International Journal of Infectious Diseases 81 (2019) 110–113

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

Candida Tropicalis renal microabscesses in a child with leukemia confirmed using nucleic acid amplification and recovery after prolonged antifungal and corticosteroid treatment

Jaime S. Rosa Duque[a,*], Kelvin K.W. To[b], Alan K.S. Chiang[a], Godfrey C.F. Chan[a], Rosana W.S. Poon[b], Kwok-Yung Yuen[b], Shau-Yin Ha[a], Daniel K.L. Cheuk[a]

[a] Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[b] Department of Microbiology, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

ARTICLE INFO

Article history:
Received 28 November 2018
Received in revised form 1 February 2019
Accepted 8 February 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Renal abscess
Candida
Leukemia
Nucleic acid amplification
Polymerase chain reaction

ABSTRACT

We report the first case of microabscesses detected by polymerase chain reaction (PCR) amplification of nucleic acid from ultrasound-guided aspirated fluid in a three-year old boy with acute lymphoblastic leukemia and febrile neutropenia during induction chemotherapy. Fever persisted despite effective antifungal treatment. The addition of corticosteroid therapy successfully controlled the suspected immune reconstitution inflammatory syndrome (IRIS). This case highlights the utility of PCR and adjunctive corticosteroid in the approach of *Candida tropicalis* renal microabscesses in leukemic patients undergoing chemotherapy.

Introduction

Disseminated Candidal infections can occur in immunocompromised hosts such as patients receiving chemotherapy for malignancies, and *Candida tropicalis* may be involved in approximately 8% of cancer cases (Li et al., 2017). Culture of fungal abscess using traditional media may have low yield if the specimen is collected after antifungal therapy. Eradication of fungal abscess is challenging for patients whose immune systems are suppressed by high potency chemotherapeutics (Ashrafi et al., 2015; Rickerts et al., 2013). Here we describe a child with leukemia whose renal microabscesses due to *Candida tropicalis* appeared during the post-neutropenic phase. The diagnosis was verified using nucleic acid amplification by polymerase chain reaction (PCR) and treatment required adjunctive systemic corticosteroid therapy.

Case presentation

A three-year-old boy presented with several weeks of fever and bloody diarrhea, pallor, and petechiae. Peripheral white blood cell count (WBC) was 34.3×10^9/L, neutrophils 0.69×10^9/L, blast cells 30.0×10^9/L (87.5%), hemoglobin 7.3 g/dL, and platelets 11×10^9/L. Bone marrow examination established the diagnosis of precursor B cell acute lymphoblastic leukemia (ALL) with hyperdiploidy. He was started on induction chemotherapy according to the low risk Chinese Children Cancer Group (CCCG) ALL 2015 protocol, which included dexamethasone (days 1–4), prednisolone (days 5–35), vincristine (days 5, 12, 19, 26), daunorubicin (day 5), L-asparaginase (alternate day on days 6–24), and intrathecal methotrexate, cytarabine, and hydrocortisone (days 5, 19).

The patient defervesced after 2 days of piperacillin-tazobactam and metronidazole (chemotherapy day 2) and antibiotics were then stopped after 7 days, but his fever recurred on chemotherapy day 17. Blood culture was obtained again and piperacillin-tazobactam was resumed. Repeat blood culture the next day revealed yeast and subsequently confirmed to be *Candida tropicalis*. Liposomal amphotericin B was added immediately. Blood cultures obtained the next day and subsequently were all negative. Only small amounts of urinary leukocyte esterase and WBCs of 10–50/μL were detected once after 35 days of induction and 1 day before

Abbreviations: ALL, acute lymphoblastic leukemia; CCCG, Chinese Children Cancer Group; CRP, C-reactive protein; IRIS, immune reconstitution inflammatory syndrome; PCR, polymerase chain reaction; WBC, white blood cell count.

* Corresponding author at: Department of Paediatrics and Adolescent Medicine, Room 115, New Clinical Bldg, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong.
E-mail address: jsrduque@hku.hk (J.S. Rosa Duque).

https://doi.org/10.1016/j.ijid.2019.02.002

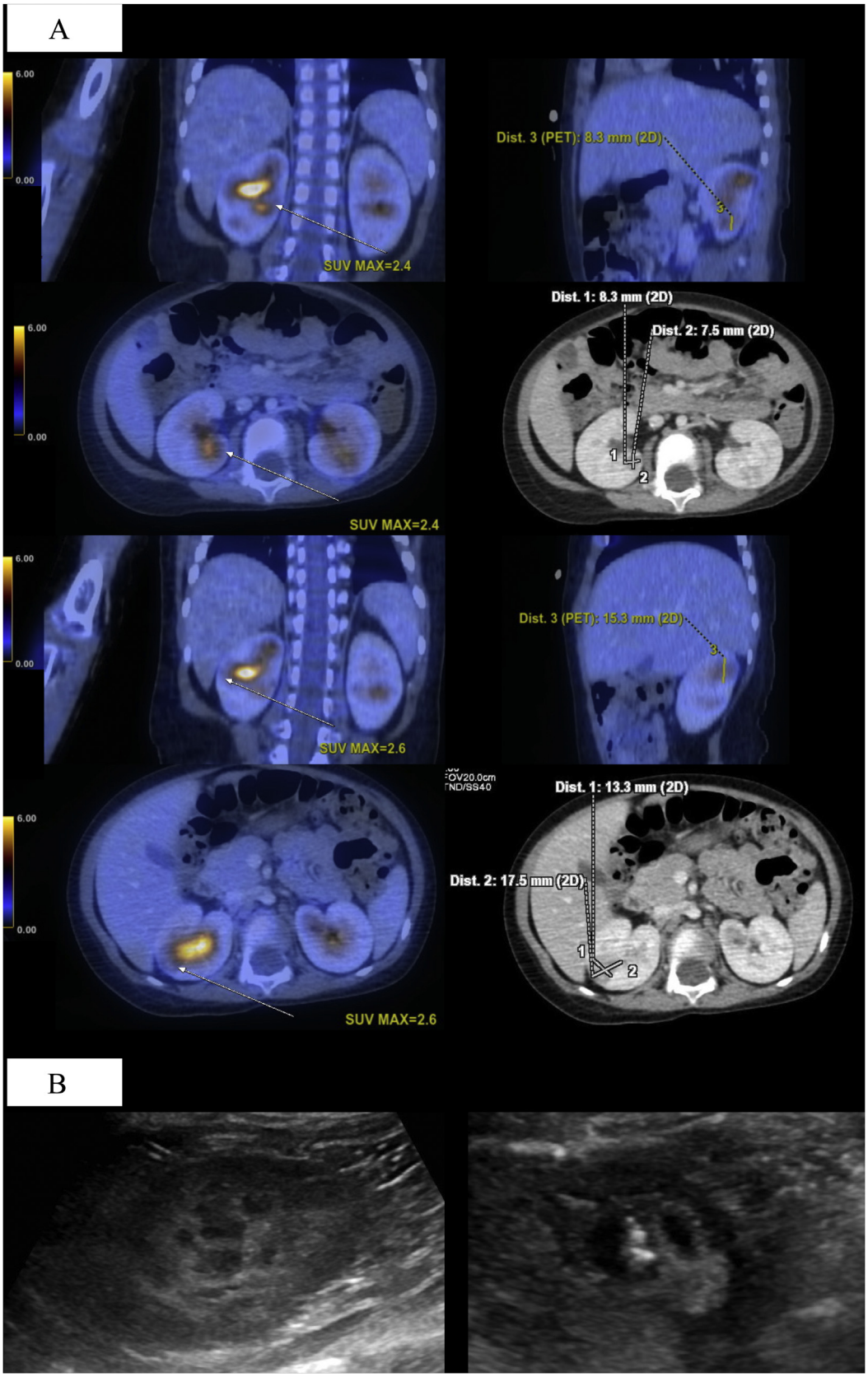

Figure 1. (A) Coronal, sagittal, and transverse views from PET-CT of the abdomen were performed which revealed more hypermetabolic, heterogenous, low attenuation in the renal parenchyma of the right kidney than left kidney. (B) Conventional microbiological cultures from ultrasound-guided aspiration of fluid within multicystic (right upper pole) and smaller hypoechoic (left middle pole) microabscesses were negative, but *Candida tropicalis* was identified using the PCR method.

consolidation chemotherapy phases despite multiple screening attempts, and there was no detectable growth on urine culture. Liposomal amphotericin B was given for a total of 26 days and changed to micafungin and then fluconazole. However, his fever persisted despite interruption of chemotherapy and prolonged antimicrobial therapy that included piperacillin-tazobactam, vancomycin, meropenem, and amikacin. All cultures remained negative and there was no clinical focus of infection. Therefore, a whole-body PET-CT was obtained 3 weeks after the positive blood culture, which revealed hypermetabolic, heterogeneous low attenuation in both renal parenchyma, consistent with pyelonephritis, but there was no apparent abscess (Figure 1A). Multicystic lesions on the right upper pole and smaller hypoechoic lesions at the left middle pole were visualized by ultrasound 4 weeks later and after recovery of the neutrophil count, suggestive of microabscesses (Figure 1B). Bacterial and fungal cultures of the ultrasound-guided aspirated fluid the following week were negative. However, PCR of this aspirated fluid was positive for *Candida tropicalis* (Figure 1B). The assay was performed using primer sequences that targeted the specific *ITS* gene of fungi from a previous published protocol. A sample mixture was amplified with our thermal cycler, and the PCR product was purified by the QIAquick gel extraction kit (Qiagen, Germany) and sequenced twice with the ABI Prism3700 DNA analyzer (Applied Biosystems, Foster City, CA, USA) (To et al., 2012; White et al., 1990). The patient was continued on micafungin, but the fever persisted despite resolution of his neutropenia. Fever due to immune reconstitution inflammatory syndrome (IRIS) was suspected, and therefore systemic corticosteroid was started on day 74. He defervesced the next day, and chemotherapy was resumed. Subsequently, micafungin was reduced to twice weekly and the corticosteroid was tapered off slowly during the consolidation phase. C-reactive protein (CRP) gradually decreased from 8.31 (<0.76) mg/dL and then remained negative since four weeks before the end of the consolidation phase. Both medications were given for approximately 8 months, until the maintenance phase. A repeat ultrasound demonstrated resolution of previous renal abscesses at the start of his maintenance phase. Currently, he is on maintenance chemotherapy which will last for 2.5 years from the date of diagnosis. His leukemia has been in remission and he did not experience other infections.

Discussion

Prompt treatment of candidemia in immunocompromised hosts such as those with leukemia receiving anti-neoplastic, immunosuppressive therapies is important since mortality can reach as high as 30% (Li et al., 2017). Species include *Candida parapsilosis complex*, *Candida tropicalis*, *Candida glabrata complex*, *Candida lusitaniae*, and *Candida famata*, and post-neutropenic candidiasis of the urinary system is much less common than hepatosplenic involvement although it has been reported in children with leukemia (Li et al., 2007, 2017). PCR appears to have a more rapid identification and higher diagnostic sensitivity for candidemia in blood samples compared to conventional culture methods (Ashrafi et al., 2015; Rickerts et al., 2013). However, the utility of PCR for detection of Candidal infections in visceral organs remains unclear since the thick cell wall of fungi within human tissues may theoretically create a barrier that interferes with binding and amplification of intracellular nucleic acid material (Ashrafi et al., 2015; Yong et al., 2009). A recent study using a two-step *in situ* RT-PCR procedure in a murine model enabled localization and detection of *Candida tropicalis* in kidney sections (Yong et al., 2009). To the best of our knowledge, our patient is the first case of human *Candida tropicalis* microabscesses occurring within visceral organs detected by PCR.

IRIS occurs most commonly as inflammatory manifestations during anti-retroviral treatment of human inmmunodeficiency virus (HIV) (Martin-Blondel et al., 2012). Recent reports and studies have also observed chronic disseminated candidiasis-related IRIS in other immunocompromised conditions such as in haematological malignancies and after stem cell transplantation (Chaussade et al., 2012; Jang et al., 2018; Kocacik Uygun et al., 2018). The pathogenesis of this phenomenon is thought to be due to rapid recovery and overactive response of T lymphocytes and granulocytes during adequate antimicrobial treatment of the infection (Chaussade et al., 2012; Jang et al., 2018; Martin-Blondel et al., 2012). The patient's positive PCR and negative culture results together suggest that the fevers were due to IRIS after leukocyte recovery rather than another uncontrolled infection or metastatic masses, a notion that was further supported by rapid resolution of symptoms only after the addition of systemic corticosteroids. A corticosteroid dose equivalent to $\geq$0.5 mg/kg prednisone for several weeks to months was usually required and our patient defervesced one day after starting this therapy (Chaussade et al., 2012; Jang et al., 2018). CRP also trended down gradually from 8.31 to 1.34 mg/dL. A slow corticosteroid taper appeared to be important to prevent inflammatory rebound (Chaussade et al., 2012; Jang et al., 2018). When we attempted to wean the patient off corticosteroids after 10 days, his fever returned, and CRP temporarily returned to 3.47 mg/dL despite gradual resolution of his Candidal abscesses as apparent on repeat ultrasound scans. Therefore, his corticosteroid was tapered much more slowly over 8 months, with each step of dose reduction dependent on his clinical status, phase of his chemotherapy, and CRP trend. This case highlights the value of PCR and adjunctive corticosteroid treatment in the approach to renal microabscesses due to *Candida tropicalis* in paediatric ALL.

Ethical approval

Consent has been obtained and no approval was required for this case report.

Statement of contribution

Jaime S Rosa Duque was involved in the clinical care, interpretation of results, and writing of the manuscript.

Kelvin KW To was involved in the clinical care, interpretation of results, and writing of the manuscript.

Alan KS Chiang was involved in the clinical care, interpretation of results, and writing of the manuscript.

Godfrey CF Chan was involved in the clinical care, interpretation of results, and writing of the manuscript.

Rosana WS Poon was involved in designing the PCR for the internal transcribed spacer of the *Candida tropicalis* gene, analysis of the sequencing result, and writing of the manuscript.

Kwok-Yung Yuen was involved in the clinical care, interpretation of results, and writing of the manuscript.

Shau-Yin Ha was involved in the clinical care, interpretation of results, and writing of the manuscript.

Daniel KL Cheuk was involved in the clinical care, interpretation of results, and writing of the manuscript.

Statement of conflicts of interest

Jaime S Rosa Duque declares no conflicts of interest (Conflicts of interest: none).

Kelvin KW To declares no conflicts of interest (Conflicts of interest: none).

Alan KS Chiang declares no conflicts of interest (Conflicts of interest: none).

Godfrey CF Chan declares no conflicts of interest (Conflicts of interest: none).

Rosana WS Poon declares no conflicts of interest (Conflicts of interest: none).

Kwok-Yung Yuen declares no conflicts of interest (Conflicts of interest: none).

Shau-Yin Ha declares no conflicts of interest (Conflicts of interest: none).

Daniel KL Cheuk declares no conflicts of interest (Conflicts of interest: none).

Funding

None.

References

Ashrafi M, Nabili M, Shokohi T, Janbabaie G, Hedayati MT, Ali-Moghaddam K. A real time PCR assay on blood for diagnosis of invasive candidiasis in immunocompromised patient. Curr Med Mycol 2015;1(1):35–41.

Chaussade H, Bastides F, Lissandre S, Blouin P, Bailly E, Chandenier J, et al. Usefulness of corticosteroid therapy during chronic disseminated candidiasis: case reports and literature review. J Antimicrob Chemother 2012;67(6):1493–5.

Jang YR, Kim MC, Kim T, Chong YP, Lee SO, Choi SH, et al. Clinical characteristics and outcomes of patients with chronic disseminated candidiasis who need adjuvant corticosteroid therapy. Med Mycol 2018;56(6):782–6.

Kocacik Uygun DF, Uygun V, Daloglu H, Ozturkmen SI, Karasu GT, Hazar V, et al. Immune reconstitution inflammatory syndrome after DLI in a SCID patient after hematopoetic stem cell transplantation. J Pediatr Hematol Oncol 2018;40(3):e179–81.

Li D, Xia R, Zhang Q, Bai C, Li Z, Zhang P. Evaluation of candidemia in epidemiology and risk factors among cancer patients in a cancer center of China: an 8-year case-control study. BMC Infect Dis 2017;17(1):536.

Li WY, Wu VC, Lin WC, Chen YM. Renal Candida tropicalis abscesses in a patient with acute lymphoblastic leukemia. Kidney Int 2007;72(3):382.

Martin-Blondel G, Mars LT, Liblau RS. Pathogenesis of the immune reconstitution inflammatory syndrome in HIV-infected patients. Curr Opin Infect Dis 2012;25(3):312–20.

Rickerts V, McCormick Smith I, Mousset S, Kommedal O, Fredricks DN. Deciphering the aetiology of a mixed fungal infection by broad-range PCR with sequencing and fluorescence in situ hybridisation. Mycoses 2013;56(6):681–6.

To KK, Lau SK, Wu AK, Lee RA, Ngan AH, Tsang CC, et al. Phaeoacremonium parasiticum invasive infections and airway colonization characterized by agar block smear and ITS and beta-tubulin gene sequencing. Diagn Microbiol Infect Dis 2012;74(2):190–7.

White TJ, Bruns T, Lee S, Taylor JW. Amplification and direct sequencing of fungal ribosomal RNA genes for phylogenetics. San Diego, CA: Academic Press; 1990. p. 315–22.

Yong VC, Ong KW, Sidik SM, Rosli R, Chong PP. A modified in situ RT-PCR method for localizing fungal-specific gene expression in Candida-infected mice renal cells. J Microbiol Methods 2009;79(2):242–5.