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CASE REPORT

A Case of Pediatric Acute Lymphoblastic Leukemia with Invasive Candidiasis: Short Review

S. P. Verma · B. Dubashi · P. Narayanan · D. Basu · T. K. Dutta · K. M. Dhanraj

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Abstract Mortality rate associated with invasive fungal infections is very high. Early suspicion for fungal infections is important during intensive chemotherapy for acute leukemia. Empirical treatment with antifungals amphotericin B or caspofungin should be started if patient is not responding to broad spectrum antibiotics and if expected duration of neutropenia is prolonged. We are reporting a 3 years old girl child with diagnosis of pre-B acute lymphoblastic leukemia who developed invasive candidiasis with typical clinical and radiological findings during induction chemotherapy. *Candida* non-*albicans* was isolated and she was treated with amphotericin B followed by caspofungin. Patient deteriorated after initial response and succumbed to death. Species identification and sensitivity pattern of fungus can help in selecting appropriate antifungal drug.

Keywords Invasive candidiasis · Acute lymphoblastic leukemia · *Candida* non-*albicans*

This 3-year old girl presented in June 2012 at JIPMER with fever off and on and progressive abdominal distension for 2 months. Fever was high grade intermittent associated with significant lethargy. There was no history of headache, vomiting, cough, expectoration, chest pain, diarrhea, abdominal pain or any urinary symptoms. Patient developed progressive paleness of body over 2 months. There was no history of bleeding, join pain or arthralgia. At presentation blood pressure was 100/70 mm of Hg and pulse rate was 126/minute regular. Patient had marked pallor, facial puffiness and multiple cervical and axillary lymph nodes, maximum 2.0 × 1.5 cm in size. Systemic examination showed moderate hepatosplenomegaly.

Hemogram showed Hb = 11.3 gm/dl, TLC-5400/cmm and platelets-5000/cmm differential count showed 60 % blasts with morphololgy suggestive of lymphoblast. Bone marrow aspiration differential showed 90 % blasts. Bone marrow flocytometry showed positivity of CD19, CD34, HLA-DR, CD10 and cCD79 suggestive of pre-B acute lymphoblastic leukemia. CSF examination was normal. Baseline chest X-ray was normal and USG abdomen showed hepatosplenomegaly.

Patient was started on tumor lysis measures followed by MCP-841 acute lymphoblastic leukemia (ALL) induction protocol. Initially patient tolerated chemotherapy well and became afebrile from day-3 onwards. Day-20 of induction therapy patient developed high grade fever in background of severe neutropenia (ANC $< 100/mm^3$). Bacterial and fungal blood cultures were sent. Patient was started on empirical IV antibiotics (ceftazidime and amikacin). After two days patient developed papulonodular skin rashes all over the body predominantly on extremities (Fig. 1) with progressive splenomegaly. Peripheral smear did not show any blasts. There was no evidence of oral *candida* and fundus examination was normal. She was started empirically on amphotericin B. Blood culture showed *candida* non-*albicans*. FNAC from skin lesions showed budding yeast. *Candida* sub-species identification and drug sensitivity pattern could not be done due to unavailability of test. Abdominal and chest CT scan was done to look for any invasive fungal infection which revealed splenic and renal involvement (Figs. 2, 3). Amphotericin B was continued for 6 weeks. WBC count started rising on day-5 of starting antifungal treatment. Patient gradually became asymptomatic. Repeat

S. P. Verma (✉) · B. Dubashi · P. Narayanan · D. Basu · T. K. Dutta · K. M. Dhanraj
JIPMER, Pondicherry, India
e-mail: spverma1998@gmail.com

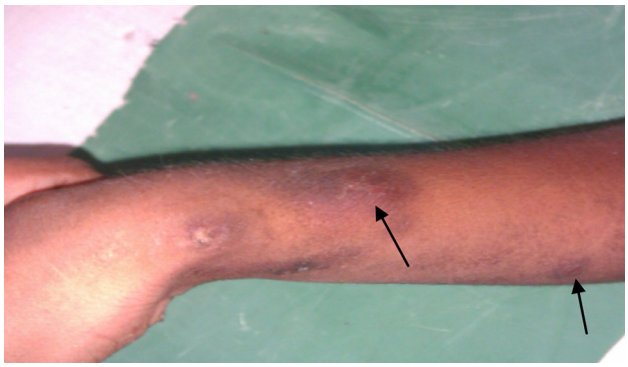

Fig. 1 Papulonodular skin lesions on forearm. Lesions were mainly limited to upper and lower limbs

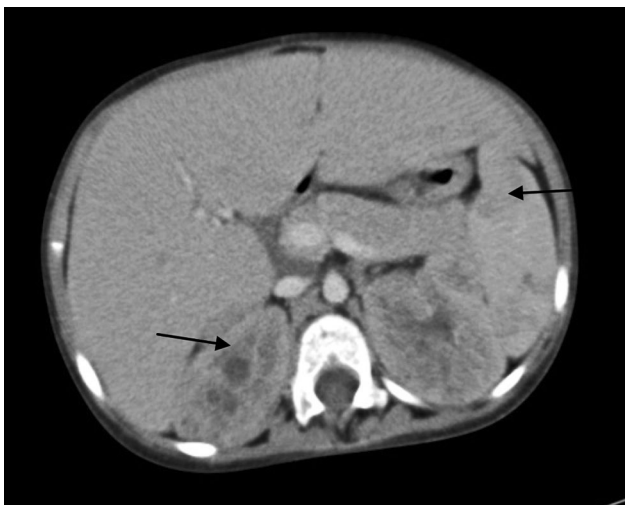

Fig. 2 CECT abdomen showing multiple hypo echoic lesions in both kidneys and spleen suggestive of fungal invasion

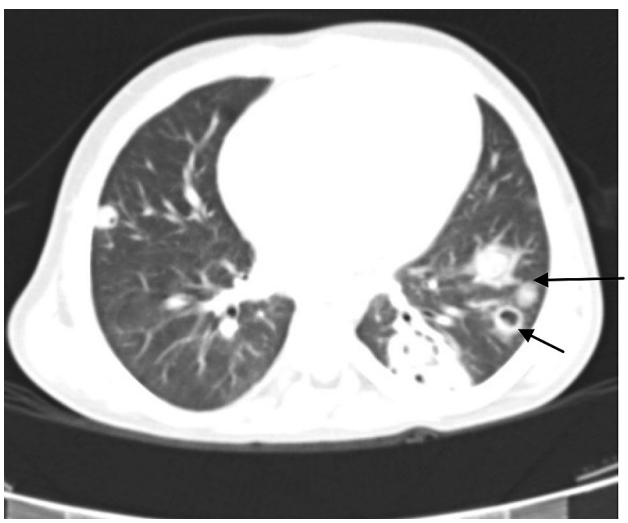

Fig. 3 CT thorax showing multiple nodular opacities and small cavitory lesions in both lungs

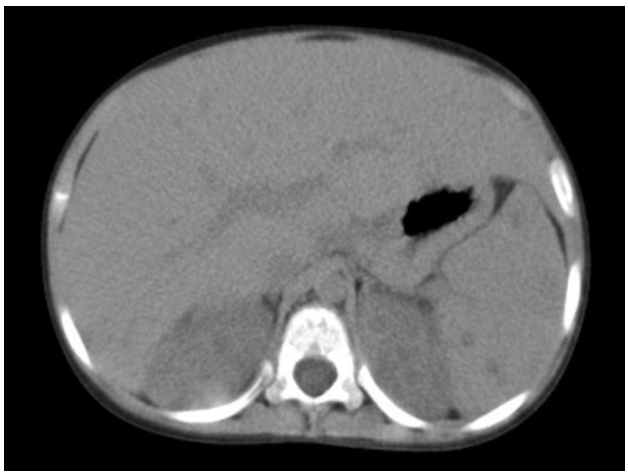

Fig. 4 CT thorax showing partial resolution of fungal lesions following 3 weeks of amphotericin B therapy

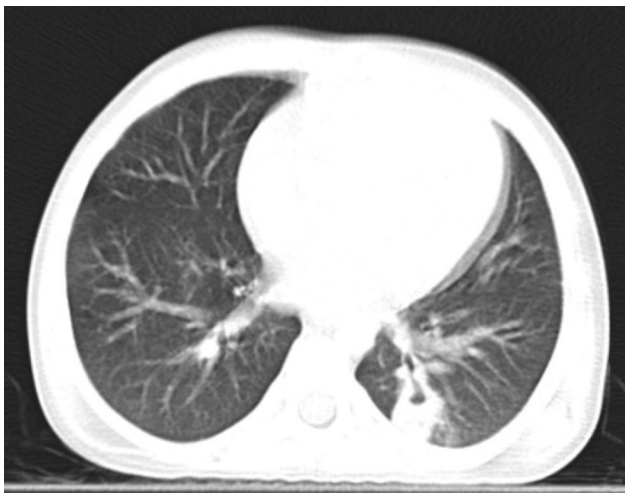

Fig. 5 CT abdomen showing partial resolution of fungal lesions following 3 weeks of amphotericin B therapy

CT after 3 weeks of antifungal therapy showed partial resolution of the initial findings (Figs. 4, 5). Patient started having intermittent fever again and caspofungin was started. She received caspofungin for 4 weeks but did not recover. She developed seizures and had a very downhill course and expired during hospital stay.

Discussion with Review of Literature

ALL is a common pediatric malignancy. Almost 85 % of all pediatric ALL are pre-B ALL. Pre-B ALL in pediatric patients has good prognosis with overall survival up to 80 %. Patients of acute leukemia are immunocompromized. Chemotherapy related neutropenia makes them more immunocompromized and they are prone for variety of

bacterial and fungal infections. Among fungal infections aspergillus, *candida albicans* and non-*albicans* are common in immunocompromized neutropenic patients. Invasive candidiasis includes candidemia, disseminated candidiasis with deep organ involvement, endocarditis and meningitis excluding less severe infections like oral or esophageal candidiasis. Invasive candidiasis is reported to be associated with mortality of 40–50 % in adults [1, 2]. *Candida* in a blood culture should never be viewed as a contaminant. Prompt search should be done for the source of the fungemia. Candidemia can be a manifestation of disseminated candidiasis in many patients while for others it reflects indwelling IV catheter colonization [3].

Candida spp. are important pathogenic organisms in pediatric ICU patients, critically ill patients, and those who are immunocompromised [4]. Immuno-suppressed patients with hematologic malignancies, organ or stem cell transplants and those receiving chemotherapy are at special risk for candidemia [2]. Neutropenia is common in these conditions and these patients are usually getting steroids. Central venous catheters, broad spectrum antibiotics and extensive gastrointestinal mucosal damage are other risk factors [2]. The mortality rate is low (~20 %) in children in contrast to mortality in adults [5]. Usually the infecting strain is part of the host's colonizing flora.

Penetration through the gastrointestinal tract mucosa is probably the most common mechanism for entering into blood stream. Various studies have also shown that colonization of catheters with *Candida* species is an independent predictor of candidemia. Non-*albicans candida* spp. are nowadays becoming more important cause of candidemia [6]. The non-albicans species now account for about 40–60 % of cases of candidemia and hematogenously disseminated *candida* infection [7]. This probably has occurred due to excess use of fluconazole in 1980s [8]. It is important to monitor this trend toward increasing non-albicans isolates and their susceptibility patterns as fluconazole use increases.

Clinical clues to the occurrence of hematogenous spread of *Candida* include characteristic eye lesions, skin lesions, and, less commonly, muscle abscesses. Skin lesions are sudden onset painless pustules on an erythematous base; they can occur on any area of the body. The lesions vary from tiny pustules to nodular lesions, several centimeters in diameter, and appear necrotic in the center. Macular rather than pustular lesions can occur in severe neutropenia. Our patient had 1–2 cm pustulonodular lesions which later on became papulonodular. Lesions were present all over body but predominantly on limbs. Our patient did not have any eye signs or muscle abscesses. Fine needle aspiration of skin lesions showed *candida* (Fig. 6).

The clinical manifestations of candidemia may be indistinguishable from severe bacterial infection. Disseminated candidemia can give rise to visceral microabscesses in various organs like liver, spleen, kidney, lung, brain and heart sometimes leading to multiorgan failure. Hepatosplenic involvement is most common. Our patient has renal and splenic involvement but no liver involvement.

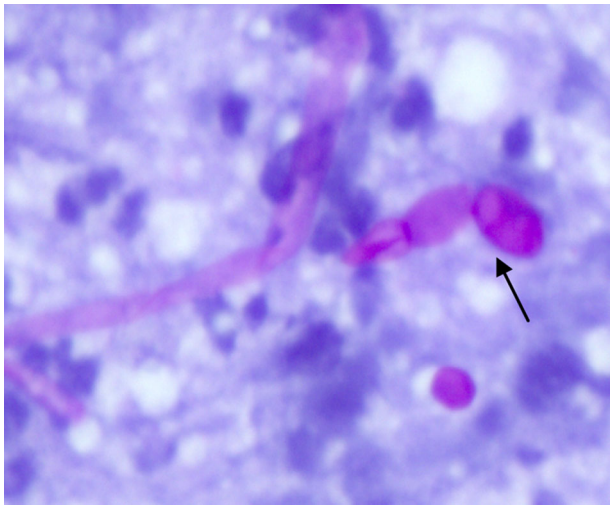

Fig. 6 FNAC from skin nodular lesion showing budding yeast

Candidal chorioretinitis can occasionally be seen in immunocompromized children and neonates. Patients may develop tender, warm and swollen muscles due to micro abscesses formation and special stains shows budding yeast with pseudohyphae.

Gold standard for the diagnosis of candidemia is a positive blood culture although it takes time (1–2 days for culture and 1–2 days for species identification). Blood culture techniques are relatively insensitive with only 50 % positivity in autopsy proven disseminated cases [9, 10]. Recent introduction of lysis-centrifugation method improved detection rates of yeast in comparison to blood culture systems. Recent modifications in culture media has lead to high positivity [11]. Clinician should have a high index of suspicion based upon clinical judgement and empirical antifungal (amphotericin B) should be started early while awaiting fungal culture reports. As in our patient presence of skin lesions was one of the clinical features suggestive of underlying *candida* infection. Several studies have shown that early treatment with an antifungal agent is associated with improved survival [12, 13].

All intravascular catheters should be removed in a patient with candidemia. Removal of catheter is associated with early clearance of fungemia [14]. Antifungals available for treatment of *candida* infections in pediatric patients are amphotericin B, azoles (fluconazole, voriconazole) and echinocandins. Amphotericin B is cidal and has good activity against *candida* except C. lusitaniae. It is USFDA approved for empirical antifungal treatment in febrile neutropenia.

In general young children tolerate amphotericin B better than adults. Typical dose of amphotericin B in older infants and children is 1 mg/kg body weight.

Azoles are static antifungal drugs. Fluconazole is good treatment option for *candida albicans* and also used for prophylactic antifungal therapy in prolonged neutropenic situations. Its efficacy in non-*albicans candida* species like *C. glabrata* and *C. cruzei* is limited. Voriconazole can take care of both *candida albicans* as well as *C. glabrata* and *C. cruzei* [15, 16]. The recommended dose of fluconazole for children is 6–12 mg/kg/day, and for voriconazole 7 mg/kg every 12 hourly (up to 12 years of age) and 4 mg/kg every 12 h above 12 years of age.

Echinocandins (caspofungin, micafungin, anidulafungin) are especially effective against candida and also aspergillus. Caspofungin is USFDA approved for empirical antifungal treatment in febrile neutropenia. These are cidal drugs and recommended for invasive candidiasis. Echinocandins appear to be safe and effective in pediatric patients although data is fewer than adult [17]. For moderate and severe candida infection echinocandins should be preferred as initial drug while fluconazole can be used in mild and stable cases or if the sensitivity pattern is known.

Our patient developed skin lesions, renal, splenic and lung lesions suggestive of invasive fungal infection in background of severe chemotherapy related neutropenia. Blood culture and FNAC from skin lesions showed candida non-albicans. Central venous catheter was removed and patient was started on amphotericin B. Initially patient responded and became afebrile with partial resolution of radiological findings after 3 weeks of IV amphotericin B. With recurrence of fever she was started on caspofungin but did not improve and expired following a seizure episode.

Conclusion

Mortality rate associated with invasive fungal infections is very high. Early suspicion for fungal infections is important during intensive chemotherapy for acute leukemias. Empirical treatment with antifungals amphotericin B or caspofungin should be started if patient is not responding to broad spectrum antibiotics and the duration of neutropenia is expected to be prolonged. Species identification and sensitivity pattern of fungus if available can help in selecting appropriate antifungals.

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