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Candidemia Diagnosed from Peripheral Blood Smear: Case Report and Review of Literature 1954–2013

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Abstract
Background Yeast with pseudohyphae or those that have been phagocytized by white blood cells are coincidentally found in peripheral blood smears. The clinical diagnostic value and outcome of candidaemia diagnosed from peripheral blood smears (CPBSs) are unclear.
Case Presentation A 45-year-old man with diabetes and panhypopituitarism for 20 years received 10 mg of hydrocortisone and 100 μg of levothyroxine sodium hydrate daily. He has been admitted seven times because of adrenal failure triggered by infections and was admitted for pneumonia. On day 56, some budding yeast was found microscopically in a peripheral blood smear with May–Giemsa staining. Some of them were phagocytized by white blood cells. The two blood cultures yielded *Candida parapsilosis*. Despite antifungal treatment and removal of an intravenous catheter, on day 98 (42 days after the candidaemia diagnosis), the patient died.
Conclusion We analysed 36 cases including the present case. Almost all CPBS patients (96.5 %, $n = 29$) were using an intravenous catheter. The most frequently isolated species was *C. parapsilosis* (35.1 %), followed by *C. albicans* (29.7 %). The overall mortality rate was 53.6 % ($n = 28$). The time from the discovery of yeast-like pathogens using peripheral blood smears to death ranged from a few hours to 93 days (median 19 days). The present results suggest that intravenous catheter use and the underlying conditions of patients are responsible for CPBSs. The detection of yeast in peripheral blood smears suggests advanced infections with uncontrollable complications, which means a poor prognosis. Rapid detection methods besides blood culture are needed.

Keywords *Candida parapsilosis* · Candidaemia · Peripheral blood smear

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Introduction

Candida spp. are the third or fourth most common isolate in patients with bloodstream infections. The prevalence of non-albicans *Candida* species has increased in recent years [1]. Although the diagnostic

gold standard for candidaemia is blood culture, yeast with buds, pseudohyphae, or that have been phagocytized by white blood cells in peripheral blood smears can be visible microscopically [2]. *Candida* is the most common genus among yeast isolated from blood culture. However, the clinical diagnostic value and outcome of candidaemia diagnosed from peripheral blood smears (CPBSs) are unclear.

Case

The patient was a 45-year-old man with diabetes, blindness, hemiplegia, and panhypopituitarism due to complications from a craniopharyngioma brain surgery at the age of 17 years. He received a daily dose of 10 mg of hydrocortisone and 100 μg of levothyroxine sodium hydrate. He had been admitted to our hospital seven times owing to severe adrenal failure triggered by severe infectious diseases such as urinary tract infections with septicaemia. He was admitted because of community-acquired pneumonia with hypoxia. Intravenous cefepime followed by cefotiam was administered, and his pneumonia was resolved on day 28. On day 32, he was administered total parenteral nutrition via an intravenous catheter because of dysphagia. On day 56, he had a high fever, and budding yeast was found microscopically in a peripheral blood smear using May–Giemsa staining. Some of the yeast had been phagocytized by white blood cells (Fig. 1). Two sets of blood cultures were soon performed. The intravenous catheter indwelling from day 32 to 56 was removed immediately, and intravenous fluconazole was administered in the same day, since candidaemia was highly suspected. The two sets of blood cultures grew *Candida parapsilosis*. Species identification of this isolate was confirmed by using internal transcribed spacer 1 and 2 and 26S rRNA D1/D2 region gene sequencing [3]. The minimum inhibitory concentrations (MIC) of the antifungals against this strain were as follows: amphotericin B (MIC 1 μg/mL), fluconazole (MIC 1 μg/mL), and micafungin (MIC 2 μg/mL) according to the Clinical and Laboratory Standards Institute M27-A3 method using an Eiken DP kit (Eiken, Japan). Laboratory data are given in Table 1. The (1 → 3) β-D-glucan level (Fungitec G-test MK, Nissui, Tokyo, Japan, cutoff level 20 pg/mL) was 3612 pg/mL on day 56, increased to 6606.8 pg/mL on day 84, and again increased to 20,053.3 pg/mL on day 98. Severe complications due to candidaemia (i.e. infective endocarditis, abscess, vertebral osteomyelitis) were not detected in the clinical examination. However, infective endocarditis due to *C. parapsilosis* was possible according to modified Duke's criteria. Despite the intravenous fluconazole (400 mg/day, from day 56 to day 79), following liposomal amphotericin B (3 mg/kg/day, day 80 to day 98), the consecutive blood cultures still yielded *C. parapsilosis*, and the yeast was detected persistently in peripheral blood smears. The patient's circulation dynamics and respiratory status had been unstable. He died on day 96 (42 days after the candidaemia diagnosis). An autopsy was not performed.

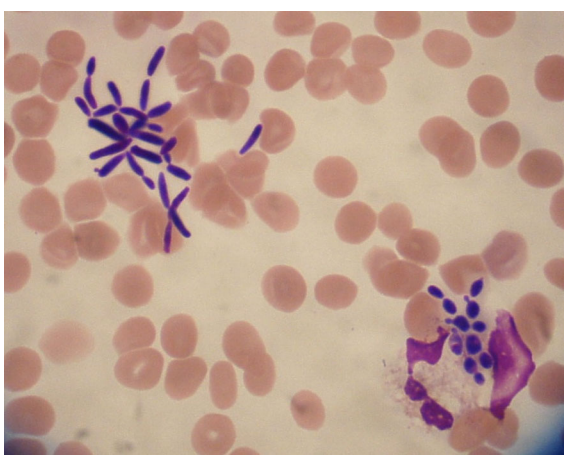

Fig. 1 Yeast-like organism (*Candida parapsilosis*) was phagocytized by white blood cells in a peripheral blood smear (May–Giemsa stain)

Discussion/Review of Literature

The yeast most often associated with *Candida* includes *Cryptococcus*, *Rhodotorula*, and *Trichosporon* in clinical settings. *Candida* is the most common cause of fungaemia and the third or fourth most common cause of central line associated blood stream infections. In a neonatal study, Benjamin et al. [4] found that catheter removal improved mortality (10 vs. 31 % in patients without catheter removal) in *C. parapsilosis* candidaemia. In contrast, a similar mortality was found with or without catheter removal in *C. albicans* candidaemia (35 vs. 48 %, respectively). Thus, *C. parapsilosis* candidaemia is strongly associated with catheter-related blood stream infection [5] similar to

Table 1 Laboratory data on admission and the first day of positive yeast for blood culture

	On admission	Blood culture; *C. parapsilosis* (day 56 after admission)
WBC (/μL)	7720	15,820
Neutrophil (%)	70.2	76.8
RBC (/μL)	570×10^4	433×10^4
Hb (g/dL)	18.2	12.4
Hct	54.1	39.2
PLT (/μL)	10.9×10^4	1.8×10^4
LDH (IU/L)	214	651
Serum creatinine (mg/dL)	0.72	0.55
CRP (mg/dL)	0.29	18.54
(1 → 3) β-D-glucan (pg/ml)	n.d.	3617

n.d. not done

this case. The *Candida* concentration in the blood of patients with candidaemia is usually low [$\sim$10 colony-forming units (CFU)/mL^2], and the detection of candidaemia by using peripheral blood smear examination requires a yeast concentration of at least 1×10^5 CFU/mL^2. Therefore, the positive microscopic findings of yeast-like fungi (*Candida* species) in peripheral blood smears suggest extremely progressive fungaemia. Interestingly, previous reports have suggested that high *Candida* concentrations in blood caused a leucocyte miscount with an automated haematology analyser [6, 7]. All abnormal values of leucocyte counts obtained using an automated analyser are routinely re-examined under the microscope by a laboratory technician in the Tokyo Women's Medical University (TWMU) Hospital.

We reviewed the available literature through PubMed and ICHUSHI-Web of the Japanese Medical Abstract Society (http://www.jamas.or.jp/) during 1954–2014 using the keywords 'candida', 'Monilia', which had been named as a *Candida* species, 'peripheral blood', and 'smear', which revealed 36 cases of CPBSs, including the present case. Of the 28 publications containing these cases, 24 were in English [6, 8–31], and four were in Japanese [32–35]. The patient characteristics are given in Table 2.

The mean age of the patients in these cases was 63 years (range 27-week prematurity to 80 years). Sixteen CPBS cases (67.7 %, $n = 24$) occurred in men. Underlying conditions included neoplasm (58.8 %) such as leukaemia (23.5 %) [12, 15, 16, 19, 34], and low body weight in infants (13.8 %) [6, 13, 24, 25]. Almost all CPBS patients (96.5 %, $n = 29$) were using an intravenous catheter. The most frequently isolated species was *C. parapsilosis* (35.1 %) [6, 12, 16–19, 22, 25, 28, 34, 35] followed by *C. albicans* (29.7 %) [6–11, 21, 24, 29, 33]. Regarding treatment, 72 % ($n = 22$) of patients were empirically treated with polyene (amphotericin B or liposomal amphotericin B). The overall mortality as described in the literature was 53.6 % ($n = 28$) in patients with CPBSs. The time from the discovery of yeast-like pathogens using peripheral blood smears to death ranged from a few hours to 93 days (median 19 days). Although few descriptions of complications caused by candidaemia were found among them, two deceased patients with CPBSs had infective endocarditis [8] or peritonitis [9]. For candida endocarditis, a recent study of *C. parapsilosis* candidaemia found an associated endocarditis rate of 5.9 %. The sensitivity of echocardiogram is still limited for making diagnosis of endocarditis. In addition, performing image inspection (i.e. CT, MRI) may be impossible due to extremely severe clinical condition in patients with CPBSs. Thus, uncontrollable complications, such as endocarditis, in patients with CPBSs may be underestimated. For febrile leukaemic patients undergoing remission induction or consolidation chemotherapy, CPBSs have shown a longer mean length of candidaemia (16.2 vs. 5.4 days, $p = 0.06$), higher rate of positive blood cultures during candidaemia (81 vs. 47 %, $p < 0.00003$), and earlier recovery of candida species from blood cultures (3.9 vs. 6.5 days, $p = 0.03$) [19]. These results suggest that CPBS occurs due to the burden of *Candida* species provided by the intravenous catheter into blood and that diagnosis is often delayed.

To our knowledge, this is the largest multilanguage literature review for CPBSs. CPBS is a rare but fatal disease affecting all age groups. The present results suggest that intravenous catheter use and the underlying condition of patients are responsible for CPBSs. The detection of *Candida* species in peripheral blood smears suggests advanced disseminated infections with uncontrollable complications, whether they were detectable or not in clinical examinations, caused by the burden of *Candida* species in the blood, which is indicative of poor prognosis. Although blood

Table 2 Candidaemia diagnosed from peripheral blood smears (CPBSs): review of the literature from 1954 to 2013

Case	Age	Gender	Underlying disorder	IVC	Chemotherapy/ antibiotics	Candida species	Complication due to candidaemia	Treatment	Outcome	Survival days	Year	Reference no.
1	42	M	Panhypopituitarism	Yes	Corticosteroid	*C. parapsilosis*	n.f.	FLCZ	Died	46	2006	Recent case
2	27 weeks	n.d.	LBWI	Yes	n.d.	*C. albicans*	n.d.	n.d.	n.d.	n.d.	1990	[6]
3	28 weeks	n.d.	LBWI	Yes	n.d.	*C. parapsilosis*	n.d.	n.d.	n.d.	n.d.	1990	[6]
4	52	n.d.	Short bowel syndrome	Yes	n.d.	*C. tropicalis*	n.d.	n.d.	n.d.	n.d.	1990	[6]
5	22	n.d.	Rectal adenocarcinoma	Yes	n.d.	*C. albicans*	n.d.	n.d.	n.d.	n.d.	1990	[6]
6	33	M	Aplastic anaemia	Yes	Aureomycin	*C. albicans*	IE (biopsy)	n.d.	Died	93	1954	[8]
7	36	M	Intestinal obstruction	Yes	KM + CPH + CP	*C. albicans*	Abscess	AMB + 5FC	Recovered	n.d.	1971	[9]
8	18	M	Malabsorption	Yes	n.d.	*C. albicans*	Peritonitis	AMB + 5FC	Died	19	1971	[9]
9	63	M	Intestinal obstruction	Yes	GM + CPH + CP	*C. albicans*	n.d.	AMB	Died	46	1973	[10]
10	76	M	Sigmoid colon cancer	Yes	n.d.	*C. albicans*	n.d.	AMB + 5FC	Recovered	n.d.	1977	[11]
11	52	M	CLL	Yes	PC + GM	*C. parapsilosis*	n.d.	AMB	Died	22	1986	[12]
12	25 weeks	F	LBWI	Yes	PC + GM	*C. pesudotropicalis*	n.d.	5FC	Recovered	n.d.	1987	[13]
13	72	F	n.d.	Yes	n.d.	*C. glabrata*	n.d.	AMB	Recovered	n.d.	1988	[14]
14	28	M	CML HSCT	Yes	BU + CY	*C. tropicalis*	n.d.	LAMB	Recovered	n.d.	1990	[15]
15	50	M	AML HSCT	Yes	Carmustine,VP16,MEL	*C. parapsilosis*	n.d.	AMB	Recovered	n.d.	1988	[16]
16	31	M	SAA HSCT	Yes	IPM + AMK	*C. parapsilosis*	n.d.	FLCZ	Recovered	n.d.	1994	[17]
17	74	F	PCa	Yes	GM + PC + Metro	*C. parapsilosis*	n.d.	n.d.	n.d.	n.d.	1992	[18]
18	n.d.	n.d.	Leukaemia	n.d.	n.d.	*C. parapsilosis*	n.d.	n.d.	Recovered	n.d.	1994	[19]
19	n.d.	n.d.	Leukaemia	n.d.	n.d.	*C. parapsilosis*	n.d.	n.d.	Recovered	n.d.	1994	[19]
20	n.d.	n.d.	Leukaemia	n.d.	n.d.	*C. guillermondii*	n.d.	n.d.	Recovered	n.d.	1994	[19]
21	n.d.	n.d.	Epidermatological Cancer	n.d.	n.d.	*C. glabrata*	n.d.	AMB	Died	n.d.	1995	[20]
22	80	M	Volvulus surgery	Yes	AMPC/CVA Metro	*C. albicans*	n.d.	FLCZ	Died	2	1998	[21]
23	7 m	F	Hepatoblastoma	Yes	n.d.	*C. parapsilosis*	n.d.	LAMB, FLCZ	Recovered	n.d.	2003	[22]
24	16	M	Ewing's sarcoma	n.d.	ADR + CY, Auto	*C. tropicalis*, *C. krusei*	n.d.	LAMB	Died	1	2004	[23]
25	0	M	LBWI	Yes	n.d.	*C. albicans*	n.d.	AMB	Died	12	2005	[24]
26	0	n.d.	LBWI	Yes	n.d.	*C. parapsilosis*	n.d.	AMB	Died	42	2008	[25]
27	30	F	Rectal cancer	Yes	n.d.	*C. tropicalis*	n.d.	n.d.	Died	'Few hours'	2009	[26]
28	65	M	GCa	Yes	n.d.	*C. glabrata*	n.d.	n.d.	Died	'Rapidly'	2009	[27]
29	33	M	IVDU (heroin for 5 years)	None	None	*C. parapsilosis*	n.d.	LAMB	Recovered	n.d.	2011	[28]
30	77	F	Pemphigus	Yes	n.d.	*C. albicans*	n.d.	FLCZ	Died	n.d.	2012	[29]
31	17	F	HSD	Yes	n.d.	*C. glabrata*	n.d.	ADFG	Recovered	n.d.	2012	[30]

Table 2 continued

Case	Age	Gender	Underlying disorder	IVC	Chemotherapy/antibiotics	Candida species	Complication due to candidaemia	Treatment	Outcome	Survival days	Year	Reference no.
32	n.d.	n.d.	n.d.	Yes	n.d.	*C. krusei*	n.d.	AMB	Recovered	n.d.	1988	[31]
33	2	M	Langerhans histiocytosis	Yes	n.d.	*C. guillermondii*	n.d.	AMB	Died	13	1997	[32]
34	59	F	Anorexia nervosa	Yes	None	*C. albicans*, *C. glabrata*	n.d.	n.d.	Died	11	2005	[33]
35	17	F	AML	Yes	n.d.	*C. parapsilosis*	n.d.	MCFG, VRCZ	Died	40	2010	[34]
36	26	M	Endstage germ cell tumour	Yes	None	*C. parapsilosis*	STI	n.d.	n.d.	n.d.	2011	[35]

CLL chronic lymphoid leukaemia, *LBWI* low birth weight infant, *AML* acute leukaemia, *SAA* systemic AA amyloidosis, *HSCT* haematopoetic stem cell transplantation, *Pca* pancreas cancer, *Gca* gastric cancer, *IVDU* intravenous drug user, *HSD* Hirschsprung's diseases, *LH* Langerhans histiocytosis, *AN* anorexia nervosa, *KM* kanamycin, *CPH* cephalosporin, *CP* chloramphenicol, *GM* gentamycin, *PC* penicillin, *BU* busulfan, *CY* cyclophosphamide, *CM* carmustine, *VP16* etoposide, *MEL* melphalan, *IPM* imipenem, *AMK* amikacin, *AMPC/CVA* ampicillin/clavulate acid, *ADR* adriamycin, *Auto* autologous transplant, *AMB* amphotericin B, *5FC* flucytosine, *LAMB* liposomal AMB, *FLCZ* fluconazole, *ADFG* anidulafungin, *MCFG* micafungin, *VRCZ* voriconazole, *n.d.* not described, *n.f.* not found, *IE* infective endocarditis, *STI* soft tissue infection

culture remains the 'gold standard' diagnostic procedure in candidaemia, test sensitivity in patients with febrile neutropenia ranged from 25 to 71 % in autopsy studies [36]. However, new generation sequencing with polymerase chain reaction–electrospray ionization mass spectrometry techniques can detect 93.3 % of bacteraemia/candidaemia in culture-negative blood samples obtained from critically ill patients [37]. Further investigation, rapid detection methods, and fewer pseudo-positive factors besides blood culture are needed.

In conclusion, a favourable clinical outcome in patients with multiple risk factors for candidaemia requires an appropriate diagnosis with blood culture, appropriate clinical management including the removal of prosthetic materials such as intravenous catheters, the identification of any complications, and strong communication between the physician and clinical laboratory.

Limitations

This report contains two limitations. First, mortality is derived from small numbers of reported cases from English or Japanese literature. Second, the identification of yeast-like pathogens by using peripheral blood smears may be incidental, which is partly dependent on individual skill.

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