Singapore Med J 1999; Vol 40(8):533-536

Successful Treatment of *Candida Albicans* Endocarditis in a Child with Leukemia – A Case Report and Review of the Literature

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ABSTRACT

Candida species is now being increasingly recognised as an important cause of endocarditis especially in immunocompromised patients. A case of *Candida albicans* endocarditis in a child with acute lymphoblastic leukemia (ALL) is reported. The child did not have a central venous catheter at any time. Treatment consisted of intravenous amphotericin B and fluconazole for 3 weeks followed by oral fluconazole for 2 weeks. No surgical resection was necessary. We highlight here the importance of echocardiography in the management of prolonged febrile neutropenia and discuss the dilemma of continuing chemotherapy in such patients.

Keywords: *Candida* sepsis, leukemia, endocarditi, febriie neutropenia, fluconazole

INTRODUCTION

Candida species is now being increasingly recognised as an important cause of endocarditis. The groups of patients at highest risk of this infection are intravenous drug abusers, immunosuppressed patients, those with prosthetic heart valves and patients with long-term in dwelling catheters[1,2].

We report a case of *Candida albicans* endocarditis in a child with acute lymphoblastic leukemia who did not have an indwelling catheter. This case report serves to highlight the importance of "screening" echocardiography in the management of prolonged febrile neutropenia and documents successful treatment of this rare infection without the need for a surgical resection. The dilemma of administering chemotherapy to leukemic patients with *Candida* endocarditis is also discussed.

CASE REPORT

A 4-year-old boy was diagnosed to have an isolated bone marrow relapse of acute lymphoblastic leukemia (ALL) FAB-L1 in December 1996 when he presented with hepatosplenomegaly and leukocytosis while still receiving oral maintenance chemotherapy for acute lymphoblastic leukemia, diagnosed 18 months earlier. A check bone marrow examination revealed 90% blasts. He underwent BFM 86-ALL relapse protocol chemotherapy and on the fourth day of the induction prophase, while on daily oral prednisolone, he developed high grade fever. And during this time, he had just completed a 48-hour infusion of cytosine arabinoside 3000 mg/m^2/day.

Examination did not reveal any source of infection. No oral thrush was detected and there were no mouth ulcers. Blood culture was performed with the Bactec NR 630 system using an aerobic Paeds Plus medium and an anaerobic NR 17A medium. He was started empirically on intravenous ceftazidime and amikacin (day 1). Further chemotherapy for his relapse ALL was discontinued. Apart from anorexia, he remained fairly well. However, as his fever did not subside after 48 hours of antibiotic therapy, another set of blood culture was taken. A full blood count at this time revealed an absolute neutrophil count (ANC) of 0.4 x 10^9/L and platelets of 35 x 10^9/L. Ceftazidime was then changed to imipenem. No isolate was obtained.

He remained febrile on the fifth day, ie. after 72 hours of imipenem and amikacin treatment. He was still neutropenic with an ANC of 0.2 x 10^9/L and platelet count was at 49 x 10^9/L. Physical examination revealed hepatosplenomegaly (no change from size at presentation) and oral ulceration. No cardiac murmur was present. Scrapings from the oral mucosa did not reveal the presence of herpes virus. Blood was sent for bacterial and fungal cultures and his antibiotics were changed empirically to ciprofloxacin and netilmicin. The third set of blood cultures subsequently yielded budding yeast cells, *pseudohyphae* and characteristic *chlamydococonidia*. The yeast was identified as *Candida albicans* on the basis of a positive 2-hour germ-tube test. Amphotericin B was started, with an initial dose of 0.25 mg/kg/day gradually increasing to 1.0 mg/kg/day over 4 days. On the eleventh day, ie. 4 days after commencing amphotericin B, he developed tender swelling of both cheeks and malar areas. Computerised tomography of the head revealed

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mucosal thickening with air-fluid level in both maxillary antra consistent with sinusitis. A posterior nasal swab did not yield any growth on culture. This infection improved clinically and radiologically over the following ten days. However, he became increasingly unwell with hypotension, tachypnoea and poor urine output on the thirteenth day and was transferred to the paediatric intensive care unit (PICU).

His condition continued to deteriorate and he developed respiratory failure for which he required mechanical ventilation. Chest radiography at that time revealed bilateral opacities consistent with adult respiratory distress syndrome. He also needed inotropic support to maintain his blood pressure. Although his sinusitis showed clinical improvement, he remained febrile after a week's therapy of amphotericin B . At that time, he showed evidence of renal impairment with the serum creatinine level rising to 76 μmol/L. A fourth set of blood culture taken on the thirteenth day still yielded *Candida albicans*; no bacteria was isolated. Intravenous fluconazole 10 mg/kg/day was then added on the fourteenth day.

A thorough investigation was done to find a septic focus and this included repeat chest radiographs, an ultrasonogram of the abdomen and echocardiography. The transthoracic echocardiogram done on the fifteenth day revealed vegetation in the right atrium. Abdominal ultrasonogram did not reveal any evidence of hepatosplenic candidiasis. On the twenty-sixth day, ie. after 18 days of amphotericin B (maximum dose 1.2 mg/kg/day) and 12 days of i.v. fluconazole 200 mg (15 mg/kg) daily, his temperature returned to normal and he was weaned off ventilatory and inotropic support.Two further sets of blood cultures taken on the twenty-second and twenty-fifth days, were negative.

An echocardiogram performed at this time showed that the vegetation was no longer present. He continued to receive both antifungal agents intravenously for a total of 21 days . The patient then recommenced his ALL induction chemotherapy; continuing oral fluconazole for a further 2 weeks.

At follow-up 12 months later, echocardiography did not reveal any abnormality and his ALL was in remission.

DISCUSSION

The paucity of case reports stresses the rarity of *Candida* endocarditis in leukemic patients. A MEDLINE search to as far back as 1970, yielded only 22 case reports (Table I). In our patient, echocardiographic abnormalities and evidence of septic emboli (presumed *Candida* sinusitis) support the diagnosis of endocarditis. In addition *Candida albicans* was isolated from two sets of blood cultures.

Leukemic patients are theoretically at low risk for developing endocarditis due to their prolonged periods of thrombocytopenia, which was also present in our patient. However, the actual level of circulating platelets required to initiate the nidus on which infection occurs in endocarditis is not known and perhaps very few platelets are sufficient[2].

Our patient had no obvious risk factor for endocarditis eg. indwelling atrial catheter, central venous cannulation and diseased or prosthetic heart valves[1,2]. However, leukemic patients per se are immunocompromised and thus are susceptible to fungal infections, which may either follow a first encounter with the organism or result from proliferation of a commensal when host defences are down. Many factors can also facilitate these infections including mucous membrane damage by

Table I – Reported cases of *Candida* endocarditis in patients with leukemia 1970 – 1997

Author	Cases	Isolate	Underlying disease	Treatment	Outcome
Girmenia et al[13]	1	*C parapsilosis*	AML	Fluconazole x 4 weeks G-CSF	Died of AML
	1	*C parapsilosis*	AML	Amphotericin B Fluconazole removal of CVC	Died of AML
Leung et al[1]	1	*C krusei*	AML	Amphotericin B removal of CVC	Died of fungemia
Ihde et al[14]	12	NA	leukemia	NA	All died of disseminated extensive fungal infection
	4	NA	lymphoma	NA	
Crofts et al[15]	1	*C guilliermondi*	ALL	Valve replacement Ampho B x 3 weeks Flucytosine x 6 months	Survived
Klingspor et al[16]	1	*C albicans*	AML	Valve replacement CVC removal Ampho B and flucytosine for 4 weeks	Survived

NA = not available
AML = acute myeloid leukemia
ALL = acute lymphoblastic leukemia
CVC = central venous catheter

chemotherapy, disruption of skin integrity by intravenous cannulation and the use of steroids and broad-spectrum antibiotics; factors which were all present in our patient. This case highlights that a high index of suspicion for fungal infections, including endocarditis in febrile neutropenic patients is required. This is especially so if prolonged use of broad-spectrum antibiotics fails to resolve persistent fever and when no obvious focus of infection is found. In this situation, aggressive investigations including abdominal ultrasonography and echocardiography (ideally transoesophageal) to find occult sources of infection is warranted.

Although two-dimensional echocardiography has improved the detection rate of *Candida* vegetations to approximately 85%[3], a negative study does not necessarily rule out its presence. Lesions less than 2 mm in diameter are below the level of accurate resolution and in fungal endocarditis, the infective process may be mural interstitial or destructive rather than vegetative[4].

In fungal endocarditis as in bacterial endocarditis, systemic embolisation to and subsequent involvement of distant organs may occur. Emboli to the skin may manifest as papules, ulcers and nodules of various sizes[5]. The detection of ocular involvement requires meticulous eye-ground examination, including that of the peripheral retina to be performed in suspected cases[6,7].

Amphotericin B is the drug of choice for the treatment of *Candida* endocarditis. In many instances, successful management of these cases has required surgical resection and concurrent replacement of the diseased valve[1,15,16]. Flucytosine should be added if there is CNS involvement including *Candida* endopthalmitis[8]. Wells et al reported successful treatment of a case of *Candida* endocarditis in a native valve with a course of fluconazole monotherapy[9]. We elected to use a combination of amphotericin B and intravenous fluconazole for the initial 3-week course to eradicate the infection and a 2-week course of oral fluconazole to prevent recurrence. Unlike previously reported cases[15,16], apparent successful therapy was achieved in our patient without the need for surgical resection.

It is also a dilemma for physicians managing these patients to decide when it is 'safe' to recommence chemotherapy. It is unwise to delay chemotherapy unnecessarily; however, the accompanying myelosuppression with administration of chemotherapy may lead to relapse of the fungemia and possibily the endocarditis. There is no published consensus on this matter apart from anecdotal reports. Experience from two European centres[13,16-18] and that of our own show that it is safe to recommence chemotherapy once defervescence has occurred and blood cultures are negative.

Late recurrence of *Candida* endocarditis has been reported by several authors[10,11], all of whom have questioned the curability of this infection. In a literature review by Johnston et al[12], 5 cases of late recurrent *Candida* endocarditis were found occurring between 17 months to 7 years after apparently adequate courses of amphotericin B; thus emphasising the role of prophylaxis. Fluconazole, a potent triazole compound, permits once-daily oral administration without major side effects and is a suitable agent for preventing recurrence. However, the exact duration of treatment required is not known as there appears to be neither reliable clinical nor microbiological indicator which may help to predict which patients with *Candida* endocarditis are at risk of developing late recurrence of this infection.

Klingspor et al found that the determination of antibody titres against *Candida* eg. using the Directigen 1-2-3(R) *Candida* antigen test may be of value in assessing the efficacy of antifungal treatment[16]. A sudden rise in the IgM titre suggests active infection and this method, although unproven, may be useful when following-up patients with *Candida* endocarditis.

However, until a satisfactory method for predicting the outcome for these patients is available, despite apparent resolution of the infection, an indefinite follow-up period with periodic echocardiographic examination may be necessary.

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