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CASE REPORT

Rhodotorula fungaemia: a life-threatening complication of indwelling central venous catheters

Rhodotorula-Fungämie: Eine lebensbedrohliche Komplikation bei zentralvenösen Verweilkathetern

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Schlüsselwörter. *Rhodotorula*, Fungämie, Katheter.

Summary. A 30-year-old woman receiving total parenteral nutrition via an indwelling central venous catheter for an intestinal motility disorder developed fever, tachycardia, tachypnea, and hypotension. Multiple blood cultures drawn through the catheter prior to these events, as well as a peripheral blood culture obtained earlier, grew the red yeast *Rhodotorula rubra*. The patient was critically ill for over one month but eventually recovered with therapy including the systemic antifungal agents amphotericin B and flucytosine and removal of the catheter. Although *Rhodotorula* has generally been regarded as having low pathogenicity, this case emphasizes the serious nature of *Rhodotorula* sepsis and suggests the need for both systemic antifungal therapy and removal of a colonized indwelling catheter.

Zusammenfassung. Eine 30-jährige Frau, wegen einer intestinalen Motilitätsstörung über einen zentralvenösen Verweilkatheter vollständig parenteral ernährungspflichtig, entwickelte Fieber, Tachykardie, Tachypnoe und Hypotonie. Aus mehrmaligen Blutkulturen, über den Katheter vor dem Auftreten dieser Symptome gewonnen, sowie aus einer davor angelegten peripheren Blutkultur wurde die rote Hefe *Rhodotorula rubra* angezüchtet. Die Patientin verblieb über einen Monat lang in kritischem Zustand, erholte sich jedoch unter Therapie mit den systemischen Antimykotika Amphotericin B und Flucytosin und nach Entfernung des Katheters. Obgleich *Rhodotorula* allgemein als nur geringgradig pathogen angesehen wird, belegt dieser Fall den ernsthaften Charakter der *Rhodotorula*-Sepsis sowie die Notwendigkeit der systemischen Antimykotika-Therapie und der Entfernung des Katheters.

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Introduction

Rhodotorula is a red-coloured yeast which has rarely been implicated as a cause of clinically significant infection in humans. With the expanded use of indwelling central venous catheters for administration of therapeutic and nutritional agents has come the observation of increased numbers of cases of catheter-associated fungaemia with *Rhodotorula* species [1, 2]. Additionally, several cases of infection involving invasion of tissues have been reported, including cases in which *Rhodotorula* has been cultured from an aortic valve, cerebrospinal fluid, and bone marrow [3–5]. In general, this yeast has been felt to be of low pathogenicity, with only two deaths thought to be related to fungal infection among those with culture-proven fungaemia [2–4]. This has led to uncertainty regarding the need to treat persons found to have *Rhodotorula* fungaemia either with antifungal agents or by

removal of the catheter [1, 2]. Most reported cases of catheter-related fungaemia have involved patients with underlying neoplastic disease. We report a case of catheter-related *Rhodotorula* sepsis, which was life-threatening and involved a patient without a neoplasm or apparent compromise of host immunity.

Case history

A 30-year-old woman was admitted to the University of Michigan Medical Center in February 1990 with a several day history of increasing abdominal pain, nausea, vomiting, and fever (40.0 °C). In 1987, the patient had been diagnosed as having familial visceral neuropathy manifested as chronic idiopathic intestinal pseudo-obstruction with intermittent nausea, vomiting, postprandial abdominal pain, and a weight loss from 59.1 to 38.2 kg over the two years prior to diagnosis [6]. The patient remained symptomatic during a brief trial of enteral feeding combined with cisapride, and thus hyperalimentation via a permanent indwelling Hickman catheter was initiated. She did well on total parenteral nutrition, such that she was able to maintain her weight at or above 53.2 kg, and her serum albumin rose from a value of 2.2 g dl^{-1} at the time of diagnosis to 3.7 g dl^{-1} at the time of this admission. Her Hickman catheter had most recently been replaced in September 1989 in conjunction with antibiotic therapy for a catheter-associated infection.

Upon admission, the patient was found to be in no acute distress. Blood pressure was 106/60 mmHg, pulse 108 beats/min, and temperature 38.4 °C. Physical examination showed mild erythema and induration of the skin surrounding the catheter site, but was otherwise unremarkable. The white blood cell count (WBC) was 9700 mm^{-3}, and haemoglobin was 12.7 g dl^{-1}, stable from previous values. Evidence for mild cholestasis was attributed to central hyperalimentation.

Based upon the history and several previous presentations of catheter-associated infection, a presumptive diagnosis of line-related infection was made. Multiple blood cultures were drawn, both via the catheter and peripherally, and therapy with vancomycin and ceftazidime was initiated. Within two days, blood cultures obtained both peripherally and from the catheter were found to be growing methicillin-sensitive coagulase-negative staphylococci. Ceftazidime was discontinued, and vancomycin was changed to cefazolin. The patient defervesced and subjectively improved, and the indwelling catheter was retained in place.

Within four days, the original blood culture drawn from a peripheral vein was found to be growing a yeast identified as *Rhodotorula rubra*. However, because the original culture only grew a single colony of yeast and since there was continued clinical improvement with treatment for infection due to coagulase-negative staphylococci, the yeast was interpreted to be a contaminant, and no antifungal therapy was begun. Additional blood cultures were obtained from a peripheral site and through the Hickman catheter, the latter yielding *R. rubra* (>1000 colonies ml^{-1}) within two days. *Staphylococcus* was never observed again in any blood cultures.

Thirteen days after admission, the patient was afebrile and felt well. However, because a total of two blood cultures had yielded *R. rubra* over eleven days, antifungal therapy with amphotericin B (MIC 0.05 μg ml^{-1}) was initiated. The central catheter was not removed because of lack of intravenous access. She tolerated amphotericin B well in escalating doses to 25 mg daily and remained afebrile.

On the 21st hospital day, the patient developed a temperature of 39.9 °C, with a pulse of 160 beats/min, respirations of 28/min, and blood pressure of 52/30 mmHg. Intravenous fluids and pressors including dopamine and norepinephrine were given. The Hickman catheter was removed, cefazolin was discontinued, and broad-spectrum antibacterials, consisting of vancomycin and gentamicin, were initiated. The next day piperacillin was added to the antimicrobial regimen. That same day she suffered a cardiopulmonary arrest, but was successfully resuscitated, intubated, and begun on mechanical ventilation. Later that day, two additional blood cultures, obtained through the catheter one week earlier, yielded *R. rubra* (30 and 15 colonies/ml, respectively). Amphotericin B was increased to 45 mg daily (0.85 mg kg^{-1} daily) and flucytosine (MIC 0.2 μg ml^{-1}) was added at a dose of 1500 mg every 6 h.

The WBC rose to 19,600 mm^{-3}, with 47% segmented neutrophils and 40% bands, and subsequently peaked at 37,200 mm^{-3}. Bilateral diffuse air-space disease, consistent with adult respiratory distress syndrome, was noted on chest roentgenograms. For 8 days, the patient required the use of pressors to maintain adequate systemic blood pressure. She remained critically ill for over one month with daily maximal temperature exceeding 37.8 °C for 32 days. She gradually improved and was extubated after 38 days of ventilatory support. Amphotericin B was given

for 29 days (total dose 1121 mg) and flucytosine was given for 21 days. After removal of the Hickman catheter, numerous blood cultures failed to grow *R. rubra* or any other microorganisms. This included three sets of blood cultures (anaerobic and aerobic) obtained from peripheral veins on the day of the patient's acute decline (21st hospital day), as well as five additional sets of cultures obtained from peripheral sites over the next month. Additionally, one set of blood cultures obtained through the Hickman catheter just prior to its removal remained negative. Following extubation, the patient required continuing inpatient care and rehabilitation for more than six weeks. Another Hickman catheter was placed, and she was discharged from the hospital 107 days after admission. No further infection with *R. rubra* has been observed.

Mycology

Blood cultures were performed with a Du Pont ISOSTAT microbial system (E. I. du Pont de Nemours & Company, Wilmington, DE, USA) with the sediment plated on chocolate agar. In order to enhance the isolation of fungi following the initial positive culture for *Rhodotorula*, sediment from subsequent blood cultures was plated on Emmon's modification of Sabouraud glucose agar and brain–heart infusion (BHI) agar with 6% sheep's blood added. The initial isolate was found to produce pink colonies on chocolate agar, suggesting that it was *Rhodotorula*. Microscopic examination disclosed oval-shaped, budding, encapsulated yeast. The sugar assimilation pattern on an API20C strip demonstrated that the yeast was *R. rubra*.

Susceptibilities were performed using macrobroth dilution assays, with antibiotic medium 3 broth (Difco Laboratories, Detroit, MI, USA) used for amphotericin B testing and yeast nitrogen base broth (Difco) used for the flucytosine testing. The inoculum for each tube was 1×10^4 CFU ml^{-1} and incubation was performed at 37 °C for 18 h. The range of dilutions for both antifungals was 250 μg ml^{-1} to 0.01 μg ml^{-1} with the endpoint for both assays being the first clear tube.

Discussion

Yeast of the genus *Rhodotorula* belong to the family *Cryptococcacae* and are normal flora of skin and gastrointestinal tract [7, 8]. They may also be found in soil, air, and water, in cheese and milk, and on common household items, such as shower curtains and bathtub grout. Members of the genus *Rhodotorula* resemble yeast of the genus *Cryptococcus* in that they are round to oval-shaped, demonstrate budding, form a capsule, produce urease, and are non-fermentative. The two genera may be differentiated by coral red pigment produced by *Rhodotorula* and assimilation of inositol by *Cryptococcus* [8]. The most frequently isolated species is *R. rubra*.

Rhodotorula has been an uncommon infectious agent in humans, and animal studies have suggested that it possesses little pathogenicity [3, 9]. With the increasing use of indwelling central venous catheters, however, more cases of fungaemia have been observed. In a recent review from a large metropolitan hospital specializing in the treatment of neoplastic disorders, 23 cases were felt to have clinically significant fungaemia associated with permanent intravenous catheters [2]. Of these cases, 20 had an underlying neoplasm. Five patients were treated with catheter removal only, five received antifungal therapy only, and thirteen underwent catheter removal in addition to receiving antifungal therapy. All of these patients were reported to have survived without recurrence of *Rhodotorula* fungaemia. Earlier reports identified thirteen other cases of culture-proven *Rhodotorula* fungaemia, including one patient who died with *Rhodotorula* endocarditis found at autopsy and another who died with *R. rubra* meningitis documented post mortem [1–4, 9–11]. Several other deaths occurred but were not felt to be secondary to fungal infection. Of these earlier cases of fungaemia, four patients, including the patient with *Rhodotorula* endocarditis who later died, were reported to have experienced a clinically significant episode of hypotension, suggestive of Gram negative bacillary sepsis. Two of the three patients who survived septic shock recovered with removal of the indwelling device and no antifungal therapy [1, 11].

In vitro susceptibility testing of *Rhodotorula* to antifungal agents has been performed in a limited number of cases [1, 2, 4, 5]. All isolates tested appear to be susceptible to flucytosine, amphotericin B, and ketonazole, with moderate susceptibility observed to miconazole and itraconazole. Although some isolates appear to be moderately susceptible to fluconazole, others have demonstrated MIC values in excess of 100 μg ml^{-1} [2].

It is unlikely that coagulase-negative staphylococci were the etiologic agents responsible for this patient's life-threatening illness, since they were never isolated after the initial cultures and the

patient promptly responded to antistaphylococcal therapy. The septic syndrome developed nearly two weeks after coagulase-negative staphylococci had been isolated from the blood. Similarly, it is quite doubtful that the illness was caused by amphotericin B therapy, since the patient remained afebrile for the first week of therapy, developed fever without any correlation to amphotericin B administration, and remained febrile for weeks following the cessation of antifungal therapy. The most likely etiology for the patient's severe illness was infection with *R. rubra*, which was isolated from one peripheral and three catheter-drawn blood cultures over a total period of two weeks.

The patient described here differs in several respects from most of those reported previously with *Rhodotorula* fungaemia. First, this patient had no underlying neoplasm or apparent immunosuppressive disorder. Second, the severity of illness observed was greater than in most other patients who have developed fungaemia with this yeast. Unlike most other patients previously reported, our patient was critically ill for many weeks, despite prolonged antifungal therapy and catheter removal one week after the initiation of amphotericin B. Several factors may have contributed to our patient's severe illness. The delay of almost two weeks from the time that a blood culture specimen containing *Rhodotorula* was first obtained until amphotericin B treatment was begun, and the further delay until the infected catheter was removed, probably contributed to the severity of infection. Additionally, it is tempting to speculate that her non-compromised immune status, exemplified by leukocytosis and left shift early in the course of infection, culminated in a vigorous host response to the yeast, with effects on the host similar to those seen in Gram negative bacillary sepsis.

Optimal management of patients with indwelling catheters infected with *Rhodotorula* has not been well defined. Pien *et al.* [1] noted that three of five survivors of *Rhodotorula* fungaemia had not received antifungal therapy and advised that infected intravenous devices be removed but that antifungal therapy be initiated only if fungaemia persisted [1]. More recently, Kiehn *et al.* [2] have advocated antifungal therapy in all cases of *Rhodotorula* fungaemia, despite their observation that five patients survived with catheter removal alone. These authors also suggested that antifungal treatment without removal of the catheter may be appropriate in some cases.

A recent review of catheter-associated fungaemia, in which *Candida* species accounted for over 98% of cases, concluded that indwelling catheters should be removed in all instances of fungaemia, noting a negative outcome in nine of eleven cases (82%) in which antifungal therapy was given without catheter removal [12]. Although conclusions of that study were drawn largely on the basis of experience with *Candida* species (infections with *Rhodotorula* species were not observed), we believe that our experience with the patient described here illustrates the potential for severe, life-threatening illness due to *Rhodotorula* infection, similar to that seen with *Candida* fungaemia. Therefore, we advocate both removal of indwelling intravenous catheters infected with *Rhodotorula* and treatment with systemic antifungal agents. We believe this constitutes the most prudent approach to management of a relatively uncommon but potentially life-threatening infection.

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