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Case report

Candida glabrata meningitis and endocarditis: a late severe complication of candidemia

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SUMMARY

We report an unusual case of *Candida glabrata* meningitis and endocarditis in a young Caucasian woman with a prosthetic aortic valve and suffering from a dissecting thoraco-abdominal aortic aneurysm. *C. glabrata* was isolated from culture of the cerebrospinal fluid. Candida infection of the central nervous system is an uncommon manifestation of disseminated infection due to *Candida* species. Our case report also highlights the intrinsic resistance of *C. glabrata* to azoles.

1. Introduction

Candida glabrata, formerly known as *Torulopsis glabrata*, is a monomorphic yeast that commonly colonizes the gastrointestinal and genitourinary tracts. For many years *C. glabrata* was considered a relatively non-pathogenic saprophyte of the normal flora of healthy individuals and was not readily associated with serious infection in humans. However, following the widespread and ever-increasing use of immunosuppressive therapies together with broad-spectrum antibiotic treatment, the frequency of mucosal and systemic infections caused by *C. glabrata* has increased significantly in hospitalized patients worldwide. *C. glabrata* currently represents the second most common cause of fungal infections of the bloodstream, oropharynx, and urinary tract after *Candida albicans*.[1]

Risk factors include antibacterial agents, steroids, malnutrition, diabetes mellitus, intravenous catheters, and immunosuppression. Differently from *C. albicans*, *C. glabrata* appears to have evolved a stealth strategy based on evasion of the immune response and persistence without causing severe damage. Accidental or iatrogenic breaches of natural barriers via trauma, catheters, surgery, or parenteral nutrition appear to be the preferred routes by which *C. glabrata* reaches the bloodstream and invades tissues.[2] Upon expression of adhesins, *C. glabrata* is able to attach and colonize host tissues as well as abiotic surfaces, where it develops as multilayered biofilm structures. Biofilm development contributes to increased resistance to antifungal agents and results in persistent infection. Persistent infections are facilitated by the ability of *C. glabrata* to survive and replicate inside the phagosome of phagocytes, similar to *Mycobacterium spp.*[3]

2. Case report

We report the case of a 42-year-old woman admitted to the Institute of Infectious Diseases, "Paolo Giaccone" University Polyclinic in Palermo because of continuous-remittent fever (maximum body temperature 38.5 °C), headache for 15 days, and confusion, disorientation, diplopia, and vomiting for a few hours.

She had a history of an extended, large (67 mm × 25 mm), and dissecting aneurysm (Stanford type A) of the thoraco-abdominal aorta (involving the ascending portion up to the initial section of the left iliac) and had undergone replacement of the ascending aorta and aortic valve 4 months earlier. At that time a febrile increase in temperature on the 10th postoperative day led to treatment with broad-spectrum antimicrobials and her condition improved. Two sets of blood cultures were drawn and yielded *C. glabrata*. Oral fluconazole was administered, as suggested by in

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vitro susceptibility testing, but the treatment was discontinued after 10 days.

At the current admission, the patient was febrile (body temperature 37.7 °C), with an oxygen saturation of 96% by pulse oximetry while breathing room air, blood pressure of 100/60 mmHg, and a heart rate of 73 bpm. On physical examination, she showed signs of meningeal irritation, mild confusion, and diplopia. On cardiac auscultation a 3/6 systolic murmur all over the precordium and a metallic click sound created by the mechanical aortic valve prosthesis were heard.

Laboratory signs underlined a neutrophilic leukocytosis (white blood cell count (WBC) 26.75×10^9/l with 89.2% neutrophils), mild anaemia (haemoglobin 11.1 g/dl), and progressive renal failure (uremia 158 mg/dl, creatinine 2.3 mg/dl, and glomerular filtration rate (GFR) 25 ml/min/1.73 m^2). Lactate dehydrogenase was 1016 IU/l, D-dimer 3445 ng/ml, C-reactive protein 15.49 mg/dl, international normalized ratio (INR) 1.52, and activated partial thromboplastin time 25.0 s. Other laboratory parameters were within the normal range.

An electrocardiogram showed tachycardia, left bundle branch block, and a first-degree atrioventricular block. A brain computed tomography (CT) scan was performed and was negative. A chest CT scan revealed right basal thickening. An abdominal CT scan showed a thoracic and abdominal aortic aneurysm (5.6 cm in size). Transoesophageal echocardiography (TEE) showed a vegetation of the prosthetic aortic valve, characterized by a thickening and irregularity of the contour of the sewing ring. TEE also showed a dissecting thoraco-abdominal aneurysm. Three sets of blood cultures were collected on the day of admission and empirical antimicrobial therapy was started immediately with intravenous (IV) daptomycin 500 mg daily, IV rifampin 300 mg every 12 h, and IV gentamicin 80 mg every 8 h for a prosthetic valve infection. The initial empirical therapy was given for a total treatment duration of 10 days.

Seven days after the beginning of treatment, the persistence of fever, preceded by chills and headache, prompted a lumbar puncture; the physicochemical results revealed turbid cerebrospinal fluid (CSF) containing WBC 3.0×10^6/l with 60% neutrophils and 40% lymphocytes, glucose 40 mg/dl (serum glucose 130 mg/dl), and protein 90 mg/dl. Yeasts were not observed on direct microscopy of the CSF. Blood cultures, urine cultures, and culture of the catheter tip were all negative. Multiple blood cultures were negative for bacteria and fungi.

C. glabrata was isolated from the CSF culture. To assess the sensitivity to antifungals, a broth colorimetric microdilution method was used (Fungifast AFG) that allows susceptibility testing to five antifungals. The minimum inhibitory concentrations for amphotericin, fluconazole, itraconazole, and voriconazole were 0.5, 8, 0.125, and 1 μg/ml, respectively. IV therapy was started with liposomal amphotericin B (3 mg/kg/daily) for 4 weeks and then oral fluconazole 400 mg daily was administered. The patient responded well to therapy and her temperature normalized on the third day of liposomal amphotericin B. A re-culture of the sample was carried out, confirming the isolation of *C. glabrata*. The rapid defervescence of the patient after initiation of antifungal therapy attested to the possible role of *C. glabrata* in the pathogenesis. The patient was discharged and treatment was continued with oral fluconazole.

A lumbar puncture after treatment was not performed due to the improved clinical condition of the patient. Thirteen months after admission a transthoracic echocardiogram showed no residual vegetation, while the patient was in good condition. The diplopia had also resolved. Lifelong therapy with oral fluconazole is expected to be necessary.

3. Discussion

Candida infection of the central nervous system (CNS) is an uncommon manifestation of disseminated infection due to *Candida* species. It may arise in the context of systemic candidiasis, as a complication of a neurosurgical procedure (especially after CSF shunt placement), or as an isolated chronic infection. Clinicopathological forms of Candida infection of the CNS include meningitis and diffuse cerebritis with microabscesses, parenchymal abscesses, and vasculitis. Meningitis is the most common presentation. Most cases are due to *C. albicans*, with few reports of *C. glabrata* and other species causing infection.[4]

Risk factors for the development of CNS candidiasis are immunosuppression, previous treatment with antibiotics or corticosteroids, preterm birth, recent abdominal surgery, neurosurgery and insertion of CSF derivative systems, intravenous drug use, and intravascular catheters. Candida meningitis is due to haematogenous spread from a distant focus, as has been described in previous studies. In our case the starting focus of infection was presumed to be the vegetative endocarditis on the prosthetic valve. Both the endocarditis and meningitis can be considered late consequences of the candidemia revealed during the previous admission. Insufficient treatment with antifungals may have allowed the yeast to structure a biofilm over the prosthetic surface. From a clinical perspective, the most important feature of Candida biofilms is their role in increasing tolerance to conventional antifungal therapy. Biofilms of non-albicans *Candida* species have also been shown to exhibit reduced antifungal susceptibility.[5]

C. glabrata may be intermediately resistant to all azoles, and about 20% of strains develop resistance during therapy and prophylaxis with fluconazole. Fortunately, in our case the strain isolated from the CSF culture was fully susceptible in vitro. Intravenous amphotericin B was used successfully as first-line treatment, as recommended by the Infectious Diseases Society of America 2009 guidelines for the treatment of systemic candidiasis. Regular follow-up and chronic fungal suppression with oral fluconazole are expected to be necessary lifelong to prevent relapses of the infection.

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