A young boy with diabetic ketoacidosis and non-resolving pneumonia

Rakesh Kodati [1], Narendra Kumar Narahari[1], Anuradha Tadepalli[2], Nishika Madireddy[2], Bhaskar Kakarla[1] and Paramjyothi Gongati[1]

[1]Department of Pulmonary Medicine, Nizam's Institute of Medical Sciences, Hyderabad, India. [2]STAR Hospitals, Hyderabad, India.

Corresponding author: Rakesh Kodati (kodatirakesh@gmail.com)

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Classic radiological signs of invasive fungal disease, especially pulmonary mucormycosis in a predisposed individual should alert the physician to initiate empiric anti-fungal therapy. https://bit.ly/40gt4Hm

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A 16-year-old boy presented to us with a history of high-grade fever associated with chills, dry cough and anorexia for the past 3 weeks. He had altered mentation in the form of excessive drowsiness of 5 days' duration. He had no comorbid illnesses. He was treated as community-acquired pneumonia with oral antibiotics (amoxicillin–clavulanate and azithromycin) followed by intravenous antibiotics (piperacillin–tazobactam). No clinical response was seen despite 2 weeks of therapy and he was referred to us.

On examination, the pulse rate was 120 beats per min, respiratory rate was 25 breaths per min, blood pressure was 110/70 mmHg, and temperature was 38.9°C (102°F). Saturation on pulse oximetry was 92% while breathing room air. Chest auscultation revealed right mammary, infraclavicular, infra-axillary and infrascapular crepitations. He was drowsy but arousable. There were no meningeal signs or focal neurological deficits. The rest of the systemic examination was unremarkable. A plain chest radiograph was performed in the emergency unit (figure 1).

Task 1

Describe the findings on the chest radiograph?

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A contrast-enhanced computed tomography (CT) was arranged as he had no response to initial therapy. Blood investigations revealed neutrophilic leukocytosis (12 500 cells per mm^3; absolute neutrophil count 11 250 cells per mm^3), high blood glucose levels (420 $mg \cdot dL^{-1}$), and normal renal and liver parameters. Urine ketones were positive and his blood gas parameters revealed high anion gap metabolic acidosis (pH 7.20, bicarbonate (HCO_3^-) 15 $mmol \cdot L^{-1}$, arterial carbon dioxide tension 24 mmHg, anion gap 20) with mild hypoxaemia (oxygen tension 64 mmHg) and hypokalaemia (potassium 3.2 $mmol \cdot L^{-1}$). Haemoglobin A1C was 13%. HIV by enzyme-linked immunosorbent assay was negative. A diagnosis of diabetic ketoacidosis with non-resolving pneumonia and hypoxic respiratory failure was made. He was started on intravenous fluids, *i.v.* insulin infusion and potassium correction.

Task 2

What does the CT scan of the thorax show (figure 2)?

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The patient underwent flexible bronchoscopy under conscious sedation. It showed blackish endobronchial mucosa in the right bronchial tree distal to the opening of right upper lobe bronchus (figure 3a). The

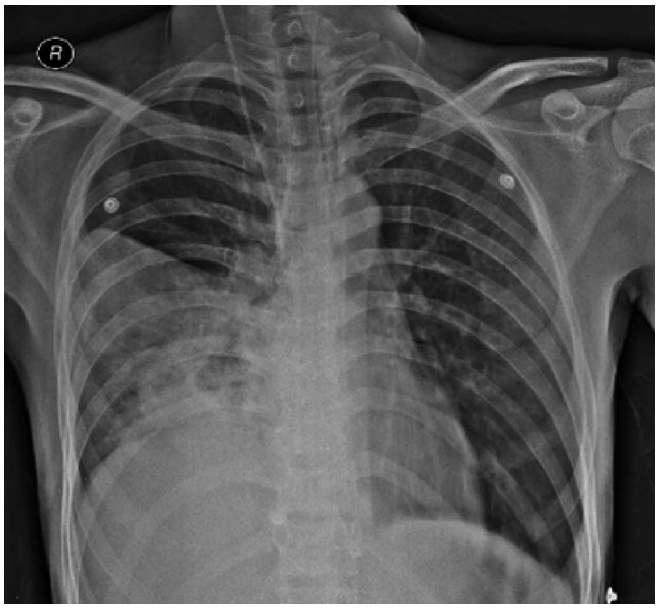

FIGURE 1 Chest radiograph at the time of admission.

bronchial mucosa was oedematous and had a few whitish membranes seen in the right lower lobe (figure 3b). Bronchoalveolar lavage (BAL) was carried out along with biopsy of the membranes without any complications.

Task 3

What is your provisional diagnosis after bronchoscopy at this point in time?

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He was started on empirical antifungal therapy with *i.v.* liposomal amphotericin B (5 $mg \cdot kg^{-1}$), pending diagnostic confirmation. Serum electrolytes and renal function were closely monitored. His blood glucose levels were controlled and sensorium improved. He was switched to subcutaneous insulin therapy and started on oral feeds. His fever spikes continued despite 5 days of antifungal therapy. BAL fluid analysis and biopsy reports were obtained and are shown in figure 4.

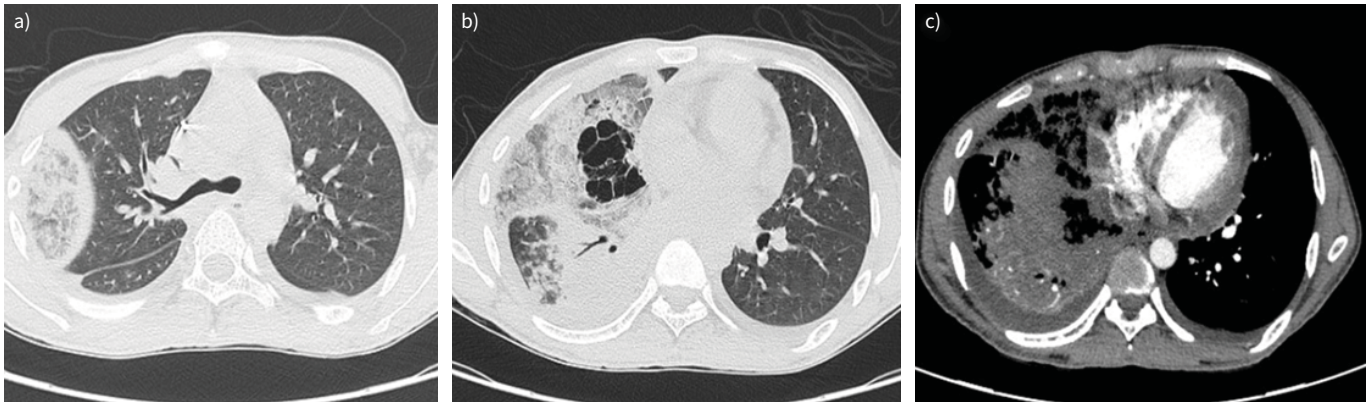

FIGURE 2 Computed tomography of the chest: a) lung window at the level of carina; b) lung window at the level of pulmonary veins entering the left atrium; and c) mediastinal window.

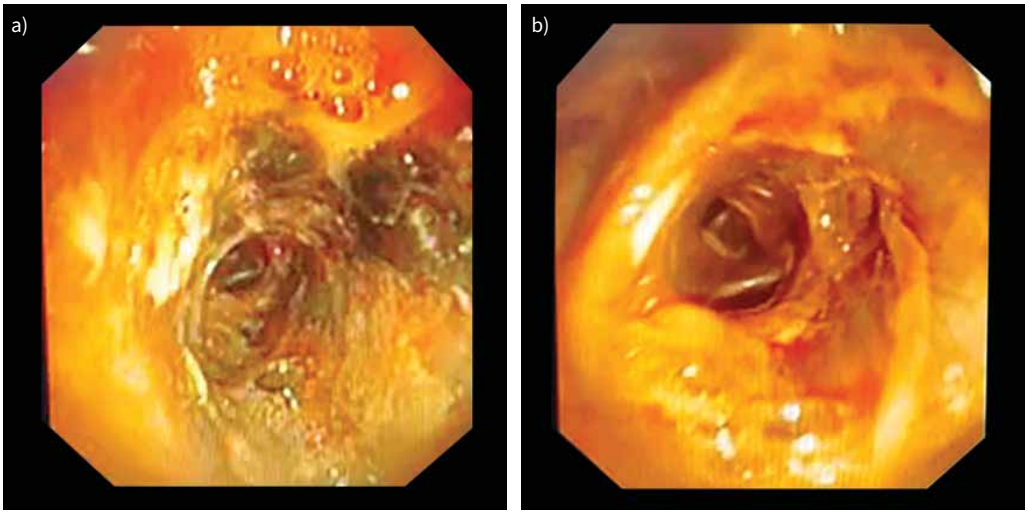

FIGURE 3 Flexible bronchoscopy showing a) blackish endobronchial mucosa at the opening of right bronchus intermedius and b) whitish necrotic mucosal membranes in the distal segments of right lower lobe.

Task 4

What does the microbiological and histopathological examination of bronchoscopic specimens show?

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The diagnosis of pulmonary mucormycosis was confirmed. He was continued on *i.v.* liposomal amphotericin B. The culture on Sabouraud's dextrose agar grew mycelial colonies, identified to be *Rhizopus arrhizus*. Consultation with a thoracic surgeon was sought for lung resection surgery.

Task 5

What is the preferred treatment for this patient?

a) Liposomal amphotericin B
b) Isavuconazole
c) Combination of liposomal amphotericin B and isavuconazole
d) Lung resection surgery only
e) Liposomal amphotericin B and lung resection
f) Isavuconazole and lung resection

Go to Answers >>

He underwent right pneumonectomy with partial pericardiectomy. Post-surgical resection, amphotericin B was continued for 4 weeks. He had a significant clinical response, and the antifungal was switched to oral posaconazole (300 mg every 12 h on the first day, then 300 mg once daily). He remained well at 3-month follow-up.

Discussion

Mucormycosis refers to infections caused by fungi of the order Mucorales. Most human infections are caused by *Rhizopus* spp., with *Rhizopus arrhizus* being the most common organism. The other clinically relevant organisms within the order Mucorales include: *Mucor* spp., *Lichtheimia* spp., *Rhizomucor* spp., *Actinomucor* spp., *Apophysomyces* spp., *Cunninghamella* spp., *Saksenaea* spp., and *Syncephalastrum* spp. [1, 2].

The disease is characterised by infarction and necrosis of the host tissues due to invasion of the fungal hyphae. The most common clinical presentation is rhino-orbital-cerebral infection presenting as sinusitis with local spread. Cutaneous/soft tissue, pulmonary, gastrointestinal, central nervous system and disseminated mucormycosis are also seen. Suspected mucormycosis requires urgent intervention because of the rapidly progressive and destructive nature of the infection.

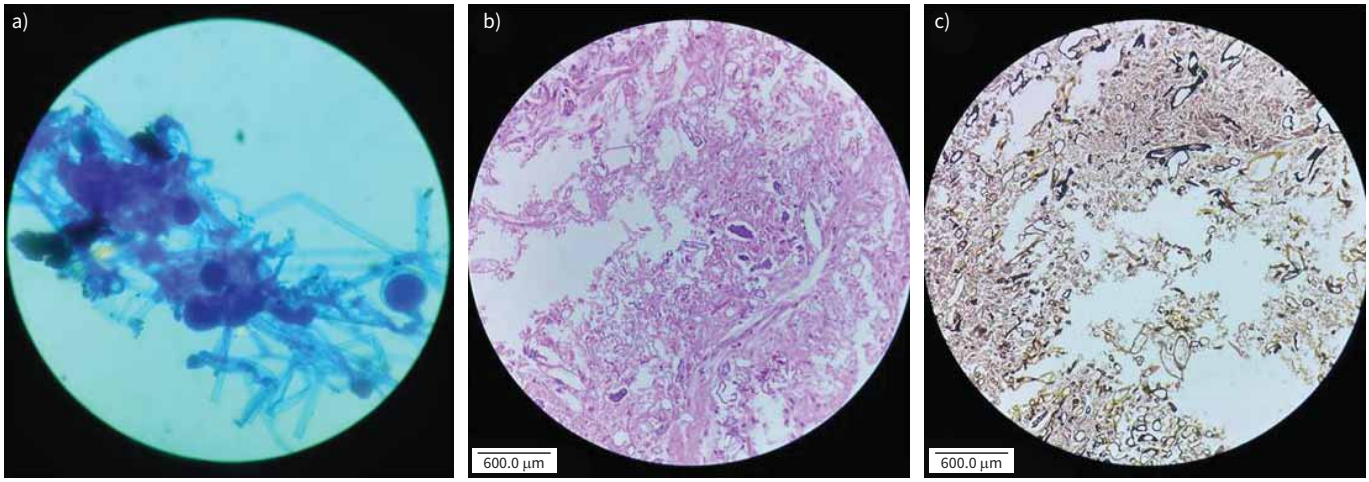

FIGURE 4 a) Lactophenol blue stain of the bronchoalveolar lavage specimen; b) histopathological examination of the bronchial membrane (haematoxylin and eosin stain, 400× magnification); and c) Gomori's methenamine silver stain (400× magnification).

Almost all patients with invasive mucormycosis have some underlying disease that both predisposes to the infection and influences the clinical presentation. Diabetes mellitus, particularly with ketoacidosis, is a common predisposing condition. Neutropenia, haematological malignancy, solid organ transplantation, haematopoietic stem cell transplantation, and deferoxamine therapy are the other risk factors. The low PH and hyperglycaemia in diabetic ketoacidosis causes dysfunction of phagocytes with impaired chemotaxis and defective intracellular killing by both oxidative and nonoxidative mechanisms. The acidosis also causes dissociation of iron from iron sequestering proteins, resulting in increased levels of free iron which enhances fungal survival and virulence [3]. There was a recent surge of cases of mucormycosis diagnosed with or within 3 months of coronavirus disease 2019 (COVID-19), labelled as of COVID-19-associated pulmonary mucormycosis (CAPM).

The clinical course of the infection is usually fast progression, but there are rare descriptions of indolent disease. There are certain radiological signs on CT scan that suggest the presence of invasive mould disease in an appropriate clinical setting. Reversed halo sign (RHS), thick-walled cavity, bird's nest sign (BNS), vessel occlusion sign (VOS), mycotic aneurysm, large consolidation or necrotising pneumonia, and multiple large nodules (nodules >1 cm) and serial imaging showing a cavity with an air-fluid level were suggestive of CAPM [4]. RHS is a CT appearance of central ground-glass opacity within a ring- or crescent-shaped rim of consolidation in the lung parenchyma. BNS refers to the appearance created by a RHS with associated irregular and intersecting areas of stranding or irregular lines within the area of ground-glass opacity. Infarction of the lung tissue at the centre, with greater amounts of haemorrhage at the periphery of the lesion is the underlying pathogenesis. VOS on CT angiography is defined as an interrupted vessel at the border of a focal lesion without depiction of the vessel inside the lesion or peripheral to the lesion. RHS and BNS are also seen in various clinical conditions, including cryptogenic organising pneumonia, bacterial pneumonia, paracoccidioidomycosis, tuberculosis, sarcoidosis, granulomatosis with polyangiitis and pulmonary infarction [5]. However, the presence of these signs in an immunocompromised host makes invasive fungal disease more likely than other conditions. Also, greater thickness of the rim (1 cm) of the lesion and the presence of an associated pleural effusion points towards fungal pneumonia [6].

The diagnosis is usually made by microbiological and histopathological examination of clinical samples (sputum, BAL, bronchial or lung biopsy). Direct microscopy with fluorescent stains (Calcofluor White or Blankophor) and culture for species identification is recommended. Demonstration of broad ribbon-like aseptate or pauci-septate hyphae with an irregular pattern of branching is characteristic of mucormycosis [7].

Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy. Elimination of predisposing factors is also critical for better outcomes. In the index case diabetic ketoacidosis was the underlying culprit, which was addressed, along with pneumonectomy and antifungal therapy. Liposomal amphotericin B is the therapy of choice. When liposomal amphotericin B is not available, other lipid formulations of amphotericin B could be used. Once a complete or partial

response is achieved, maintenance treatment with isavuconazole or posaconazole should be initiated. Delaying antifungal therapy is associated with increased mortality, especially among patients with haematological malignancy [8]. Obtaining tissue for analysis can be challenging in certain circumstances, which necessitates relying on radiographic findings in a susceptible host.

Currently there is no sufficient evidence suggesting the benefit of combination antifungal therapy over a single drug [9]. The duration of antifungal therapy should be highly individualised. It is usually continued until resolution of signs and symptoms, and radiographic improvement of the active disease [10]. When feasible, therapy should also continue until reversal of underlying immunosuppression has been achieved.

Conclusion

Pulmonary mucormycosis is an uncommon but life-threatening invasive mould infection occurring in immunosuppressed patients. Diabetes mellitus patients, especially subjects with diabetic ketoacidosis, are at high risk for acquiring the infection. Radiological signs like RHS and BNS on CT of the thorax should alert the physician to start empirical antifungal therapy, pending diagnostic confirmation.

Answer 1

The chest radiograph demonstrated right mid and lower zone inhomogeneous opacity with blunting of the costophrenic angle. A central venous line is seen in the internal jugular vein. The abnormal radiograph was suggestive of consolidation in the right lung and pleural effusion.

<< Go to Task 1

Answer 2

The CT scan shows a round lesion in the right upper lobe with central ground-glass opacities surrounded by rim of consolidation suggestive of reversed halo sign (figure 2a). Right middle lobe consolidation with central break down and irregular, intersecting areas of stranding or irregular lines within the lesion suggestive of bird's nest sign (figure 2b). Mild right pleural effusion and pericardial effusion seen on mediastinal window (figure 2c).

<< Go to Task 2

Answer 3

Invasive fungal disease, probably pulmonary mucormycosis involving the right lung with pleuropericardial effusion. Diabetes mellitus and diabetic ketoacidosis is the underlying predisposing factor.

<< Go to Task 3

Answer 4

Lactophenol blue mount of the BAL specimen showed fungal hyphae with sporangiophores and spherical sporangia (figure 4a). Histopathology of the membrane showed numerous broad aseptate hyphae in the background of fibrocollagenous stroma consistent with zygomycetes (figure 4b). Gomori's methenamine silver stain highlighted the fungal hyphae (figure 4c).

<< Go to Task 4

Answer 5

e. Aggressive surgical debridement of involved tissues with clean margins along with antifungal medications is the preferred treatment. Liposomal amphotericin B is the drug of choice for initial therapy.

<< Go to Task 5

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