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Case report

Pleural empyema due to *Rhodotorula mucilaginosa*: A rare yet severe complication of a previously undiagnosed cancer patient

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ABSTRACT

Rhodotorula mucilaginosa (*R. mucilaginosa*) has been increasingly recognized as an emerging opportunistic pathogen causing invasive fungal infection, mainly in immunosuppressed patients. We report the case of a previously undiagnosed lung cancer patient with a pleural empyema due to *R. mucilaginosa*.

Background

Over the past few decades, there has been an increase in the number of cases of invasive fungal infection, mostly caused by common agents such as *Candida* species or *Aspergillus* species; however, some less common agents such as *Rhodotorula* species have been recognized as emerging pathogens [1]. *Rhodotorula* species are ubiquitous encapsulated yeasts with worldwide distribution belonging to the phylum *Basidiomycota*, subphylum *Pucciniomycotina*, class *Cystobasidiomycetes* and order *Cystobasidiales*. Although these yeasts can be found as part of the normal human flora in moist areas of the skin, nails and respiratory, gastrointestinal and genitourinary tracts [2,3], they have also been increasingly associated with human infection, mainly in immunosuppressed patients, such as those with human immunodeficiency virus infection and solid organ [1,2,4–6] or hematological [7,8] malignancies. The human infections most often caused by *Rhodotorula* species comprise (1) systemic infection, including fungaemia associated with intravenous catheters, broad-spectrum antimicrobial use and/or previous surgery, and endocarditis; (2) central nervous system infection, including meningitis and ventriculitis; (3) ocular infection, including keratitis and endophthalmitis; and (4) intraabdominal infection, including peritonitis in patients undergoing continuous ambulatory peritoneal dialysis [2–5,9–11]. Among the more than 40 species of the genus *Rhodotorula*, *Rhodotorula mucilaginosa* (*R. mucilaginosa*), formerly known as *Rhodotorula rubra*, is the most common cause of human infection, followed by *Rhodotorula glutinis* and *Rhodotorula minuta* [2,3,9,10]. *Rhodotorula* species culture reveals soft, smooth, moist to mucoid salmon-pink to coral-red colonies (due to the production of carotenoid pigment) [1,5,6,12], which are characterized by a rapid growth rate and mature appearance after 4 days of incubation. Microscopy reveals large spherical to elongate budding yeast-like cells or blastoconidia, rarely with the formation of true hyphae or pseudohyphae [4]. Traditionally, species identification was carried out through semi-automated systems based on biochemical tests, such as sugar assimilation pattern and urease production. More recently, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) and sequencing of the ITS and/or D1/D2 regions also allowed the identification of clinically relevant *Rhodotorula* species. The patients with *Rhodotorula* species infection should be treated with systemic antifungal

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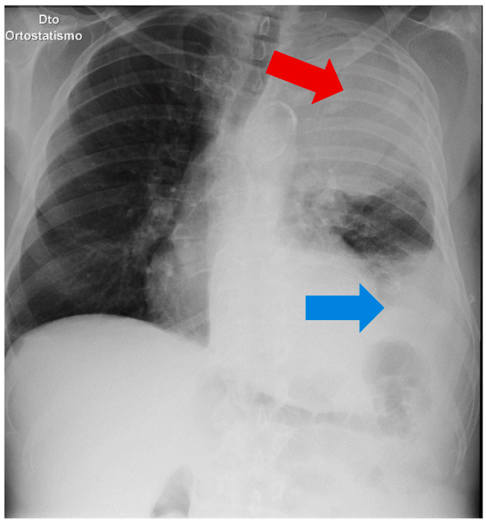

Fig. 1. Chest radiography showing a mass-like opacity in the upper third of the left lung (red arrow) and a moderate volume pleural effusion (blue arrow); mediastinal shift is also observed.

therapy; however, as these yeasts seem to be intrinsically resistant to most azoles [1,11] and echinocandins, the antifungal therapy of choice is amphotericin B, and the addition of flucytosine may be helpful.

We report the case of a previously undiagnosed lung cancer patient with a pleural empyema due to *R. mucilaginosa*.

Case report

An 84-year-old Portuguese man was admitted to the emergency department due to left pleuritic chest pain with a few days of evolution. Further interrogation revealed a 6-month history of productive cough and involuntary weight loss, as well as a 1-month history of haemoptysis. Past medical history included arterial hypertension, dyslipidaemia, hypertensive and ischemic heart disease with reduced ejection fraction, and benign prostatic hyperplasia. He denied smoking habits and he had no relevant family history of cancer. On physical examination, the patient was afebrile and haemodynamically stable, cardiac auscultation was normal and pulmonary auscultation of the left hemithorax revealed abolished respiratory sounds in the upper and lower thirds, and slightly diminished respiratory sounds in the middle third. Arterial blood gas analysis did not reveal respiratory failure. Laboratory tests showed a normal white blood cell count (leukocytes = 7760 μL), normocytic and normochromic anemia (hemoglobin = 8.2 g/dL; mean corpuscular volume = 85.1 fL; mean corpuscular hemoglobin = 27.5 pg) and thrombocytosis (platelets = 460,000 μL), as well as slightly elevated serum inflammatory markers (C-reactive protein = 109.65 mg/dL) and normal lactate dehydrogenase (LDH) enzyme activity (LDH = 155 units/L). Chest radiography showed a large pulmonary mass concerning the left upper lobe and blunting of the lower half of the left hemithorax, suggesting a moderate volume pleural effusion (Fig. 1). Chest computed tomography (CT) scan was then performed and it revealed a large heterogeneous mass in the upper lobe of the left lung (13.4 cm × 11.1 cm) with mediastinal invasion and vascular incarceration, as well as chest wall invasion (Fig. 2). A post-obstructive pneumonia and a moderate volume left pleural effusion were also identified. Abdominal CT showed a nodule of the left adrenal gland (20 mm) of probable secondary affiliation. The patient was hospitalized to investigate the etiology of the lung mass and to manage both the post-obstructive pneumonia and the pleural effusion.

Table 1
Light's criteria for exudative pleural effusion calculation. LDH: lactate dehydrogenase.

Laboratory tests results		
Total serum protein	6.8	g/dL
Pleural fluid protein	3.77	g/dL
Serum LDH	155	units/L
Pleural fluid LDH	83	units/L
Upper limit of normal serum LDH	225	units/L
Light's criteria results		
Pleural fluid protein to serum protein ratio = 0.55		
Pleural fluid LDH to serum LDH ratio = 0.54		
Pleural fluid LDH to upper limit of normal serum LDH ratio = 0.37		

A diagnostic thoracentesis was performed with citrus yellow pleural fluid outlet. The cytological examination revealed an increased total nucleated cell count (total nucleated cells = 2893/μL) and a differential cell count with predominance of mononuclear leukocytes (mesothelial cells = 405/μL, neutrophils = 347/μL, lymphocytes = 636/μL, monocytes = 231/μL and macrophages = 1273/μL). The cytochemical examination showed proteins = 3.77 g/dL and LDH = 83 units/L, fulfilling Light's criteria for exudative effusion (pleural fluid protein to serum protein ratio > 0.5; Table 1); adenosine deaminase (ADA) levels were normal (ADA = 18.2 units/L).

Pleural fluid was also collected into a blood culture vial and immediately sent to the Microbiology Service at room temperature, where it was introduced into the BD BACTEC™ FX (Becton Dickinson) blood culture system. After 91.5 h of incubation, the vial was flagged as positive and the microscopic examination of the smear by Gram stain revealed the presence of oval budding yeast cells surrounded by a transparent halo, suggesting the presence of a capsule (Fig. 3). After 24 h of incubation at 35 ± 2 °C in 5% CO_2, the subculture in chocolate agar revealed the presence of soft, smooth,

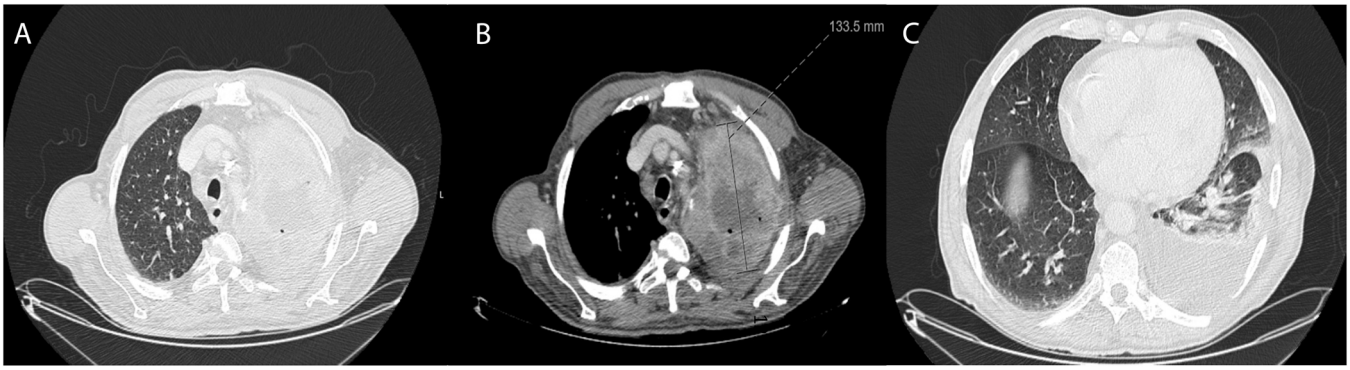

Fig. 2. Chest CT scan confirming the presence of a large heterogeneous mass in the upper lobe of the left lung with mediastinal invasion and vascular incarceration, as well as chest wall invasion (A: lung window; B: mediastinal window; note the presence of central tumor necrosis; C: moderate volume pleural effusion, causing passive atelectasis of the left lower lobe).

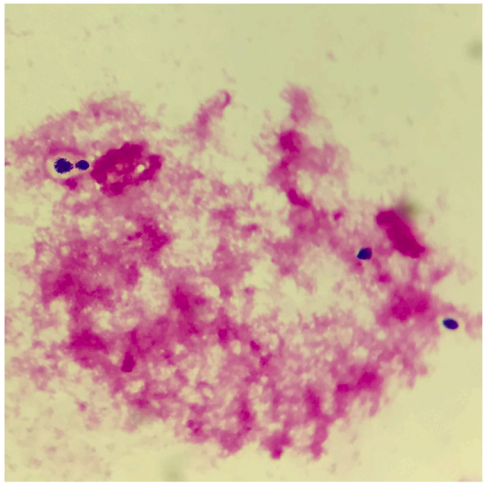

Fig. 3. Microscopic examination of the blood smear by Gram stain after 91.5 h of incubation into the BD BACTEC™ FX (Becton Dickinson) blood culture system.

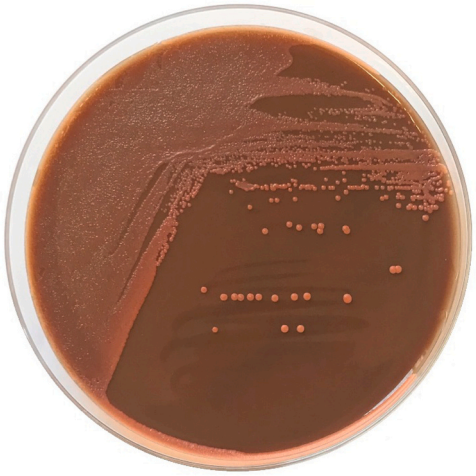

Fig. 4. Macroscopic appearance of *R. mucilaginosa* colonies in chocolate agar after 24 h of incubation at 35 ± 2 °C in 5% CO_2.

moist and slightly mucoid salmon-pink colonies (Fig. 4), which were then identified by MALDI-TOF MS on VITEK® MS (bioMérieux) as *R. mucilaginosa* (Fig. 5). Due to the expected resistance to most azoles and echinocandins, we decided not to perform antifungal susceptibility testing and the patient started empirical systemic antifungal therapy with liposomal amphotericin B 3 mg/kg/day.

In parallel, a diagnostic bronchial biopsy was also performed. The histopathological examination identified an adenosquamous carcinoma of the lung (PDL-1 positive, ALK negative and NGS negative), a rare subtype of non-small cell carcinoma of the lung.

The case was discussed in the multidisciplinary group of thoracic tumors where it was decided that, after completing the ongoing course of systemic antifungal therapy, the patient would initiate palliative targeted systemic therapy. However, although there was a considerable decrease in serum inflammatory markers, chest radiography performed after 10 and 14 days on liposomal amphotericin B showed that pleural effusion gradually progressed, resulting in left hemithorax white-out and requiring a new thoracentesis. At this point, he presented significant renal toxicity due to the systemic antifungal therapy, which led to the decision to cease it. Furthermore, he also developed a hospital-acquired pneumonia due to multidrug-resistant *Klebsiella pneumoniae* and worsened his medical state with the onset of heart failure, acidaemia and type 2 respiratory failure refractory to non-invasive ventilation. Due to the severity of the clinical condition, the presence of various comorbidities and the high level of care dependency, the patient was proposed for comfort measures only and he deceased 5 weeks after hospitalization.

Discussion

R. mucilaginosa, previously considered non-pathogenic, has been increasingly recognized as an emerging opportunistic pathogen. In fact, up to 40% of *R. mucilaginosa* infections have been described in immunosuppressed patients [2]. In this subset of patients, previous colonization offers a significant risk factor for the development of severe infection, which is associated with a high mortality rate [5,11]. In this particular case, although there is no way to corroborate it, we consider that our patient's respiratory tract was previously colonized by *R. mucilaginosa*, and that some host factors, such as advanced age and the presence of a previously undiagnosed lung

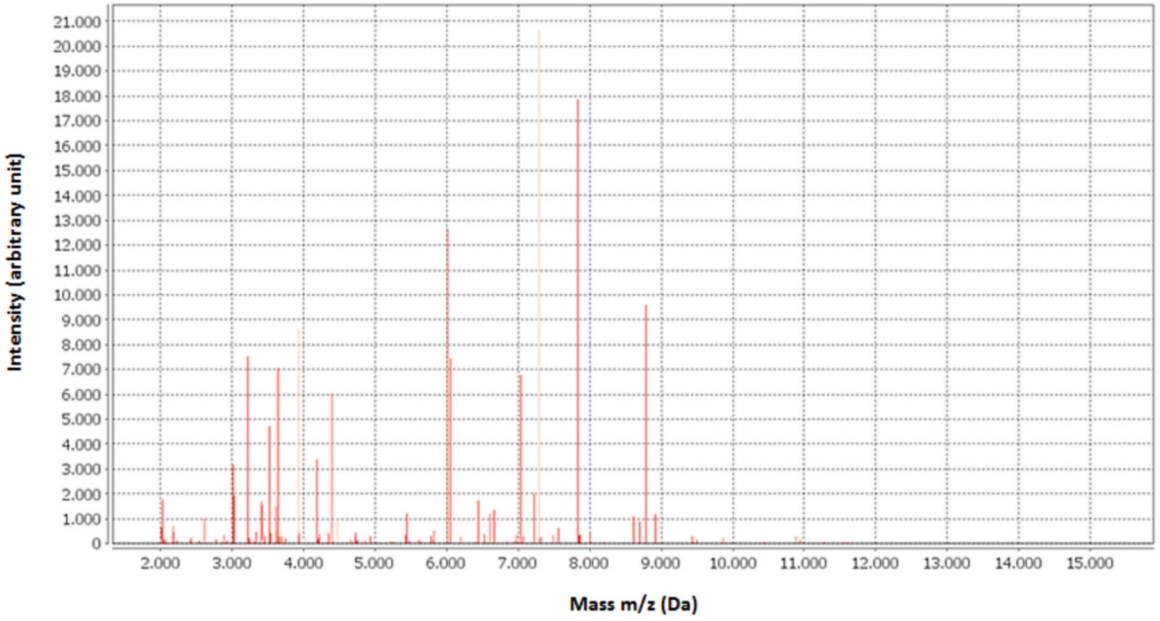

Fig. 5. Mass spectrum of *R. mucilaginosa* acquired by MALDI-TOF MS on VITEK® MS (bioMérieux), with an identification rate of 99.9%.

cancer, contributed to the onset of this infection. Moreover, since the patient had a large and locally advanced tumor mass, we believe that it may have broken the natural defense barriers of the respiratory tract and reduced blood flow to surrounding normal tissues, which, together, enabled the progression of the infectious process.

Although the antifungal resistance mechanisms are not widely recognized, in vitro susceptibility studies have shown that *R. mucilaginosa* is generally resistant to most azoles [1,11] and echinocandins, suggesting that these are intrinsic resistances; on the contrary, *R. mucilaginosa* is commonly susceptible to amphotericin B and flucytosine [1,2]. Even though amphotericin B is considered the first-line antifungal therapy [6,11], it is often associated with significant adverse effects and toxicity, especially nephrotoxicity. In the most severe cases, such as the formerly described for our patient, this can prevent the maintenance of systemic fungal therapy and even compromise clinical outcomes.

Conclusion

This case report illustrates that, despite the timely microbiological diagnosis and the unceasing communication between the laboratory and the clinic, infection due to emerging opportunistic pathogens such as *R. mucilaginosa* is, in fact, associated with a poor outcome.

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

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Consent

Written informed consent was obtained from a relative of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Ana Isabel Ferreira, Hugo Cruz and Ridhi Ranchor: Draft of the paper, critical review and approval of the final version of the paper. Bruno S. Silva, Joana Serôdio, Virgínia Lopes and Maria Helena Ramos: Critical review and approval of the final version of the paper.

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