Genitourinary Manifestations of Epstein-Barr Virus Infections

Randi Leigh, MD, MPH, and Paul Nyirjesy, MD

Corresponding author
Paul Nyirjesy, MD
Department of Obstetrics and Gynecology, Drexel University College of Medicine, 245 North 15th Street, New College Building, 16th Floor, Philadelphia, PA 19102, USA.
E-mail: pnyirjes@drexelmed.edu

Current Infectious Disease Reports 2009, **11:**449–456
Current Medicine Group LLC ISSN 1523-3847

Epstein-Barr virus (EBV) is best known as the organism responsible for the syndrome of acute infectious mononucleosis. Transmission of EBV most commonly occurs through oral secretions. EBV has also been isolated from the female genital tract, where its role is poorly understood. This article reviews the available literature and data regarding EBV in the female genital tract and discusses areas of consensus and controversy. The primary manifestation of EBV seems to be vulvar ulcers, which are underrecognized. Diagnosis relies on appropriate serologic testing. Management includes local care and may require pain and corticosteroid medications. Although EBV is present elsewhere in the female genital tract, its pathogenic role in the cervix, uterus, fallopian tubes, and ovaries is poorly understood.

Introduction

Epstein-Barr virus (EBV) is a lymphotrophic, double-stranded DNA virus from the Herpesviridae family that is best known as the cause of infectious mononucleosis (IM). It is ubiquitous in the adult population, with a worldwide prevalence of 90% to 98% [1,2]. The incidence of symptomatic infection in the United States is approximately 50 cases per 100,000 persons per year among all age groups and is higher in adolescents [3]. The diagnosis of EBV may be made clinically in patients with the syndrome of acute IM characterized by the classic triad of fever, pharyngitis, and lymphadenopathy (LAD). Although most clinicians regard EBV as the cause of a systemic illness with generalized manifestations, a recent case in our practice raised our awareness of the genitourinary manifestations of EBV, and led to this review of EBV and the female genital tract.

Epstein-Barr Virus and Acute Genital Ulcers

Case

A 14-year-old premenarchal female presented with a large, extremely painful, vulvar ulcer, which had developed over the previous 4 days on her left inner labium minus. She noted several days of genital burning followed by the development of a "blood blister" a few days later. Evaluations during visits to an emergency department and her health care provider yielded unremarkable bacterial cultures and negative herpes simplex polymerase chain reaction (PCR). Despite empiric treatment with acyclovir and trimethoprim-sulfamethoxazole, her symptoms worsened significantly, and she had difficulty voiding because of severe pain when urine touched the ulcer. She also noted a mild pharyngitis, small oral ulcers, and fever for the preceding week. She denied a history of sexual contact. Her medical history was negative except for a history of aphthous oral ulcers. Additional questioning revealed close contact with a classmate who was recently hospitalized for IM.

Examination revealed mild oropharyngeal erythema and three oral aphthous ulcers along with cervical and submandibular LAD. She had no splenomegaly. Vulvar examination was remarkable for a 4 cm × 1.5 cm ulcer with a purulent exudate and well-demarcated border on the left inner labium minus, immediately next to the urethral meatus. Her white blood cell count was 8700/μL, with a differential of 26% neutrophils, 43% lymphocytes, and 6% monocytes. Her platelet count was 177,000 per unit. Her liver function test results were mildly elevated with an aspartate aminotransferase level of 32 U/L and alanine aminotransferase of 32 U/L. Herpes simplex virus (HSV) types 1 and 2 IgG antibodies were negative. Although the heterophile antibody test was negative, other EBV serologies revealed a positive test for EBV viral capsid antigen (VCA) IgM, elevated EBV nuclear antigen (EBNA) IgG, and positive quantitative blood PCR for EBV DNA (2458 copies/mL, reference < 200).

Based on these results, a diagnosis of acute IM and an EBV-associated genital ulcer (EBVU) was made. After starting prednisone, 20 mg daily for 14 days, symptoms improved rapidly over the next 5 days. The ulcer healed fully over the next 4 weeks. Convalescent titers 4 months later revealed negative HSV IgG serologies, a negative test for EBV VCA IgM, and positive tests for EBV VCA IgG

Table 1. Signs and symptoms reported in 39 cases of Epstein-Barr virus–induced vulvar ulcers

Signs and symptoms	Present	Total documented	Among cases with documentation, %
Reported symptom			
Fever	32	33	97
Sore throat	18	21	86
Headache	7	7	100
Fatigue	10	10	100
Arthralgia/myalgia	6	6	100
Leukorrhea	3	3	100
Dysuria	14	16	88
Genital prodrome (pain and/or pruritus)	4	4	100
History			
History of recurrent oral ulcers	3	4	75
Physical examination findings			
Cervical lymphadenopathy	22	28	79
Inguinal lymphadenopathy	10	17	59
Pharyngitis/tonsillitis	12	15	80
Organomegaly	2	16	13
Oral ulcers	4	4	100
Description of ulcer			
Size of dominant ulcer ≥ 1 cm	16	38	42
Solitary ulcer	2	29	7
Two or more ulcers	27	29	93
Bilateral	9	14	64
Labia minora only	25	34	74
Necrotic/exudative appearance	20	20	100

(*Data from* Cheng et al. [1], Barnes et al. [4••], Portnoy et al. [10], Halvorsen et al. [11••], Pelletier et al. [12], Taylor et al. [13], Farhi et al. [14••], Svedman et al. [15], Llanos et al. [18], Hernandez-Nunez et al. [20], Brown and Stenchever [23], Hudson and Perlman [26], Johnson and Landry [27], Logeart et al. [28], Nicolas et al. [30], Groulier et al. [33], Lorenzo and Robertson [34], Tenorio et al. [36], McKenna et al. [37], Sisson and Glick [48], DeKlotz and Frieden [49].)

and EBNA. One year after initial presentation, the patient had a recurrence of her ulcer, which responded within a few days to a 7-day course of prednisone.

Clinical presentation

Our review identified 39 cases of EBVU published between 1966 and 2009, 34 in women between the ages of 10 and 23. Table 1 summarizes the pertinent clinical features of EBVU. Five patients were premenarchal, 7 had reached menarche, and 27 had no documentation of pubertal status. Of 29 patients for whom sexual histories were documented, 72% denied sexual activity. Associated symptoms were often prodromal and ranged from 1 day to several weeks before ulcers appeared. Although one third developed the classic syndrome of IM, only two developed the syndrome before the appearance of a vulvar lesion. In most patients, EBVU demonstrated a preference for the labia minora. Lesions tended to be large (0.3–4 cm) and well circumscribed, with violaceous margins. In the nine bilateral cases, five had a symmetric or "kissing" pattern.

Modes of transmission

EBV is thought to be transmitted to oropharyngeal epithelial cells and circulating B cells via infected oral secretions. Once B-cell infection is established, EBV migrates into the lymphoid tissues and establishes latency in memory B cells. Prolonged viral shedding of EBV from epithelial cells may occur for up to 18 months after the resolution of symptomatic infection [4••,5]. In a large prospective study, 90% of healthy seropositive participants demonstrated viral shedding at least once, whereas 25% demonstrated viral shedding on multiple tests over 15 months [6]. Furthermore, in highly concentrated salivary samples, the virus can be identified in up to 100% of healthy seropositive individuals, suggesting that the virus is never truly latent [7].

In the genital tract, EBV DNA was isolated by PCR from samples taken from the cervix and vagina of women, the urethra and anal mucosa of men and women, and the coronal sulcus of uncircumcised males [8]. In 1994, Taylor et al. [9] isolated EBV DNA by PCR from cervical

samples in 42% of women with normal Pap smears and 36% of women with abnormal findings. A possible explanation for these results is that the virus might be present in cell-free form, in lymphocytes, or in cervical squamous epithelial cells [9]. Among the cases we reviewed, EBV was isolated by culture (n = 1) [10], by PCR of vulvar biopsies (n = 3) [11••,12] or ulcer swab (n = 1) [13], and by in situ hybridization (n = 2) [13,14••]. Although other attempts to isolate EBV using the same methods failed [4••,13,14••,15], it is clear that EBV virus is present in the male and female genital tracts, including sites of EBVU, during acute and latent infection. It is unknown whether genital epithelial cells are infected by direct inoculation, circulating B lymphocytes, hematogenous spread, another route, or some combination thereof.

The presence of EBV in the genital tract, along with the knowledge that EBV infects epithelial cells at other body sites, led to the hypothesis that EBV may be sexually transmitted. One study of EBV transmission in HIV-infected men who have sex with men provides convincing evidence that sexual transmission of EBV is possible among this group [16]. Studies failed to provide substantial evidence to either refute or confirm heterosexual transmission of EBV. However, sexual transmission does not appear to be a necessary prerequisite for genital or gynecologic manifestations of EBV. In fact, most cases of EBVU occur in young women who deny a history of any sexual activity.

Although the question of whether EBV can be transmitted through vaginal intercourse is important, an equally relevant question is whether it can infect genital epithelium via contact with salivary secretions. Free EBV virus, infected oropharyngeal epithelial cells shed into salivary secretions, or infected B lymphocytes in saliva may all serve as possible vectors. Thus, orogenital transmission and self-inoculation via salivary secretions are potential routes of EBV infection that cannot be ruled out based on available data. Most investigations of EBV in the genital tract failed to explore patients' sexual histories in sufficient detail to answer this question with certainty [17••]. Only seven of the cases (18%) reviewed specifically addressed whether a patient who was "not sexually active" had ever engaged in oral sex, and only three patients had done so. An even smaller number of patients specifically reported on other sexual behaviors and practices, including digital-genital stimulation and masturbation. A better understanding of how EBV enters the female genital tract is desirable because this information has the potential to affect understanding of EBVU epidemiology and the role of EBV in genitourinary and gynecologic pathology.

Epstein-Barr virus–associated ulcers: underrecognized disorder vs increasing incidence

With clinicians largely unaware of the possibility that EBV can cause acute genital ulcers (AGUs), it is well accepted that EBVU is an underrecognized disorder [4••]. Presumptive diagnoses of herpes likely contribute to missed cases of EBVU. Furthermore, as demonstrated by at least two cases, a history of confirmed herpes does not exclude the possibility of EBVU [14••,18]. More than a dozen reports describe women with AGUs in whom the possibility of EBVU was not explored, including a small number of women in whom exhaustive workups failed to identify any cause [19••,20,21]. It remains unknown if EBVU can occur as a result of reactivated latent infection. In multiple cases of women with AGU of unknown etiology, testing revealed an otherwise negative workup and serologies consistent with past EBV infection (anti-VCA IgG or anti-EBNA IgG positive), although no clear linkage was offered for these findings [19••,20,21,22]. Excluding our case and that of a 19-year-old sexually active patient with confirmed EBVU who reported suffering a similar episode of AGU at age 12, before coitarche [19••], reports of EBVU fail to address recurrence.

Although the growing number of case reports of EBVU may reflect a greater awareness of the condition, it may also be the result of increasing incidence. Adolescents and young adults are now engaging in oral sex more frequently and at younger ages than in the past [23]. If direct inoculation of the genital epithelium via infected salivary secretions occurs, then changes in sexual behavior trends among the group most susceptible to symptomatic EBV infection may be increasing genital manifestations of EBV. However, it is also possible that the increase in EBVU cases may reflect an overall increase in the number of complicated cases of EBV infection over the past three decades [24,25].

Pathophysiology of acute genital ulcers secondary to Epstein-Barr virus

Two hypotheses are proposed to explain the pathophysiology of EBVU [5,10]. The virus itself may cause the ulcers. According to this theory, infected cells undergo cytolysis and cause epithelial erosion and eventually ulceration. A more likely explanation is that the ulcers are caused by the host immune response, in which immune complex deposition results in complement fixation and reactive localized inflammation, then cell lysis. Consistent with this theory, biopsies collected from 11 patients demonstrated pathologic findings of vasculitis, thrombosis of superficial blood vessels, and nonspecific mixed dermal infiltration [1,4••,11••,12,14••,18,26–29]. EBVUs may simply be one of many mucocutaneous manifestations of EBV infection. The large number of possible sites of involvement (including the skin and nasal, oral, esophageal, and gastric mucosa) supports the idea that the host response to infection causes the ulcer.

Of note, our literature review revealed only one case of a penile ulcer attributed to EBV [30]. The most likely reason for this gender discrepancy is that less keratinized tissue (eg, the labia minora, where most EBVUs occur), is more vulnerable to ulceration than the more keratinized epithelium of the male genitalia. It is also possible that female sex hormones serve as catalysts in ulcer formation. Exogenous estrogen and progesterone are associated with

other, nonulcerating cutaneous lesions including the vasculitic panniculitis erythema nodosum, and vulvar ulcers secondary to progesterone autoimmune dermatitis and estrogen hypersensitivity were observed [31].

Diagnosis

A thorough history in patients presenting with AGU is important and should include a detailed sexual history, use of soaps and detergents, current and recent medications, travel history, and sick contacts. The differential diagnosis is extensive and beyond the scope of this review. A summary of clinical clues that may help distinguish EBVU from other key diagnoses is provided in Table 2. Notably, the timing of signs and symptoms associated with EBVU may vary, with many appearing days after the presentation of the ulcer. Rash may be a particularly important sign in patients with EBVU. Although 3% to 19% of all patients with acute EBV infection develop a maculopapular rash [7], this sign is observed in more than 70% of patients with acute EBV who receive antibiotics, particularly amoxicillin [5]. EBVU may be distinguished from HSV ulcers by their rapid enlargement despite treatment with antiherpetic agents. EBVU also tend to be larger, deeper, and more necrotic than ulcers caused by herpes.

Numerous diagnostic tests can help clinicians distinguish among EBVU, HSV, and other causes of AGU. Patients with EBVU demonstrate laboratory findings typical for acute IM, including atypical lymphocytosis, mild thrombocytopenia, and mild elevations in liver transaminases [7]. Culture or PCR of the lesion for HSV can help distinguish EBVU from HSV, and provide guidance for counseling sexually active patients. HSV and cytomegalovirus (CMV) serology during the acute and convalescent periods also should be considered. Selection of other tests should be based on findings from the history and physical examination, and may include tests for syphilis and HIV, and for rare causes of AGU including adenovirus, influenza and coxsackie viruses, typhoid and paratyphoid, toxoplasmosis, tuberculosis, *Mycoplasma pneumoniae*, and others [4••,20,32].

EBV serology should be performed in the acute *and* convalescent phases of illness. Wide variation may occur in the types of antibodies produced and the timing of their appearance during primary EBV infection [6]. The presence of IgM antibodies against EBV VCA in the absence of antibodies against EBNA is diagnostic of acute EBV infection. Anti-VCA IgM typically forms during the first 2 weeks of illness and peaks several weeks later. However, it is worth noting that the ulcer preceded anti-VCA IgM antibodies in three cases [11••,33,34]. Anti-VCA IgG and anti-EBNA antibodies typically form during the third to sixth week after the onset of infection and may persist for life. Nonspecific heterophile antibodies may also form; however, as in our case, they can give a false-negative result during the first 2 weeks of infection. Moreover, 70% to 80% of patients develop anti–early antigen (EA) antibodies during the acute phase of infection. Persistence of anti-EA antibodies for more than 6 months is unusual and may be a marker of an aberrant immune response. A rapid test for EBV and serum PCR for EBV DNA are newer methods being used with increasing frequency [7]. Because of variations in the timing and type of antibody production during primary EBV infection and the possibility of false-positive and false-negative test results, convalescent serology performed at least 10 to 14 days after the initial presentation and repeated several months after the acute phase are helpful in confirming the diagnosis.

Culture of ulcers for EBVU was attempted, but was successful in only one of five cases. Also useful is PCR for EBV DNA from the ulcer, or immunohistochemistry and indirect immunofluorescence from a biopsy. Nucleic acid hybridization techniques are the only methods that differentiate between the two known strains of EBV. These latter methods are not currently used but may become more important with improved understanding of the differences between EBV strains. Biopsy findings are often nonspecific and nondiagnostic, but provided clinically useful information in 36% (4/11) of the cases reviewed, with EBV DNA isolated in three specimens by PCR [9,10,35] and with one in which the pathologist noted a "prominent starry sky pattern" similar to that observed in the EBV-induced cancer Burkitt's lymphoma [29].

Management

EBVU is typically a self-limited condition. However, among the 20 case reports that described healing time, the mean time to complete resolution of the ulcer was approximately 20 days, with one lasting 10 weeks [4••]. Although supportive treatment of EBVU is the norm, a range of management options is available.

Topical therapy and pain management

A moisturizing barrier (eg, zinc oxide ointment) may provide local relief. Patients with severe dysuria may need to urinate while directing a stream of water onto the vulva or while in a sitz bath. Low-potency topical steroids, silver sulfadiazine, topical lidocaine, fusidic acid, and estrogen cream have been used in the treatment of EBVU with variable benefit [18,26]. A broad range of analgesics, including narcotics, were used in the cases reviewed.

Antimicrobials

Eighteen patients in the case reports reviewed had negative bacterial cultures of ulcers, but one grew *Pseudomonas aeruginosa* [36] and another *Staphylococcus aureus* [37]. Although bacterial superinfection appears rare, antibiotic therapy may be considered in patients with markedly necrotic or purulent ulcers. Broad-spectrum agents with coverage for genitourinary pathogens should be selected.

Antiherpetic agents for acute EBV infection appear to have little clinical efficacy. Although acyclovir therapy reduces oropharyngeal EBV shedding, the quantity of virus and rate of viral shedding return to pretherapeutic levels soon after patients stop taking the medication [4••,17••].

Table 2. Distinguishing Epstein-Barr virus–associated ulcers from other common causes of acute genital ulcers

Features	EBVU	HSV	Syphilis	Chancroid	Lymphogranuloma venereum
History					
Mean age, *y*	14–17	Seroprevalence increases with age; sharpest increase at ages 19 and 29	25–29	≥ 35	Unknown
Incubation period	0 d–3 wk (mean, 8 d)	2–7 d	1–12 wk	1–14 d	3 d–6 wk
Fever	Yes	Yes	Rare in primary infection	Occasionally mild fever	Yes
Pain/dysuria	Yes	Yes	Rarely	Yes	Occasionally
Favored location	Labia minora	Labia majora, labia minora, perianal, vaginal walls, cervix	No preference; can appear on vagina, cervix, perineum, anus	Labia majora, labia minora, perianal; rarely affects vagina or cervix	Commonly causes rectal ulcers; isolated genital/vaginal ulceration rare
Other	+ Sick contacts; + history of oral ulcers in many cases	Primary infection may be asymptomatic	Chancre is associated with primary syphilis	Endemic in Africa, Asia, Caribbean; rare in United States, most outbreaks in cities	Very rare in United States; associated with proctocolitis (ie, rectal bleeding or purulent discharge, tenesmus)
Physical examination					
Appearance of primary lesion	Large, vesicular, "punched-out" ulcer; often necrotic or pseudomembrane forming	Small (but multiple small ulcers may coalesce), vesicular	Papular chancre	Papular (occasionally pustule forming)	Papular or vesicular (occasionally pustule forming)
Number of lesions	Solitary or multiple; commonly one dominant and several satellite ulcers	Multiple, occasionally coalescing	Usually solitary	Usually multiple, occasionally coalescing	Usually solitary
Diameter, *cm*	0.1–4.0	0.1–0.2	0.5–1.5	0.2–2.0	0.2–1.0
Depth	Deep	Superficial	Superficial or deep	Deep	Superficial or deep
Color/appearance	Violaceous/purplish, irregular borders, often with central necrosis	Reddish blisters → small ulcers	Indurated, nontender, reddish-brown, elevated, sharply demarcated; may coalesce and form plaques	Purulent base, irregular borders	Vesicle or papule → painless ulcer; severe cases may result in vulvar elephantitis
LAD	Cervical > inguinal; unilateral or bilateral	Firm, tender, bilateral, inguinal	Firm, tender, bilateral	Tender, usually unilateral, occasionally suppurative	Tender, loculated, usually unilateral, occasionally suppurative
Laboratory					
Diagnostic gold standard	EBV VCA IgM+ and EBNA IgG-; + serum PCR for EBV DNA	+ HSV culture or PCR (serum or from ulcer swab)	+ RPR or VDRL plus + FTA-ABS or TP-PA or TPHA; + dark-field exam	+ Culture for *Haemophilus ducreyi*	+ Culture for *Chlamydia trachomatis* followed by genotyping

EBNA—Epstein-Barr virus nuclear antigen; EBV—Epstein-Barr virus; EBVU—Epstein-Barr virus–associated ulcer; FTA-ABS—fluorescent treponemal antibody absorption; HSV—herpes simplex virus; LAD—lymphadenopathy; PCR—polymerase chain reaction; RPR—rapid plasma reagin; TPHA—*Treponema pallidum* hemagglutination assay; TP-PA—*Treponema pallidum* particle agglutination; VCA—viral capsid antigen; VDRL—Venereal Disease Research Laboratory test.
(*Adapted from* Sisson and Glick [48] and Taylor et al. [50].)

Antiviral therapy has limited impact on the numbers of circulating EBV-infected B lymphocytes, and, most importantly, antiviral medications do not provide relief from EBV symptoms [7]. They are not recommended for acute EBV infection, nor do data exist to support their use for EBVU.

Systemic corticosteroids

The use of corticosteroids in treating acute EBV infection is controversial. In patients with severe pharyngitis, steroids reduce swelling and pain within 24 hours of initiating therapy [38••]. A recent Cochrane review of seven randomized clinical trials found strong evidence to suggest that steroids may shorten the length of stay in hospitalized patients with EBV, decrease the time until resumption of normal activities, and reduce the severity of sore throat pain [2,38••]. Current guidelines recommend steroids primarily to treat complicated EBV infection, defined as airway compromise, thrombocytopenia, and certain neurologic and cardiac complications [7]. Steroid therapy in mild EBV infection is linked to septicemia and to neurologic and other complications [7]. Concerns also exist that muting the normal host immune response to EBV may predispose some patients to EBV-linked cancers (eg, Burkitt's lymphoma) [38••,39••]. The effect of systemic corticosteroids on EBV relapse is unknown.

No apparent difference in average healing times of the ulcer(s) was observed between patients who did or did not receive steroid therapy. Although steroids may not reduce healing time, they appear to significantly reduce the severity and duration of pain from EBVU; this is consistent with findings in patients with severe EBV infection, who typically report marked symptomatic improvement within 24 hours of their first steroid dose [38••]. Among the cases we reviewed, one patient who received steroids experienced a recurrence and one patient remained asymptomatic and free of recurrence 1 year after EBVU diagnosis. No information about follow-up was provided for the remaining five patients who received steroids. The efficacy of steroids in EBVU is difficult to assess because of variations in dose, duration of treatment, and timing of therapy initiation. That EBVU might constitute a new criterion for complicated EBV is worth considering, because 21% of cases required hospitalization during the course of the illness. With regard to recommended doses, Jenson [2] suggests oral prednisone, 40 mg/d for 1 to 3 days. The studies included in the Cochrane review describe starting doses of steroids between 5 and 25 mg/d [38••].

Epstein-Barr Virus in the Lower Female Genital Tract: Vaginal, Cervical, and Uterine Manifestations

Several studies confirm the presence of EBV in the cervical secretions of healthy women [8,13,17••,31,35,39••,40]. Shedding of EBV from the female genital tract is more common among EBV-immune women who are sexually active, particularly those with sexually transmitted infections [8,31,35,40]. Apart from ulcers, data are sparse regarding clinical and pathologic significance of EBV in the lower female genital tract.

Vaginal ulceration from EBV infection is extremely rare. Our review revealed a case of a 21-year-old patient with EBVU who had multiple superficial vaginal ulcerations 48 hours after her initial presentation [27]. Because speculum examinations are usually deferred in premenarchal girls, the actual frequency of vaginal ulceration in patients with EBVU may be higher.

Although other herpes viruses (eg, HSV and CMV) are known to cause cervicitis, the data for EBV are more tenuous [17••]. EBV was found in the cervical secretions of 6 of 15 women (40%) with acetowhite lesions who showed signs of nonspecific inflammation (cervicitis) on colposcopy [41]. Young et al. [29] describe three women with cervical and uterine pathology suspicious for EBV involvement, including one woman with a chief complaint of vaginal bleeding who had cervical involvement with a confirmed diagnosis of acute EBV. In addition, significant debate occurs regarding the role of EBV in cervical carcinogenesis. Although the human papillomavirus (HPV) was identified as the main causative agent in cervical cancer, most patients with HPV-induced dysplasias do not develop cancer. That other factors play a role in cervical carcinogenesis is widely accepted, and EBV is considered a possible cofactor. Several studies explored the possible correlation between HPV and EBV infection in women with cervical dysplasia. In one study, EBV DNA was isolated from 55% of samples taken from women with cervical cancer and only 26% of samples from women with no known cervical pathology [39••]. Thoe et al. [42] isolated EBV DNA from 63% of tissue samples taken from women with a diagnosis of cervical cancer and none from healthy controls. Other studies fail to link coinfection with EBV and HPV to changes suggestive of cervical carcinogenesis [43]. Even where evidence was identified for a role for EBV in cervical dysplasia, the question persists whether the relationship between EBV and cervical cancer is causal. In summary, not enough evidence exists to prove or exclude that EBV acts as a cofactor in the development of gynecologic malignancies.

Finally, a few cases of EBV-induced malignancies arising in the lower female genital tract were reported. These include a recent case report of extranodal lymphomatoid granulomatosis initially involving the uterine cervix [44], and a report by Goker et al. [45] of an HIV-negative patient with multiple gynecologic malignancies including endometrial adenocarcinoma and vulvar intraepithelial neoplasia. An extensive immunologic workup of the patient in the Goker et al. [45] report revealed only a positive test for EBV VCA IgG.

Upper Genital Tract

The role of EBV in upper genital tract pathology is even less well-defined. Most notable is EBV's association with primary Burkitt's lymphoma of the ovary, of which more

than a dozen case reports exist. Many of these cases were discovered during pregnancy, and in a few, the primary ovarian tumor was recognized before other, extraovarian manifestations of disease [46]. Based on epidemiologic data [47], some researchers speculate that EBV plays a role in the development of ovarian epithelial cell tumors. A recent preliminary study evaluating the risk of epithelial ovarian cancer in relationship to age at IM diagnosis found that women with elevated IgG anti-VCA antibodies had a 5.3-fold increased risk of ovarian cancer. The study also found an association between ovarian cancer risk and EA antibody titers. Because the presence of EA antibody is considered suggestive of an atypical response to EBV, this finding may explain why disease develops in some, but not all, EBV-exposed individuals [47–50].

Conclusions

EBV remains an underappreciated cause of AGU, and prompt recognition can lead to more appropriate patient counseling and care. Although controversial, systemic corticosteroids may help decrease the severity of symptoms and should be considered for large, painful ulcers. Despite the ubiquity of the organism in the global population, its role in causing EBVU and possibly other disease in the female genital tract remains relatively unstudied. Important questions remain about mode of transmission and the role of host factors in causing genital disease.

Acknowledgments

The authors thank Clifton Burt, Stephanie Doupnik, and Benjamin Kummer for their help in translating medical articles for this review.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Cheng SX, Chapman MS, Margesson LJ, et al.: **Genital ulcers caused by Epstein-Barr virus.** *J Am Acad Dermatol* 2004, **51:**824–826.
2. Jenson HB: **Acute complications of Epstein-Barr virus infectious mononucleosis.** *Curr Opin Pediatr* 2000, **12:**263–268.
3. Auwaerter PG: **Infectious mononucleosis in middle age.** *JAMA* 1999, **281:**454–459.
4.•• Barnes CJ, Alió AB, Cunningham BB, Friedlander SF: **Epstein-Barr virus-associated genital ulcers: an under-recognized disorder.** *Pediatr Dermatol* 2007, **24:**130–134.

This article is a case report that includes thorough discussions of possible mechanisms of ulceration in EBVU and treatment considerations.

5. Ikediobi NI, Tyring SK: **Cutaneous manifestations of Epstein-Barr virus infection.** *Dermatol Clin* 2002, **20:**283–289.
6. Hollier LM, Grissom H: **Human herpes viruses in pregnancy: cytomegalovirus, Epstein-Barr virus, and varicella zoster virus.** *Clin Perinatol* 2005, **32:**671–696.
7. Katz BZ, Miller G: **Epstein-Barr virus infections.** In *Krugman's Infectious Diseases of Children,* edn 11. Edited by Gershon AA, Hotez PJ, Katz SL. Philadelphia: Elsevier; 2004. Available at http://www.MDconsult.com. Accessed June 2009.
8. Naher H, Gissmann L, Freese UK, et al.: **Subclinical Epstein-Barr virus infection of both the male and female genital tract—indication for sexual transmission.** *J Invest Dermatol* 1992, **98:**791–793.
9. Taylor Y, Melvin WT, Sewell HF, et al.: **Prevalence of Epstein-Barr virus in the cervix.** *J Clin Pathol* 1994, **47:**92–93.
10. Portnoy J, Ahronheim GA, Ghibu F, et al.: **Recovery of Epstein-Barr virus from Genital Ulcers.** *N Engl J Med* 1984, 966–967.
11.•• Halvorsen JA, Brevig T, Aas T, et al.: **Genital ulcers as initial manifestation of Epstein-Barr virus infection: two new cases and a review of the literature.** *Acta Derm-Venereol* 2006, **86:**439–442.

This article reviews relevant data regarding some symptoms associated with EBVU and healing time in multiple cases.

12. Pelletier F, Leblanc L, Estavoyer JM, et al.: **Ulcere de Lipshutz au cours d'une primo-infection a virus Epstein-Barr [in French].** *Ann Dermatol Venereol* 2002, **129:**904–907.
13. Taylor S, Drake SM, Dedicoat M, Wood MJ: **Genital ulcers associated with acute Epstein-Barr virus infection.** *Sex Transm Infect* 1998, **74:**296–297.
14.•• Farhi D, Wendling J, Molinari E, et al.: **Non-sexually related acute genital ulcers in 13 pubertal girls.** *Arch Dermatol* 2009, **145:**38–45.

This article is a descriptive prospective study of 13 immunocompetent adolescent females with AGUs, four of whom were diagnosed with EBVU. The article includes a detailed review of 24 cases of EBVU. The prospective nature of the study supports the notion that the incidence of EBVU is likely higher than was once thought.

15. Svedman C, Holst R, Johnsson A: **Ulcus vulvae acutum, a rare diagnosis to keep in mind.** *Eur J Obstet Gynecol Reprod Biol* 2003, **115:**104–105.
16. van Baarle D, Hovencamp E, Dukers NH, et al.: **High prevalence of Epstein-Barr virus type 2 among homosexual men is caused by sexual transmission.** *J Infect Dis* 2000, **181:**2045–2049.
17.•• Pagano JS: **Is Epstein-Barr virus transmitted sexually?** *J Infect Dis* 2007, **195:**469–470.

This article discusses the controversy about whether EBV is sexually transmitted and explores the data supporting this theory.

18. Llanos AN, Climent VD, Eguinoa JE, Lllave EP: **Epstein-Barr virus primary infection: a poorly known cause of acute genital ulcers [in Spanish].** *Revista Clinica Espanola* 1996, **196:**570–571.
19.•• Huppert JS, Gerber MA, Deitch HR, et al.: **Vulvar ulcers in young females: a manifestation of aphthosis.** *J Pediatr Adolesc Gynecol* 2006, **19:**195–204.

This article describes a prospective study of young women with vulvar ulcers. The authors explore the etiology and discusse important treatment considerations, including corticosteroids, in the setting of AGU.

20. Hernandez-Nunez A, Cordoba S, Romero-Mate A, et al.: **Lipchutz ulcers—four cases.** *Pediatric Dermatology* 2008, **25:**364–367.
21. Deitch HR, Huppert J, Hillard PJA: **Unusual Vulvar Ulcerations in Young Adolescent Females.** *J Pediatr Adolesc Gynecol* 2004, **17:**13–16.
22. Pardo A, Figueroa JP: **Acute vulvar ulcer or Lipschutz disease [in Spanish].** *Revista Chilena de Obstetricia Gynecologico y Ginecologica* 1966, **31:**219–221.
23. Brown ZA, Stenchever MA: **Genital ulceration and infectious mononucleosis: a report of a case.** *Am J Obstet Gynecol* 1977, **127:**673–674.

24. Tattevin P, Tulzo YL, Minjolle S, et al.: **Increasing incidence of severe Epstein-Barr virus-related infectious mononucleosis: surveillance study.** *J Clin Microbiol* 2006, **44:**1873–1874.
25. Morris MC, Edmunds EJ: **The changing epidemiology of infectious mononucleosis?** *J Infect* 2002, **45:**107–108.
26. Hudson LB, Perlman SE: **Necrotizing genital ulcerations in a premenarcheal female with mononucleosis.** *Obstet Gynecol* 1998, **92:**642–644.
27. Johnson TR, Landry MS: **College blues and hues.** *Obstet Gynecol* 2007, **109:**1447–1448, 1461–1462.
28. Logeart I, Blondon H, Caulin C: **Acute ulceration of the vulva during a primary Epstein-Barr virus infection [in French].** *Presse Medicale* 1998, **27:**571–572.
29. Young RH, Harris NL, Scully RE: **Lymphoma-like lesions of the lower female genital tract: a report of 16 cases.** *Int J Gynecol Pathol* 1985, **4:**289–299.
30. Nicolas X, Ansart S, Jaffuel S, et al.: **Genital ulcerations due to Epstein-Barr virus primary infection [in French].** *Revue de Medecine Interne* 2005, **26:**913–916.
31. Anderrson-Ellstrom A, Bergstrom T, Svennerholm B, Milsom I: **Epstein-Barr virus DNA in the uterine cervix of teenage girls.** *Obstet Gynecol Scand* 1997, **76:**779–783.
32. Lampert A, Assier-Bonnet H, Chevallier B, et al.: **Lipschutz's genital ulceration: a manifestation of Epstein-Barr virus primary infection.** *Br J Dermatol* 1996, **135:**663–665.
33. Groulier JL, Pellegrin JL, Marchal C et al.: **Genital ulceration in infectious mononucleosis [in French].** *Presse Medicale* 1986, **15:**2167.
34. Lorenzo CV, Robertson WS: **Genital ulcerations as presenting symptom of infectious mononucleosis.** *J Am Board Fam Pract* 2005, **18:**67–68.
35. Kantakamalakul W, Kanyok R, Naksawat P, Puthavathana P: **Prevalence of type specific Epstein-Barr virus in the genital tract of genital herpes suspected patients.** *J Med Assoc Thai* 1999, **82:**263–267.
36. Tenorio V, Parra C, Uriz S, et al.: **Febre I ulcers genitals en una nena de 2 anys [in Catalan/Spanish].** *Pediatria Catalana* 2004, **64:**88–89.
37. McKenna G, Edwards S, Cleland H: **Genital ulceration secondary to Epstein Barr virus infection.** *Genitourin Med* 1994, **70:**356–357.
38.•• Candy B, Hotopf M: **Steroids for symptom control in infectious mononucleosis.** *Cochrane Database Syst Rev* 2006, **3:** CD004402.
This article is a comprehensive review of the data available on use of corticosteroids in acute EBV infection and the data in support of and against this treatment modality.
39.•• Santos NBM, Villanova FE, Andrade PM, et al.: **Epstein-Barr virus detection in invasive and pre-invasive lesions of the uterine cervix.** *Oncol Rep* 2008, **21:**403–405.
The authors report compelling data to support a link between Epstein-Barr virus and cervical carcinogenesis.
40. Gradlione A, Vercillo R, Napolitano M, et al.: **Prevalence of human papillomavirus, cytomegalovirus, and Epstein-Barr virus in the cervix of healthy women.** *J Med Virol* 1996, **50:**1–4.
41. Voog E, Ricksten A, Stenglein M, et al.: **Are acetowhite lesions of the cervix correlated to the presence of Epstein-Barr virus DNA?** *Int J STD AIDS* 1997, **8:**432–436.
42. Thoe SYS, Wong KK, Pathmanathan R, et al.: **Elevated secretory IgA antibodies to Epstein-Barr virus (EBV) and presence of EBV DNA and EBV receptors in patients with cervical carcinoma.** *Gynecol Oncol* 1992, **50:**168–172.
43. Lattario F, Furtado YL, Silveira FA, et al.: **Evaluation of DAPK gene methylation and HPV and EBV infection in cervical cells from patients with normal cytology and colposcopy.** *Arch Gynecol Obstet* 2008, **277:**505–509.
44. Melegh Z, Sutak J, Whiteway A, et al.: **Lymphomatoid granulomatosis of the uterine cervix.** *Pathol Res Pract* 2009, **305:**371–374.
45. Goker BO, Bese T, Ilvan S, et al.: **A case with multiple gynecological malignancies.** *Int J Gynecol Cancer* 2005, **15:**372–376.
46. Magliore LK, Pettker CM, Buhimschi CS, Funai EF: **Burkitt's lymphoma of the ovary in pregnancy.** *Obstet Gynecol* 2006, **108:**743–745.
47. Littman AJ, Rossing MA, Madeleine MM, et al.: **Association between late age at infectious mononucleosis, Epstein-Barr virus antibodies, and ovarian cancer risk.** *Scand J Infect Dis* 2003, **35:**728–735.
48. Sisson BA, Glick L: **Genital ulceration as a presenting manifestation of infectious mononucleosis.** *J Pediatr Adolesc Gynecol* 1998, **11:**185–187.
49. DeKlotz CMC, Frieden IJ: **Picture of the month quiz case. Vulvar ulcerations resulting from acute Epstein-Barr virus infection.** *Arch Pediatr Adolesc Med* 2008, **162:**86–87.
50. Taylor SN, Martin DH, Leone P, et al.: **Chancroid, genital herpes, lymphogranuloma venereum and syphilis.** In *Current Diagnosis and Treatment of Sexually Transmitted Diseases*. Edited by Klausner JD, Hook EW. New York: McGraw-Hill; 2007:69–75, 84–92, 108–116, 119–142.