

Clinical characteristics and prognoses of pulmonary mucormycosis in four children

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ABSTRACT

Importance: Pulmonary mucormycosis is life threatening and carries a poor prognosis. Identification of factors that improve prognosis is urgently necessary.

Objective: To analyze the clinical features and outcomes of pulmonary mucormycosis in children.

Methods: A retrospective analysis of clinical data of four cases with pulmonary mucormycosis was conducted in Beijing Children's Hospital from January 2017 to December 2018.

Results: Underlying diseases were identified in all four cases (diabetes in three individuals and a hematological malignancy in one individual). The predominant clinical manifestations were fever, cough, chest pain and hemoptysis. Imaging features included consolidation or nodules with cavities. All four cases were treated with liposomal amphotericin B, one case underwent lobectomy, and three cases received a full course of posaconazole. All four cases were cured.

Interpretation: Patients with pulmonary mucormycosis often have underlying diseases. Imaging features are relatively characteristic. Treatment with liposomal amphotericin B at an early stage and a sufficient course of posaconazole for maintenance significantly improves prognosis.

KEYWORDS

Pulmonary mucormycosis, Liposomal amphotericin B, Posaconazole, Prognosis

INTRODUCTION

Mucormycosis is an opportunistic infection caused by fungi of the order Mucorales. It has emerged as a rare but severe disease. Almost all patients with invasive mucormycosis have an underlying disease that both predisposes them to infection and influences clinical presentation; these include diabetes, hematological malignancy, voriconazole therapy, and neutropenia.¹ Mucormycosis can be characterized by infection of the rhino-orbital-cerebral area, lungs,

gastrointestinal tract, skin and kidneys. The disease progresses quickly, with rapid invasion of blood vessels and multi-organ dissemination. Previous studies indicated a poor prognosis of mucormycosis in adults, especially of pulmonary mucormycosis and disseminated mucormycosis, with case mortality over 90%.^{2,3} Although prognoses have improved due to improvements in early diagnosis and comprehensive treatment, overall mortality is still over 50% in adults.⁴ The prognoses of children with mucormycosis pneumonia were better, but mortality was still over 30%.^{5,6} However, four children with pulmonary

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mucormycosis in our hospital all survived. Here, we summarized the clinical features and treatment of these four cases.

METHODS

Four children were diagnosed with pulmonary mucormycosis in Beijing Children's Hospital from January 2017 to December 2018, including two proven and two probable cases. All cases met the criteria outlined in the guidelines for the diagnosis and treatment of invasive pulmonary fungal infections in children of the Respiratory Diseases Subspecialty Group, Society of Pediatrics, Chinese Medical Association.⁷ Similar diagnostic criteria were outlined in the European consensus (the revised 2008 EORTC/MSG definitions).⁸

This was a retrospective analysis. Clinical data were collected for all four children including age, sex, underlying diseases, clinical manifestations, imaging data, pathogen identification, treatment, and prognosis.

RESULTS

Clinical features

The four patients included one male and three females, and their ages ranged from 2 to 13 years. All four patients had underlying diseases: three patients had diabetic ketosis, and one patient had acute lymphoblastic leukemia and was treated with voriconazole chemotherapy. All four children had fever and cough with little sputum. The three diabetic patients also presented with drowsiness, coma, and dehydration, and were diagnosed with diabetic ketoacidosis. Two of the three patients had no previous

history of diabetes mellitus. The third patient presented with massive hemoptysis (more than 1100 mL within 2 days). The fourth patient had a pulmonary embolism and presented chest pain and dyspnea. Two patients had moist rales and one also had wheezing (Table 1).

Imaging findings

Lung consolidation in the right lower or left upper quadrant was apparent in all four cases. Cavities inside areas of consolidation or nodules were observed in three patients. The third patient presented with a reversed halo sign accompanied by pulmonary hemorrhage and pseudoaneurysm formation (Figure 1). The fourth patient had pulmonary embolism and hydropneumothorax. Moreover, one patient presented with typical tissue granuloma under bronchoscopy (Figure 2).

Pathogenic examination

Mucormycosis was confirmed using lung tissue from lobectomy in the third patient (Figure 3) and necrotic tissue from the bronchial lumen in the fourth patient. *Rhizopus* was cultured from bronchoalveolar lavage fluid of the first patient, and the mycelium of Mucorales was identified in the bronchoalveolar lavage fluid smear of the second patient.

Treatment and prognosis

Liposomal amphotericin B was administered to all four cases (2–4 mg·kg⁻¹·d⁻¹). Liposomal amphotericin B monotherapy was used to treat the first patient, and combination therapy with liposomal amphotericin B and posaconazole was initially given to the second, third, and fourth patients. The third patient underwent lobectomy

TABLE 1 Specific information of four children with pulmonary mucormycosis

Patient	Gender/ Age (years)	Underlying disease or risk factor	Symptoms and signs	Chest CT	Pathogen obtaining	Treatment	Prognosis
1	Male/2	Diabetes	Fever Cough Moist rales	Consolidation Nodules Cavities	BALF culture	Amphotericin B liposomes	Cured
2	Female/13	Diabetes	Fever Cough	Consolidation Cavities	BALF smear	Amphotericin B liposomes posaconazole	Cured
3	Female/13	Diabetes	Fever Cough Hemoptysis Moist rales Wheeze	Consolidation Cavities Spherical lesions Pseudoaneurysm Hemorrhage Reversed halo sign	Tissue from lobectomy	Lobectomy Amphotericin B liposomes posaconazole	Cured
4	Female/2	Malignant hematoma; voriconazole therapy	Fever Cough Chest pain Dyspnea	Consolidation Hydropneumothorax	Necrotic tissue from bronchoscopy	Amphotericin B liposomes Posaconazole	Cured

BALF, bronchoalveolar lavage fluid.

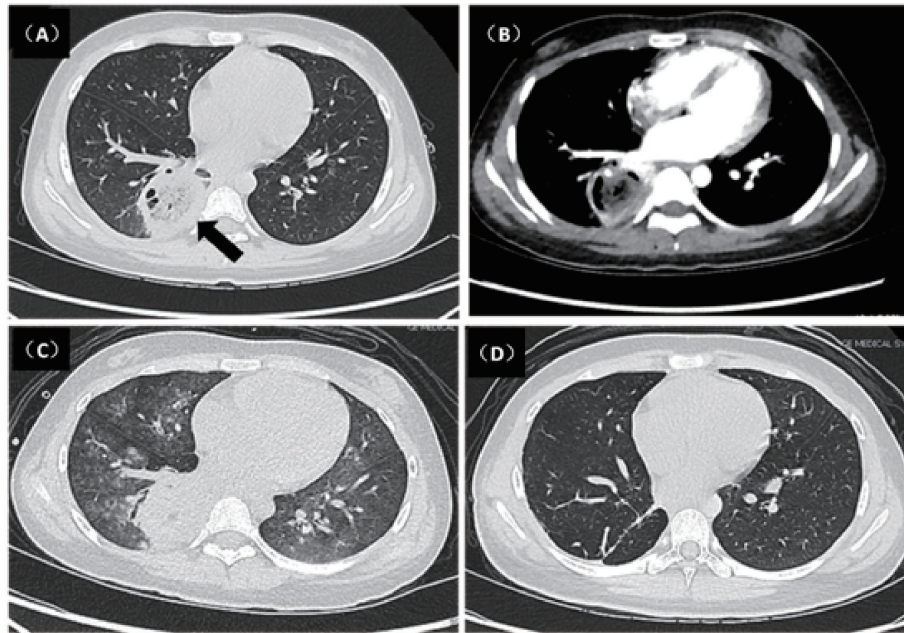


FIGURE 1 Chest CT findings of the third patient with pulmonary mucormycosis. (A) On admission: consolidation with cavities (the arrow points to reversed halo sign). (B) On admission: pseudoaneurysm formation. (C) Hemoptysis: ground-glass opacity. (D) After lobectomy and 10-month antifungal therapy.

due to massive hemoptysis, and the second, third, and fourth patients were given a full course of posaconazole maintenance treatment until symptoms and signs disappeared completely and imaging improved significantly (> 34 kg, 200 mg four times daily; ≤ 34 kg, 24 mg·kg⁻¹·d⁻¹ given in four doses; total treatment course longer than 6 months). All four cases were cured. Symptoms and signs disappeared, and the lesions were essentially absorbed as observed by radiography. All patients were followed up for more than 6 months without recurrence.

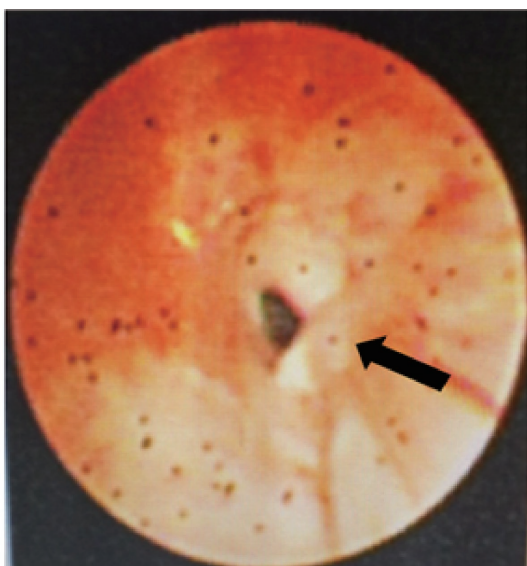


FIGURE 2 Tissue granuloma under bronchoscopy of one patient with pulmonary mucormycosis.

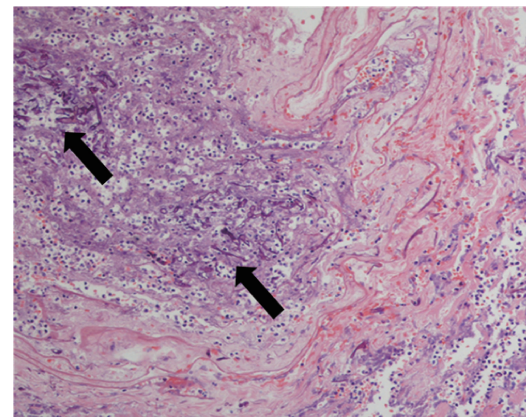


FIGURE 3 Lung tissue pathological findings of the third patient with pulmonary mucormycosis (Hematoxylin-eosin stain; the arrows point to the mycelium of mucorales).

DISCUSSION

Mucormycosis is an opportunistic and invasive infection caused by fungi of the order Mucorales. Almost all cases with mucormycosis are complicated by underlying diseases such as diabetes mellitus, hematological malignancies and transplantation. In Europe and the United States, diabetes is mostly associated with rhino-orbital-cerebral mucormycosis, while patients with hematological malignancies tend to develop pulmonary mucormycosis.^{2,5} However, among the four cases with pulmonary mucormycosis described here, only one patient had an underlying hematological malignancy. The other three patients had diabetic ketoacidosis, then

developed respiratory symptoms, and then finally evidence of Mucorales infection was detected. A hyperglycemic environment is a risk factor for Mucorales growth. Fever and cough were the most common clinical manifestations of pulmonary mucormycosis. A 13-year-old girl presented with massive hemoptysis and pseudoaneurysm. Pseudoaneurysm formation is the most serious sign of mucormycosis, due to the invasive and selective effect of Mucorales on blood vessels.

Galactomannan was not detected in any of the four cases because Mucorales do not produce these cell wall components.⁹ The imaging findings were basically consistent with literature reports, showing characteristic nodules or masses accompanied by cavities. Based on the ESCMID and ECMM joint clinical guidelines for mucormycosis outlined in 2013 and 2016,^{10,11} reversed halo sign (a focal area of ground-glass attenuation surrounded by a ring of consolidation) was suggested to differentiate mucormycosis from aspergillosis with moderate strength. However, we only observed the typical reversed halo sign in the third patient, and not in the other three children. One patient presented with typical tissue granuloma under bronchoscopy, which has not been reported in the previous literature. This is consistent with the pathological changes that occur during mucormycosis. In recent years, researchers have paid more attention to molecular diagnosis of mucormycosis, especially PCR detection. These tools are helpful for early diagnosis of mucormycosis and can improve tissue diagnosis and characterization of culture-negative invasive mold infections.^{12,13}

Treatment of pulmonary mucormycosis include three points: elimination or control of the underlying diseases, surgery and antifungal therapy. Control of underlying diseases is strongly recommended in the European guidelines. All three of our patients with diabetes were treated with strict blood glucose control and diabetes maintenance therapy. In patients with mucormycosis, surgery is strongly recommended whenever possible. Antifungal therapy is divided into two stages: initial therapy and maintenance therapy. The first line treatment is generally liposomal amphotericin B, while posaconazole was recommended for maintenance therapy. Combination therapy with antifungal drugs is recommended with marginal strength in the guidelines.^{10,11} Moreover, a meta-analysis of adult patients with mucormycosis suggested that initial treatment with combination antifungals did not reduce 90-day mortality when compared with liposomal amphotericin B monotherapy.¹⁴ However, patients in the combination therapy group were sicker than those in the monotherapy group. It is strongly recommended in the European guidelines that maintenance treatment should continue until complete response demonstrated on imaging and permanent reversal of predisposing factors.

Poor prognoses were reported for adult mucormycosis, with mortality as high as 87% in the 20th century in the United States.² However, with the early diagnosis, early application of potent antifungal drugs and surgical treatment, the prognosis of mucormycosis has improved. Mortality in 25 cases with pulmonary mucormycosis dropped to 56% in a retrospective study from 2009 to 2017 in China.⁴ A study in America showed that delays in amphotericin B treatment resulted in almost a two-fold increase in mortality at 12 weeks post-diagnosis (83% vs 49%).¹⁵ Liposomal amphotericin B was given to all four of the cases described here. The first and second patients were treated with liposomal amphotericin B within the first 2 weeks of illness, and their pulmonary lesions were relatively mild. The third and fourth patients were treated with liposomal amphotericin B starting one month after disease onset. One patient developed pseudoaneurysm and pulmonary hemorrhage, and the other developed pulmonary embolism and hydropneumothorax. Thus, the two patients who experienced delays in liposomal amphotericin B treatment developed severe pulmonary complications, indicating the importance of early treatment. We were delighted that all four children survived in our study, and that their symptoms and signs disappeared completely. Their lesions were basically absorbed as shown by imaging. All patients were followed up for more than 6 months without recurrence. There may have been several reasons for the positive outcomes in these patients. Firstly, the prognoses of children with mucormycosis may be better than those of adults. Secondly, liposomal amphotericin B or surgery at early stages of disease can improve prognosis. Thirdly, a full course of treatment with posaconazole may play a vital role in improving long-term prognosis. Furthermore, although retrospective studies in adults have shown that combination therapy does not improve mortality, children may benefit from it, especially children with severe mucormycosis pneumonia.

Therefore, clinicians should vigilantly watch for mucormycosis pneumonia, and fully understand its clinical characteristics and risk factors. At the first medical contact with suspected cases, smears and cultures of bronchoalveolar lavage fluid or histopathology of lung tissue should be performed as soon as possible to ensure the early administration of sensitive antifungal drugs. Meanwhile, lobectomy should be performed whenever possible. Considering the limitations of the small numbers of cases in our study, there may have been some bias. More reliable data on optimal treatment of pulmonary mucormycosis in children and analysis of prognostic factors will depend on larger samples and multi-center studies.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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