Vulvar Vestibulitis Syndrome: A Post-infectious Entity?

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Vulvar vestibulitis syndrome, a condition characterized by inflammation of the vaginal introitus, causes chronic vulvar pain, particularly with intercourse. It occurs in at least 15% of women with chronic vulvovaginal symptoms, and it is a common cause of sexual dysfunction and resulting comorbidities. Because 80% of women with vulvar vestibulitis syndrome describe an acute onset of symptoms, an infectious etiology has been suspected but never proven. Initially, human papillomavirus infection was thought to be the cause, but recent controlled studies dispute this earlier supposition. Vulvovaginal candidiasis may play an important role in the development of this condition.

Introduction

Idiopathic vulvar vestibulitis syndrome (VVS) is a condition characterized by unexplained chronic vulvar pain, sexual dysfunction, and psychological disability. Exact data about the prevalence of VVS remain scarce, but VVS is present in as many as 15% of patients referred to tertiary-care centers for the evaluation of chronic vaginal and vulvar symptoms [1•].

Women with VVS present with a primary complaint of dyspareunia, particularly in association with penetration. By and large, these symptoms occur in women who had comfortable, pain-free intercourse, then gradually or acutely developed this problem. Other activities that involve contact with the introital area—such as inserting a tampon, wearing tight clothes, or riding a bicycle—may cause pain. Patients also note variable amounts of burning, irritation and itching during their daily activities. Symptoms are almost completely localized to the vulvar vestibule.

If a patient has experienced, for at least six months, the symptoms collectively called "Friedrich's criteria"—a history of vulvar pain on attempted intromission during intercourse, focal areas of erythema confined to the vulvar vestibule, and tenderness upon palpation of these areas with a cotton-tipped applicator—a diagnosis of VVS is appropriate. Unfortunately, because VVS is a condition with which most clinicians are unfamiliar, some patients may have suffered these symptoms for years before being properly diagnosed.

Multiple etiologies have been suggested for VVS. Proposed etiologies have included prior vulvovaginal candidiasis [2], a hypersensitivity reaction to chemicals, human papillomavirus (HPV) infection [3], high levels of urinary oxalates [4], and neurological dysfunction. However, controlled studies to evaluate the etiology of this syndrome have failed to establish a definitive cause [5,6••].

As can be expected when the cause is unknown and has been attributed to such a wide variety of diseases, many treatment options have been proposed for VVS. The treatment of last resort is partial vestibulectomy. This surgery has a failure rate of about 25% [7•], causes considerable discomfort, and is relatively expensive. Recurrence rates, beyond one year after surgery, are generally unknown.

Because of these factors, medical management is the treatment option of first recourse. The success rate associated with interferon injection is low, at about only 18% [8]. In the treatment of 72 women with VVS, Nyirjesy and Halpern [9] described a sequential approach, using, in order, the following modalities: topical lidocaine, topical desoximethasone cream, low doses of oral amitriptyline, a low-oxalate diet combined with calcium citrate pills, and interferon injections. If the patient's symptoms failed to resolve with a particular modality, her treatment progressed to the next one in the sequence. Overall, 48 patients (66%) VVS responded to this approach, but it is unclear which modality provided what level of results. Biofeedback therapy of the pelvic floor musculature has allowed as many as 79% of patients to resume coitus [10]. At present, the few prospective and the retrospective studies of the treatment of VVS have been small and uncontrolled. Thus, no treatment stands out as particularly effective.

Is VVS a Sequelum of Infection?

Preliminary studies have suggested that women with VVS have a local elevation of inflammatory cells [11] and pro-inflammatory cytokines [12••], suggestive of a hyper-immune response. Histopathology of cells from the

vestibular area of women with VVS has demonstrated a chronic, predominantly lymphocytic, inflammatory infiltrate [13,14]. A moderate-to-severe level of inflammation is present in 60% to 100% of women with VVS. The degree of inflammation seems to be greater beneath the squamous epithelium than beneath the vestibular glands [14]. In two studies that examined controls without VVS, such inflammation seems to be, for the most part, absent [15,16]. Although Pyka and colleagues observed mast cells in only 21% of patients [13] with VVS, others have noted increased numbers of mast cells in VVS patients, compared with controls [11]. However, other findings consistent with allergic reactions, such as increased numbers of eosinophils, are not usually present [11].

In terms of local cytokine production, Foster and Hasday [12••] found that vulvar and vestibular tissue obtained from women with VVS contain twice the tissue concentrations of interleukin (IL)-1β ($P = .02$) and tumor necrosis factor (TNF)-α ($P = .07$), compared with tissue from women undergoing rectocele repair. Of interest, both the degree of inflammation found on histology and the concentration of IL-1β and of TNF-α in the tissue were higher in the vulvar area than in the vestibular area, among both VVS patients and controls. The authors believe that the higher levels of these two cytokines are responsible for the localized pain and tenderness that VVS patients exhibit.

Taken in aggregate, these findings of a hyperimmune response are consistent with some sort of infectious or post-infectious process; or they may indicate the presence, in the affected area, of some persistent antigen, which drives the VVS process. Patient histories also suggest that an infectious process may play a role in the development of VVS. In an early study of the epidemiology of VVS, Peckham and colleagues [17] described 67 women whose cases adhered to strict definition of VVS. Of these patients, 80% described an acute onset, 75% had been treated for vaginal infections prior to developing dyspareunia, and none showed evidence of a vaginal infection by the time of the study evaluation. The acute nature of onset suggests that infection plays a role in the development of VVS; however, because the typical patient receives multiple treatments before the appropriate diagnosis of VVS is made, it is difficult to identify the precipitating cause in these cases.

Is VVS Caused by HPV or Some Other Microbe?

Efforts to identify an infectious cause of VVS immediately focused on HPV. In 1988, Turner and Marinoff [18] described seven cases of VVS, in each which HPV DNA was found in tissue specimens Subsequent studies found HPV DNA in 30% to 100% of patients with VVS. However, the findings of more recent studies, which used polymerase chain reaction (PCR) to detect HPV, have led to a re-evaluation of the link between VVS and HPV. Wilkinson and colleagues [19] found HPV (types 6, 11, 16, and 18) in only 3 of 31 VVS biopsies. Marks and colleagues [20] compared VVS patients with and without PCR-detected HPV DNA, and found their cases to be clinically identical; their findings suggest that HPV, if present, may be an innocent bystander in VVS. Finally, a study from Israel found HPV in 54% of VVS patients and only 4% of controls [21]; however, the women in the control group were undergoing vaginal operations for various benign causes or episiotomy repair. Hybridization tests for HPV types 6, 11, 16, 18, and 33 were negative in 39% of women, and no one HPV type was consistently found in the other positive samples. It is not clear whether the control group was appropriately matched for potential confounding factors. Furthermore, differences in PCR techniques used to detect HPV may account for some study-result differences.

Studies investigating other possible infectious etiologies for VVS generally found microbes, at an expected prevalence rate; but not all of these studies included control groups. For example, although no controls were included, culture identified an expected prevalence of microbes in 57 cases of VVS. Organisms included *Ureaplasma urealyticum* (18%), *Gardnerella vaginalis* (14%), and *Candida* species (9%). *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Mycoplasma hominis* were not detected [5]. Recognizing that in situ staining techniques are relatively insensitive, it should also be noted that such stains for *Candida* [13,15], gram-positive bacteria [13], and *Mycobacterium* [13] have uniformly been negative.

Is *Candida albicans* a Potential Cause of VVS?

In 1989, Ashman and Ott [2] noted that *Candida albicans* antigens cross-react with certain antigens in vulvovaginal tissue. They suggested that an effective immune response against *C. albicans* is aborted by this cross-reactivity and that, after repeated infections, susceptible patients become hyperreactive to the cross-reactive antigens, and the patient develops VVS in the absence of active *Candida* infection. *Candida*, a commensal microorganism known to cause the most common clinical infections of the vulva and vagina, is certainly a likely candidate as a possible cause of VVS. Yet, despite the fact that Ashman and Ott initially proposed it more than a decade ago, this hypothesis has yet to undergo rigorous evaluation.

Clinically—in women who are culture-positive for recurrent vulvovaginal candidiasis (RVVC) and who respond to long-term–maintenance oral antifungal therapy—we have observed that their symptoms and signs rapidly and completely response or that residual dyspareunia and findings consistent with idiopathic VVS remain, despite negative vaginal-yeast cultures. In a third group, the presence of candidiasis is not established by culture, but patient history strongly suggests that an episode of VVC immediately preceded the development of VVS. These observations support Ashman and Ott's

hypothesis and suggest that *Candida* may indeed play a role in the development of VVS.

Epidemiological studies of the relationship between VVS and VVC have yielded conflicting results. In most studies of VVS patients, the researchers did not look for the presence of *Candida* by microscopy or culture. While *Candida* species were found in 9% of women in one report [5], Nyirjesy and Halpern found *Candida* species, by culture, in 24% of women with VVS [9]. In a case-control study, VVS was strongly associated (odds ratio = 4.9, 95%; confidence interval = 1.4, 18.0) with a history of physician-diagnosed candidiasis [6••]. The discrepancies in these findings may be related to the small number of patients in each of the three studies, but are also due to the methods used to detect *Candida*. For example, *Candida* was diagnosed by culture only once in one of the three studies [5], by culture multiple times in one study [9], and by patient history of physician-diagnosed VVC in one [6••]. Thus, a possible link between *Candida* and VVS has not been adequately explored.

We recently conducted a prospective, randomized, double-blind, placebo-controlled study of 4% cromolyn cream to treat VVS (Nyirjesy, Unpublished data). In this study, 12 of 34 patients (35%) with symptoms and signs of VVS were treated with fluconazole, because of culture-proven VVC. Three of 22 other patients not receiving fluconazole during the 3-month study period developed VVC during treatment. Of the 15 infections, 14 were from *C. albicans*. Hence, of 56 patients with VVS under observation, 27 (almost 50%) had documented VVC immediately before or shortly after enrollment. Although the number of patients in this study was small, these observations are similar to those we have made relative to other subjects we treat with VVS, and suggest that VVC and VVS frequently coexist.

Furthermore, with the advent of PCR to detect *Candida*, it is clear that traditional culture techniques greatly underestimate the presence of yeast in symptomatic women. For example, in a general gynecology clinic study of a patient population with possible VVC, cultures for *Candida* were positive in 32.8% of patients, but PCR was positive in 49.2% [22•]. The true incidence of VVC in VVS patients may be much greater than the already high percentage noted in certain studies. These observations suggest that VVC may play a significant role in VVS, and that this relationship should be further investigated.

Local Immune Response in RVVC and Correlation with VVS

In women with RVVC, local immune factors appear to play a role in the relapse of candidiasis, which occurs often [23]. For example, anti-*Candida* immunoglobulin (Ig) E antibodies are often present in vaginal secretions of women with RVVC, but not in secretions of control women [24]. An increased IgE specific for *Candida* implies that these women have been sensitized to *Candida* antigen and are expressing a T-helper (Th)-2 cytokine-driven response. The implications of this finding apply both to the level of response that is possible to *Candida* antigen and to an abnormal host that produces an exaggerated immune response.

Local factors other than increased levels of IgE may play an important role in RVVC. Fidel *et al.* [25] longitudinally examined women during both acute episodes of RVVC and remission, studying skin-test reactivity and in vitro peripheral blood lymphocyte (PBL) responses to multiple *Candida* and non-*Candida* antigens. They found decreased delayed *Candida*-specific skin test reactivity during acute episodes of vaginitis, but in vivo PBL responses generally did not differ from those of controls. Further, most women with reduced delayed skin-test reactivity to *Candida* antigen during acute episodes of RVVC reacquired normal reactivity following successful eradication of symptomatic candidiasis. This finding suggests that transient reduction of skin-test reactivity is a consequence of systemic immune response to *Candida* antigens released into the circulation from a local *Candida* infection, rather than a predisposing RVVC factor. These findings also suggest that, in RVVC, changes in local and not systemic cell-mediated immunity (CMI) may predispose women to relapse.

Another implication of these data is the capacity of *Candida* to influence local immune responses. In the study, 30% of women who showed a delayed skin response at 48 hours during the acute infection demonstrated a wheal-and-flare reaction 20 minutes after the introduction of *Candida* antigen [25]. This rapid response implies that IgE and immediate hypersensitivity responses may also play a role in the pathology of RVVC.

It is largely unknown whether women with VVS exhibit local immune changes similar to those observed in women with RVVC. However, if such changes occur, they could explain how *Candida* contributes to VVS. For example, increased numbers of mast cells, noted in the vestibular mucosa of women with VVS, could allow binding of IgE antibodies and facilitate the local release of histamine and prostaglandins. That would explain the erythema, inflammation and possibly the increased nerve response present in vestibulitis. Alternatively, *Candida* antigens may leak from the vagina, interact with inflammatory cells at the vestibule mucosa, and cause a local hyperinflammatory response at the mucosa or from within the vestibular glands.

Possible Genetic Factors for Both RVVC and VVS

Although changes in local immunity may contribute to the pathology of RVVC, epidemiological data suggest that other host factors, particularly genetic factors, may also be important. For example, women with idiopathic RVVC were less likely than controls to have a Lewis antigen

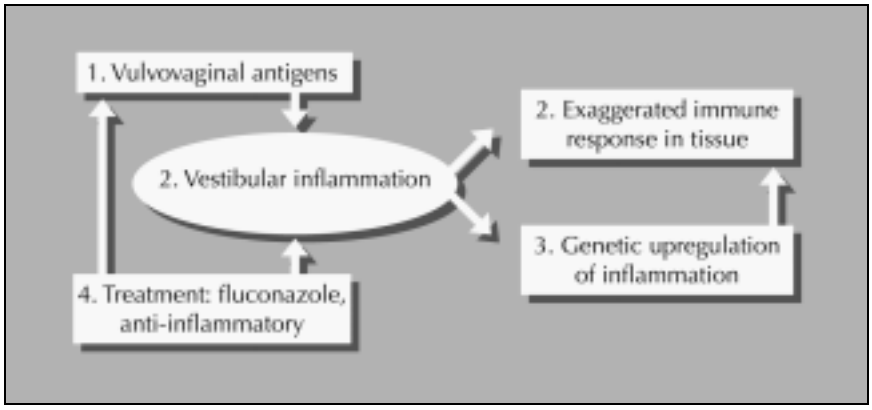

Figure 1. Paradigm of vulvar vestibulitis syndrome

secretor status [26], and the absence of secretor status is estimated to be the underlying cause of RVVC in approximately 20% of women with this disorder. It is believed that secretor substances reflect the ability of *Candida*-antigen ligands or adhesins to adhere to receptor sites. Nonsecretors fail to provide soluble substances that bind to *Candida* adhesins, thus allowing *Candida* to better adhere to epithelial cells. It is possible in RVVC, as it is in urinary tract infection, that nonsecretor individuals are more likely to become colonized with *Candida* and be more vulnerable to infection.

Patients with VVS have not been studied for associations between disease and factors such as ABO blood type, Lewis secretor status, or HLA-haplotype. However, epidemiological data suggest that genetic factors also may play an important role in VVS, which almost exclusively affects whites [6••,17]. Our own clinical experience with VVS corroborates what is reported elsewhere. Additionally, one study shows that women with VVS are more likely than controls to have a homozygous form of allele 2 of the gene encoding for the IL-1 receptor antagonist [27••]; this allele is associated with greater biological activity of IL-1. This finding suggests that genetic factors are at play in the development of VVS.

Clinical Implications of VVS as a *Candida*-related Syndrome

Figure 1 summarizes our view of VVS, and strongly suggests that potential treatments for VVS have not been adequately explored. For example, if the vulvovaginal antigens that drive this hyperimmune response are *Candida* antigens, prolonged-maintenance antifungal therapy in patients who are *Candida*–culture-positive may help alleviate symptoms. In published [9] and unpublished studies, fluconazole has been used to treat patients in such a way. However, these studies were not designed to evaluate fluconazole therapy, but rather the outcome of patients after they had received fluconazole, failed to respond, and then received other treatments. However, if *Candida* does indeed contribute to the symptoms of VVS, one could understand the necessity of treating yeast infections very aggressively in the setting of VVS.

However, Figure 1 suggests that—even with effective antifungal therapy—many women with VVS will continue to have chronic inflammation once the process of VVS has begun. Corticosteroid therapy seems a logical step to treat the local inflammation, regardless of etiology. Conversations with health-care providers who regularly treat VVS reveal that many empirically treat patients with corticosteroid therapy, on a trial basis, before attempting more aggressive therapy. However, published reports of outcomes after corticosteroid therapy are sparse, and opinions vary as to effectiveness. In a study of 68 patients treated with topical 0.25% desoximethasone cream, twice daily for four weeks, Nyirjesy and Halpern [9] reported a positive response—defined as a one in which the patient said that her symptoms had diminished to an acceptable or nonexistent level—in 34%. No controlled studies have been performed to evaluate corticosteroid therapy further.

Conclusions

The suggested framework for the etiology of VVS provides opportunities for further study of this condition. Issues that require further investigation include the role of *Candida* and other microbes in this condition, and possible interventions or combinations of interventions.

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