



Note

Fungemia and interstitial lung compromise caused by *Malassezia sympodialis* in a pediatric patient



Clarisa Aguirre^a, Cristina Euliarte^a, Jorge Finquelievich^b,
María de los Ángeles Sosa^c, Gustavo Giusiano^{c,*}

^a Hospital Pediátrico Dr. Avelino Castelán, Resistencia, Argentina

^b Centro de Micología, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

^c Instituto de Medicina Regional, Facultad de Medicina, Universidad Nacional del Nordeste, Resistencia, Argentina

ARTICLE INFO

Article history:

Received 18 June 2013

Accepted 14 January 2014

Keywords:

Malassezia sympodialis

Interstitial lung compromise

Fungemia

Pediatric patient

ABSTRACT

A case of fungemia with interstitial lung compromise caused by *Malassezia sympodialis* is reported in an obese pediatric patient on long-term treatment with inhaled corticosteroids for asthma. The patient was hospitalized due to a post-surgical complication of appendicitis. The patient was treated with amphotericin B for 3 weeks, with good clinical evolution and subsequent negative cultures.

© 2013 Revista Iberoamericana de Micología. Published by Elsevier España, S.L.U. All rights reserved.

Fungemia con compromiso intersticial causada por *Malassezia sympodialis* en un paciente pediátrico

RESUMEN

Presentamos un caso de fungemia con compromiso intersticial causado por *Malassezia sympodialis* en un paciente pediátrico obeso, asmático y con tratamiento prolongado con corticosteroides inhalados, que fue hospitalizado debido a una complicación posquirúrgica de una apendicectomía. El paciente fue tratado con anfotericina B durante 3 semanas con buena evolución clínica y negativización de los cultivos subsecuentes.

© 2013 Revista Iberoamericana de Micología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Palabras clave:

Malassezia sympodialis

Compromiso pulmonar intersticial

Fungemia

Paciente pediátrico

Malassezia species are components of the normal microbiota of human skin and of many warm-blooded animals but, for still unknown reasons, these yeasts are able to change their saprophytic state and invade the *stratum corneum* as pathogens.^{2,3,10,11,15} These yeasts have been involved in the pathogenesis of a variety of dermatological disorders. Furthermore, in the immunocompromised host, including critically ill neonates, *Malassezia* may cause a number of invasive infections ranging from very mild to life-threatening ones.^{2,6,21}

We present a case of fungemia with interstitial lung compromise caused by *Malassezia* in a pediatric patient.

Case

A 7-year-old male patient afflicted with both obesity and moderate asthma, with long-period inhaled corticosteroids and under beta-2-agonist therapy, was hospitalized in July 2009 with acute abdomen. The diagnosis revealed phlegmonous appendicitis. Twenty-four hours after surgery, evidence of acute lower respiratory tract infection (ALRI) caused by a respiratory syncytial virus (RSV) was observed. RSV was detected by indirect immunofluorescence (IFI) of nasopharyngeal aspirate. As a complication, resulting from severe coughing, the patient showed diaphragm

* Corresponding author.

E-mail addresses: gustavogiusiano@yahoo.com.ar, ggiusiano@hotmail.com (G. Giusiano).

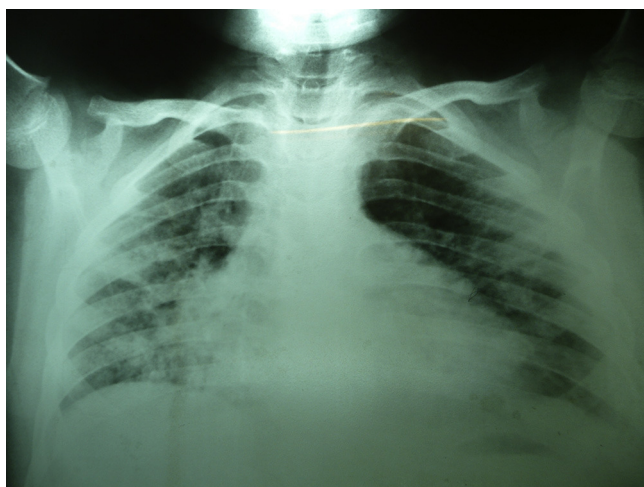


Fig. 1. Rx: diffuse bilateral alveolar-interstitial infiltrates. Diffuse reticulonodular patterns particularly in lower lobes. Cardiac area looks bigger than normal.

eventration. The patient underwent reoperation and was treated with ceftriaxone 100 mg/kg/day and metronidazole 30 mg/kg/day EV. Five days later, due to poor clinical and infection recovery, a new antibiotic scheme with imipenem 50 mg/kg/day and vancomycin 40 mg/kg/day was indicated. Prior to antibiotic scheme, samples drawn from conventional blood and urine cultures were negative.

In spite of the antibiotic treatment the patient developed moderate respiratory distress, high fever and low oxygen saturation level. Auscultation revealed decreased air entry, bilateral subcrepitant rales and disseminated sibilant bronchi. The abdomen was bloated, depressible upon deep palpation and the surgical wound showed no signs of phlogosis.

Laboratory studies showed the following counts: leukocytes ($21,900/\text{mm}^3$), 74% segmented, 1% band neutrophils, 1% eosinophils, 22% lymphocytes and 2% monocytes. The hemoglobin concentration was 11 mg/dl, platelet count $167,000/\text{mm}^3$, and the sedimentation rate was >120 mm. The X-ray showed diffuse bilateral alveolar-interstitial infiltrates (Fig. 1). The CT scan also revealed pleural effusion of 16 mm (Fig. 2).

After 24 days of hospitalization, due to moderate respiratory distress with manifestations consistent with multifocal pneumonia and oxygen requirement through nasal cannula, the patient was

admitted in ICU (intensive care unit). Imipenem and vancomycin intake was interrupted. Treatment with beta-2 agonist, hydrocortisone, ranitidine, ciprofloxacin was initiated intravenously.

Prior to indicating ciprofloxacin treatment, new samples were collected for conventional urine and blood cultures and catheter tip culture. To exclude fungal infection, blood culture was performed by lysis-centrifugation. In order to rule out other etiologies, samples of respiratory secretions were obtained serially and the PPD test was carried out. As broad-based budding yeasts were observed on stains in material obtained from lysis-centrifugation, a differential medium for *Malassezia* was included. Five days later, a lipophilic yeast growth was obtained; 48 h later *Malassezia sympodialis* was identified. Amphotericin B deoxycholate 1 mg/kg/day was indicated (accumulated dosage 20 mg/kg). No adverse effects with amphotericin B were observed.

Immunodeficiency markers were studied: HIV testing, protein electrophoresis, immunoglobulin dosage, lymphocyte subsets and complements were performed. These studies showed normal parameters. All other microbiological studies including PPD test were negative.

As a consequence of this finding, this fungus bearing was sought. *Malassezia sympodialis* was also isolated from the patient's skin. The patient's clinical history reported hyperpigmented lesions of the skin recorded since 2005, located mainly in the inguinal area, assumed as superficial mycoses and treated with topical antifungals but with poor response.

Seven days after starting antifungal treatment new samples for lysis-centrifugation blood culture were collected, which were negative. The patient's condition evolution was favorable; he responded to the 21-day antifungal treatment positively. Imaging studies were normal 3 months later (Fig. 4).

The patient was never under mechanical ventilation.

Blood culture and molecular identification

Blood cultures were performed on modified Dixon's medium at 32°C for 7 days.⁹ *Malassezia* isolate (IMR-M-735) was identified by PCR-RFLP.¹³

For DNA extraction, cellular lysis was performed by a boiling-thermic shock combination. One loopful of yeasts was suspended in 80 μl of distilled water and boiled for 5 min at 100°C , then frozen for 10 min at -70°C and finally boiled again for 5 min at 100°C . The

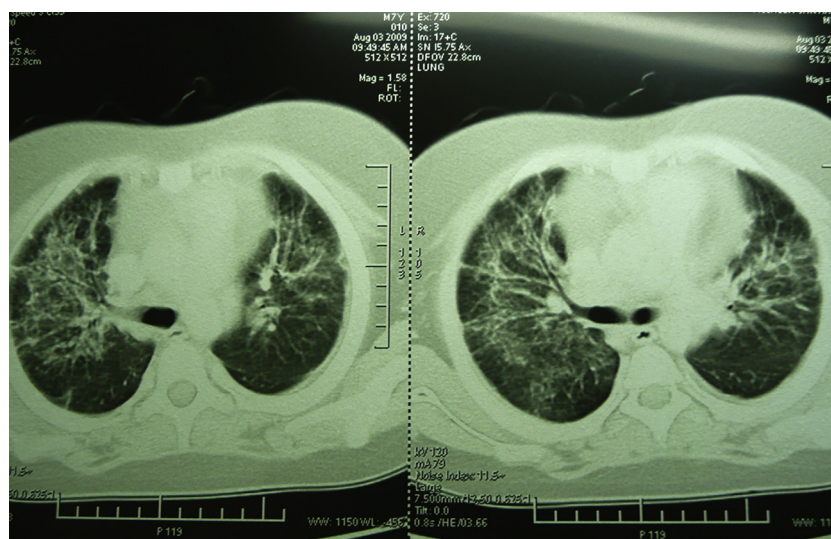


Fig. 2. CT scan: diffuse bilateral interstitial infiltrate, more evident in the right lung, is shown, as well as left pleural effusion of 16 mm. Regular diffuse septa thickening, areas of mild ground-glass attenuation and pericardial effusion are also shown.

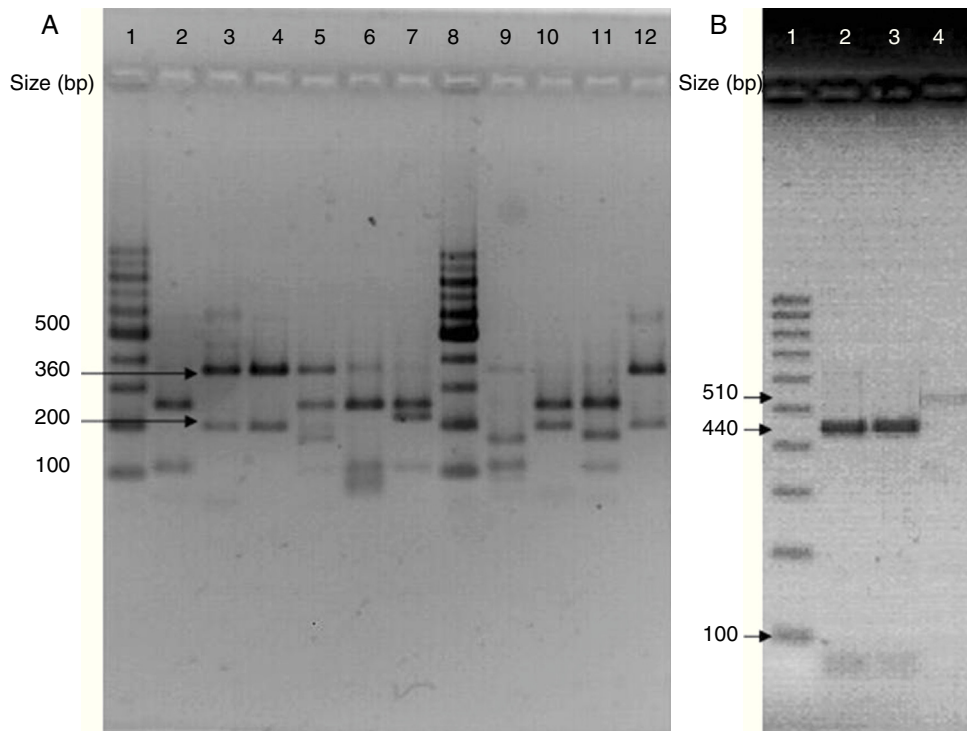


Fig. 3. (A) Visualization of 26S rDNA products after digestion with *Cfo* I (Lane 1–12: 100 bp ladder, CBS 7019 *M. furfur*, CBS 7222 *M. sympodialis*, CBS 9169 *M. dermatitis*, CBS 9558 *M. nana*, CBS 7956 *M. slooffiae*, CBS 10533 *M. pachydermatis*, 100 bp ladder, CBS 9725 *M. yamatoensis*, CBS 9432 *M. japonica*, CBS 7876 *M. obtusa*, and IMR-M-735). (B) Digestion with *Mbo* I (Lanes 1–4: 100 bp ladder, IMR-M-735, CBS 7222 *M. sympodialis* and CBS 9169 *M. dermatitis*).

crude DNA suspension (extract) was stored at -20°C , until its use for the analysis.

Amplification was performed by using generic primers, forward 5'-TAA CAA GGA TTC CCC TAG TA-3' and reverse 5'-ATT ACG CCA GCA TCC TAA G-3'. The primers successfully amplified the target part of 26S rDNA from all tested *Malassezia* strains, providing a single PCR product of the expected size (approximately 580 bp).¹³ Amplified DNA products were subjected to restriction fragment length polymorphism (RFLP) using *Cfo* I (Promega) in a first identification step. Whenever the restriction pattern produced by *M. sympodialis* or *Malassezia dermatitis* appeared, additional *Mbo* I (Fermentas) was used (Fig. 3).⁷ CBS 7019 *Malassezia furfur*, CBS 7222 *M. sympodialis*, CBS 9169 *M. dermatitis*, CBS 9558 *Malassezia nana*, CBS 9432 *Malassezia japonica*, CBS 10533 *Malassezia pachydermatis*,

CBS 9725 *Malassezia yamatoensis*, CBS 7876 *Malassezia obtusa* and CBS 7956 *Malassezia slooffiae* were included as reference strains.

Discussion

Malassezia colonizes the skin and scalp of healthy individuals. This colonization increases from adolescence, when the sebaceous glands increase their activity and the concentration of lipids in the skin raises.^{2,3,11,15} On the other hand, these opportunistic yeasts may cause invasive infections in immunocompromised patients.^{3–6,21,23} The first case reported of peritonitis caused by lipophilic yeast was in 1979 by Wallace.²² In our case, overweight and long-term use of inhaled corticosteroids, as well as surgical stress, were factors that allow our patient to be considered as an immunocompromised patient.

Malassezia infections are more common in warm climate regions.² Our city is located in a subtropical region with a high annual average temperature and humidity, which facilitate colonization by *Malassezia* in its inhabitants. As evidenced by outbreak investigations, the cutaneous commensal biota of the patient or healthcare workers is the usual source of the infecting organisms. This colonization by *M. sympodialis* could be one of the causes that may lead to subsequent infection. In addition, it has been reported that genetic factors may predispose to dermatological diseases related to *Malassezia*.^{2,10} Our patient might have some sort of susceptibility, taking into account his long-lasting history of mycoses (lasting for years). A history of prior cutaneous infections caused by the same fungus makes it almost impossible to think of a possible horizontal transmission of infection.

Malassezia sepsis and pneumonitis have been described in children and adults with central venous catheters and in patients with preceding surgery, such as in our case.^{6,17–19,21} *Malassezia* fungemia is usually associated with lipid-solution administration through venous catheters.^{1,5,8,12,18,20,21,23} But reports evaluating the

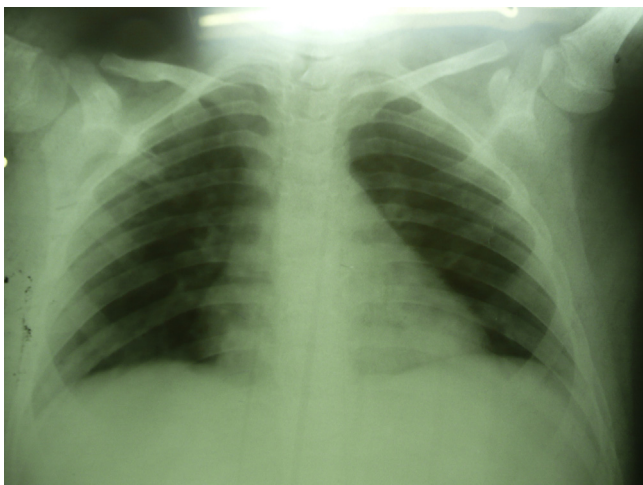


Fig. 4. Rx performed three months after the fungemia.

colonization of central venous catheters by *Malassezia* species have demonstrated a colonization rate of 0.7% in unselected hospitalized adults despite not receiving parenteral lipid nutrition.²¹ Our patient was not on intralipids but his skin colonization, the prolonged hospitalization, the broad-spectrum antibiotic treatment and the central venous catheter could have acted as risk factors, but not the parenteral nutrition. We agree with some authors who emphasize that colonization and the presence of a central line appear to be mandatory prerequisites for fungemia and that the administration of parenteral lipids may act as a facilitating factor.^{5,21}

Unfortunately, the catheter could not be cultured for the isolation of *Malassezia*, since the patient was referred exclusively for bacteriological studies. It was probably colonized by the same *M. sympodialis* found in the child's skin, but epidemiological typing to identify clonal relations of isolates was not made.

In critically ill patients, clinical status is difficult to determine. In infants hospitalized in intensive care units with central catheters, parenteral nutrition with lipids and broad spectrum antibiotics treatment, who develop fever, pulmonary infiltrates, leukocytosis, thrombocytopenia and negative conventional cultures for bacteria and fungus, *Malassezia* should be thought as one of the likely etiologic agents.^{1,5,18,20} However, individual cases lacking the typical risk factors have been reported.^{14,24} In adults, when fever is the only clinical symptom presented by the patient,⁵ and some may be asymptomatic, a differential diagnosis should be conducted to elucidate other opportunistic infections.²⁰ Systemic spread appears to be limited to the lungs.¹⁷ When dealing with critically ill patients, it is difficult to observe the pathological role of *Malassezia*, since several aggravating factors are combined.²³

Our patient developed high fever and respiratory distress with hypoxemia. Initially, we took into account the probable fungal etiology because of his history of prolonged hospitalization, broad-spectrum antibiotic therapy and both abdominal surgeries. On the other hand, microbiological studies confirmed viral infection with RSV and viral infections can favor or predispose the fungal infection. Subsequently, persistent fever and negative cultures suggested the performance of a differential culture for the isolation of *Malassezia*. Although the frequency of *Malassezia* infections is low, this highlights the importance of determining its likely etiology and preparing the laboratory appropriately for differential diagnosis, since this fungus can only be isolated in special culture media not used in laboratory routine.^{3,9}

Treatment includes catheter and lipid-solution administration removal and antifungal therapy.^{21,23} Our patient was treated with amphotericin B for 3 weeks, with good clinical response confirmed by subsequent negative cultures. Surely, the removal of central venous catheter in this case was a cornerstone of the treatment.¹⁶

The majority of invasive infections reported in literature have been associated with *M. furfur* and *M. pachydermatis*. The first is a lipophilic yeast commonly isolated from humans and the latter, *M. pachydermatis*, is a zoophilic yeast not lipo-dependant, occasionally isolated from human skin.^{6,17–19,21} This is a relevant case since we have not found any report of sepsis and interstitial lung compromise caused by *M. sympodialis*, one of the lipo-dependent species of the genus. Also, it is essential to take into account other predisposing factors than the sole presence of parenteral lipidic nutrition.

The revision of the genus *Malassezia* opened up new questions about the pathogenicity of *Malassezia* species. Further studies will be necessary to avoid subdiagnosis and to understand the relationship of these species with the environment and with associated pathologies.

References

- Alpert G, Bell LM, Campos JM. *Malassezia furfur* fungemia in infancy. Clin Pediatr. 1987;26:528–31.
- Ashbee HR, Evans EG. Immunology of diseases associated with *Malassezia* species. Clin Microbiol Rev. 2002;15:21–57.
- Batra R, Boekhout T, Guého E, Cabañez FJ, Dawson TL Jr, Gupta A. *Malassezia* Baillon, emerging clinical yeast. FEMS Yeast Res. 2005;5:1101–13.
- Chrysanthou E, Broberger U, Petrini B. *Malassezia pachydermatis* fungaemia in a neonatal intensive care unit. Acta Pediatr. 2001;90:323–7.
- Dankner WM, Spector SA, Fierer J, Davis CE. *Malassezia fungemia* in neonates and adults: complication of hyperalimentation. Rev Infect Dis. 1987;9:743–53.
- Gaitanis G, Magiatis P, Hantschke M, Bassukas I, Velegraki A. The *Malassezia* genus in skin and systemic diseases. Clin Microbiol Rev. 2012;25:106–41.
- Giusiano G, Sosa MA, Rojas F, Toma Vanacore S, Mangiaterra M. Prevalence of *Malassezia* species in pityriasis versicolor lesions in northeast Argentina. Rev Iberoam Micol. 2010;27:71–4.
- González-Cuevas A, Alayeto J, Juncosa T, García-Fructuoso MT, Moreno J, Latorre C. Sepsis neonatal por *Malassezia furfur*. Rev Iberoam Micol. 1999;16:157–60.
- Guillot J, Guého E, Lesourd M, Midgley G, Chévrier G, Dupont B. Identification of *Malassezia* species. A practical approach. J Mycol Med. 1996;6:103–10.
- Gupta AK, Batra R, Bluhm R, Boekhout T, Dawson T. Skin diseases associated with *Malassezia* species. J Am Acad Dermatol. 2004;51:785–98.
- Gupta AK, Kohli Y, Summerbell RC, Faergemann J. Quantitative culture of *Malassezia* species from different body sites of individuals with or without dermatoses. Med Mycol. 2001;39:243–51.
- Marimón JM, García-Arenzana JM, Gil A, Paisán L. Infección asociada a catéter por *Malassezia furfur* en un niño prematuro. Enf Inf Microbiol Clin. 1995;13:572.
- Mirhendi H, Makimura K, Zomorodian K, Yamada T, Sugita T, Yamaguchi H. A simple PCR-RFLP method for identification and differentiation of 11 *Malassezia* species. J Microbiol Methods. 2005;61:281–4.
- Myers JW, Smith RJ, Yuounberg G, Gutierrez C, Berk SL. Fungemia due to *Malassezia furfur* in patients without the usual risk factors. Clin Infect Dis. 1992;14:620–1.
- Nakabayashi A, Sei Y, Guillot J. Identification of *Malassezia* species isolated from patients with seborrheic dermatitis, atopic dermatitis, pityriasis versicolor and normal subjects. Med Mycol. 2000;38:337–41.
- O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, Lipsett PA, Masur H, Mermel LA, Pearson ML, Raad II, Randolph AG, Rupp ME, Saint S, Healthcare Infection Control Practices Advisory Committee (HICPAC). Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52:162–93.
- Redline RW, Dahms BB. *Malassezia* pulmonary vasculitis in an infant on long-term intralipid therapy. N Engl J Med. 1981;305:1395–8.
- Shek YH, Tucker MC, Viciano AL, Manz HJ, Connor DH. *Malassezia furfur* disseminated infection in premature infants. Am J Clin Pathol. 1989;92:595–603.
- Sizun J, Karangwa A, Giroux JD, Masure O, Simitzis AM, Alix D, et al. *Malassezia furfur*-related colonization and infection of central venous catheters. A prospective study in a pediatric intensive care unit. Intensive Care Med. 1994;20:496–9.
- Surmont I, Gavilanes A, Vandepitte J, Devlieger H, Eggermont E. *Malassezia furfur* fungaemia in infants receiving intravenous lipid emulsions. A rarity or just underestimated? Eur J Pediatr. 1989;148:435–8.
- Tragiannidis A, Bisping G, Koehler G, Groll AH, Minireview. *Malassezia* infections in immunocompromised patients. Mycoses. 2009;53:187–95.
- Wallace M, Bagnall H, Glen D, Averill S. Isolation of lipophilic yeast in sterile peritonitis. Lancet. 1979;2:956.
- Weiss SJ, Schoch PE, Cunha BA. *Malassezia furfur* fungemia associated with central venous catheter lipid emulsion infusion. Heart Lung. 1991;20:87–90.
- Wurst RM, Knospe WN. *Malassezia furfur* fungemia in a patient without the usual risk factors. Ann Intern Med. 1988;109:432–3.