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Risk Factors for Candidemia in Cancer Patients: a Case-Control Study

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Risk factors for candidemia were analyzed in a case-control study of 30 cancer patients with candidemia and 58 controls. In a univariate analysis, previous surgery, neutropenia, central catheterization, chemotherapy, specific antibiotic treatments, and peripheral cultures positive for *Candida* spp. were associated with a significantly increased risk of candidemia. In a multivariate logistic model, the significant risk factors for candidemia were positive peripheral cultures for *Candida* spp. ($P = 0.02$), central catheterization ($P = 0.03$), and neutropenia ($P = 0.05$). These results should help to identify cancer patients with a high risk of candidemia, who should be given early systemic antifungal therapy.

In several studies the poor prognosis of infections caused by *Candida* organisms in cancer patients (2, 4, 6, 9, 11–13) has been emphasized. In those patients with proven deep-organ infection, the mortality rate reaches 95% (11).

Intravenous antifungal therapy with amphotericin B is initiated empirically in patients presenting one or several characteristics that are thought to be risk factors for candidiasis or candidemia, e.g., neutropenia, chemotherapy, antibiotic treatment, positive fungal surveillance cultures, or central intravenous catheterization (4, 11, 14). Because these factors are often present in the absence of deep fungal infection, many patients are overtreated. For instance, 40% of patients with acute leukemia but without systemic candidiasis are given amphotericin B unnecessarily (4). Positive serological tests do not constitute a reliable indication of a deep-seated fungal infection (12) and are of little value for diagnosis in immunocompromised hosts (5). Methods for the detection of *Candida* antigens or metabolites (7) have low sensitivity (1) and low positive predictive value (8), and the value of surveillance cultures for an early diagnosis remains unclear (11).

We report here the results of a case-control study of cancer patients with candidemia that was designed to identify clinical and microbiological risk factors for this infection.

MATERIALS AND METHODS

All the inpatients admitted between 1 June 1982 and 31 December 1985 to Institut Gustave-Roussy, a 420-bed cancer reference center, were included in the study. Case patients were defined as patients with two or more blood cultures positive for the same *Candida* spp. recovered within 72 h. The surveillance period for a case patient was defined as the time that elapsed between admission and the day on which the first positive blood culture was drawn. Two controls were matched with each case. These controls were chosen among patients of the study population who had not had any blood culture positive for *Candida* spp.; who had not been treated with flucytosine, ketoconazole, or intravenous amphotericin B; and who had been hospitalized for a period of at least as long as the surveillance period of the matched case patient. Case patients and controls were matched for primary diagnosis, ward, year of hospitalization, age (±5 years), and duration of surveillance. For the controls, the surveillance period was defined as starting on the day of admission and ending after a number of days equal to that of the surveillance period of the matched case patient. Clinical charts and microbiological data of both case patients and controls were reviewed throughout the surveillance period.

Urine, skin, and oropharyngeal surveillance cultures were obtained frequently and plated onto Sabouraud glucose agar containing 50 mg of gentamicin (Bio-Mérieux, Charbonnières-les-Bains, France) per liter. They were incubated for 7 days at 25°C. Fungi were counted in feces by plating 0.1 ml of serial 10-fold dilutions of fecal samples. On removal, all catheters were cultured onto blood agar by the semiquantitative technique described by Maki et al. (10). At least three blood samples were obtained for culturing at the onset of all febrile episodes (over 38.5°C for 6 h or more) and inoculated into flasks containing 100 ml of brain heart infusion broth (10 ml of blood per flask). The minimum time between blood sample collections was 2 to 3 h. Flasks were ventilated on arrival in the laboratory, and their contents were subcultured every other day on malt agar (Roche Septi-Chek system; F. Hoffmann-La Roche, Basel, Switzerland). Isolates of *Candida* spp. were identified by using the API system (API system S.A., La-Balmes-les-Grottes, France).

Data were managed and checked by the PIGAS system (18) and analyzed by multivariate logistic regression for matched case-control studies (3). Likelihood ratios and predictive values were calculated as described previously (15).

RESULTS

For the years 1982, 1983, 1984, and 1985, 3, 6, 12, and 9 cases of candidemia, respectively, were included in the study. The organisms identified were 24 strains of *Candida albicans*, 4 strains of *C. tropicalis*, and 1 strain each of *C. pseudotropicalis* and *C. krusei*. Underlying diseases of the case patients were leukemia in 10 patients, lymphomas in 9 patients, and solid tumors in 11 patients. Two adequate controls without candidemia were available for 28 of the 30 cases.

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TABLE 1. Characteristics of 30 case patients with candidemia and 58 matched controls

Characteristic	Cases	Controls	*P* value
Sex (% males)	50	48	>0.10
Age (yr; mean ± SD)	30 ± 19	31 ± 20	>0.10
Duration of cancer (mo, mean [range])	21 (0–186)	14 (0–97)	>0.10
No. of cultures/site (mean [range]) in[a]:			
Oropharynx	2.3 (0–11)	1.6 (0–11)	>0.10
Skin	1.1 (0–8)	0.7 (0–8)	>0.10
Feces	2.8 (0–10)	1.9 (0–11)	>0.10
Urine	6.1 (0–61)	2.4 (0–20)	>0.10
Venous catheters	0.8 (0–7)	0.3 (0–4)	0.06
Blood	15.3 (1–74)	6.8 (0–106)	0.02
Associated bacteremia with[b]:			
Gram-positive cocci	5	1	
Gram-negative bacilli	2	3	
Anaerobes	1	0	

[a] During the surveillance period.
[b] Bacteremia that occurred in the same hospital stay in which candidemia occurred. For the eight cases of associated bacteremia in the case patients and four in the controls, the *P* value was 0.02.

Characteristics of case patients and controls are given in Table 1. Sex ratio, age, and the time that elapsed since diagnosis of the underlying disease and the start of the study were not significantly different in case patients and controls, nor were the numbers of oropharyngeal, fecal, urine, and skin cultures made during the surveillance periods. The number of samples from catheters that were cultured was larger for the case patients than for the controls, blood samples were cultured significantly more often in the case patients, and associated bacteremia was significantly more frequent.

In Table 2 it is shown that some clinical, therapeutic, and microbiological characteristics were significant risk factors for candidemia: the clinical risk factors were previous surgery and the durations of neutropenia and central catheterization; the therapeutic factors were exposure to chemotherapy and some antibiotic treatments; and the microbiological factors were the recovery of a *Candida* sp. from surveillance culture sites (oropharynx or feces). The mean fecal concentrations of *Candida* spp. were not significantly different, however, in the colonized case patients and colonized controls (4.1 ± 1.2 versus 3.5 ± 1.1 $\log_{10}$ CFU/g of feces).

Results from a multivariate analysis (Table 3) showed that, when considered together, only colonization of at least one site by a strain of *Candida* sp., central catheterization, and neutropenia were associated with a significantly increased risk of candidemia. Likelihood ratios calculated for these three characteristics (Table 2) expressed the odds that their presence would be expected in a patient with candidemia (as opposed to one without). The highest of these likelihood ratios was colonization by *Candida* spp.

The mortality associated with invasive disease in patients with candidemia could not be precisely assessed since an autopsy was not performed on most patients. Nevertheless, we found that only 50% of the 30 patients (cases) with candidemia survived the episode. Significantly more control patients (76%; $P = 0.02$) were alive at the end of the hospital stay in which the surveillance period was included. When the patients who survived were compared with those who did not for all the factors given in Tables 1 and 2, the only significant difference between the two groups was the time that elapsed between the diagnosis of the underlying cancer and the diagnosis of candidemia (median, 6 months in survivors versus 15 months in nonsurvivors; $P = 0.05$ by the Wilcoxon rank test). Associated bacteremia was more frequent (although not significantly) in patients who died during the candidemia episode (4 of 15) than in those who survived the candidemia episode (2 of 15).

DISCUSSION

We chose to study patients with candidemia rather than patients with histological diagnosis of disseminated candidiasis because (i) premortem histological diagnosis of disseminated candidiasis is difficult, in that surgical biopsies of infected sites are often impossible to perform and blind needle biopsies are unrewarding (2), and (ii) 79% of patients with candidemia caused by *C. albicans*, *C. tropicalis*, *C. pseudotropicalis*, or *C. krusei* have proven disseminated fungal disease (12). In studies in which conventional blood culture systems were used, only 35% of the patients with disseminated candidiasis were found to have positive blood cultures for *Candida* spp. (11); however, the agar slide blood culture bottles used in our study (Roche Septi-Chek system) have been shown to be significantly more sensitive than conventional blood culture bottles in detecting *C. albicans* bacteremia (19, 20).

Although it could not be strictly proven, it is unlikely that our control patients had disseminated candidiasis. No blood for culture was drawn from some control patients during the surveillance period, but they remained afebrile. No blood culture from the other control patients was positive for *Candida* spp. These blood samples could not have been sterilized by systemic antifungal therapy, since controls were chosen among patients who did not receive such a treatment. In the multivariate analysis, we found that treatment with antibiotics was not an independent risk factor that was significantly associated with candidemia. The same result has been observed by others in non-cancer patients with candidemia (J. E. Bross, S. Hurewitz, and G. H. Talbot, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 738, 1986).

Factors associated with invasive fungal disease have been analyzed in a population that was restricted to patients undergoing induction therapy for acute myelogenous leukemia (17). Only 55% of the fungi isolated were *Candida* spp. Prolonged chemotherapy and fungal colonization were the major risk factors associated with the ultimate development of invasive fungal disease, as was the case in our study. Negative peripheral cultures have also been found to be associated with the absence of systemic disease due to *C. tropicalis* and *C. albicans* (16). Conversely, positive peripheral cultures have been associated with systemic disease caused by *C. tropicalis* but not by *C. albicans* (16). It is usually concluded from these results that routine surveillance cultures for *Candida* spp. are not recommended. In groups of patients in which the prevalence of candidemia is high, however, results of such cultures might be helpful in deciding which therapy is to be used. For instance, it is usually recommended that neutropenic patients with acute leukemia and fever refractory to antibacterial agents should be treated with systemic amphotericin B (4, 14). The prevalence of disseminated *Candida* infection is estimated to be

TABLE 2. Matched relative risks of candidemia in case patients and controls for each individual characteristic

Characteristic	% Cases (n = 30)	% Controls (n = 58)	Matched relative risk[a]	P value	Likelihood ratio[b]
Neutropenia					
1–7 days	21	18	9.2	0.02[c]	1.2
>7 days	52	26	17.4		2.1
Radiotherapy	28	30	0.8	>0.10	
Abdominal surgery	20	4	9.7	0.01	
Central catheter					
1–14 days	30	17	3.3	0.02[c]	1.0
>14 days	40	24	4.2		1.9
Parenteral nutrition	30	16	2.9	0.09	
Drug exposure					
Corticosteroids	23	29	0.6	>0.10	
Chemotherapy >5 days	41	20	6.1	0.01	
Cephalosporins	67	45	2.2	0.07	
Carboxyureidopenicillins	30	5	7.9	0.01	
Aminoglycosides	87	47	10.0	0.0001	
Erythromycin	3	14	0.2	0.08	
Vancomycin	40	16	3.5	0.02	
Antifungal prophylaxis[d]	23	16	1.7	>0.10	
Positive culture for *Candida* spp. from[e]:					
Oropharynx	27	9	6.3	0.01	
Feces	33	12	4.8	0.01	
Skin	7	2	ND[f]	ND	
Urine	10	3	2.6	>0.10	
Central intravenous catheter	10	0	ND	ND	
At least one site	53	17	10.2	0.001	3.5

[a] Estimated by a logistic regression model (3).
[b] Calculated only for characteristics significantly associated with candidemia in Table 3 (16).
[c] Chi-square test for the trend (3).
[d] Included only oral nonabsorbable antifungal agents.
[e] During the surveillance period.
[f] ND, Not done (values were too small).

60% in these patients (4). Calculations from the data given in Table 2 indicate that, given that prevalence, the positive predictive value of a surveillance culture which grows *Candida* spp. organisms reaches 83%.

We observed a 50% mortality rate in our patients with candidemia. This is similar to that given in other reports: 79% (12), 72% (9), and 52% (6). This mortality rate was significantly higher than that observed in controls without candidemia. Therefore, our results will help to quantify the risk of candidemia in cancer patients.

TABLE 3. Matched relative risks in 30 case patients with candidemia and 58 controls in a multivariate analysis

Characteristic	Matched relative risk[a]	95% confidence interval[a]	P value
Central catheter	6	1–39	0.03
Colonization by *Candida* spp.[b]	12	1–119	0.02
Neutropenia	45	0–>1,000	0.05
Abdominal surgery	20	0–>1,000	0.07
Antibiotic treatment	2	0–27	0.26

[a] Estimated by a logistic regression model and adjusted on all the other characteristics of the table (3).
[b] From at least one site.

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