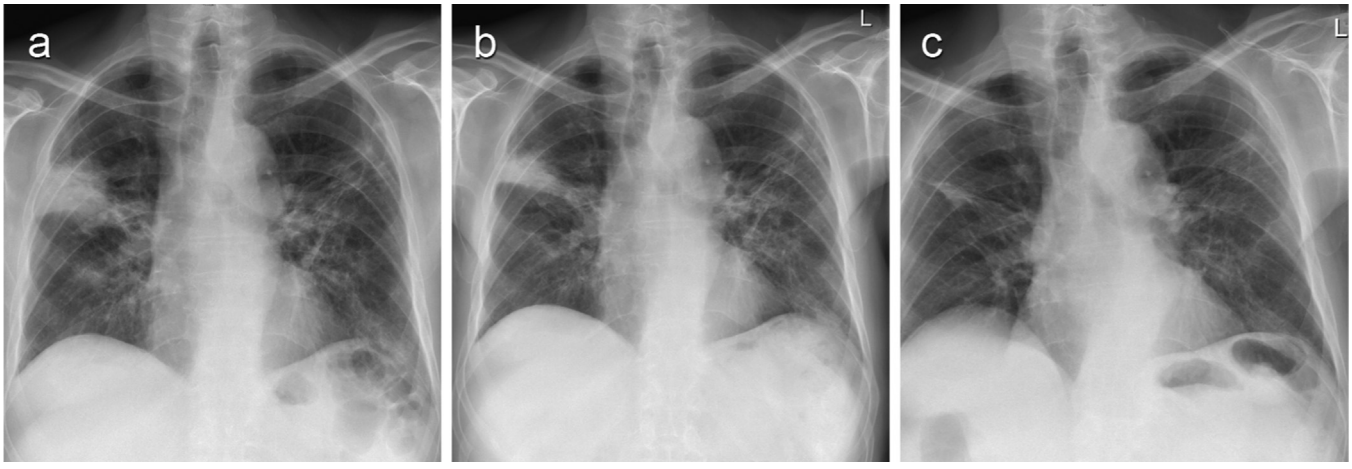

Fig. 6. a: Chest radiography before corticosteroid treatment (day + 316). **b:** Chest radiography after 14 days of prednisolone therapy (at 40 mg/day) **c:** Chest radiography after 8 months of prednisolone therapy (at 5 mg/day).

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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