High rate of vaginal infections caused by non-\textit{C. albicans} \textit{Candida} species among asymptomatic women

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A prospective observational study of patients attending a gynecological clinic and those referred to a clinic for genitourinary infections was undertaken with the purpose of evaluating the relative prevalence of non-\textit{C. albicans Candida} species among \textit{Candida} isolates from the vagina in different clinical settings in an area with high occurrence of vulvovaginal candidiasis. The rate of non-\textit{C. albicans Candida} species was 44.5% among asymptomatic women, 19.4% among those with sporadic vaginitis and 21% among patients with chronic vaginal symptoms ($p<0.001$ for asymptomatic vs. pooled symptomatic women). No increase in the rate of non-\textit{C. albicans Candida} was observed during a period of 4 years (1995–1998) despite a 1.57-fold increase in the sales of azole antifungal agents. Unlike some previous reports we could not document an association of non-\textit{C. albicans Candida} species with chronic vaginal symptoms or increased use of azole antifungal agents. The significantly higher rate of these yeasts in asymptomatic women is in accord with the known tendency of non-\textit{C. albicans Candida} species to cause mild symptoms.

Keywords azole antifungal agents, non-\textit{C albicans Candida} species, vulvovaginal candidiasis

Introduction

\textit{Candida} is one of the most common causes of vaginal infection [1], and the incidence of vulvovaginal candidiasis has continued to increase during the last decade [2]. According to earlier reports \textit{C. albicans} was the cause of 80–95% of cases of symptomatic fungal vulvovaginitis, whereas other \textit{Candida} species, such as \textit{C. glabrata}, \textit{C. parapsilosis} and \textit{C. tropicalis}, were responsible for the remaining cases [3,4]. More recently, an increase in the isolation rate of non-\textit{C. albicans} species, particularly \textit{C. glabrata}, has been reported [5–8], a shift that was explained by a widespread use of over-the-counter drugs [9]. Other than the epidemiological importance of reporting changes in prevalence of pathogens and investigating the possible causes, documenting this new trend might have therapeutic implications, because non-\textit{C. albicans} species appear to be less responsive to azole therapy than \textit{C. albicans} [8,10,11]. We sought, therefore, to evaluate the relative prevalence of non-\textit{C. albicans Candida} vaginal infections in different clinical settings in an area with high prevalence of vulvovaginal candidiasis [12].

Materials and methods

The study population was composed of three groups of women: (a) asymptomatic women who were seen at a gynecological clinic in Bat-Yam, Israel, between 15 November 1994 and 15 June 1995 for routine check-up or for prescription of contraceptives, and who did not have vulvovaginal symptoms in the preceding 6 months or more; (b) women who presented to the same clinic during the same period with acute vulvovaginal symptoms (at least one of the following: vaginal discharge, itching, burning); and (c) women referred for chronic vulvovaginal complaints to a clinic for genitourinary infections at the E. Wolfson Hospital, Holon, Israel, from January 1995 through December 1998. Holon and Bat-Yam are neighboring towns in the Tel Aviv area and have similar populations. The two clinics served both towns’ citizens equally. The patients were representative of a non-promiscuous middle-class population (88% had $\leq 1$ sexual partners in the preceding year). Each patient
underwent an evaluation that included a standardized questionnaire (covering demographic information, medical history, sexual practice, history of vaginitis and vaginal symptoms), a pelvic examination and vaginal pH determination. Vaginal smears were obtained for Gram staining, saline and potassium hydroxide microscopy, and fungal culture. The specimens for culture were plated on Sabouraud agar (Difco Laboratories, MI, USA), and cultures were incubated at 35 °C for 48–72 h. Positive growth was evaluated for germ tube formation after incubation of the yeast-human serum suspension at 35 °C for 2 h. Germ tube-negative isolates were identified with the ID 32C identification system (Biomerieux, Marcy-l’Etoile, France). No attempt was made to rule out contaminating yeasts because of their presumed rarity.

Patients with multiple positive cultures were included only once. Patients with *C. albicans* isolates were compared with patients who carried non-*C. albicans Candida* strains using the GraphPad Prism version 2.0 statistical software package (Intuitive Software for Science, San Diego, CA, USA). Categorical data were analyzed for significance by means of a $\chi^2$ test. For comparison of means the unpaired $t$-test was used.

**Results**

One hundred and seventy-eight patients were evaluated at the gynecological clinic. *Candida* species were isolated in 71 women (39.8%). The isolation rate was 33% (33/100) among the asymptomatic women and 48.7% (38/78) among the symptomatic patients. Isolates from 58 patients were available for species identification. The prevalence of non-*C. albicans Candida* strains was 31.4% (18/58). The 18 non-*C. albicans* isolates included 11 *C. glabrata*, three *C. parapsilosis* and four other species (one each of *C. krusei*, *C. guilliermondii*, *C. famata* and *Saccharomyces cerevisiae*). Of the 58 isolates, 27 belonged to asymptomatic women, 12 (44.5%) of which were non-*C. albicans* strains; 31 isolates were recovered from symptomatic patients, six (19.4%) of which were non-*C. albicans* strains (Table 1). The difference in the rate of non-*C. albicans Candida* species in the two groups was statistically significant ($\chi^2$, $p<0.01$).

During the 4-year study period, approximately 1000 patients with chronic vaginal symptoms were seen at the clinic for genitourinary infections; *Candida* was isolated in 110. Non-*C. albicans Candida* was detected in 23 (21%) of the patients: there were 12 cases of *C. glabrata*, four cases of *C. parapsilosis*, three cases of *C. tropicalis*, two of *C. krusei* and two cases involving other species (*C. norvegiensis* and *Saccharomyces cerevisiae*). In three patients, *C. albicans* and non-*C. albicans* species were isolated concomitantly, and in another five cases they were isolated on separate occasions. The patients yielding mixed isolations were evaluated as non-*C. albicans* cases. When the rate of non-*C. albicans Candida* species in asymptomatic women was compared to that in all symptomatic patients (acute and chronic combined), the difference was highly statistically significant ($\chi^2$, $p<0.01$).

Table 2 shows the annual isolation rate of non-*C. albicans* species in patients with chronic vaginal complaints between 1995 and 1998. The rate of isolation of non-*C. albicans* strains had decreased over the years; however, the difference was statistically insignificant.

Table 3 shows some epidemiological and clinical characteristics of the patients with non-*C. albicans Candida* and those with *C. albicans*. There were no statistically significant differences between the two groups in mean age, mean years of schooling, parity (percentage of women that were ever pregnant and mean number of pregnancies), parity (percentage of women that had children and mean

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**Table 1** Proportion of non-*C. albicans Candida* species in patients with different categories of symptoms

<table>
<thead>
<tr>
<th>Site</th>
<th>Nature of patients’ symptoms*</th>
<th>No of Candida isolates</th>
<th>Proportion of non-<em>C. albicans</em> Candida isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynecological clinic</td>
<td>No symptoms</td>
<td>27</td>
<td>44.5%†</td>
</tr>
<tr>
<td></td>
<td>Acute symptoms</td>
<td>31</td>
<td>19.4%†</td>
</tr>
<tr>
<td>Clinic for genitourinary infections</td>
<td>Chronic symptoms</td>
<td>110</td>
<td>21%</td>
</tr>
</tbody>
</table>

*See text for details; †$p<0.01$
number of children), contraceptive methods, use of hygienic devices, use of antibiotic agents in the preceding month, use of antifungal agents and prevalence of diabetes mellitus.

**Discussion**

The results of the present study are unique in several aspects. We have shown that in asymptomatic women the rate of non-*C. albicans Candida* isolation from the vagina was significantly higher than that in patients with vaginal symptoms. This finding should not surprise us if we consider that the typical clinical presentation of non-*C. albicans Candida* infections is characterized by milder symptoms than those caused by *C. albicans* vaginitis [Q1, 13–15]. One should thus expect non-*C. albicans Candida* colonization to be more often asymptomatic than *C. albicans* infection would be. Moreover, clinical experience has thought us that in a considerable proportion of symptomatic patients with positive vaginal smears and cultures for non-*C. albicans Candida* species, symptoms may persist after therapy despite laboratory eradication of the fungus, leading to the conclusion that the symptoms were unrelated to the colonization, which was in fact asymptomatic. A similar trend was described by Oriel et al. [16] in a small group of patients with *C. glabrata*, more than half of whom were asymptomatic. Redondo-Lopez et al. [11] reported that 42% of *C. glabrata* cases in their series of patient attending a vaginitis clinic were associated with symptomatic vaginitis, whereas 30% of the cases were totally asymptomatic with normal physical examination. In the remaining 27%, the role of *C. glabrata* in causing symptoms was unclear because of concomitant pathologies. In a study conducted in the 1970s among asymptomatic women [17], non-*C. albicans* fungi accounted for 27.7% of all fungal species recovered from the vagina. Although the study did not include a control group of symptomatic women, the above-reported rate of non-*C. albicans* spp. was markedly higher than those reported at the same period for symptomatic patients (~6%) [15] or unselected women (~16%) [15,18]. We are not aware of any previously reported sound study comparing the prevalence of non-*C. albicans Candida* of the vagina in asymptomatic and symptomatic women.

Our finding of very similar rates of non-*C. albicans Candida* infections in patients with sporadic vaginitis (less than three episodes in the preceding year) and in those with chronic disease challenges previous claims about the increase risk of non-*C. albicans Candida* infections in patients with chronic vaginitis. The association of non-*C. albicans Candida* infection with chronic vaginitis was evoked in a number of studies [6,7,13,19], three of which [7,13,19] emanated from a single center (one of these [13] being confined to the study of *C. glabrata* infection). The fourth study [6] evaluated only patients with chronic vaginal symptoms and found by contrast that patients with symptoms of > 3-year duration were somewhat more common (30%) in the *C. albicans* group than among patients with non-*C. albicans* infection (26%). In the series of Redondo-Lopez et al. [11], only 9% of patients with *C. glabrata* vaginitis suffered recurrent symptomatic episodes. One should be attentive to the possibility that published data may be marred by selection bias due to the referral basis of population studied. We have overcome this obstacle by studying women from different clinical settings and various clinical presentations. The present study is to our knowledge the only one to compare a population of women with acute sporadic symptoms to a group of patients with chronic or recurrent complaints.

In contrast with previous studies [5–8], we did not find an increase in the prevalence of non-*C. albicans Candida* vaginitis from 1995 to 1998. In fact, a consistent decline in the rates of non-*C. albicans Candida* species was observed over the study years despite an increase in azole sales in Israel during the same period. However, the sample size was small and the observed trend was
statistically insignificant. Consumption of fluconazole grew 2.6-fold, that of clotrimazole 1.3-fold and that of other azoles 1.6-fold. Although the expanding use of azoles has been held responsible for the increase in rates of non-C. albicans Candida infections [9], it apparently had no effect on the present study population. Moreover, no difference was observed in the previous use of antifungal agents between patients with non-C. albicans infection and those infected with C. albicans. The potential impact of antifungal agents might have been dissipated by the high rate of asymptomatic carriers of non-albicans strains who used these drugs markedly less than did symptomatic patients. It should also be noted that two other factors which may increase the prevalence of non-C. albicans Candida infections, namely HIV infection and over-the-counter availability of vaginal antifungal agents [1,7,9], were not pertinent in our case. Our results are, thus, in accordance with those of two large multicenter studies that failed to demonstrate any increase in the prevalence of vaginitis caused by non-C. albicans species [20,21]. Finally, we could not confirm previously reported associations of non-C. albicans Candida vaginitis with a variety of factors such as older age [13], lower socioeconomic status [13], use of tampons [13] and diabetes mellitus [22].

References

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