Non–Sexually Related Acute Genital Ulcers in 13 Pubertal Girls

A Clinical and Microbiological Study

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Objective: To describe the clinical and microbiological features of acute genital ulcers (AGU), which have been reported in virgin adolescents, predominantly in girls.

Design: Descriptive study. We collected data on the clinical features, sexual history, blood cell count, biochemistry, microbiological workup, and 1-year follow-up.

Setting: Departments of dermatology of 3 university hospitals in Paris.

Patients: Thirteen immunocompetent female patients with a first flare of non–sexually transmitted AGU.

Main Outcome Measures: Clinical and microbiological data, using a standardized form.

Results: Mean age was 16.6 years (range, 11-19 years). Eleven patients denied previous sexual contact. A fever or flulike symptoms preceded AGU in 10 of the 13 patients (77%), with a mean delay of 3.8 days before the AGU onset (range, 0-10 days). The genital ulcers were bilateral in 10 patients. The final diagnosis was Epstein-Barr virus primary infection in 4 patients (31%) and Behçet disease in 1 patient (8%). No other infectious agents were detected in this series.

Conclusions: We recommend serologic testing for Epstein-Barr virus with IgM antibodies to viral capsid antigens in non–sexually related AGU in immunocompetent patients. Further microbiological studies are required to identify other causative agents.

Arch Dermatol. 2009;145(1):38-45

The most common causes of acute genital ulcers (AGU) are herpes simplex virus (HSV) and aphthosis. Since the beginning of the 20th century, several cases of virgin patients with AGU that were not consistent with HSV infection or aphthosis were reported. In 1913, Lipschütz1 proposed a classification of nonvenereal AGU in 3 categories. Two categories fall in the pattern of aphthosis, being idiopathic or secondary to Behçet disease or Crohn disease. The third type of AGU was described as sudden, gangrenous, self-limiting, with nonrelapsing ulcers, occurring mainly in non–sexually active girls and young women and associated with systemic signs evocative of infection. During the 20th century, nonherpetic AGU has been associated with several infectious diseases, including salmonellosis1-3 and infectious mononucleosis.4

However, the etiological diagnosis of AGU remains a difficult one, partly because of the large array of potential precipitating factors,5 many of which are probably underrecognized by clinicians. Moreover, when considering the literature on this issue since the seminal study by Lipschütz,¹ we suspected that in fact several distinct nosological entities may have been reported under the entry Lipschütz’s ulcer, thus further hampering the understanding of this syndrome. We therefore suggest avoiding this appellation, and propose herein major and minor criteria to designate a peculiar clinical situation that requires prompt diagnosis and management, often in an emergency context: the first flare of AGU in an immunocompetent patient without any context of sexually transmitted disease (STD) or aphthosis. Our aim was to describe the clinical and microbiological features of the first flare of AGU in a series of these patients.

STUDY DESIGN AND PATIENTS

We designed a descriptive study of 13 consecutive immunocompetent patients with a first...
flare of non-sexually related AGU. Patients referred to the departments of dermatology of 3 university hospitals in Paris from January 1, 1996, through December 31, 2006, were prospectively included if they presented with 5 major and 1 of 2 minor criteria. Major criteria included (1) presenting with a first flare of AGU; (2) being younger than 20 years; (3) absence of sexual contact during the past 3 months; (4) absence of immunodeficiency; and (3) acute course of the genital ulcer (ie, abrupt beginning and healing without scarring within 6 weeks). Minor criteria were related to the symptomatology of the genital lesions, which may present in the following 2 possible patterns: (1) 1 or several deep, well-delimited, painful ulcers, with a necrotic and/or fibrinous center or (2) a bilateral “kissing pattern” (a mirror-like varicella distribution).

The exclusion criteria were (1) a history of genital aphthosis or STD; (2) clinical or microbiological evidence of genital herpes or another STD; and (3) immunodeficiency. Given its high incidence in the general population, a history of oral aphthosis was not an exclusion criterion. Because this was a descriptive, noninterventional study, the project did not require approval by an institutional review board.

DATA COLLECTION

We collected the following data: age, sex, sexual history, complete clinical examination, symptomatology of the genital ulcers, time to healing of the genital lesions, blood cell count, biochemistry (measurement of liver enzyme levels and kidney function), and results of a search for infectious agents including human immunodeficiency virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), syphilis, and toxoplasmosis. The presence of HSV was investigated by means of repeated serologic examinations and/or local swabbing (for culture and/or polymerase chain reaction). In some cases, other laboratory workups were implemented, including genital mucosal biopsy for histopathological examination (in 5 patients).

One year after the flare of AGU, a standardized form was sent to the patients to assess occurrence of relapses of AGU or other medical problems.

LITERATURE REVIEW

We conducted an extensive and systematic MEDLINE search using the key words acute and genital or vulgar and ulcers or ulcer vasculum acutum or Lipschitz. We further searched all references in the retrieved articles. Thus, we collected a total of 32 relevant articles on the topic.

REPORT OF A CASE

In March 2000, a previously healthy 19-year-old woman presented with painful AGU, odynophagia for 10 days, and intense fatigue for 2 days. She denied previous sexual contact at repeated interviews. On physical examination, her temperature was 40°C and she had pharyngeal edema, lymphadenopathies, and vulvar ulcers (Figure, A, and Table 1). Her hymen was intact. At day 10, she developed a grayish white membranous tarsilitis, with enlarged and swollen cervical lymph nodes. Pharyngeal culture results were negative for group A streptococci. Cefpodoxime proxetil therapy was then started with substitution of josamycin at day 13. At day 25, she developed a rash of the 4 extremities, consisting of scattered erythematous small papules that resolved spontaneously within a few days. Fatigue persisted until day 37. At day 65, she presented with several painful aphthoid ulcerations of the tongue that healed within 15 days.

Sero logic test results for CMV, human immunodeficiency viruses 1 and 2, parvovirus B19, hepatitis B and C viruses, syphilis (Treponema pallidum) hemagglutination test (TPHA) and VDRL tests), toxoplasmosis, and p24 antigenemia were negative at different sampling times.

At day 7 of the ulcers, findings were positive for IgM antibodies to the EBV capsid antigen (VCA) and negative for IgG antibodies. At day 15, findings for IgM and IgG anti-VCA antibodies were strongly positive, whereas those for anti-EBV nuclear antigen (EBNA) were negative, confirming primary infection with EBV. Other biological variables are summarized in Table 1.

The Tzanck test showed no cytopathogenic effect. Histopathological examination of a mucosal biopsy specimen showed a necrotic epithelium and a polymorphic dermal infiltrate that consisted of neutrophils and mononuclear cells expressing preferentially the CD8 antigen (Figure, B). Results of in situ hybridization revealed EBV transcripts (EBV-encoded small RNA [EBER] and BamHI H left frame 1 [BHLF-1 RNA]) (Figure, C), whereas immunohistochemistry revealed EBNA-2 and BamHI Z EBV replication activator (ZEBRA) proteins (Figure, D). Quantification of EBV was performed at sequential intervals in the serum samples and in the vulvar lesion.

At day 6, the serum load of EBV was in the range of the serum loads commonly found in patients with EBV primary infection (373 copies/mL), whereas the EBV load was higher in the mucosal swab (1737 copies/mL). The serum EBV load remained high at day 15 (336 copies/mL) and decreased to less than 3 copies/mL at day 24, without any subsequent flare of serum EBV load during the 4-month virological follow-up.

The CD8 cells specific for EBV were quantified at different times, using an interferon γ enzyme-linked immunospot assay (IFN-ELISPOT kit; Dianclone Research, Besançon, France). At day 21, a weak response against latent (EBNA-3A, EBNA-3C, and latent membrane protein 2 [LMP-2]) and lytic (EBV immediate-early gene product BMLF-1) antigens was detected. At day 65, the response against BMLF-1 displayed a 10-fold increase (257 spot-forming cells per 10⁶ peripheral blood mononuclear cells). At 6 months, the BMLF-1 response diminished and was replaced by a strong response against the LMP antigen (217 spot-forming cells per 10⁶ peripheral blood mononuclear cells).

Six months later, the patient remained free of symptoms, findings for anti-EBNA antibodies were positive at high titers, and blood lymphocyte levels were within the reference range. One year later, she had not experienced a relapse.

RESULTS

From 1996 to 2006, 13 patients (including the case described in the preceding section) were included in a clinical and virological study (Table 1). Unless otherwise indicated, data are expressed as mean (SD).
DEMOGRAPHIC DATA

All of the patients were female. Mean age was 16.6 (2.8) years (median age, 18 years; range, 11-19 years). Eleven of 12 patients (92%) denied previous sexual contact. Patient 12 had had previous sexual intercourse, although not during the 3 months before the AGU.

CLINICAL PRESENTATION AND MICROBIOLOGICAL DATA

Seven of the 13 patients (54%) had prodromic tonsillitis, which occurred with a mean delay of 8.6 (6.0) days before the AGU onset (median delay, 7 days; range, 3-18 days). A fever or flulike symptoms preceded AGU in 10 of 13 patients (77%), with a mean delay of 3.8 (3.1) days before the AGU onset (median delay, 3 days; range, 0-10 days).

The genital ulcers were bilateral in 10 of 13 patients (77%), with a peculiar kissing pattern in 9 of 10 (90%). Nine of 13 patients had a medical history of transient oral erosions, diagnosed as aphthae.

The AGU was associated with an EBV primary infection in 4 of 13 patients (31%). Biological mononucleosis syndrome (hyperbasophilic atypical lymphocytes) was present in 3 of the 4 patients with EBV primary infection (75%) vs 1 of the 7 patients without EBV primary infection (14%) (P = .09). No other infectious agents were detected in any of the 13 patients; all patients who underwent testing had negative serologic findings for HIV (12 patients) and syphilis (6). All patients who underwent testing had repeated negative test results or a formerly acquired immunity profile for HSV (10 patients), CMV (12), and toxoplasmosis (6) antibodies. The kissing pattern of the ulcerations was present in all 4 of the patients with EBV primary infection (100%) vs 3 of the 9 patients without EBV primary infection (56%).

Figure. Clinical and virological findings in patient 1. A, Acute necrotizing genital ulcerations of the labia minora, with a kissing pattern. B, Immunostaining with anti-CD8 antibodies shows infiltrating lymphocytes expressing CD8 (red) (original magnification X20). C, In situ hybridization with an Epstein-Barr virus (EBV)-encoded small RNA probe shows 2 cells with positive reactions (arrows) (original magnification X40). D, Immunostaining with anti-BamHI 2 EBV replication activator antibodies shows 1 cell with a positive reaction (nuclear, red) (original magnification X100).
Table 1. Thirteen Immunocompetent Female Patients Presenting With a First Flare of AGU

<table>
<thead>
<tr>
<th>No.</th>
<th>Features of Genital Ulcers</th>
<th>Lymph Node Findings</th>
<th>Systemic Signs</th>
<th>Blood Cell Count</th>
<th>HSV Workup Findings</th>
<th>Serum EBV Workup Findings</th>
<th>Genital EBV Workup Findings</th>
<th>Duration of AGU, d</th>
<th>Final Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Deep kissing-pattern, 5- to 20-mm necrotizing ulcers on labia minora, with well-defined edge; moderate edema</td>
<td>+ (Bilateral, cervical and inguinal)</td>
<td>Fluffy symptoms (fever and fatigue; purpuric micropapular acral rash; oral erosions; cytolytic hepatitis)</td>
<td>Lymphopenia</td>
<td>Serologic: –</td>
<td>Serocconversion of EBNA antibodies in ≤ 6 mo; PCR for EBV on serum, +</td>
<td>Valacyclovir hydrochloride, cefpodoxime proxetil, josamycin</td>
<td>17</td>
<td>EBV PI</td>
</tr>
<tr>
<td>2</td>
<td>Necrotic 1-cm kissing-pattern ulcers on labia minora; edema</td>
<td>– None</td>
<td>Within reference range</td>
<td>Serologic: IgG+, IgM–</td>
<td>EBNA: IgG+, IgM–</td>
<td>–</td>
<td>Cefpodoxime</td>
<td>28</td>
<td>Idiopathic AGU</td>
</tr>
<tr>
<td>3</td>
<td>Multiple, geographic, 2-cm, soft and tender kissing-pattern ulcers on labia minora</td>
<td>+ (Bilateral, inguinal, tender)</td>
<td>Fluffy symptoms (fatigue, fever, and headache); oral erosions</td>
<td>Lymphopenia; no AL</td>
<td>Serologic: –</td>
<td>Serocconversion of EBNA antibodies in ≤ 20 d</td>
<td>Valacyclovir</td>
<td>15</td>
<td>EBV PI</td>
</tr>
<tr>
<td>4</td>
<td>Multiple kissing-pattern ulcers on labia minora; edema</td>
<td>– Fluffy symptoms (fever); cytolytic hepatitis</td>
<td>Within reference range</td>
<td>Serologic: –</td>
<td>VCA: –; PCR for EBV on serum: –</td>
<td>–</td>
<td>_valacyclovir</td>
<td>15</td>
<td>Behçet disease (6 mo after AGU: relapsing bowel aphthosis, pseudofolliculitis, arthritis)</td>
</tr>
<tr>
<td>5</td>
<td>Ulcer on right labium minus</td>
<td>+ (Bilateral inguinal)</td>
<td>Fluffy symptoms (fatigue and fever); Fluffy symptoms (fever); cytolytic hepatitis</td>
<td>Lymphocytosis count, 4200/µL; AL, 3%</td>
<td>Serologic: IgG–, IgM–</td>
<td>EBNA antibodies: – (twice in ≤ 36 d)</td>
<td>NA</td>
<td>None</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>Asymmetric necrotic ulcers on labia minora; edema</td>
<td>– Fluffy symptoms (fever); cytolytic hepatitis</td>
<td>Within reference range</td>
<td>Serologic: –</td>
<td>VCA and EBNA: – (twice in ≤ 37 d)</td>
<td>–</td>
<td>Aminocillin</td>
<td>35</td>
<td>Idiopathic AGU</td>
</tr>
<tr>
<td>7</td>
<td>Symmetric kissing-pattern ulcers on labia minora</td>
<td>– Fluffy symptoms (fever); cytolytic and cholestatic hepatitis</td>
<td>Leukocytosis (lymphocyte count, 10,100/µL; AL, 18%; thrombocytopenia (platelet count, 129,000/µL)</td>
<td>Serologic: consistent with ancient acquired immunity; culture and PCR negative on genital swabs</td>
<td>None</td>
<td>Serocconversion of VCA antibodies in ≤ 14 d</td>
<td>(Culture, PDR)</td>
<td>None</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>Kissing-pattern ulcers on labia minora</td>
<td>– Fluffy symptoms</td>
<td>Leukocytosis (WBC count, 12,800/µL; AL, &gt; 50%)</td>
<td>Serologic: HSV1 and HSV2 tests: IgM–, IgG–</td>
<td>NA</td>
<td>Valacyclovir</td>
<td>15</td>
<td>Idiopathic AGU</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Necrotic symmetric kissing-pattern ulcers on labia minora and majora</td>
<td>– Fluffy symptoms (fever and myalgias); cytolytic hepatitis</td>
<td>Leukocytosis (WBC count, 12,800/µL; AL, &gt; 50%)</td>
<td>Serologic: HSV1 and HSV2 tests: IgM–, IgG–; culture: –</td>
<td>NA</td>
<td>Valacyclovir</td>
<td>15</td>
<td>EBV PI</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Large necrotic kissing-pattern ulcers on labia minora; edema</td>
<td>– Fluffy symptoms, abdominal pain, and diarrhea; cytolytic hepatitis</td>
<td>Fluffy symptoms (WBC count, 12,800/µL; AL, &gt; 50%)</td>
<td>NA</td>
<td>VCA: IgG+, IgM–</td>
<td>–</td>
<td>(Culture)</td>
<td>None</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Small necrotic ulcer on right labium minus</td>
<td>– Abdominal pain</td>
<td>Within reference range</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>(IHC)</td>
<td>Aminocillin</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>Necrotic bilateral kissing-pattern ulcers on labia minora with marked edema</td>
<td>+ (Cervical and inguinal)</td>
<td>Fluffy symptoms (fever)</td>
<td>Within reference range</td>
<td>Serologic: consistent with ancient acquired immunity; culture: –</td>
<td>MNT: –; VCA: IgG+, IgM–</td>
<td>NA</td>
<td>None</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>Painful ulcer of the right labium minus</td>
<td>+ None</td>
<td>NA</td>
<td>Serologic: –</td>
<td>VCA: –; EBNA: –</td>
<td>NA</td>
<td>Valacyclovir</td>
<td>15</td>
<td>Idiopathic AGU</td>
</tr>
</tbody>
</table>

Abbreviations: AGU, acute genital ulcers; AL, atypical lymphocytes; CMV, cytomegalovirus; EBNA, Epstein-Barr virus (EBV) nuclear antigen; HSV, herpes simplex virus; IHC, immunohistochemistry; ISH, in situ hybridization; MN, mononucleosis; MNT, monospot test (heterophile antibody); NA, not assessed (or not reported); PCR, polymerase chain reaction; PI, primary infection; VCA, viral capsid antigen; WBC, white blood cell; +, positive; –, negative.

SI conversion factors: To convert lymphocytes and WBCs to × 10^9/L, multiply by 0.001; platelets to × 10^11/L, multiply by 0.001.
A medical history of oral erosions diagnosed as aphthae was present in 1 of the 4 patients with EBV primary infection (25%) vs all 8 of those without EBV primary infection (100%) (P = .02).

Cytolytic hepatitis was present in 3 of the 4 patients with EBV primary infection (75%) vs 3 of the 7 without EBV primary infection (43%).

Results of the histopathological examination were not helpful for the diagnosis in any of the 5 patients who underwent mucosal biopsy and usually showed a nonspecific lymphocytic inflammatory dermal infiltrate.

FOLLOW-UP

Six patients were treated with valacyclovir hydrochloride (46%) and 4 with a β-lactamine (31%). The mean delay before healing was 16.8 (7.4) days (median delay, 15 days; range, 8-35 days), without a significant difference according to the final diagnosis (EBV primary infection vs other AGU).

Three patients (23%) experienced 1 relapse of AGU during the following year. None of them was diagnosed as having EBV primary infection during the first flare of AGU. One of them was later diagnosed as having Behçet disease.

COMMENT

The first flare of a nonherpetic AGU in an immunocompetent patient without an STD is a difficult etiological problem that is often diagnosed in excess as genital herpes or aphthosis or even sexual abuse in young patients. We presented herein a series of 13 consecutive cases of AGU in female patients younger than 20 years, and we showed that one-third of these AGUs were associated with EBV primary infection.

Unlike herpes and aphthosis, AGUs related to EBV primary infection are typically associated with the absence of further relapse of genital ulcers. This clinical syndrome should lead to an oriented microbiological workup in search of previously reported causative infectious agents, including EBV, CMV, salmonella, and toxoplasmosis. Our study confirms that the most frequently reported infectious agent associated with a first flare of nonherpetic AGU is EBV.

We retrieved 18 articles that reported 24 cases of a first flare of AGU associated with EBV primary infection, including 15 cases in girls without previous sexual contact (Table 2). All cases were confirmed by serologic test results consistent with EBV primary infection. In 4 cases, local workup identified EBV on the genital lesions.

In 2006, Huppert et al reported a series of 20 cases of presumed non–sexually transmitted AGU in female patients aged 10 to 19 years. Systemic signs such as fever, malaise, and headache were reported by 19 of 20 patients. Two of them had IgM antibodies to VCA (10%), and 2 had possible evidence of acute CMV infection. Summary rather than detailed individual data were provided; thus, peculiar findings in the 2 patients with associated EBV primary infection were not available. Other laboratory findings were nonspecific. The median duration of pain was 10 days, and 15 patients (75%) healed by 21 days. Huppert et al considered that most of these cases of AGU were possibly genuine genital aphthae. However, the inclusion criterion in their series was AGU with negative HSV test results and, therefore, that these cases might be different from those in our series, which may explain the lower rate of EBV-related AGU reported in the series by Huppert et al. For example, 3 of their patients had a history of AGU, whereas this feature was an exclusion criterion in our series.

In the highlighted case from our series of patients, we demonstrated the presence of EBV in mononuclear cells infiltrating the vulva. We showed the expression of both RNA (EBER and BHLF-1) and proteins (EBNA-2 and ZEBRA), suggesting that EBV may replicate in the mucosa, or at least that a part of the lytic cycle could occur. However, the proportion of EBV-positive cells was low, suggesting that the ulceration results more from an immune reaction associated with EBV than from a direct cytopathogenic effect of the virus itself. Moreover, in our series, as in others, most of the pubertal non–sexually active patients with AGU had no evidence of associated acute systemic infection. Therefore, it might be hypothesized that AGU in these patients result from a reaction nonspecific inflammatory process. This may explain why AGU have been described with a large spectrum of acute infection, such as CMV, influenza, salmonella, and toxoplasmosis.

In addition, some authors have suggested that these peculiar forms of AGU in non–sexually active adolescents are a clinical form of primary genital aphthosis.

In 24 previously published cases of EBV primary infection associated with AGU, mean age was 15.1 years, which is similar to our findings, and 23 of 24 patients (96%) were female. In our series, 92% of the patients denied previous sexual contact; in the literature, 17 of 24 patients (71%) had never had sexual contact; 4 (17%) had had sexual intercourse and 3 (13%) had had only orogenital (2 patients) or digital-genital (1) contact. On clinical examination, 8 of 22 previously published cases of AGU (36%) had a kissing pattern of ulcers, 13 (59%) had sore throat, 16 (73%) had lymphadenopathy, and all had systemic signs, the most common being fever (20 of 22 [91%]) and fatigue (14 of 22 [64%]). In our study, the mean duration of genital lesions was 17 days, which is comparable to the duration of 19 days reported in the literature. This healing delay is comparable to that of 12 to 16 days reported for genital herpes primary infection.

In 9 of the 21 reported cases (43%), acyclovir was introduced before the correct diagnosis of EBV primary infection was made (5 of 13 [38%] in our series); this reflects that genital herpes is the most commonly suspected differential diagnosis. Indeed, genital herpes should always be ruled out first in a patient with AGU. However, the clinical presentation of genital herpes is different, with smaller and superficial erosions often coalescing in a polycyclic pattern, and this differential diagnosis can be confirmed by genital polymerase chain reaction or culture.

A much-debated question is how the EBV reaches the genital mucosa in AGU. Four modes of transfer of EBV to the genital mucosa may be discussed. First, potential transmission via genital-genital contact has been hypothesized, given that EBV shedding has been identified in...
Table 2. Previously Reported Cases of First Flare of AGU Associated With EBV in Female Patients Without Previous Sexual Contact

<table>
<thead>
<tr>
<th>Source</th>
<th>Age, y</th>
<th>Features of AGU</th>
<th>Lymph Node Findings</th>
<th>Systemic Signs</th>
<th>Blood Cell Count</th>
<th>HSV Workup</th>
<th>EBV Serologic Findings</th>
<th>Local EBV Workup Findings</th>
<th>Treatment</th>
<th>Duration of AGU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnes et al, 2007</td>
<td>14</td>
<td>Painful, well-circumscribed, deep, 1- to 2-cm bilateral labial ulcers</td>
<td>+ (Anterior cervical)</td>
<td>Fever, tonsillitis, myalgias, fatigue, vomiting, headaches, blurry vision, dizziness, cholestatic and cytolytic hepatitis</td>
<td>Lymphocytosis (lymphocyte count, 4092/µL; AL, 19%)</td>
<td>Serologic and genital PCR: −</td>
<td>VCA: IgM +, IgG +</td>
<td>Genital EBV: −</td>
<td>Cephalexin hydrochloride, naproxen sodium, prednisone (20 mg/d)</td>
<td>70 d</td>
</tr>
<tr>
<td>Cheng et al, 2004</td>
<td>16</td>
<td>Multiple painful ulcers, 1 cm in diameter with ragged edges and central granulation tissue on labia minora</td>
<td>+ (Tender, cervical and inguinal)</td>
<td>Fatigue, headache</td>
<td>Elevated monocyte levels</td>
<td>NA</td>
<td>MNT: −; VCA: IgM +</td>
<td>NA</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Cheng et al, 2004</td>
<td>10</td>
<td>Multiple ulcers, 0.3 to 2.5 cm in diameter</td>
<td>−</td>
<td>Fever, elevated transaminase level</td>
<td>Leukocytosis (WBC count, 17 000/µL; AL detected (number NA))</td>
<td>Culture and pathological study on lesion biopsy specimen: −</td>
<td>MNT: +; VCA: IgM +</td>
<td>NA</td>
<td>Antibiotics</td>
<td>NA</td>
</tr>
<tr>
<td>DeKlotz and Perlman, 1996</td>
<td>12</td>
<td>Bilateral large, deep, pseudo-membranous and exudative ulcers on labia minora</td>
<td>−</td>
<td>Fever</td>
<td>NA</td>
<td>Culture of ulcer: −</td>
<td>VCA: IgM −, IgG +</td>
<td>EBNA: IgG −</td>
<td>−</td>
<td>None</td>
</tr>
<tr>
<td>Groulier et al, 1996</td>
<td>13</td>
<td>Painful ulcer on labia majora; edema</td>
<td>+ (Bilateral cervical and inguinal)</td>
<td>Fever, headache, cytolytic hepatitis</td>
<td>Leukocytosis (WBC count, 12 000/µL; lymphocytes, 61%; AL, 12%)</td>
<td>HSV serologic: weakly +</td>
<td>Strongly positive MNT:</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hudson and Perlman, 1996</td>
<td>13</td>
<td>Multiple necrotizing ulcers with fibrous exudates on labia minora</td>
<td>+ (Bilateral inguinal)</td>
<td>Fatigue</td>
<td>WBC count within reference range; AL, 5%</td>
<td>Culture of ulcer: −</td>
<td>MNT and IgM and IgG VCA findings consistent with acute MN</td>
<td>NA</td>
<td>Acyclovir sodium, cefotaxin sodium, amoxicillin + clavulanate potassium</td>
<td>NA (=25 d)</td>
</tr>
<tr>
<td>Lampert et al, 1996</td>
<td>13</td>
<td>Pruritic and painful 2-cm bluish black ulcer of left labium minus, covered by a dirty adherent membrane and surrounded by other smaller ulcers</td>
<td>+ (Enlarged and swollen cervical)</td>
<td>High fever, myalgias, fatigue</td>
<td>Leukocytosis (WBC count, 11 700/µL); lymphocytes, 46%; AL, 10%</td>
<td>Genital culture: −</td>
<td>VCA: IgM −, IgG +; EBNA: IgG −; VCA (2 mo later): IgM −, IgG +</td>
<td>Acyclovir, amoxicillin + clavulanate</td>
<td>“Few weeks”</td>
<td></td>
</tr>
<tr>
<td>Lorenzo and Roberts, 2005</td>
<td>18</td>
<td>Multiple, large, painful, hemorrhagic, necrotic, ulcerated lesions on labia minora</td>
<td>+ (Cervical)</td>
<td>Fever</td>
<td>Leukocytosis (WBC count, 5000/µL; AL, 24%; thrombocytopenia (platelet count, 130 000/µL))</td>
<td>Serologic and direct fluorescent antibody tests: −</td>
<td>MNT and IgM and IgG VCA findings consistent with acute MN</td>
<td>NA</td>
<td>Acyclovir, ciprofloxacin hydrochloride, prednisone</td>
<td>22 d</td>
</tr>
<tr>
<td>McKenna et al, 1994</td>
<td>13</td>
<td>Very large, deep ulcers on labia minora with vivid purple borders</td>
<td>+ (Marked, generalized)</td>
<td>Fever</td>
<td>Presence of AL</td>
<td>Genital culture: −</td>
<td>VCA: IgM +</td>
<td>NA</td>
<td>Acyclovir</td>
<td>NA</td>
</tr>
<tr>
<td>Navarro Llanos et al, 1996</td>
<td>14</td>
<td>Painful 2-cm ulcer on left labium majus with soft, erythematous edge and clean center</td>
<td>−</td>
<td>Fever, malaise, headache</td>
<td>Within reference range</td>
<td>HSV tests: IgM −, IgG + (at days 5 and 60)</td>
<td>MNT: +; VCA: IgM +, IgG +</td>
<td>NA</td>
<td>Topical fusidic acid</td>
<td>20 d (no relapse during 16-mo follow-up)</td>
</tr>
<tr>
<td>Pelletier et al, 2002</td>
<td>15</td>
<td>Ulcers on labia minora</td>
<td>+ (Cervical)</td>
<td>Rulike symptoms (fatigue, fever, chills), cytolytic and cholestatic hepatitis</td>
<td>Leukocytosis (WBC count, 6 000/µL; AL, 24%); thrombocytopenia (platelet count, 88 000/µL)</td>
<td>Serologic: consistent with previous acquired immunity (IgM −, IgG)</td>
<td>VCA: IgM −, IgG +; EBNA: IgG − (lately converted)</td>
<td>PCR for EBV DNA on lesion biopsy specimen: +</td>
<td>Macrolide</td>
<td>NA (=28 d)</td>
</tr>
</tbody>
</table>

(continued)
male semen\textsuperscript{33} and in the uterine cervix.\textsuperscript{32} Second, transmission via oral-genital contact is suggested by previous reports of long-term salivary shedding of EBV after infectious mononucleosis in healthy adults.\textsuperscript{33,34} These 2 hypotheses seem unlikely because 92% of the patients in our series had had no previous sexual contact. Third, shedding of EBV in the urine has been shown during and after infectious mononucleosis\textsuperscript{35} as well as in healthy adults.\textsuperscript{36} Fourth, a hematogenous spread of EBV-infected lymphocytes\textsuperscript{14,16,23} or Langerhans cell precursors\textsuperscript{37} has been reported. Furthermore, the EBV may provoke a cytotoxic immune response, and hematogenous routes are the most likely ones and definitely promote one of these hypotheses, the urinary infection via oral-genital contact is suggested by previous investigations, treatment, and anxiety. Patients should be informed that this rare form of acute mononucleosis is self-limiting and seldom relapses. Supportive care primarily aimed at pain relief is indicated in all cases. Systemic corticosteroids have been administered by some authors for peculiarly painful or long-lasting AGU,\textsuperscript{9} but evidence-based data on the efficacy-safety balance are lacking. Despite showing in vitro activity, acyclovir demonstrated no clinical benefit in a meta-analysis of 339 patients.\textsuperscript{19} The nature of the immunoglobulin was not specified.

**Table 2. Previously Reported Cases of First Flare of AGU Associated With EBV in Female Patients Without Previous Sexual Contact** (continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>Age, y</th>
<th>Features of AGU</th>
<th>Lymph Node Findings</th>
<th>Systemic Signs</th>
<th>Blood Cell Count</th>
<th>HSV Workup Findings</th>
<th>EBV Serologic Findings</th>
<th>Local EBV Workup Findings</th>
<th>Treatment</th>
<th>Duration of AGU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelletier et al.\textsuperscript{21} 2002</td>
<td>17</td>
<td>Painful punched-out–appearing ulcers with fibrous center on labia minora.</td>
<td>+ (Cervical)</td>
<td>Flu-like symptoms (fatigue, fever), cytolytic hepatitis</td>
<td>NA</td>
<td>VCA: IgM+, IgG+; EBNA: IgG+</td>
<td>PCR for EBV DNA on lesion biopsy specimen: +</td>
<td>Amoxicillin</td>
<td>NA (&lt;28 d)</td>
<td></td>
</tr>
<tr>
<td>Svedman et al.\textsuperscript{22} 2004</td>
<td>14</td>
<td>Extremely painful, deep ulcer on left labium majus.</td>
<td>−</td>
<td>Fatigue, fever, oral ulcers</td>
<td>PCR for HSV DNA: −</td>
<td>VCA: IgM+, IgG+; EBNA: IgG+</td>
<td>MNT: −; EBNA EIA: −; VCA: IgM+</td>
<td>NA</td>
<td>Prednisone 14 d</td>
<td></td>
</tr>
<tr>
<td>Taylor et al.\textsuperscript{23} 1998</td>
<td>14</td>
<td>Deep, painful kissing-pattern ulcers, 1 cm in diameter, on labia minora.</td>
<td>+ (Tender, generalized)</td>
<td>Elevated lymphocytosis; numerous AL</td>
<td>Culture and direct fluorescent antibody test: −</td>
<td>NA</td>
<td>PCR for EBV DNA: +</td>
<td>Ayclovir</td>
<td>14 d</td>
<td></td>
</tr>
<tr>
<td>Wilson, et al.\textsuperscript{24} 1999</td>
<td>10</td>
<td>15-mm painful kissing-pattern ulcers on labia minora; edema</td>
<td>+ (Small anterior cervical)</td>
<td>Fever (temperature, 39.5°C), nausea, anorexia, headache, myalgias</td>
<td>NA</td>
<td>DIF on swab of ulcers: −</td>
<td>MNT: +</td>
<td>Ayclovir</td>
<td>&lt;2 wk</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AGU, acute genital ulcers; AL, atypical lymphocytes; DIF, direct immunofluorescence; EBNA, EBV nuclear antigen; EBV, Epstein-Barr virus; EIA, enzyme immunoassay; HSV, herpes simplex virus; MNT, monospot test (heterophile antibody); NA, not assessed (or not reported); PCR, polymerase chain reaction; VCA, viral capsid antigen; WBC, white blood cell; +, positive; −, negative.

SI conversion factors: To convert lymphocytes and WBCs to \(10^9/L\), multiply by 0.001; lymphocyte percentage to a proportion of 1, multiply by 0.01; platelets to \(10^9/L\), multiply by 0.001.

The diagnosis of AGU related to EBV primary infection should be based essentially on VCA-IgM results. The histopathological examination of the mucosal biopsy specimen performed in 5 of our 13 patients showed only nonspecific inflammatory dermal infiltrates. We therefore consider this invasive diagnostic method as probably not relevant in most cases of AGU.

Primary infection with EBV is largely underrecognized cause of AGU, leading patients to unnecessary investigations, treatment, and anxiety. Patients should be informed that this rare form of acute mononucleosis is self-limiting and seldom relapses. Supportive care primarily aimed at pain relief is indicated in all cases. Systemic corticosteroids have been administered by some authors for peculiarly painful or long-lasting AGU,\textsuperscript{9} but evidence-based data on the efficacy-safety balance are lacking. Despite showing in vitro activity, acyclovir demonstrated no clinical benefit in a meta-analysis of 339 patients with EBV primary infection.\textsuperscript{19}

Our series of consecutive patients is the first, to our knowledge, to permit an estimation of the rate of EBV primary infection among patients with AGU in the absence of STD, although the small size of our series does not allow for a definite estimation. The analysis of the present series and of the previous reports\textsuperscript{9,11,13,14,16,18-24} yields several messages for the clinician. (1) Acute mononucleosis should always be in a clinician's differential diagnosis of AGU, especially when there is no context of sexual transmission and no history of genital aphthosis. (2) Failure to consider causes other than genital aphthosis or herpes may expose patients and their family to un-
REFERENCES


