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POSTMORTEM CANDIDEMIA: MARKER OF DISSEMINATED DISEASE

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Abstract

Aim—The significance of finding *Candida* species in heart blood cultures obtained at postmortem examination has never been studied. Therefore, we describe the findings of autopsy patients with postmortem candidemia and compare them to autopsy patients with antemortem candidemia.

Method—Twenty-three patients with *Candida* species isolated from heart blood at autopsy were identified over a ten-year period. These patients were compared to 10 autopsy patients found during the same time period with antemortem blood cultures isolating *Candida* species, but not positive postmortem heart blood cultures. Ante- and postmortem records were reviewed.

Results—All 23 patients with *Candida* species isolated from postmortem blood culture had one or more antemortem risk factors for disseminated candidiasis such as positive antemortem blood cultures, isolation of *Candida* from sterile internal sites, neutropenia, recent abdominal surgery, broadspectrum antibiotic administration or the use of central venous catheters or other invasive devices. Eight patients had histologic proof of invasive candidiasis in addition to the positive heart blood cultures. This group did not differ with respect to risk factors from 10 autopsy patients with disseminated candidiasis and antemortem blood cultures with *Candida* species. However, all the patients with antemortem candidemia had histologic evidence of disseminated candidiasis at autopsy.

Conclusion—Candidemia, when documented by heart blood culture performed at autopsy or by antemortem blood culture, is an insensitive, but highly specific indicator of disseminated candidiasis.

Keywords

Candida; disseminated candidiasis; candidemia; postmortem; autopsy

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INTRODUCTION

Candida species are important opportunistic pathogens that can invade the vascular space giving rise to metastatic lesions in many organs (disseminated candidiasis).(1) A finding of *Candida* species in blood culture should prompt immediate empiric treatment and removal of central venous catheters as *Candida* species are no longer considered “contaminants” in blood culture.(2) However, postmortem studies of patients with hematological malignancies established that a significant number of patients with histological evidence of disseminated candidiasis did not have antemortem blood cultures with *Candida* species.(3, 4) Although the term disseminated candidiasis implies bloodborne spread of the microorganism to sterile sites, it is well accepted that in the case of *Candida*, antemortem blood culture is an insensitive indicator (~50%).(5) The, detection of these fungi in the blood is difficult and their presence in postmortem blood cultures has never been studied. We therefore studied 23 patients with postmortem candidemia to determine the significance of this finding.

METHODS

Postmortem examination

Patients with postmortem blood cultures with *Candida* were identified in a previous study of candidemia (6) approved by the University of Arizona Institutional Review Board. However, the patients with postmortem candidemia were not reported in that communication as the significance of the finding was unknown at the time. This led to the present investigation.

Postmortem evaluations were performed in the autopsy suite at the University Medical Center (UMC) in Tucson Arizona. Solid organ and bone marrow transplants are performed regularly at this center. Immunocompromised patients now constitute a large proportion of autopsy patients. Following review of the clinical record the body was opened utilizing a standard “Y” incision. The chest plate was removed exposing the organs of the thorax and lower neck. A dissection plane was exposed between the structures of the posterior mediastinum and the thoracic spine allowing an antero-infero removal of the thoracic block and visualization of the superior and inferior vena cava, as is standard in the En Bloc autopsy technique.(7)

Heart blood culture is standard procedure for all full autopsies performed at UMC. Using sterile technique a 20 cc. syringe with a 10-gauge needle was introduced into the lumen of the inferior vena cava and blood aspirated and injected into a BacT/Alert culture bottle (bioMerieux, Hazelwood, MO). Tissue sections of the lungs, liver, spleen and kidneys were obtained and processed in 4% neutral buffered formalin.

Histology

Hematoxylin-eosin (H&E) stained sections were examined for preliminary identification of fungal microorganisms. Gomori methenamine silver (GMS) staining was performed on the spleen, liver and kidney, to detect fungi. Two reviewers examined each H&E and GMS stained slide independently. Slides found positive for *Candida* species (presence of yeasts and/or pseudohyphae or true hyphae) were then examined by a third reviewer who confirmed or rejected the finding.

Microbiology

The BacT/Alert blood culture system was used. In early years of the study some blood culture isolates were identified as “yeasts not *Candida albicans* or *Cryptococcus*” because determining *Candida* species at that time was labor intensive and its significance in

postmortem blood cultures, unappreciated. This designation was made after identifying yeasts on the gram stain of the blood culture, growing the yeast overnight on Sabouraud's agar and performing a germ tube test as well as a urea tube test to rule out *Cryptococcus*. The finding of "yeasts not *Candida albicans* or *Cryptococcus*" was therefore, virtually synonymous with "*Candida* species other than *C. albicans*." This is confirmed by blood culture data. For example, from June 1997 through June 2006 there were 1164 blood cultures that isolated non-filamentous fungi. This represented 231 patients with *Candida* identified to species level. Ninety-four patients had *C. albicans* on blood culture and 137 that had non-*albicans* species. There were 4 patients with yeasts that could not be separated from *Candida* species using the tests outlined above, one with *Hansenula polymorpha* and one with *Saccharomyces cerevisisiae*. (Two patients were infected with *Rhodotorula* species, but these were identified by their production of pigment on Sabouraud's agar). Therefore, the likelihood that one of the "yeasts not *Candida albicans* or *Cryptococcus*" would be a *Candida* species (and not a confounder) is >60:1.

Culture of tissue such as lung for evidence of disseminated candidiasis was not utilized because of the lack of specificity of these cultures in the postmortem state. (8, 9)

RESULTS

General comments

From January 1997 to September 2008 there were 1655 partial or full autopsies performed and 39 autopsies (2%) noted candidemia, candidiasis or disseminated candidiasis in the formal autopsy report. Of these 39 individuals, 20 had histological evidence of disseminated candidiasis and of these, 10 had antemortem blood cultures that isolated *Candida* species. These 10 patients did not have postmortem heart blood cultures that isolated *Candida* species. However, 23 autopsy patients during this time period cultured *Candida* species from postmortem heart blood culture. Two of these patients had antemortem blood cultures that were positive for *Candida* species.

Patients ranged in age from stillborn to 90 years. Autopsy was performed from as short as 2 hours and twenty minutes to as long as 4.5 days following death (Table 1).

Patients with *Candida* species in heart blood culture at postmortem

Patients had many comorbidities, some well known to predispose to disseminated candidiasis such as acute leukemia in three patients all of who had neutropenia induced by chemotherapy before death (patient #1,2,19) (Table 1). Additionally, patients #1 and 2 had positive antemortem blood cultures with *C. krusei* and *C. albicans*, respectively.

Sixteen of the patients received from one to four antibiotics before death. Six of the patients did not have medication records to review (they were from other hospitals) and one patient, a stillborn (patient # 8) did not receive antibiotics. Twenty-one patients had one or more central catheters or invasive tubes, which could have provided portals of entry of the fungus to the blood stream. Twelve Patients #3–7, 10–15 and 20 had likely gastrointestinal portals of entry of *Candida* (Table1). Three patients were pediatric cases (#8,9 and 10). Eight of 23 patients had histological evidence of invasive disseminated disease with *Candida* species.

Autopsy patients that had antemortem blood cultures, but not heart blood cultures that isolated *Candida* species

Only 10 of the 20 patients with evidence of disseminated candidiasis at autopsy had antemortem blood cultures with *Candida* species (similar to rates found in the past (3)) (Table 2). These patients as a group did not appear to have risk factors different than those

with heart blood cultures that were positive at postmortem. However, all of the 10 patients had histological evidence of disseminated candidiasis.

DISCUSSION

Postmortem blood cultures: colonization, contamination or pathogenicity?

Morris et al. in the most comprehensive study of the role of postmortem blood culture bacteriology (10) contends that there were four ways by which a positive blood culture could arise postmortem. First, a truly positive result, i.e., the microorganism invading in life and reaching target organs or fluids before death; second, agonal spread, microorganisms invading as the patient is in the process of dying where natural barriers are weakened by ischemia; third, postmortem translocation, e.g., from the gut to the blood in putrefying tissue. Fourth, is contamination of the specimen similar to that encountered with blood cultures antemortem. The authors concluded in a review of over 5000 autopsies that the second and third possibilities rarely occur (10) and that contamination (fourth possibility) may occur, but rates would likely be similar to those of antemortem blood cultures of 4–6%. (11) In conclusion, they regarded postmortem blood culture isolates as highly specific for disease.

Dolan et al. also concluded that agonal spread of microorganisms did not occur (12) and others point out that the positivity rate of postmortem blood cultures does not increase as a function of time after death and that postmortem blood cultures provide reliable cultures corresponding to antemortem disease.(13) Hove and Pencil concluded, like Morris et al., after comparing antemortem and postmortem blood cultures that the two were equivalent. (14) One study found an incidence of about 4% of postmortem heart blood cultures with *C. albicans* from 396 autopsies. (15)

Postmortem candidemia: A specific finding

Disseminated candidiasis remains a clinical diagnosis even in an era of powerful diagnostic tools.(5) Unfortunately blood culture is insensitive (~50%) and therefore other ancillary data must be brought to bear to establish the diagnosis antemortem.(5) The term disseminated candidiasis implies microorganism spread through the vascular system to sterile organs such as the kidneys, liver, spleen, retina and occasionally the heart valves and brain. However, unlike bacteremias, candidemia is difficult to detect and is not a constant feature of the illness although PCR may increase the sensitivity of documenting disease.(16) Maksymiuk et al. found that only 35% of 188 cancer patients with disseminated candidiasis at autopsy had antemortem blood cultures positive for *Candida* species.[3] The data from the two groups of autopsy patients reported here are very similar in respect to risk factors for disseminated candidiasis yet, one group (Table 1), had heart blood cultures positive at postmortem whereas the second group (Table 2) had antemortem blood cultures only that isolated *Candida* species. The only difference between the two groups was that those with positive antemortem blood cultures had histology that confirmed the disseminated nature of the disease. However, this is to be expected as the candidemia was present in detectable numbers for a longer time before death in those patients than in the patients with only postmortem blood cultures with *Candida*. Even so, there were two patients with postmortem candidemia that also had antemortem blood cultures that were positive for *Candida* species.

Results of pediatric autopsies also underscore the insensitivity of blood culture in disseminated candidiasis. Hughes, in a study of 109 fatal cases of candidiasis in children, found that 89% of the cases had more than one organ involved, yet antemortem blood cultures were of `limited diagnostic aid".(17) Among 28 recent pediatric autopsies there were seven cases in which the autopsy findings would have altered the premortem care, the

majority being due to *Aspergillus* and *Candida* that went undocumented by blood culture. (18) Disseminated candidiasis is common in neonates. In a report of 2027 neonatal autopsy cases, 6.6% of the cases had candidiasis.(19) This included 8 fetuses ranging in age from 22 to 40 weeks of which 5 cases had evidence of *Candida* in the brain, heart, lungs, liver, kidneys or intestines and the fungus was listed among the causes of death in all 8 cases. A study in Spain found that among 20,565 admissions to 27 different neonatal units, 118 or 0.57% of the total admissions had disseminated candidiasis, usually denoted as “sepsis”.(20)

The fact that many of the heart blood cultures were polymicrobial (9 of 23 or 39%) cannot be used as evidence of contamination. Polymicrobial blood cultures in which one microorganism is a *Candida* species is in fact, quite common (~20%) in the antemortem state [6] and therefore it would not be surprising to see a high incidence of polymicrobial blood cultures in postmortem blood cultures as well. The historical confusion about the meaning of finding yeasts in otherwise sterile tissue and blood culture carries over into the autopsy suite. As a recent example, an autopsy study found yeasts compatible with *C. glabrata* in the lungs and kidneys which was termed “transitory fungaemia”.(21) This type of categorization has no clinical correlate and most authorities would contend that the evidence represents disseminated candidiasis. Pathologists at our institution mentioned postmortem candidemia as possibly contributing to the death of only 7 of the 23 patients found to have *Candida* species in their postmortem heart blood cultures.

In conclusion this report demonstrates that postmortem candidemia is likely a reliable indicator of undetected premortem candidemia and may have contributed to the death of these patients. The 23 patients in our study had documented postmortem candidemia and multiple well known risk factors for candidemia including neutropenia, broadspectrum antibiotic use, the presence of central venous catheters or other invasive devices and recent abdominal surgery. Eight patients had postmortem histological evidence of dissemination. This group did not differ from 10 patients with antemortem candidemia.

The “take home message” is that postmortem candidemia is a reliable indicator of premortem candidemia and should be a part of the postmortem report.

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Table 1
Characteristics of patients with postmortem candidemia

The results of microbiology and postmortem histology are included. Patients 14 and 15 and 19–23 had "yeasts not *Candida albicans* or *Cryptococcus*," i.e., synonymous with *Candida* species not *albicans*.

Case	Age/Sex	Heart blood culture	Risk for disseminated candidiasis	Results of histological examination
1	3/F	*C. krusei; Enterococcus*	AL; neutropenia	pseudo-membraneous colitis with invading yeasts
2	75/M	*C. albicans; Enterococcus; Xanthomonas*	AL; neutropenia	
3	70/F	*C. albicans; S. aureus*	perforated viscus; peritonitis	GMS: yeasts and filamentous forms perforating through the serosa
4	72/F	*C. albicans*	peritonitis	yeasts in gastric wall and peritoneum
5	68/M	*C. albicans*	ruptured abdominal aorta; sepsis; abdominal surgery	GMS: yeasts and pseudohyphae in spleen
6	79/M	*C. albicans*	surgical repair of ruptured thoracic and abdominal aorta	
7	90/M	*C. albicans*	thoracic and abdominal aortic repair; necrotic colon; colectomy; DIC	
8	Still born/F	*C. glabrata*	prematurity	
9	4 days/F	*C. albicans*	high-risk twin; DIC; neonatal ICU for 4 days	
10	5 mon ths/F	*C. albicans*; CNS	ischemic bowel; 75% removed	
11	61/F	*C. pseudo-tropicalis* and *C. krusei*	widespread carcinomatosis of peritoneum; ascites; sepsis	
12	54/F	*C. albicans*	diabetes; G.I. hemorrhage; pneumonia	
13	65/F	*C. albicans*	severe *C. difficile* colitis; pneumonia	
14	86/F	yeast; CNS	dead bowel; colectomy; abdominal surgery	GMS: yeasts and pseudohyphae in spleen
15	75/F	yeast	G.I. ulcerations; pneumonia	GMS: yeasts and pseudohyphae in spleen
16	50/F	*C. glabrata*	ESRD; gangrene of leg; pneumonia	lung abscess with yeasts in lung and vascular tissue
17	52/M	*C. glabrata*	OHT; recurrent pneumonias	
18	88/F	*C. glabrata*	pneumonia	
19	73/M	yeast; CNS	AL; neutropenia; pneumonia	
20	58/F	yeast; *Enterococcus*	peritonitis	yeasts in muscle and bowel
21	72/F	yeast; CNS	metastatic pancreatic cancer	
22	90/M	yeast	aspiration pneumonia; *C. difficile* colitis; ESRD	
23	23/F	*yeast*	BMT; pneumonia	

Abbreviations: G.I: gastrointestinal; BMT: bone marrow transplant; OHT: orthotopic heart transplant; CNS: coagulase-negative *Staphylococcus;* AL: acute leukemia; DIC: disseminated intravascular coagulation; ICU: intensive care unit; ESRD: end stage renal disease; GMS: Gomori methenamine silver stain.

Table 2
Characteristics of autopsy patients with antemortem candidemia

The postmortem histology results are included. Postmortem heart blood cultures however, did not isolate *Candida* species from these patients.

Case	Age/Sex	Antemortem blood culture	Risk for disseminated candidiasis	Results of histological examination
1	Premature, 25 weeks /F	*C. albicans, E. coli, P. aeruginosa*	Prematurity	Fungi invading myocardium, kidney, intestines
2	Premature, 29 weeks/F	*C. albicans*, CNS	Prematurity, hyaline membrane disease	Twin of Case 1; fungal sepsis
3	10 years/M	*C. glabrata*	ALL, chemotherapy	Fungi involved in erosive esophagitis
4	56 years/M	*C. albicans*	Severe erosive esophagitis and gastritis	Fungi involved in erosive esophagitis and gastritis
5	3 years/M	*C. tropicalis*	ALL	Fungal sepsis
6	24 years/M	*C. albicans*	Severe, erosive colitis	Fungi involved in erosive colitis and pseudomembrane
7	20 years/M	*C. glabrata*	CML, chemotherapy, bone marrow transplant	Fungi involved in pyelonephritis
8	74 years/M	*C. albicans*	Small bowel resection	Fungi involved in pyelonephritis
9	3 years/M	*C. albicans, Enterococcus* species	HSCT	Fungi involved in erosive colitis
10	29 years/M	*C. albicans*, CNS	Liver transplant	Fungi invading myocardium, kidneys, adrenals, spleen, prostate

Abbreviations: ALL: acute lymphocytic leukemia; CML: chronic myelogenous leukemia; HSCT: hematopoetic stem cell transplantation; CNS: coagulase-negative *Staphylococcus*.