An unusual case of recurrent vaginal discharge: Diagnostic and therapeutic dilemma

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Abstract
Abnormal vaginal discharge is common among the females of the reproductive age group. Vulvovaginitis caused by azole-resistant Candida albicans is rare. Recurrent vulvovaginal candidiasis (RVVC) causes significant patient distress and morbidity. The vaginal microflora is a complex micro-ecological environment comprising different microbiological species in variable quantities and relative proportions. Any disturbance in the aforesaid causes vaginitis, for instance, aerobic vaginitis (AV) results from the displacement of healthy vaginal Lactobacillus species with aerobic pathogens. We report AV with RVVC caused by C. albicans resistant to even second generation azoles which has not been previously reported to the best of our knowledge.

Key words: Aerobic vaginitis, azole-resistant Candida albicans, recurrent vulvovaginal candidiasis, vaginal discharge

Introduction
Abnormal vaginal discharge is frequent among women of the reproductive age group, usually related to bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis. Less than 5% females with VVC experience recurrent VVC (RVVC), that is, four or more episodes of symptomatic VVC in a year. Candida albicans is the most common cause of VVC,[1] whose resistance to azoles is rare. Aerobic vaginitis (AV) results from the displacement of healthy vaginal Lactobacillus species with aerobic pathogens (Enterococcus faecalis, Escherichia coli, Staphylococcus aureus, and Group B Streptococci) triggering localized vaginal inflammatory immune response. We report an interesting case of AV with RVVC caused by C. albicans resistant to even second generation azoles in an immunocompetent female which has not been previously reported to the best of our knowledge.

Case report
A 22-year-old unmarried sexually active, immunocompetent female presented with thick, nonfoul smelling vaginal discharge associated with itching and burning sensation for 1 week. She developed recurring episodes of symptomatic vaginitis during the last year. She was not on any drugs (antibiotics, corticosteroids, or oral contraceptives pills), had no significant past medical or family history including atopy. The patient had single regular asymptomatic healthy male sex partner. General physical examination was normal. Genital examination showed curdy white vaginal discharge [Figure 1], vulval and labial erythema, edema and erosions over labia majora. Per speculum examination did not show any signs of cervicitis. Vaginal pH was 4, wet mount and whiff test were negative. Microscopy revealed abundant pseudohyphae and spores (KOH and gram stained vaginal smears examination). Routine hematological and biochemical tests along with serum blood glucose, serological screening for HIV, syphilis and hepatitis B, and urinalysis were normal. VVC was our presumptive diagnosis which we treated with oral fluconazole 150 mg single dose, clotrimazole vaginal pessaries 100 mg daily for 6 days and general measures. The patient reported reduced vaginal discharge and partial symptomatic relief followed by aggravation. In view of RVVC, we prescribed oral fluconazole 150 mg three doses every 3rd day followed by the maintenance regime of weekly 150 mg oral fluconazole. After each course of antifungal therapy, her symptoms initially improved, and then recurred few days later. Oral itraconazole and sertaconazole vaginal pessary were tried. Three months later, she presented with profuse, foul smelling yellowish vaginal discharge which was associated with marked pruritus [Figure 2]. Vaginal pH was 5.5; wet mount and whiff test were negative. Microscopy revealed abundant pseudohyphae and spores (KOH and gram stained vaginal smears examination) along with markedly reduced lactobacilli, presence of polymorphs, Gram-positive cocci in clusters, Gram-negative bacilli, and absence of clue cells (Gram stain). The diagnosis of RVVC with AV was...
Table 1: Differences between aerobic vaginitis and bacterial vaginosis

| Bacterial vaginosis                                                                 | Aerobic vaginosis                                                                 |
|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Caused by overgrowth of anaerobes                                                  | Caused by overgrowth of aerobes                                                  |
| Gardnerella vaginalis, Mobiluncus                                                 | Group B streptococci, Escherichia coli, Staphylococcus aureus, Enterococcus faecalis |
| Pauci-symptomatic, no features of vaginitis or inflammation                       | Red inflamed vagina, burning, pain or dyspareunia (12%)                          |
| Watery gray leucorrhea                                                             | Yellow discharge (70%)                                                            |
| Fishy smell elicited or enhanced by the addition of 10% KOH (seen in 80%)         | Foul smell not elicited or enhanced by the addition of 10% KOH (seen in 20%)     |
| Clue cell-positive, lactobacillus-negative smears, n Nugent score >6, absence     | Clue cell negative, lactobacillus-negative smears, abundant leukocytes            |
| of leukocytes                                                                      | Vaginal succinate levels not increased                                           |
| Vaginal succinate levels (produced by anaerobes) increased                         | Vaginal pH is raised, usually above 6                                            |
| Vaginal pH raised, above 4.5                                                       |                                                                                  |

Figure 1: Presence of curdy white vaginal discharge

Figure 2: (a) Presence of yellowish vaginal discharge near posterior fourchette. (b) Presence of yellowish vaginal discharge smearing vaginal walls

considered. The clinical signs of vaginitis (red inflamed vagina, yellowish discharge, and dyspareunia) along with laboratory findings (raised pH, decreased lactobacilli, increased vaginal leukocytosis, and absence of clue cells) justified the diagnosis of AV [Table 1].

C. albicans (resistant to fluconazole, itraconazole, voriconazole, and posaconazole) and methicillin-resistant Staphylococcus aureus (MRSA) were isolated from high vaginal swab. Topical amphotericin B vaginal gel and betadine local washes were tried with slight improvement. Oral linezolid 600 mg twice daily for 7 days was given for MRSA in accordance with culture and sensitivity, and she reported marked reduction within 2 days. The patient has not developed any recurrence for the past 5 months.

Although RVVC affects only a minority of patients, it causes significant patient distress and psychological morbidity. Vaginal triazole-resistant C. albicans isolates are extremely rare in nonimmunocompromised women.[3]

To our knowledge, only two cases of vulvovaginitis due to fluconazole-resistant C. albicans have been reported to date.[3] We report the first case of second-generationazole-resistant C. albicans vulvovaginitis in an HIV seronegative female. The alternatives to azoles are few, like nystatin pessaries, boric acid vaginal suppositories, and amphotericin vaginal gel, thereby making it difficult to treat.

The vaginal microflora is a complex micro-ecological environment comprising different microbiological species in variable quantities and relative proportions.[4] In 2002, Donders et al. defined a new clinical entity AV according to bacteriological, immunological, and clinical characteristics.[3]

The prevalence of AV varies from 7% to 12%. AV is characterized by yellow to green offensive (rotten odor in severe cases) vaginal discharge associated with red, inflamed vagina with erosions and/or ulcers, dyspareunia, increased vaginal pH, reduction or absence of lactobacilli, and presence of leukocytes, and parabasal or immature epithelial cells in vaginal smears. Phase contrast microscopy is preferred for smear examination. AV may explain failure to treat all vaginal discharge cases with possibility of trichomonas, candida, or BV.

Mixed infection of AV with VVC, BV, or TV has been described. Local treatment of AV may include topical antibiotic, steroid, or estrogen. Although in severe cases for rapid relief, especially in infections with Group B streptococci or MRSA oral amoxicillin-clavulanic acid or moxifloxacin may be employed.[6] Sangeetha et al. reported that β–lactams/β–lactamase inhibitor combinations, vancomycin, and linezolid were more effective against all Gram-positive isolates, whereas the Gram-negative isolates were more sensitive towards β–lactams/β–lactamase inhibitor combination, aminoglycosides, and meropenem.[7] Besides treatment failure, lack of identification, and appropriate management may result in complications such as pelvic inflammatory disease, infertility, preterm birth, premature rupture of membranes and chorioamnionitis due to the high production of interleukin-6, interleukin-1β, and leukemia inhibitory factor in the vaginal fluid.[8]

We report an interesting case of azole-resistant C. albicans with coexisting AV in an immunocompetent female which is quite rare.

Our case highlights the need for individual-based approach in patients of recurrent vaginal discharge as there could be coexisting rare entities such as AV which are not commonly considered and thereby pose a diagnostic and therapeutic challenge.
Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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