Original Article

Outcomes of early anti-fungal therapy with aggressive surgical resection in pulmonary mucormycosis

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ABSTRACT

Objectives: The standard management protocols are lacking in the management of pulmonary mucormycosis (PM). The present study aims at reporting our clinical experience and proposing an algorithm for the management of PM. **Materials and Methods:** This is a retrospective analysis of a prospectively maintained database at a dedicated thoracic surgical unit in New Delhi, India, over 7 years. An analysis of demographic characteristics and perioperative variables including complications was carried out. Various parameters were analyzed to assess the factors affecting mortality after surgical intervention. **Results:** Out of total 19 patients, 15 were males (78.9%) and 4 females (21.1%), with a mean age of 43.8 years (range, 19–72 years). Chronic kidney disease (status postrenal transplant on immunosuppressant therapy) was the most common predisposing factor in 11 patients (57.8%). All patients were initially started on antifungal therapy, and after 7–8 days, the response was assessed by computed tomography scan of the chest, and based on that, 15 patients (78.9%) were operated (surgical group) and the rest 4 (21.1%) were not (nonsurgical group). In the surgical group, lobectomy was required in 12 (80%) and pneumonectomy in 3 patients (20%). Postoperative complications occurred in 5 patients (33.3%). There were 3 perioperative deaths (within 90 days of surgery) (20%). Poor Eastern Cooperative Oncology Group performance status (>2) and longer duration of symptoms (>2 weeks) were independent predictors of mortality after surgery. The survivors in the surgical group are doing well. However, all four patients in the nonsurgical group died due to disease progression. **Conclusion:** After few days of initiation of antifungal therapy, aggressive surgical resection must be performed (wherever feasible) to improve survival outcome in patients with PM.

KEY WORDS: Amphotericin B, management protocol, mortality, pulmonary mucormycosis, surgery

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INTRODUCTION

Mucormycosis is an infective disease, caused by the filamentous fungi of the order – Mucorales, class – Zygomycetes, and genus – *Mucor*, *Rhizopus*, and *Rhizomucor*.[1] Due to the ubiquitous nature of these fungi, all humans are exposed to them. However, only the immune-compromised develop clinical disease.[2] Uncontrolled diabetes mellitus (DM), prolonged use of corticosteroids, immunosuppressive therapy for solid organ and hematopoietic cell transplantation, and

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conditions causing neutropenia are the common risk factors.[3]

Pulmonary mucormycosis (PM) occurs due to the inhalation of fungal spores into the alveoli. This causes a rapidly progressive infection that leads to pneumonia. The hallmark of this infection is angioinvasion leading to thrombotic infarction and necrosis of lung parenchyma.[4] Due to the aggressive invasive nature of the infection, it can spread locally to surrounding structures (lymph nodes, chest wall, mediastinum, blood vessels, and diaphragm)[5] and also to the distant organs (hematogenously).[6,7] Clinical presentation includes cough, fever, shortness of breath, and occasionally massive hemoptysis.[8]

Early diagnosis, control of underlying comorbidities, antifungal therapy with amphotericin B,[9,10] and aggressive resection of the involved structures are the four cornerstones of PM management. There is enough evidence in the literature to prove the superiority of combined therapy (medical and surgical) over any single (medical or surgical) therapeutic modality.[11,12] However, due to the lack of standard management protocols, the mortality associated with this disease continues to be high. In addition, there are no universally accepted consensus/guidelines regarding the management of this complex clinical condition. The present study aims at reporting our clinical experience of managing PM with special emphasis on principles of surgery, operative outcomes, postoperative complications, and long-term survival. Based on institutional experience, we have also proposed an algorithm for the management of this highly lethal infective disease.

MATERIALS AND METHODS

Study population

This retrospective analysis included 19 patients treated for PM from March 2012 to December 2019 at the department of thoracic surgery in a tertiary referral center in New Delhi, India.

Preoperative evaluation

- Evaluation of general condition and disease extent – Included a detailed history, physical examination, evaluation of comorbidities and complete blood count, renal profile including serum electrolytes, and coagulation profile. All patients underwent computed tomography (CT) of the chest to assess the disease extent. The diagnosis of mucormycosis was made by demonstration of aseptate, filamentous, irregularly wide branching fungal hyphae in the biopsy from the lung parenchymal lesion done by CT or ultrasound guidance. In situations where lung biopsy was not possible, broncho-alveolar lavage from the involved lobe/lung was done and the resultant bronchoalveolar fluid was subjected to microbiological analysis
- Optimization of underlying condition – All patients had detailed evaluation of underlying conditions such as DM, chronic kidney disease (CKD), posttransplant status on immunosuppressive therapy, and chronic steroid usage. For postrenal transplant patients, the dosages of immunosuppressive medications were modified as per the advice of the transplant-physician. Electrolyte and blood sugar abnormalities were corrected. Nephrologist's opinion was sought in all cases of CKD, to optimize the kidney status. Patients were infused 20% human albumin and/or various blood components to correct low albumin levels, low hemoglobin, low platelets, or elevated prothrombin time/international normalized ratio. Nutritional and physiotherapy counseling was done by dedicated personnel attached to the thoracic surgery unit, and it was supervised on a daily basis. This goes a long way in improving their performance status
- Functional evaluation – Predictive postoperative lung function was assessed using pulmonary function tests, diffusion capacity, and ventilation/perfusion scan (selectively in patients likely to require pneumonectomy). Cardiac function was assessed in all patients by echocardiography, and when indicated, coronary angiogram was also done.

Antifungal therapy

The management protocol was as per our institutional policy. All patients were started on injection amphotericin B (Intravenously) till a cumulative dose of 1–1.5 g and oral posaconazole therapy (200 mg thrice a day). This therapy was continued for a duration of 7–8 days and then CT of the chest was repeated to assess the treatment response.

Surgical technique

All patients who underwent surgical resection were operated through posterolateral thoracotomy. The details of surgery are summarized in Table 1. In view of invasive

Table 1: Perioperative details of surgical cohort (*n*=15)

Characteristics	Frequency
Extent of surgery	
Lobectomy	12
Right upper lobe	1
Right upper + middle lobe	2
Right lower lobe	5
Right middle + lower lobe	2
Left upper lobe	1
Left lower lobe	1
Pneumonectomy	3
Right	2
Left	1
Additional structures resected	
Diaphragm resection	5
Chest wall resection	1
Postoperative ICD duration (days) (mean±SD)	6.1±3.2
Hospital stay (days) (mean±SD)	8.1±4.3
Postoperative complications (%)	5 (33.3)
Perioperative mortality (<90 days) (%)	3 (20)

SD: Standard deviation, ICD: Intercostal drain

nature of the disease, a principle of *"when in doubt, take it out"* was always adhered to, wherein no attempt was made to separate the structures adherent to the infected lung tissue, but resected *en bloc* with the infected tissue. Painstaking efforts were made in all the cases to resect all visible infected tissue as far as possible and achieve complete resection. Systematic mediastinal lymph node dissection was performed in all cases as the disease is known to spread to the lymph nodes.

- Lung involvement – Anatomical lung resection was done, i.e., either lobectomy or bilobectomy or pneumonectomy, depending on the extent of lung involvement
- Diaphragmatic involvement – In cases where diaphragm was infiltrated by the infection, a full-thickness resection of the same with 1-cm circumferential margin was performed and the resultant defect in the diaphragm was closed primarily [Figure 1]
- Chest wall involvement – In patients where lung abscess was infiltrated or ruptured into the adjacent chest wall, *en bloc* resection of the involved ribs and intercostal muscles was performed. Reconstruction was not done in such cases as all the defects were posteriorly located, i.e., paravertebral, and the number of ribs in all cases resected was ≤2
- Pleural contamination – Complete parietal pleurectomy was performed in patients where abscess had ruptured into the pleura causing its contamination.

Postoperative care

Patients were extubated at the end of the surgery whenever possible. Patients who required postoperative ventilation were shifted to intensive care unit and kept on ventilator till they were extubated. Injectable amphotericin B was restarted 6 h after surgery. Supervised chest physiotherapy was continued after the surgery to maintain good lung expansion. Special attention was paid to adequate nutritional intake, and patients unable to take enough orally were administered appropriate diet through nasogastric tube. Effective pain relief was achieved by continuous epidural analgesia supplemented by intravenous medications. The chest drains were removed when. Duration of chest tube, hospital stay, and other complications were monitored and recorded.

Follow-up

The first follow□up was done at 2 weeks from discharge. Further follow-up protocol included clinical examination and chest X-rays at 1 month, 3 months, 6 months, and yearly thereafter.

Statistical analysis

Statistical analysis was carried out using Stata 14.0 software (StataCorp LLC, College Station, TX, USA). Continuous variables were presented as mean with standard deviation. Categorical variables were expressed as frequencies with percentages. Linear regression analysis was performed to analyze the factors affecting mortality. For all statistical tests, $P < 0.05$ was taken as "clinically significant."

RESULTS

Demographic characteristics

Out of total 19 patients, there were 15 males (78.9%) and 4 females (21.1%), with a mean age of 43.8 years (range, 19–72 years). The major underlying cause which predisposed these patients to PM was CKD with status postrenal transplant on immunosuppressant therapy in 11 patients (57.8%), followed by DM in 7 patients (36.8%) and chronic liver disease status postliver transplant in 1 patient (5.2%). The disease was more common on the right side (11 patients, i.e., 57.8%). Bilateral presentation was seen in 4 cases (21.1%). The mean duration of symptoms was 2.1 weeks. On radiological evaluation with CT of the chest, pneumonia of the lobe/lung was the most common morphological presentation in 9 patients (47.3%), followed by lung cavitation/lung abscess in 8 patients (42.1%) and diffuse parenchymal infiltrates in 2 patients (10.5%) [Table 2].

Treatment modalities and outcomes

All the 19 (100%) patients were initially started on antifungal therapy, and after 7–8 days, the response was assessed by CT scan of the chest. Out of these, 15 patients (78.9%) were operated whereas the rest 4 (21.1%) were considered not suitable for surgery, due to bilateral diffuse lesions in 2, extensive mediastinal invasion in 1, and upper lobe lesion invading apical chest with engulfment of brachial plexus and subclavian vessels in 1 patient. These patients were continued on maximum dosages of antifungal therapy, but all of them died within 2 months due to disease progression. In the surgical cohort, lobectomy was required in 12 (80%) and pneumonectomy in 3 patients (20%). Along with lung parenchyma, diaphragm was the most common additional structure that was resected in 5 patients (33.3%) followed by chest wall in a single patient (6.6%). In all cases who required pneumonectomy, the bronchial stump was reinforced with pericardial fat pad. Postoperative complications occurred in 5 patients (33.3%). The most common complication was prolonged air leak (>7 days) in 3 patients, residual

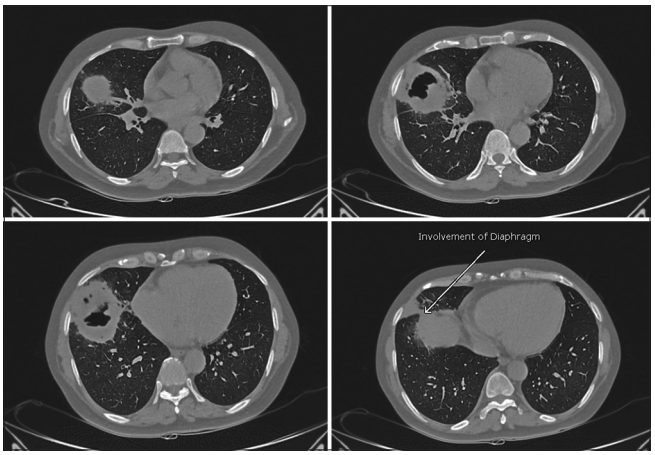

Figure 1: Pulmonary mucormycosis with diaphragm involvement

Table 2: Demographic details and disease characteristics

Characteristics	Frequency
Male (%)	15 (78.9)
Female (%)	4 (21.1)
Age (years) (mean±SD)	43.8±12.1
Duration of symptoms in weeks (mean±SD)	2.1±2.4
Predisposing condition	
Chronic kidney disease (postrenal transplantation on immunosuppression)	11 (57.8)
Diabetes mellitus	7 (36.8)
Postliver transplantation on immunosuppression	1 (5.2)
Side of the disease	
Right side	11 (57.8)
Left side	4 (21.1)
Bilateral	4 (21.1)
Radiological features	
Pneumonia	9 (47.3)
Cavitation	8 (42.1)
Diffuse infiltrates	2 (10.5)
Type of intervention	
Antifungal therapy alone	4 (21)
Antifungal + surgical therapy	15 (79)

SD: Standard deviation

pleural collection in 1 patient, and wound infection in another patient. There were 3 perioperative deaths (within 90 days of surgery) (20%). One patient had on-table cardiac arrest, was revived but developed multi-organ failure, and expired on the 3rd postoperative day. The other two patients continued to be in fungal sepsis and expired 20 days and 1 month after surgical intervention [Table 1 and Figure 2].

Factors influencing "mortality" in the surgical cohort

Poor Eastern Cooperative Oncology Group performance status (>2) and longer duration of symptoms (>2 weeks) were independent predictors of mortality after surgery in patients with PM [Table 3].

DISCUSSION

PM was first described by Furbringer from Germany in 1876.[13] In recent times, the incidence of this infectious complication is rapidly increasing. This is due to increase in the usage of immunosuppressive medications used for solid organ transplantation and hematopoietic cell transplantation, hematological malignancies, and various conditions associated with prolonged use of corticosteroids.[14-16] PM is an extremely aggressive infection due to the angioinvasive and thrombotic nature causing tissue necrosis.[4] Due to this property, it causes pneumonia, pulmonary infarction, and necrosis, which spreads rapidly to contiguous structures such as the mediastinum, heart, blood vessels, and lymph nodes or disseminates hematogenously to other organs.[7] This is why timing of starting antifungal therapy has a major influence on the ultimate outcome of the disease. The cornerstones of PM treatment are (1) early diagnosis, (2) reversal of the underlying factors, (3) antifungal therapy, and (4) surgical resection. A high index of suspicion is the key for an early diagnosis. Due to the difficulties in the diagnosis of the disease, the initiation of antifungal medications should be done at the earliest suspicion, as delaying the initiation of antifungal therapy is associated with poor clinical outcomes. A study by Chamilos *et al*. quantified the benefit of early initiation of polyene antifungal therapy. They reported that if treatment was initiated within 5 days of symptoms of mucormycosis, survival was markedly improved compared to initiation at ≥6 days after symptoms (83% vs. 49% survival).[9] Various other studies also evaluated and confirmed the beneficial effects of early initiation of amphotericin B in mucormycosis.[17,18] In addition, underlying disease status should be controlled to achieve optimal outcomes, i.e., reducing the dosage of steroids or aggressive diabetes management with control of acid-base balance or altering the dosage of immunosuppressants.

Antifungal therapy alone is not sufficient to eliminate the disease completely. The blood vessel thrombosis with necrosis results in poor penetration of the antifungal agents to the site of infection.[6] Therefore, surgical resection of involved, necrotic tissues is critical for complete eradication of mucormycosis.[8] Hence, the definitive treatment of this disease is antifungal therapy combined with aggressive surgical resection.[19] Surgical resection along with perioperative antifungal cover has been proven to improve clinical outcomes.[20,21] The role of surgery should be considered as an adjunct to antifungal therapy rather than an alternative and in cases of complications such as hemoptysis, empyema, or bronchopleural fistula.[22] The extent and timing of surgical resection necessary to maximize the outcomes of PM have never been defined. However, it depends on the extent of disease involvement and the general condition of the patient. The principles of surgical resection include aggressive resection of all involved tissue to achieve clear margins[23] with complete mediastinal lymph nodal dissection. Perioperative antifungal therapy is critically essential. Surgical resection in such cases is really challenging because of two reasons – dense pleural adhesions and angioinvasion. The dense adhesions of lung parenchyma to the surrounding structures could be the result of poor immunological status leading to the aggressive spread of fungi.[24] In addition, these changes also cause great difficulty in distinguishing the normal anatomical layers. Due to these dense hilar adhesions and unclear anatomy, in three patients who underwent pneumonectomy in this series, the pulmonary artery and vein ligation had to be done by intrapericardial route, as the lung hilum was totally frozen with no differentiation between different vascular structures. Patients who have bilateral multilobar involvement or extensive mediastinal involvement are not candidates for surgery. They should be continued on antifungal therapy. However, they have a dismal outcome, with most of them succumbing to the disease over the next few weeks.

The most common presenting symptoms are dry cough, fever, chest pain, shortness of breath, and occasionally

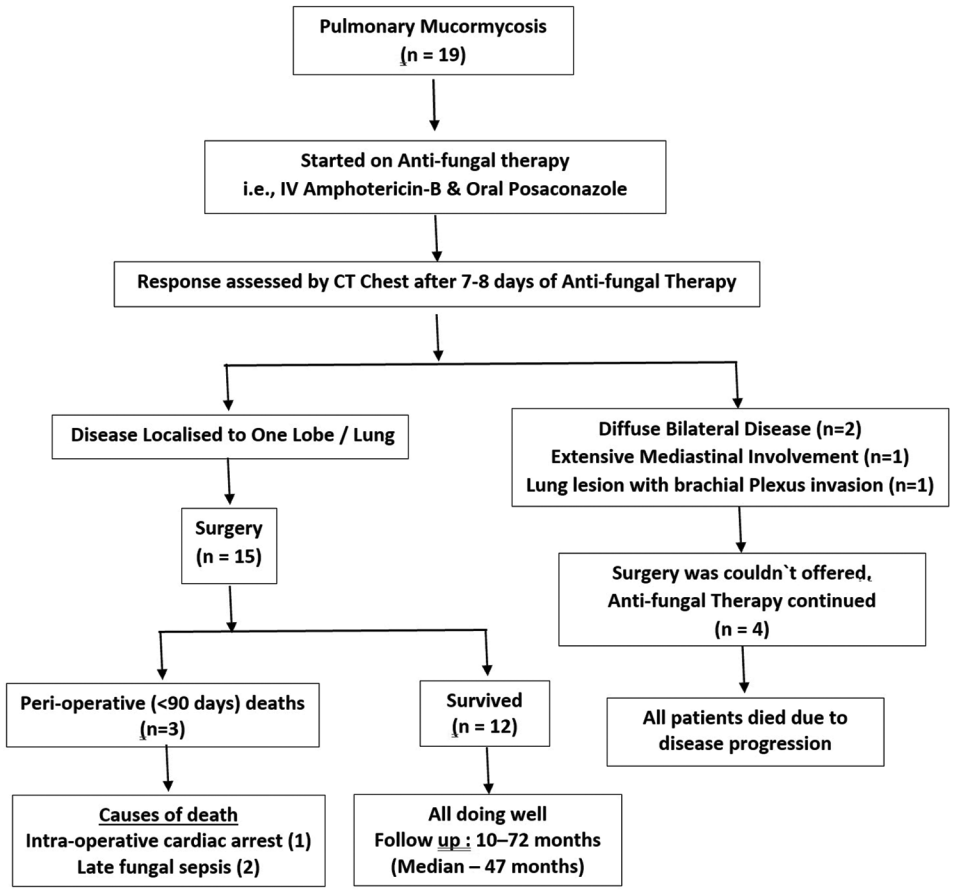

Figure 2: Flowchart of management of pulmonary mucormycosis in the study population

Table 3: Analysis of factors affecting mortality in surgical cohort (*n*=15)

Variables	Characteristics	Number of patients	Mortality	*P* (univariate analysis)	*P* (multivariate analysis)
Age of patient (years)	≤40	10	2	0.24	0.72
	>40	5	1		
ECOG Performance Scale#	>2	4	3	0.01	0.04
	≤2	8	0		
Type of surgery	Pneumonectomy	3	2	0.08	0.11
	Lobectomy	12	1		
Duration of symptoms (weeks)	≤2	5	3	0.02	0.04
	≥2	10	0		

ECOG: Eastern Cooperative Oncology Group, #Performance status of the patient is a scientifically proven factor which can affect the postoperative mortality of the patient. This method is usually used in oncology patients. However, we extended the same method in our study to analyze the morality which is proven to be significant.

hemoptysis.[25] The radiological features of PM are mostly nonspecific with manifestations of parenchymal infiltrates, nodules, cavitation, atelectasis, effusion, hilar, or mediastinal lymphadenopathy.[26] In some cases, CT of the chest shows "reverse halo sign," i.e., a focal round area of ground-glass attenuation surrounded by ring of consolidation.[27] In the present study, lobar pneumonia was the most common radiological manifestation, followed by lung abscess. These findings were similar to the observations by previous studies.[28] The definitive diagnosis can only be made by demonstration of the characteristic broad nonseptate hyphae in sputum or bronchoalveolar lavage (BAL) fluid or lung biopsy.[29,30] In our series, BAL was able to diagnose PM in 36.8% of cases, whereas in the rest 63.3% of cases, diagnosis was proved by lung biopsy.

Earlier studies reported an overall survival rate in the range of 30%–50%.[6,11] However, the overall survival (surgical + nonsurgical patients) in the present study was 63.1% which is higher than earlier reports. In addition, the survival rate in the surgical group (80%) was also similar to the previous studies. Poor performance status and longer duration of symptoms (>2 weeks) were the poor prognostic factors affecting the survival. Therefore, based on our institutional experience, we recommend the

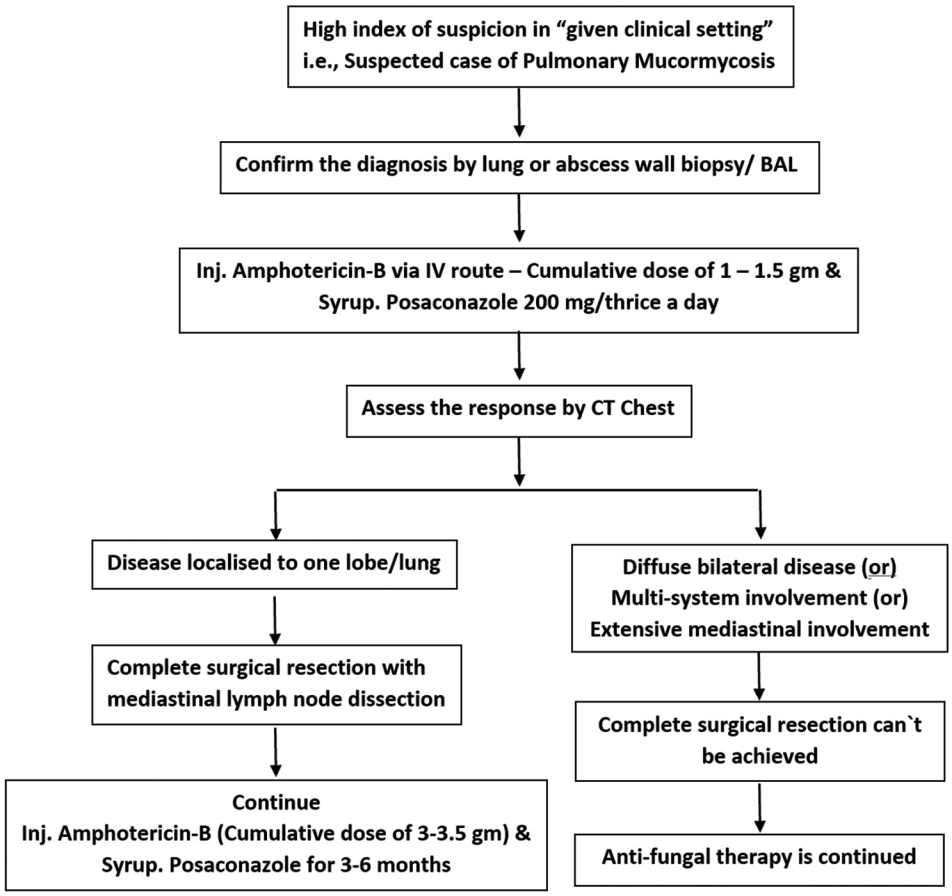

Figure 3: "Centre for Chest Surgery" protocol for management of pulmonary mucormycosis

"Centre for Chest Surgery protocol" [Figure 3] for effective management of PM.

The present study had various limitations. Major limitation of the study is it`s retrospective nature. The second limitation is the lack of well-matched control group (i.e., patients managed by nonsurgical methods having similar characteristics of surgical group). Consequently, this is likely to cause a number of biases, including selection, detection, and performance bias. Third, there was no analysis directed at survival in relation to various species of order Mucorales. Finally, the power of this study is also limited by small cohort of patients, which may also question the significance of multivariate analysis used to assess factors affecting mortality.

CONCLUSION

The prevalence of PM is going to be more and more in the future. A high index of suspicion is the key for early diagnosis. Antifungal therapy should be started at the earliest, even before establishing the confirmatory diagnosis with optimization of underlying risk factors. Antifungal therapy alone is not adequate for the complete eradication of the disease. After 7–8 days of antifungal therapy, aggressive surgical resection must be performed (wherever feasible) with prolonged postoperative antifungal treatment to improve long-term survival. The present study emphasizes the feasibility, safety, and efficacy of surgical intervention in patients with PM.

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Conflicts of interest
There are no conflicts of interest.

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