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SHORT COMMUNICATION

Candidemia in acute leukemia patients

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Abstract Fungal infections are an important cause of morbidity and mortality in patients with acute leukemia (AL). Candidemia, once rare, is now a common nosocomial infection because of the intensity of chemotherapy, prolonged neutropenia, administration of broad-spectrum antibiotics and use of central venous catheters (CVC). We retrospectively identified patients treated for AL from 6/86 to 6/95 who also had candidemia. We describe 28 patients (incidence 6.3%) with a median age of 39 years, 24 of whom were on remission induction and 4 on postremission chemotherapy. All patients had CVC and empiric antimicrobial therapy, 4 had been given prophylactic antifungal drugs, and 2 had parenteral nutrition. Neutropenia was profound (median leukocyte nadir 200/μl, median duration 19 days). *Candida* was isolated in blood cultures 10 days (median) after the start of neutropenia. The clinical presentation included fever (100%), respiratory symptoms (71.4%), skin lesions (39.2%) and septic shock (17.8%). Amphotericin B was given to 17 patients and liposomal amphotericin to 5 patients. Infection resolved in 18 patients (64.2%), 10 of whom were in complete remission. Mortality from candidemia was 17.8% (5/28). In conclusion, fungal infections are responsible for death in a significant number of patients. In our series treatment success was related to its rapid onset and to the recovery of neutropenia.

Key words Candidemia · Neutropenia · Acute leukemia

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Introduction

Fungal infection is an important cause of morbidity and mortality in immunocompromised patients. Its incidence has risen steadily and considerably in the last decades in AL patients as a result of the intensity of chemotherapy, prolonged neutropenia, cellular immune deficiency, rupture of natural barriers, and better supportive care (use of CVC, broad-spectrum antibiotics and parenteral nutrition). These factors favor the occurrence of candidemia among immunocompromised hosts in particular. Its incidence is 4–12% [1, 4]. There is a growing concern about its high mortality rate (46–75%) [9, 15]. Antifungal prophylaxis, by diminishing the burden of *Candida* in the intestinal flora, may lower the incidence of candidemia and disseminated candidiasis [17]. On the other hand, triazoles may favor the emergence of certain species, such as *C. krusei* and *C. glabrata* [2, 10, 11], without any real reduction in the incidence of candidemia [10]. Preliminary data on the usefulness of colony-stimulating factors in prophylaxis or as an adjuvant to therapy [17] need to be confirmed. Optimal management of candidemia is still controversial, but amphotericin B remains the preparation of choice for neutropenic patients, although its toxicity limits its generalized use [12]. Unfortunately, there are

few comparative studies examining lipid formulations of amphotericin B and with flucytosine. Retrospective analyses suggest some advantage of the association with flucytosine, but more adverse effects and higher costs [11]. Resolution of the neutropenia and complete remission of the hematologic malignancies are associated with a favorable outcome [17], although this is not accepted by all authors [8]. We report the incidence, risk factors, clinical features, therapy and outcome of candidemia in AL patients at our institution.

Patients and methods

We retrospectively reviewed all files from patients with AL treated from April 1986 to April 1995 and selected those with candidemia. Candidemia was defined as the presence of at least one positive blood culture for *Candida*. Yeasts were identified by means of the API (ID32C) System. The presence of the following predisposing factors for candidemia was recorded for each case: duration and depth of leukopenia, defined as leukocytes ‹1000/μl; previous administration of broad-spectrum antibiotics; parenteral nutrition; and indwelling CVC. Clinical manifestations, type and dosage of antifungal drugs used, and adverse effects of treatment were evaluated. Outcome was recorded as cure, for complete clinical resolution with subsequent negative blood cultures, or as failure, for any other outcome, including visceral localizations. Chronic disseminated candidiasis was diagnosed in patients with persistent fever after neutrophil recovery, abdominal symptoms, elevated serum alkaline phosphatase, and demonstration on CT scan of multiple hepatosplenic microabscesses, with or without histopathologic documentation.

Results

Of the 442 AL patients, 28 had candidemia (incidence 6.3%); 15 were male and 13 female, median age was 39 years (range 13 to 72), and AL was nonlymphoblastic in 19 and lymphoblastic in 9. Patients were nursed on an open ward; 24 were on a remission induction course (their first course in 11 cases) and the remaining 4 on postremission therapy. Treatment included high-dose cytarabine in 12 cases. Antifungal prophylaxis was not routinely used. Among the known predisposing factors for candidemia, all patients had long-lasting profound neutropenia, had indwelling CVC, and had been given broad-spectrum antibiotics, but only 2 had parenteral nutrition (Table 1).

Respiratory tract symptoms predominated in clinical presentation (Table 2), although only 6 patients had positive findings in the chest roentgenogram, consisting of diffuse bilateral interstitial infiltrates, homogeneous consolidations, and pleural effusions. The relationship of these findings to candidemia could not be definitely established by tissue biopsy, because of thrombocytopenia, and other methods (CT scan in 4 patients, bronchoalveolar lavage in 2) were inconclusive; no concurrent infections were diagnosed.

Table 1 Predisposing factors

Factor	$n=28$
Central venous catheter	28 (100%)
Parenteral nutrition	2 (7.1%)
Broad-spectrum antibiotics	28 (100%)
Leukopenia (<1000/μl)	28 (100%)
Median nadir (range)	200 (100–600)
Median duration (range)	19 (5–45)

Table 2 Clinical features

	No. of cases (%)
Fever	28 (100%)
Skin lesions	11 (39.2%)
Myalgia and arthralgia	5 (17.8%)
Respiratory symptoms	20 (71.4%)
Septic shock	5 (17.8%)
Endocarditis	1 (3.5%)
Endophthalmitis	1 (3.5%)

Candida was isolated from the blood between days 4 and 30 of the chemotherapy course, after a median of 10 days with leukocytes ‹1000/μl. Median number of positive blood cultures was 2 (range 1–7) per patient. *C. parapsilosis* was isolated in 5 cases, *C. albicans* in 3, *C. tropicalis* in 3, *C. krusei* in 3 and in the remaining 14 the *Candida* spp. were not further characterized.

Amphotericin B (0.5–1.5 mg/kg per day) was given to 17 patients, liposomal amphotericin (2.5–4 mg/kg per day) to 5 patients (1 of these with added flucytosine), and itraconazole to 1 patient. No antifungal therapy was given to 5 patients; this was due to spontaneous cure in 2 cases, both with AL in complete remission, and to death from *Candida* sepsis before candidemia was recognized in 3 cases. Side effects of amphotericin B were rigors and fever despite premedication in 13 patients, hypokalemia in 14, and a rise in serum creatinine (WHO grade ‹3) in 9.

The outcome was cure in 18 of 28 patients (64.2%), 10 of whom were in complete remission of AL. Cure was achieved with liposomal amphotericin in 4 patients and with amphotericin B in 14. The remaining 10 cases were classified as failures: 5 (17.8%) died from *Candida* sepsis and 5 progressed to chronic disseminated candidiasis. The CVC was removed from 10 patients (4 of them demonstrating line colonization by the same *Candida* species as was found in the blood): 7 of these were cured and in 3 the treatment failed.

There was no significant difference between cure and failure cases in the dose of amphotericin (mean 1.07 mg/kg per day versus 1.2) or in the mean duration of fever before treatment with amphotericin was begun (11 versus 9 days).

Discussion

The candidemia rate of 6.3% found in our AL patients is similar to rates published in the literature [1, 4, 16]. The growing incidence of non-*albicans* species has recently been stressed and reaches 46% of fungal infections in some studies [19]; this change is probably related to the prophylactic use of triazoles. In our series, one third of the cases in which the species of *Candida* was identified were affected by *C. parapsilosis*, which has been associated with exogenous contamination from CVC and with parenteral nutrition [3, 13, 14, 18]. As for other predisposing factors, all our patients had been given broad-spectrum antibiotics and aggressive chemotherapy (nearly half with high-dose cytarabine), which results in prolonged neutropenia and rupture of mucosal barriers.

The mortality rate of candidemia is high (46–75%) [7, 9, 15] unless neutropenia resolves. Antifungal prophylaxis was unable to reduce its incidence or mortality rate in neutropenic patients in randomized trials [20], except in the case of bone marrow transplantation [5, 6]. Our patients did not have routine prophylaxis, and most were treated with amphotericin B, which remains the drug of choice in neutropenic patients. The removal of CVC in candidemia is controversial, except in the case of tunnel infection or persistence of positive blood cultures after appropriate therapy [1, 14]. Only 7 of our 18 cured patients had their CVC removed, indicating that response is possible without removal. The excellent cure rate (64%) found in our series probably stems from early empirical treatment with amphotericin B as much as from resolution of neutropenia and remission of the underlying leukemia in the majority of patients.

References

1. Anaissie E (1992) Opportunistic mycoses in the immunocompromised host: experience at a cancer center and review. Clin Infect Dis 14 [Suppl 1]:43–53
2. Anaissie E, Bodey GP, Kantarjian H, David O, Barnett K, Bow E, Defelice R, Downs N, File T, Karam G, Potts D, Shelton M, Sugar A (1991) Fluconazole therapy for chronic disseminated candidiasis in patients with leukemia and prior amphotericin B therapy. Am J Med 91:142–150
3. Branchiani ML, Pfaller MA, Rhine-Chalberg J, Frenpong T, Isenberg D (1994) Genotypic variation and slime production among blood and catheter isolates of *Candida parapsilosis*. J Clin Microbiol 32:452–456
4. Edwards JE, Filler JS (1992) Current strategies for treating invasive candidiasis: emphasis on infections in non-neutropenic patients. Clin Infect Dis 14 [Suppl 1]:106–113
5. Freifeld AG (1993) The antimicrobial armamentarium. Hematol Oncol Clin North Am 7:813–864
6. Goodman JL, Winston DJ, Greenfield RA (1992) A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 326:845–851
7. Hay RJ (1991) Overview of the treatment of disseminated fungal infections. J Antimicrob Chemother 28:17–25
8. Kauffman CA, Bradley SF, Ross SC, Weber DR (1991) Hepatosplenic candidiasis: successful treatment with fluconazole. Am J Med 91:137–141
9. Komshian SV, Uwaydahak AK, Sobel JD, Crane LR (1989) Fungemia caused by *Candida* species and *Torulopsis glabrata* in the hospitalised patient: frequency, characteristics and evaluation of factors influencing outcome. Rev Infect Dis 11:397–390
10. Meilroy MA (1991) Failure of fluconazole to suppress fungemia in a patient with fever, neutropenia and typhlitis. J Infect Dis 163:420–421
11. Meunier F, Aoun M, Bitar N (1992) Fungal infections in immunocompromised hosts. Clin Infect Dis 14 [Suppl 1]:20–25
12. Moreau P, Milpied N, Fayette N, Ramee JF, Harousseau JL (1992) Reduced renal toxicity and improved clinical tolerance of amphotericin B mixed with intralipid compared with conventional amphotericin B in neutropenic patients. J Antimicrob Chemother 30:535–541
13. Pfaller MA (1995) Epidemiology of candidiasis. J Hosp Infect 30:329–338
14. Raad II, Bodey GP (1992) Infectious complications of indwelling vascular catheters. Clin Infect Dis 15:197–210
15. Rex JH, Bennet JE, Sugar AM, Pappas PG, Van der Horst CM, Edwards JE, Washbirn RG, Scheld NM, Karchmer AW, Dine AP, Levenstein MJ, Webb Q (1994) A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. N Engl J Med 331:1325–1330
16. Schaffner A, Schaffner M (1995) Effect of prophylactic fluconazole on the frequency of fungal infections, amphotericin B use and health care costs in patients undergoing intensive chemotherapy for hematologic malignancies. J Infect Dis 172:1035–1041
17. Uzun O, Anaissie E (1995) Antifungal prophylaxis in patients with hematologic malignancies: a reappraisal. Blood 8:2063–2072
18. Ween JJ Jr (1992) *Candida parapsilosis*: epidemiology, pathogenicity, clinical manifestations and antimicrobial susceptibility. Clin Infect Dis 14:756–766
19. Wingard JR (1995) Importance of *Candida* species other than *C. albicans* as pathogens in oncology patients. Clin Infect Dis 20:115–125
20. Winston DJ, Chandrasckar PH, Lazarus HM (1993) Fluconazole prophylaxis of fungal infections in patients with acute leukemia: results of a randomized placebo controlled double blind multicenter trial. Ann Intern Med 118:495–503