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Case Report

A Rare Systemic Fungal Infection (Cladophialophora) Masquerading Invasive Candidiasis in a Patient with B-Acute Lymphoblastic Leukaemia

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ABSTRACT

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in childhood and its incidence peaks during the first 2–5 years of life.The long-term survival of patients with ALL has increased to ~90% with risk-directed therapy and improved supportive care. However, incidence of mould infections caused by *Aspergillus* species, and other emerging mould opportunistics, such as *Zygomycetes* and *Fusarium* species and non-albicans Candida species have progressively been noted to increase particularly in patients with ALL. Here, we present a case of B-ALL with rare fungal infection (*Cladophialophora*) masquerading invasive Candidiasis which led to diagnostic delay and chemotherapy interruptions, but the patient achieved good overall outcome.

Keywords: *Cladophialophora*, B-acute lymphoblastic leukaemia, Rare invasive fungus, Mimic, Yeast like

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in childhood which peaks during the first 2–5 years of life due to the expression of early or prenatally acquired somatic mutations in immature lymphoid cells, many of which inherited germline cancer predisposition polymorphisms or variants.[1] The long-term survival of patients with ALL has increased to ~90% with risk-directed therapy and improved supportive care but at the cost of increased risk of infections.[2,3] Treatment-related mortality in ALL trials is reported to be 2–4%, predominantly from infections.[3] Until two decades ago, infections by Candida were the most common fungal pathogen in patients treated for ALL but with fluconazole as prophylaxis and the application of more intensive treatment protocols, including allogeneic hematopoietic stem cell transplantation, a shift toward the advent of invasive aspergillosis has been noted.[4] However, nowadays along with the increased incidence of mould infections, non-albicans Candida species incidence has also increased in ALL patients.[5] Here, we present a case of B-ALL with rare fungal infection (*Cladophialophora*) masquerading invasive Candidiasis.

CASE REPORT

At the age of 1 year 7 months, a girl child developed fever which was high grade associated with chills but were not associated with any cough or loose motions but were associated with

neck swelling which was 2*2 cm, non-tender, not adhered to skin or deep structures. Physical examination revealed submandibular lymphadenopathy and rest of systemic examination was unremarkable. Complete blood count done showed haemoglobin – 9.9 g/dL, total leucocyte count – 20800/cumm and platelet count – 36000/cumm. Peripheral blood film showed leucocytosis with marked prominence of lymphocytes with few blastic cells. Workup was done for infectious causes and Weil–Felix test, Widal test, Malaria antigen test and Epstein–Barr virus viral capsid antigen immunoglobulin M were found negative. Human immunodeficiency virus, hepatitis B surface antigen and anti-hepatitis C virus antibody were non-reactive.

Bone marrow aspiration and biopsy revealed near-total replacement of marrow by blast cells (95%) with high N: C ratio, scattered cytoplasm, no auer rods/granules and marked paucity of normal haematopoiesis suggestive of acute leukaemia. Flowcytometric immunophenotyping analysis showed increased blasts in CD45 negative area expressing bright CD19, CD10, CD34, CD38, HLADR, CD58 and CD79a with dim CD20 along with aberrant expression of CD66c. Blasts were negative for cMPO, sCD3,cCD3, CD7,CD13, CD14,CD33, CD64 and CD117 consistent with precursor B-cell acute lymphoblastic leukaemia (CALLA Positive). Deoxyribonucleic acid(DNA) index was 1.2 (high hyperdiploid) and S-phase fraction was 5.8% on DNA ploidy analysis on bone marrow aspirate sample. Karyotyping revealed no abnormality. Leukaemia translocation panel was negative for BCR-ABL, t(12;21)(ETV6-RUNX1), t(4;11) (MLL-AF4), t(1;19)(TCF3-PBX1), t(9;11)(MLL-AF9) and t(11;19)(MLL-ENL). Cerebrospinal fluid revealed no malignant cells. Hence, she was treated as pre-B-cell acute lymphoblastic leukaemia-intermediate risk central nervous system 1 and was started on Berlin-Frankfurt-Munich (BFM) 2002 protocol from April 2020 after family counselling and informed consent. No evidence of tumour lysis was seen.

She developed neutropenic fever and *Escherichia coli* sepsis during induction phase I chemotherapy which was treated with antibiotics. She also developed multiple nodular densities in the periphery of the lung abutting the underlying pleura in the left upper lobe, left lower lobe and right middle lobe with ground glassing in the adjacent lung parenchyma. Computed tomography abdomen showed hepatomegaly with fatty liver, and multiple rim enhancing hypodense lesions in both lobes of liver. Bronchoalveolar lavage (BAL) done showed trace detected for Gene Xpert Mycobacterium tuberculosis so she was started on four drug antitubercular therapy from June 2020 but withheld on August 2020 in view of culture negativity and non-response to anti tubercular therapy (ATT) after 2 months. Repeat contrast-enhanced computed tomograpghy (CECT) chest and abdomen revealed regression of the cavitatory lesions of the chest but persistence of the hypodense rim lesions in liver and kidney. Post-induction phase I day 33 marrow was in remission and measurable residual disease (MRD) was negative. After a delay of 20 days, she was started on phase II induction chemotherapy. Day 78 bone marrow aspiration and biopsy revealed that a cellular marrow with 3% blasts and MRD was negative. Fungal smear from the hepatic lesions revealed fungus with pseudohyphae. She was started on antifungal (Liposomal Amphotericin) from July 2020. Her consolidation chemotherapy was delayed in view of hepatorenal fungal infection. She developed peripherally inserted central catheter (PICC) line site sepsis so line was removed and pus swab was sent also showed fungus with pseudohyphae. Due to persistent fever, Inj Micafungin was added in place of amphotericin along with fluconazole after 3 weeks. She received Methotrexate consolidation from August 2020. Serum cryptococcal antigen was negative. She was given intravenous immunoglobulin therapy monthly in view of severe infections. CECT chest and whole abdomen done for evaluation of fever showed small hypodensity in the left upper lobe and mild ground-glass densities in the bilateral lower lobes. Abdomen shows hepatomegaly with multiple (at least three) hypodense lesions in both lobes of liver and multiple hypodense poorly peripherally enhancing lesions in parenchyma of bilateral kidneys. The hypodense lesions in liver and kidney were grossly stable in size since last imaging although necrotic component was found to be increased. Micafungin and fluconazole were stopped and voriconazole started from September 2020 as blood culture and pus cultures revealed *Cladophialophora* species. She completed reinduction phase I of chemotherapy and developed COVID in November and was given supportive care and recovered. After recovery from COVID, she received phase II reinduction followed by maintenance chemotherapy. At present, she is doing well off therapy.

DISCUSSION

The prevalence of invasive fungal infection (IFI) in children with ALL is reported to range between 4 and 35%, depending on era, chemotherapy protocol, risk category and prophylaxis regimen.[6] In an early Australian study, the IFI prevalence in children with high-, standard- and low-risk ALL was 35%, 30% and 6%, respectively.[6]

In a large and multi-centre study of IFI in children with ALL, the overall IFI prevalence was 9.7% with significantly higher prevalence in relapsed or refractory ALL compared to non-relapsed disease (23.5% vs. 6.2%). IFIs were more in high risk (HR) chemotherapy protocols compared to standard risk SR (14.5% vs. 7.3%) and most infections occurred during the dose-intensive chemotherapy phases. Across all groups, mould infections occurred more frequently than non-mould infections. A UKALL2001 protocol-based study found that the IFI rate was significantly higher in children treated with a more intensive chemotherapy regimen (11% vs. 4%). Similarly,

the study also showed that the majority of IFI occurred in the dose-intense treatment phases of induction, consolidation and delayed intensification, which are typically associated with prolonged periods of neutropenia and high-dose steroids.

Similarly, in our case study, the child developed *Cladophialophora* fungal infection during intensive phase of chemotherapy for B-ALL and due to late diagnosis on culture, our patient was treated empirically with ATT and antifungal therapy for possible Candidiasis which was later on diagnosed as *Cladophialophora* infection. Due to complicated infections during induction, we worked up for immunodeficiency disorders, but no underlying deficiency was detectable in our patient.

Among the most prevalent causes of human infection by dematiaceous septated moulds are *Bipolaris* spp., *Cladophialophora bantiana*, *Dactylargallopava*, *Alternaria* spp., *Exophiala* spp., *Phialophora* spp. and *Curvularia* spp.[7] In normal host, localised lesions of skin and subcutaneous tissues following a penetrating injury are common but sinusitis, pneumonia and disseminated infection in immunocompromised patients by these moulds. In the absence of a therapeutic standard, the practical approach to therapy is a combination of surgery with systemic antifungal chemotherapy consisting of high-dose amphotericin B. Broad-spectrum antifungal triazoles such as itraconazole or voriconazole or posaconazole have consistent and potent antifungal activity *in vitro* that appears to be fungicidal and may provide alternative therapies.[8]

An important consequence of IFI is that the relatively longer duration of time for treatment of this severe infection causes a significant delay in the primary treatment of ALL. The optimal time for restarting chemotherapy in these patients is not clear, which poses a great dilemma for the physician. The decision for timing chemotherapy is generally made on an individual basis depending on the extent of the fungal disease and the status of the primary disease. Similarly, we also delayed chemotherapy for 10–15 days after induction in view of active infection and delays of few days later on during starting of consolidation also. Despite delays in chemotherapy, our patient achieved remission and MRD negativity at day 33 and day 78 of our protocol and she successfully tolerated the whole intensive chemotherapy regimen and she has completed maintenance and she is asymptomatic and performing well.

CONCLUSION

IFIs are becoming common during intensive phases of chemotherapy in ALL induction and need consideration for empirical antifungal therapy along with detailed workup for diagnosing it early. The decision for timing chemotherapy should be individualised depending on the extent of the fungal disease and the status of the primary disease to achieve better outcome.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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