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Original Research Paper

Hematology

PULMONARY BLASTOMYCOSIS IN CHILDREN WITH RELAPSE ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE REPORT

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ABSTRACT **Background:** Blastomycosis is rare fungal infection in Indonesia, South East Asia. However, this infection can be found in immunocompromised children. Host susceptibility plays a role in pathogenesis. Children with acute lymphoblastic leukemia (ALL) who get chemotherapy is immunocompromised and prone to fungal infection. Pulmonary blastomycosis often misdiagnosed with Community Acquired Pneumonia (CAP) or Pneumocystis pneumonia (PCP) in patient with ALL. We should be aware of this infection because it may cause morbidity and mortality of patient with severe immunosupression. **Methods:** We present a case of 5 year-old boy who came to the hospital with shortness of breath. This patient was also diagnosed as relapse acute lymphoblastic leukemia and was treated with 3rd week of induction phase of chemotherapy of ALL High Risk (HR) protocol. **Result:** Culture of the organism was performed and showed Blastomyces dermatitidis. **Conclusion:** We should be aware of the possibility of pulmonary blastomycosis infection in patient with ALL who get chemotherapy. Careful consideration and early detection of this infection may help to improve survival.

KEYWORDS : Pulmonary Blastomycosis, All, Children, Immunocompromised

INTRODUCTION

Blastomycosis refers to disease caused by dimorphic fungus *Blastomyces dermatitidis*. Blastomycosis is endemic in the Ohio and Missisipi River valley, and near the Great Lakes and southeastern parts of United States. The spectrum of illness ranging from subclinical infection to acute or chronic pneumonia. Immunocompromised children may progress to fulminant multilobar pneumonia and acute respiratory distress syndrome (ARDS) (Chapman *et al*, 2008).

Infection of *B. dermatidis* started with inhalation of conidia into the lungs. After conidia are inhaled, they pass into the lower respiratory tract. The conidia can be phagocytized by bronchopulmonary mononuclear cells and killed by neutrophils and macrophages. This phenomenon happens in the asymptomatic infection in some individuals.

Alveolar macrophages have been shown to inhibit the transformation of conidia to the pathogenic yeast form. This is a critical step in terms of pathogenesis, because the yeast form, which posseses a thick capsule, is hardly to ingest and kill by phagocytes. Polymorphonuclear leukocytes are ineffective against the yeast form. If the host responses fail to contain the infection, conidia will convert to the yeast form and proliferate which result in symptomatic pulmonary infection (Ahsani, 2014).

Acute lymphoblastic leukemia is the most common hematologic malignancies in children. The primary treatment for ALL in the developing countries is chemotherapy. The principle of chemotherapy is to eliminate the leukemic cells as many as possible. However, chemotherapy can also damage the immune system by reducing of infection fighting white blood cells such as netrophils, macrophages and lymphocytes. This is why children with acute lymphoblastic leukemia who get chemotherapy will be immuno compromised and have risk to get fungal infections.

The average annual incidence of blastomycosis in areas of endemicity ranges from 1 to 2 per 100 000, and up to 10% of blastomycosis cases occur in children. (Frost *et al*, 2017). The data about incidence of pulmonary blastomycosis in the pediatric ALL is still limited. However Rubnitz *et al,* 2004, mentioned that invasive fungal disease during ALL induction therapy has been reported to account > 70% of induction related mortality.

The writer belief this is the first publication in our country that report pulmonary blastomycosis in children with acute lymphoblastic leukemia.

Case Presentation

A 5-year-old boy came to the hospital with the chief complain of shortness of breath and fever. Patient was diagnosed as ALL at 2 year and 6 months based on bone marrow aspiration which showed lymphoblast 80%. Immunophenotyping showed B lineage ALL, then patient started ALL Standard Risk (SR) protocol. At week 112 (a week before end of therapy), patient complained of bone pain, abdominal enlargement due to hepatosplenomegaly. We performed peripheral blood smear which showed 39% of lymphoblast and 91% of lymphoblast on the bone marrow aspiration result. We diagnosed this patient as very early relapse ALL and decided to give ALL High Risk (HR) protocol. ALL HR protocol has higher dose of chemotherapy than ALL SR protocol. It consist of methrotexate intrathecal, vincristine, prednison, high dose methrotexate, daunorubicine, cyclophospamide, citarabine, leunase and 6-MP. In our protocol we do not give infection prophylaxis. Three weeks after start of induction phase, patient complained of fever and shortness of breath. Laboratory finding showed leukocytosis with high CRP level (>150, normally < 5). Chest X ray showed bilateral pneumonia, and we gave Ceftriaxone for 5 days. After 5 days, there was no improvement in respiratory distress and evaluation of chest X ray showed the increasing of infiltrates bilaterally.

The respirologist then decided to do chest CT scan and bronchoalveolar lavage (BAL) culture. The result of chest CT scan showed multiple cavities with fungus ball in the both

lungs, bilateral pneumonia with multiple nodules on the right lung and necrosis of inferior lobe of the right lung leads to aspergillosis.

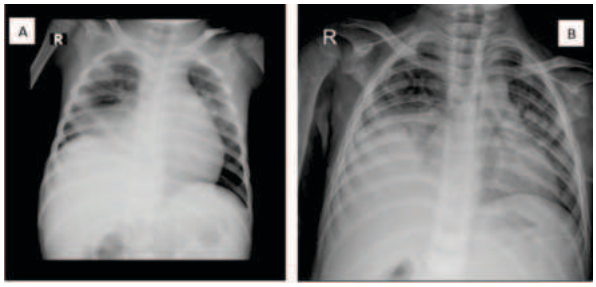

Figure 1. Chest X ray at the first visit when patient diagnosed as pneumonia (A). Chest X ray evaluation after got 5 days of antibiotics (B)

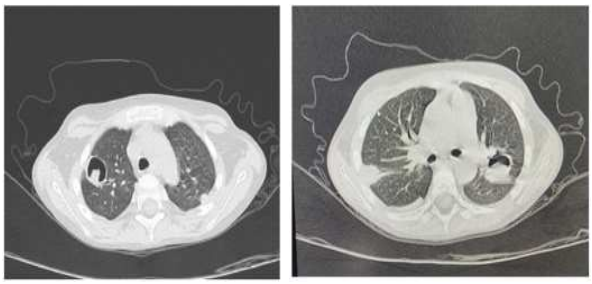

Figure 2. Chest CT scan showed cavities on both lungs with fungus balls.

Patient managed with possible aspergillus infection and treated with pre-emptive therapy using micafungin. We chose micafungin based on availability in our hospital. After 10 days, patient condition did not significantly improved and BAL culture result showing the growth of Blastomyces sp. Patient diagnosed as severe blastomycosis and we changed the treatment to voriconazole for 14 days and then switched to itraconazole for 6 weeks. Clinical condition of patient improved, no more fever and less effort of breathing. However, chest indrawing still persisted and patient need oxygen 1-2 liter per menit to maintain good saturation. After 2 weeks administration of voriconazole, we evaluate the CT thorak as showed below:

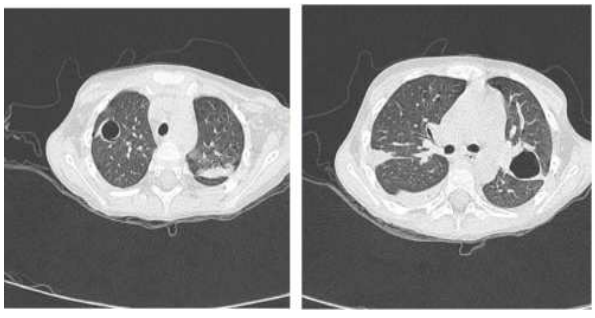

Figure 3. Chest CT scan after 2 weeks administration of voriconazole. Multiple cavities in the superior lobe of the lungs bilateral. Compared to the previous chest CT, there were no more fungus ball appearance inside the cavities.

Due to patient condition, chemotherapy of relapse ALL was postponed until the condition improved. However, after four weeks without chemotherapy, the leukocytes reached 200.000/μL and showed lymphoblast 59% on the peripheral blood smear. Patient also suffered from bleeding due to trombocytopenia. Supportive care were given to the patient with hyperhydration, monitoring for tumor lysis syndrome and educate the patient about the poor prognosis and the risk of giving chemotherapy with his respiratory issue. Parents chose to give no more chemotherapy and we start palliative treatment for this patient.

DISCUSSION

We described a case of rapid progressive pulmonary blastomycosis in an immunocompromised patient with relapsed ALL. Blastomyces exists in the mycelial form in the environment. Disrupted mycelia release conidia that can be inhaled by humans. Conidia changed to yeast form in vivo rapidly and manifested as clinical symptoms of Blastomycosis. The portal of entry is respiratory tract and may spread to affect other organ (Helen *et al*, 1992).

The mean age at diagnosis was 12.9 ±4.6 years and the youngest patient was 5 months old. Clinical characteristic of blastomycosis vary from asymptomatic infection to pulmonary and extrapulmonary infection (bone, cutaneus, genitourinary and central nervous system). Children with blastomycosis 78 % have isolated pulmonary infection and the rest is extrapulmonary infection. Systemic findings, including fever, poor oral intake, elevated WBC count, elevated CRP level were significantly correlated with isolated pulmonary infection (Frost *et al*, 2017).

Immunocompromised patients are particularly susceptible to rapid progression and dissemination of infection, which may result in fatal outcome. Patient with ALL has abnormal proliferation of lymphocytes B and T. T cells from bone marrow of ALL patient are functionally anergized. They express different markers of memory and activation and lack the ability to express CD40L and CD25 molecules. CD40L molecules appear on T lymphocytes only after complete activation. Failure to detect CD40L on activated T cells support the hypothesis that some T-lymphocytes are anergized. The apoptotic rate is increase in the CD4 and CD8 subsets and the Th2 phenotypes in the CD4 population predominates (Yotnda *et al*, 1998). Blastomycosis is fungal infection and the activity of CD4 T cells against fungal infection in immunocompetent individuals has been very well characterized. Because of abnormal proliferation and anergized T cell in patient with ALL, the fungal infection of Blastomyces can not be eliminated properly and could became disseminated disease.

Based on Verma *et al*, 2016 chemotherapy also caused short-term depletion of all main subtypes of circulating lymphocytes (3-6 months), and prolonged (>9 months) depletion of B and CD4+ T cells. In the fungal infection, cell mediated immunity will be induced by recognition of conidia by dendritic cell through TLR4. T helper 1 cells will be activated and induce inflammatory process. Th1 cells is subset of CD4 T cells, produce interferon -gamma, IL-1 and TNF beta, which activate macrophages and are responsible for cell mediated immunity (Ahsani, 2014). In this report, the immunocompromised condition of patients induced by chemotherapy of relapsed ALL and also caused by ALL itself due to abnormal function of T lymphocytes.

Blastomycosis often mimics other disease in human, which may result in significant delay of diagnosis and treatment. At first, our patient was also diagnosed as CAP with differential diagnosed with PCP and aspergilus based on chest CT scan. The diagnosis of Blastomycosis in our patient was confirmed after 28 days of hospitalization based on culture of BAL. Common chest radiological patterns in blastomycosis include alveolar infiltrates, solitary pulmonary nodules, lung mass with or without cavitation, interstitial infiltrates, mediastinal lymphadenopathy, and pleural involvement Alveolar infiltrates are more common in acute presentation, whereas mass like lesions are more common in chronic presentation. Chest CT scan similarly shows a broad range of findings: mass lesions, consolidation with air bronchogram, intermediate-sized nodules, satellite lesions around mass or consolidation, pleural thickening, small effusions, and cavitation. There is no pathognomonic radiological pattern in blastomycosis. (Sarkar *et al*, 2014).

The previous research also mentioned that 5 of 114 pediatric patiens with blastomycosis died due to isolated pulmonary disease and acute respiratory distress syndrome as result of Blastomyces infection (Frost *et al*, 2017). Mortality rate of Blastomycosis associated with advanced age, chronic obstructive pulmonary disease, cancer, African American ethnicity. When ARDS occurs, mortality rate has range of 50-89% (Chapman *et al*, 2008). In Indonesia, the case fatality rate will be much higher since we can not test for resistancy pattern, limited alternative of antifungal drugs and we can not do Therapeutics Drug Monitoring (TDM).

CONCLUSION

ALL is characterized by state of immunodeficiency caused by abnormal function of T lymphocytes. Chemotherapy of ALL will also cause depletion of circulating T lymphocytes. Blastomycosis is one of invasive fungal infection that should be aware in patient with severe immunodeficiency. It mimics other disease, which may cause delay in the diagnosis and treatment. Early detection of Blastomycosis by doing chest CT scan and culture should be done to confirm the diagnosis. Immediate and proper treatment of Blastomycosis may improve survival for children with immunodeficiency.

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