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ORIGINAL RESEARCH

Clinical Characteristics and Prognoses of Mucormycosis in Four Children

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Background: Mucormycosis is a fatal invasive fungal infection that commonly affects immunocompromised children. The aim of our study was to investigate the clinical manifestations, treatments, and prognosis of pediatric patients with mucormycosis.

Methods: We conducted a retrospective search in Shenzhen Children's Hospital from July 2013 to July 2023 for all patients with mucormycosis. The clinical manifestation, pathogen detection, radiology, treatments, and prognosis were analyzed.

Results: Four cases were identified. Underlying conditions included acute myeloid leukemia with myeloid sarcoma (n = 1), thalassemia (post-allogeneic hematopoietic stem cell transplantation; n = 1), systemic lupus erythematosus (n = 1), and bilateral nephroblastoma (post-bilateral nephrectomy; n = 1). Two patients were disseminated mucormycosis, one case was pulmonary mucormycosis, and one case was cerebral mucormycosis. Fever, cough, and dyspnea were the main clinical symptoms of pulmonary mucormycosis, headache was the main clinical symptom of cerebral mucormycosis. Lung CT findings included consolidation, multiple nodules, halo sign, air crescent sign, and pleural effusion. The contrast-enhanced CT showed pulmonary artery and pulmonary vein occlusions in two patients and pseudoaneurysm in two patients. Amphotericin B formulations were administered as first-line therapy in all cases; in three cases, Triazole was administered in combination with amphotericin B.

Conclusion: Mucormycosis is a life-threatening disease involving multiple systems. Aorta pseudoaneurysm is a rare and fatal complication, enhanced CT can assist in diagnosis. Early diagnosis and appropriate therapeutic strategies are needed.

Keywords: children, immunocompromised, mucormycosis, pseudoaneurysm

Background

Mucormycosis is caused by *Mucoraceae*, which are ubiquitous in the environment and have become important pathogens among immunocompromised children. The underlying diseases in mucormycosis include hematological and solid organ tumors, hematopoietic stem cell and solid organ transplants, immunosuppressive therapy, and neutropenia.[1]

Mucormycosis includes sinusitis, cutaneous, pulmonary, gastrointestinal, disseminated, and other uncommon rare forms.[2] The involvement of two or more non-contiguous sites is defined as disseminated mucormycosis. It is rare in children. *Mucorales* can invade blood vessels and disseminate through hematogenous routes. Prakash H reported that 13% of mucormycosis patients present with disseminated disease.[3]

In this study, we aimed to analyze the clinical data of four patients with mucormycosis in our hospital to provide helpful information for clinical research.

Materials and Methods

Study Design

Pediatric patients diagnosed with mucormycosis from July 2013 to July 2023 at Shenzhen Children's Hospital were enrolled in the study. The electronic medical records, imaging, and pathogen information were collected for all cases.

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Diagnostic Methods

Metagenomic next-generation sequencing was performed on the four patients. Specimens included bronchoalveolar lavage fluid from one patient, CSF-cerebrospinal fluid and peripheral blood from one patient, peripheral blood and bronchoalveolar lavage fluid from one patient, and hydrothorax and bronchoalveolar lavage fluid from one patient.

Ethical Issues

All aspects of the study were performed in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration. The study protocol was approved by the Ethical Committee of Shenzhen Children's Hospital (number 201601304). Written informed consent was obtained from all of the participants guardians.

Results

Patient Characteristics

Four pediatric cases of mucormycosis were included in the study. The median age was 10.2 years (range, 5.6–11.9 years). Underlying conditions included relapsed acute myeloid leukemia (AML) with myeloid sarcoma (n = 1), thalassemia (post-allogeneic hematopoietic stem cell transplantation; n = 1), systemic lupus erythematosus (SLE) (n = 1), and bilateral nephroblastoma (post bilateral nephrectomy; n = 1). Three patients were undergoing chemotherapy, and one patient underwent hematopoietic stem cell transplantation (HSCT). The median duration of neutropenia before mucormycosis was 29.5 days (range, 0–201 days). The patient characteristics were in Table 1.

Clinical Manifestation and Pathogens

All four patients presented with prolonged fever and cough, dyspnea in three cases, chest and back pain in one case, and headache in one case. Thoracic computed tomography (CT) was performed in all patients. CT findings were consolidation, nodules, halo sign, air crescent sign, and pleural effusion. Three patients received contrast-enhanced CTs, in which two patients showed pulmonary artery and pulmonary vein occlusions. The enhanced CT scan of the descending aorta (at the level of the fifth thoracic vertebrae to the ninth thoracic vertebrae) in one patient showed two tuberoid expansions outward from the lumen, with uniform internal density, the larger one had a neck width of about 35mm and a maximum cross-section size of about 43mm x 35mm, the smaller one had irregular shape and a neck width of about 7mm, indicating a pseudoaneurysm of the descending aorta. Another patient's enhanced CT scan showed a circular soft tissue density shadow below the aortic arch, with irregular shape and enhanced blood pool, with a size of 44mm x 30mm x 30mm, indicating the rupture of a pseudoaneurysm. One patient evaluated by craniocerebral magnetic resonance imaging and enhancement showed a hemorrhagic infarction in the left occipital lobe. Two patients with massive bloody pleural effusion underwent closed thoracic drainage. Bronchoscopic lavage was performed in all four cases; a grey, gelatinous substance and grayish-brown necrotic mass occluded the middle lobe of the right lung in one patient and the base lobe of the left lower lung in another. The pathogens were molecularly confirmed by mNGS in all patients, and one case was also confirmed by pathology. Pathogens included *Cunninghamella bertholletiae* (n = 2), *Rhizomucor pusillus* (n = 1), and *Rhizopus microspores* (n = 1). The specimen origins included alveolar lavage fluid (BALF; n = 1), blood and BALF (n = 1), blood and CSF (n = 1), and hydrothorax and BALF (n = 1). All patients received antifungal therapy. The radiographic, bronchoscopic, and pathological features are shown in Figure 1.

Treatment

The treatment modalities are summarized in Table 2. In all cases, liposomal amphotericin (L-AmB; n = 1) or amphotericin B (AmB; n = 3) were administered as first-line therapies. Three patients treated with AmB received doses of 5–6 mg/kg/day, and one patient was treated with L-AmB at a dose of 5 mg/kg/day. In three cases, combination antifungal therapy was used, comprising L-AmB or AmB with triazole (posaconazole or isavuconazole).

Outcome

All patients died, including two within 6 weeks of diagnosis. The median day from mucormycosis diagnosis to death was 31 days (range, 12–98 days).

Table 1 Patient Demographics and Microbiological Data in Four Pediatric Patients with Mucormycosis

No.	Sex	Age (Years)	Underlying Condition	Phase Of Therapy	Duration of Neutropenia (Days)	Clinical Presentation	Sites of Involvement	Diagnostic Method	Specimen	Pathogen	Imaging
1	F	5.6	Bilateral nephroblastoma	Consolidation	38	Prolonged fever, cough and dyspnea	Lung angiocardiopathy	mNGS	BALF	*Cunninghamella bertholletiae*	Lung CT: multiple nodules, halo sign, and air crescent sign. Contrast-enhanced CT: aortic arch dissection with ruptured pseudoaneurysm.
2	F	11.3	Relapsed AML with myeloid sarcoma	Consolidation	201	Prolonged fever, cough, and headache	Brain	mNGS	PB CSF	*Rhizomucor pusillus*	Craniocerebral MRI and enhancement: hemorrhagic infarction.
3	F	11.9	SLE	Consolidation	0	Prolonged fever, cough and dyspnea	Lung	mNGS, Pathology	Hydrothorax BALF	*Rhizopus microsporus*	Lung CT: consolidation and massive pleural effusion. Contrast-enhanced CT: pulmonary artery and pulmonary vein occlusions.
4	M	8.1	Thalassemia	Allogeneic HSCT	20	Prolonged fever, cough, dyspnea, and chest and back pain	Lung angiocardiopathy	mNGS	PB BALF	*Cunninghamella bertholletiae*	Lung CT: consolidation and massive pleural effusion. Contrast-enhanced CT: pseudoaneurysm of the descending aorta, pulmonary artery and pulmonary vein occlusions.

Abbreviations: AML, acute myeloid leukemia; SLE, systemic lupus erythematosus; HSCT, hematopoietic stem cell transplantation; mNGS, metagenomics next generation sequencing; CSF, cerebrospinal fluid; PB, peripheral blood; BALF, bronchoalveolar lavage fluid; CT, computerized tomography; MRI, magnetic resonance imaging.

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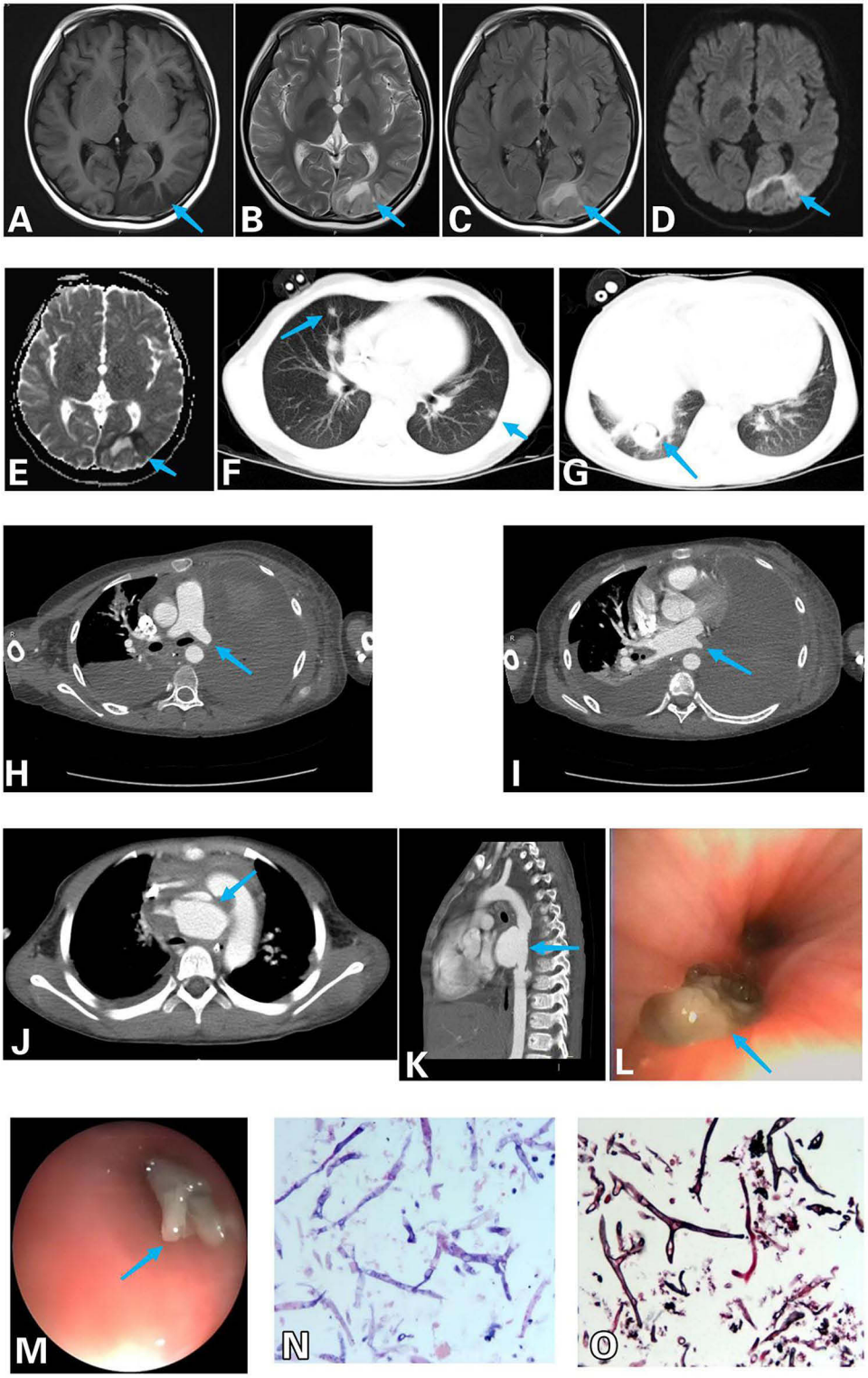

Figure 1 (**A**–**E**) Magnetic resonance imaging of patient No. 2. (**A**) The left occipital lobe showed an irregular gyrus with an abnormal signal shadow and a low signal on T1WI (arrow). (**B**) Slightly high signal on T2WI (arrow). (**C**) Slightly high signal on FLAIR (arrow). (**D**) Limited DWI diffusion (arrow). (**E**) Limited DWI diffusion (arrow). (**F**) Computed tomography (CT) of patient No. 1 showing multiple pulmonary nodules and marginal halo sign (arrow). (**G**) Computed tomography (CT) of patient No. 1 showing air crescent sign (arrow). (**H**) Enhanced CT of patient No. 3 showing left pulmonary artery occlusion, left atelectasis and left pleural effusion (arrow). (**I**) Enhanced CT of patient No. 3 showing left pulmonary vein occlusion (arrow). (**J**) Enhanced CT of patient No. 1 showing aortic arch dissection with ruptured pseudoaneurysm (arrow). (**K**) Enhanced CT of patient No. 4 showing a pseudoaneurysm of the descending aorta (arrow). (**L**) Bronchoscope of patient No. 4 showing a grayish-brown necrotic mass occluding the middle lobe of the right lung (arrow). (**M**) Bronchoscope of patient No. 1 showing a gelatinous substance occluded the base lobe of the left lower lung (arrow). (**N**) Alveolar lavage fluid pathology of patient No. 3 showing typical hyphal morphology. *Mucorales* hyphae were at least 6–16 μm wide, ribbon-like, pauci-septate, with subrectangular branching (HE 20X). (**O**) Alveolar lavage fluid pathology of patient No. 3 showing typical hyphal morphology. *Mucorales* hyphae were at least 6–16 μm wide, ribbon-like, pauci-septate, with subrectangular branching (PASM 20X).

Table 2 Treatments and outcomes of Four Pediatric Patients with Mucormycosis

No,	Antifungal Prophylaxis	First-Line Antifungal Treatment	Second-Line Antifungal Treatment	Surgical Debridement Procedures	Outcome	Time to Death from Mucormycosis Diagnosis
1	Voriconazole caspofungin	L-AmB, 5 mg/kg/d	None	None	Death	12
2	Voriconazole caspofungin	AmB, 5 mg/kg/d	L-AmB, 5 mg/kg/d posaconazol susp	None	Death	98
3	Voriconazole	AmB, 6 mg/kg/d posaconazole susp	None	None	Death	15
4	Caspofungin	AmB, 5 mg/kg/d posaconazole susp	AmB, 5 mg/kg/d IV isavuconazole	None	Death	47

Abbreviations: AmB, amphotericin B; L-AmB, liposomal amphotericin; susp–oral suspension.

Discussion

Mucormycosis is a fatal invasive infection that manifests in different clinical forms and occurs in patients with a variety of risk factors. Adult populations at risk of mucormycosis include patients with diabetes mellitus, surgical patients, those with burns or trauma, and patients undergoing deferoxamine therapy, in children hematologic malignancy and hematopoietic stem cell transplant are significant risk factors.[4] The majority of patients with hematological malignancy and mucormycosis in various studies had acute myeloid leukemia (48% in the ECMM study,[5] 46% in Italy,[6] 34% in France,[7] and 42% in a global review by Jeong et al).[8] The incidence among HSCT recipients varies widely, from 0.08% to 0.69%.[9] In this study, we report on four patients diagnosed with mucormycosis, one with relapsed acute myeloid leukemia, one with nephroblastoma, and one who underwent HSCT. Prolonged neutropenia is the risk factor for mucormycosis.[10] Three of the four patients in our study had underlying neutropenia. The median duration of neutropenia before mucormycosis diagnosis was 29.5 days.

Mucormycosis is traditionally classified into 6 major clinical forms: ①rhinocerebral, ②pulmonary, ③cutaneous, ④gastrointestinal, ⑤disseminated, ⑥miscellaneous. In adult patients, Rhino-orbital-cerebral mucormycosis (ROCM) was the most common manifestation, followed by cutaneous and pulmonary mucormycosis.[8] In children, The most common pattern of mucormycosis was cutaneous, followed by gastrointestinal, rhinocerebral, and pulmonary mucormycosis.[11] Pulmonary mucormycosis occurs often in neutropenic patients. The clinical manifestations of pulmonary mucormycosis are nonspecific and indistinguishable from those of other pulmonary fungi. The common symptoms are fever and nonproductive cough.[12] Three of the four children in our study with pulmonary mucormycosis presented with prolonged fever, cough, and dyspnea. Pulmonary mucormycosis can have endobronchial involvement and cause airway obstruction, resulting in lung collapse. Pulmonary mucormycosis can also invade hilar blood vessels and cause massive hemoptysis.[2] Three patients with pulmonary mucormycosis underwent tracheoscopy, in which two patients were found to have a discharge blockage in the distal trachea.

The molecular mechanism of mucormycosis involves *Mucorale*s invading the endothelium by specifically recognizing the host receptor glucose-regulator protein 78 (GRP78), which triggers host cell injury and subsequent hematogenous dissemination of the fungus, causing vessel thrombosis and tissue necrosis.[13] The manifestations of cerebral mucormycosis are typically meningitis, infarctions secondary to vasculitis, abscesses, or aneurysms.[14] Direct invasion from rhino-orbital structures or through hematogenous spread leads to cerebral mucormycosis.[15] The patient in our study with cerebral mucormycosis presented with a headache, and an MRI showed hemorrhagic cerebral infarction. There was no involvement of the paranasal sinuses on computed tomography or MRI, but mNGS of cerebrospinal fluid and peripheral blood all tested positive for *Rhizomucor pusillus.*

Artery pseudoaneurysm is another fatal complication of disseminated mucormycosis. Pulmonary artery pseudoaneurysm, carotid artery pseudoaneurysm, subclavian artery pseudoaneurysm, and pseudoaneurysm in spleen have been

reported.[16–19] Aorta pseudoaneurysm was never reported before. One patient in our study experienced chest and back pain during the treatment of pulmonary mucormycosis, and enhanced CT showed a pseudoaneurysm of the descending aorta. Another patient with aortic arch pseudoaneurysm died due to aneurysm rupture.

Early diagnosis is a challenge in mucormycosis. The gold standard is a histopathological examination, including direct examination and culture, which has a positive rate of approximately 50%.[20] In recent years, molecular biology techniques, including polymerase chain reaction (PCR) and metagenomics next-generation sequencing, have been widely used for the diagnosis of mucormycosis. Metagenomics next-generation sequencing (mNGS) refers to the direct extraction of nucleic acids from samples, construction of a metagenomic sequencing library, and sequencing. The results are culture-independent, and mNGS is particularly useful for non-cultivable or uncommon microbiological organisms.[21] In our study, mNGS of BALF, PB, and CSF were employed to diagnose mucormycosis.

Timely initiation of antifungal therapy for mucormycosis is essential to improve survival. AmB and its lipid formulations were the first FDA-approved drugs for treating mucormycosis infections.[22] Current guidelines suggest the standard daily dose of L-AmB is 5 mg/kg/day.[23] Two of the four patients in our study were treated with L-AmB at 5 mg/kg/day. Newer triazoles (posaconazole and isavuconazole) have better activity against *Mucorales*. A synergistic effect between polyenes and posaconazole has been demonstrated in vitro studies.[24] Three of the four patients with mucormycosis in our study received combination therapy consisting of L-AmB or AmB with triazole (isavuconazole or posaconazole). Surgical resection of necrotic tissues is the core of mucormycosis therapy. Endovascular embolization, surgical resection, or a combination of both has been successfully used in the treatment of mucormycosis-associated aneurysms.[18,25] In two of the four patients with aortic aneurysm, unfortunately, there was no chance of further treatment.

Mucormycosis is a fatal infection in immunocompromised patients. Early diagnosis and appropriate combination therapeutic approach are very important to improve the prognosis of mucormycosis.

Conclusions

In this study, we report four children diagnosed with mucormycosis. Mucormycosis is a life-threatening disease involving multiple systems. *Mucorales* rapidly invades blood vessels, leading to blood spread, thrombosis of the vessels, and subsequent tissue necrosis, which are the hallmarks of mucormycosis. Aorta pseudoaneurysm is a rare and fatal complication that was never reported before, chest and back pain may indicate a pseudoaneurysm of the aorta, Enhanced CT can assist in diagnosis. Combination of L-AmB/AmB and triazole antifungal therapy and surgical interventions may improve survival.

Abbreviations

AML, Acute myeloid leukemia; mNGS, Metagenomics next generation sequencing; CSF, Cerebrospinal fluid; PB, Peripheral blood; BALF, Bronchoalveolar lavage fluid; SLE, Systemic lupus erythematosus; HSCT, Hematopoietic stem cell transplantation; AmB, Amphotericin B; L-AmB, liposomal amphotericin.

Data Sharing Statement

The key information and data generated and analyzed during this are given in this article.

Ethics Approval and Consent to Participate

Ethical approval for this study was obtained from the Ethical Committee of Shenzhen Children's Hospital (Shenzhen, Guangdong Province, China) under registration number 2016013. All of the experiments were performed under the relevant guidelines and regulations. Guardians of all of the children included in this study provided written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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