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ORIGINAL ARTICLE

Colony morphologies, species, and biotypes of yeasts from thrush and denture stomatitis

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Abstract

Objective. To study the species and phenotypic characteristics of yeasts, i.e. colony morphology, biotypes, and biotype relatedness, and the oral distribution of yeasts, in thrush and denture stomatitis**.** ***Material and Methods.*** Yeast colony morphology was observed under a stereo-microscope and photographed with a digital camera. Genus, species, and biotypes of the yeast isolates were identified by using a commercial kit, ID 32C. Yeast biotype dendrograms were generated by Spotfire software and SPSS 15.0 for Windows. ***Results.*** Multiple colony morphologies were observed among the yeasts from both thrush and denture stomatitis. One genus, 6 species, and 21 biotypes were identified among the yeasts from thrush, while 2 genera, 7 species, and 20 biotypes were identified among the yeasts from denture stomatitis. Considerable similarities in predominant species, biotypes, and biotype clustering profiles were shown among the yeasts from thrush and denture stomatitis. However, *Candida dubliniensis* was identified exclusively in subgingival areas and biotype 7347340215 of *C. albicans* was identified more frequently in palate and sulci in thrush. ***Conclusions.*** A diversity of species and phenotypes was found among the yeasts in thrush and denture stomatitis. Candidal commensals were predominant in thrush and denture stomatitis, but the observation of divergent *Candida* species and biotypes, constituting 23% of all the yeast isolates, should not be ignored.

Key Words: *Biotype, colony morphology, denture stomatitis, thrush, yeasts*

Introduction

Oral candidosis is an opportunistic infection predominately caused by *Candida albicans* together with related *Candida* species [1]. In general, oral candidosis can be categorized as primary oral candidosis that is confined to oral and perioral tissues and secondary forms where oral candidosis is a manifestation of generalized systemic mucocutaneous candidal infection [2]. Thrush is the most common form of oral candidosis. Antibiotic therapy or immunosuppression can predispose to thrush, especially in neonates and terminally ill patients. It is characterized by soft, creamy-colored and elevated plaques that are easily wiped off from the buccal mucosa, dorsal tongue, and palate. Denture stomatitis, which affects 28–65% of denture wearers [3–5], is a common candidal infection secondary to long-standing occlusion of part of the oral mucosa by a denture. The characteristic feature is uniform bright erythema or granular hyperplasia of the upper denture-bearing area and limited by the denture margin. Three major general factors may predispose to oral candidosis, i.e. the immune status of the host, the oral mucosal environment, and *C. albicans* and particular strains of this species [6].

Yeast identification and classification in oral candidosis are important for infection diagnosis, understanding of the pathogenesis, and treatment. There are several studies on molecular typing of yeast isolates from HIV patients with oral thrush and from healthy carriers [7–9]. These studies have revealed the genetic relatedness between yeasts of oral candidosis from HIV and yeasts from healthy oral cavities. Commensal candidal species in the oral cavity of healthy individuals may become the prevalent agents of subsequent oral candidosis in compromised hosts [8,9], and these species likely undergo genetic "shuffling" during disease

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progression [7]. Using molecular typing of *C. albicans* strains from denture stomatitis, researchers have found that similar genotypes can be detected in individuals with and without denture stomatitis, suggesting that denture stomatitis is due to the outgrowth of commensal strains of *C. albicans* [10,11]. It is of interest to compare the phenotypic characteristics of the yeasts in thrush and denture stomatitis, and to find the connection, if any, between the phenotypic characters and genotypic characters from a previous study [12].

The objectives of the present study were to: 1) investigate colony morphology, genera, species, and biotypes of oral yeasts from thrush and denture stomatitis, 2) analyze the biotypic relatedness of the yeast isolates in thrush and denture stomatitis, and 3) assess the distribution of the species and predominant biotypes among different oral sites.

Material and methods

Yeast sampling

Yeasts were sampled from the palate, buccal mucosa, and gingival sulci/periodontal pockets of 19 patients with thrush, and in addition to these sites, from the fitting surface of the dentures of 22 patients with denture stomatitis [12]. The thrush patients comprised 13 males and 6 females aged 9 to 84 (57.7 ± 20.3 SD) years who had undergone head/neck radiation and chemotherapy because of neck or head cancers. The denture stomatitis patients comprised 9 males and 13 females aged 50 to 94 (70.4 ± 10.8 SD) years who wore complete or $^{3}/_{4}$ partial removable dentures and who had not been treated with any corticosteroids, immunosuppressive agents, cytotoxic chemotherapy, or irradiation therapy in the previous 3 months, were not pregnant, and did not suffer from endocrinal disorders, malignancies, immunodeficiencies, or malnutrition.

Palate, buccal mucosa, and denture were sampled by streaking these locales with sterile cotton-tipped swabs (Selefatrade, Spånga, Sweden). Subgingival plaque samples were collected by inserting two sterile paper points (Roeko, Munich, Germany) into two to four gingival sulci/periodontal pockets for 15 s after removing supragingival plaque. The sample(s) from each oral site was streaked directly onto one Sabouraud dextrose agar plate at the chairside. The plates were incubated aerobically at 37°C for 3 days.

Colony morphology

After incubation on Sabouraud dextrose agar, yeast colony morphology was observed under a stereomicroscope (Stemi SV.6; Zeiss, Germany) (×5) and photographed with a Kodak DC 120 digital camera (Eastman 6 Kodak Co., Rochester, NY, USA). Colonies exhibiting distinct morphologies on each plate were picked, subcultured, transferred to liquid Todd Hewitt with dimethyl sulfoxide (DMSO), and stored at −80°C pending further use. The criteria for assessing colony morphology were based on colony form, margin, and surface [13].

Yeast collection, cultivation, and isolation were performed by one examiner (XS).

Yeast biotyping

The subcultures of 105 yeast isolates from thrush and 91 isolates from denture stomatitis were biotyped. Genus, species, and biotype of the yeast isolates were identified using the ID 32C kit (bioMérieux, Craponne, France) based on 29 assimilation tests (carbohydrates, organic acids, and amino acids), one susceptibility test (cycloheximide), one colorimetric test (esculin), and a negative control. Inoculation was processed using a Vitek System ATB 1574 robot (bioMérieux), and the strip was incubated aerobically at 30°C for 48 h. The strip was read by a mini API instrument (bioMérieux), the growth being determined as positive or negative based on the presence or absence of turbidity. The results of each reaction were transferred into numerical codes that gave the biotype profile of the each yeast isolate after treatment in a database (API, bioMérieux).

Nine type strains (*C. albicans* CBS 562, *C. dubliniensis* CBS 7987, *C. parapsilosis* CBS 604, *C. tropicalis* CBS 94, *C. glabrata* CBS 138, *C. krusei* CBS 573, *C. norvegensis* CBS 1922, *C. inconspicua* CBS 180, and *S. cerevisiae* CBS 1171) (Centraalbureau Voor Schimmelcultures (CBS), Delft, The Netherlands) were used as references in the study.

Dendron computer-assisted biotype analyses

Yeast biotype relatedness was analyzed using the Spotfire software (http://www.spotfire.com/products/gallery.cfm) and SPSS 15.0 for Windows. Hierarchical cluster analysis was applied for analyzing biotype relatedness among the yeast isolates, which compared the 30 biochemical test results from each isolate by using an agglomeration schedule. The dendrograms were generated based on the squared Euclidean distance computed between all pairs of the collected isolates. A threshold was chosen arbitrarily at the similarity of 90% (2.5 of 25 rescaled distance clusters combined) for strain clustering.

Results

Yeast isolates were identified from the oral cavities of all 19 thrush patients and 20 out of the 22 denture stomatitis patients. These yeast isolates exhibited multiple colony morphologies in the primary cultures on Sabouraud dextrose agar, e.g. fuzzy,

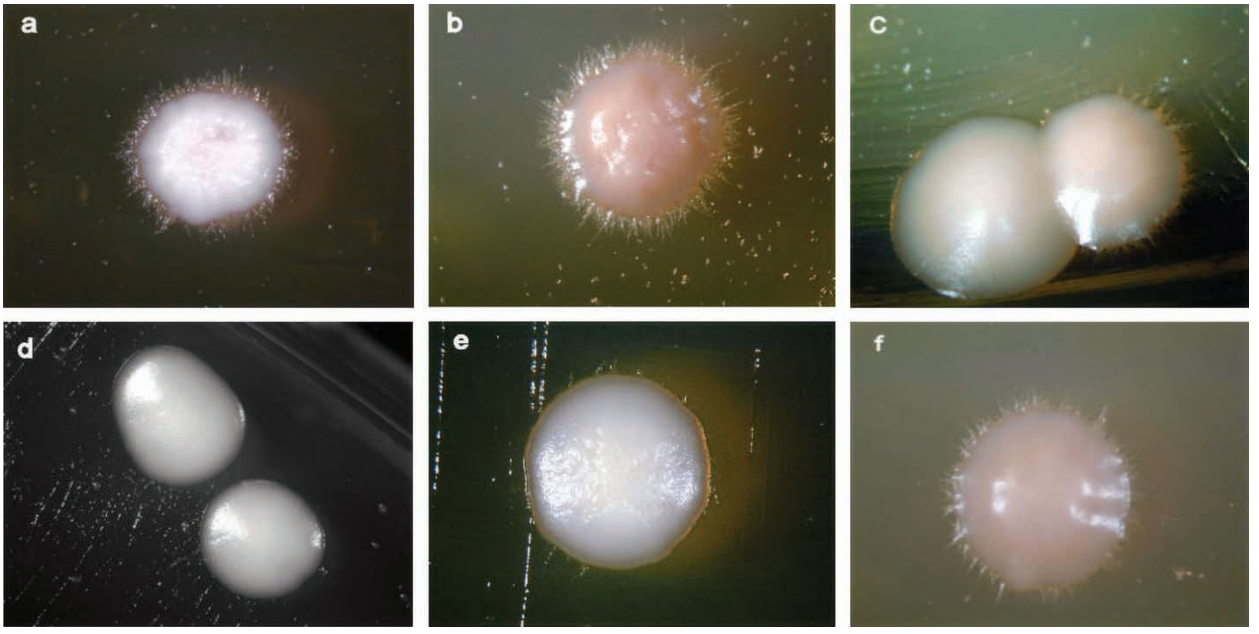

Figure 1. Diverse colony morphologies of the yeasts from thrush and denture stomatitis. Species and biotype of the colonies: *C. albicans*, biotype 7347340215 (a); *C. albicans*, biotype 7347340215 (b); *C. albicans*, biotype 7347340211 (c); *C. albicans*, biotype 7347340015 (d); *C. tropicalis*, biotype 7357750115 (e); *C. albicans*, biotype 7347340215 (f).

filamentous, or even margin, with rough or smooth surfaces, and white or pink color under the stereomicroscope (Figure 1).

In the case of thrush, all 105 yeast isolates were classified into one genus, *Candida*, 6 species and 21 biotypes (Table I). *C. albicans* was the predominant species followed by *C. tropicalis*, *C. glabrata*, *C. dubliniensis*, *C. utilis*, and *C. guilliermondii*. Biotypes 7347340015 and 7146340015 of *C. albicans* were the most frequently identified biotypes followed by biotypes 7347340215 and 7346340015.

In denture stomatitis, all 91 yeast isolates were classified into two genera: *Candida* and *Saccharomyces*, 7 species and 20 biotypes (Table I). *C. albicans* was the most dominant species, followed by *C. tropicalis*, *C. glabrata*, *C. inconspicua*, *C. dubliniensis*, *C. parapsilosis*, and *Saccharomyces cerevisiae*. Biotype 7347340015 was the most frequently identified biotype of *C. albicans* followed by biotype 7146340015, 7147340015, 7347340215, and 7346340015.

Dendrograms were generated based on the similarity of the biotypes of the yeast isolates from thrush and denture stomatitis (Figure 2). At 90% similarity, four biotype clusters were found among the yeasts in thrush. The four clusters included 91.4% of the thrush isolates, the species *C. albicans*, *C. glabrata*, and *C. tropicalis*, and the predominant biotypes, i.e. 7347340015 in cluster I, 7146340015 in cluster II, and 7347340215 in cluster I of *C. albicans*.

Three biotype clusters were found among the yeasts from denture stomatitis at 90% similarity. These clusters included 90.1% of the denture stomatitis isolates; the species *C. albicans* and *C. glabrata* were the most predominant as well the biotypes 7347340015 in cluster I, 7146340015 in cluster II, and 7147340015 in cluster I of *C. albicans*.

The species and biotypes from various oral sites of the thrush and denture stomatitis patients are presented in Table II. *C. albicans* was the most predominant species in all the oral sites of the two patient groups. *C. dubliniensis* was detected only in the subgingival area of both groups.

The biotypes 7347340015, 7146340015, and 7347340215 of *C. albicans* were predominant in all the oral sites, and biotype 7347340215 was found more frequently in palate and sulci in the thrush patients. The biotypes 7146340015 and 7347340015 of *C. albicans* dominated in all the sites in denture stomatitis.

Discussion

The lesions of creamy white patches or small yellow spots on palatal or buccal mucosa surfaces were detected in all 19 thrush patients who had received radiation therapy for neck and head cancer. Generalized simple inflammation was seen under the denture fitting surface in the 22 denture stomatitis patients who wore a complete or partial denture.

Diverse colony morphologies were seen in the yeasts from thrush and denture stomatitis, whereas morphologies of the smooth type were seen in yeasts from healthy oral cavities in our previous study [14]. These results are in agreement with the observations by Hellstein et al. [15] and Maffei et al. [16] who observed a significant difference in colony phenotypic characteristics among the isolates recovered from diseased versus healthy sites. Slutsky et al. [17] demonstrated that cells switched among seven

Table I. Frequency of oral yeast biotypes identified from thrush and denture stomatitis.

	% of patients		% of isolates	
Species, biotype	Thrush ($n=19$)	Denture stomatitis ($n=22$)	Thrush ($n=105$)	Denture stomatitis ($n=91$)
C. albicans	17 (89.5%)	20 (90.9%)	87 (82.9%)	77 (84.6%)
7146240015	0	1 (4.5%)	0	1 (1.1%)
7146340015	9 (47.4%)	7 (31.8%)	15 (14.3%)	18 (19.8%)
7146340215	1 (5.3%)	0	1 (1%)	0
7147340015	2 (10.5%)	6 (27.3%)	3 (2.9%)	11 (12.1%)
7147340215	1 (5.3%)	1 (4.5%)	5 (4.8%)	3 (3.3%)
7166340015	0	1 (4.5%)	0	1 (1.1)
7167340015	0	1 (4.5%)	0	1 (1.1%)
7346340015	4 (21.1%)	3 (13.6%)	11 (10.5%)	9 (9.9%)
7346340215	1 (5.3%)	0	1 (1%)	0
7347340015	9 (47.4%)	9 (40.9%)	23 (21.9%)	18 (19.8)
7347340211	1 (5.3%)	0	1 (1%)	0
7347340215	8 (42.1%)	5 (22.7%)	26 (24.8%)	11 (12.1%)
7347350035	0	1 (4.5%)	0	1 (1.1%)
7347740015	1 (5.3%)	1 (4.5%)	1 (1%)	2 (2.2%)
7367340015	0	1 (4.5%)	0	1 (1.1%)
C. tropicalis	4 (21.1%)	3 (13.6%)	7 (6.7%)	3 (3.3%)
5377750515	1 (5.3%)	0	1 (1%)	0
7157750115	0	1 (4.5%)	0	1 (1.1%)
7167340315	1 (5.3%)	0	1 (1%)	0
7367340115	0	1 (4.5%)	0	1 (1.1%)
7367340135	0	1 (4.5%)		1 (1.1%)
7377350315	1 (5.3%)	0	1 (1%)	0
7377740315	1 (5.3%)	0	1 (1%)	0
7377750115	1 (5.3%)	0	3 (2.9%)	0
C. glabrata	2 (10.5%)	2 (9.1%)	6 (5.7%)	6 (6.6%)
1000001	2 (10.5%)	2 (9.1%)	6 (5.7%)	6 (6.6%)
C. dubliniensis	2 (10.5%)	1 (4.5%)	2 (1.9%)	1 (1.1%)
7042100015	1 (5.3%)	0	1 (1%)	0
7142100015	0	1 (4.5%)	0	1 (1.1%)
7142140011	1 (5.3%)	0	1 (1%)	0
C. utilis	1 (5.3%)	0	2 (1.9%)	0
4271250301	1 (5.3%)	0	1 (1%)	0
4271250311	1 (5.3%)	0	1 (1%)	0
C. guilliermondii	1 (5.3%)	0	1 (1%)	0
5577352117	1 (5.3%)	0	1 (1%)	0
C. inconspicua	0	1 (4.5%)	0	2 (2.2%)
200010005	0	1 (4.5%)	0	2 (2.2%)
C. parapsilosis	0	1 (4.5%)		1 (1.1%)
5547350317	0	1 (4.5%)		1 (1.1%)
S. cerevisiae	0	1 (4.5%)		1 (1.1%)
5260000001	0	1 (4.5%)		1 (1.1%)

colony phenotypes, i.e. between "original smooth", "star", "irregular wrinkle", "ring", "mottled", "fuzzy", and "revertant smooth" in the "3153A switching system", while Soll et al. [18] demonstrated unmyceliated–heavily myceliated colony transition and white-opaque colony transition. Some of these colony morphologies were observed in our study on periodontitis [14], e.g. "original smooth", "star", "irregular wrinkle", "mottled", "fuzzy", and "revertant smooth", unmyceliated, and heavily myceliated. It has been suggested that an association between multiple colony morphologies and virulence behaviors of yeasts exists in invasion, adhesion, tissue destruction, host defense evasion, as well as acquisition of antimicrobial resistance in candidal infections [19,20].

In the present study we identified 1 genus, 6 species, and 21 biotypes in 105 yeast isolates from thrush, and 2 genera, 7 species, and 20 biotypes in 91 isolates from denture stomatitis. In our previous study we identified 1 genus, 2 species, and 11 biotypes in 58 isolates from the oral cavities of 45 healthy individuals [14]. Common species and biotypes represented over 77% of the yeast isolates in thrush and denture stomatitis and 95% of the yeasts in oral health [14], whereas unique species and biotypes represented 23% of the isolates in thrush and denture stomatitis. These results demonstrated more diverse yeast species and biotypes in thrush and denture stomatitis than in oral health, which corresponds with the diversity in colony morphology. Accordingly, several studies have

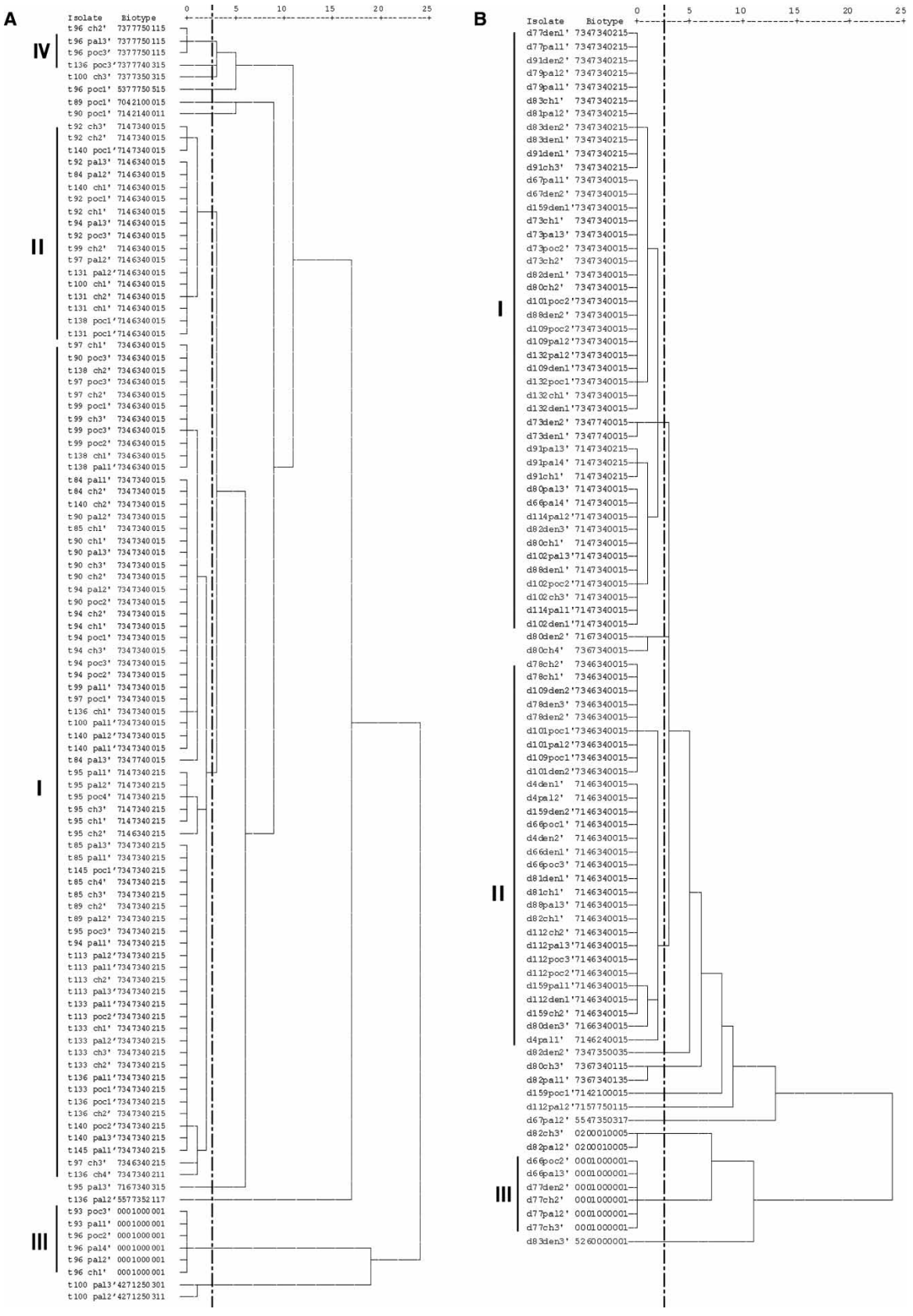

Figure 2. Dendrogram of yeast isolates and biotypes from thrush (A) and denture stomatitis (B).

demonstrated more candidal biotypes in diseased subjects than in non-diseased subjects [14,15,21]. Phenotypic plasticity might explain why *Candida* species from active infection tend to show a higher prevalence of different phenotypes than those from healthy subjects [15,20,22]. Phenotypic switching provides *Candida* species with an extraordinary level of phenotypic variability so that every colonizing

Table II. Oral distribution of yeast species and biotypes in thrush and denture stomatitis.

	Thrush		Denture stomatitis	
Oral site	Species and predominant biotype	Frequency in patients (%) ($n=19$)	Species and predominant biotype	Frequency in patients (%) ($n=22$)
Buccal mucosa	*C. albicans*	16 (84.2%)	*C. albicans*	11 (50.0%)
	7347340015	6 (31.6%)	7146340015	4 (18.2%)
	7146340015	5 (26.3%)	7347340015	3 (13.6%)
	7347340215	5 (26.3%)		
	C. tropicalis	2 (10.5%)	*C. tropicalis*	1 (4.5%)
	C. glabrata	1 (5.3%)	*C. glabrata*	1 (4.5%)
			C. inconspicua	1 (4.5%)
Palate	*C. albicans*	17 (89.5%)	*C. albicans*	17 (77.3%)
	7347340215	8 (42.1%)	7146340015	4 (18.2%)
	7347340015	6 (31.6%)	7147340015	4 (18.2%)
	7146340015	5 (26.3%)	7347340015	4 (18.2%)
	C. tropicalis	2 (10.5%)	*C. tropicalis*	2 (9.1%)
	C. glabrata	2 (10.5%)	*C. glabrata*	2 (9.1%)
	C. utilis	1 (5.3%)	*C. inconspicua*	1 (4.5%)
	C. guilliermondii	1 (5.3%)	*C. parapsilosis*	1 (4.5%)
Sulci/periodontal pockets	*C. albicans*	13 (68.4%)	*C. albicans*	7 (31.8%)
	7347340215	6 (31.6%)	7346340015	4 (18.2%)
	7146340015	3 (15.8%)	7146340015	2 (9.1%)
	7346340015	3 (15.8%)	7347340015	2 (9.1%)
	7347340015	3 (15.8%)		
	C. tropicalis	2 (10.5%)	*C. glabrata*	1 (4.5%)
	C. glabrata	2 (10.5%)	*C. dubliniensis*	1 (4.5%)
	C. dubliniensis	2 (10.5%)		
Denture fitting surface			*C. albicans*	18 (81.8%)
			7347340015	6 (27.3%)
			7146340015	5 (22.7%)
			C. glabrata	1 (4.5%)
			S. cerevisiae	1 (4.5%)

population provides enrichment in response to selective pressure in the process of rapid adaptation. Switching affects a variety of metabolic activities which have been implicated in virulence, including bud-hypha transition, antigenicity, adhesion, sensitivity to neutrophils and oxidants, secretion of proteinase, and drug susceptibility. Studies demonstrate that cells from white colonies are less hydrophobic and more adhesive than cells from opaque colonies; cells from white colonies are also more resistant to neutrophils and other cell-free oxidants; cells from opaque colonies possess phase-specific surface antigens, secrete two phase-specific aspartyl proteinases, and exhibit higher resistance to antifungal agents [22,23].

In addition to the diversity in species and biotypes, a similarity in predominant species and biotypes has been demonstrated from the yeasts in thrush and denture stomatitis. *C. albicans*, *C. tropicalis*, and *C. glabrata* dominated in both groups. *C. albicans* was the most predominant species, being detected in 89.5% of thrush patients, 90.9% of denture stomatitis patients, and in 84.2% of oral health subjects in the previous study [14]. Most isolates of *C. albicans* fell into cluster I and II biotypes, all the isolates of *C. glabrata* into cluster III, and the *C. tropicalis* isolates were dispersed in and out of the clusters. *C. tropicalis* is a major cause of septicemia and disseminated candidosis, especially in patients with lymphoma, leukemia, and diabetes. It is postulated that the pathogenicity of *C. tropicalis* is mainly due to variation in the carbohydrate assimilation ability [24,25]. *C. dubliniensis* appeared only in the subgingival areas of the thrush and denture stomatitis subjects, corresponding with our previous finding from marginal periodontitis [14]. Other studies also report the appearance of *C. dubliniensis* in periodontal pockets and discuss its unique role in subgingival areas [26–28].

There was a similarity in the predominant biotypes and biotype clustering profiles among the yeasts in thrush and denture stomatitis, with the exception of biotype 7347340215 of *C. albicans*, which was recovered more frequently from palate and gingival sulci in thrush. Interestingly, these predominant biotypes in thrush (71.5% isolates) and denture stomatitis (73.7% isolates) were also found as the dominant biotypes in oral health (75.8% isolates) [14], except that biotype 7147340015 of *C. albicans* was less frequently recovered from thrush. A number of studies even demonstrate the absence of phenotypic and genetic

hypervirulent *C. albicans* strains in disease [29,30]. Nevertheless, the present study indicated that 23% of the yeasts isolates were divergent in thrush and denture stomatitis compared to in healthy sites [14].

When comparing the biotypic profile with the genotypic profile generated from the same groups of yeasts by Random Amplification of Polymorphic DNA in our previous study [12], no obvious association between the biotypic and genotypic clusters of the yeasts in thrush and denture stomatitis was revealed. Whether the results from such phenotyping and genotyping methods can be compared remains unclear [31–33].

In conclusion, diversity of species and phenotypes has been found among the yeasts in thrush and denture stomatitis. Our findings together with ample evidence from other studies suggest that candidal commensals are predominant in thrush and denture stomatitis, but divergent *Candida* species and biotypes, constituting 23% of all the yeast isolates, should not be ignored.

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