Treatment of Desquamative Inflammatory Vaginitis With Vitamin D: A Case Report

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Desquamative inflammatory vaginitis (DIV) is a well-described but poorly understood vaginitis associated with yellow vaginal discharge and vulvovaginal pruritus, burning, and dyspareunia. Although etiologies of an inflammatory, infectious, and hormonal nature have been proposed, response to therapy has been inconsistent and complete resolution of symptoms has been disappointing. We propose that DIV is a mucous membrane manifestation of vitamin D deficiency that results in desquamation of the vaginal epithelium and discharge. Moreover, we suggest that the loss of this epithelium leads to altered vaginal pH levels, mucous membrane fragility, inflammation, and secondary infection. Because vitamin D is a known transcriptional activator, we suggest that vitamin D is necessary for the synthesis of specific vaginal structural proteins, such as cytokeratins. Vitamin D deficiency results in decreased amounts of these proteins, resulting in loss of epithelial structural integrity and desquamation. Correction of the vitamin D deficiency ultimately leads to regeneration of the vaginal epithelium and cessation of desquamation.

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Desquamative inflammatory vaginitis (DIV) is a chronic genital problem of undetermined etiology.[1-5] Symptoms include discharge with odor, vulvovaginal pruritus, burning, and dyspareunia. Physical examination of the genital area is remarkable for vulvar erythema, which can be focal, patchy, or generalized. The vaginal discharge is yellow-green and can be copious. The volume of the discharge increases at ovulation and decreases just prior to menstruation. It can be malodorous, though the odor is not usually described as fishy. Examination of the discharge generally reveals an elevated pH level (>4.5; reference range, 7.35–7.45), while the results of a vaginal wet mount reveal many polymorphonuclear leukocytes and vaginal epithelial cells. Direct microscopy reveals the absence of normal genital flora. Culture of discharge specimens most commonly demonstrates group B streptococci; however, other organisms also have been identified.[1-3,5] It is intriguing to note that in a small subpopulation of individuals, the purulent discharge grows no organisms at all—neither pathogenic organisms, such as the group B streptococci, nor normal lactobacilli. Initial therapy has included vaginal corticosteroids[1] and antibiotics such as clindamycin and cephalexin.[5] However, some individuals require hormone replacement therapy for sustained symptom relief, while others fail to respond to all interventions.[5]

We have a long-standing interest in vulvovaginal disorders and have developed a clinical practice with more than 3000 annual outpatient visits. This population is selected for the more unusual forms of vaginitis, such as DIV. Over the past few years, we have noted an association between DIV and women with vitamin D deficiency. We describe this association in a patient as well as the resolution of DIV symptoms. Circulating levels of 25-hydroxyvitamin D in this patient initially were deficient at 22 ng/mL (reference range, 32–100 ng/mL). Treatment with vitamin D and calcium led to complete resolution of the discharge and eradication of group B streptococci. These observations lend support to the notion that DIV may represent a vaginal manifestation of vitamin D deficiency and treatment of the deficiency can resolve the symptom of vaginal discharge.

Case Report

A 36-year-old white woman presented in July 2002 for evaluation of a long-standing history of vaginal discharge. Complaints also included pruritus, burning, and dyspareunia; however, the major complaint

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was that of vaginal discharge described as copious amounts of yellow-green mucus with a foul odor on a daily basis. Although the discharge was described as chronic and unremitting, the amount of discharge increased markedly at the midpoint of the menstrual cycle and decreased with the onset of menses. The patient's medical history was unremarkable for gastrointestinal disease, including celiac disease, but she did describe multiple daily bowel movements. She denied the use of any medications, including oral contraceptives. Her menstrual pattern was regular and she denied problems with fertility. However, she did report that the problem began after her second pregnancy, delivery, and subsequent breast-feeding.

Initial physical examination of the vulva revealed erythema and vaginal discharge, which was thick and yellow. Vaginal culture at this time revealed no pathogenic yeast or fungi. A diagnosis of DIV was made, and the patient was empirically started on a therapeutic regimen of oral cephalexin 500 mg administered 4 times daily for 2 weeks.[5] She returned 4 weeks later and reported a slight decrease in her discharge. Repeat vaginal culture again failed to identify pathogenic organisms of any type. Oral cephalexin was decreased to 500 mg twice daily and vaginal boric acid 600-mg capsules every other day was added to her treatment plan. Two weeks later, the discharge had decreased in amount but was still present and yellow. Vaginal culture remained negative for pathogenic organisms. The patient's therapeutic regimen was switched to 100-mg clindamycin phosphate per 2.5 g suppository (vaginal ovules) twice weekly alternating days with 25-μg estradiol vaginal tablets twice weekly. The discharge continued with this treatment plan, but it was less than when she initially presented for examination. Substantial symptoms recurred in March 2004, at which time the vaginal culture was positive for group B streptococci. The patient initially was started back on oral cephalexin 500 mg twice daily and then switched to alternating days of vaginal clindamycin phosphate and estradiol, with improvement in her symptoms. However, the discharge never completely resolved. The patient was not seen for 6 months; however, in March 2005, her symptoms became unbearable, with substantial vulvovaginal pruritis and burning that again was associated with copious amounts of yellow discharge. Culture of the vaginal discharge again demonstrated the presence of group B streptococci. Blood tests at this time demonstrated a 25-hydroxyvitamin D level of 22 ng/mL, a 1,25 dihydroxyvitamin D level of 48 pg/mL (reference range, 16–65 pg/mL), an intact parathyroid hormone level of 38.9 pg/mL (reference range, 10–50 pg/mL), a serum calcium level of 9.0 mg/dL (reference range, 8.5–10.5 mg/dL), and a serum phosphorus level of 3.6 mg/dL (reference range, 2.3–4.7 mg/dL). The patient then was given oral ergocalciferol 50,000 IU 3 times weekly as well as a daily dose of calcium citrate 630 mg; 4 weeks later, the discharge had improved. Vaginal culture still demonstrated group B streptococci. She was switched to oral ergocalciferol 50,000 IU once weekly and maintained on calcium citrate.

In May 2005, 8 weeks after she had started on the supplemental vitamin D (ergocalciferol) and calcium citrate, her symptoms showed a substantial improvement for the first time, with a minor amount of clear white discharge evident only at the midpoint of her menstrual cycle. In the absence of either antibiotics or vaginal estradiol, her culture was negative for group B streptococci. She was continued on the same therapeutic program of vitamin D (ergocalciferol) and calcium citrate, and in June 2005, she was totally symptom free. Her vaginal culture demonstrated normal vaginal flora and an absence of group B streptococci. Repeat blood testing was performed at this time, demonstrating a 25-hydroxyvitamin D level of 49 ng/mL. The patient was seen in July 2006 and was symptom free on her maintenance therapeutic regimen of oral ergocalciferol 50,000 IU once weekly and calcium carbonate 1000 mg daily with cholecalciferol 2000 IU, which was initiated in June 2005. Her vaginal culture at this time demonstrated abundant normal genital flora and an absence of group B streptococci. It was suggested that the patient change her weekly ergocalciferol therapy (vitamin D_2) to vitamin D_3 (cholecalciferol), but she adamantly refused because she did not want to change the medication plan that she believed had stopped the discharge that had affected her for years.

Comment

DIV is an uncommon but well-described chronic vaginitis of uncertain etiology.[1-5] In a single case report, we revealed 2 important new insights into the pathophysiology and treatment of this disease. First, we demonstrated an association between the disease and vitamin D deficiency. Second, and more importantly, we showed the resolution of DIV symptoms and the deficiency state through a treatment plan that used pharmacologic amounts of vitamin D in association with the standard daily requirement of elemental calcium (1000–1500 mg). This plan is a well-established medical regimen currently in use for the treatment of osteomalacia. We suggest that these observations raise the possibility that DIV represents a disorder of keratinization and vitamin D may be necessary

to maintain the functional integrity of the vaginal mucous membrane.

DIV initially was described in a single case report by Scheffey and colleagues[1] in 1956 whereby the patient demonstrated a clinical response to local treatment with corticosteroids. More descriptive information about DIV was provided by Gray and Barnes.[2] They reported that DIV was a rare form of vaginitis that was noted in a large group of women with vaginal discharge. Gardner[3] described 8 cases of DIV in women with normal circulating levels of estrogen. However, the author described certain features of atrophic/"estrogen-deficient" vaginitis that occurred in the DIV population, including an absence of normal genital flora, diminished vaginal acidity, and the absence of a consistent bacterial pathogen. Of interest, Gardner[3] commented that "none of the 8 patients had a dietary deficiency," though the specific nutritional deficiencies that had been examined were not reported. The most comprehensive analysis of women with DIV was performed by Sobel[5] in 1994. These data demonstrated a response to vaginal clindamycin in many women, suggesting a role for a bacterial pathogen, such as group B streptococci. However, postmenopausal women required supplemental estrogen therapy to maintain remission, which is a puzzling observation if the cause of the disease was infectious.[5] Dermatologists have treated DIV with combinations of corticosteroids and clindamycin with good success,[6] though it has not been an effective treatment plan for our patient population. Moreover, all of these clinical descriptions failed to demonstrate a model of disease pathogenesis with a cogent therapy that would reverse the overall pathogenic process.

The nature of our clinical practice in the Manhattan area has provided us with a population of individuals with rarer forms of vaginitis. With more than 3000 annual outpatient visits, DIV is a relatively common problem in our patients. Of all the interventions described to date, we, like other physicians treating patients with DIV, found all the current therapeutic regimens to be disappointing, including clindamycin, cephalexin, corticosteroids, and estrogens. Our most successful regimen, which was first used with this patient, involved the initial use of a systemic antibiotic, such as oral cephalexin, followed by vaginal clindamycin phosphate with vaginal estradiol, which was somewhat useful. We rarely had success with topical or systemic corticosteroids; in fact, we had the impression that they worsened the overall condition. We also found that vaginal clindamycin phosphate could worsen vaginal burning, and oral clindamycin frequently led to diarrhea, which necessitated a change in antibiotic.

Vitamin D deficiency is most commonly associated with bone disease, manifesting as rickets in children and osteomalacia in adults, and is an established risk factor for hip fracture in elderly patients.[7] Although vitamin D deficiency is thought to be a rare problem in Western societies, certain individuals appear to be at risk, including individuals with gastrointestinal tract problems that predispose them to malabsorption, such as celiac disease and Crohn disease, and individuals that use the medications phenytoin and isoniazid. Finally, an age-related decline in vitamin D levels is well-documented.[7] As we began to note the association between vitamin D deficiency and DIV, it also was interesting to note the amount of vitamin D necessary to reverse the process and the time frame required for the symptoms to abate. The reference range of circulating concentration of vitamin D, as measured in the form of 25-hydroxyvitamin D, is controversial and the subject of much debate.[8] Hollis[8] suggested that a circulating 25-hydroxyvitamin D level of 32 ng/mL should be considered the lower level of the reference range. Our experience, as demonstrated here, would support that contention. Moreover, we found that the DIV symptoms required the circulating 25-hydroxyvitamin D levels to reach approximately 50 ng/mL before subsiding. Although this value is well within the reference range, it is on the higher side. In our patient, the long-term maintenance plan required her to use 2000 to 4000 IU of supplemental vitamin D (cholecalciferol) daily with 1000 mg of elemental calcium in the carbonate form. This amount is well beyond the current dietary intake recommendations of 400 IU of vitamin D,[9] but it lies well within the range that has been shown to be safe in humans.[8] Resolution of the DIV symptoms in our patient required 8 to 12 weeks. This observation is in accordance with the observations of Heaney and colleagues[10]; they demonstrated that a steady-state level of vitamin D (cholecalciferol) and calcium was achieved in 90 days, independent of the daily dose of vitamin. We believe that this finding reflects the time necessary to resolve the underlying problem within the epithelium, which may require regeneration of the entire vaginal mucous membrane. However, we were astonished when this could be accomplished by the use of vitamin D (cholecalciferol) in the absence of antibiotics, estradiol, or corticosteroids. Although we used vitamin D_2 to obtain a therapeutic effect, it should be noted that vitamin D_3 should be the agent of choice because vitamin D_2 substantially up-regulates the catabolism of both forms of the vitamin, thus decreasing the effective potency of coadministered vitamin D_3.[11,12] However, as with our patient, there is substantial reluctance

of patients to stop taking vitamin D_2 because they believe it led to the "cure" of their vaginitis.

Conclusion

We have demonstrated in a single case report an association of vitamin D deficiency with DIV, and further demonstrated resolution of the vaginal discharge when the circulating concentration of vitamin D returned to reference range, albeit the higher concentrations of the reference range. We propose that DIV represents a disorder of keratinization and that decreased levels of vitamin D lead to epithelial desquamation and secondary inflammation and infection. In many ways, DIV mimics a blistering disorder, which is an observation that supports the contention of some dermatologists that DIV represents a blistering disorder related to lichen planus, pemphigus vulgaris, and mucous membrane pemphigoid.[6,13,14] These data suggest that vitamin D, a known transcriptional activator, may induce the expression of important structural proteins in the vaginal epithelium, such as the cytokeratins, and that vitamin D deficiency leads to an altered program of keratinocyte differentiation, resulting in vaginal desquamation. Studies are in progress to determine if this is the case and to identify which structural proteins in the vaginal epithelium are regulated by vitamin D.

REFERENCES

1. Scheffey LC, Rakoff AE, Lang WR. An unusual case of exudative vaginitis (hydrorrhea vaginalis) treated with local hydrocortisone. *Am J Obstet Gynecol.* 1956;72:208-211.
2. Gray LA, Barnes ML. Vaginitis in women: diagnosis and treatment. *Am J Obstet Gynecol.* 1965;92:125-136.
3. Gardner HL. Desquamative inflammatory vaginitis: a newly defined entity. *Am J Obstet Gynecol.* 1968;102:1102-1105.
4. Oates JK, Rowen D. Desquamative inflammatory vaginitis. a review. *Genitourin Med.* 1990;66:275-279.
5. Sobel JD. Desquamative inflammatory vaginitis: a new subgroup of purulent vaginitis responsive to topical 2% clindamycin therapy. *Am J Obstet Gynecol.* 1994;171: 1215-1220.
6. Murphy R, Edwards L. Desquamative inflammatory vulvovaginitis [letter]. *Br J Dermatol.* 2001;145:74.
7. Chapuy MC, Arlot M, DuBoeuf F, et al. Vitamin D_3 and calcium to prevent hip fracture in the elderly women. *N Engl J Med.* 1992;327:1637-1642.
8. Hollis BW. Circulating 25 hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr.* 2005;133: 317-322.
9. Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, Fluoride*. Washington, DC: National Academy Press; 1997.
10. Heaney RP, Davies KM, Chen TC, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr.* 2003;77: 204-210.
11. Trang H, Cole DE, Rubin LA, et al. Evidence that vitamin D_3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D_2. *Am J Clin Nutr.* 1998;68: 854-858.
12. Armas LA, Hollis BW, Heaney RP. Vitamin D_2 is much less effective than vitamin D_3 in humans. *J Clin Endocrinol Metab.* 2004;89:5387-5391.
13. Edwards L, Friedrich EG Jr. Desquamative vaginitis: lichen planus in disguise. *Obstet Gynecol.* 1988;71 (6, pt 1):832-836.
14. Pelisse M. The vulvo-vaginal-gingival syndrome. a new form of erosive lichen planus. *Int J Dermatol.* 1989;28: 381-384.