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Unusual invasive candidiasis by *Candida glabrata* in a patient with systemic lupus erythematosus: Case report

Elenice Gomes Ferreira, Isabele Carrilho Jarros, Flávia Franco Veiga, Jakeline Luiz Corrêa, Raíssa Bocchi Pedroso, Melyssa Negri, Terezinha Inez Estivalet Svidzinski

ABSTRACT

Introduction: Systemic *Candida glabrata* infections have increased dramatically over the years. However, few studies have associated them with autoimmune diseases, such as systemic lupus erythematosus.

Case Report: We report the case of a patient with systemic lupus erythematosus, admitted with gastrointestinal complaints and oral bleeding. She had an unfavorable clinical evolution with renal failure, requiring hemodialysis and invasive ventilatory support, and fungal septic shock followed by death. The culture grown on the central venous catheter was negative for fungi, but the yeast *C. glabrata* was observed in all other cultures, as regarding a fungal infection (urine and blood) as for monitoring colonization (tongue and tracheal secretion). The high similarity between the isolated yeasts strongly suggested a common origin of the colonizing yeasts of the oral cavity and respiratory tract, as well as those involved in the infection.

Conclusion: This finding confirms that nosocomial infection by *C. glabrata* is a reality today and it should not be neglected; furthermore, the management of patients with systemic lupus erythematosus should be rethought because the imbalance of the organic response makes patients susceptible to infections, such as invasive candidiasis.

Keywords: Candidemia, *Candida glabrata*, Sepse, Systemic lupus erythematosus, Tongue coating

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INTRODUCTION

Invasive fungal infections caused by the *Candida* genus have been among the severe nosocomial infections of most concern in recent years. They are associated with high morbidity and mortality, especially in critically ill patients hospitalized in intensive care units (ICU) [1–3]. These infections have a significant economic impact due to their severity [4].

They are opportunistic infections generally associated with neutropenia, hematological malignancy, cancer, inflammatory bowel disease, diabetes mellitus, and chronic obstructive pulmonary disease [3]. Few studies have associated them with autoimmune diseases, such as systemic lupus erythematosus (SLE), and the published

case reports generally indicate *Candida albicans* as the cause [5]. Nonetheless, *C. glabrata* infections have increased dramatically over the years [6, 7]. According to Rodrigues et al. [8], the frequency of this species within the genus *Candida* is 14–15% and it has the highest mortality rate, which has been attributed to its resistance to antifungals [9]. Moreover, its ability to form biofilms has also been considered relevant in this context [8].

Interestingly, Pieralisi et al. [10] proposed that a tongue coating is the visual manifestation of a polymicrobial biofilm formed on a biotic surface (tongue) and that this condition is a potential gateway and a means of spreading microorganisms that cause fungal infections. This report presents a case of invasive candidiasis (IC) by *C. glabrata* in a patient with SLE, studied by isolating this species from blood, urine, the tongue coating, and endotracheal secretion.

CASE REPORT

A 58-year-old woman coming from another hospital, receiving oxygen therapy and using a central venous catheter (CVC) in the jugular and a bladder catheter, was admitted to the ICU of a public hospital in Maringá, Paraná, Brazil. She had a history of constipation for 15 days, with abdominal pain and distension. Her medical history included systemic lupus erythematosus (SLE). She received a clinical diagnosis of sepsis and the APACHE II score at admission was 38 points, representing approximately 85% risk of death.

In the first five days of hospitalization, her general condition worsened, and she exhibited mental confusion, groaning, delirium, drowsiness, and fever, requiring mechanical ventilation and infusion of vasoactive drugs. The patient progressed to renal failure (required hemodialysis) and received mechanical ventilation (MV) for 32 days, 16 days via an endotracheal tube (ETT) and the remaining days via a tracheostomy tube.

The patient's oral cavity had poor care and hygiene conditions, and it presented some alteration such as tongue coating, bleeding, partial tooth loss and lesions appeared on the lips during the endotracheal intubation (Figure 1).

Microbiological cultures were done from blood, urine, catheter tip, and urine. The results of these tests can be analyzed together with the evolution of laboratory markers for the clinical follow-up of the patient, the subsequent confirmation of candiduria and an increase in C-Reactive Protein (CRP), with a progressive decrease in the number of leukocytes, compatible to an IC picture (Figure 2).

This patient participated in a study that investigated the colonization of the upper tract by yeast in critically ill patients. Hence, in the mornings of the days corresponding to 48 and 96 hours of intubation, materials from the back of the tongue and tracheobronchial secretion were also collected for investigating culture of yeasts. The yeast identification, antifungal susceptibility test, and analysis of genetic similarity (RAPD) of the isolates were performed by following previously described methods [11, 12].

The culture of the CVC was negative for fungi but showed growth of the bacteria *Acinetobacter baumannii*. The yeast *C. glabrata* was found in all other cultures, both while monitoring the colonization (tongue and tracheal secretion) and diagnosing infections (urine and blood). Since yeasts were isolated from the bloodstream, hence antifungal treatment with fluconazole was carried out for four days. After identifying the species as *C. glabrata* and isolating it from urine, amphotericin B was administered for seven days. Despite this, the patient died after 37 days of hospitalization.

The analysis of genetic similarity by Random Amplification of Polymorphic DNA (RAPD) using the Primers ERIC-2 and OPE-3 and the phenogram generated by BIONUMERICS 7.6.3 revealed 100% of similarity between the isolated from the hemoculture and uroculture, indicating that the yeasts were identical, and these were considered related (80% similarity) in comparing to those from colonization (tongue and secretion) (Figure 3).

All isolates were susceptible, *in vitro*, to fluconazole and to amphotericin B, with minimal inhibitory concentration varying between (0.25 and 4 µg/mL) and (0.125 and 0.250 µg/mL), respectively.

DISCUSSION

This article reports a fatal case of IC by *C. glabrata*, which was isolated with high rates of similarity between the strains from the infection and colonization, in a patient who had SLE as the underlying disease.

The rate of hospitalization of SLE patients with severe infection has increased substantially, and the need for

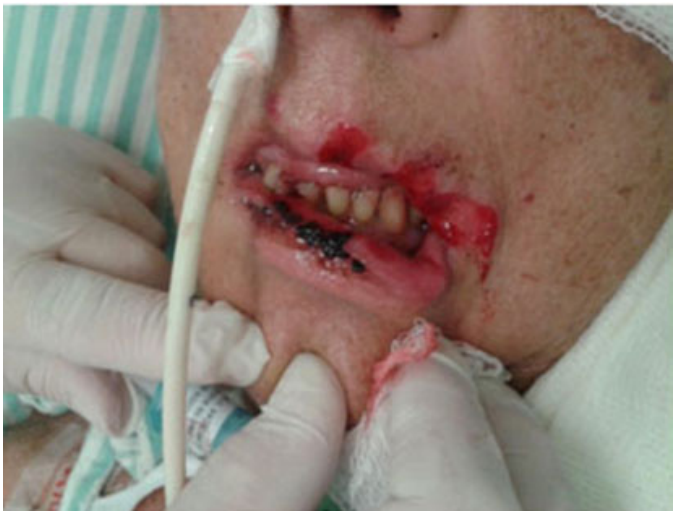

Figure 1: Ulcerative lesions on lips with active bleeding in the upper region.

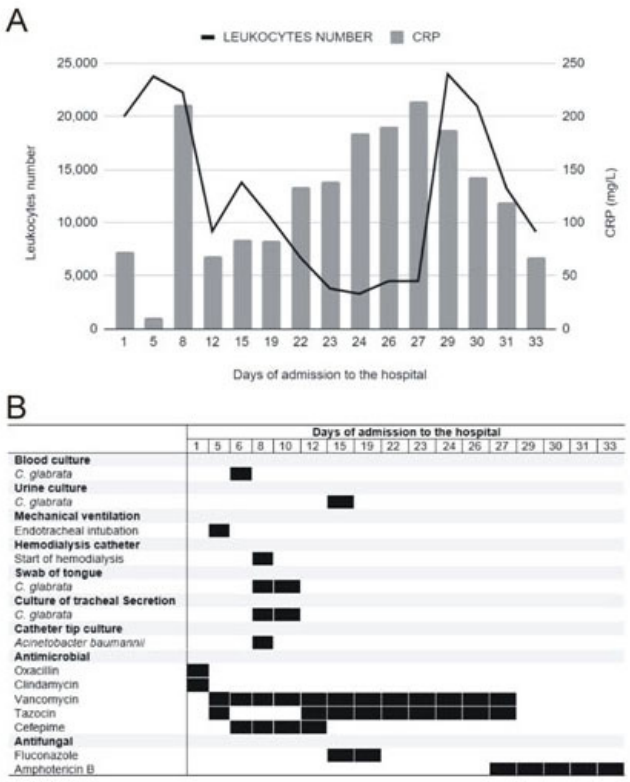

Figure 2: Representation of the main events that occurred during the patient's hospitalization.

Figure 3: UPGMA grouping phenogram of *Candida glabrata* isolated from tongue (H12A1 and H12A2) and endotracheal secretion (H12B1 and H12B2) in both (1 indicates 48 h and 2 = 96 h after intubation); H12Hemo = blood culture and H12Uro = urine culture. Primers ERIC-2 and OPE-3 were used and the phenogram was generated by BIONUMERICS 7.6.3.

intensive care reflects the patient's fragility [13]. The gastrointestinal complaints that motivated hospitalization were abdominal pain, chronic constipation, and epigastric pain. Despite being non-specific, these symptoms are among the most frequent in SLE [14, 15].

Systemic lupus erythematosus is a multisystem autoimmune disease with a heterogeneous and complex presentation. It has been associated with a host–microbiome interaction [16]. A microbiome is composed of large microbial communities that colonize the human organism and are essential to ensure several immunological modulating factors. Dysbiosis, i.e., an imbalance of this microbiota, may cause dysregulation of the immune system [17]. Although the genus *Candida* naturally belongs to the microbiota of the oral and gastrointestinal cavities, the infection may be preceded by an increase in the proliferation of these microorganisms, which may contribute to their translocation into the bloodstream, giving rise to candidemia [18]. Moreover, studies indicate that patients with SLE have a lower diversity of the intestinal microbiome, resulting in general patterns of dysbiosis, which seem to contribute to the immune pathogenesis of nephritis [19]; this may justify the renal failure of the patient on day 8 after admission.

This patient had bleeding in the oral cavity on admission, which may be evoluted to lesions on the lips during the ETT use, in fact oral ulceration during hospitalization occurs in 20–50% of patients with SLE [20], when associated with inadequate oral hygiene conditions. These are predisposing factors of local dysbiosis, which can make the tongue more susceptible to colonization by yeast [21]. Therefore, it is possible that a tongue coating, i.e., the organization of this yeast in the form of a biofilm [10], confers virulence onto *C. glabrata*, with a sufficient risk factor for the translocation of this microorganism to lower airways. Interestingly, *C. glabrata* isolated from the tongue coating showed 100% similarity to the yeast isolated from the tracheobronchial secretion.

Intensive Care Unit admission exposes the patient to multiple risk factors for candidemia or IC, such as long-term use of broad-spectrum antibiotics, CVC, parenteral nutrition, length of hospital stay, mechanical ventilation for more than seven days, hemodialysis, and immunocompromising conditions [1–3].

The patient was exposed to these factors mainly because of ventilatory support, which may have favored the colonization by yeasts; *C. glabrata* was observed in tracheobronchial secretion after 48 hours of ETT use. Studies show that mechanically ventilated critical patients soon experience dysbiosis in the respiratory tract [22]. The prevalence of *Candida* spp. in tracheobronchial secretions is well known. They have a high capacity to form biofilms in ETT [11] and have been associated with severe clinical outcomes [23, 24].

A laboratory dosage of CRP is a useful marker for sepsis, with its rapid increase indicating infection. High CRP and a high number of circulating leukocytes indicate bacterial infection, which initially responded to broad-spectrum antibiotic therapy with escalation. However, these markers soon rose again, possibly due to candidemia.

Therefore, on day 12, treatment with antifungal agents was initiated due to the positive result of blood culture for yeasts, with fluconazole being administered for four days. The subsequent confirmation of candiduria

caused by this same species and an increase in CRP, with a progressive decrease in the number of leukocytes, indicated that it was a case of IC, and treatment with amphotericin B was started. This strategy translated into changes in the laboratory profile with an increase in the number of leukocytes and consequent decrease in CRP. However, the outcome was unfavorable, with the patient dying on day 37.

Although it is very difficult to define the origin of such infectious process, the non-observation of yeast in the CVC, the main source of yeast in IC, combined with the high similarity among the isolated yeasts strongly suggest a common origin of the yeasts colonizing the oral cavity and respiratory tract, and those involved in the infection.

CONCLUSION

This case report shows that nosocomial infection by *C. glabrata i*s a reality today; hence, it should not be neglected. It also shows that the management of patients with SLE must consider IC as a risk factor because regardless of the location of the infection origin, the patient exhibits an imbalance in the organic response and is hence vulnerable to severe infections.

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Author Contributions

Elenice Gomes Ferreira – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Isabele Carrilho Jarros – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Flávia Franco Veiga – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jakeline Luiz Corrêa – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Melyssa Negri – Conception of the work, Design of the work, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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