MINI REVIEW

Rhodotorula an emergent pathogen

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ABSTRACT

The indiscriminate use of antibiotics conditioned by the constant appearance of new diseases and the re-emergence of others has caused an increase in antimicrobial resistance and the association of bacterial infections and viral and fungal infections. Although Candida and Aspergillus species cause the bulk of these infections, a growing proportion of infections are caused by less prevalent pathogens like the Rhodotorula species. Rhodotorula is an emerging opportunistic fungal pathogen. Rhodotorula, a basidiomycetous yeast, is found in nature; and has been isolated from several environmental sources as well as dairy products. They can also as commensal yeast on the skin, nails, and mucous membranes of humans. It is important to mention that mening-itis, fungemia, ventriculitis, endocarditis, peritonitis, endocarditis, endophtalmitis, keratitis, lymphadeniis, oral ulcer and infections of devices, such as catheters and contact lenses have all been related to Rhodotorula. The most effective antifungal agents against R. mucilaginosa are amphotericin B and flucytosine. Fluconazole resistance has been observed in all strains of Rhodotorula. In immunocompromised patients, early identification and chemotherapy are critical for preventing disease spread. Prevention methods aim to reduce identified risk factors. It is necessary to implement control and prevention measures to reduce morbidity and mortality rates due to Rhodotorula species. Its resistance to azoles leaves us with few therapeutic options to deal with it.

Key words: *Rhodotorula, Fungemia, immunocompromised patients*

INTRODUCTION

It is a fact proven by science that microorganisms have been the first to populate the earth and will certainly persist in it long after the disappearance of humans. Man has always relied on nature to make his scientific discoveries and has obtained from her the necessary resources for his evolution. The deterioration of the environment, a cumulative effect of centuries due to human activity, has caused an imbalance in the relationships established by these microorganisms with man. The indiscriminate use of antibiotics conditioned by the constant appearance of new diseases and the re-emergence of others has caused an increase in antimicrobial resistance and the association of bacterial infections with viral and fungal infections. In the last few decades, fungal infections linked to healthcare assistance have become a major medical concern. Although Candida and Aspergillus species cause the bulk of these infections, a growing proportion of infections are caused by less prevalent pathogens like the Rhodotorula species [1]. Some authors have referred to these fungi as emerging pathogens. Many of them were thought to be laboratory contaminants and/or of poor virulence. Rhodotoruliosis is a sporadic, non-contagious, opportunistic mycotic disease. Rhodotorula, a basidiomycetous yeast, is found in nature; and has been isolated from several environmental sources as well as dairy products. It was once thought to be non-pathogenic. It has emerged as an opportunistic etiological agent in the last two decades, particularly in immunocompromised hosts. They can also be present in the skin, nails, and mucous membranes as commensal yeasts. It is important to mention meningitis, fungemia, ventriculitis, endocarditis, peritonitis, endocarditis, endophthalmitis, keratitis, lymphadenitis, oral ulcer and infections of devices, such as cathetersand contact lenses have all been related to Rhodotorula [2-5]. It is also been found as a saprophyte on the skin, vaginal, and respiratory samples, as well as a colonizing organism on hemodialysis machines and bronchoscopes. [3,4]. The objective of this work is to contribute to the knowledge of rhodotoruliosis as an emerging infectious disease.

Development Etiology

Rhodotorula is a basidiomycetous yeast belonging to the phylum Basidiomycota and the family Sporidiobolaceae. The genus Rhodotorula has 34 species of which Rhodotorula glutinis, R. mucilaginosa, and R. minuta are the most frequent. Rhodotorula species are nutritionally non-fastidious, grow well on a variety of media, and have a quick growth rate. The morphology of the colony has been described as soft, smooth, moist, and occasionally mucoid. Pseudohyphae are rare, and they appear as round or oval budding cells under microscopy. Occasionally, a faint capsule forms. Urease is produced by Rhodotorula species, although they do not ferment carbohydrates. Due to the presence of carotenoid pigments, most Rhodotorula species generate pink to coral colonies on Sabouraud dextrose agar, although they can also be orange to red on Sabouraud dextrose agar [6].

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Epidemiology

Rhodotoruliosis is reported in several countries of the world.The disease often occurs in sporadic form however, outbreaks have also been recorded. Rhodotorula species are implicated as a cause of fungaemia, endocarditis, meningitis, peritonitis, keratitis, oral ulcers, and central venous catheter infection [7]. The species can be isolated from a range of sources in nature, including air, soil, salt water, plants, dairy products, and the home environment (e.g., shower curtains, bathtub grout) [8]. It is also possible that this opportunistic fungus can contaminate laboratory specimens [9]. A systematic review of Rhodotorula infections from the literature showed from the 128 cases, 79% were fungemia (103 cases), 7% eye infections (nine cases) and 5% (six cases) peritonitis associated with continuous ambulatory peritoneal dialysis. 87% 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% [9]. In a study conducted in a Colombian hospital from 2008 to 2011, 150 isolates of Rhodotorula spp. in superficial mycoses were mostly obtained from the nails of patients [10]. Manzano et al. showed in their investigation of onychomycosis-causing yeasts isolated, that one case was related to Rhodotorula glutinis [11]. R glutinis is part of the saprophytic flora of the skin and mucous membranes of man and is found widespread in humid environments: shower curtains, pipes, toothbrushes, floors, etc., and in medical supplies (catheters, IV solutions, dialysis). In hospitalized patients, Rhodotorula spp are found colonizing the digestive and genital mucosa with a frequency of 10.3%, this being significantly higher than in the control population [12]. Specifically, analyzing the percentage of yeasts by genus and species isolated in different body areas of the human being, Rhodotorula spp supposes: that in the skin of out-of-hospital individuals 17%<143) of them in the oral cavity of hospitalized patients 4.9%<144) of the same, in the anorectal area of hospitalized patients the 88% [12]. Rhototorula mucilaginosa is prominent basidiomycetous yeast that is found in a variety of natural habitats, including living or decomposing plant constituents, soil, and diverse aquatic environments, including fresh waters, estuaries, and coastal waters, as well as Open Ocean and deep-sea environments. It can also be found in harsh conditions, such as hyper acidic waters and uranium environs. Rhototorula mucilaginosa has been found in peanuts, Apple cider, cherries, fresh fruits, fruit juices, cheeses, sausages, edible molluscs, and crustaceans. Although eating yeast-contaminated food may not cause opportunistic infection directly, there is growing worried that food may be an underappreciated source of environmental pathogens. Recently, was reported an outbreak of Rhodotorula mucilaginosa in the neonatal intensive care unit. Rhodotorula glutinis complex has also been isolated from a range of substrates and is found all over the world. Air, fresh water, seawater, terrestrial settings, food and beverages, animals, and humans are all known sources of this saprobic fungus. Rhodotorula minuta has been recovered less frequently in natural environments than in R. Rubra and R. glutinis complex [2]. A case of meningitis caused by Rhodotorula rubra in an HIV-infected patient has been reported in Russia, in a study carried out in Colombia, its association was observed in 10% with cases of cancer patients with neutropenia [13,14]. This species was found in the air, in seawater (including the deep sea), and in freshwater. Infection due to Rhodotorula can occur through inhalation and also by accidental inoculation of the fungus through abraded skin. Natural infection due to Rhototorula species has been described in humans. The source of infection is exogenous and the infection may be acquired through the respiratory tract. However, the fungus can also enter the body of the host via wound, abrasion or injury on the skin [1].

Pathogenesis

The pathophysiology of Rhodotorula infection has not been investigated. As previously stated, there is nearly always underlying immunosuppression and/or the presence of a foreign body. Invasive infections may occur as a result of environmental contamination of an inserted prosthetic device, but it appears more likely that the organism is an opportunist that colonizes and infects at-risk patients by taking advantage of immune compromising conditions, and indwelling devices, and exposure to broad-spectrum antibiotics [2].

Clinical manifestations

Because Rhodotorula is such a common and saprophytic fungus, its isolation from non-sterile human sites, particularly mucosal membranes, has been a source of debate in the medical community. Rhodotorula species have been linked to a variety of diseases, including fungaemia. The first report of fungemia caused by Rhodotorula was published in 1960. Increased use of more aggressive treatment modalities, such as intensive care unit admissions, central venous catheter use, short- and long-term parenteral nutrition, broad-spectrum antibiotics, organ transplants, and chemotherapy, was related to an increase in Rhodotorula fungemia linked to catheters. Endocarditis, meningitis, ventriculitis, keratitis, endophthalmitis, and peritonitis are some of the other clinical symptoms other than fungaemia. There is also a case of lymphadenitis attributed due to Rhodotorula mucilaginosa in a man with a well-controlled HIV infection and a case of pelvic infection with bilateral hydrosalpinx was caused by Rodotorula glutinis [2]. Two cases of fungemia produced by this yeast were reported in Cuba: one in the province of Holguín, the sample from a blood culture of a neonatology patient with associated risk factors, and the other in the province of Cienfuegos, a two-month-old infant of age with a history of preterm delivery and infections of viral aetiology [15,16]. Also in Japan, a case of asymptomatic fungemia due to Rhodotorula spp [17].

Identification

Isolation of Rhodotorula species from non-sterile sites such as skin, sputum, or stool is more likely to be due to colonization. The isolation of Rhodotorula species from sterile site samples, such as blood, peritoneal fluid or cephalo spinal fluid, is generally suggestive of infection, especially in patients without indicative symptoms of infection [18]. On Sabouraud dextrose agar with chloramphenicol, the fungus can be easily isolated from clinical samples. The microscopic morphology of Rhodotorula isolates is studied by using PHOL or the Narayan stain, which includes 6 mL dimethyl sulfoxide, 4.0 mL glycerin, and 0.5 mL 3% methylene blue solution. As Pal sunflower seed medium, APRM agar, PHOL stain and Narayan stain are cheaper than other media and stains, it is, therefore, advised that Microbiology and Public Health laboratories should routinely employ these media and stains for the study of fungi including Rhodotorula. Rhodotorula species found in sterile environments, such as blood, peritoneal fluid, or CSF are frequently symptomatic. Since yeast cells may usually be observed by microscopic examination, morphological and biochemical confirmation of the diagnosis should be sought. They differ from Cryptococcus species in that they cannot assimilate inositol, and they differ from Candida species in that they produce coloured colonies and lack pseudohyphae.

Colony colouration, confirming biochemical tests (e.g., lack of carbohydrate fermentation, urease production), and the absence of ballistospore generation should all lead to a particular mycological identification of Rhodotorula. Identification by biochemical and enzymatic criteria carbohydrate assimilation: The patterns of assimilation of sugars (glucose, lactose, sucrose, maltose, galactose and raffinose) allow the identification of the different species of Candida spp, Rhodotorula rubra, Trichosporon spp. and Geotrichum spp. Interpretation: Positive: colour change of the culture medium towards yellow. Biochemical characteristics of Rhodotorula rubra: positive glucose, raffinose, maltose and sucrose.

Identification by nutrient assimilation

There are different semi-automated identification systems based on panels or galleries that contain nutrients, such as Auxacolor, Uni Yeast-Tek, API 20 C AUX, Galeria ID 32C, and Vitek System. Among the automatic systems, we have Vitek 2 System, Biolog YT MicroPlate, and Rapid Yeast Identification Panel MicroScan.There are also rapid yeast identification systems using biochemical and enzymatic tests, such as Rapid Yeast Plus System, and Fungiscreen 4H [19].

Susceptibility of patrons and treatment

Rhodotorula species are susceptible to amphotericin B and flucytosine in vitro, resistant to fluconazole and caspofungin, and have varying susceptibility to voriconazole. Amphotericin B is the first choice drug for Rhodotorula infections [12]. There are published studies on the in vitro susceptibility of Rhodotorula spp. to systemic antifungals. Isolates are usually sensitive to amphotericin B and 5-fluorocytosine but resistant to fluconazole (MIC90 256 mg/l). Itraconazole is moderately active (MIC90 of 1 mg/l), with the MIC of voriconazole being four times higher than that of itraconazole. In a study carried out, 35 isolates of R. glutinis and 61 of R. mucilaginosa were collected, and more than 50% were resistant to the azoles studied, especially R. mucilaginosa [20]. In another investigation carried out in Spain on the absence or severe reduction in the amount of ergosterol in the fungal membrane and its replacement with other sterols as potential antifungal resistance mechanisms in fungi, the presence of ergosterol was demonstrated in 3 isolates of Rhodotorula mucilaginosa and this was sensitive to Fluconazole, Itraconazole, Voriconazole, and Amphotericin B [21]. The therapy of Rhodotorula fungemia in humans is still debatable. Recovery requires the resolution of coexisting neutropenia. The removal of the central venous catheter is usually sufficient, and systemic antifungal treatment is rarely necessary. Rhodotorula is a low-virulence fungus with a low mortality rate. As a result, most Rhodotorula fungemia patients in the literature survived with or without antifungal treatment. Amphotericin B or one of its lipid formulations appears to be the medication of choice based on available in vitro susceptibility data. The most effective antifungal agents against R. mucilaginosa are amphotericin B and flucytosine. Fluconazole resistance has been observed in all strains of Rhodotorula. Cross-resistance to other azole medications is not common, however, itraconazole, voriconazole, and posaconazole resistance are found in more than 60% of the strains. This yeast species is also resistant to echinocandins. A lot of studies have been discussed about the importance of the genus Rhodotorula in the field of biotechnology and its vital applications in the future of the industry, recent studies confirmed the ability of genus Rhodotorula such as Rhodotorula minuta and Rhodotorula glutinis to synthesise metal nanoparticles. One of the most vital applications of metal nanoparticles, especially silver nanoparticles, in the field of medicine is using these nanoparticles as antimicrobial agents. One study from Egypt obtains a Rhodotorula strain a promising new biological source for the synthesis of silver nanoparticles having potent antimicrobial activity against a wide range of pathogenic bacteria and fungi [22].

Control and prevention

Minimizing risk factors is an important part of preventing Rhodotorula species infections. There is no indication of Rhodotorula species is transmitted from person to person. However, Rhodotorula spp. can infect healthcare professionals' hands. Standard infection control precautions, such as hand washing and thorough skin cleansing and preparation before invasive treatments, should be emphasized in the absence of particular evidence. As the fungus can enter through the abraded skin, it is, therefore, advised to avoid traumatic injury to the skin. Further, proper medical attention should be given to skin injury. In immune-compromised patients, early identification and chemotherapy are critical for preventing disease spread. Prevention methods aim to reduce identified risk factors. Thus, in the face of colonization in high-risk patients, it is advisable to establish antifungal prophylaxis. Prophylaxis is not without risk since, in turn, it can select strains resistant to azoles. Furthermore, performing antifungal susceptibility testing helps to understand the contribution of antifungal resistance to therapeutic failure. The administration of cytokines and growth factors can palliate the intensity of neutropenia and shorten its duration, although there is no proven evidence that the incidence of fungal infections decreases with the use of these drugs. On the other hand, hygiene measures for both the patient and his room and bathroom may contribute to preventing horizontal transmission. It is also important to have easy access to handwashing by health personnel. In addition, it is recommended that high-risk patients (bone marrow recipients, haematological patients, etc.) be admitted to rooms with the highest levels of environmental safety (positive air pressure, food sterility control, etc.) [23].

CONCLUSIONS

Rhodotorula is an emerging opportunistic fungal pathogen. Fungemia caused by this microorganism has increased due to the use of invasive procedures in accordance with technological development in the world. It is frequently isolated in immunocompromised patients and its transmission can be through health personnel. It is necessary to implement control and prevention measures to reduce morbidity and mortality rates due to Rhodotorula species. Its resistance to azoles limits the use of therapeutic options. Therefore it is necessary to focus on the implementation of control and preventive measures to reduce morbidity and mortality rates due to Rhodotorula species.

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