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## Case report

## A case of Covid-19-associated invasive pulmonary mucormycosis in a pediatric patient with a newly diagnosed diabetes

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## ABSTRACT

Mucormycosis is a rare, potentially life-threatening disease that is growing during the Covid-19 pandemic. This study reports a case of an 11-year-old patient with fatal Covid-19-related pulmonary mucormycosis and diabetes mellitus with ketoacidosis. The diagnosis was set post mortem. It was based on histochemical detection of the causative agent. Massive hemoptysis due to erosion of a large pulmonary vessel caused mechanical asphyxia and lethal outcome. Pulmonary mucormycosis may be highly suspected in patients with long-term Covid-19, poorly controlled diabetes mellitus with ketoacidosis, and corticosteroid therapy. Early diagnosis and treatment with Amphotericin B are potentially curative options for this invasive fungal infection and can lead to better outcome.

## 1. Background

Mucormycosis (previously called zygomycosis) is a general term for a group of rare invasive infections caused by molds called mucormyces, order Mucorales [1]. The Covid-19 pandemic has led to increase in mucormycosis. According to data from a multicenter retrospective study across India Covid-19-associated mucormycosis (CAM) prevalence has been 0,27% among hospitalized Covid-19 patients [2]. Mucormycosis is an aggressive life-threatening infection that most commonly affects immunocompromised individuals and carries a significant risk of mortality. It is an angioinvasive disease. Vascular invasion by hyphae and subsequent thrombosis cause rapid necrosis of the involved tissue [3]. Clinical presentation is classified according to the organ involvement. It can be: rhino-cerebral – the most common; pulmonary; cutaneous; gastrointestinal; disseminated [4]. Pulmonary mucormycosis is often a rapidly progressive disease characterized by fever, non-productive cough, chest pain, dyspnea, and less often haemoptysis [5]. Predisposing factors for CAM include: poorly controlled diabetes mellitus especially associated with ketoacidosis; long-term corticosteroid therapy; hemochromatosis; prolonged hospitalization; neutropenia; hematologic malignancies; solid organ transplantation; trauma [6].

Diagnosis of mucormycosis is challenging because the symptoms are common to many other diseases. The overall mortality rate improved from 84% in the 1950's to 47% in 1990's. Nowadays decreased risk of mortality - 29–38% - is associated with early treatment with Amphotericin B lipid formulation [7].

**The aim** of this study is to highlight the need for a high clinical suspicion for fungal infection in pediatric patients with Diabetes mellitus and Covid-19 infection.

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## 2. Case presentation

SNM was an 11-year-old boy who presented to the clinic of Infectious diseases on Aug. 30-th, 2021 with a 3-month history of increased thirst, frequent urination, unexplained weight loss of about 10 kg and frequent respiratory infections. He was managed as an outpatient. Blood analysis and chest X-ray screening were not made. In the last week he had low-grade fever, abdominal pain and fatigue. The patient was admitted in a generally bad condition, febrile with a fruity scented breath and deep gasping breathing. The blood and urine changes were consistent with those of diabetic ketoacidosis. There were mild elevated inflammatory markers as CRP 122,5 mg/L, leucocyte count  $30,1 \cdot 10^9/L$  with shift to the left – 73% of neutrophils, 14% of lymphocytes and fibrinogen 4,9 g/L. The arterial blood gas tests were normal. Oxygen saturation was 96–98% on room air. Both the rapid antigen test and the PCR test were positive for SARS-CoV-2. Auscultation findings included wheezing and fine moist rales in the lung basis.

Chest X-ray and CT images revealed bilateral ground-glass opacities of the 9<sup>th</sup> and 10<sup>th</sup> lung segments, enlarged thymus and a congenital malformation – double tracheal carina. Treatment with Ceftriaxone, Methylprednisolone, Antistenocardin was initiated. The patient was treated symptomatically as well.

Blood glucose levels and metabolic acidosis were monitored and corrected. Based on the consultation with pediatrician-endocrinologist a strategy for diabetes mellitus treatment was recommended. The patient was discharged after a hospital stay of 18 days in a general improved condition, afebrile with reduced cough. Further treatment with Clarithromycin and immunomodulatory drugs had been prescribed.

Three days later – on Sep, 20<sup>th</sup> the patient worsened suddenly with fever, cough and shortness of breath. He was admitted again with clinical manifestation of an acute respiratory distress. Respiratory rate was 38–48/min, heart rate –148/min, RR 120/80 mm Hg. He was hypoxemic with a SpO<sub>2</sub> of 78–80% on room air and with a SpO<sub>2</sub> 98% on 6 L Oxygen. Auscultation findings included a great amount of wheezing, crackling and bubbling rales. Electrocardiography and echocardiography, blood tests, including CRP, leucocytes and fibrinogen were normal. Treatment with Methylprednisolone, Budesonide, Oxygen via mask, Meropenem, Furosemide, Aspirin and Captopril was started. Even with this aggressive therapy clinical signs of an acute respiratory distress progressed.

CT images showed an endotracheal pericarinal solid lesion with a density of 40 Hounsfield units in the lower tracheal segments. It was adjacent to the right tracheal wall and protruded into the bifurcation and the right main bronchus. The tracheal lumen in the middle segments was narrowed to 4,3 mm. Fig. 1a and b.

CT images arose a suspicion of solid neoplasma, corpus alienum tracheae and benign inflammatory or fibrous adhesions. The need of surgical treatment was discussed. Massive hemoptysis due to erosion of a large pulmonary vessel causes mechanical asphyxia and death.

The case was diagnosed with mucormycosis post mortem. Autopsy revealed a greyish-white solid lesion located near the tracheal bifurcation, ranged in size from 4,0 to 4,1 cm. It protruded into the luminal surface of the trachea caused necrosis of the tracheal wall and eroded an arterial vessel. A congenital malformation – double carina, enlarged thymus and enlarged chest lymph nodes with central necrosis were identified. Tissue necrosis is the hallmark of mucormycosis. Vascular involvement of a large arterial vessel may be a cause of fatal hemoptysis. Samples of the endotracheal lesion and the affected lymph nodes were analyzed. The prompt diagnosis was set on ground of the histochemical detection of the etiological agent. Figs. 2 and 3. The presented case is a good illustration for rapid arterial invasion in pulmonary mucormycosis causing fatal hemoptysis.



Fig. 1a. CT of the lungs, axial projection. Deformed and stenosed carina.



Fig. 1b. CT on the lungs, coronary reconstruction. Stenotic changes in the distal part of the trachea, carina and main bronchi.

### 3. Discussion

Mucormycosis is a rare life-threatening fungal disease and early detection of the infection is the key of treatment. Current knowledge of pediatric mucormycosis is based on case-reports and small series reported over several decades. Contemporary data on a large cohort of patients is lacking [8]. In children zygomycosis may occur in a similar settings to those seen in adults. Median age is 13 years with a slight predominance of female [8]. Mean age of adult patients with CAM, predominantly males is 57,5 (22–86) years [1,9]. The described case is an 11-year-old boy. Covid-associated mucormycosis patients are classified according to timing of onset: early  $\leq 7$  days after Covid-19 diagnosis and late  $\geq 8$  days after Covid –19 diagnosis [2]. The median time to CAM diagnosis is 18 (11–27) days. Clinical signs include: fever, cough, dyspnea and hemoptysis [10]. The onset of CAM in our patient was unknown, but clinical manifestations were similar. Most of the sources available in the literature comment on isolated cases of tracheal involvement in invasive mucormycosis. It is a rare form of the disease with high mortality due to non-specific clinical manifestations and various predisposing factors [11].

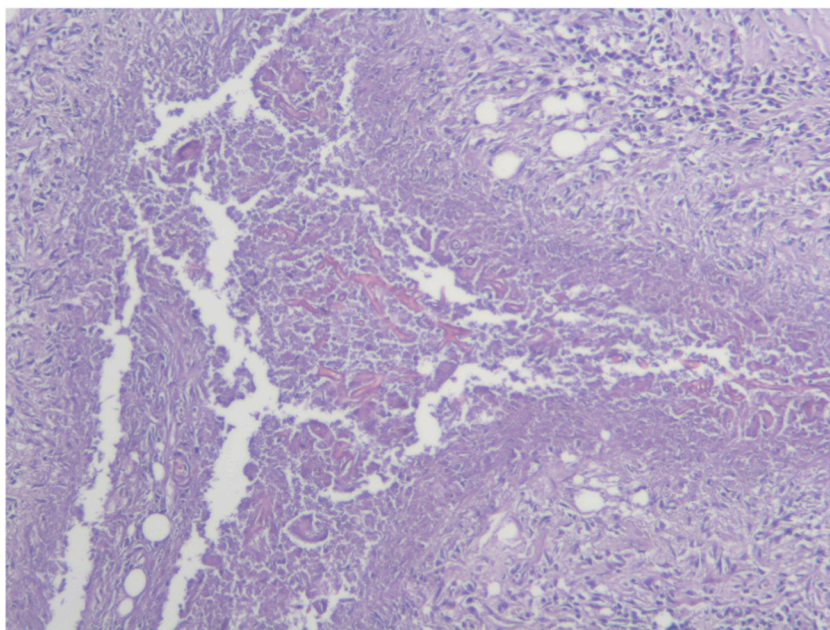
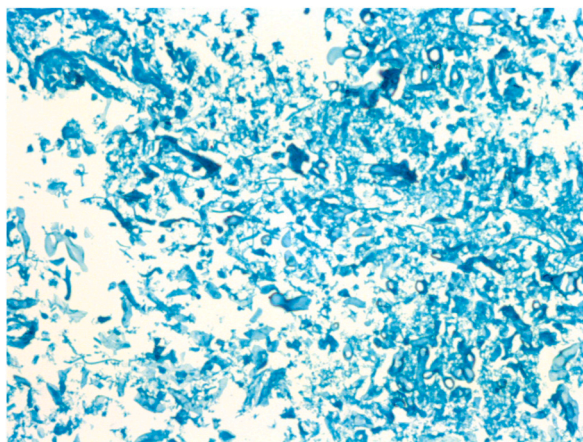


Fig. 2. Mucormycosis granuloma with central necrosis mycotic right-angle branchings in trachea. H&E Magnification  $\times 200$ .



**Fig. 3.** Mucormycosis - pseudomembrane over the bronchial mucosa containing cellular debris from necrotic mucosa, fibrin and fungal particles. Grocott Magnification  $\times 200$ .

Recent reports suggest that patients with Covid-19 associated pulmonary mucormycosis have a mortality rate 46–96% [12]. Mucorales are observed in rather heterogenic pediatric population with a wide spectrum of organ involvement. Disseminated mucormycosis present in 38%, lung mucormycosis – in 19% [8]. Patients with malignant hematological disorders and severe neutropenia are at great risk for developing pulmonary mucormycosis [13]. The progression of lymphopenia correlates with Covid-19 severity [14]. Our patient was not neutropenic. On admission he had a mild lymphopenia – 14,2%, which was corrected within a week.

Severe Covid-19 is currently managed with systemic corticosteroids. Opportunistic fungal infections are of concern in such condition. Uncontrolled diabetes mellitus is the most commonly reported underlying risk factor for CAM. Comorbidity of diabetes mellitus and mucormycosis is 9–36% [15]. Some authors report comorbidity of 50% [16].

SNM presented to the clinic of Infectious diseases with newly diagnosed diabetes mellitus with ketoacidosis. He was treated with a Methylprednisolone in a daily dose of 1 mg per kg body weight for a period of 8 days. Imaging features in pulmonary mucormycosis are non-specific. Radiological manifestation include infiltrates, exudation, consolidation, cavities and nodules [17]. The initial radiological image and chest CT scan showed bilateral changes of the “ground glass opacities” which are most often consistent with Covid-19. Imaging findings that suggest the diagnosis play an important role in the management of these patients but the gold standard for the diagnosis of pulmonary mucormycosis is histopathology [18]. In the reported case the etiological agent was detected histochemically in samples of the affected tissue.

Treatment usually consists of antifungal medications, surgery and controlling underlying immunocompromising conditions. Amphotericin B lipid formula is the drug of choice and needs to be initiated so early as possible [19]. SNM was not treated with Amphotericin B as the diagnosis was set post mortem.

Diagnosis of Mucormycosis remains challenging. Histopathology, direct examination and culture remain mainstay although the newer tools like genetic-molecular methods are improving [20]. The identification of the exact species that cause mucormycosis is not straight forward due to the difficulty of isolating the fungus in culture media. However regardless of the causative species and clinical presentation therapeutic management is the same [21].

#### 4. Conclusion

Mucormycosis has emerged as a rare but frequently fatal invasive fungal disease. The epidemiology and management of pediatric pulmonary mucormycosis is poorly described. The initial work up to the patient did not include mucormycosis as a part of differential diagnosis and delayed treatment. No such case has been described so far. In our opinion this is the first diagnosed case of Covid-19 associated pulmonary mucormycosis in a pediatric patient. In the current pandemic the comorbidity of Covid-19 infection, diabetes mellitus especially in ketoacidosis and prolonged steroid therapy is a serious risk for this rare fungal infection. None of the listed underlying conditions and medications like steroids and broad-spectrum antibiotics should be ignored in assessing a Covid-19 positive patients of any age. Inter professional management consisted of high-trained specialists sometimes is not enough for the benign prognosis. A combined approach of treatment – antifungal and surgery is associated with improved outcomes in adults and children.

#### Submission declaration and verification

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Liliya Pekova, Svetla Angelova and Maya Gulubova. The first draft of the manuscript was written by Liliya Pekova and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

We declare that the material described is not under publication or consideration for publication elsewhere.

## Declaration of competing interest

There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

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