Rhodotorula infection. A systematic review of 128 cases from literature

Felipe F. Tuon & Silvia F. Costa

Department of Infectious and Parasitic Diseases, School of Medicine, University of São Paulo, Brazil.

Summary

Rhodotorula is an emerging opportunistic pathogen, particularly in immunocompromised patients. Many cases of fungemia associated with catheters, endocarditis, peritonitis, meningitis, and endophthalmitis are infections incited by this yeast. The main purpose of this study was to review all cases of Rhodotorula infection reported in the literature and to describe risk factors, underlying conditions and outcome. From 128 cases, 79% were fungemia (103 cases), 7% eye infections (nine cases) and 5% (six cases) peritonitis associated with continuous ambulatory peritoneal dialysis. Eighty seven percent of Rhodotorula infections are associated with underlying immunosuppression or cancer. The most common isolated risk factor associated with Rhodotorula infection was the use of a central venous catheter, which was found in 83.4% of Rhodotorula fungemia (86 cases). Rhodotorula mucilaginosa was the most common species of fungemia (74% of cases), followed by Rhodotorula glutinis with 7.7%. The species was not identified in 17% of the cases of fungemias. Amphotericin was the drug of choice in the treatment of fungemia and most of the eye infections were treated with topical amphotericin, although all patients lost their vision. All peritonitis cases associated with continuous ambulatory peritoneal dialysis needed to have the Tenckoff catheter changed. The overall mortality of Rhodotorula infection was 12.6%.

Key words

Rhodotorula, Fungemia, Central venous catheter, Immunosuppressed

Infección por Rhodotorula. Revisión de 128 casos

Resumen

Rhodotorula es un patógeno emergente oportuno, especialmente presente en pacientes inmunodeprimidos. Este microorganismo está involucrado en numerosos casos de fungemia asociada a catéteres, endocarditis, peritonitis, meningitis y endoftalmitis. El propósito del presente estudio fue revisar todos los casos de infecciones por Rhodotorula publicados en la literatura, describiendo los factores de riesgo. De 128 casos, el 79% (103 casos) correspondían a fungemias, el 7% (nueve casos) a infecciones oculares y el 5% (seis casos) a peritonitis asociada con diálisis peritoneal ambulatoria continua. El 87% de las infecciones se asociaban con inmunosupresión o cancer. El factor de riesgo más importante asociado a infección por Rhodotorula fue el uso de catéter venoso central, encontrado en el 83.4% de los casos de fungemia (86 casos). Rhodotorula mucilaginosa fue la especie encontrada en la mayor parte de los casos de fungemia (74%), seguida de Rhodotorula glutinis (7.7%). La identificación de la especie no fue posible en un 17% de los casos de fungemia. El tratamiento de elección en las fungemias fue la anfotericina B, y la mayor parte de las infecciones oculares fueron tratadas tópicamente con anfotericina B, si bien todos los pacientes sufrieron pérdida de la visión. Todos los casos de peritonitis asociados a diálisis peritoneal continua ambulatoria requirieron el cambio del catéter Tenckoff. La mortalidad debida a la infección por Rhodotorula fue del 12.6%.

Palabras clave

Rhodotorula, Fungemia, Catéter venoso central, Inmunosuprimido
Rhodotorula is a basidiomycetous yeast in the fungal family Sporidiobolaceae (Phylum Basidiomycota) [17]. Widespread in nature and isolated from environmental sources and products [1,48], it was previously considered non-pathogenic. During the last two decades, however, it has emerged as an opportunistic etiologic agent, particularly in immunocompromised patients [27]. Fungemia associated with catheters, endocarditis, peritonitis, meningitis, and endophthalmitis is one of the most common infections reported in the literature [63]. This yeast fulfills the criteria of an emerging pathogen [27].

Although several publications have described this yeast as a cause of human mycoses, there is no review in the literature regarding the epidemiology, risk factors and outcome related to Rhodotorula infection. A previous systematic review was published, but only central venous catheter-associated fungemias were evaluated [69]. The main purpose of this study was to review all cases of human Rhodotorula infection reported in the literature, and to describe the risk factors, underlying conditions and outcomes for the different forms of Rhodotorula infection.

Methods

A careful search of all articles about Rhodotorula infections published in the MEDLINE, EMBASE and LILACS was performed (until January, 2006). The search terms (key word) were “Rhodotorula”, “fungal infections”, “fungal endophthalmitis”, “fungal eye infection”, “fungal peritonitis”, “yeast infection”, “fungemia”, “fungaemia”, “fungal meningitis”, “fungal abscess”, “fungal central nervous system infection” and “fungal endocarditis”. The reviews of “fungal infections” or “emergent fungal infections” were included in this search. No limitations were placed on language or types of studies published. A detailed examination of the references from all articles chosen in the first selection was performed for ascertainment of additional case reports. The studies were initially selected by two physicians independently. Disagreements were resolved by consensus.

The classification of Rhodotorula infection was based on epidemiologic data and anatomical location. Epidemiologic data included: 1) isolation of the yeast from a previous sterile site; 2) information regarding age and gender; 3) underlying conditions; 4) current and previous therapies and; 5) outcome. No contact was made with the original authors. We checked the clinical findings, age and gender of all cases to avoid overlapping cases.

Rhodotorula infection was stratified by anatomical location (blood, peritoneum, meningitis and eye) according to the following criteria: 1) a blood stream infection required at least one criteria published by Garner et al. [21], which was defined as one positive culture for Rhodotorula either from the central venous catheter (CVC) tip or the peripheral blood; 2) fungal peritonitis in patients on CAPD (Continuous Ambulatory Peritoneal Dialysis) was determined by a positive peritoneal fluid culture and at least two of the three following criteria which included abdominal pain, a cloudy peritoneal fluid, and/or a cell count from the peritoneal fluid with more than 100 neutrophils per mm³ [60]; 3) fungal meningitis was defined by positive culture with pleocytosis and clinical signs of meningitis [46]; 4) diagnostic criteria of eye Rhodotorula infection were described previously by Thomas [68].

Epi Info 2000 was used to develop a database of all clinical information and underlying conditions, previous medications, any kind of immunosuppression, invasive procedures, antifungal therapy, year of publication, and outcome. Previous antibiotic use was accepted if a broad spectrum antibiotic was used for at least one week prior to yeast identification. We considered overall mortality in this systematic review. No statistical test was performed.

Results

A total of 1233 articles were found. However, 1092 articles were excluded because no Rhodotorula infection was identified. From 141 articles, only 128 cases were included in our database because they fulfilled the inclusion criteria. The other cases were excluded because inclusion criteria for Rhodotorula infection were not adequate.

The mean age was 34.5 years (range 1-74 years) and sixty five percent of all cases of Rhodotorula infection occurred in males. Fungemia was documented in 103 cases (79% of the Rhodotorula infections). Among fungemia patients, 86 cases were associated with CVC (66% of Rhodotorula infection) [2,3,5,8,9,16,24,28,29,39,40,42,44,54,55,57,58,65,66,71,72]. Other cases of fungemia were endocarditis (seven cases) [19,36,41,43,51,55,64] and in ten patients the source of the fungemia was not evident [30,31,36,37,40,63,66] (Table 1). The mortality of Rhodotorula fungemia was 14.4%. Fungemia not associated with CVC had a higher mortality than endocarditis and CVC fungemia (20% vs. 14.2% vs. 13.5%).

After fungemia, eye infection, with a total of nine cases, was the second most common Rhodotorula infection (endophthalmitis, keratitis and corneal infections) [4,7,26,38,45,47,53,59,61] followed by six cases (5% of Rhodotorula infection) of peritonitis associated with CAPD [12,14,56,67].

The most common eye Rhodotorula infection was keratitis, which had a good prognosis with topical antifungal treatment. Endophthalmitis caused by Rhodotorula had a worse prognosis as all patients lost vision and required either a vitrectomy or enucleation (Table 2).

A total of five cases of meningitis and one case of ventriculitis were described. The underlying conditions were AIDS (two cases), meningioma (one case) and acute lymphoblastic leukemia (one case); only one patient had no underlying disease.
predisposing factor. In the patient with ventriculitis, the underlying condition was the use of an intraventricular catheter. The outcome for meningitis was good, with only two deaths. One of these cases was not attributed to Rhodotorula infection and the outcome was progressive coma due to leukemic infiltration of central nervous system (Table 3). Although neither considered nosocomial nor related to an invasive procedure, four cases of meningitis appear to have been healthcare-related.

All Rhodotorula peritonitis cases were associated with chronic renal failure and patients on CAPD in the presence of a Tenckoff catheter. In the six cases published, only one patient had not received antibiotics prior to developing fungal peritonitis. The prognosis of Rhodotorula peritonitis was death in one case due to hospital associated pneumonia (not attributed to Rhodotorula infection). All patients required removal of their Tenckoff catheter and hemodialysis (Table 4).

Other unusual sites of Rhodotorula infection described in the literature were hydrosalpingitis [23], an orthopedic prosthesis infection [11], and two cases of disseminated Rhodotorula infection with bone marrow isolation of the agent [50,62].

Immunosuppression was found in 40% of patients with Rhodotorula infection. The causes of immunosuppression were corticosteroid use (13 cases - 10%), neutropenia (20 cases - 15%), AIDS (nine cases - 7%) and malnutrition (12 cases - 9%). Solid neoplasm was found in 13.2% of patients with Rhodotorula infection (17 cases) and hematological neoplasm in 32.8% (42 cases). Twelve transplanted patients developed Rhodotorula infection (11 cases of bone marrow, one case of lung and one case of kidney transplantation) [19,50]. The interval of Rhodotorula infection after organ transplant was 1.6 years. All cases were attributed to immunosuppressive drugs. Although 87% of patients with Rhodotorula infection had an underlying immunosuppression or cancer, the most common isolated underlying condition associated with Rhodotorula infection was the use of a CVC found in 83.4% of Rhodotorula fungemia (86 cases). Only five patients with Rhodotorula fungemia had no underlying disease, although all these patients had previous use of broad spectrum antibiotics. Thirty-eight percent of patients with Rhodotorula infection used broad spectrum antibiotics and 15.1% were receiving parental nutrition. The underlying conditions associated with each form of Rhodotorula infection are described in tables 1-4.

Rhodotorula mucilaginosa was the most common species of fungemia (74% of cases) followed by Rhodotorula glutinis in 7.7%. The species was not identified in 17% of the cases of fungemia.

Seventy-one percent of patients with Rhodotorula fungemia associated with CVC received specific therapy. The most common antifungal used was amphotericin B and the treatment duration ranged from 14 to 41 days with a mean total dose of 1,318 mg. Seven patients received fluconazole; 5-fluorocytosine was used in two patients. Four patients used the combination of amphotericin with 5-fluorocytosine. The overall mortality of Rhodotorula infection was 12.6%.

### Table 2. Ocular infections caused by Rhodotorula spp.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Agent</th>
<th>Sex/Age</th>
<th>Disease</th>
<th>Previous Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>Romano</td>
<td>R. mucilaginosa</td>
<td>M/29</td>
<td>Keratitis</td>
<td>None</td>
<td>TA + nystatin</td>
</tr>
<tr>
<td>1973</td>
<td>Segal</td>
<td>R. mucilaginosa</td>
<td>F/29</td>
<td>Keratitis</td>
<td>None</td>
<td>TA + nystatin</td>
</tr>
<tr>
<td>1992</td>
<td>Casolari</td>
<td>R. glutinis</td>
<td>M/40</td>
<td>Keratitis</td>
<td>None</td>
<td>TA + SA + 5-FC</td>
</tr>
<tr>
<td>1992</td>
<td>Gregory</td>
<td>R. minuta</td>
<td>F/71</td>
<td>Endophthalmitis</td>
<td>None</td>
<td>Ketoconazol</td>
</tr>
<tr>
<td>1999</td>
<td>Panda</td>
<td>Rhodotorula spp.</td>
<td>M/55</td>
<td>Corneal infection</td>
<td>None</td>
<td>TA</td>
</tr>
<tr>
<td>2001</td>
<td>Piana</td>
<td>R. minuta</td>
<td>M/27</td>
<td>Endophthalmitis</td>
<td>HCV</td>
<td>TA + Ketoconazol</td>
</tr>
<tr>
<td>2002</td>
<td>Merkur</td>
<td>R. mucilaginosa</td>
<td>M/26</td>
<td>Endophthalmitis</td>
<td>AIDS</td>
<td>SA + TA</td>
</tr>
<tr>
<td>2003</td>
<td>Bawazeer</td>
<td>Rhodotorula spp.</td>
<td>F/63</td>
<td>Keratitis</td>
<td>None</td>
<td>TA</td>
</tr>
<tr>
<td>2005</td>
<td>Lifshitz</td>
<td>R. mucilaginosa</td>
<td>M/78</td>
<td>Keratitis</td>
<td>None</td>
<td>SA + TA</td>
</tr>
</tbody>
</table>

SA: Systemic amphotericin; TA: Topical amphotericin; HCV: Hepatitis C infection; 5-FC: 5-fluorocytosine

### Table 3. Central nervous system infections caused by Rhodotorula spp.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Agent</th>
<th>Sex/Age</th>
<th>Diagnosis</th>
<th>Previous Disease</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>Pore</td>
<td>R. mucilaginosa</td>
<td>M/14</td>
<td>Meningitis</td>
<td>ALL</td>
<td>AmphotB</td>
<td>Death</td>
</tr>
<tr>
<td>1987</td>
<td>Donald</td>
<td>R. mucilaginosa</td>
<td>F/32</td>
<td>Ventriculitis</td>
<td>Meningioma</td>
<td>5-FC</td>
<td>Cure</td>
</tr>
<tr>
<td>1996</td>
<td>Gymurieva</td>
<td>R. mucilaginosa</td>
<td>M/39</td>
<td>Meningitis</td>
<td>AIDS</td>
<td>5-FC</td>
<td>Cure</td>
</tr>
<tr>
<td>1998</td>
<td>Huttova</td>
<td>R. mucilaginosa</td>
<td>M/13</td>
<td>Meningitis</td>
<td>Neuroblastoma</td>
<td>Miconazole</td>
<td>Cure</td>
</tr>
<tr>
<td>1999</td>
<td>Ahmed</td>
<td>R. mucilaginosa</td>
<td>F/65</td>
<td>Meningitis</td>
<td>AIDS</td>
<td>Miconazole</td>
<td>Death</td>
</tr>
<tr>
<td>2001</td>
<td>Lanzafame</td>
<td>R. glutinis</td>
<td>M/69</td>
<td>Meningitis</td>
<td>None</td>
<td>AmphotB</td>
<td>Cure</td>
</tr>
</tbody>
</table>

5 FC: 5-Fluorocytosine; AmphotB: Amphotericin B; ALL: Acute lymphocytic leukemia

### Table 4. Peritonitis associated with CAPD caused by Rhodotorula spp.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Agent</th>
<th>Sex/Age</th>
<th>Disease</th>
<th>Previous Antibiotic</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Eisenberg</td>
<td>R. mucilaginosa</td>
<td>M/16</td>
<td>CRF</td>
<td>Yes</td>
<td>C+IPA</td>
<td>Cure + Hemodialysis</td>
</tr>
<tr>
<td>1983</td>
<td>Eisenberg</td>
<td>R. mucilaginosa</td>
<td>M/50</td>
<td>Diabetes</td>
<td>Yes</td>
<td>C+IPA</td>
<td>Cure + Hemodialysis</td>
</tr>
<tr>
<td>1995</td>
<td>Pennington</td>
<td>R. mucilaginosa</td>
<td>M/99</td>
<td>No</td>
<td>Yes</td>
<td>C+IPA</td>
<td>Death</td>
</tr>
<tr>
<td>2004</td>
<td>Soylu</td>
<td>Rhodotorula spp.</td>
<td>F/4</td>
<td>No</td>
<td>No</td>
<td>C+IPA</td>
<td>Cure + Hemodialysis</td>
</tr>
</tbody>
</table>

C: Removal the Tenckoff catheter; IPA: Intraperitoneal amphotericin; SA: Systemic amphotericin; CRF: Chronic renal failure
Discussion

The first case of Rhodotorula infection, a patient with endocarditis, was reported in 1960 by Louria [41]. After this first case, several articles have been published and an increase in the number of Rhodotorula infections has been reported, mainly in the last two decades. However, this increase could be a publication bias after the recognition of Rhodotorula as a pathogen. Another explanation is the dramatic expansion in new modalities of treatment related to critical care medicine and transplantation, short and long term CVC with or without parental nutrition, broad spectrum antibiotics, and chemotherapy. Rhodotorula is the etiological agent in 0.5 to 2.3% of all cases of fungemia described in some epidemiologic studies [3,22,32,33,52].

Rhodotorula is a yeast which produces mucoid colonies with a characteristic carotenoid pigment and is widely distributed in the environment [17]. Previously considered a low virulence organism in comparison to Candida or Trichosporon, Rhodotorula must be considered a potential pathogen in patients with immunosuppression and CVC [25,62]. Patients with hematological neoplasms who are both neutropenic and have long term CVC use are at risk for Rhodotorula infection. In a study that included 101 CVC-related infections, Rhodotorula constituted 8.9% of the cases [54]. In a previous large outbreak in a hospital, Rhodotorula and Candida spp. constituted 54% and 20% of the infections, respectively [19].

The resistance mechanism of Rhodotorula has been described as very high (MIC > 64 μg/ml) for fluconazole. Despite the low MICs to voriconazole and posaconazole, there is no clinical experience with these drugs, however they may have potential efficacy.

Currently amphotericin B appears to be the drug of choice for Rhodotorula infection, although seven patients treated with fluconazole and one treated with miconazole responded. There are no prospective studies that have evaluated antifungal treatment for Rhodotorula infections.

Patients on CAPD have an incidence of peritonitis of about one episode per patient-year [49]. Fungal peritonitis is a relatively uncommon complication of peritoneal dialysis and although it accounts for less than 5% of all peritonitis episodes in patients on CAPD, it contributes significantly to morbidity, drop out from the CAPD program, and mortality [6]. Contamination of the dialysis catheter with these ubiquitous organisms from the environment serves as a portal of entry [49]. Patients receiving CAPD are at risk for Rhodotorula peritonitis and, as are those who have previously received antibiotics for bacterial peritonitis. Rhodotorula is easily recovered from the peritoneal fluid, thereby providing early identification and antifungal therapy. Eighty percent of patients who survived their Rhodotorula peritonitis dropped out of the CAPD program and were started on hemodialysis, which increased the risk of other infections.

Endogenous fungal endophthalmitis has increased owing to widespread use of immunosuppressive therapy, parental nutrition, injectable drug use, and AIDS [59]. Candida and Aspergillus are the most common organisms [34]. Rhodotorula seldom causes ocular infections and most common cases described include keratitis and endophthalmitis. Dacryocystitis and corneal lamellar graft infection were also reported [47,53]. Although the therapy of Rhodotorula eye infections is not well-defined, some reports recommend that endophthalmitis should be treated with systemic antifungals, and some keratitis cases clear with topical treatment [4,7]. The worst outcomes requiring enucleation occurred in two patients, both with underlying conditions and drug abuse histories [45,59].

It appears Rhodotorula meningitis should be considered a hospital infection, as five cases of central nervous system infections were nosocomial, including a case of ventriculitis. One case of community-acquired infection was reported in 2001 [35], although it is difficult to explain how Rhodotorula gets access to cerebral spinal fluid without a barrier leak, such as a catheter or neoplasm, in a non-hospitalized patient. Rhodotorula spp. appear to be emerging yeasts, although some infections not documented histopathologically appear doubtful [50]. Immunosuppression and CVC appear to be risk factors. Correct identification is necessary for appropriate managements, as Rhodotorula spp. are resistant to some antifungal agents such as fluconazole and the echinocandins. Reports of Rhodotorula infections resolving without the use of specific antifungal treatment may suggest their low virulence in immunocompetent individuals. Additional studies including an immunosuppressed model, and prospective randomized trials in humans are need to better understand this intriguing infection and to determine optimal management.

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References


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