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진행성 비소세포폐암 환자에서 발생한 *Rhodotorula* 패혈증 1예

Sepsis Due to *Rhodotorula mucilaginosa* in a Patient with Advanced Non-Small Cell Lung Cancer

배태원[1] · 이재현[1,3] · 조용곤[1,2,3] · 김달식[1,3] · 최삼임[1,3] · 이혜수[1,2,3]
Tae Won Bae, M.D.[1], Jaehyeon Lee, M.D.[1,3], Yong Gon Cho, M.D.[1,2,3], Dal Sik Kim, M.D.[1,3], Sam Im Choi, M.D.[1,3], Hye Soo Lee, M.D.[1,2,3]

전북대학교 의학전문대학원 진단검사의학교실[1], 전북대학교병원 병원체자원은행[2], 전북대학교병원 의생명연구원[3]
Department of Laboratory Medicine[1], Chonbuk National University Medical School, Jeonju; Chonbuk National University Hospital Branch[2] of National Culture Collection for Pathogens, Jeonju; Research Institute of Clinical Medicine[3] of Chonbuk National University-Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, Korea

Rhodotorula species are round to oval-shaped, multilateral budding, encapsulated yeasts that produce urease and do not ferment carbohydrates. *Rhodotorula* species form characteristic salmon-pink colored colonies owing to carotenoid pigment production. These yeasts form a part of the normal flora of moist skin and are found in the environment. *Rhodotorula* was traditionally considered a contaminant but is now progressively recognized as a human pathogen, especially in immunocompromised patients with central venous catheters. However, isolation of *Rhodotorula* species from blood has been very rarely reported in Korea. We report a case of sepsis due to *Rhodotorula mucilaginosa* infection in a patient who had received chemotherapy and supportive care for non-small cell lung cancer.

Key Words: Sepsis, *Rhodotorula mucilaginosa*, Fungemia

INTRODUCTION

Rhodotorula species are known as contaminants because of their omnipresence in the environment such as in the air, soil, lakes, and ocean water. Due to their ubiquitous and saprophytic nature, the isolation of *Rhodotorula* from nonsterile sites such as the skin, sputum, urine, and feces has often been of doubtful clinical significance. However, it has been considered as pathogen, particularly in patients with leukemia or other solid tumors [1] and there were two cases of *Rhodotorula* bacteremia in Korea [2, 3].

Corresponding author: Hye Soo Lee
Department of Laboratory Medicine, Chonbuk National University Medical School, 20 Geonjiro, Deokjin-gu, Jeonju 54907, Korea
Tel: +82-63-250-1218, Fax: +82-63-250-1200, E-mail: leehs@jbnu.ac.kr

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CASE REPORT

A 77-yr-old woman presented to the hospital with cough and dyspnea. Two years ago, she was diagnosed with non-small cell lung cancer and had been treated with wedge resection and several rounds of combined chemotherapy and radiation therapy.

In the present visit, her initial diagnosis was bronchopneumonia with pleural effusion. Empirical antibiotic therapy by intravenous piperacillin/sulbactam was started. She was stable and afebrile during the intravenous antibiotic treatment. Findings of computed tomography of the chest and abdomen suggested multiple metastases in the liver, lymph nodes in the lesser omentum, and left supraclavicular lymph nodes.

On day 22 of hospitalization, she developed fever of up to 38.1°C without any evident source and her vital signs and labora-

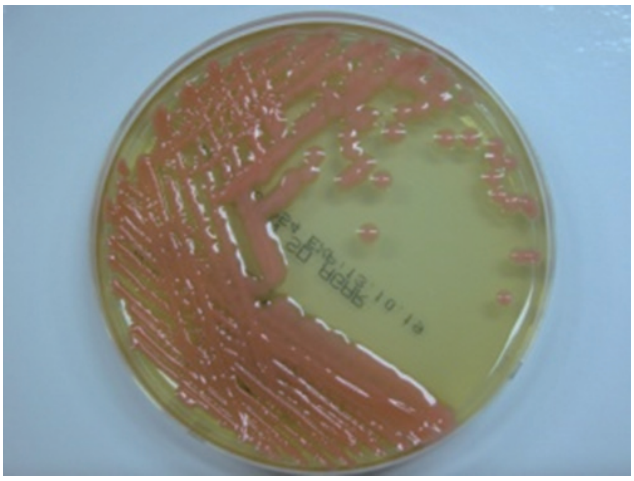

Fig. 1. *Rhodotorula mucilaginosa* on Sabouraud's dextrose agar (30°C, 5 days).

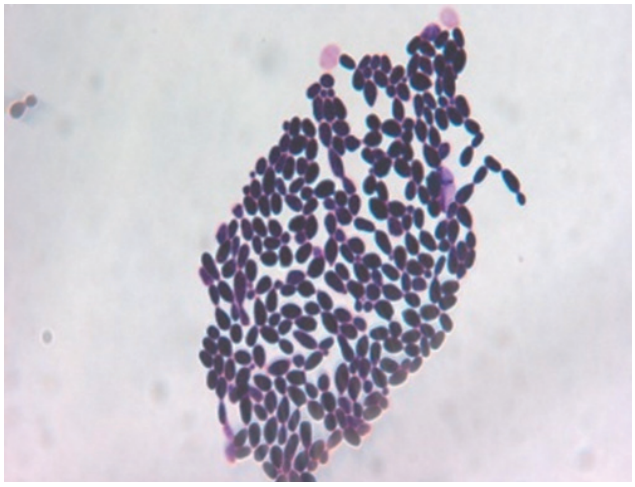

Fig. 2. Gram stain of *Rhodotorula mucilaginosa* (magnification: ×1,000).

tory findings were as follows: pulse rate, 90/min; respiratory rate, 20/min; blood pressure, 140/80 mmHg; leukocyte count, 12,550/mm^3 (neutrophils: 83.5%); Hb, 11.5g/dL; platelet count, 137,000/mm^3; erythrocyte sedimentation rate (ESR), 63 mm/hr; and C-reactive protein (CRP) level, 43.08 mg/L. Two peripheral blood samples were drawn and cultured. Based on the culture results, the antibiotic regimen was changed to meropenem and arbekacin. Within 1 day of initiating the new regimen, the patient's fever subsided and she remained afebrile. On day 27 of hospitalization, the patient again developed a fever of up to 38.3°C. Two sets of peripheral blood samples were cultured, and the findings were as follows: pulse rate, 110/min; respiratory rate, 20/min; blood pressure, 140/85 mmHg; leukocyte count, 8,500/mm^3 (neutrophils: 86.2%); ESR, 57 mm/hr; and CRP level, 38.23 mg/L. However, her condition worsened and she died on day 34 of hospitalization.

Aerobic cultures of blood samples drawn during the first episode of fever flagged positive 5 days after incubation; these were subcultured. The isolates gave rise to smooth, mucoid, glistening, pink to coral red colonies (Fig. 1). Gram staining revealed globose and elongated budding yeasts without any pseudohyphae (Fig. 2). The Vitek2 system (BioMerieux Inc., Hazelwood, USA) identified the isolated colonies as *Rhodotorula glutinis/mucilaginosa* (90% probability). Therefore, we performed molecular identification by sequencing the internal transcribed spacer (ITS) sequence of the ribosomal transcript. The ITS region was amplified using the primer sets ITS1 (5′-TCCGTAGGTGAACCTGCGG-3′) with ITS1-F (3′-CTTGGTCATTTAGAGGAAGTAA-5′) and ITS4 (5′-TCCTCCGCTTATTGATATGC-3′) with ITS4-B (3′-CAGGAGACTTGTACACGGTCCAG-5′). The amplicons showed 98.85% similarity with the ITS region of *R. mucilaginosa* (NR_073296.1), confirming that the isolated fungus was *R. mucilaginosa*.

In addition, aerobic cultures of blood samples collected during the second episode of fever were also positive after 4 days of incubation, and the same microorganisms were identified. Antifungal susceptibility tests revealed that the isolate was susceptible to amphotericin B (minimum inhibitory concentration, MIC 0.5 μg/mL) and voriconazole (MIC 1.0 μg/mL) and resistant to fluconazole (MIC 32 μg/mL), casopofungin (MIC >8 μg/mL), and micafungin (MIC >8 μg/mL).

DISCUSSION

Rhodotorula species are the fourth most common non-candida yeast isolated from clinical specimens (4.2% of 8,821 isolates) [4]. The first case of *Rhodotorula* fungemia was reported in 1960 by Louria et al. in a patient with endocarditis [5]. Since then, a number of *Rhodotorula* infections have been reported. Recent studies have showed that the incidence of *Rhodotorula* fungemia is from 0.5% to 2.3% in Europe [6] and USA [7].

The major risk factors of *Rhodotorula* infection are prolonged use of central venous catheters in patients with a hematologic or solid malignancy, prolonged use of corticosteroids and/or cytotoxic drugs [7, 8], and long-term used of broad-spectrum antibiotics [7]. The most prevalent species was *R. mucilaginosa*, formerly

known as *R. rubra*, followed by *R. glutinis*. Our patient had been treated with cytotoxic agents eight times and broad-spectrum antibiotics daily for two months before admission, but no catheter was used.

Since *Rhodotorula* is not a common cause of infection, there are no definite treatment guidelines for *Rhodotorula* fungemia. In many cases, patients have been treated effectively with removal of the indwelling catheter and/or appropriate antifungal agents [2, 3, 7]. One in vitro study revealed that *Rhodotorula* species were reliably susceptible to amphotericin and flucytosine, but resistant to fluconazole and echinocandin; and susceptibility to new triazoles such as itraconazole, voriconazole and posconazole is not predictable [9, 10]. The presumed mechanism of resistance to echinocandin is inhibition of access to the site of drug action in the fungal cell wall [11]. Although *Rhodotorula* species are less virulent than *Candida* and *Cryptococcus* species, the associated mortality rate was 12.6% in the largest systematic review [12]. In the current case, no catheter was inserted and only peripheral IV line was used. Before the antifungal susceptibility test, fluconazole was empirically administered two days after the second *Rhodotorula* isolation. However, given the high resistance to fluconazole and poor activity of echinocandin, amphotericin B may have been more beneficial in the current case. In contrast, there have been two reports of successful fluconazole treatment of *Rhodotorula* fungemia in cases in which fluconazole resistance was observed in vitro [13, 14].

In summary, we reported a case of *R. mucilaginosa* septicemia in a patient with advanced NSCLC in which long-term administration of broad-spectrum antibiotics may have contributed to this opportunistic infection. This is the first report of non-catheter-related sepsis due to *R. mucilaginosa* in Korea. Currently, amphotericin B is recommended as first-line therapy for *Rhodotorula* infection, but further evaluation of the effectiveness of new triazoles (e.g., voriconazole) based on antifungal susceptibility tests are required to determine appropriate therapy. Furthermore, correct and rapid identification of *Rhodotorula* species with antifungal susceptibility tests is also necessary.

요 약

*Rhodotorula*는 협막에 싸여진 원형 또는 난원형의 효모균으로 다발성(multilateral) 출아를 보이며, 요소분해 효소를 생성하고 탄수화물은 발효하지 않는다. *Rhodotorula*는 카로티노이드 색소를 생성하기 때문에 특징적인 연어살색 집락을 보인다. *Rhodotorula*는 자연환경에 분포하고 습윤한 피부에서 정상균무리로 존재하기 때문에 흔히 오염균으로 간주하였으나 최근에는 면역기능저하환자, 특히 중심정맥카테터를 삽입하고 있는 환자를 중심으로 병원균으로 인식되고 있는 추세이다. 그러나 아직 한국에서는 *Rhodotorula* 패혈증이 매우 드물게 보고되고 있는 바, 저자들은 항암치료 및 보존적 치료를 받아오던 비소세포폐암 환자에서 *Rhodotorula mucilaginosa*에 의한 패혈증이 발생하였기에 증례로 보고한다.

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