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Case Report

Rhodotorula Fungaemia in a Preterm Infant with umbilical Venous Catheter and Parenteral Nutrition Intraperitoneal Extravasation

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Abstract

Rhodotorula species are emerging opportunistic fungi causing fungaemia in patients with underlying diseases of immunosuppression and the presence of central venous catheters (CVCs). The association between *Rhodotorula* fungaemia and indwelling CVCs in adults, paediatrics and neonates is well recognised. *Rhodotorula* infection in the preterm neonate has been reported with variable management. We report the clinical presentation, course, management and outcome of *Rhodotorula* infection in an immunocompromised preterm neonate in a tertiary neonatal unit with a CVC and parenteral nutrition extravasation into the abdomen.

Keywords: *Rhodotorula*; Umbilical Venous Catheter; Preterm; Parenteral Nutrition: Intra-Abdominal Extravasation

Abbreviations

CPAP: Continuous Positive Airway Pressure; UVC: Umbilical Venous Catheter; TPN: Total Parenteral Nutrition; EBM: Expressed Breast Milk; PICC: Peripherally Inserted Central Catheter; CVC: Central Venous Catheters

Case Presentation

A 31+4 weeks gestation female weighing 1660 grams was delivered vaginally. Apgar scores were 8 and 8 at 1 and 5 minutes. Continuous positive airway pressure (CPAP) support was required at birth. Umbilical venous catheter (UVC) was inserted under aseptic technique and position confirmed with abdominal X-ray. The line tip was at level of thoracic vertebrae 8 overlying the liver. Intravenous Benzyl penicillin and Gentamicin was started for suspected infection after obtaining blood cultures from the UVC. Total parenteral nutrition (TPN) (standard 10% solution) via UVC with SMOFlipid® emulsion was administered.

Fever developed at 6 hours of life with an axillary temperature of 38.4°C. Blood cultures were repeated and fever persisted till 25 hours of age. Infant was not septic on examination. Fever subsided and antibiotics were discontinued by 48 hours of age as initial blood cultures were negative. Expressed Breast Milk (EBM) feeds were started and TPN through the UVC continued.

At 69 hours of life, she developed abdominal distension and clinically deteriorated requiring intubation. Gastric aspirates were milky and meconium had been passed. Blood cultures were repeated, feeds withheld and intravenous Amoxicillin, Gentamicin, Flucloxacillin and Metronidazole started based on local guidelines for suspected necrotising enterocolitis and sepsis. Abdominal X-ray showed UVC tip at level of thoracic vertebrae 10 overlying the liver with dilated bowel loops. The UVC was removed and Peripherally Inserted Central Catheter (PICC) inserted. Prophylactic intravascular fluconazole was started at 6mg/kg twice weekly following unit policy for PICC lines.

Repeat abdominal X-rays showed evidence of abdominal ascites and no free air in the abdomen. Antibiotics were adjusted to Ceftazidime, Vancomycin and Metronidazole on the discretion of attending consultant. Laboratory investigations showed a minimal drop in platelet count to 125,000 and an increase in total white cell counts with normal neutrophil and lymphocyte counts.

Abdominal distension improved within 24 hours and ascites was managed conservatively in view of improving clinical condition. She was extubated on day 4 of life, EBM feeds restarted and antibiotics discontinued after 48 hours as blood cultures showed no growth. Abdominal ultrasound on day 4 showed intra-abdominal fluid in the left flank and echogenic debris suggestive of TPN leak via UVC. A 20mm hyper-echoic lesion was noted in the left lobe of the liver suggesting acute intra-parenchymal haemorrhage most likely due to TPN necrosis.

On day 7 of life, growth of yeast was reported on blood culture performed at 6 hours of age, after 5 days of incubation at 37°C. Subcultures on Sabouraud glucose agar plates identified *Rhodotorula mucilaginosa*. Infant was re-cultured and fluconazole dose adjusted to treatment dose (loading 20mg/kg followed by 6mg/kg once daily). This was changed to intravenous Amphotericin B liposomal formulation the following day at dose of 2mg/kg once daily.

Unfortunately the yeast failed to grow on SensititreYeastOne® susceptibility plates. Repeat blood cultures showed no fungal growth and as her clinical condition was stable, Amphotericin B was discontinued after 5 days of treatment. PICC line was removed after remaining in situ for 8 days. Catheter tip culture did not grow *Rhodotorula*. The infant was discharged home at 28 days, weighing 2275grams.

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Discussion

Systemic fungal infections have a high mortality rate up to 40% in very low birth weight infants [1]. Most neonatal systemic fungal infections are due to Candida species, in particular Candida albicans occurring in 5% of low birth weight infants [2]. Risk factors for neonatal fungaemia include use of intravenous TPN (in specific intralipid solutions) [2]. Other risk factors include prematurity (gestation below 32 weeks), broad-spectrum antibiotics i.e. third-generation cephalosporins, presence of CVCs, prolonged duration of endotracheal intubation, surgically invasive procedures and corticosteroids use [3]. This case report highlights prematurity, the presence of UVC and TPN as risk factors for *Rhodotorula* infection. Broad-spectrum antibiotics were used in our case; however, the fungaemia was identified on cultures collected prior to cephalosporin use and hence will not be considered a risk factor.

The incidence of *Rhodotorula* infection is 0.5% and 2.3% in USA and Europe [4]. It is the fourth most common non-candidal invasive fungus reported by the ARTEMIS antifungal surveillance program [5].

Rhodotorula species are unicellular saprophytic yeasts, previously thought to be non-pathogenic [6]. They belong to the family Sporidiobolaceae which contains 46 species. Only 3 cause infection in humans; R. mucilaginosa (formerly *R. rubra), R. minuta*, and *R. glutinis* [7]. *Rhodotorula* colonies are salmon pink in colour due to carotenoid pigments and show rapid growth on Sabouraud Dextrose Agar (SDA) [8]. The fluorescence in situ hybridisation technique for species identification shows cross-reactivity between *Rhodotorula* and Candida glabrata and C. krusei. Polymerase chain reaction provides higher sensitivity and specific identification for fungi in blood samples [3].

Rhodotorula species are natural environmental inhabitants found in air, soil, lakes, ocean water and colonise plants, animals and humans [4]. The species have been identified in air samples from tertiary hospitals in Northern Brazil [4] and shows a strong affinity with plastic [8].

Experimental studies in rats displayed susceptibility to infection after intense immunosuppression using cyclophosphamide. The species produces a biofilm which may play a role in the association with CVCs, particularly with R. mucilaginosa and R. Minuta [9]. Environmental contamination of invasive prosthetic devices at the time of insertion may act as point of entry into the host and conditions that compromise immunity may make the organism pathogenic [8].

The first report of human infection was in 1960 [10] and the last two decades have seen a dramatic increase in *Rhodotorula* infection demonstrating the association between infection, immunodeficiency and the presence of CVCs [6].

Invasive *Rhodotorula* infections present as fungaemia in 79% of cases making blood cultures the mainstay of diagnosis. 87% of infections occur in patients with immunosuppression or cancer. The most common risk factor identified is the presence of a CVC seen in 83.4% of fungaemia cases and R. mucilaginosa is the most common species isolated (74%). Meningitis, endophthalmitis, endocarditis, and peritonitis are among the most common infections associated with fungaemia. TPN use was also seen in 15% of infections [11]. Zaas et al. reported 10 cases of CVC related *Rhodotorulainfection*, two were neutropenic and 17% received TPN [12]. The overall mortality rate for *Rhodotorula* infection is 12.6% and 14.4% for *Rhodotorula* fungaemia. CVC-fungaemia had lower mortality than non-CVC fungaemia (13.5% *vs* 20% respectively) [11].

To our knowledge, there are no literature reports describing association between TPN intraperitoneal extravasation through UVC and R. Mucilaginosa fungaemia in a preterm neonate. TPN use is a risk factor for *Rhodotorula* fungaemia and we can thus extrapolate that intraperitoneal spillage of TPN increases the chances of fungaemia.

Literature for *Rhodotorula* infection in preterm neonates is lacking. Perniola et al. reported four preterm cases of R. mucilaginosa with indwelling catheters since birth during an infection outbreak [13]. The report showed no mortality. Gestational age ranged between 28 to 31 weeks. Two infants were neutropenic. All infants received intravenous liposomal Amphotericin B and duration of therapy ranged from 8 to 13 days but dose were not mentioned. Two infants had CVC removed early (day 8 and 24) and two removed late (day 38 and 45). None of the catheter tip cultures were positive and repeat blood cultures were negative. All *Rhodotorula* isolates showed fluconazole resistance. Our case report shows a similar outcome with clinical resolution of infection following Amphotericin B therapy and UVC removal although treatment duration was shorter. Lack of sensitivities from the *Rhodotorula* isolate makes us unable to determine if Fluconazole resistance was reproduced in this case.

In vitro testing of the *Rhodotorula* species with the Clinical and Laboratory Standards Institute (CLSI) methodology identifies Amphotericin B and Flucytosine to be the most active agents [8]. MICs for R. mucilageinosa ranged from 0.125-0.25 ug/mL and 0.25-1ug/mL for Flucytosine and Amphotericin B respectively [12]. The species shows resistance to echinocandins with high MIC50 >8ug/mL and Fluconazole resistance (MIC50 >128ug/mL) [14]. Although the mechanism of resistance has not been reported, the consistently high MICs suggest intrinsic resistance to echinocandins and triazoles [9].

The drug of choice for *Rhodotorula* systemic infection in neonates appears to be Amphotericin B. The duration of treatment in literature varies between 14 to 41 days [11]. Concerns over Amphotericin B's nephrotoxicity profile and hypokalaemia have limited its use. The lipid formulation is reported to have less toxicity with equal effectiveness. The recommended dose for Amphotericin B liposomal formulation is 1mg/kg that can be increased to 3mg/kg once daily [15]. The Neonatal Candidiasis Study Group did not reach a consensus for the duration of therapy in neonates with systemic fungal infections [2]. However, for neonatal candidaemia, Hsieh E. recommended that therapy be continued for 21 days after microbiological clearance [16]. This data could be extrapolated to treatment for *Rhodotorula* infections ranging between 14 to 21 days, guided by clinical severity. Blood clearance of *Rhodotorulais* hastened by CVC removal and should be part of treatment strategy to decrease mortality [3].

Advances in neonatal medicine have led to increasing survival rates of very low birth weight and extremely low birth weight infants [17]. Risk factors for systemic fungal infections, in particular use of CVCs with or without parenteral nutrition are inadvertently

increasing incidences of severe infection with rare opportunistic yeasts. *Rhodotorulais* recognized as a cause of severe fungal sepsis in neonates and its identification should be treated appropriately with liposomal Amphotericin B and CVC removal.

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