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Case Report

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Emergence of Azole Resistant Candida Glabrata as An Important Cause of Hospital Acquired Infection: Its Risk Factors and Impact

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Abstract

Candida spp. colonizes the human host and coexist with members of human microbiome. Candida glabrata are aggressive pathogen, have many virulence factors that lead to serious recurrent candidiasis. Their ability to form complex biofilm, inability to form hyphae and inability to secrete hydrolase lead to antifungal resistance. Candidemia is the fourth most common bloodstream infection [1]. Candidemia remains a major source of mortality and morbidity. Mortality among patients with invasive candidiasis is as high as 40%, even when patients receive antifungal therapy [2]. More than 90% of invasive diseases are caused by the 5 most common Candida spp. C. albicans, C. glabrata, C. tropicalis, C. parapsilosis and C. krusei [3]. The distribution of Candida species has been changing over the last decade, with a decrease in the proportion of C. albicans and an increase in C. glabrata and C. parapsilosis. More than 50% of blood stream infections are caused by non-albicans Candida [4,2]. The largest proportional increase in the USA is in C. glabrata, which accounts for one third or more of all candidemia isolates [5-7]. C. glabrata are associated with high mortality. Candida glabrata develops acquired resistance following exposure to antifungal agents [8]. 50% of C. glabrata are resistant to fluconazole [9,10]. Furthermore, 9% of C. glabrata that are resistant to fluconazole are also resistant to the echinocandins [8,11].

Case history

A 32-yr. old female with a past medical history of cholecystectomy with common bile duct injury treated with hepaticojejunostomy reconstruction, colostomy, incisional hernia, small bowel obstruction presented with a chronic non-healing enterocutaneous fistula and failure to thrive. The patient had constant 10/10 abdominal pain in the left lower quadrant. Eating aggravated her pain and discharge from the fistula.

Figure 1: Figure showing a fistula in the left lower abdomen.

She had significant weight loss. She denied any history of recurrent fever, night sweats, diarrhea or melena. On examination she was cachectic and had left lower quadrant tenderness.

Laboratory investigations were significant for anemia of chronic disease (Hb 12.6 g/dL, hematocrit 36.5%, ferritin 444 ng/ml, serum Iron 25 mcg/dL, TIBC 188 mcg/dL, transferrin 135 mg/dL) and malnutrition (prealbumin 4.8 mg/dL). Anti-HIV 1 and HIV 2 antibody, HBsAg, and anti HCV antibody were non-reactive. PPD test was negative. Rest of the laboratory test were:

WBC count of 11300 / cmm, adequate platelets, sodium of 134 mEq/L, potassium of 3.2 mEq/L, bicarbonate of 29 mEq/L.

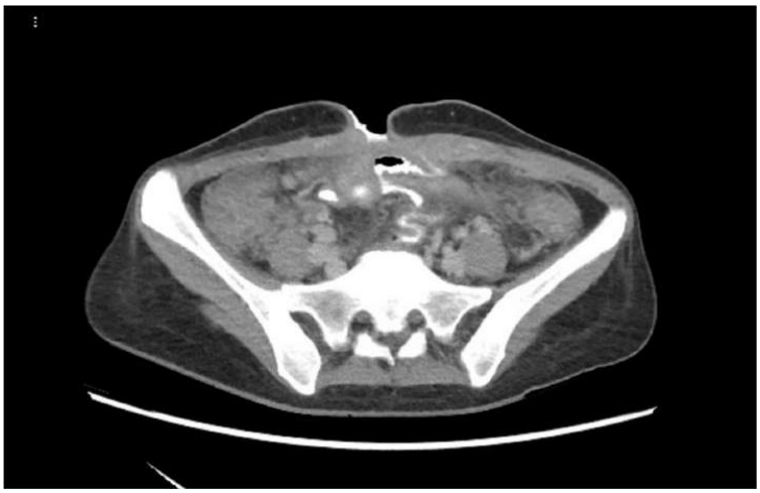

Figure 2: Linear hyperattenuating area extending from the structures inside to the anterior abdominal wall/median surgical wound consistent with enterocutaneous fistula evident.

CT scan abdomen and pelvis was significant for coloproctitis and a fistula from small bowel through the anterior abdominal wall. The patient was initially managed conservatively with total parenteral nutrition (TPN) and several ACELL and VAC (Vacuum assisted closure) applications. Her electrolytes were monitored and replaced. A midline was placed for TPN. During the hospital course she developed three episodes of infection ESBL E. coli UTI (Extended spectrum beta lactamase resistant E. coli urinary tract infection), ESBL. E. coli Pneumonia and Enterococcus UTI for which she was treated with ertapenem and vancomycin respectively. Fistulogram confirmed presence of two fistulas (figure 3) involving both jejunum and colon. The patient continued to have high fistula output and emesis with diet thus predisposing her to fluid electrolyte imbalance and malnutrition (low prealbumin). She also had recurrent episodes of bowel obstruction. The midline was removed with every fever spike but had to be replaced to continue her nutrition. Chronic intestinal failure secondary to short bowel syndrome (because of history of recurrent abdominal surgery leading to dense intraabdominal adhesions) was high in the differential which was thought to hinder her recovery. Gastroenterologist was consulted. Stool calprotectin was 446, thus increasing her likelihood of Crohn's disease. Colonoscopy could not be done as patient had recurrent infections.

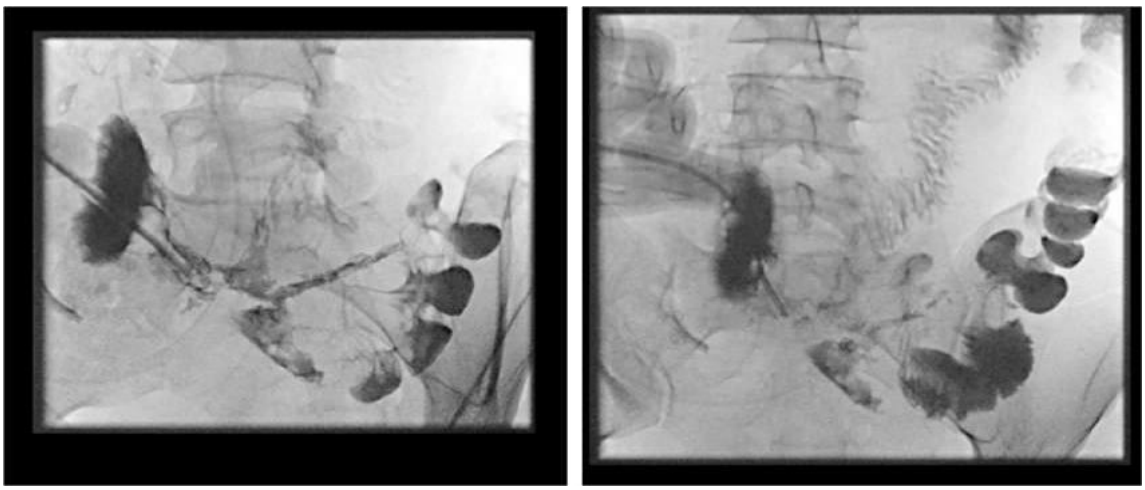

Figure 3: Fistulogram showing enterocutaneous fistula involving both jejunum and colon.

On hospital day 57 patient had a fever spike of 104, tachycardia, and hypotension. Preliminary blood culture was positive for yeast. Patient was started empirically on caspofungin. Ophthalmology was consulted to rule out

endophthalmitis. Final blood culture showed Candida glabrata. Caspofungin was continued, repeated surveillance cultures were negative and antifungals were continued for 14 days. Patient had a repeat C. glabrata fungemia which was managed similarly as before. Patient improved with treatment and midline was placed to start TPN. Her discharge improved with regular follow up and VAC therapy and ACELL treatment. She needed to change her colostomy bag every three days and starting tolerating enteral nutrition. She gained 20 pounds and her prealbumin improved to 19. She was transferred to a tertiary care center for surgery of her complex fistula.

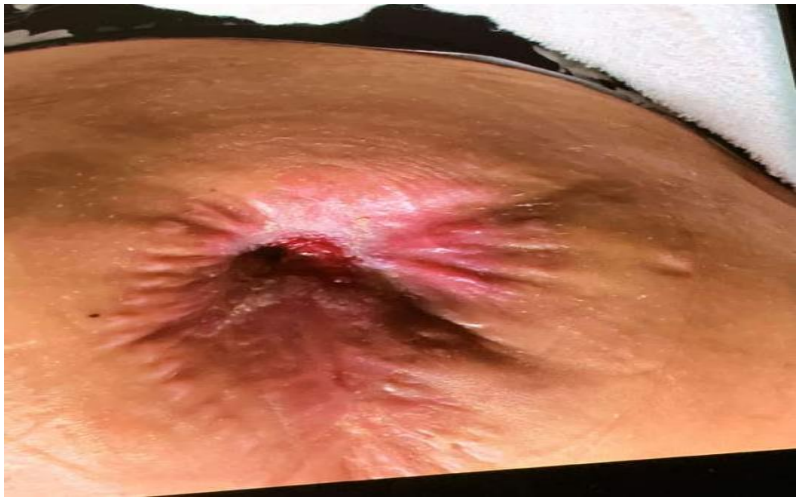

Figure 4: Figure showing the fistula after VAC and multiple ACELL treatment.

Discussion

C. glabrata lacks the ability to form hyphae and pseudo hyphae. Hence initially it was classified under a separate genus Torulopsis and was later accepted in the genus Candida.

C. glabrata fungemia is most often seen in older adults with low immunity or in patients with cancer. There has also been incidence of hospital acquired infections in preterm newborns [12].

The spectrum of infections ranges from non-nosocomial vulvovaginal infections (complicated vulvovaginal candidiasis and recurrent vulvovaginal candidiasis) to severe, life-threatening invasive candidiasis. C. glabrata has emerged as an important hospital-acquired pathogen with a mortality rate of 49% [12]. Few decades ago, it was considered as a non-pathogenic saprophyte of the normal flora of healthy individuals. However, following the widespread and increased use of immunosuppressive therapy together with broad–spectrum antibiotic and antifungal therapies, the frequency of mucosal and systemic infections caused by C. glabrata has grown significantly. No unique clinical features are associated with C. glabrata. Often, the only manifestation is persistent fever in a patient whose condition is deteriorating and who is unresponsive to antimicrobial agents and has negative blood cultures.

C. glabrata secrete phospholipases, lipases, and hemolysins that contribute towards an extreme aggressiveness resulting in a low therapeutic response and serious recurrent candidiasis [12]. But pathogenicity was mainly attributed to moderate production of biofilm. They have the ability to form a compact biofilm structure in different multilayers with proteins, carbohydrates (e.g., β-1,3 glucans), and ergosterol in their matrixes. The biofilms help them to adhere to the surface to catheters. So central venous catheter removal with negative daily cultures are of great importance in treating these infections. Biofilms also help them to disseminate which leads to secondary metastatic infection in kidney, lungs, spleen, liver, eyes, bones. These result in persistent fungaemia [12].

Multiple studies have been done to identify the risk factors for nosocomial C. glabrata blood stream infection. Hospital environment favors infection owning to interplay of carriage via the health care personnel hands which favor colonization and presence of risk factors [13].

Clearly identified risk factors are: length of stay, use of total parenteral nutrition, broad spectrum antibiotics, central lines, abdominal surgery with particular risk among patients who have anastomotic leakage or have had repeat laparotomies, acute necrotizing pancreatitis, hematologic malignant disease, solid-organ transplantation, solid-organ tumors, hemodialysis, glucocorticoid use or chemotherapy for cancer, candida colonization, particularly if multifocal, mechanical ventilation > 48 hrs, multiple blood transfusions, APACHE II score of >10 [2].

Single risk factor is unlikely to predict invasive candidiasis, since all of these are very common in the hospital setting. Paphitou et al. [14] performed a retrospective review of all surgical ICU patients who stayed 4 days or longer over a year in a unit in the United States. Their findings showed that patients that had a combination of diabetes mellitus, new onset hemodialysis, use of total parenteral nutrition, and broad-spectrum antibiotics had a rate of invasive candidiasis of 16%, compared with 5% of patients that did not have the combination. Another study by Malani et al. [15] showed that the mean age ⩾ 60 years old, use of broad-spectrum antibiotics were present in 86%, use of central intravenous catheters in 77%, stay in an ICU in 48%, renal insufficiency in 46% and receipt of parenteral nutrition in 45%.

Risk assessment strategies are thus used which increase pretest likelihood of candidiasis. When a single uncommon risk factor, or a combination of two or more common risk factors are present there is a reasonable chance of developing the disease. It also demonstrated the rapidity with which these risk factors were achieved decided the type of candidiasis. It was day 8 in the no colonization group and LC groups and day 4 in the invasive candidiasis group. Risk factors can be divided into early and late. Early risk factors present at admission or at day 3 like total parenteral nutrition or central catheter previous SICU admissions or surgical procedures. Late risk factors hemodialysis, persistent leukocytosis, fever or hypothermia while taking antibiotics, use of broad-spectrum antibiotics, solid tumor, and lack of nutritional support. Central catheter for more than 72 hours and use of mechanical ventilation on day 4 were significant predictors. The NEMIS Prospective Multicenter Study a prospective multicenter cohort study showed that independent risk factors like abdominal surgery was associated with higher risk (7.1). Vancomycin, or an antibiotic agent with activity against anaerobic organisms (including combinations of imipenem, metronidazole, clindamycin, and the extended-spectrum penicillins/β-lactamase-inhibitor drugs, such as ticarcillin/clavulanate, piperacillin/tazobactam, and ampicillin/sulbactam) were associated with increased risk.

Sensitivity of blood culture ranges from 21 to 71% (11). Cultures may establish a diagnosis during the period when candida resides in the bloodstream, cultures of blood obtained from patients with deep seated infections often yield negative results. Candida mannan antigens and anti mannan antibodies and β-d-glucan are the primary surrogate markers for invasive candidiasis (16–18). Nguyen et al. reported that an in-house PCR assay had a sensitivity of 89% [19]. Most of these tests are limited by low specificity. Because of the high mortality of invasive candidiasis, it's imperative to identify high risk patients which increase the pretest likelihood of disease in that population.

In terms of treatment echinocandin was associated with better survival rates and greater clinical success in invasive candidiasis when compared to triazoles or amphotericin B [20]. Triazoles are preferred in the treatment of meningitis, endophthalmitis, and urinary tract as echinocandins cannot penetrate the barriers. Catheter Removal at any time point was associated with a reduction in mortality and higher clinical success rates [21-23]. As per 2016 Update by the Infectious Diseases Society of America choice of empiric antifungal therapy is decided on the basis of neutropenic vs non neutropenic patient. An echinocandin is the initial antifungal therapy for non neutropenic critically ill patient. Fluconazole, intravenous or oral, an acceptable alternative to an echinocandin as initial therapy in selected patients who are not critically ill. Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant isolates. Transition from an echinocandin to fluconazole (usually within 5-7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (e.g. C. albicans), and have negative repeat blood cultures following initiation of antifungal therapy. In neutropenic catheter removal is decided on an individual basis, ophthalmological evaluation is minimal during neutropenia, hence it performed within the first week after recovery from neutropenia.

Prophylaxis has also been tested in multiple trials. It has been shown that fluconazole prophylaxis in patients with recurrent abdominal surgery, recurrent gastrointestinal perforations or anastomotic leakage reduced the incidence of candidemia by approximately 50% [7]. But this strategy has not been shown to improve survival [24,25]. The major challenge is to select individual patients or subgroups that will benefit most from prophylaxis in order to limit the number needed to treat and to avoid emergence of resistance.

Conclusion

Candida glabrata are important cause of Hospital Acquired Infection in our time. Spectrum of manifestation can range from low grade fever to fulminant shock. Unlike Candida albicans they are associated with higher mortality and are usually resistant to azoles. MIC (minimum inhibitory concentration) is high for Amphotericin B as well. Resistance to echinocandins have also been reported. But this organism has not been extensively studied in terms of virulence, pathogenesis and host defense factors. Through our report we urge readers for the above. Also, the most important risk factor for the emergence of this species is use of broad-spectrum antibiotic. Hence this underlines the urgency of antibiotic stewardship to prevent emergence of azole resistant non albicans candida.

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Conflict of Interest

The author would like to report that she has no conflict of interest in the above work.

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