Early detection of pulmonary fungal infection by CT scan in pediatric ALL patients under chemotherapy or in post-transplantation period with primary complaint of chest pain

Göğüs ağrısı ile başvuran pediatrik akut lenfoblastik lösemi olgularında kemoterapi sırasında ya da kök hücre nakli sonrası gelişen pulmoner fungal enfeksiyonun bilgisayarlı tomografi ile erken tayini

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Abstract

We describe herein four children with acute lymphoblastic leukemia who were diagnosed as pulmonary fungal infection after presenting with chest pain. The plain radiologic evaluations failed to reveal any positive findings, whereas computerized tomography (CT) scanning showed nodular opacification with or without cavitation. This experience suggests that chest pain may be an initial symptom of an invasive fungal infection in patients with leukemia, and CT scan of the lungs should be performed urgently for the early diagnosis and treatment, despite normal plain X-rays. *(Turk J Hematol 2010; 27: 34-7)*

Key words: Leukemia, pediatric, chest pain, fungal infection, pneumothorax

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Özet

Göğüs ağrısı yakınması ile başvuran dört pediatrik akut lenfoblastik lösemi olgusu pulmoner fungal enfeksiyon tanısı almıştır. Düz grafilerinde pozitif bulgu olmayan bu hastaların, bilgisayarlı tomografi incelemelerinde pulmoner noduler opasifikasyonlar ve bazı hastalarda kavitasyonlar pulmoner enfeksiyon yönünden uyarıcı olmuştur. Bu deneyimimiz lösemili hastalarda pulmoner invasif enfeksiyonun ilk yakınmasının göğüs ağrısı olabilecegine, düz grafiler normal olsa bile bu hastalarda bilgisayarlı tomografinin erken yapılması ile fungal enfeksiyonun erken tanı ve tedavi edilmesinin önemine dikkat cekmektedir.
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Anahtar kelimeler: Lösemi, pediatrik, göğüs ağrısı, fungal enfeksiyon, pnömotoraks

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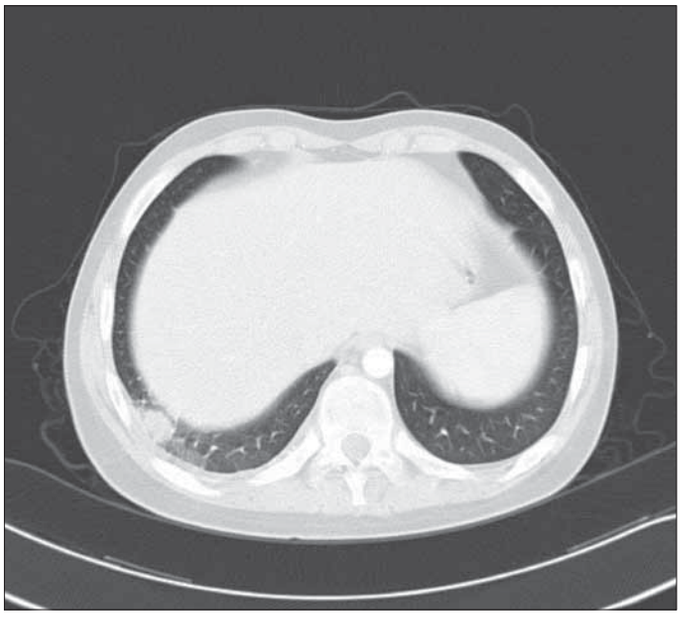

Figure 1. Peripherally localized nodule at the posterobasal segment of the right lung inferior lobe

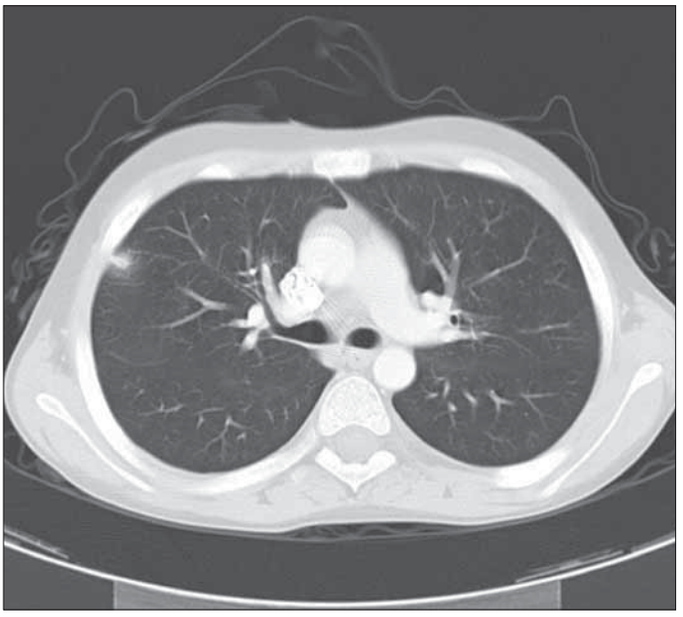

Figure 2. Bilateral mosaic pattern and a subpleurally localized nodule in the superior lobe of the right lung compatible with fungal infection

Introduction

Respiratory tract fungal infection is the most common site of invasive fungal infection in children with hematologic malignancies [1,2]. The clinical onset is not specific and usually includes prolonged fever and new or resistant pulmonary infiltrates that progress despite broad-spectrum antibacterial therapy [3]. Chest pain is a common finding of pulmonary infections of any etiology including viral, bacterial and fungal agents; however, it can also be seen in pulmonary thromboembolism and pneumothorax. Usually, roentgenographic findings do not provide any clues towards identification of the specific pathogen except in a few cases in which the late development of a cavitary lesion can suggest infection with Aspergillus species [4].

Herein, we report our experience in four children with acute lymphoblastic leukemia (ALL).

The aim of this report is to emphasize the importance of chest pain as an initial complaint of pulmonary fungal infection and the superiority of pulmonary computerized tomography (CT) scanning over plain chest X-rays in the detection of pulmonary fungal involvement, which enables early diagnosis and treatment in these immunologically compromised patients.

Case Reports

Written informed consent was obtained from all patients.

Case 1

A 16-year-old male ALL patient relapsed four months after cessation of St. Jude Total XIII treatment protocol [5], and he was placed on BFM-95 early relapse protocol [6]. However, in the 8th month of this treatment, he had a second bone marrow relapse and was started on the FLAG-IDA regimen [7]. Ten days after completion of FLAG-IDA and on the 17th day of neutropenia, while under fluconazole prophylaxis, he developed bilateral chest pain at inspiration and fever. The pulmonological examination revealed bilateral fine rales. The plain chest X-rays were normal and a pulmonary CT scan was obtained, which revealed bilateral parenchymal nodular lesions compatible with fungal infection, a peripherally localized nodule at the posterobasal segment of the right lung inferior lobe and minimal pleural and pericardial effusion (Figure 1). Liposomal amphotericin-B was initiated (3 mg/kg/day) in addition to concomitant antibacterial treatment, and the dose was later increased to 5 mg/kg/day. Sputum and blood cultures were negative. By the third week of the antifungal treatment, repeat CT scan showed partial resolution in the nodules. However, the neutropenic period continued since a remission could not be achieved, and the antifungal treatment was continued. Voriconazole was added to the antifungal treatment in the second month of antifungal treatment, since no further resolution could be achieved in pulmonary nodules and serum Aspergillus galactomannan antigen was positive by enzyme-linked immunosorbent assay (ELISA). The patient died in the third month of antifungal treatment due to progression of leukemia and sepsis.

Case 2

A 12-year-old male patient who was diagnosed as ALL at the age of six years and received St. Jude Total XIII protocol [5] had bone marrow relapse twice. The initial relapse was seven months after cessation of treatment. Due to family refusal of hematopoietic stem-cell transplantation (HSCT), the patient was placed on BFM REZ 95 protocol [6]. The patient relapsed again towards the end of the maintenance treatment. Following the FLAG-IDA regimen [7], while under fluconazole prophylaxis, he had a complaint of right shoulder pain during inspiration while afebrile and severely neutropenic (WBC was 200/mm^3). The

pulmonological examination was unremarkable. Echocardiographic evaluation and plain chest X-rays were normal; the pulmonary CT scan revealed bilateral mosaic pattern and a subpleurally localized nodule in the superior lobe of the right lung compatible with fungal infection radiologically (Figure 2). Granulocyte colony-stimulating factor (G-CSF) and liposomal amphotericin-B (3 mg/kg) were initiated, in addition to antibacterial treatment. Serum galactomannan antigen, sputum and blood cultures were negative. By the second week of the treatment, chest pain recurred and repeat pulmonary CT showed enlargement of the nodule in the superior lobe of the right lung. The antifungal treatment was intensified by increasing liposomal amphotericin-B dosage to 5 mg/kg and addition of caspofungin. Antifungal treatment could not be stopped for two months since the neutropenic period continued after completion of the chemotherapy protocol. By the end of the second month of treatment, the subpleural nodule was stable and the lung parenchyme was normal. The antifungal treatment was discontinued until the patient recovered from neutropenia. However, he exhibited a central nervous system (CNS) and later a bone marrow relapse and died due to leukemia progression, neutropenic sepsis, pleural effusion, and congestive heart failure four months after termination of antifungal treatment.

Case 3

A 13-year-old male with ALL experienced bone marrow relapse 10 months after cessation of St. Jude Total XIII high-risk protocol [5] and underwent HSCT from his HLA-matched sister at age 17; however, he developed grade III acute and then extensive chronic graft-versus-host disease (GVHD) following donor lymphocyte infusion. He was treated with prednisolone, cyclosporine A, mycophenolate mofetil, and extracorporal photopheresis. At month +19, the patient experienced extramedullary relapse in the CNS and the eye. BFM-REZ 95 protocol [6] was initiated. During treatment, he had a complaint of sharp chest pain at inspiration in the third week of induction while under fluconazole prophylaxis, and absolute neutrophil count was 9792/mm^3. The pulmonological physical examination was unremarkable. Chest X-rays were normal. Pulmonary CT scan revealed parenchymal bilateral nodular opacities. In the sputum culture, *Candida albicans* was isolated (resistant to fluconazole). Since he developed acute renal failure in a previous neutropenic fever attack while under empiric liposomal amphotericin-B treatment, caspofungin (1 mg/kg) was chosen. By the third week of antifungal treatment, the repeated CT scan showed that more than 50% of the nodules in the previous CT had disappeared and the remaining nodules had decreased in size. Nevertheless, the patient relapsed five months after diagnosis of pulmonary fungal infection and died on the 18th day of the last relapse due to resistant leukemia progression.

Case 4

Acute lymphoblastic leukemia was diagnosed in a 14-year-old male five years before. St Jude Total XIII remission-induction therapy was started [5]. The patient developed sudden right-sided chest pain and dyspnea during induction therapy on the 31st day of hospitalization, while under fluconazole prophylaxis, during the recovery phase from neutropenia (neutrophil count, 1500/mm^3). The physical examination revealed decreased breath sounds on the right side. A chest radiograph showed small right-sided pneumothorax with no evidence of pulmonary lesions. A chest tube was inserted and left until resolution of pneumothorax on the fifth day. The follow-up chest X-ray after removal of the chest tube was normal; however, CT scan was done since the etiology of pneumothorax was obscure and revealed nodular opacifications with cavitation. *Aspergillus fumigatus* was identified from bronchoalveolar lavage fluid culture. Therapy with 5 mg/kg liposomal amphotericin-B was initiated and continued for four weeks, and follow-up CT scan showed regression of the pulmonary lesions. The patient died during the maintenance phase due to intracranial bleeding following an accidental fall in the ninth month of diagnosis.

Discussion

Invasive fungal infections are increasingly being observed in immunocompromised patients, particularly in those who are neutropenic, due to the use of aggressive chemotherapeutic regimens. Aspergillus has been described as the leading pathogen in pulmonary cases [1]. Up to 70% of reported patients with invasive pulmonary aspergillosis (IPA) have been reported to suffer from acute leukemia [8]. In invasive aspergillosis, the duration of neutropenia is an accepted risk factor, and recovery from neutropenia is generally associated with a favorable outcome. However, the rapidity of granulocyte recovery may, on rare occasions, be associated with adverse sequelae [9]. Todeschini et al. [9] showed that the risk of pulmonary complications significantly increased when the neutrophil concentration was more than 4500 μL^{-1} on day 5 after deep neutropenia (neutrophil less than 100 μL^{-1}).

The incidence of aspergillosis is about 4-9% in stem cell-transplanted children [10]. Risk factors for aspergillosis in patients with hematological diseases are prolonged (>10 days) severe neutropenia (<500/ml), high-dose steroid treatment, allogeneic SCT, and strong immunosuppressive treatment especially in patients with GVHD after allogeneic HSCT [11]. In our experience, two of the cases (Cases 1 and 2) were severely neutropenic, whereas one was in the recovery period from neutropenia (Case 4) and the other had normal neutrophil count (Case 3) when they developed pulmonary fungal infection. However, the latter patient was severely immunocompromised because of chronic GVHD and was also very prone to infections because of the severe skin involvement of GVHD.

In pulmonary fungal infections, the clinical findings are nonspecific, consisting of unremitting fever, cough, chest pain, and dyspnea [8]. The most frequent presenting clinical picture has been described as cough and fever of insidious course [12]. Subira et al. [2] showed that 85% of patients had fever and 80% of those experienced respiratory symptoms as presenting symptoms and none developed pneumothorax. Excluding Case 1, who had fever in addition to chest pain, the only complaint was chest/shoulder pain during inspiration in the other cases. Interestingly, Case 4 was asymptomatic until pneumothorax developed and he remained symptom-free afterwards. Pneumothorax has been shown to be a severe complication of pulmonary mycetoma that has rarely been reported in patients with hematologic malignancies. Martino et al. [3] found that pneumothorax occurred in six (13%) of 46 episodes of pulmonary mycetoma.

The diagnostic yield of fungal culture and microscopy from bronchoalveolar lavage fluid or bronchial washings varies considerably in the literature, with an overall sensitivity of 32% and specificity of 99.7% [13]. In Case 3, sputum culture revealed *C. albicans* resistant to fluconazole. In Case 4, *A. fumigatus* was identified from bronchoalveolar lavage fluid culture. On the other hand, it has been reported that although the ELISA test does not appear to play a role in the early diagnosis of invasive aspergillosis, it is especially useful for monitoring patients receiving specific therapy [14]. However, detection of Aspergillus species in bronchoalveolar fluid by polymerase chain reaction (PCR) enables early diagnosis of IPA [15]. In a recent study, the radiological appearance of early IPA diagnosed with the aid of PCR testing was found to be correlated with mainly discrete small nodules with halo and focal ground-glass appearance in the thoracic CT scans [16].

Subira et al. [11] showed that chest X-rays are not useful for the early diagnosis of IPA [2]. Thoracic CT scan findings of macronodules, halo signs, and cavitary lesions with an air crescent sign are highly indicative of IPA. In the presented cases, CT scanning showed nodular opacifications with or without cavitation, which were consistent with fungal infection. A CT scan is considered to be one of the most important procedures for early diagnosis of IPA, and several authors have shown that the use of early CT may improve survival [2]. In our series, none of the patients had a diagnostic sign of fungal infection on plain chest X-rays and all had pulmonary fungal infection diagnosis through pulmonary CT scanning. Notably, none of the patients died due to fungal infection but from other causes, and the early detection of fungal infection might have contributed to the improvement in the fungal infection. CT scanning may also be helpful for exclusion of pulmonary thromboembolism in patients with chest pain.

All four patients were under fluconazole prophylaxis when pulmonary fungal infection developed. Pulmonary fungal infection is a fulminant and highly fatal infection in patients with hematologic malignancies. The reported mortality rate is approximately 60% when it occurs during chemotherapy-induced neutropenia. Improvement in chance of survival may rely on the early recognition and prompt initiation of antifungal treatment.

In conclusion, chest pain may be the first symptom of a pulmonary fungal infection, which may not be detected with chest X-ray. Pulmonary CT scanning may be very helpful in the early diagnosis and treatment of fungal infection in an immunocompromised patient whose plain chest X-rays are normal.

Conflict of interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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