Clinical features of pulmonary mucormycosis in patients with different immune status

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Background: Pulmonary mucormycosis (PM) is a relatively rare but often fatal and rapidly progressive disease. Most studies of PM are case reports or case series with limited numbers of patients, and focus on immunocompromised patients. We investigated the clinical manifestations, imaging features, treatment, and outcomes of patients with PM with a focus on the difference in clinical manifestations between patients with different immune status.

Methods: Clinical records, laboratory results, and computed tomography scans of 24 patients with proven or probable PM from January 2005 to December 2018 in Peking Union Medical College Hospital were retrospectively analyzed.

Results: Ten female and 14 male patients were included (median age, 43.5 years; range, 13–64 years). Common presenting symptoms were fever (70.8%), cough (70.8%), sputum production (54.2%), and hemoptysis (41.7%). Radiological findings included consolidation (83.3%), ground-glass opacities (58.3%), nodules (50.0%), masses (37.5%), cavities (33.3%), mediastinal lymphadenopathy (29.2%), and halo sign (12.5%); one patient had a reversed halo sign. Seven patients (29.2%) had no obvious predisposing risk factors, and 17 (70.8%) had underlying diseases including diabetes, hematological malignancy, and use of immunosuppressants. Compared with immunocompromised patients, immunocompetent patients with PM were younger {23 [13–46] *vs.* 48 [17–64] years, P=0.023}, comprised a higher proportion of men (100.0% *vs.* 41.2%, P=0.019), had a longer disease course {34 [8–47] *vs.* 9 [2–102] weeks, P=0.033}, had a higher eosinophil count [0.66 (0.07–2.00) ×10⁹/L *vs.* 0.04 (0.00–0.23) ×10⁹/L, P=0.001], and had a lower erythrocyte sedimentation rate {12 [1–88] *vs.* 74 [9–140] mm/h, P=0.032}.

Conclusions: PM can occur in heterogeneous patients with different immune status, and the clinical phenotype differs between immunocompetent and immunocompromised patients. Because of the lack of specific clinic and imaging manifestations, aggressive performance of invasive procedures to obtain histopathological and microbial evidence is crucial for a definitive diagnosis.

Keywords: Mucormycosis; zygomycosis; lung diseases; fungal

Introduction

Mucormycosis is an invasive fungal disease that is relatively rare but often fatal and rapidly progressive (1). The incidence of mucormycosis has recently been increasing (2-5). It is the second most common invasive fungal disease, ranking second only to aspergillosis. The genera that cause most cases of mucormycosis are *Rhizopus*, *Mucor*, and *Lichtheimia* (previously *Absidia*). Common predisposing factors include hematological malignancy, diabetes, transplantation, use of corticosteroids or immunosuppressants, and trauma (2,3,6). Common clinical types of mucormycosis include rhino-orbito-cerebral (27–39%), pulmonary (20–30%), dermal (19–26%), disseminated (3–15%), and gastrointestinal types (7–8.5%) (2,5,6).

Pulmonary mucormycosis (PM) is the second or third most common clinical subtype of mucormycosis (2,6). The mortality rate of PM was relatively high in early studies (56–76%) (2,7) but has recently decreased to 29% to 38% (8-10). PM continues to be a diagnostic and therapeutic challenge because its rarity makes the performance of prospective randomized controlled trials and accumulation of substantial personal experience difficult to accomplish. Two research groups reviewed the literature regarding PM at different time points (7,8); however, current studies concerning PM are mainly case reports or retrospective case series with limited numbers of patients. In addition, most studies on PM focus on severely immunocompromised patients, especially those with hematological malignancy or neutropenia (9-15). Therefore, the present study was performed to investigate the clinical manifestations, imaging features, treatment, and outcome of patients with PM with a focus on the difference in clinical manifestations between patients with different immune status.

Methods

Diagnostic criteria for PM

The present study included patients with proven or probable mucormycosis based on the European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) criteria (16). All patients had the following microbiological or histopathological evidence of mucormycosis (1): non-septate, right-angle branching filamentous fungi of variable width (6–25 μm) on direct microscopy of clinical specimens; recovery of Mucorales species by culture of clinical specimens; or confirmation of mucormycosis by

histopathological examination of tissue specimens.

Study population

Patients with a diagnosis of mucormycosis were identified from medical records from January 2005 to December 2018 at Peking Union Medical College Hospital, a tertiary hospital in Beijing, China. Patients who fulfilled the criteria for proven or probable PM were included. Their case records and imaging findings were retrospectively reviewed. Observation indices included demographic information, clinical manifestations, predisposing conditions, radiologic findings, laboratory examination findings, diagnostic procedures, therapeutic interventions, and outcomes. Patients with PM were further divided into immunocompetent and immunocompromised groups for comparison.

The study was approved by the Ethics Committee of Peking Union Medical College Hospital (Reference number: S-K805). Due to the retrospective nature of the study and no identifying information relating to participants was included, written informed consent was waived.

Statistical analysis

SPSS 24.0 software (IBM Corp., Armonk, NY, USA) was used to analyze the data. Continuous variables are expressed as median and range, and qualitative variables are expressed as count and percentage. Categorical variables were compared by Fisher's exact test, whereas continuous variables were compared by the Wilcoxon rank-sum test or Mann-Whitney U test. Two-sided P values of <0.05 were considered statistically significant.

Results

Demographic characteristics and clinical features

A total of 34 patients met the diagnostic criteria for proven or probable mucormycosis, including 20 (58.8%) with PM, 5 (14.7%) with disseminated mucormycosis (4 of whom had lung involvement), 4 (11.8%) with gastrointestinal mucormycosis, 3 (8.8%) with rhino-orbito-cerebral mucormycosis, and 2 (5.9%) with dermal mucormycosis. Among the 34 patients with mucormycosis, 24 (70.6%) had pulmonary infection involving *Mucor* species.

The demographic and clinical manifestations of the 24 patients with PM are shown in *Table 1*. The population

Table 1 Demographics, clinical manifestations, imaging features and outcomes of 24 patients with pulmonary mucormycosis

Patient characteristic	Total (N=24)	Immunocompetent (N=7)	Immunocompromised (N=17)	P value
Age (years), median [range]	43.5 [13–64]	23 [13–46]	48 [17–64]	0.023*
Sex (male), n (%)	14 (58.3)	7 (100.0)	7 (41.2)	0.019*
Duration (weeks), median [range]	10 [2–102]	34 [8–47]	9 [2–102]	0.033*
Clinical symptoms, n (%)				
Fever	17 (70.8)	3 (42.9)	14 (82.4)	0.134
Cough	17 (70.8)	4 (57.1)	13 (76.5)	0.374
Sputum production	13 (54.2)	2 (28.6)	11 (64.7)	0.182
Hemoptysis	10 (41.7)	3 (42.9)	7 (41.2)	1.000
dyspnea	8 (33.3)	1 (14.3)	7 (41.2)	0.352
Lab tests, median [range]				
WBC (10^9/L)	7.72 (2.01–20.00)	8.32 (5.04–20.00)	7.52 (2.01–15.50)	0.383
Neutrophil (10^9/L)	5.03 (0.09–18.20)	5.84 (2.80–18.20)	3.90 (0.09–14.35)	0.294
Lymphocyte (10^9/L)	1.51 (0.85–8.22)	1.49 (0.99–2.40)	1.60 (0.85–8.22)	0.857
Eosinophils (10^9/L)	0.10 (0–2.00)	0.66 (0.07–2.00)	0.04 (0.00–0.23)	0.001*
ESR (mm/h)	63 [1–140]	12 [1–88]	74 [9–140]	0.032*
hsCRP (mg/L)	21.40 (0.17–166.00)	10.61 (0.17–70.23)	40.05 (2.10–166.00)	0.128
Radiological features, n (%)				
Consolidation	20 (83.3)	5 (71.4)	15 (88.2)	0.552
Ground glass opacity	14 (58.3)	3 (42.9)	11 (64.7)	0.393
Nodule	12 (50.0)	4 (57.1)	8 (47.1)	1.000
Mass	9 (37.5)	3 (42.9)	6 (35.3)	1.000
Cavitary	8 (33.3)	1 (14.3)	7 (41.2)	0.352
Halo sign	3 (12.5)	1 (14.3)	2 (11.8)	
Reversed halo sign	1 (4.2)	0	1 (5.9)	
Mediastinal lymphadenopathy	7 (29.2)	4 (57.1)	3 (17.6)	0.134
Pleural effusion	12 (50.0)	3 (42.9)	9 (52.9)	1.000
Invasion of mediastinum	4 (16.7)	2 (28.6)	2 (11.8)	0.552
Radiological distribution, n (%)				
Single lobe	7 (29.2)	3 (42.9)	4 (23.5)	0.374
Multi-lobe single lung	5 (20.8)	1 (14.3)	4 (23.5)	1.000
Bilateral lungs	12 (50.0)	3 (42.9)	9 (52.9)	1.000
Outcome, n (%)				
Recovery or improve	18 (75.0)	6 (85.7)	12 (70.6)	0.629
Death or loss of follow-up	6 (25.0)	1 (14.3)	5 (29.4)	0.629

*, P<0.05. WBC, white blood cell; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein.
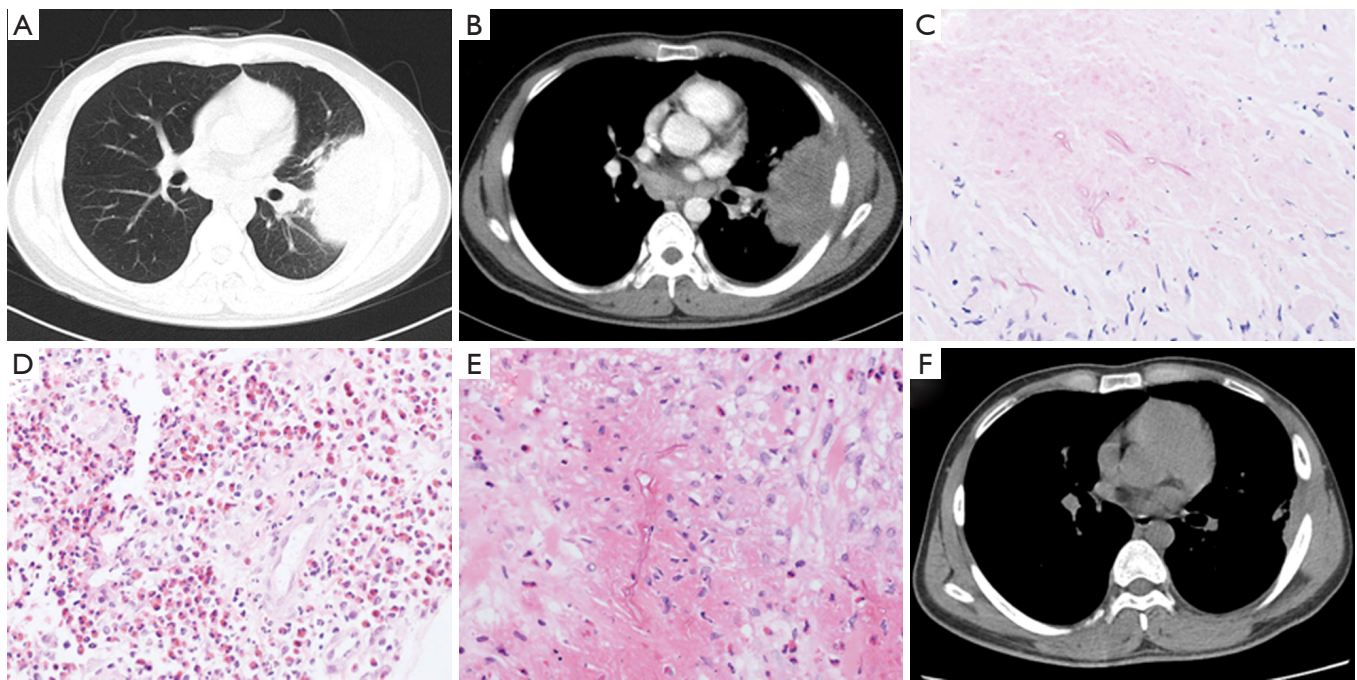
Figure 1 A 24-year-old man with disseminated mucormycosis. (A) Chest computed tomography (lung window) shows consolidation in the left lower lobe; (B) chest computed tomography (mediastinal window) shows consolidation with central necrosis, mediastinal lymphadenopathy, and invasion of the chest wall; (C) microscopic examination of lung biopsy showing necrosis in the lung tissue accompanied by an epithelioid cell response and *Mucor* hyphae with a width of 6–10 μm [hematoxylin and eosin (HE), 200×]; (D) microscopic examination of lung biopsy indicates eosinophilic infiltration (HE, 200×); (E) microscopic examination of abdominal subcutaneous nodule biopsy shows necrosis, eosinophilic infiltration, and *Mucor* hyphae with a width of 8–12 μm (HE, 200×); (F) after 14 months of treatment, the pulmonary opacity and mediastinal lymphadenopathy improved.

comprised 10 female and 14 male patients with a median age of 43.5 years (range, 13–64 years). The median duration from symptom onset to the definitive diagnosis was 10 weeks (range, 2–102 weeks). Seven patients (29.2%) had an acute course (≤1 month), 9 (37.5%) had a subacute course (1–3 months), and 8 (33.3%) had a chronic course (>3 months). Common symptoms included fever in 17 patients (70.8%), cough in 17 (70.8%), sputum production in 13 (54.2%), hemoptysis in 10 (41.7%), shortness of breath in 8 (33.3%), chest pain in 4 (16.7%), and weakness in 4 (16.7%).

Among the 24 patients with PM, 7 (29.2%) had no obvious underlying disease; 17 (70.8%) had underlying diseases, including 7 with diabetes and 7 with hematological malignancies (4 with acute myelogenous leukemia, 1 with aplastic anemia, 1 with acute lymphoblastic leukemia, and 1 with chronic lymphocytic leukemia); and 3 had received corticosteroids and/or immunosuppressants for treatment of connective tissue disease or nephropathy.

Laboratory tests

The laboratory examination findings of the 24 patients with PM are shown in *Table 1*. The median leukocyte count was 7.72 (2.01–20.00) ×10^9/L. Four patients (16.7%) had a low leukocyte count (<4×10^9/L), and seven (29.2%) had a high count (>10×10^9/L). The median neutrophil count was 5.03 (0.09–18.20) ×10^9/L. The median eosinophil count was 0.10 (0–2.00) ×10^9/L. Four patients (16.7%) had a high eosinophil count (>0.5×10^9/L). Four patients (16.7%) had a high immunoglobulin E level (>2,500 KU/L). The median erythrocyte sedimentation rate was 63 [1–140] mm/h, and the median high-sensitivity C-reactive protein level was 21.40 (0.17–166.00) mg/L.

Radiological findings

As shown in *Table 1*, the chest computed tomography (CT) manifestations included consolidation in 20 patients
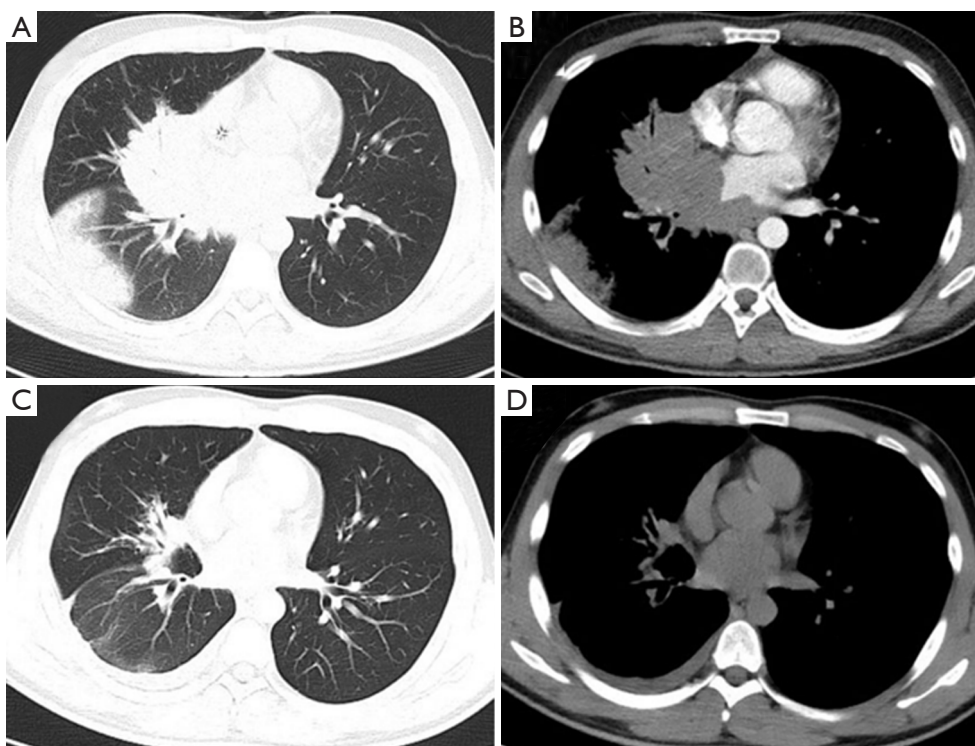
Figure 2 A 20-year-old man with pulmonary mucormycosis. (A) Chest computed tomography reveals a perimediastinal mass and subpleural consolidation in the right lung; (B) chest computed tomography (mediastinal window) shows a mass invading the mediastinum and compressing the left atrium and right lower pulmonary vein; (C,D) chest computed tomography indicates that the lesions have been significantly absorbed after 9 months of treatment.
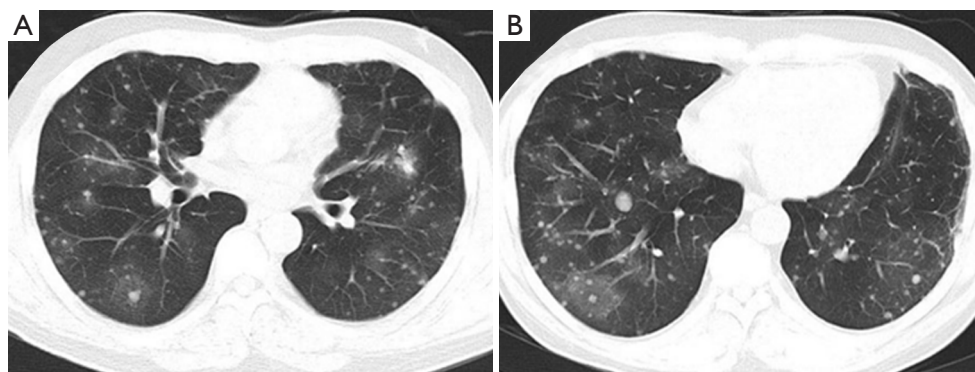

Figure 3 A 44-year-old man with pulmonary mucormycosis that manifested as massive hemoptysis. (A,B) Chest computed tomography reveals small nodules with varying sizes, randomly distributed in the bilateral lungs and superimposed on ground-glass opacities.

(83.3%), ground-glass opacity in 14 (58.3%), nodules in 12 (50.0%), masses in 9 (37.5%), cavities in 8 (33.3%), mediastinal lymphadenopathy in 7 (29.2%), pleural effusion in 12 (50.0%), interlobular septal thickening in 2 (8.3%), a halo sign in 3 (12.5%), and a reversed halo sign (RHS) in 1 (4.2%) (*Figures 1-6*). Four patients had

intrapulmonary lesions invading the mediastinum, among whom two had vessel compression (*Figure 2B*). And one had chest wall invasion (*Figure 1B*). Six patients (25.0%) had a single lesion, and 18 (75.0%) had two or more lesions. The lesion distribution was as follows: 7 patients (29.2%) had a lesion in one lobe, 5 (20.8%) had lesions in multiple lobes
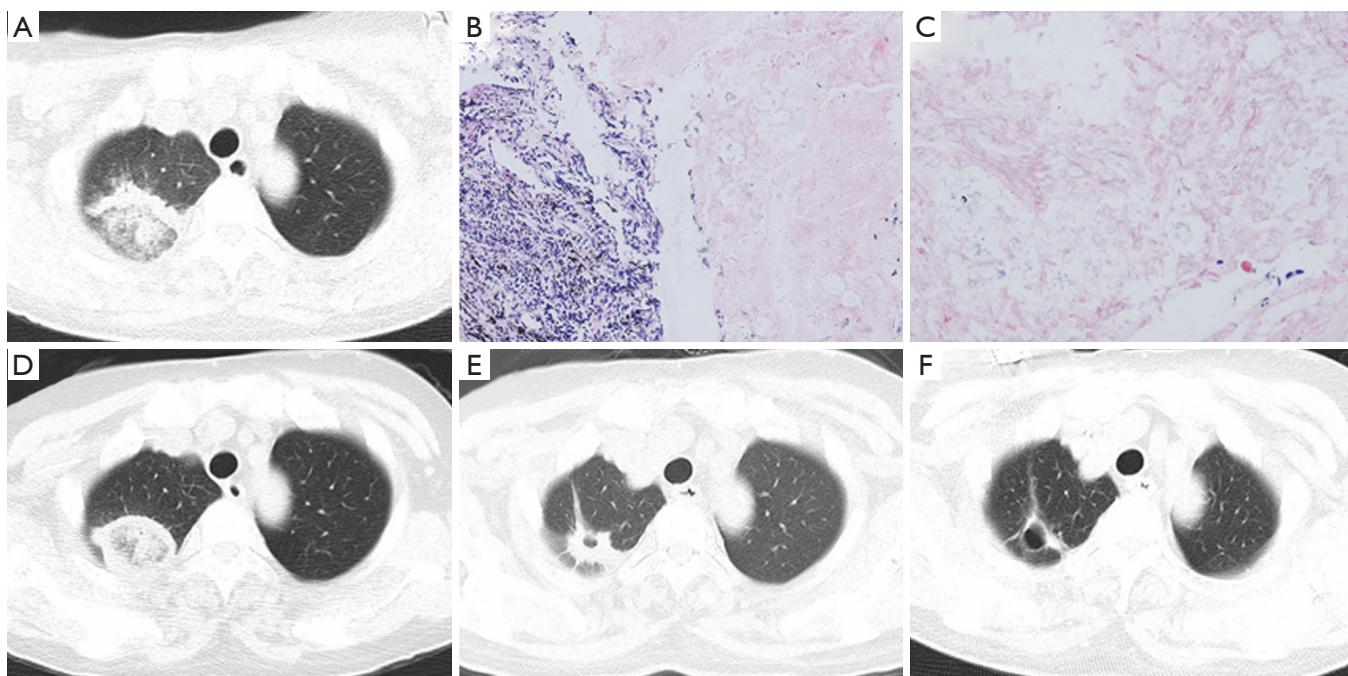
Figure 4 A 61-year-old woman with pulmonary mucormycosis and acute myeloid leukemia. (A) Chest computed tomography shows ground-glass opacity in the upper right lung, surrounded by consolidation shadow (reversed halo sign); (B) microscopic examination of a lung biopsy reveals chronic inflammation accompanied by necrosis [hematoxylin and eosin (HE), 40×]; (C) *Mucor* hyphae with a width of 6–8 μm could be observed in the lung tissue (HE, 200×); (D) chest computed tomography illustrates a clearer reversed halo sign after 2 weeks; (E) chest computed tomography illustrates a cavity in the right upper lung at month 5; (F) the lesion in the right upper lung had significantly resolved and left a thin-walled cavity after 9 months.
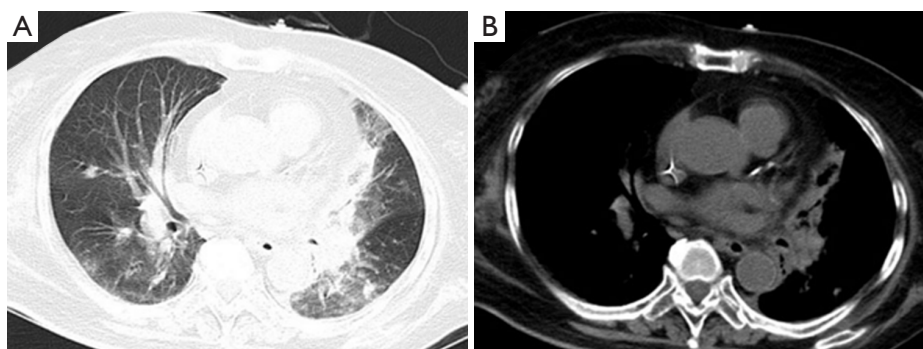

Figure 5 A 63-year-old woman with aplastic anemia and pulmonary mucormycosis. (A) Chest computed tomography shows consolidation neighboring the left heart margin as well as multiple ground glass opacities and nodules in the bilateral lungs; (B) chest computed tomography (mediastinal window) shows a lung lesion involving the pericardium.

in one lung, and 12 (50.0%) had lesions in multiple lobes in both lungs.

Diagnostic procedures

Among the 24 patients with PM, 17 (70.8%) had proven PM and 7 (29.2%) had probable PM. The diagnostic methods were histopathology in 17 (70.8%), direct microscopy of clinical specimens in 6 (25.0%), and recovery of Mucorales species from clinical specimens in 6 (25.0%) (including 3 with *Rhizopus*, 2 with *Mucor*, and 1 with *Lichtheimia* species). The procedures performed
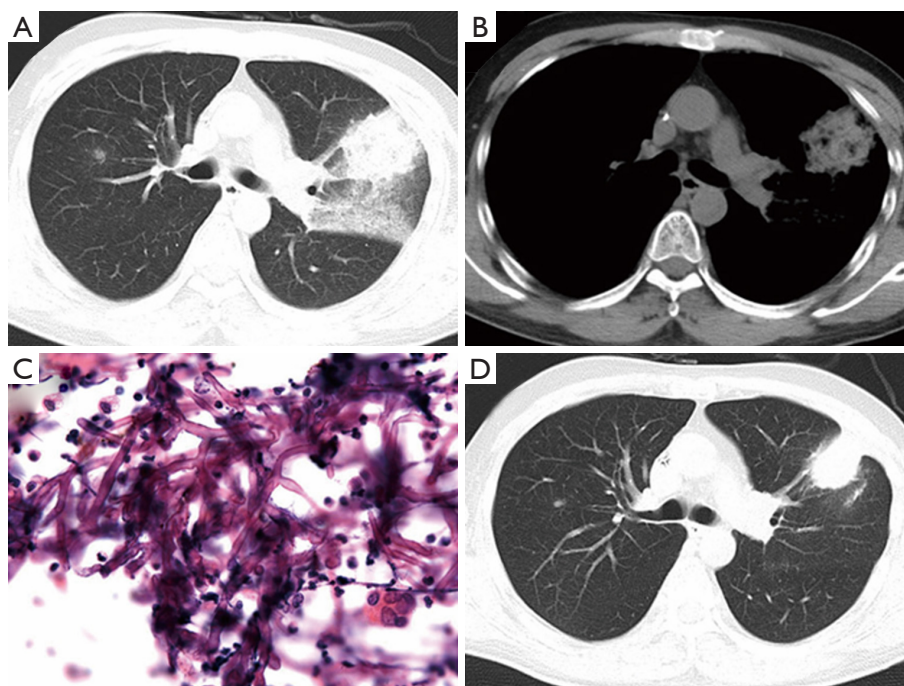
Figure 6 A 45-year-old man with acute myelogenous leukemia and pulmonary mucormycosis. (A) Chest computed tomography show a mass in the left upper lobe surrounded by a ground-glass opacity shadow (halo sign). A small nodule is also present in the right upper lobe; (B) chest computed tomography (mediastinal window) shows a mass with central necrosis in the left upper lobe; (C) direct microscopy of bronchoalveolar lavage fluid reveals non-septate, ribbon-like, right-angle branching *Mucor* hyphae with a width of ~10 µm (Gram stain, 1,000×); (D) after 4 months of treatment, chest computed tomography indicates absorption of both the mass in the left upper lung and the small nodule in the right upper lung.

to obtain specimens included bronchoscopic biopsy or bronchoalveolar lavage in nine patients, percutaneous lung biopsy in six, surgical lung biopsy in four, sputum in three, pleural effusion drainage in one, and biopsy of extrapulmonary tissue in four (*Figure 1E*).

Pathological manifestations

The pathological characteristics of the lung tissues of 17 patients with PM were as follows (*Figures 1C,D,4B,C*): chronic and/or acute inflammation in 11 patients, granulomatous inflammation in 6, epithelioid granuloma in 3, necrosis in 10, eosinophilic infiltration in 3, organizing pneumonia in 1, abscesses in 1, and granulomatous angiitis in 1. *Mucor* species were found in the tissues of all 17 patients.

Management and outcomes

Twenty-two patients (91.7%) were treated with amphotericin

B (AmB) deoxycholate. The most common adverse effect was an elevated creatinine level (n=15); other adverse effects included potassium deficiency (n=1), neutropenia (n=1), and anemia (n=1). AmB deoxycholate was stopped in four patients because of intolerance of the adverse effects. Only two patients were treated with AmB liposome. In the most recent 5 years, nine patients received posaconazole oral suspension. Only three patients underwent pulmonary lobectomy. One patient developed recurrence after surgical resection. Twelve patients improved, six were cured, three died, and three were lost to follow-up. The survival rate was 75.0%.

Comparison between immunocompetent and immunocompromised groups

The patients with PM were divided into immunocompetent and immunocompromised groups. Compared with immunocompromised patients, immunocompetent patients with PM were younger {23 [13–46] *vs.* 48 [17–64] years,

P=0.023}, comprised a higher proportion of men (100.0% *vs.* 41.2%, P=0.019), had a longer disease course {34 [8–47] *vs.* 9 [2–102] weeks, P=0.033}, had a higher eosinophil count [0.66 (0.07–2.00) *vs.* 0.04 (0.00–0.23) ×10^9/L, P=0.001], and had a lower erythrocyte sedimentation rate {12 [1–88] *vs.* 74 [9–140] mm/h, P=0.032} (*Table 1*). Only one patient in the study (immunocompromised group) had an RHS on chest CT. No significant differences in symptoms, imaging findings, or outcomes were found (*Table 1*).

Discussion

This report describes our single-center experience of patients with PM with different immune status. In contrast to previous studies, our study indicates that PM could be the most common form of mucormycosis. Additionally, PM is reportedly typically acute in onset, but the infection exhibited a subacute or chronic course in two-thirds of the patients in the present study. Moreover, the clinical features differed between the immunocompetent and immunocompromised groups.

In this study, PM with or without extrapulmonary disease occurred in 70% of all patients with mucormycosis; the lung was the sole site of infection, accounting for 55.9% of patients with mucormycosis, which is much higher than previously reported (20–30%) (2,5,6). Our results suggest that pulmonary infection could be the most common form of mucormycosis, and concurrent extrapulmonary dissemination may occur in only a minority of patients (8). Further studies are needed to confirm this.

Most published cases of PM occurred in immunocompromised patients (7,8). Our results showed the most common risk factors were diabetes and hematological malignancy, consistent with previous publications (2,6-8). Mucormycosis is rarely reported in patients without predisposing conditions (17-20). In the present study, however, nearly 30% of patients with PM had no obvious underlying disease; this proportion is much higher than previously reported (12%) (7,8). In addition, the clinical features of immunocompetent patients with PM were different: most were men, younger, presented with subacute or chronic disease, and had relatively less severe systemic inflammation compared with immunocompromised patients. The reason for the development of PM in immunocompetent patients is unclear but may be associated with individual susceptibility or exposure to a large amount of *Mucor* microorganisms with high virulence (18). Thus, mucormycosis can infect a variety of patient groups, including severely immunodeficient patients, such as those with hematological malignancies and those who have undergone transplantations; patients using immunosuppressants; patients who are only mildly immunocompromised, such as those with diabetes; and even immunocompetent patients. Patients with different immune status may have different clinical phenotypes.

The clinical manifestations of PM are nonspecific. In the present study, common symptoms included fever, cough, expectoration, and hemoptysis, which is consistent with a previous study (8). Although most patients with PM present with fulminant and rapidly progressive disease, our study revealed that a substantial number of patients can manifest chronic symptoms, as occasionally reported in the literature (21). In addition, our study showed that invasion of contiguous chest structures (chest wall, pericardium, mediastinum) is an unusual complication of PM. PM can also reportedly involve the recurrent laryngeal nerve, leading to vocal cord paralysis (22,23); compress the sympathetic chain, resulting in Horner's syndrome (24); or penetrate the bronchial wall, leading to chronic mediastinitis (25). PM can also invade the chest wall, leading to subcutaneous emphysema, or extend from the lung to abdominal organs (transdiaphragmatic mucormycosis) (26,27).

The radiologic features of PM are also nonspecific and exhibit a wide spectrum of types. In the present study, the common chest CT findings were nodules, masses, or consolidation shadows with or without cavities; these findings are consistent with previous studies (7,8,13,15). The RHS is considered a characteristic imaging finding of PM, and its incidence may reach 54% to 94% (9,12,14,28). In contrast to previous studies, the incidence of the RHS in our study group was very low (4.2%). One possible explanation could be differences in the hosts' immune status. The prevalence of the RHS among patients with PM with hematological malignancies or neutropenia is very high (9,12). While few patients in the present study had these diseases, a substantial number of patients were immunocompetent or mildly immunocompromised (i.e., diabetes). Another explanation might be that the CT scans were performed at different stages of the disease. The RHS in most patients with neutropenia occurs within the first week (9,28). In our study, however, a portion of patients presented with a chronic course, and CT was not performed in the early stage. In severely immunocompromised patients, especially those with hematological malignancies and neutropenia, the RHS is highly suggestive of early infection by Mucorales species and can be useful for preemptive

initiation of antifungal therapy (9,12,29). However, for mildly immunocompromised patients (such as those with diabetes) or immunocompetent patients, the diagnostic value of the RHS for PM remains uncertain because this nonspecific finding is commonly seen in a wide range of infectious and noninfectious pulmonary diseases (29). In the case of pulmonary tuberculosis infection, it has been noted that severe immune suppression may limit the development of a radiographically observable tuberculosis response to infection (30,31). However, this pattern was not demonstrated in our cohort of PM.

In this study, a few patients with PM had an elevated eosinophil level in the peripheral blood or infiltration of eosinophils in lung tissue. The most common etiology of an elevated eosinophil level caused by infectious disease is parasite infestation, but some fungal infections such as coccidioides also cause hypereosinophilia (32-34). Paracoccidioidomycosis, disseminated histoplasmosis, and cryptococcosis can also occasionally cause a high blood eosinophil level. Mucormycosis with increased eosinophils has occasionally been reported (35,36). The role of eosinophils in the pathogenesis of mucormycosis requires further investigation.

The diagnosis of PM is still challenging because of the nonspecific clinical manifestations and imaging features and lack of effective serum markers. Thus, the key to a definitive diagnosis is microbiological or histopathologic evidence (1). In the present study, histopathological examination of tissue specimens had the highest diagnostic yield, followed by direct microscopy or culture of clinical specimens. Therefore, active tissue biopsy is very important for early diagnosis. The biopsy specimens should be delivered for simultaneous pathological examination, direct microscopic examination, and culture (1). Bronchoalveolar lavage fluid, sputum, and pleural effusion specimens are more accessible than biopsy specimens and may also be helpful in the diagnosis. In the present study, about 60% of patients were diagnosed via bronchoscopy or percutaneous puncture, and only a few patients needed a more invasive procedure such as surgical lung biopsy. Other methods that may be helpful for early diagnosis of PM need to be explored, such as the use of molecular methods on both fresh clinical material and paraffin slides, Mucorales-reactive lymphocyte assay on peripheral blood, and quantitative polymerase chain reaction assays for circulating Mucorales detection (1,37,38).

Treatment for mucormycosis includes removal of risk factors, implementation of anti-*Mucor* therapy, and surgical resection in selective patients. The European Society for Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology recommended liposomal AmB as a first-line treatment and posaconazole as a first-line or salvage treatment (1). However, a huge gap exists between clinical practice and these guidelines because antifungal drugs are either very expensive or unavailable. Most patients in the present study were treated with AmB deoxycholate, which is not recommended in the guideline because of its substantial toxicity. Posaconazole became available in the past several years and has thus provided an alternative choice. Nonetheless, the treatment response rate in the present study was more than two-thirds, and the survival rate was slightly higher than in previous studies (2,7-9). A possible explanation is that most of the patients were immunocompetent or mildly immunocompromised. The combination of surgery with medical treatment in patients with mucormycosis is strongly recommended because surgery seems to significantly improve survival (1,2,7,9,39). However, most evidence concerning surgical treatment has been obtained from case reports or small retrospective case series (7,9,39,40). In the present study, most patients responded well to sole antifungal therapy. About three-fourths of patients had multiple lung lesions and were therefore unsuitable for surgical treatment. One patient developed recurrence after surgical resection (18). Therefore, with the emergence of more novel antifungal agents, further studies are needed to evaluate the value of surgical treatment and clarify which patients will benefit most from surgical treatment.

Our study had several limitations, mainly its small size and retrospective nature. Furthermore, because our patients had various host factors, one should be careful when applying these findings to other patients with different risk factors. Finally, because nearly 30% of the cases were probable infections, firm conclusions are difficult to make.

In conclusion, PM can occur in heterogeneous patients with different immune status, and the clinical phenotype differs between immunocompetent and immunocompromised patients. Because of the lack of specific clinic and imaging manifestations, aggressive performance of invasive procedures to obtain histopathological and microbial evidence is crucial for a definitive diagnosis.

Acknowledgments

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of Peking Union Medical College Hospital (Reference number: S-K805).

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