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CLINICAL STUDY

Vaginal *Candida parapsilosis*: Pathogen or bystander?

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Abstract

***Objective*:** *Candida parapsilosis* is an infrequent isolate on vaginal cultures; its role as a vaginal pathogen remains unstudied. This retrospective study of women with positive culture for *C. parapsilosis* sought to characterize the significance of this finding and its response to antifungal therapy.

***Methods*:** From February 2001 to August 2002, we identified all individuals with positive fungal isolates among a population of women with chronic vulvovaginal symptoms. Charts of women with *C. parapsilosis* cultures were reviewed with regard to patient demographics, clinical presentation and therapeutic response. Mycological cure, defined as a negative fungal culture at the next office visit, and clinical cure, i.e. symptom resolution, were determined for each subject.

***Results*:** A total of 582 women had positive vaginal cultures for 635 isolates, of which 54 (8.5%) were *C. parapsilosis*. The charts of 51 subjects with *C. parapsilosis* were available for review and follow-up cultures and clinical information were available for 39 (76.5%). Microscopy was positive in 9 (17.6%). Antifungal treatment resulted in mycological cure in 17/19 patients with fluconazole, 7/7 with butoconazole, 6/6 with boric acid, 1/1 with miconazole and occurred spontaneously in 6/7: 24/37 (64.9%) patients with a mycological cure experienced clinical cure.

***Conclusions*:** Although *C. parapsilosis* is often a cause of vaginal symptoms, it seems to respond to a variety of antifungal agents and may even be a transient vaginal colonizer.

Keywords: *Vaginitis, vulvovaginal candidiasis, Candida parapsilosis*

Introduction

Vaginitis is the most common reason for patient visits to obstetrician-gynecologists and accounts for over 10 million physician office visits annually [1]. Among the most common diagnosis in women presenting with vaginal irritation is vulvovaginal candidiasis(VVC); 80% to 90% of sporadic, uncomplicated cases of VVC are caused by the species *Candida albicans* [2]. However, other species may be responsible for up to 30% of recurrent VVC cases [3]. The identification of non-*C. albicans* species in vulvovaginal infection is important because some non-*C. albicans* species are resistant to the standard azole therapy used to clear the infection. The most common non-*C. albicans* species that have been implicated in recurrent VVC include *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, and *Saccharomyces cerevisiae*. To a lesser extent *Candida parapsilosis* has been identified as a vaginal isolate, but little evidence exists to support its role as a vaginal pathogen; it may simply represent colonization of the normal vaginal environment.

The identification of non-*C. albicans* species on vaginal fungal culture has become more common in recent years. This may partially be due to the increased usage of vaginal fungal cultures for accurate diagnosis of complicated or recurrent VVC, as recommended by several authors [3, 4]. Others believe that the increase in non-*C. albicans* isolates is secondary to the increased use and availability of over-the-counter antimycotic preparations [5, 6]. Regardless of the reason, a positive culture for non-*C. albicans* yeast species such as *C. parapsilosis* from a symptomatic patient may sometimes lead to treatment. However, with the less common types of yeast, determining whether treatment is appropriate and what it should consist of may not be clear.

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C. parapsilosis is a relatively infrequent isolate on vaginal fungal culture, and there have been no studies that look specifically at its relevance to symptoms. Because *C. parapsilosis* produces certain virulence factors such as acid proteinases, it has been hypothesized that this organism is a vaginal pathogen [7] but it remains relatively unstudied as a cause of VVC. The purpose of this descriptive study was to determine the prevalence of *C. parapsilosis* isolates in our population, to evaluate the symptoms experienced by women with positive vaginal cultures, to examine the effectiveness of different antifungal remedies against *C. parapsilosis* and to determine whether a negative follow-up culture was associated with the relief of vaginal complaints. In doing so, our goal was to determine whether *C. parapsilosis* represents a true vaginal pathogen.

Methods

The study population was derived from women referred by their primary care physicians for medical treatment of chronic vulvovaginal complaints at an outpatient vaginitis referral center. From February 2001 to August 2002, all individuals with positive vaginal fungal isolates were identified using office flowsheets maintained to track and notify patients of their results. All women with a positive culture for *C. parapsilosis* were selected for retrospective chart review. Data regarding demographics, medical history, symptom history, and treatment were obtained from standardized patient chart notes. Follow-up information was obtained from additional chart entries. The Institutional Review Board at Thomas Jefferson University Hospital approved the study protocol.

Two clinicians, both specialized in the treatment of chronic vulvovaginal complaints, collected data and examined all subjects throughout the study period. Saline wet-mount preparations, 10% potassium hydroxide (KOH) preparations, and vaginal pH determinations were obtained routinely for women seen at the center. Saline and KOH preparations were performed by spreading vaginal secretion samples on separate slides, adding the appropriate solutions, and then evaluating with both low- and high-power microscopy for the presence of fungal elements, altered vaginal flora, clue cells, trichomonads, vaginal cytology and white blood cells. Sterile culture swabs were used to sample the external vulvar skin and lateral vaginal sidewalls on speculum exam for yeast cultures. Three laboratories analyzed vaginal swabs for fungal isolates. The patient's insurance carrier dictated which laboratory site was used to analyze the fungal swab.

The Thomas Jefferson University laboratory (Philadelphia, PA, USA) identified yeast isolates by first plating vaginal swabs onto CHROMagar plates. If growth was seen on the CHROMagar, then a saline wet mount was prepared to confirm the presence of yeast species. Germ tube-positive species were identified as *C. albicans*. Germ tube-negative colonies were further speciated using the Rapid ID System (Remel, Lenexa, KS, USA). This presumptive diagnosis was simultaneously confirmed using cornmeal agar and urea tubes. Quest Diagnostics Laboratory (Philadelphia, PA, USA) used inhibitory mold agar for the initial plating of vaginal swabs. Germ tube-negative colonies were further isolated using Sabouraud agar. Pure colonies were then speciated using API 20 C (BioMerieux Vitek Inc., Hazelwood, MO, USA), a carbohydrate assimilation test, in conjunction with morphology testing for proper identification. Laboratory Corporation of America (New Castle, DE, USA) initially seeded Sabouraud-dextrose agar and Mycosel agar with vaginal swabs. Germ tube-positive species were confirmed as *C. albicans* by the concurrent formation of chlamydospores in cornmeal agar. Germ tube-negative colonies were further speciated using the YBC card (BioMerieux Vitek, Hazelwood, MO, USA). Confirmatory testing was performed using the API 20 C system.

Symptoms were documented at the index visit and at the follow-up visit. Follow-up visits occurred between 1 and 4 months after the initial *C. parapsilosis* culture. Intervening treatments and compliance with treatment were reviewed, as well as change in vaginal symptoms. A clinical cure was defined as complete resolution of the symptoms noted at the time of the index visit. Mycological cure was defined as resolution of *C. parapsilosis* on follow-up culture. Cases were documented as a spontaneous mycological cure if the follow-up culture did not grow *C. parapsilosis* and antifungal treatment was never initiated.

Statistical analysis was performed using EpiInfo 2002 (CDC, Atlanta, GA, USA). Two- tailed chi-square statistical analysis was carried out using the Mantel—Haenszel formula. Statistical significance was defined as a p value < 0.05.

Results

A total of 582 women had positive vaginal cultures for 635 isolates; 609 organisms were grown on pure culture and 13 cultures contained growth of mixed species. Table I shows the distribution of isolates among this patient population. Isolates positive for *C. parapsilosis* were found in 54 (8.5%) of women, 1 of whom had a culture positive for both *C. albicans* and *C. parapsilosis*. The charts of 51 patients with *C. parapsilosis* were available for review, and follow-up culture and clinical information was available in 39

Table I. Distribution of yeast isolates.

Species	Number	Percentage
Candida albicans	457	72.0%
Candida glabrata	74	11.7%
Candida parapsilosis	54	8.5%
Rhodotorula spp.	18	2.8%
Saccharomyces cerevisiae	9	1.4%
Candida lusitaniae	5	0.8%
Other species	18	2.8%

(76.5%). With the exception of 3 subjects, all women were seen for follow-up within 6 weeks of the index visit.

The median patient age was 46 years (range 19 to 86 years); 49 women (96.1%) were Caucasian and 18 (35.3%) were nulliparous. Of the 21 women (41.2%) who were menopausal, 19 (90.5%) were receiving estrogen therapy. Oral contraceptives were being used by11 (21.6%), and 21 (41.2%) had used antifungals and 10 (19.6%) had used topical steroids within 1 month of positive culture. At the time of the index visit, complaints comprised itching in 27 (53%), burning in 22 (43.1%), abnormal discharge in 11 (21.6%) and dyspareunia in 16 (31.4%) women. However, 9 (17.6%) were asymptomatic at the time of positive culture although microscopy was also positive, and of these 4 were seen for a follow-up visit.

In this study, 37 women (72.5%) had associated vulvovaginal conditions. Of these, the most common conditions were atrophic vaginitis in 11 (29.7%), irritant dermatitis in 8 (21.6%), lichen sclerosus in 8 (21.6%) and vulvar vestibulitis in 5 (13.5%). Other diagnoses included vulvodynia, herpes simplex, recurrent bacterial vaginosis and desquamative inflammatory vaginitis, and 8 women (21.6%) carried the diagnosis of two vulvovaginal conditions in addition to *C. parapsilosis* vaginitis. Between the index and follow-up visits, the only change in treatment was the institution of antifungal therapy.

A variety of antifungal regimens were used in patients with cultures positive for *C. parapsilosis*. The treatments included boric acid, 600 mg twice daily for 2 weeks, buconazole, two vaginal applicator doses 1 week apart, fluconazole, 200 mg twice weekly for 1 month, and miconazole, one applicator nightly for 7 days. The choice of antifungal agent was left to the discrimination of the clinician. Antifungal treatment resulted in mycological cure in 17/19 cases with fluconazole, 7/7 with buconazole, 6/6 with boric acid, and 1/1 with miconazole. Mycological cure also occurred spontaneously in 6/7 women, of whom 24/37 (64.9%) experienced clinical cure. Of those with associated vulvovaginal conditions, 14/26 women achieved both mycological and a clinical cures (10 with treatment and 4 without treatment), whereas 10/13 without associated vulvovaginal conditions achieved both clinical and mycological cures (9 with treatment and 1 without treatment).

Discussion

More than 80% of VVC cases are caused by the species *C. albicans*. In mild cases the organism responds to a variety of standard azole remedies, wheeas complicated or recurrent cases respond to more aggressive multiple-dose regimens. The remaining cases of vaginal candidasis are caused by non-*C. albicans* species that appear to have higher minimum inhibitory concentrations to standard azole therapies [6]. Additionally, some investigators have questioned whether some non-*C. albicans* species cause vulvovaginal symptoms at all [7, 8]. Most of these studies evaluated the non-*C. albicans* isolates collectively, without studying symptomatology or the mycotic response of minor isolates individually. To our knowledge, this is the largest study that looks exclusively at the minor isolate *Candida parapsilosis*, its prevalence, symptomatology and mycotic response.

The prevalence of *Candida parapsilosis* in our study was slightly higher (8.5%) than that previously documented. Other authors report prevalence of 5% or less for *C. parapsilosis* in symptomatic patients; however, these studies evaluate prevalence in a much smaller population than ours [3, 4]. Sood et al. report a prevalence of 12% in their study of terconazole for treatment of non-*C. albicans* vaginitis, but studied only 28 patients, 3 of whom had *C. parapsilosis* isolates [9]. Because this study was specifically a study of non-*C. albicans* cases, the 12% incidence of *C. parapsilosis* in the series may not be an accurate reflection of the incidence in larger population of women with complicated VVC. Our study may over-represent the true prevalence because of the selection bias of our population. Women seeking treatment at a vaginitis referral center may be more likely to have cultures positive for *C. parapsilosis*, because cases of uncomplicated candidiasis are eliminated from a referred population.

The symptoms experienced by women with *C. parapsilosis* infection were typical of any vulvovaginal infection. Complaints included itching (53%), burning (43.1%), dyspareunia (31.4%) and abnormal discharge (21.6%). Approximately 20% appeared to be asymptomatically colonized with *C. parapsilosis* at the index visit. Certainly, the reported complaints are not unique to VVC and could also be attributed to secondary diagnoses affecting the vulvovaginal area, which were present in 72.5% of the study population. Likewise, objective findings suggestive of candidiasis

were unhelpful in diagnosing vaginal *C. parapsilosis*, as only 17.6% of cases demonstrated yeast species on saline microscopy. In the few subjects with positive microscopy, the objective finding was not helpful in predicting whether the woman would achieve a mycotic and symptomatic cure with treatment. This underscores the usefulness of vaginal fungal cultures for deciphering the diagnostic ambiguity of vulvovaginal conditions. Without a positive fungal culture, the isolate could masquerade as a number of other conditions, eluding appropriate treatment.

When pretreatment and post-treatment symptoms were compared, the data from this study strongly suggested that vaginal *C. parapsilosis* can be a pathogen responsible for vulvovaginal complaints. Symptomatic relief was experienced by 65% of women who cleared the isolate on follow-up culture. In those who did not report symptomatic relief at their follow-up visits, 10/13 had other vulvovaginal conditions. It is possible that *C. parapsilosis* was contributing to their symptoms but that their other problems prevented complete symptomatic relief. Alternatively, it may be that *C. parapsilosis* was an innocent bystander in those cases where clearance was not associated with clinical cure. Furthermore, in women with other vulvovaginal conditions who did get better, it is possible that their improvement was not secondary to the disappearance of *C. parapsilosis*, but rather to improvement of their other conditions with further time.

Agatensi and colleagues hypothesized that *C. parapsilosis* is a potential vaginal pathogen, in that isolates demonstrate acid (aspartyl) proteinase activity [7]. This enzyme is capable of hydrolyzing mucosal IgA and interfering with the natural vaginal barrier to infection. Additionally, the isolates cultured from symptomatic subjects demonstrated significantly higher proteinase activity than control cultures. The only other candidal isolate capable of significant acid proteinase activity is *C. albicans*, a known vaginal pathogen. It seems logical that the proteolytic acitivity shared by both *C. parapsilosis* and *C. albicans* may explain their common behavior as pathogenic organisms. Additionally, women suffering with multiple vulvovaginal diagnoses, and with theoretically compromised integrity of the vaginal mucosa, may be more susceptible to infection with *C. parapsilosis* because of the acid proteinase activity of the organism. This suggestion is supported by the observation that several of the women who spontaneously cleared *C. parapsilosis* did so while receiving non-antimycotic treatment for other vulvovaginal conditions. Perhaps restoration of healthy vaginal epithelium diminishes the ability of *C. parapsilosis* to infect its host.

Despite its apparent virulent capability in the vagina, our data also suggest that vaginal infection with *C. parapsilosis* is treated and cleared from subsequent culture relatively easily. In all but 2 cases in this series, the infection cleared with a single course of antimycotic therapy. Ot these 2 cases, 1 cleared the isolate with a second antimycotic agent, and the other cleared the isolate while receiving steroid treatment for a separate vulvovaginal condition. Admittedly, there is an inherent treatment bias that may skew the results toward a relatively high mycotic response rate, in that all the women received fairly aggressive treatment regimens. The finding that *C. parapsilosis* seems to clear fairly easily with antifungal therapy is not too surprising. We did not obtain *in vitro* susceptibility testing of our isolates to various antifungal agents. However, when Lynch and Sobel evaluated 377 clinical vaginal yeast isolates, they found that the 26 *C. parapsilosis* isolates seemed to have sensitivities which were quite similar to those of the *C. albicans* isolates [10]. Interestingly, 6 subjects cleared the isolate without specific antifungal therapy.

Further study of *Candida parapsilosis* should prospectively compare mycotic response with standard single-dose azole treatment, aggressive multiple dose regimens, and no treatment. In comparing these treatment groups, it may become clear that *C. parapsilosis* does not demonstrate the inherent azole resistance displayed by other non-*C. albicans* species. The number of cases of spontaneous isolate resolution suggests that *C. parapsilosis* may have limited virulent longevity in the vaginal environment.

In summary, *Candida parapsilosis* is a significant non-*C. albicans* vaginal isolate responsible for vulvovaginal complaints. Even when it appears to be a transient vaginal colonizer, it may be associated with vulvovaginal symptoms. In symptomatic patients, antifungal treatment should be expected to achieve symptomatic cure in a large number of patients. Properly controlled studies are still necessary to determine the most efficient antimycotic treatment regimen. In view of the relative rarity of this organism, an appropriately powered, randomized controlled trial is unlikely. However, in cases with a complicated history of recurrent candidiasis, extended antifungal treatment with fluconazole, buconazole, miconazole, or boric acid is reasonable but may be more aggressive than truly necessary.

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