Prevention of Vulvovaginal Sequelae in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Vulvovaginal sequelae of Stevens-Johnson syndrome and toxic epidermal necrolysis are well documented in the literature, although little consensus exists about effective prevention strategies. This review summarizes the available literature and offers expert opinion about how to minimize long-term vaginal impairment from these rare but often devastating illnesses.
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Vulvovaginal sequelae of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are well documented in the literature, though little consensus exists about effective prevention strategies. Our gynecology service was recently consulted regarding management options for prevention of long-term sequelae in a patient with biopsy-proven SJS. In our review of the literature, we found relatively little information about the natural history of vaginal involvement in SJS and TEN and no cohesive set of guidelines to prevent gynecologic complications. This review summarizes the available literature and offers expert opinion about how to minimize long-term vaginal impairment from these rare but often devastating illnesses.

Anatomic Sequelae

Erythema multiforme, SJS, and TEN are idiosyncratic blistering diseases of the skin with overlapping clinical presentations. The latter two are defined by extent of body surface and mucosal membrane involvement. Patients typically present with an exfoliative dermatitis of the oral and vaginal mucosae. Retrospective studies of women with SJS or TEN confirm that vulvovaginal involvement is common. In one series, 70% of patients hospitalized for biopsy-proven TEN developed genital lesions, including erosive and ulcerative vaginitis, vulvar bullae, and vaginal synechiae. None of these patients was treated specifically for these lesions during the acute phase of her illness, and the time to resolution of vulvovaginal lesions ranged from 7 to 56 days.[1] Long-term anatomic sequelae such as labial agglutination and introital stenosis occurred in 18% of these women and up to 28% of women in other series.[1,2] The most common complaints were entry dyspareunia and postcoital bleeding. Other sequelae result from obstructed urinary stream and menstrual egress—urinary retention, recurrent cystitis, postvoid dribbling, hematocolpos, hematometra, and endometriosis have all been described.[1-3]

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Cytopathologic Findings

Pathologic changes such as vulvovaginal adenosis are commonly reported in women with SJS and TEN.[6,18,19] Vulvovaginal adenosis is defined by the presence of metaplastic cervical or endometrial glandular epithelium in the vulva or vagina. The macroscopic appearance of adenosis varies and can manifest as patchy or diffuse hyperemia, or cystic, ulcerative, or verrucous lesions.[4] The prevalence of vaginal adenosis in the general population is 8% and follows in utero exposure to diethylstilbestrol (DES) in up to 90% of women.[5,6] Adenosis is a common endpoint to a variety of physical and chemical insults and has been documented in women after long-term tampon or pessary use, following condylomata treatment with vaginal 5-fluorouracil or CO_2 laser vaporization, and even as a result of in utero exposure to tamoxifen, clomiphene citrate, and bisphenol A in the rodent model.[6-12]

The malignant potential of vulvovaginal adenosis in non–DES-exposed women is unknown, but transformation to adenosis with cellular atypia, squamous cell carcinoma, mucinous adenocarcinoma, and clear cell carcinoma of the vagina has been reported.[6,13-17]

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Incidence and Pathophysiology of Adenosis

The incidence of vulvovaginal adenosis secondary to SJS and TEN has not been established. Vaginal adenosis in the upper two-thirds of the vagina is thought to occur when overlying stratified squamous epithelium, originally derived from upward growth of the urogenital sinus, is damaged and embryonic rests of the underlying Müllerian ducts are exposed. Adenosis of the lower one-third of the vagina, however, is rare and, based on the embryologic origin of the urogenital sinus, should not occur.[18-20]

Several case reports of TEN note the exceptional finding of vulvar adenosis, but its etiology remains unclear. Loss of p63, a transcription factor critical in determining Müllerian cell fate and maintaining the integrity of vaginal squamous epithelium, may play a role. This tumor suppressor gene is expressed in basal cells of the vaginal and cervical epithelium, but not in uterine epithelium.[21] When p63 expression is inhibited, vaginal squamous epithelium is replaced by glandular epithelium. Immunohistochemical studies of TEN-induced vulvar adenosis demonstrate that biopsy tissue stains negative for p63.[19] Other studies have shown that cervicovaginal Malpighian epithelium can differentiate into columnar Müllerian epithelium in p63-null mice and that DES induces adenosis by estrogen receptor α-mediated inhibition of p63.[22] Similarly, the loss of epithelial p63 expression in the process of wound healing in SJS and TEN may lead to glandular development and subsequent adenosis.[19]

Adenosis may lead to vaginal stricture formation. Interestingly, in a series of patients with obstructed hemivagina-ipsilateral renal agenesis (OHVIRA) syndrome, 35% of patients developed adenosis of the resected septum.[23] Of these patients, 25% with septal adenosis developed postoperative vaginal stenosis and required

reoperation within 1 month of initial surgery. In comparison, none of the patients with specimens revealing squamous mucosa developed strictures. In patients with OHVIRA syndrome, some consider septal adenosis to be a risk factor for postoperative stenosis and malignant transformation, and, by corollary, the same may apply for vulvovaginal involvement of SJS/TEN.[23]

Topical Glucocorticoids as First-Line Therapy

Several methods to prevent vulvovaginal sequelae of SJS and TEN have been proposed. The goals of therapy should be to protect vaginal function by decreasing adhesion formation and agglutination, as well as limiting metaplastic and potentially neoplastic changes in affected tissue. Preventative strategies include the application of intravaginal glucocorticoids, the regular use of vaginal molds, and menstrual suppression during the acute phase of illness.

Class III steroid creams such as betamethasone valerate 0.1%, betamethasone dipropionate 0.05%, and hydrocortisone acetate 10% have been used intravaginally in patients with ulcerative lesions of SJS and TEN.[24] Whereas cream formulations are appropriate for external use, we prefer to use ointments for vaginal lesions, as mucosal absorption and bioavailability are higher than that of creams. Clinicians should be aware of the development of tachyphylaxis to superpotent topical steroids, which can occur as early as treatment day 4. Recovery occurs after several days of rest, which has led to alternating courses of therapy such as 3 days on, 4 days off, or 1 week on, 1 week off. Topical steroid treatment should be continued until resolution of the acute phase of illness. Our practice is to prescribe betamethasone valerate 0.1% cream every 12 hours to the vulva externally and betamethasone valerate 0.1% ointment every 12 hours to the internal vaginal mucosa via a Milex dilator (discussed below). Regular application of antifungal creams can be used as well, as even short courses of intravaginal steroids can predispose to moniliasis.

Although nearly half of the overall mortality from TEN is attributed to infection, it is unlikely that systemic absorption of topical steroids increases the risk of sepsis in these patients.[2] As such, the initiation of steroid therapy should occur at the time of diagnosis, and an effort must be made to familiarize medical staff with the importance of early intervention. Alternatively, intravaginal tacrolimus 0.1%, a calcineurin-inhibitor, has been reported to be successful in preventing vaginal stenosis in erosive lichen planus.[24] The use of tacrolimus in SJS and TEN has not been studied, however. Oral therapy with corticosteroids and other immunosuppressive agents such as cyclosporine, azathioprine, mycophenolate mofetil, and etanercept has been reserved for progressive disease.[24]

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Vaginal Molds to Disrupt Adhesion Formation

In addition to topical steroids, a soft vaginal mold should be placed prophylactically as early as possible during the acute phase of illness and used regularly until complete healing of ulcerative lesions has occurred. Our group recommends Milex vaginal dilators (Milex Products Inc., Chicago, IL). These dilators are made of latex-free, hypoallergenic silicone and come in various lengths and widths. They are available for purchase from online distributors (CooperSurgical, Trumbull, CT).

If such dilators are not immediately available, a condom filled with foam rubber or an inflatable vaginal dilator could be used for this purpose. Another option is the intermittent use of a hard vaginal dilator such as a Syracuse Medical dilator (Syracuse, NY). Regular and early use of dilator therapy is important to maintain a functional vaginal caliber and length. The mold can be coated with topical steroids and used until clinical resolution. Patients can be instructed to wear the molds for 24 hours per day, removing them only for cleansing, medication application, and toileting. For a more minimalist approach, daily insertion and removal is an option for those who find leaving the dilator in place overnight unacceptable. Early intercourse after wound epithelialization may also help reduce the incidence of stenosis.

Special consideration must be given to the virginal patient, in whom vaginal molds would be inadvisable. Instead, a suitable steroid formulation can be applied every other day via a standard vaginal applicator available through compounding pharmacies. We recommend that no dilator treatment be initiated in the pediatric patient until she is an adolescent and able to manage the dilation process without emotional trauma and significant physical discomfort.

Menstrual Suppression to Prevent Adenosis

It is reasonable to consider menstrual suppression during the healing process to decrease the risk of vaginal adenosis.[18,20] The cause of adenosis

has not been demonstrated conclusively, but may result from estrogen-dependent inhibition of p63 in squamous epithelium, the unmasking of Müllerian remnants upon epithelial damage, or from exposure of ulcerative lesions to menstrual blood with direct implantation of Müllerian-derived columnar cells.[18,22] It is well established that glandular proliferation is regulated by estrogen. As the epithelium in vaginal adenosis stains positive for estrogen receptors, in contrast to native vaginal epithelium, hormonal suppression has been proposed by some groups for symptom management.[18] This estrogen-dependent hypothesis is further supported by autopsy studies that demonstrate that development of vaginal adenosis is bimodal, arising exclusively in either neonates aged less than 1 month or in postpubertal females.[5] No cases of adenosis have been described in patients between 1 month and 12 years of age.

In patients with confirmed adenosis, gonadotropin-releasing hormone (GnRH) downregulation with goserelin acetate has been reported to significantly improve symptoms of pain.[18] A course of leuprolide acetate by intramuscular injection will effectively produce a hypoestrogenic environment and suppress menses until healing occurs, ideally administered in the luteal phase to avoid a subsequent gonadotropin flare effect and an associated heavy menses. By adding norethindrone acetate, 5 mg by mouth, once daily for hormonal add-back, menopausal symptoms will be mitigated and bone mineral density preserved.[25] Alternatively, continuous oral contraceptive pills or depot medroxyprogesterone acetate can be used for menstrual suppression.[3] The efficacy of these strategies to prevent vaginal adenosis, however, has not been evaluated by prospective study.

As noted above, vulvovaginal adenosis in non–DES-exposed women can transform into squamous, mucinous, and clear cell carcinoma of the vagina.[6,13-17] Until the natural history and malignant potential of vaginal adenosis is further characterized, patients with biopsy-proven adenosis secondary to SJS or TEN may merit close observation with colposcopy. Vulvar and vaginal punch biopsies should be considered in all patients with genital involvement of SJS or TEN once the acute phase has resolved or if symptoms persist.

Summary and Recommendations

Vulvovaginal sequelae of SJS and TEN are preventable, but prevention requires an awareness of the disease process as it relates to the female genital tract. Proper patient and medical staff education about the importance of these strategies is critical to prevent long-term vaginal sequelae. The

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Main Points

- Little consensus exists about effective prevention strategies for the vulvovaginal sequelae of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
- Erythema multiforme, SJS, and TEN are idiosyncratic blistering diseases of the skin with overlapping clinical presentations. The latter two are defined by extent of body surface and mucosal membrane involvement, and patients typically present with an exfoliative dermatitis of the oral and vaginal mucosae.
- Pathologic changes such as vulvovaginal adenosis are commonly reported in women with SJS and TEN. Vulvovaginal adenosis is defined by the presence of metaplastic cervical or endometrial glandular epithelium in the vulva or vagina. The macroscopic appearance of adenosis varies and can manifest as patchy or diffuse hyperemia, or cystic, ulcerative, or verrucous lesions.
- Several methods to prevent vulvovaginal sequelae of SJS and TEN have been proposed. The goals of therapy should be to protect vaginal function by decreasing adhesion formation and agglutination, as well as limiting metaplastic and potentially neoplastic changes in affected tissue. Preventative strategies include the application of intravaginal glucocorticoids, the regular use of vaginal molds, and menstrual suppression during the acute phase of illness.
- Biopsy of affected tissue in patients with genital involvement of SJS or TEN should be considered after resolution of the acute phase of illness, and those with pathologic evidence of adenosis may warrant close colposcopic surveillance given the association of this pathologic diagnosis with subsequent malignancy.

mainstay of prevention involves early initiation of intravaginal steroids to decrease inflammation and subsequent agglutination, dilator therapy to disrupt and prevent adhesions, and menstrual suppression to decrease formation of adenosis. Biopsy of affected tissue in patients with genital involvement of SJS or TEN should be considered after resolution of the acute phase of illness, and those with pathologic evidence of adenosis may warrant close colposcopic surveillance given the association of this pathologic diagnosis with subsequent malignancy. ■

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References

1. Meneux E, Wolkenstein P, Haddad B, et al. Vulvovaginal involvement in toxic epidermal necrolysis: a retrospective study of 40 cases. *Obstet Gynecol.* 1998;91:283-287.
2. Niemeijer IC, van Praag MC, van Gemund N. Relevance and consequences of erythema multiforme, Stevens-Johnsom syndrome and toxic epidermal necrolysis in gynecology. *Arch Gynecol Obstet.* 2009;280:851-854.
3. Wilson EE, Malinak LR. Vulvovaginal sequelae of Stevens-Johnson syndrome and their management. *Obstet Gynecol.* 1988;71:478-480.
4. Robboy SJ, Hill EC, Sandberg EC, Czernobilsky B. Vaginal adenosis in women born prior to the diethylstilbestrol era. *Hum Pathol.* 1986;17:488-492.
5. Kurman RJ, Scully RE. The incidence and histogenesis of vaginal adenosis. An autopsy study. *Hum Pathol.* 1974;5:265-276.
6. Kranl C, Zelger B, Kofler H, et al. Vulval and vaginal adenosis. *Brit J Dermatol.* 1998;139:128-131.
7. Sedlacek TV, Riva JM, Magen AB, et al. Vaginal and vulvar adenosis. An unsuspected side effect of CO_2 laser vaporization. *J Reprod Med.* 1990;35:995-1001.
8. Goodman A, Zukerberg LR, Nikrui N, Scully RE. Vaginal adenosis and clear cell carcinoma after 5-fluorouracil treatment for condylomas. *Cancer.* 1991;68:1628-1632.
9. Ketani MA, Ketani S, Kaloğlu C, Güney B. Effects of tamoxifen administration in rat vaginas: an ultrastructural and light microscopy study. *Eur J Gynaecol Oncol.* 2003;23:557-560.
10. Gorwill RH, Steele HD. The long-term effect of clomiphene citrate on vaginal epithelial differentiation in the mouse. *Reprod Toxicol.* 1988;1:263-266.
11. Dungar CF, Wilkinson EJ. Vaginal columnar cell metaplasia. An acquired adenosis associated with topical 5-fluorouracil therapy. *J Reprod Med.* 1995;40:361-366.
12. Newbold RR, Jefferson WN, Padilla-Banks E. Prenatal exposure to bisphenol A at environmentally relevant doses adversely affects the murine female reproductive tract later in life. *Environ Health Perspect.* 2009;117:879-885.
13. Scurry J, Planner R, Grant P. Unusual variants of vaginal adenosis: a challenge for diagnosis and treatment. *Gynecol Oncol.* 1991;41:172-177.
14. Veridiano NP, Weiner EA, Tancer ML. Squamous cell carcinoma of the vagina associated with vaginal adenosis. *Obstet Gynecol.* 1976;47:689-692.
15. Ruffolo EH, Foxworthy D, Fletcher JC. Vaginal adenocarcinoma arising in vaginal adenosis. *Am J Obstet Gynecol.* 1971;111:167-172.
16. Yaghsezian H, Palazzo JP, Finkel GC, et al. Primary vaginal adenocarcinoma of the intestinal type associated with adenosis. *Gynecol Oncol.* 1992;45:62-65.
17. Ghosh TK, Cera PJ. Transition of benign vaginal adenosis to clear cell carcinoma. *Obstet Gynecol.* 1983;61:126-130.
18. Emberger M, Lanschuetzer CM, Laimer M, et al. Vaginal adenosis induced by Stevens-Johnson syndrome. *J Eur Acad Dermatol Venereol.* 2006;20:896-898.
19. Noël JC, Buxant F, Fayt I, et al. Vulval adenosis associated with toxic epidermal necrolysis. *Br J Dermatol.* 2005;153:457-458.
20. Bonafe JL, Thibaut I, Hoff J. Introital adenosis associated with Stevens-Johnson syndrome. *Clin Exp Dermatol.* 1990;15:356-357.
21. Kurita T, Cunha GR. Roles of p63 in differentiation of Müllerian duct epithelial cells. *Ann N Y Acad Sci.* 2001;948:9-12.
22. Kurita T, Mills AA, Cunha GR. Roles of p63 in the diethylstilbestrol-induced cervicovaginal adenosis. *Development.* 2004;131:1639-1649.
23. Smith NA, Laufer MR. Obstructed hemivagina and ipsilateral renal anomal (OHVIRA) syndrome: management and follow-up. *Fertil Steril.* 2007;87:918-922.
24. Amankwah YA, Haefner HK, Brincat CA. Management of vulvovaginal strictures/shortened vagina. *Clin Obstet Gynecol.* 2010;53:125-133.
25. Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. Lupron Add-Back Study Group. *Obstet Gynecol.* 1998;91:16-24.