Original

The presence of fluconazole-resistant *Candida dubliniensis* strains among *Candida albicans* isolates from immunocompromised or otherwise debilitated HIV-negative Turkish patients

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Summary

The newly described species *Candida dubliniensis* phenotypically resembles *Candida albicans* in many respects and so it could be easily misidentified. The present study aimed at determining the frequency at which this new *Candida* species was not recognized in the authors' university hospital clinical laboratory and to assess antifungal susceptibility. In this study six identification methods based on significant phenotypic characteristics each proposed as reliable tests applicable in mycology laboratories for the differentiation of the two species were performed together to assess the clinical strains that were initially identified as *C. albicans*. Only the isolates which have had the parallel results in all methods were assessed as *C. dubliniensis.* One hundred and twentynine *C. albicans* strains isolated from deep mycosis suspected patients were further examined. Three of 129 *C. albicans* (two from oral cavity, one from sputum) were reidentified as *C. dubliniensis*. One of the strains isolated from oral cavity and that from sputum were obtained at two months intervals from the same patient with acute myeloid leukemia, while the other oral cavity strain was obtained from a patient who had previously been irradiated for a laryngeal malignancy. Isolates were all susceptible *in vitro* to amphotericin B, with the MIC range 0.125 to 0.5 µg/ml, resistant to fluconazole, with the MICs ≥ 64 µg/ml, and resistant to ketoconazole, with the MICs ≥ 16 µg/ml, dose-dependent to itraconazole with the MIC range 0.25-0.5 µg/ml, and susceptible to flucytosine, with the MIC range 1-4 µg/ml.

Key words *Candida dubliniensis*, Immunocompromised patients, Candidiasis, Antifungal susceptibility, Fluconazole resistance, Staib agar

Presencia de cepas de *Candida dubliniensis* entre los aislamientos de *Candida albicans* de pacientes turcos VIH negativos inmunocomprometidos o debilitados

Resumen

La especie *Candida dubliniensis*, recientemente descrita, se asemeja fenotípicamente a *Candida albicans* en muchos aspectos y puede ser fácilmente confundida e identificada erróneamente. Este estudio ha tenido como objetivo determinar la frecuencia de *C. dubliniensis* y su sensibilidad antifúngica en el laboratorio clínico de un hospital universitario. Se emplearon seis métodos basados en características fenotípicas significativas para la diferenciación de ambas especies con el fin de confirmar la identidad de los aislamientos clínicos inicialmente identificados como *C. albicans*. Los aislamientos con resultados similares por todos los métodos fueron considerados como *C. dubliniensis*. Se examinaron 129 aislamientos de *C. albicans* de pacientes con sospecha de micosis invasora. Tres de estos aislamientos, dos de la cavidad oral y uno de esputo, fueron reidentificados como *C. dubliniensis*. Uno de estos dos aislamientos orales y el aislamiento de esputo se obtuvieron con un mes de intervalo del mismo paciente con leucemia mieloide aguda, mientras que el otro aislamiento oral se obtuvo de un paciente que había sido previamente irradiado para tratar una neoplasia laríngea. Todos los aislamientos fueron sensibles *in vitro* a anfotericina B, con un

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rango de CMI entre 0,125 y 0,5 µg/ml, resistentes a fluconazol, con CMIs≥64 µg/ml, resistentes a ketoconazol, con CMIs≥16 µg/ml, de sensibilidad dependiente de la dosis para itraconazol (CMI 0,25-0,5 µg/ml) y sensibles a 5-fuorocitosina (CMI 1-4 µg/ml).

Palabras clave *Candida dubliniensis*, Pacientes inmunosuprimidos, Candidiasis, Sensibilidad a los antifúngicos, Resistencia a fluconazol, Agar de Staib

Candida dubliniensis is a newly described species of genus *Candida* that shares many phenotypic characteristics with, and is phylogenetically closed to, *C. albicans*. The novel species has been isolated mostly from oral specimens of HIV infected patients. It has also been isolated from different body sites including vaginal, fecal, lung, sputum and blood specimens and now is recognized as a minor constituent of normal human (oral) microbiota. For *C. dubliniensis*, the clinical significans seems to be its association with HIV-seropositive individuals [1-4] and its ability to rapidly develop a stable fluconazole-resistant phenotype on exposure to this antifungal *in vitro* [3,5].

C. dubliniensis forms germ tubes and chlamydoconidia that are almost indistinguishable from those of *C. albicans*. In addition, both species typically produced blastoconidia with pseudohyphae, and true hyphae [2,3]. Since many laboratories use the germ tube and chlamydoconidium formation tests as their sole method for the routine identification of *C. albicans*, isolates of *C. dubliniensis* have probably been overlooked and misidentified for a long time [6].

A variety of methods have been developped for phenotypically discrimination of isolates of *C. dubliniensis* from *C. albicans*, including among others, ability to produce germ tubes and chlamydoconidia [3], lack of growth at 45°C [7], carbohydrate assimilation profiles [2,8], ß-glucosidase activity [2,9], colony color on CHROMagar Candida medium [10,11], ability to produce rough colonies and chlamydoconidia on Staib agar [12,13], immunofluorescence [14], coaggregation with *Fusobacterium nucleatum* [15]. However all have been demonstrated being insufficient alone for accurate differentiation of the two species [6,16]. The most reliable method has been considered molecular genotypic analysis [3] but not yet used routinely by many clinical microbiology laboratories. Therefore, this retrospective study designed to use of a combination of mycological and biochemical methods developped to identify *C. dubliniensis*. The isolates only which have had the results in line with all these methods were assessed as *C. dubliniensis* to confirm their identification by a variety of techniques.

On the other hand, Sullivan and Coleman [2] established that the distribution of *C. dubliniensis* is widespread -probably world wide-, and in clinical laboratories the incidence of this yeast species is continuing to increase [3]. Despite the clinical importance, its epidemiology remains to be elucidated.

The incidence of *C. dubliniensis* and antifungal susceptibility patterns of clinical Turkish isolates have not been established yet. The present study was therefore undertaken to reevaluate *C. albicans* strains of clinical origin isolated at author's systemic mycology laboratory for the presence of *C. dubliniensis* isolates among them and to confirm and extend the previous few data about *C. dubliniensis* can be associated with carriage and infection in the absence of HIV infection. In this sample, *C. albicans* strains were reexamined through use of phenotypic criteria. The isolates reidentified as *C. dubliniensis* were also assessed for *in vitro* susceptibility against fluconazole and other commonly used antifungal agents.

In the present study, the tested strains were isolated from non-HIV-infected subjects but with malignancy and/or underlying diseases, and interestingly, three reidentified isolates were found resistant to fluconazole while detected have decreased susceptibility to azoles.

MATERIALS AND METHODS

Test organisms. One hundred and twentynine clinical *C. albicans* strains isolated from oral cavity (n= 31), respiratory tract (n= 59), vagina (n= 27) and feces (n= 12) were previously identified based on their ability to produce germ tubes and chlamydoconidia. The isolates were obtained only from debilitated and immunocompromised patients due to various causes i.e. malignancy and corticosteroids, neutropenia, extensive surgery and previous antibiotic usage, diabetes mellitus and others; whose HIV status were unknown except two HIV-seropositive ones. All isolates were mainted on two Sabouraud glucose agar (SGA) (prepared in-house) slants at 4 °C. Strains were subcultured onto SGA and were incubated at 30 °C for 24 to 48h before a second subculture on SGA. Colonies from the second subculture were used for the tests.

Germ tube and chlamydoconidia formation tests. Germ tube formation tests were performed in human serum at 37 °C for 3h. Rough (mycelial) and smooth (yeast) colony forms were assessed on *Guizotia abyssinica* creatinine agar [12]. Degree of chlamydoconidium production and their arrangement were examined on cornmeal agar which was prepared in-house supplemented with 1% Tween 80 (Sigma, USA) after 48h at 25 °C.

Fluorescence on methyl blue SGA tests. SGA with 0.01% methyl blue [17] were surface inoculated by streaking of each isolates and incubated at 37 °C in ambient air for 24 to 48h and examined under a Wood's lamp [3,10,18].

Growth at 37 °, 42 °, 45 °C. The test were performed on conventional solid media. A small portion of a single colony of each isolate was removed from SGA plate and streaked over the surface of three plates of SGA and one of which was incubated at 37 °C, the second at 42 °C, and the third was placed at 45 °C. Growth if any, on all three plates was usually assessed after 24 and 48h of incubation [6,7].

Assimilation tests. The modification of the Wickerham medium with carbohydrates and bromocresol purple (1.6%) indicator was used in tubes to investigate indicative assimilation profiles of the isolates [19]. Yeast inocula were prepared in sterile water and standardized to a turbidity equivalent to that of a 1 McFarland standard

with a spectrophotometer at 530 nm. The yeast suspension was further diluted in sterile water to yield an inoculum concentration of approximately $30x10^6$ cells/ml and was mixed for 15 s with a vortex. A negative control tube without any carbon source was included for each series of tests. Assimilation and negative control tubes were inoculated with 1 ml of a yeast suspension, incubated at 30 °C and controlled at 24, 48 or 72h. A color change to yellow was considered positive if the medium in negative control tube was purple. The incubation period was prolonged to 31 days for strains with negative reaction.

Antifungal susceptibility tests. Susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) reference broth macrodilution method [20]. Ten two fold serial dilutions of the antifungal agents were prepared. Antibiotic medium 3 (Oxoid, England) was used for testing amphotericin B (Bristol-Meyers-Squibb, USA) (0.03 to 16 µg/ml), and RPMI-1640 (Sigma) buffered with 0.165 M morpholinepropanesulfonic acid (MOPS) (Sigma) was used to prepare for testing fluconazole (Pfizer, Turkey) (0.125 to 64 µg/ml), itraconazole (Janssen Pharmaceuticals, Belgium) (0.03 to 16 µg/ml), ketaconazole (Milen, Turkey) (0.03 to 16 µg/ml) and 5-fluorocytosine (5-FC) (Sigma) (0.125 to 64 µg/ml). AmphotericinB, itraconazole and ketoconazole were dissolved in dimethyl sulfoxide, flucytosine and fluconazole were dissolved in sterile distilled water. Yeast suspensions were prepared in sterile (0.85%) saline and the turbidity of the suspensions were adjusted to match that of a 0.5 McFarland turbidity standard. A growth control tube contained drug-free medium and inoculum suspension, and a sterility control tube contained uninoculated, drug-free medium were included in each series. Inoculated test tubes were incubated at 35 °C and read at 24 h. *C. albicans* ATCC 90028 was tested used as quality control strain with each testing series. The interpretive criteria used for antifungal agents (susceptible, dose-dependent, intermediate and resistant) were those proposed by the NCCLS and by Rex *et al.* [20,21].

RESULTS

Reevaluation of clinical C. albicans *strains.* All 129 isolates produced germ tubes in serum. On *Guizotia abyssinica* creatinine agar 19 of 129 isolates formed rough colonies due to abundant mycelial growth while the others produced smooth colonies consisting of mostly yeast cells. On cornmeal-Tween 80 agar abundant chlamydoconidium production in unusual configurations in pairs, triplets or in larger clusters attached to a single suspensor cell, indicative of *C. dubliniensis* was seen in only 17 of these colonies (17/129). On methyl blue SGA 116 of 129 isolates fluoresce with a yellow color on exposure to longwave UV light and other 13 (13/17) fail to fluoresce under these conditions. In differential temperature growth test all isolates grew well at 37 °C. Very poor or no growth occured at 42 and at 45 °C in 10 of these 13 strains (10/129). Overall carbohydrate assimilation profiles of the test isolates were positive for glucose, maltose, galactose and negative for lactose, melibiose, cellobiose, inositole, raffinose and dulcitole. Only one isolate was sucrose negative and the others was positive. Trehalose assimilation was negative in five of the former 10 strains (5/129). Xylose utilisation was negative in three isolates (3/129) and was positive in all the rest. Briefly, a total of three of 129 (2.3%) isolates were positive for fluorescence, utilized both xylose and trehalose as sole carbon source and demonstrated no growth at 45 °C. Based on the whole findings three clinical *C. albicans* strains isolated two from oral cavity, one from sputum were reidentified as *C. dubliniensis*. The sucrose negative isolate was assessed as *C. stellatoidea* variant of *C. albicans*. It is worth to note that one of the strains isolated from oral cavity and that from sputum were obtained at two months intervals from the same patient with acute myeloid leukemia (AML), while the other oral cavity strain was obtained from a patient who have previously been irradiated for a laryngeal malignancy. These isolates were obtained as the sole fungus from the specimens. In this retrospective study, clnical information concerning candidiasis status for patients from whom *C. dubliniensis* isolates were recovered was not obtained.

Antifungal susceptibilities. Antifungal susceptibility tests were performed on the three isolates plus control strain according to the guideliness of NCCLS M27-A document [20] with current antifungals amphotericin B, fluconazole, itraconazole, ketoconazole and 5-fluorocytosine (5FC). Isolates were all susceptible *in vitro* to amphotericin B, with the MIC range 0.125 to 0.5 µg/ml, resistant to fluconazole, with the MICs ≥ 64 µg/ml, and resistant to ketoconazole, with the MICs ≥ 16 µg/ml, dose-dependent to itraconazole with the MIC range 0.25-0.5 µg/ml, and susceptible to 5 FC, with the MIC range 1-4 µg/ml.

DISCUSSION

C. dubliniensis is a newly recognized fungal pathogen predominantly causing mucosal disease in AIDS patients and has become a significant cause of infections in humans including abdominal infections and fungemia [5,15-22]. Although preliminary studies indicate that most strains of *C. dubliniensis* are susceptible to presently available antifungal agents, fluconazole-resistant strains have been detected [5,23]. Several investigators suggested that fluconazole resistance may be induced in patients as a result of treatment with the drug protracted periods [23]. Thus, there is an increasing interest in *C. dubliniensis* regarding incidence, drug resistance, pathogenesis, and epidemiology of infections caused by this newly recognized pathogen. The present study aimed at determining the frequency at which this new *Candida* species was not recognized at authors' laboratory and to assess antifungal susceptibility.

In practise, identification and classification of *Candida* species has depended to a large extent on the analysis of a limited number of physiological traits and morphological features. Because *C. dubliniensis* and its close relative *C. albicans* share many phenotypic characteristics in common and the lack of a sole reliable predictive characteristic stimulated recent development methods for discriminating between *C. albicans* and *C. dubliniensis*. Recently Tintelnot *et al.* [24] has reevaluated previously described discriminatory criterion and proposed a flow scheme based on phenotypic markers for identifying *C. dubliniensis*. Similarly, in the present study six method were used together to eliminate as possible the false positive results and the isolates only which have had the parallel results in all methods were assessed as *C. dubliniensis.*

One hundred and twentynine germ-tube and chlamydoconidia positive yeast strains isolated from deep mycosis suspected patients were further examined. Three of 129 *C. albicans* (2.3%) were found by the process of reidentification. In a prospective study [4] in the United States, six of 699 yeasts (0.9%) isolated were *C. dubliniensis,* five from HIV-seropositive patients and one from a patient whose HIV status was unknown. In another study a total of 15 (1.2%) isolates from 12 patients were

identified as *C. dubliniensis* by the same authors. Ten of the patients were found to be immunocompromised including HIV infected or AIDS and cancer patients receiving chemotherapy and patients awaiting transplantation [25].

In a recent study by Polachek *et al*. [26] five *C. dubliniensis* isolates recovered from separate HIV-negative hospitalized patients in Jerusalem, Israel, one from urine samples and the remaining four were recovered from upper respiratory tract and oral samples of non-HIV infected patients. Meis *et al*. [27] added their data for the year 1999, from Netherlands, a prevalence of 0.8%. They obtained this new species from 11 patients, of them six were HIV negative, and of five patients, no antibodies against HIV were tested since there was no clinical suspicion for HIV-related disease. In a large scale retrospective study by Odds *et al*. [6], it was reported that among the 2.589 yeast isolates examined 52 isolates were identified as *C. dubliniensis*. These findings indicate that *C. dubliniensis* isolates from clinical material predate the AIDS epidemic and that this species has been isolated in the past from HIV-negative subjects.

In this study, three (2.3%) *C. dubliniensis* strains were identified using phenotypical criteria. However, since phenotipic-based identification methods are not as accurate as molecular genotypic discrimination, there is the possibility that there may be a small number of additional isolates of *C. dubliniensis* in our strain collection.

In the present study three *C. dubliniensis* strains were obtained from two immunocompromised patients, one with AML and the other have previously irradiated. The findings is in accordance with the results previously reported by Odds *et al*., Meis *et al*., Jabra-Rizk *et al*. [4,6,25,27]. Several recent studies have shown that it is more prevalent in HIV negative individuals than previously thought. Several studies have reported that *C. dubliniensis* is found as a commensal organism in HIV negative individuals and it can cause various forms of candidiasis in this group. All these studies confirm that *C. dubliniensis* might be associated with carriage and infection in the absence of HIV infection.

In this study all *C. dubliniensis* isolates were found susceptible to amphotericin B and 5FC, dose dependent-susceptible to itraconazole and resistant to fluconazole. All isolates showed high MIC values against ketoconazole. Although preliminary studies indicate that most strains have been susceptible to conventional antifungals, fluconazole resistant strains have also been reported [5,23,25-34]. Fluconazole-resistant strains of *C. dubliniensis* are easily obtained *in vitro* and this fact could be a complication if this resistance develop during treatment with this drug [16,25,28]. Furthermore several reports describing fluconazole resistance have also reported strains that exhibited increased expression of multidrug resistance transporters [5,23].

The cross-resistant phenotypes could be a complication if this resistance develop during treatment with these drugs. In the present study three *C. dubliniensis* strains were found *in vitro* resistant to fluconazole and also to ketoconazole, and dose-dependent against itraconazole. Considering the usual prophylactic usage of fluconazole for the patients with malignancy we speculate thar these species possibly developped resistance to azoles because of repeatedly exposure to the drug. However these isolates were found susceptible to 5FC and amphotericin B that might be the alternatives to azole drugs for the treatment of infections by them.

All these studies confirm that *C. dubliniensis* can be associated with carriage and infection in the absence of HIV infection and fluconazole-resistant strains are easily derived *in vitro*. As the immunocompromised population continues to grow in numbers, it might be important for epidemiological aspects to determine patient populations with which *C. dubliniensis* is associated and to establish its prevalence in different patient groups. In conclusion, regarding the potential for the development of resistant strains of *C. dubliniensis* the data obtained in this study could be added the previous similar ones to emphasize the need of proper identification of germ-tube and chlamydoconidia positive yeasts. Additional studies are necessary to determine the incidence and prevalence of *C. dubliniensis* among the various susceptible populations, especially in invazive and systemic mycoses suffering patients and for therapeutic purposes as well.

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