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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

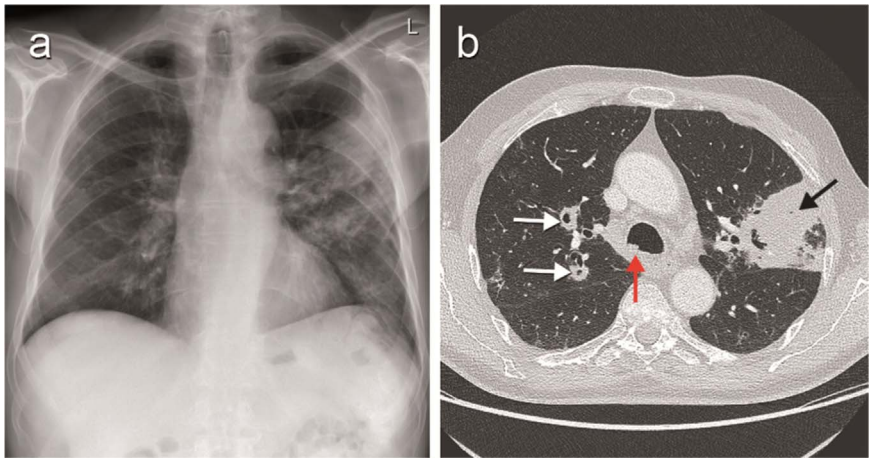


**Fig. 1. a:** Chest radiograph showing opacities in the left upper lobe, lingula and lower lobe. **b:** Contrast-enhanced computed tomography of the chest showing left upper lobe consolidation (segment 2, black arrow), right upper lobe cavities within foci of consolidation, measuring up to 1.5 cm in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