Pulmonary mucormycosis: A case report and review of the literature

XI-MING WANG¹, LING-CHUAN GUO², SHENG-LI XUE³ and YAN-BIN CHEN⁴

Departments of ¹Radiology, ²Pathology, ³Hematology and ⁴Respiratory Medicine, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, P.R. China

Received February 1, 2015; Accepted February 19, 2016

DOI: 10.3892/ol.2016.4370

Abstract. The current study reports the case of a 15-year-old male who presented to The First Affiliated Hospital of Soochow University (Suzhou, Jiangsu, China) with a 3-day history of anergy and epistaxis. The patient was diagnosed with T-cell acute lymphoblastic leukemia according to the results of a bone marrow examination and received chemotherapy. During the agranulocytosis period, the patient developed pneumonia of the right upper lung (RUL). Once complete remission was achieved, the patient underwent a lobectomy of the RUL, together with amphotericin B therapy, following the confirmation of pulmonary mucormycosis by the histopathological results. The patient experienced 12 months of uneventful follow-up post-surgery.

Introduction

Mucormycosis is an opportunistic infection that is caused by Mucorales fungi of the Zygomycetes class. The term zygomycosis, the previous designation for infections caused by fungi of the order Mucorales, is no longer appropriate due to a recent taxonomic reclassification that abolished Zygomycetes as a class (1). Mucorales fungi are ubiquitous, saprophytic and not fastidious fungi located in soil or decaying organic matter, with three genera that are known to be human pathogens, namely, Rhizopus, Absidia and Mucor. The optimal temperature for growth is 28 to 30°C under aerobic conditions, with an incubation period of 2 to 5 days. Incubation begins with inhalation of the spores or their direct inoculation into abraded skin (2). Six distinct clinical presentations of mucormycosis are now recognized: Rhinocerebral, cutaneous, pulmonary, gastrointestinal and central nervous system mucormycosis, and a miscellaneous form involving the bones, breasts, mediastinum and kidneys. The first case of pulmonary mucormycosis was described in 1876 by Furbringer (3). The estimated incidence of the disease is 1.7 cases per million people per year in the United States (4). In a review of 116 cases of mucormycosis, 22% were pulmonary mucormycosis (5). However, the incidence of pulmonary mucormycosis has increased with the development of modern medicine. Numerous predisposing clinical factors have been described, including uncontrolled diabetes mellitus, diabetic ketoacidosis, chemotherapy, hematological malignancies (leukemia and lymphoma), immunosuppressive therapy, acquired or congenital neutropenia, antibiotic therapy, metabolic acidosis due to chronic salicylate poisoning, elastoplast bandages, renal failure, a prolonged post-operative course, solid tumors, solid organ transplantation, agammaglobulinemia and burns (6-8). It is well known that iron metabolism has a key role in mucormycosis pathogenesis. Therefore, patients in an iron overload state, including those individuals undergoing deferoxamine chelation therapy, are uniquely predisposed to mucormycosis (9). Only 6.25% patients do not have any underlying risk factor (10,11). In patients with hematological malignancies, mucormycosis most commonly affects the lungs (58-81%) (12). A previous single-center autopsy study over a 15-year period in patients with hematological malignancy reported a significant 3-fold increase in the incidence of autopsy-proven mucormycosis cases, from 0.9-3%, during the study period (13). The present study reports the case of a patient with a definite histological diagnosis of pulmonary mucormycosis.

Case report

A previously healthy 15-year-old male was admitted to The First Affiliated Hospital of Soochow University (Suzhou, Jiangsu, China) in January 2012 with a 3-day history of anergy and epistaxis. There was no history of hemoptysis, fever, chills, night sweats, chest pain, diabetes mellitus or weight loss. The patient reported no history of steroid use. Physical examination showed a well-developed male with facial pallor and fresh petechia on the lower limbs. The patient had a temperature of 36.7°C (normal range, 36-37°C), a pulse rate of 80 beats/min (normal range, 60-100 beats/min), a respiratory rate of 20 breaths/min (normal range, 12-20 breaths/min) and a blood pressure of 120/60 mmHg (normal range, <130/85 mmHg). Further physical examination results were unremarkable. The chest radiograph
showed no abnormalities (Fig. 1). A full blood count revealed a hemoglobin level of 76 g/l (normal range, 120-150 g/l), a platelet count of 1.5x10⁹/l (normal range, 100-300x10⁹/l) and a white blood cell count of 1.24x10¹¹/l (normal range, 4.00-10.00x10⁹/l), with 1.24x10⁹/l neutrophils (normal range, 1.80-6.30x10⁹/l), 2.98x10⁹/l lymphocytes (normal range, 1.10-3.20x10⁹/l), and 9.3x10⁹/l precursor cells and juvenile cells (normal range, 0 cells). Bone marrow examination revealed 89.1% of the naive population were T lymphocytic cells (normal range, 0%). The patient was therefore diagnosed with T-cell acute lymphoblastic leukemia (T-ALL). At 3 days post-evaluation, the patient received induction chemotherapy with an IVP regimen (10 mg idamycin on days 1-4; 4 mg vindesine once a week for four weeks; and 10 mg dexamethasone every day).

On the 15th hospital day the patient developed a fever, with a temperature of 39°C. Computed tomography (CT) scans showed right upper lobe (RUL) infiltration (Fig. 2). The white blood cell count was 0.3x10⁹/l and the neutrophil count was 0.03x10⁹/l. Throat swab, blood, urine and sputum cultures for bacteria and fungus were repeatedly obtained, but did not reveal any pathogens. Sputum smears for acid-fast bacilli were negative, and galactomannan testing (GM) for diagnosing invasive aspergillosis was negative. The patient clinically improved following intravenous meropenem (0.5 g; every 8 h), teicoplanin (3 mg/kg; every 12 h), amphotericin B (1 mg on day 1, then add 5 mg every day until 0.5 mg/kg/day reached) and caspofungin (70 mg on day 1, then 50 mg/day) empirically.
for one week, however, radiography showed progression of the infiltrating lesion in the RUL (Figs. 3-5). Following chemotherapy with L-asparaginase (10,000 units every other day, three times), the patient had a white blood cell count of 8.27x10⁹/l, a hemoglobin level of 84 g/l and a platelet count of 195x10⁹/l. Bone marrow morphology showed complete remission had been attained. The patient underwent a lobectomy of the RUL at 40 days post-admission, during which the infected area and necrotic tissue were resected. During surgery, a mass measuring 5x5x5 cm was revealed arising from the posterior segment of the RUL, which was tightly adherent to the chest wall. The pulmonary hilar lymph nodes were slightly enlarged. Histological study of the mass using hematoxylin and eosin staining revealed features consistent with pulmonary mucormycosis. The mass was composed of a large amount of right-angled branching, broad, non-septate hyphae. Epithelioid cells and an intense chronic inflammatory reaction were noted (Fig. 6). The patient experienced 12 months of uneventful follow-up post-surgery; however, the patient died from septic shock 13 months following surgery.

Written informed consent was obtained from the patient for the publication of the study.

Discussion

The present study reports the case of a young boy with T-ALL that developed agranulocytosis following chemotherapy at the same time as pneumonia. RUL infiltration progressed after empirical antibiotic therapy, which included antifungal agents. Surgery was the first choice of treatment for the patient and, fortunately, pulmonary mucormycosis was diagnosed subsequent to the lobectomy, so amphotericin B therapy was continuously provided. The patient’s pulmonary mucormycosis was successfully treated.

Pulmonary mucormycosis occurs due to the inhalation of fungi spores into the bronchioles and alveoli, which typically results in the rapid progression of pneumonia or endobronchial disease. Rarer results include endobronchial lesions and complications associated with airway occlusion. Hemoptysis commonly occurs with vascular invasion, which can occasionally be fatal. The symptoms of pulmonary mucormycosis are typically non-specific, even at late stages of infection, and may include fever, dyspnea, coughing and chest pain. Rare cases can present as progressive subcutaneous emphysema, Pancoast syndrome, Horner’s syndrome, or chronic mediastinitis and bronchial perforation (7,14-17).

The radiological manifestations of pulmonary mucormycosis are mostly non-specific. An abnormal chest roentgenogram result is present in >80% of patients (18). The reported findings include consolidation, cavitation, the air-crescent sign, the halo sign, the reversed halo sign, solitary or multiple pulmonary nodules or masses, bronchopleural fistulae, pulmonary artery pseudoaneurysms, lymphadenopathy and pleural effusion. Cavitation is observed in as many as 40% of cases, but the air-crescent sign is uncommon. CT can show findings that alter the management or diagnostic approach in as many as 26% of patients (19-24). The presence of the air-crescent sign often portends a poor prognosis if surgical therapy is delayed. Similar to invasive pulmonary aspergillosis, pulmonary mucormycosis is detected with the highest sensitivity when using high-resolution chest CT to determine the extent of the disease. This technique also usually finds evidence of the infection earlier than standard chest radiographs (2,4,9). The right lung is more commonly involved than the left, and there is a predilection for the involvement of the upper lobes, although the reason for this remains unknown. The present case reported a lesion in the RUL, as in the majority of the cases in the literature (25).

Histopathologically, vascular invasion with tissue necrosis and neutrophilic infiltration of the tissue is common to all types of mucormycosis. Diagnosis is achieved by demonstrating broad (diameter, 6-16 µm), non-septate (coenocytic), ribbon-like hyphae, with right-angled branching in a tissue biopsy specimen stained with routine hematoxylin and eosin. Special fungal stains are usually not necessary for diagnosis. The less common and less specific features of pulmonary mucormycosis include bronchial invasion, pneumonia, lung abscesses and granulomatous pneumonitis (20,21).

As pulmonary mucormycosis demonstrates rapid clinical progression and is often fatal, patient survival is dependent on an early diagnosis. Mucorales fungi are ubiquitous saprophytic fungi that grow in decaying organic matter, particularly fruit with a high sugar content, soil and manure. Although the fungi are able to grow in anaerobic, aerobic and microaerophilic conditions, clinical specimen cultures often prove to be negative, making the diagnosis difficult. There has previously been no serological test for mucormycosis. The symptoms, signs and radiographic manifestations of pulmonary mucormycosis are non-specific. Pulmonary mucormycosis is associated with bacterial pneumonia in 30% of cases, which can delay the diagnosis of the fungal infection (26). Diagnostic options are largely limited to the clinical and radiographic findings, together with staining and culture. A definitive diagnosis depends on the identification of mucoraceous hyphae in affected tissues (9,21); diagnostic techniques used to achieve this identification include percutaneous needle biopsy, open lung biopsy and pleural fluid culture. Fiberoptic bronchoscopy is a useful diagnostic method, and an adequate bronchoalveolar lavage specimen provides enough diagnostic material to form a cytological diagnosis (27). The differential diagnosis of the
Pulmonary mucormycosis presenting as Persistent cavitations in pulmonary, 1. outcome than medical therapy alone (surgical develops in a patient with hematological disease (fungal sepsis, respiratory failure and hemoptysis (Delays in the diagnosis result in a lethal clinical course due to In total, <50% of patients are diagnosed premortem (If untreated, survival beyond 2 weeks is distinctly unusual (rapidly fatal illness, with an overall mortality rate of 76%, which massively hemoptysis, surgery should be performed as soon as to one lung (lower mortality rates in published series of patients with resection of the involved areas of the lung and treatment of the underlying disease, is the mainstay of treatment (25). Despite the risk of renal toxicity, amphotericin B (1-1.5 mg/kg/day) remains the gold-standard antifungal agent used against mucormycosis. Oral posaconazole is also recommended, but these two types of drugs are often ineffective without surgical intervention (9,10,30-32). Voriconazole is ineffective against mucormycosis (33). Although the therapy duration is not well defined, a total cumulative dose of 1.5 g of amphotericin is usually sufficient in the selective group of patients who respond only to amphotericin therapy (34). Surgical therapy, such as wedge resection, lobectomy and pneumonectomy, in combination with medical therapy, has been associated with lower mortality rates in published series of patients with Mucor infection, particularly in patients with disease confined to one lung (35-38). In order to prevent dissemination and erosion into the vessels, which can result in potentially fatal massive hemoptysis, surgery should be performed as soon as possible (39).

Unlike pulmonary aspergillosis, pulmonary mucormycosis has a prognosis and outcome that have not significantly improved over the last decade, mainly due to the difficulty in forming an early diagnosis and the limited activity of current antifungal agents against Mucorales (9,11). Pulmonary mucormycosis is a rapidly fatal illness, with an overall mortality rate of 76%, which increases to 95% with extrathoracic dissemination (57,9,40-43). If untreated, survival beyond 2 weeks is distinctly unusual (40). In total, <50% of patients are diagnosed premortem (18). Delays in the diagnosis result in a lethal clinical course due to fungal sepsis, respiratory failure and hemoptysis (44,45). The outcome is typically fatal when pulmonary mucormycosis develops in a patient with hematological disease (41). Combined surgical/medical treatment may provide a better survival outcome than medical therapy alone (46).

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