



Pulmonary Aspergillosis Silently Presenting as Pneumothorax in Children with Leukemia: A Report of Three Cases

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Abstract

Keywords

- ▶ leukemia
- ▶ pediatric oncology
- ▶ pneumothorax
- ▶ pulmonary aspergillosis

Aspergillosis causes invasive pulmonary disease in patients with hematological malignancies. Children with invasive pulmonary aspergillosis (IPA) usually have nonspecific radiographic findings unlike cavitory lesions commonly seen in adults. Pneumothorax due to rupture of peripheral fungal lesion may be a severe complication in patients with neutropenia. Here, we describe three children during induction chemotherapy for B-lymphoblastic leukemia with pneumothorax as a presenting feature of pulmonary aspergillosis.

Introduction

Invasive pulmonary aspergillosis (IPA) is a potentially fatal opportunistic infection in patients with hematological malignancies and stem cell transplant recipients.^{1,2} Acute necrotizing bronchopneumonia, hemorrhagic pulmonary infarction, and lung abscess have been described in a large retrospective review of culture documented aspergillus infection in pediatric cancer patients but none of them manifested with pneumothorax.³ We describe our observations of three children with B-lymphoblastic leukemia (B-ALL) who developed spontaneous pneumothorax that represented the first sign of IPA.

Case Description

Case 1

A 7-year-old male presented with fever, pallor, hepatomegaly, and splenomegaly. He was diagnosed with B-ALL and started on remission induction chemotherapy as per the

Indian Childhood Collaborative Leukemia Group (ICiLe) protocol under the intermediate-risk arm.⁴ On day 22 of induction, child complained of difficulty in breathing and chest pain on left side. On physical assessment, the trachea was shifted to the right and hyperresonant percussion note on left hemithorax. Chest radiography showed lucent area in left lung field with absent bronchovesicular marking suggesting a pneumothorax with tracheal shift to right (▶Fig. 1). An emergent chest tube thoracostomy was performed. Contrast-enhanced computed tomography (CECT) showed bilateral patchy areas of consolidation involving left lower lobe, left upper lobe, and right lower lobe.

Serum galactomannan (GM) level was analyzed by immune-enzymatic sandwich microplate assay and was found to be optical density index of 0.85. Any value of >0.5 optical density index is considered positive by the assay. Blood culture was negative. The patchy consolidation resolved after 6 weeks of amphotericin B deoxycholate therapy at dose of

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Fig. 1 Pneumothorax with tracheal shift to right

1 mg/kg/day once daily. In retrospect, it was noticed that there was rapid recovery of neutrophil counts from 500 to 1,500 cells/ μ L within 48 hours when child developed pneumothorax. At the end of induction, bone marrow was in remission and minimal residual disease was $<0.01\%$.

Case 2

A 9-year-old female presented with fever and easy fatigability since 4 weeks. Physical examination revealed pallor; cervical, axillary, and epitrochlear lymphadenopathy; hepatomegaly; and splenomegaly. The child was diagnosed with B-ALL having hyperdiploidy and chromosome 6q deletion. Remission induction chemotherapy was started as per the ICiCLE protocol under the intermediate-risk arm. Second week of induction was complicated by reversible posterior leukoencephalopathy syndrome (RPLS). On day 30 of induction, child developed pleuritic chest pain on the right side. Chest radiograph suggested right pneumothorax which was confirmed on CECT thorax. There were multiple ill-defined heterogeneously enhancing nodules of varying size in bilateral lung fields in random distribution. Few cavitory lung lesions were observed in the anterior basal segment of right lower lobe. The child was started on amphotericin B deoxycholate with suspicion of invasive fungal infection. There was a recent neutrophil count recovery from 600 to 1,100 cells/ μ L when child had developed pneumothorax. Two days later, a small subcutaneous swelling was noted on anterior abdominal wall in the left iliac region. It was firm and tender on examination. The specimen obtained by needle aspiration was sent for microbiological evaluation which revealed septate fungal elements. Serum GM was positive with an index value of 2.11. There was modest improvement on CECT thorax after 3 weeks of therapy, with

persistence of lung nodules in bilateral lung fields. Pneumothorax resolved spontaneously. Serum GM was negative (optical density index of 0.30) after 6 weeks of amphotericin B. Despite a challenging course of remission induction complicated by RPLS and invasive aspergillosis (IA) with pneumothorax, the child was able to achieve a post induction minimal residual disease of $<0.01\%$.

Case 3

A 9-year-old male with fever since 2 weeks had pallor, cervical lymphadenopathy, and organomegaly. On evaluation, child was diagnosed with B-ALL with hyperdiploidy and started on induction chemotherapy as per the ICiCLE protocol. On day 28, the child developed right-sided chest pain on deep inspiration. There were decreased chest excursions and diminished breath sounds on right hemithorax. Chest radiography showed collapse of right lung with lucent area in peripheral lung field with absent bronchovesicular marking suggesting a pneumothorax. Needle decompression of pleural space was performed followed by chest tube thoracostomy. CECT thorax showed patchy areas of consolidation in right lower lobe. Serum GM assay was positive. Child responded well after 3 weeks of amphotericin B dosage and achieved remission at the end of induction.

Discussion

The incidence of invasive fungal infections (IFIs) has increased over the last few years along with the increased number of immunocompromised patients.⁵ Timely diagnosis and prompt initiation of antifungal treatment are crucial for care.⁶ Spontaneous pneumothorax in children receiving remission induction chemotherapy for leukemia is seldom encountered. Pneumothorax occurs in approximately 13% of adults who have pulmonary fungal infection while receiving chemotherapy for hematological malignancies. But the incidence of pneumothorax due to IPA in pediatric age is not known, since it is exceedingly rare.

IPA is categorized as “proven,” “probable,” and “possible” based on clinical, microbiological, and radiological criteria as per the revised European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) consensus definition.⁷ In this report, we describe pneumothorax as the first manifestation in one “proven (case 2)” and two “probable (cases 1 and 3)” cases of IPA. Bacterial blood cultures were negative, and fungal blood cultures were sent for testing but showed no growth in all the three cases.

Bronchoalveolar lavage could not be performed in patients due to prevailing clinical conditions and resource constraints. All the patients were on fluconazole for primary antifungal prophylaxis since beginning of the induction therapy. Voriconazole was continued as secondary prophylaxis after discontinuation of amphotericin B. Steroids were continued at second or third dose, and further induction was resumed once patients were clinically stable along with antifungal therapy.

Opportunistic infections during the early phase of leukemia treatment are a two-fold blow. They not only hamper the timely delivery of cytotoxic agents but are also difficult to treat and often lethal. The German ALL–Berlin–Frankfurt–Muenster (BFM) study group reported that fungal infections were responsible for one-fifth of fatal infections in pediatric ALL patients.⁸

Aspergillus was implicated in two-thirds of those with invasive fungal infection.⁸ Corticosteroids and prolonged neutropenia are known risk factors for this.⁹ Pulmonary aspergillosis presents with fever, pleuritic chest pain, and hemoptysis. Corticosteroids may mask the common presenting symptoms of IPA, mainly fever and cough. In a large survey of patients with IPA, typical manifestations were significantly less common in patients receiving steroids.¹⁰ The occurrence of spontaneous pneumothorax may be the first manifestation of subpleural fungal infection in patients with leukemia. Poor nutrition, presence of subpleural lesion, bouts of excessive coughing, and prolonged corticosteroid therapy are various precipitating factors. Pleural lesions were seen in cases 2 and 3.

In review of radiological findings in children with IPA consolidation, perihilar infiltrates, multiple small nodules, peripheral nodular masses, and pleural effusions have been described but no findings have been suggestive of pneumothorax.¹¹ In a multicenter retrospective analysis of pediatric invasive pulmonary aspergillosis, the most common diagnostic radiologic finding was of nodules.¹² Children with proven IPA commonly have nonspecific changes on CECT compared with halo sign, air crescent formation, or cavitation seen in adults.⁸ Rare possible complications of pulmonary aspergillosis include bronchopericardial fistula, pericarditis, tension pneumopericardium, and pericardial tamponade.¹³

A temporal correlation between neutrophil count recovery and occurrence of pneumothorax in patients with invasive fungal pneumonia has been demonstrated.¹⁴ The neutrophils are attracted to site of infection by chemotactic factors. Along with its microbicidal activity, neutrophils release reactive oxygen intermediates and proteolytic enzymes like collagenase and elastase. These cytolytic molecules cause collateral damage by destruction of surrounding pulmonary parenchyma. This might explain the paradoxical clinical deterioration with neutrophil recovery observed in two of the cases (1 and 2) we described.

Early suspicion of aspergillosis helped us to start appropriate antifungal agent early, with favorable outcome during a crucial period of remission induction. The advent of biomarker tests such as the GM enzyme immunoassay (GM-EIA) provides a potential adjunct for noninvasive diagnosis of IA.¹⁵ A limitation to our approach was that histopathologic or cytopathologic evidence of mold could not be proven in cases 1 and 3. Bronchoalveolar lavage and fungal DNA polymerase chain reaction (PCR) could not be performed due to resource constraints.

Conclusion

Our observation helps us to be vigilant for sudden deterioration and pneumothorax in children with ALL on induction

therapy. A possibility of IPA should be considered when encountered with pneumothorax in children with leukemia on intensive chemotherapy. Based on clinical and radiological observations, recent recovery of neutrophil counts and presence of subpleural or peripheral lesion may increase the likelihood of pneumothorax.

Note

The manuscript has been read and approved by all the authors, and the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms.

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Conflict of Interest

None declared.

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