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Study of morphological characteristics, pathogenicity and drug resistance of *Candida glabrata* as increasing opportunistic yeast

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ABSTRACT

Recent decades can be a milestone in the advancement of medical science with the help of modern tools and drugs including use of antibiotics, corticosteroids, immunosuppressive drugs, different types of transplantation, etc. Furthermore, with industrialization of human society and change of their lifestyle, some human diseases have prevailed, such as increasing in mental illness, AIDS, diabetes, Lupus Erythematous, etc. Besides all of mentioned cases, the way has been opened to expanse of opportunistic infections and the emergence of less common cases. Candidiasis is a common fungal disease that in recent decades has been encountered with changes of type of etiologic agent and patterns of drug resistance. Candida glabrata can be accounted as emerging species with specific changes, therefore it is necessary to know this organism and make efforts to eliminate it. In this paper we try to introduce some of the most common disease of C. glabrata, its appearance changes, and also some of the most prominent causes of its disease increasing.

Key words: *Candida glabrata*, Candidiasis, Non-albicans *Candida*.

INTRODUCTION

Cryptococcus glabrata was identified in 1917 by Anderson. In 1938 renamed to *Torulopsis glabrata* [1]. In 1962, *C. glabrata* was introduced as a non-pathogen saprophyte and as normal flora in healthy individuals [2]. It produces small, smooth, white and pale colonies on Sabouraud-Dextrose Agar medium, which are seen on direct experiment like yeasts without hyphae, pseudohyphae, chlamidoconidia and blastoconidia of ovoid form. In Corn Meal Agar medium containing Tween 80, yeast cells with quite ovoid buds can be seen. *C. glabrata* is one of the most common

species which can be found on the human body surface and it is removed occasionally from the skin and urine [3]. It is known as one of the opportunistic species of human surface and visceral fungal diseases [4].

Common diseases of *C. glabrata*

1 - Diseases related to the mouth and esophagus

C. glabrata infection usually appears as the thrush [5]. In 2005 with study on 110 patients suffering from thrush, 24% of cases were detected with *C. glabrata*, while in 1980 this case had been reported nearly 4.1% [6]. Although in recent years *Candida albicans* has been introduced as the main factor causing the Candida infection but the incidence of the infection has been reported to increase due to *C. glabrata*.

2 - Vulvovaginal Candidiasis (VVC)

C. glabrata has been isolated from 10 to 20 % of women of most places in the world [8]. The rate of non-albicans species involved in VVC has increased from 9.9% in 1988 to 17.2% in 1995[9]. 10 to 33 percent of relapsing forms of VVC is due to non-albicans species such as *C. glabrata*, *C. tropicalis*, *C. kruseii* , and *C. parapsilosis* [10]. This species has been introduced as the most common non-albicans species causing VVC (covering more than 34.5% of the cases) [2]. Uncontrolled diabetes can lead to increased vaginal Candida colonization. Type II diabetes increases vaginal infection potency with *C. glabrata*. Treatment of relapsing forms of VVC in individuals suffering with diabetes, especially those with colonized *C. glabrata*, is very difficult or impossible [11]. Outbreaks of this disease in women, who have used low doses of fluconazole for a long time, have been reported [5].

3 - Urinary Candidiasis

Candida species are isolated from 10% of urine cultures. This rate is higher in hospital centers [12]. *Candida* species cover more than 13 to 26 % of hospital urinary tract infections [13]. About 50 % of Candida isolates from urinary cultures are non-albicanse *Candida* species, commonly *C. glabrata. C. glabrata* is involved in 25 to 35 % of Candidurea [12, 13, 14].

4 - Blood infection and systemically infection

C. glabrata was introduced in 1999, as the fourth most common causes of Candidemia behind *C. albicanse*, *C. parapsilosis* and *C. tropicalis*. This infection is increased from 14 % to 18 % from 1992 to 2001 in USA and In addition, some researchers reported that this species was introduced as the second most common causes with more than 24 % of total Candidemia in USA from 1997 to 2001. In 2004 this species was introduced as the main cause of Candidemia [2]. Mortality rates in Candidemia patients due to *C. glabrata*, was reported from 50% in cancer patients to 100 % in bone marrow recipients.

5 – Endophthalmitis

Incidence of this disease is probably one of the most recent reported diseases related to *C. glabrata*. About 12 cases of this type of fungal infections have been reported since 1978 to 2010 [15].

RESULTS AND DISCUSSION

The reason of *C. glabrata* efficiency rather than other non-albicans species of Candida

1 - Ability of Adhesion and form biofilms

C. glabrata has less ability to adhere to oral keratinocytes cells and twofold greater ability to bind to synthetic acrylic surfaces (dentures and catheters) in comparison with *C. albicans*, this is why this species is the most common species of Candida which has been isolated from the mouths of elderly and may cause oral thrush [2].

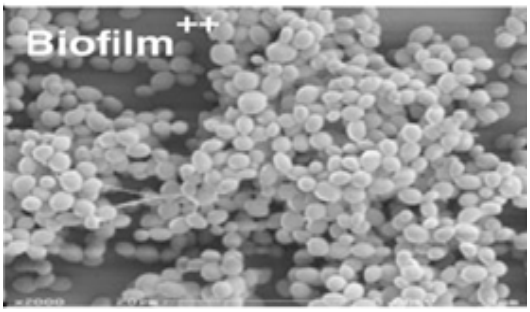

Figure 1 - Biofilm formation of *C. glabrata*

According to researches, all non-albicanse *Candida* species are able to produce biofilms. The production of biofilms in *C. glabrata* is less intensive in comparison with *C. parapsilosis* and *C. tropicalis*. Based on data from Scanning Electron Microscopy (SEM), the reason of this difference refers to the extracellular matrix of these fungal species. So that, the extracellular matrix of *C. parapsilosis* is composed of high carbohydrates and low protein. In contrast, in *C. tropicalis* matrix, the level of both carbohydrate and protein is low. Interestingly, in *C. glabrata* cell matrix, the level of both protein and carbohydrates is high [16]. Therefore *C. glabrata* has the ability of biofilm formation. This property increases through increasing of serum levels and inflammatory factors. Cell surface hydrophobicity (CSH) of *C. glabrata* is 4 times higher in comparison with *C. albicans*. According to previous researches, the adhesion rate of *C. glabrata* increases in presence of preservative substances. C. *glabrata* has the maximum adhesion rate in presence of methylparaben, propylparaben and sorbate. These substances are used in formulations of most gels or vaginal ointments [17].

2 - Production of extracellular Hydrolyses

These enzymes are including serine-, cysteine-, metalo- and aspartyl- proteinases [2, 18]. Furthermore, it has been proved that unlike isolated strains of *C. glabrata* from mucosal infections, 41% of isolated *C. glabrata* species from blood infections are able to produce phospholipases, which indicates the importance of this enzyme in causing this type of infections [2].

3 - The performance of phenotypic Switching phenomenon and filaments production

No reports of these phenomenons have been observed in *C. parapsilosis* and *C. tropicalis*. Lack of hyphae production has been assumed as *C. glabrata* identifying factor for a long time (Fig. 2). It has been recently seen that *C. glabrata* is able to create four colonies with different phenotypes on the medium containing copper sulfate, spontaneously and reversibly. These phenotypes are: white, light brown, dark brown and very dark brown.

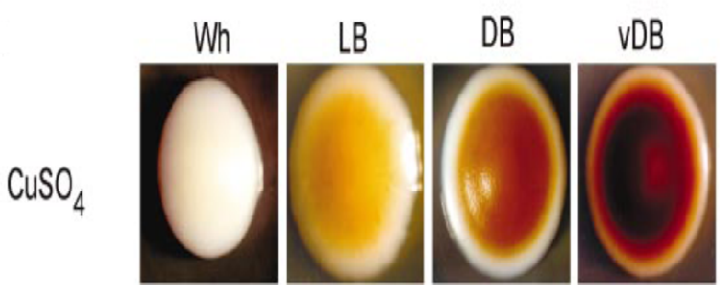

Figure 2 - The capability of producing four colonies with different phenotypes on medium containing copper sulfate.

Moreover, recently the capability of producing pseudohyphae and even germ tube has been observed in *C. glabrata* using Calcofluor white and electron microscopy [2, 19].

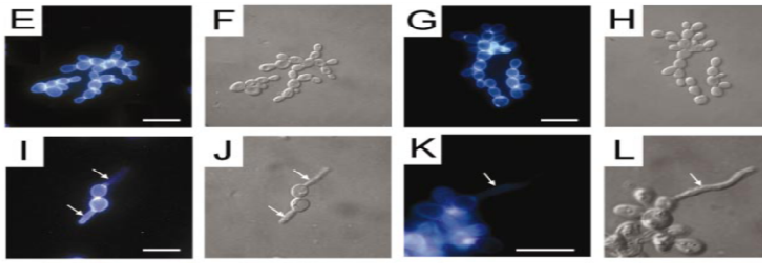

Figure 3 - Observing the capability of producing pseudohyphae (E-H) and germ tube (I-L) in *C. glabrata*

4 - Reaction with the host immune system

Studies have shown that infection with *C. albicans* increases production of MG – CSF، TNF ،IL - 8 ، and IL – 1 in host animal, while, the production of these factors is very weak in *C. glabrata* infections [2]. In addition, production level of vaginal S-IgA in *C. glabrata* infections is much less in comparison with *C. albicans* infections [5, 18]. Phagocytic activity of endothelial cells during infection with *C. glabrata* is much lower than *C. albicans* infections [5].

5 - Drug resistance

C. glabrata is intrinsically resistant to a vast range of anti-fungal compounds such as human beta-defensins (HBD), histatin (hsn), and magainins, while no resistance has been seen for other Candida species [2]. Furthermore, intrinsic and acquired resistance to azoles compounds has been well proven for *C. glabrata* [18].

In 1998 about 68 % of isolated *C. glabrata* species from hospital infections were resistant to the fluconazole. It was reported in 2003 that 72 % of the mentioned isolates were resistant to both fluconazole and itraconazole [2]. Fluconazole MIC (Minimum Inhibitory Concentration) for *C. glabrata* has been reported almost 16 time more than *C. albicans* [20]. In a study which was conducted from 1999 to 2005, it was recognized that prescription of Fluconazole to treat candidemia exchange *C. glabrata* to *C. albicans* [21].

C. tropicalis and *C. glabrata* are 10 times less sensitive against miconazole in comparison with *C. albicans*. According to In Vitro Studies, miconazole and clotrimazole are not effective on non-albicanse species. While according to a study on 250 strains of *C. albicans* in 1993, none of them was resistant to ketoconazole, itraconazole and clotrimazole [9].

New azoles including Voriconazol, Rilopirox, and Eberconazol are effective on *C. glabrata* and *C. kruseii* [10].

***C. glabrata* resistance mechanisms:**

1-Possessing cdr1 and cdr2 pumps and also ABC efflux pump, this species with consuming energy is capable to drive out drugs and antifungal azoles from cells [2, 5].

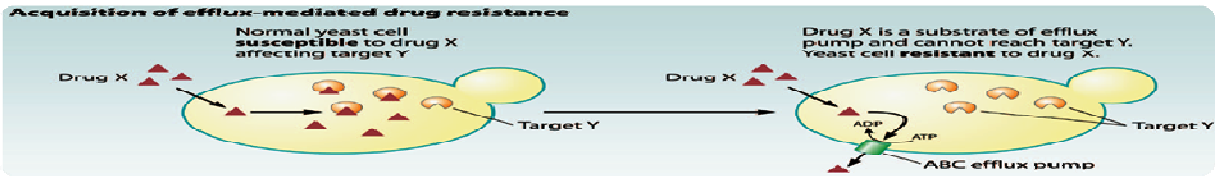

Figure 4 - The expel of drugs from ABC efflux pump of *C. glabrata* cells and increasing drug resistance.

2- This fungus, when faced with effective drugs on ergosterol, increases ergosterol biosynthesis. So that expression increasing of CgERG11 gene, coding Lanostrol 14 demethylase enzyme, increases the expression rate of ergosterol [2].

3-Mutations in antifungal drug targets [5].

4-Mutation of C14 Sterol demethylase enzyme [20].

5-Unlike other Candida species *C. glabrata* has a haploid genome which helps to increase its resistance [5, 18].

Given the prevalence increasing of *C. glabrata* and also *C. glabrata* resistance increasing in recent decades and considering that fluconazole is commonly used to treat fungal infections, it is better to take steps to identify and correct diagnosis of this species. Also it would be useful that during the isolation of Candida by using chrome agar medium, Corn Meal Agar medium containing Tween 80 and germ tube test, give some information on the proper administration of anti-fungal agent to Physician. Perhaps the use of the drug fluconazole susceptibility disc is the best way to advance this goal.

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