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Rhodotorula Fungemia of an Intensive Care Unit Patient and Review of Published Cases

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Abstract *Rhodotorula* species are commensal yeasts that have emerged as a cause of life-threatening fungemia in severely immunocompromised patients. A case of *Rhodotorula mucilaginosa* fungemia in a 48-year-old woman that had undergone consecutive abdominal surgeries due to ovarian cancer and bowel necrosis while she was receiving fluconazole prophylaxis is presented. Several risk factors were identified such as presence of central venous catheters, solid organ neoplasm, abdominal surgery and administration of antibiotics. Identification was performed using commercial systems. The yeast was resistant to fluconazole, posaconazole and voriconazole and to echinocandins, whereas MIC to amphotericin B was 1.5 mg/L. Furthermore, published cases of *Rhodotorula* spp fungemia during the last decade are reviewed. In conclusion, *Rhodotorula* spp must be considered a potential pathogen in patients with immunosupression and central venous catheters. Correct identification is mandatory for appropriate management, as *Rhodotorula* spp are resistant to antifungal agents, such as fluconazole and echinocandins.

Keywords *Rhodotorula* spp · *Rhodotorula* mucilaginosa · Fungemia · Risk factors · Antifungals

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Introduction

Rhodotorula species are commensal yeasts that belong to Urediniomycetes class of Basidiomycota phylum and are distributed in Microbotryum, Sporidiobolus and Erythrobasidium clades [1]. Members of the genus *Rhodotorula* show a marked ubiquity and have been isolated from human feces, urine, nails, skin, sputum, digestive tract and adenoids [2]. Although the first report on *Rhodotorula* fungemia dates back to 1960 [3], during the last two decades *Rhodotorula* spp have emerged as cause of catheter-related fungemia, sepsis, and invasive disease in severely immunocompromised patients [4]. In the ARTEMIS surveillance project, *Rhodotorula* spp were the fourth most common non-candidal of yeasts isolated from clinical specimens, whereas *R. mucilaginosa* (formerly *R. rubra*) was the commonest cause of *Rhodotorula* spp fungemia followed by *R. glutinis* and *R. minuta* [5]. In this study, a fatal case of *R. mucilaginosa* fungemia at a critically ill ICU patient and review of all published cases of *Rhodotorula* spp fungemia during the last decade is presented.

Case Report

A 48-year-old woman was admitted to emergency department complaining for abdominal pain and distension (ileus). Symptoms originated from colorectal invasion and obstruction due to ovarian cancer.

The patient was nursed in the General Surgery department. Extensive surgery was performed, and the affected part of the bowel was removed. Unfortunately, bowel necrosis complicated the post-surgery clinical course resulting in bowel perforation and fecal peritonitis. Additional bowel excision was performed, and the patient was transferred to intensive care unit with mechanical ventilization. After 2 weeks of stay in ICU, *Klebsiella pneumoniae* was isolated from blood. The isolate produced carbapenemases and among all other agents tested (Vitek2, Biomerieux, Marcy l'Etoile, France) was susceptible only to colistin (MIC < 0.5 mg/L) and tigecycline (MIC $= 2$ mg/L). In spite of antibiotic administration (colistin), *K. pneumoniae* continued to be isolated from consecutive blood cultures for the following 3 weeks. Additionally, the patient was receiving fluconazole as prophylaxis due to immunosupression. Finally, 2 days after the last *K. pneumoniae*-positive blood culture, a fungus was isolated. Creamy, coral red-colored colonies were visible after 2 days of incubation on blood agar and Sabouraud agar plates at 37 °C. Germ tubes test was negative, while urease test was positive. The strain was identified as *R. rubra* by API 20C AUX (Biomerieux, Marcy l'Etoile, France) and *R. mucilaginosa* in Vitek2 YST (code number 4116 141413121511; probability of species identification 90 %) (Biomerieux, Marcy l'Etoile, France). Susceptibility test was performed with *E* test strips, and MICs were the following: 1.5 mg/L for amphotericin B, 0.064 mg/L for flucytocine, over 256 mg/L for fluconazole, 0.032 mg/L for ketoconazole, 0.75 mg/L for itraconazole, 0.25 mg/L for posaconazole, 1.5 mg/L for voriconazole and over 32 mg/L for caspofungin, anidulafungin and micafungin, respectively (Figs. 1, 2). Unfortunately, the patient did not receive any antifungal agent besides fluconazole and she died 1 day after fungus retrieval from blood cultures.

Discussion

Although *Rhodotorula* is of low virulence organism as compared to *Candida* and *Trichosporon*, it must be considered a potential pathogen in patients with immunosupression and central venous catheters (CVCs) [6, 7]. Most cases of *Rhodotorula* infections (79 %) are presented as catheter-related fungemia [6, 8], endocarditis and meningitis [5]. From 1960, over 134 cases of *Rhodotorula* fungemia have been described. Such cases have been extensively presented on several studies until 2001 [9, 10]. In addition, reviews on selected groups of patients, such as those having central catheter (8), hematological malignancy patients [11] and patients undergoing hematopoietic stem cell transplantation [12] have been conducted. In Table 1, clinical presentation, underlying disease, risk factors, microbiological data, therapeutic approach

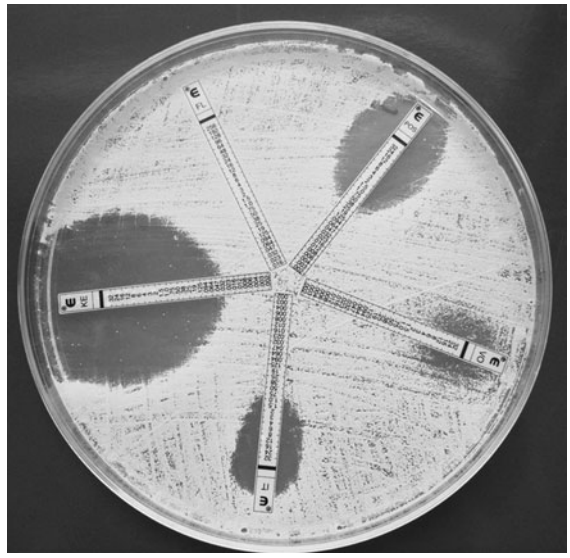

Fig. 1 Susceptibility testing to azoles

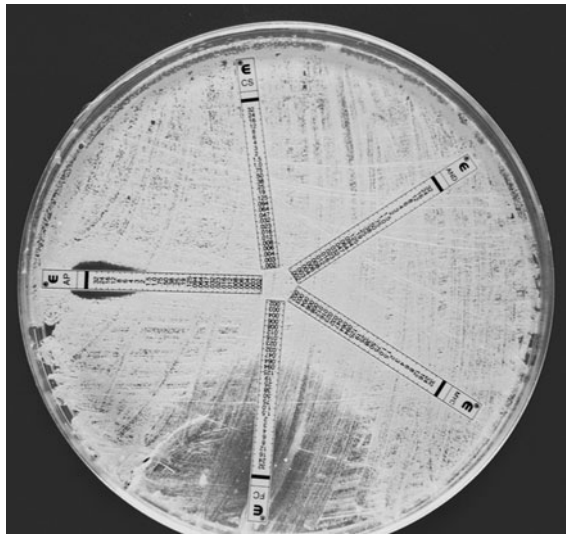

Fig. 2 Susceptibility testing to amphotericin B, flucytosine and echinocandins

Table 1 Published cases of *Rhodotorula* spp fungemia (2001–2011)

Author, year [references]	spp	Age/sex	Signs and symptoms	Underlying conditions	Risk factors	Px	Susceptibility testing (mg/L)	Treatment	Out come
Samonis [10]	m	76/M	Fever, chills, tachy-cardia/pnea, GI signs	Colon cancer, GI mucositis	chemoTx, N, antibiotics			rhG-CSF, N resolution	S
Petrocheilou-Paschou [13]	m	21/F	Fever	NHL, autologous PBSCT	CVC, chemoTx, N, TPN, antibiotics	FL	AmB 0.25, FL > 256, KE 0.25, FC 0.06, IT 1	LAmB, cath R, N resolution	S
Navarro [14]	m	55/M	Pancytopenia	Kidney transplantation, diabetes mellitus	Steroids, immunosuppressive agents, antibiotics			AmB lipid complex	S
Chung [15]	m	64/M	Fever	AML	CVC, chemoTx, N, antibiotics			AmB, cathR	D[a]
	m	15/F	Fever	AML	CVC, chemoTx, N			AmB, neutropenia resolution	S
Krcmery [16]	m	Child		Cancer					
Zaas [17]	m	23		HIV, intravenous drug use	CVC, CD4 < 50		*R. mucilaginosa*: AmB 0.25–1, FC 0.125–0.25, IT 0.5–4, VO 1- > 8, PO 0.5–2, FL 32- > 64, CS 16- > 16, MYC > 64 *R. glutinis*: AmB 0.25–1, FC 0.125–0.25, IT 1–4, VO 4–8, PO 1–2, FL 32- > 64, CS 16- > 16, MYC > 64	FL then AmB	S
	g	7		Glioblastoma multiform, autologous BMT	CVC, TPN, steroids			AmB	S
	m	43		Acute leukemia	CVC, N			cathR	
	m	Neonate		Congenital heart disease	TPN			AmB	
	m	54		Crohn's disease, kidney transplant	CVC, TPN, steroids, immunosupressive agents			FL cathR	S
	g	29		Short-bowel syndrome	CVC, TPN			FL cathR	S
	m	4		Neuroblastoma	CVC, N			AmB	S
	m	32		Gastroparesis	CVC, TPN			FL, cathR	S
	m	31		Cystic fibrosis, lung transplant	Steroids, immunosuppresive agents			AmB lipid complex, cathR	S
	m	35		Sickle cell disease	CVC			FL, then AmB, cathR	S

Table 1 continued

Author, year [references]	spp	Age/sex	Signs and symptoms	Underlying conditions	Risk factors	Px	Susceptibility testing (mg/L)	Treatment	Out come
Hsueh [18]	g	51/M	Fever–2 episodes	Nasopharyngeal carcinoma-bone metastases	CVC, antibiotics	FL	AmB 0.125, FL > 256, KE 0.25, IT 8, FC 0.06	FL, cathR	S
Lo Re III [19]	m	34/M	Fatigue and chills without fever, 2 episodes	Short-bowel syndrome, juvenile RA	CVC, TPN, steroids, immunosupressive agents			FL, cathR; Recurrence LAmB, cathR	S
Maeder [20]	m	53/M	Endocarditis	Aortic homograft				Surgery and FL, then AmB, then IT	S
Pasqualotto [21]	spp	10/F	Fever, chills, cyanosis, exanthem, endocarditis	Relapsed ALL	CVC, chemoTx, N			AmB and FC and rifampicin, cathR	S
	spp	16/F	Fever, mucositis	Relapsed AML, autologous HSCT	CVC, chemoTx, N, antibiotics, bacteremia			AmB and FC	S
	spp	16/F	Febrile neutropenia	Ewing sarcoma of the jaw	CVC, chemoTx, N			AMB and FC, cathR	S
Perniola [22]	m	Neonate/F	Lethargy, tachycardia, respiratory distress, GI signs	VLBW	Vascular central line, N, bacteremia	FL	AmB 0.25, FL > 256, IT 2, VO 2, KE 0.25, FC 0.125	LAmB cathR	S
	m	Neonate/M	Lethargy, respiratory distress	VLBW	Vascular central line, bacteremia			LAmB, cathR	S
	m	Neonate/F	Lethargy, tachy-cardia, GI signs	LBW	Vascular central line, bacteremia	FL		LAmB, cathR	S
	m	Neonate/F	Lethargy, tachy-cardia, respiratory distress, GI signs	ELBW	Vascular central line, N, bacteremia	FL		LAmB, cathR	S
Lunardi [23]	m	12/M		Leukemia	CVC, chemoTx, N, steroids, antibiotics			AmB, cathR	D
	m	16/F		Leukemia, BMT	CVC, chemoTx, N, steroids, antibiotics	FL		AmB and FC, cathR	S
	m	17/F		Ewing sarcoma	CVC, chemoTx, N, antibiotics			AmB and FC, cathR	S
	m	48/M		Bowel tumor, enterectomy	CVC?, TPN			cathR	S
	m	46/F		Lyposarcoma	CVC, chemoTx, N, antibiotics			cathR	S
	m	34/M		Testicular cancer	CVC, chemoTx, N, antibiotics	FL		FL cathR	D
	m	18/M		Leukemia	CVC, chemoTx, N, steroids, antibiotics, fusariosis			AmB, VO, cathR	D

Table 1 continued

Author, year [references]	spp	Age/sex	Signs and symptoms	Underlying conditions	Risk factors	Px	Susceptibility testing (mg/L)	Treatment	Out come
Neofytos [24]	m	31/M	Sickle cell crisis	Sickle cell disease	CVC		AmB < 0.5, FL > 64, VO < 2, CS > 16	FL; Recurrence VO	S
Kofteridis [25]	g	64/M	Fever		Antibiotics, bacteremia		FL 1.5, FC > 32	FL	S
	g	65/M	Fever		Antibiotics, pneumonia		FL 1.5, FC > 32	FL	S
Pamidimukkala [26]	g	20/F	Fever, sepsis, meningoencephalitis	Systemic lupus erythematosus	Mild N, antibiotics, malnutrition		AmB < 0.5, FC < 0.5, FL 64, IT > 4		D
Riedel [27]	g	54/M		Liver-kidney transplant, hypertension, diabetes, gout	CVCs, immunosupressive agents, steroids, antibiotics[b]	FL	VO < 0.06, FL R	VO, cathR; MYC (concomitant candidemia)	D (R. infection cured)
De Almeida [28]	m	53/M		NHL BMT	CVC	N (3 patients), antibiotics (11 patients), bacteremia (7 patients) 2 patients received Px	AmB 0.25–1, IT 0.03- > 8, VO 0.06–4, FL > 64	AmB, cathR	S
	m	8/F		Aplastic anemia BMT	CVC			cathR	S
	m	7/M		CNS tumor				None	S
	m	47/M		Cirrhosis	CVC, pneumonia			AmB, cathR	D
	m	39/F		Acute leukemia	CVC			AmB, cathR	S
	m	58/M		Burkii lymphoma BMT	CVC			AmB, cathR	D
	m	43/M		NHL	CVC			AmB, cathR	S
	m	21/F		Hodgkin's Lymphoma	CVC			AmB, cathR	S
	m	19/M		Liver abscess due to *S. aureus*				None	?
	m	3/M		Falciform anemia				None	S
	m	70/M		Short bowel	CVC			FL, cathR	S
	m	53/M		NHL	CVC			?	?
	m	53/M		Acute leukemia	CVC			AmB, cathR	S
	m	14/M		NHL BMT	CVC			AmB, cathR	S
	m	51/M		Acute leukemia BMT	CVC			AmB, cathR	S
	m	50/M		NHL BMT	CVC			AmB, cathR	S
	m	9/M		Acute leukemia BMT	CVC			AmB, cathR	S
	m	41/F		HD	CVC			AmB, cathR	S
	m	48/F		Acute leukemia BMT	CVC			AmB, cathR	S
	m	Neonate/M		Congenital liver disease	CVC, candidemia			None	D

Table 1 continued

Author, year [references]	spp	Age/sex	Signs and symptoms	Underlying conditions	Risk factors	Px	Susceptibility testing (mg/L)	Treatment	Out come
	m	7/M		Aplastic anemia BMT	CVC, *P. jiroveci* pneumonia			cathR	D
	m	47/F		Acute leukemia BMT	CVC			cathR	S
	m	55/M		NHL BMT	CVC			FL, AmB, cathR	S
	m	67/M		NHL	CVC			None	S
	m	37/M		NHL	CVC			FL, AmB, cathR	S
Garcia-Suarez [29]	m	54/M	Asymptomatic, 2 episodes	MM autologous peripheral blood stem cells transplantantion	CVC, chemoTx, N, steroids, antibiotics, *E. coli* bacteremia (2nd episode)	FL CS	AmB 0.12, FC 0.12, FL > 64, IT > 8, VO > 8, PO 4, CS 16	IT; Recurrence CS then LAmB, cathR	S
Pulvirenti [30]	g	79/M	Fever	Diabetes, cirrhosis	CVC, antibiotics			VO	S
Mori [12]	m	49/M	Fever	MDS allogenic HSCT	CVC, immunosupressive agents, steroids	FL MYC	AmB 0.25, FC < 0.12, FL > 64, MYC > 16, VO 8, IT 1	AmB	S[c]
Al-Obaid [31]	m	4/F	Low-grade fever	ALL	CVC		AmB 0.023, FC 0.016, FL > 256, VO 2, PO > 32, CS > 32	VO, cathR	S
Duggal [32]	m	Neonate	Respiratory failure, sepsis, GI signs (second episode)	Low gestational age	CVC, antibiotics, *K. pneumonia* bacteremia (second episode)		AmB 1.5–3, VO 0.38 CS > 16, FL > 256	FL, then AmB; Recurrence VO	S
	m	50/F	Fever	Traffic accident, neurosurgery	CVC, antibiotics		AmB 0.5, VO > 32	AmB, cathR	S
Our case	m	48/F		Ovarian cancer, surgery	CVC, antibiotics, bacteremia, TPN, intubation	FL	AmB 1.5, FC 0.064, FL > 256, IT 0.75, KE 0.032, VO 1.5, PO 0.25, CS, MYC > 32	None	D

AML acute myelogenous leukemia, *ALL* acute lymphoblastic leukemia, *AmB* amphotericin B, *BMT* bone marrow transplant, *cathR* catheter removal, *chemoTx* chemotherapy, *CS* caspofungin, *CVC* central venous catheter, *D* death, *ELBW* extremely low birth weight, *FC* flucytosine, *F* female, *FL* fluconazole, *g R. glutinis*, *GI* gastrointestinal, *HD* Hodgkin Disease, *HSCT* hemopoietic stem cell transplantation, *IT* itraconazole *KE* ketoconazole *LAmB* liposomal amphotericin B, *LBW* low birth weight, *m R. mucilaginosa*, *M* male, *MYC* micafungin, *N* neutropenia, *NHL* non-Hodgkin lymphoma, *PBSCT* peripheral blood stem cell transplantation, *Px* antifungal prophylaxis, *RA* rheumatoid arthritis, *rhG-CSF* recombinant human granulocyte colony–stimulating factor, *S* survival, *spp* species, *TPN* total parenteral nutrition, *VLBW* very low birth weight, *VO* voriconazole

[a] Due to *K. pneumoniae* bacteremia (*R. mucilaginosa* was treated)

[b] Ventilator-associated pneumonia, CMV viremia, *C. difficile* colitis, *C. glabrata* candidemia

[c] Died later of invasive systemic aspergillosis

and outcome of seventy cases published between 2001 and 2011 is presented [10, 12–32]. During the last decade, 46 cases are reported in adults, seventeen in children below 18 years, and seven in neonates.

Patients with solid tumors and hematological malignancies [11], especially those undergoing bone marrow transplantation [12] as well as patients with AIDS, are considered as those at high risk of systemic *Rhodotorula* infection [5, 33]. As presented in Table 1, the majority of adults had malignancies; specifically, twenty-one patients had hematological malignancies and six solid tumors, whereas four patients had undergone solid organ transplantation.

Published cases involving children are few and involve almost exclusively children with hematological malignancies or solid tumors.

The presence of central venous catheters has been closely associated with *Rhodotorula* fungemia [8]. *Rhodotorula*, as a fungus that is normally present on the skin, adheres to the catheter and colonizes it [33]. Administration of chemotherapeutic agents, immunosuppressive agents, steroids and associated neutropenia represents major risk factors [8, 28]. Patients who have abdominal surgery, cirrhosis, autoimmune diseases or burns are also at risk [5]. Previous antibiotic use and parenteral nutrition is also associated with *Rhodotorula* infection [6, 19, 28]. Use of broad spectrum antibiotics and exposure to cytotoxic agents probably contribute to the increase in gastrointestinal colonization and to damage of the intestinal mucosa, although the role of gastrointestinal tract as a source of *Rhodotorula* fungemia is not well documented [10, 28]. In a report of *R. mucilaginosa* outbreak in a neonatal intensive care unit [22], all neonates were premature and had a vascular central line. Also, three out of four neonates were on fluconazole prophylaxis. Although cultures were taken from hands of personnel, parenteral nutrition bags and objects, no source was found; even cultures of catheter tips were negative. Of the patients reported with *Rhodotorula* fungemia during the last decade, 81.4 % had a central line in place, 38.6 % were receiving chemotherapy, immunosuppressive agents, steroids or had neutropenia, 30 % were receiving antibiotics, and 20 % had a concomitant infection, most commonly bloodstream infection. Furthermore, a considerable number (four) of patients had gastrointestinal malformations, such as short-bowel syndrome. Our patient had several risk factors such as solid organ neoplasm, abdominal surgery, presence of CVC, total parenteral nutrition and prolonged antibiotic administration.

Our isolate was identified as *R. mucilaginosa*, which is the most common species causing fungemia (74–75 %), followed by *R. glutinis* (6–7.7 %) [6, 8]. Also, among the reviewed seventy cases, 59 were identified as *R. mucilaginosa*, eight as *R. glutinis*, whereas three were unidentified.

Overall mortality is reported to be 15 % [5]. During the last decade, ten out of seventy patients with *Rhodotorula* fungemia died, corresponding to a mortality rate of 14.3 %. In addition, in two cases, death was not attributed to *Rhodotorula* infection.

Several *in vitro* studies have been carried out in order to predict i*n vivo* response of *Rhodotorula* fungemia to antifungal agents. Susceptibility testing of twenty-nine *Rhodotorula* strains revealed that only one was resistant to amphotericin B having MIC $>$ 1 mg/L, whereas 27 strains were susceptible to flucytosine [34]. Susceptibility to azoles such as itraconazole and voriconazole was limited; 55 and 72.4 % of strains had MICs $>$ 1 mg/L, respectively, whereas MIC to fluconazole was consistently $>$4 mg/L [34]. Finally, ravuconazole appeared to be the most active drug of the azoles group; 93 % of strains were inhibited by $\leq$4 mg/L [34]. In another study where 210 *Rhodotorula* strains were tested, 49 % were resistant to fluconazole and 37.3 % to voriconazole [35]. Diekema et al. [36] tested 64 *Rhodotorula* spp strains against eight antifungals and revealed that all strains were susceptible to flucytosine and ravuconazole, 63 (98 %) of strains were susceptible to amphotericin B (most strains were clustered around a value of 1 mg/L), and voriconazole, 25 (39 %) and 16 (25 %) were susceptible to itraconazole and posaconazole, respectively, whereas fluconazole and caspofungin were inactive. Our strain was susceptible to flucytosine. MIC to amphotericin B was relatively high (1.5 mg/L), whereas the strain was resistant to fluconazole, posaconazole and voriconazole according to the revised break points for *Candida* spp [37]. Echinocandins appeared completely inactive, as previously described [11, 12, 29, 38].

Our patient was also receiving fluconazole as prophylaxis. Antifungal prophylaxis can be administrated to adults in ICUs who are at high risk of invasive candidosis [5]. Because of intrinsic resistance of *Rhodotorula* spp to triazoles and echinocandins, patients receiving fluconazole and caspofungin are

prompt to develop breakthrough *Rhodotorula* fungemia (23). In a study involving twenty-nine cases of hematological malignancy patients, thirteen were receiving prophylaxis with fluconazole when they developed *Rhodotorula* fungemia [6].

Resolution of neutropenia, especially chemotherapy induced, is crucial for recovery from the infection [9, 10]. Taking into account that many cases are proven to be catheter related (either positive cultures of catheter tips or recurrence of infection until catheter is removed) [13, 15, 18, 19, 29, 31], catheter removal seems a reasonable choice. As shown in Table 1, catheter removal was adequate for the elimination of infection in five cases. Regarding the use of antifungals, amphotericin B was the agent of choice and was used alone or in combination with catheter removal in 57 % of reported cases. Surprisingly, seven patients were successfully treated with fluconazole; isolated strains were either susceptible to fluconazole [25] or resistant [17, 18, 28]. Voriconazole has been used in some cases alone or with catheter removal with good results [24, 27, 30–32]. Flucytosine has been also used as a second agent because of persistent positive blood cultures, despite several days of monotherapy with amphotericin B [21].

Increasing awareness by physicians and microbiologists along with improved and more aggressive therapeutic approach of critically ill patients or patients with malignancies have led to the emergence of *Rhodotorula* spp as a noteworthy pathogen. Although the optimal therapy remains to be defined, a conservative approach combining amphotericin B with catheter removal should be considered to prevent serious complications, especially in immunosuppressed patients [28]. Correct identification is obligatory for appropriate management, as *Rhodotorula* spp are resistant to antifungal agents, such as fluconazole and echinocandins.

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