Symptomatic Vulvovaginitis Due to Fluconazole-Resistant Candida albicans in a Female Who Was Not Infected with Human Immunodeficiency Virus

Azoles that are active against mycoses are an important advance in the management of serious fungal infections. Recent reports of clinical resistance and failure associated with triazole therapy have been of considerable concern [1-8]. Candida albicans isolates with high-level resistance to azoles (including fluconazole) have been identified, particularly in patients with advanced HIV infection. These isolates are of concern because they may represent the first step in a series of events leading to resistance. The selection of resistant isolates seems to be independent of azole usage. Many of the isolates tested are resistant to fluconazole (MIC, > 40 μg/mL), itraconazole (MIC, 0.39 μg/mL), and flucytosine (MIC, 0.63 μg/mL) and that they were susceptible to anidulafungin (MIC, 0.8 μg/mL) and voriconazole (MIC, 0.03 μg/mL) [9].

The patient was a 38-year-old female with a 3-month history of continuous yeast vaginitis who was referred to the Vaginitis Clinic at Wayne State University (Detroit) on 3 March 1995. Before the referral, the patient had experienced only occasional episodes of candidal vaginitis. Symptoms at presentation included pruritus, vulvovaginal burning, and dyspareunia. During the 3 months before presentation, the patient had received over-the-counter topical antifungal agents as well as prescribed terconazole and fluconazole (150 mg orally daily) for 1 month.

A pelvic examination revealed erythema and edema of the vulva and vagina, with extensive vulvar excoriation. Examination of the cervix and a bimanual pelvic examination did not reveal any abnormalities. The vaginal pH was 4.3, and a test for amine was negative. Microscopic examination of vaginal secretions in saline revealed no increase in polymorphonuclear neutrophils, no clue cells, and no trichomonads; however, numerous yeast blastospores as well as pseudohyphae were seen. On the assumption that the patient had azole-susceptible C. albicans vulvovaginitis, she was initially treated with fluconazole (150 mg administered every 4th day; three doses total). Culture of vaginal specimens yielded C. albicans.

The patient returned to the clinic 2 weeks later, at which time her condition was only marginally improved (she still had signs of vulvovaginitis); microscopic examination of vaginal secretions in 10% KOH revealed yeast, and culture of a vaginal specimen again yielded C. albicans. While susceptibility tests were being performed, she was treated with clotrimazole vaginal suppositories (100 mg daily for 7 days).

The patient returned to the clinic 10 days later, at which time she was still uncomfortable and had persistent clinical signs of vulvovaginitis; microscopic examination of vaginal secretions in 10% KOH again revealed yeast, and culture of a vaginal specimen again yielded C. albicans. There was no question of lack of compliance with her medications. The patient received therapy with boric acid (600-μg vaginal capsule twice daily for 2 weeks). She returned to the clinic after 17 days; at that time she was asymptomatic and a pelvic examination did not reveal any abnormalities. The results of all laboratory studies (including cultures) were negative, and follow-up examination 6 weeks later revealed that she was clinically and mycologically cured.

In vitro susceptibility tests performed according to NCCLS (National Committee for Clinical Laboratory Standards) methodology [9] revealed that the vaginal C. albicans isolates were susceptible to amphoterin B (MIC, 0.01 μg/mL), miconazole (MIC, 0.05 μg/mL), and fluconazole (MIC, 0.63 μg/mL) and that they were resistant to fluconazole (MIC, > 40 μg/mL), itraconazole (MIC, 6.25 μg/mL), and ketoconazole (MIC, 3.12 μg/mL). The C. albicans isolates had intermediate susceptibility to clotrimazole (MIC, 0.39 μg/mL). All three isolates were compared with use of CHEF (contour-clamped homogeneous electric field) typing (data not shown) and found to be an identical C. albicans clone.

To our knowledge, azole-resistant C. albicans has not been previously reported as a cause of vulvovaginitis. We recently reported the results of susceptibility testing of over 500 vaginal yeast isolates, including 300 isolates of C. albicans, obtained from patients in our clinic; no evidence of azole resistance was observed [10]. Our patient's case demonstrated high-level resistance to fluconazole as well as cross-resistance to ketoconazole and itraconazole, drugs that she had not received. She had received a prolonged course of daily fluconazole for 1 month.

We believe that our case is an example of fluconazole resistance that was associated with the development of cross-resistance to other azoles in a vaginal strain of C. albicans in an immunocompetent patient who was not exposed sexually or otherwise to a reservoir that might have selected for resistance in C. albicans. Unfortunately, the specimen of C. albicans isolated before the course of fluconazole was administered was not available to determine preexposure susceptibility; thus, it is unclear at which stage resistance to fluconazole developed. Since superinfection with a resistant isolate is unlikely, it is possible that our patient was initially infected with a fluconazole-resistant strain or that resistance developed during topical azole therapy or under the selective pressure...
of long-term fluconazole therapy. We suggest that clinicians should institute measures for detecting fluconazole resistance in otherwise healthy patients.

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References

Serum Levels of Penicillin in Basic Trainees in the U.S. Army Who Received Intramuscular Penicillin G Benzathine

The most important advent in the treatment of streptococcal pharyngitis and the prevention of primary and secondary rheumatic fever as well as the control of these diseases has been the development of intramuscular penicillin G benzathine (PGB), which became available in the United States in 1952. A single intramuscular injection of PGB (with the dosage adjusted according to weight) produces serum levels of penicillin G that are relatively low but that are inhibitory for essentially all strains of group A β-hemolytic streptococci (GABHS) for up to 4 weeks [1]. Because of these advantages and since compliance was assured, intramuscular PGB evolved as the “gold standard” for the treatment of streptococcal pharyngitis and the agent of choice for controlling outbreaks of streptococcal infection and preventing primary rheumatic fever in basic trainees in the military [2].

It is surprising that there have been no reports of studies of serum penicillin levels in highly active basic trainees in the military who received the standard 1.2 million units of intramuscular PGB at the beginning of their training; PGB has been used to control streptococcal infection in these populations of young adults with great success since the mid-1950s [2]. This study was undertaken to provide this information.

Study subjects were newly arrived army recruits who reported to Fort Sill, Oklahoma, for 8 weeks of basic training. An integral part of basic training is strenuous exercises involving daily calisthenics (including sit-ups and push-ups) and a 2-mile run three times weekly. Ongoing monitoring of streptococcal infection in trainees prompted routine administration of 1.2 million units of intramuscular PGB to the entire cohort of several hundred soldiers in each training cycle shortly after they arrived at the training center. Members of the study training cycle were counseled as to the purpose of the study, and 125 volunteers signed informed consent forms. All participants received 1.2 million units of PGB (bicillin L-A, lot 2931727 [expiration date, January 1995]; Wyeth-Ayerst Laboratories, Philadelphia), in the upper outer gluteal region with use of a 3.2-cm, 20-gauge needle on the morning of 3 March 1994. The assay of this lot by Wyeth-Ayerst Laboratories revealed that each 2-mL injection contained 1,248,200 units of PBG.

Ten-mL samples of venous blood were drawn from each participant at 1, 7, 14, 21, and 28 days after the penicillin injection. Immediately after the samples were obtained, sera were separated and frozen at −80°C. All samples were submitted for assay for determination of penicillin concentration within 1 week after the final sample (day 28) was collected.

An assay for determination of serum penicillin concentration was performed with use of an agar diffusion method that was previously described [3]. Validation of the assay was performed in triplicate, and the minimum concentration of penicillin that could be detected was 0.006 µg/mL. Any sample below 0.006 µg/mL was considered to be 0.005 µg/mL for analysis. The upper limit of the sensitivity of the assay was considered to be anything that could be achieved by serum dilution.

Linear regression modeling (SuperANOVA software, Abacus Concepts, Berkeley, CA) was used to relate penicillin concentrations at varied intervals after the injection to the independent vari-