Nonsexually acquired acute genital ulceration: A commonly misdiagnosed condition

El-Shahat Farag Ahmed, MD

Department of Dermatology and Andrology, Faculty of Medicine, Mansoura, Egypt

ABSTRACT
Nonsexually acquired acute genital ulceration (NSAGU) is a rare benign condition in vulvar dermatology which may be very painful with marked emotional distress especially among non-sexually active peripubertal girls. It is often misdiagnosed, over-investigated, and under-reported. Recognition of NSAGU is important so that patients receive appropriate and timely treatment and prognostic counseling, involving their parents as needed. It is essential that patients with NSAGU are not given a misdiagnosis of, or treated empirically for, sexually transmitted herpes simplex virus (HSV) infection. An accurate diagnosis of NSAGU will prevent invasive investigations and provide reassurance to the patients and their families. More than 70% of NSAGU are idiopathic. The remaining cases may be related to a preceding systemic illness or caused by direct cytotoxic infection. Contrary to the common belief, the association of NSAGU with EBV is rare. Girls and their parents should be reassured that their ulcers are not infectious, communicable, or sexually transmitted. No formal treatment guidelines for this condition exist. The main lines of treatment include pain control measures, wound care, topical potent steroids and systemic steroids.

KEY WORDS: Genital ulcers; Lipschütz ulcer; ulcus vulvae acutum, aphthous ulcer, vulvar

INTRODUCTION
Nonsexually acquired genital ulceration (NSAGU) is defined as vulvar ulcers that do not have an identifiable etiology, based on clinical, histopathologic serologic, and microbiologic findings. However, in very rare occasions, Epstein-Barr virus (EBV) was identified in the base of the ulcer. It is characterized by sudden painful genital ulceration occurring mostly in young and virgin girls with malaise, fever and other systemic symptoms. This distressing syndrome is rare and may be presented to dermatologists, gynecologists or pediatricians. It is often misdiagnosed as a sexually transmitted disease or even as a sign of child abuse, and commonly over-investigated. It may be considered as a variant of complex aphthosis or a separate entity. The onset may be preceded by an acute systemic illness. The ulcers commonly very painful and can cause considerable emotional distress or psychic trauma. NSAGU is under-recognized by health care providers and its pathogenesis is not fully understood. However it is a benign condition that may present as an acute or recurrent but not progressive event. No consistent treatments protocols have been described yet. In any case of acute genital ulcer (AGU), herpes simplex virus must be excluded.

History
NSAGU or “ulcus vulvae acutum” was first described by the German dermatologist Lipschütz...
in 1913. Lipschütz proposed a classification of nonvenereal acute genital ulcer (AGU) in 3 categories. Two categories fall in the pattern of aphthosis, being idiopathic or secondary to Behcet disease or Crohn disease. The third type of AGU was described as sudden, gangrenous, selflimiting, with nonrelapsing ulcers, occurring mainly in non-sexually active girls and young women and associated with systemic signs suggestive of infection. During the 20th century, nonherpetic AGU has been described to be associated with several infectious diseases, including salmonellosis and infectious mononucleosis.

**Nomenclature**

Several names were proposed for this condition. Older names include Lipschutz ulcer (still used by some), “ulcus vulvae acutum”, vulvar apthous ulcer (still used by some), and complex aphthosis. The term “complex aphthosis” was introduced in 1985 by Jorizzo et al describing recurrent oral and/or genital aphthae in the absence of systemic illness to set it apart from Behçet disease. Recently, complex aphthosis, as it affects the genital area, has been renamed “nonsexually acquired genital ulceration”. The term “acute genital ulcer” (AGU) was coined by Farhi et al, in 2009.

**Pathogenesis**

Despite its historical longevity, this condition is not well recognized and its cause is poorly understood. In many cases, no identifiable cause was identified. Over 70% of all reported patients were ultimately diagnosed with idiopathic vulvar ulcers or idiopathic vulvar aphthosis. Some cases were reported to be preceded or accompanied with systemic infection such as infectious mononucleosis (EBV), influenza, cytomegalovirus infection, mumps, paratyphoid fever, and mycoplasma pneumonia. Other reported preceding illnesses include viral gastroenteritis, viral upper respiratory tract illness, and streptococcal pharyngitis. The development of genital ulceration in those cases can be attributed to a nonspecific reactive inflammatory response to systemic infection. This type of reactive dermatosis is analogous to the mucocutaneous lesions of erythema multiforme, pathergic lesions in Behçet disease and pyoderma gangrenosum, and erythema nodosum. Pelletier et al proposed that cytotoxic T lymphocytes are recruited in response to systemic viral illness and mediate the inflammation that results in genital ulceration. Alternatively, the ulceration may be mediated by immune complexes produced during the acute phase of infection causing localized vascular immune complex deposition, microthrombosis, and subsequent tissue necrosis. Although the presentation of NSAGU may suggest an infectious etiology, no viral, bacterial, or fungal pathogen was identified for over 75% of patients in 4 case series. Farhi et al have suggested that acute and recurrent NSAGU may differ in cause with the former being reactive, possibly with a viral origin and therefore able to be assumed to be unlikely to recur.

Although EBV has been reported as a precipitant of AGU, based on the recent literature review, it is a rare occurrence. Since 1977, less than 50 EBV-linked cases have been reported. Most of EBV-related cases were preceded or associated with acute systemic EBV infection or infectious mononucleosis (IMN) based on serological data without any evidence of EBV in
the ulcer base and thus can be considered as a reaction process. In a very few cases, EBV was identified in the ulcer base by in situ hybridization, culture or PCR. The mechanism of ulceration in the later cases can be attributed to a direct cytotoxic or cytolytic effect EBV replication in the vulvar epithelium and the associated inflammatory reaction.

Farhi et al. and Huppert et al., respectively reported the incidence of EBV related-AGU among acute genital ulcers in adolescent women to be approximately 30% and 10%. Many other authors reveal very rare or no association at all.

EBV is a ubiquitous virus, and both the oropharynx and urogenital tract have been shown to harbor EBV even in the absence of symptoms. A much-debated question is how the EBV reaches the genital mucosa in AGU. EBV might reach the site of ulceration via hematogenous spread from the patient’s own oropharyngeal infection or through autoinoculation with natural reservoirs of EBV including saliva, urine, or cervico-vaginal fluid. Autoinoculation can occur in healthy girls or more commonly with preceding IMN. The only study that implies a different etiology is a Turkish study that concluded that chronic irritation from tight-fitting synthetic clothing led to the development of the lesions.

**Relation to aphthosis**

Many authors believe that by definition, NSAGU is a variant of idiopathic aphthosis or complex aphthosis. Other authors claim that NSA-GU is better to be classified as a separate entity or special subset of vulvar aphthae due to some reasons including rarity of the condition, rare recurrence, severe pain in many cases, and occurrence mainly in peripubertal girls.

**Epidemiologic and demographic information**

NSAGU are reported most commonly in young virgin girls in the peripubertal age period. However it can occur at any age and in sexually active women. It was reported in 65-year-old women and in a 17-month-old girl. It was also reported in twin sisters. Patients with NSAGU are characteristically non-sexually active, non-abused, and not immunosuppressed. Fear and shame may prevent patients from seeking care, and providers may fail to recognize this unique subset of patients or give a wrong diagnosis. All of these factors may explain the rarity of this diagnosis. However, a recent study has reported that it may represent around 30% of vulvar ulcerations.

**Clinical presentation** (Fig. 1-5)

NSAGU is characterized by abrupt onset of solitary or multiple painful genital ulcerations on the external genitalia, most often the labia minora of adolescent girls. Most of patients reported prodromal flu-like symptoms preceding the AGU such as low-grade fever, myalgia, and headache. Prodromal symptoms is very rare in recurrent cases. It is possible that fever may be part of the

**Fig. 1** Multiple vulvar ulcers with yellow base as seen on initial presentation.
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Fig. 2 Acute necrotizing genital ulcerations of the labia minora, with a kissing pattern.

Fig. 3 Multiple hemorrhagic and necrotic pseudovesicles and edema involving the introitus, fourchette and labia minora.

Fig. 4 Multiple, small, sharply demarcated ulcers in patient with negative microbiologic studies consistent with herpetiform aphthae.

Fig. 5 Large ulcers on labia minora and majora with thick white pseudomembrane on patient’s right.

Genital aphthosis phenomenon rather than necessarily indicative of a preceding infection. The onset is typically acute, with ulceration developing within hours of the first sign of discomfort. Most patients with recurrent disease relate that the pain precedes the ulceration and some indicate that attacks are precipitated by sexual intercourse. \(^1\)-\(^4\),\(^11\),\(^19\)

The ulcer is characteristically painful or very painful in most cases. Dysuria is common. Pain may prevent walking or urination and some patients may require urinary catheterization for pain control. Such vulval ulcers commonly cause severe emotional distress and psychic trauma among patients and their families.\(^2\),\(^3\) The psychic trauma commonly exaggerated by the behavior of many treating physicians who manage the case empirically as sexually transmitted HSV infection.

Keratinized, hairbearing, as well as mucosal skin can be involved. Reported sites include the lower vagina, introitus, fourchette, labia minora, labia majora, and perineal body. The most common location is the medial aspect of the labia minora, often presenting bilaterally on opposing labial surfaces as “kissing aphthae”.\(^11\) Most reports
describe lesions greater than 1 cm in diameter, but the size varies.\textsuperscript{1-4} Ulcers similar to simple aphthous ulcers (one or few small ulcers) or herpitriform aphthous ulcers (many small superficial ulcers) were also reported.\textsuperscript{2} Some patients may present with small abortive lesions (such as symptomless vulvar petechiae) which may be passed without medical consultation.\textsuperscript{12} Occasionally, patients initially present with dark red or black pseudovesicles that may then develop an eschar with underlying painful ulcer.\textsuperscript{2} In contrast to women with an isolated first episode of AGU, women with recurrent genital ulcers or those with both oral and genital aphthae are designated as having complex aphthosis provided that there is no other features of Behcet disease (BD).\textsuperscript{2} Ulcers are typically shallow (1 to 2 mm deep) with well-demarcated, ragged borders. Borders can become overhanging and heaped up, sometimes simulating an ulcerated malignant tumor. Necrotic ulceration may develop in some cases. The base of the ulcer ranges from black, necrotic tissue, to gray or yellow adherent exudates (pseudomembrane). The surrounding skin is usually erythematous, edematous, warm, and tender. Edema of the labia minora may be severe, obscuring the ulceration. Associated regional lymphadenopathy and cellulitis can occur.\textsuperscript{1-4,11} More than 50% of patients give history of recurrent oral aphthous ulcers which is not temporally related to the episode of AGU.\textsuperscript{1-4,11}

**Histopathology**

Histopathology is non-specific and is not helpful in diagnosis. It is better avoided as it can be traumatic for a patient already in severe pain, particularly young girls. It may exaggerate the emotional stress and psychic trauma of the patient and parents.\textsuperscript{3,4,11} The main role of the biopsy is to exclude other pathology in clinically suspicious cases. Histopathological findings are nonspecific including reactive epithelial hyperplasia, epidermal ulceration, abscess formation, and granulation tissue response.\textsuperscript{1-4,11} Periodic acid-Schiff and Gram stains were negative for micro-organisms. Electron microscopic findings suggest that microthrombi in epidermal blood vessels lead to ischemia, necrosis, and ulceration of the dermis.\textsuperscript{17}

**Work-up**

The most important aspect of the evaluation of a patient with acute genital ulcer in women is a complete history and physical examination.\textsuperscript{1-4,11} The workup should start with a sensitive sexual history, which is performed confidentially and includes questions on sexual activity and potential abuse. Some clinicians consider that a probing sexual history is not always necessary in clinically classic cases as it is often psychologically distressing for young nonsexually active adolescents and their parents.\textsuperscript{1-4} The review of systems should include queries to uncover other systemic illnesses, with particular attention to ocular, neurologic, gastrointestinal, and genitourinary symptoms. Obtaining a detailed history may not reveal an underlying etiology, and this should not discourage the patient or physician. Patients and parents should be reassured that vulvar aphthae are similar to oral aphthae in that a cause is often not identified.\textsuperscript{1-4} The clinician should perform a full physical examination looking for oral and skin lesions. Although vaginal lesions may be present, documenting them does not change the patient’s management and thus a speculum exam in sexually
active women is not recommended unless the patient requires general anesthesia for evaluation. A careful history and meticulous physical examination should exclude local trauma, sexual injury or abuse, and local application of caustic substances. Physical examination also should include particular attention to signs or symptoms of an underlying associated systemic condition: BD, human immunodeficiency virus (HIV), malabsorption, ulcerative colitis, Crohn’s disease (CD), cyclic neutropenia, periodic fever syndromes, and leukemia. This is particularly indicated in recurrent cases.

An extensive laboratory work-up is often undertaken, creating great anxiety on the part of the patient and parents, and generating enormous, unnecessary medical expense. These searches are usually useless and should be tailored to the history and examination.

Excluding HSV with lesional viral culture or PCR is the most important laboratory investigations which must be done in any case. Because of the limited sensitivity of viral culture, PCR is preferred. False negative and false positive results can occur even with culture and PCR. Combination of culture and PCR give the best results. IgG-based serological tests (detect type-specific glycoprotein) may be helpful only if culture or PCR are not available. Older assays that do not accurately distinguish HSV-1 from HSV-2 antibody (despite claims to the contrary) remain on the market and should not be requested. However, even with type specific serological tests, false positive and false negative results can occur.

Given the low rate of infection-associated AGU, infectious work-up should be limited. For a primary episode of AGU with nonspecific prodromal symptoms, no further infectious workup (other than HSV testing) need to be performed. Viral serology may be important from research point of view, but does not assist in management and is very expensive. So, based on current literature, EBV and CMV is not routinely recommended. However, a limited infectious evaluation, including serologies (EBV, CMV, influenza, mycoplasma) may be considered only in patients with more severe systemic symptoms, including persistent fever, extreme fatigue, swollen lymph nodes, or persistent or severe sore throat.

To evaluate for recent infectious mononucleosis, IgG and IgM antiviral capsid antigen for EBV is recommended. The heterophile antibody (monospot) test should not be used due to its low sensitivity and specificity. To evaluate for CMV infection, IgG and IgM antiviral capsid antigen for CMV is recommended. The test results may be helpful in reassuring patients and counseling them about future recurrences. Because syphilis and chlamydial and gonorrheal infections do not classically cause painful acute genital ulcerations, testing for these conditions is indicated only if clinical suspicion exists. Screening for HIV should be limited to sexually active or high-risk patients. Routine bacterial and fungal cultures reveal skin flora or nonpathogenic bacteria and do not add benefit. Microbiologic testing is not routinely recommend for a first episode of uncomplicated AGU.

In contrast to women with an isolated first episode of AGU, women with recurrent genital ulcers or those with both oral and genital aphthae are designated as having complex aphthosis. Those women require a thorough history, mucocutaneous examination, and laboratory studies to rule out underlying diseases including Behçet’s
disease, Crohn’s disease, HIV, PFAPA syndrome, MAGIC syndrome, and folate deficiency. Suggested labs include iron, folate, and vitamin B12 levels, and a biopsy of the vulvar lesion may be indicated. Furthermore, consultations with gastroenterology, rheumatology, neurology, and ophthalmology are recommended if there is clinical suspicion of BD or CD. If the evaluations are normal, those patients with recurrent ulcers may be deemed to have primary complex aphthosis. Excluding of BD may not be possible on the first episode. Continuous management to assess for the evolution for BD is essential, since patients may initially present with vulvar aphthae, and later meet criteria for BD. Neutropenia and hematologic deficiencies should be ruled out with a complete blood count with differential, serum iron, folate, zinc, and vitamin B12. As the results of genital biopsy are likely to show nonspecific inflammatory changes and necrosis, a biopsy should only be performed when a specific dermatologic condition is suspected.

**Differential diagnosis**

Other conditions may present with acute and recurrent vulvar ulcers and it is important to differentiate these from NSAGU. However, the appearance and history of NSAGU is sufficiently characteristic to allow a clinical diagnosis in most cases. Acute genital ulcer may be sexually transmitted or nonsexually transmitted. Sexually transmitted infections such as HSV, syphilis, lymphogranuloma venereum, and chancroid are well-known causes of AGU. HSV is the most common of these sexually transmitted infections and it is important to remember that nonsexual transmission of either type 1 or type 2 HSV can occur. Chancroid is very painful as HSV, but very rare. Syphilis, lymphogranuloma venereum, and granuloma inguinal are painless and usually chronic.

It is important to take a thorough sexual history, including screening for abuse, recognizing that patients may be reluctant to share these intimate details. Initial history of nonsexual contact may not always be reliable in at least 10% of cases. Non-sexually transmitted ulcers are numerous including isolated aphthous ulcer, (?) Iron, folate, vitamin B12 deficiency), complex aphthosis, BD, MAGIC syndrome, Crohn’s disease (knife cut” ulcers or fissures), HIV-associated aphthous ulcers, fixed drug eruption, trauma, burn (thermal or chemical), non-sexual transmission of HSV1 or HSV2, cyclic neutropenia, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis), bullous diseases, pyoderma gangrenosum, erythema multiforme major, pyoderma gangrenosum, SJS/TEN. Langerhans cell histiocytosis and leukemia may have similar vulvar manifestations.

Herpes simplex virus 1 and 2 is the most common treatable cause of acute genital ulcer. HSV2 is almost invariably sexually transmitted with very rare possibility of nonsexual transmission. Acute genital ulcer due to HSV1 can result from sexual or nonsexual transmission by autoinoculation with hands contaminated with saliva or through oral sex. HSV must be excluded in any case of acute genital ulcer whether first or recurrent episodes. The best diagnostic test is PCR with or without serology as mentioned before. Many cases of acute genital ulcers, especially recurrent cases, are misdiagnosed as recurrent genital herpes depending on false positive nonspecific serological tests.
Vulvar aphthosis is another etiology that should be included in the differential diagnosis of vulvar ulcers. Many dermatologic vulvar specialists believe that by definition, NSAGU is a variant of aphthosis as previously mentioned in this review. Complex aphthosis is characterized by recurrent oral and/or genital aphthae in the absence of systemic illness. Complex aphthosis can further be classified as primary (idiopathic) or secondary due to another illness. Recently, complex aphthosis, as it affects the genital area, has been renamed “nonsexually acquired genital ulceration”.

Behçet disease is a complex multisystem disease with variable vessel vasculitis. Diagnostic criteria include one major criterion—recurrent oral aphthae plus at least 2 of: genital aphthae, synovitis, posterior uveitis, cutaneous pustular vasculitis, or meningoencephalitis. Patients may also develop arthritis, gastrointestinal lesions, vasculitis, and central nervous system involvement. Because of the absence of a diagnostic confirmatory test, it may take 6-8 years from development of the first ulcer to establish a diagnosis of Behçet’s disease.

Ulcers associated with Crohn’s disease (CD) are classically long “knife cut” lesions in the genitocrural folds or interlabial creases. This presentation is almost pathognomonic for CD. Patients with CD will likely also report abdominal pain, diarrhea, rectal bleeding, loss of appetite, and weight loss. Histologic findings of noncaseating granulomas help to establish the diagnosis. Fistulous tracts from Crohn’s disease may resemble ulcers, but close examination reveals the tract itself. Any patient with gastrointestinal symptoms must be referred to gastroenterologist for colonoscopy.

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 idiopathic genital aphthosis. Acute vulvar fixed drug eruption can present as confluent erosive vulvovaginitis, however, if offending drug is continued, it can progress to ulceration. Nonsteroidal anti-inflammatory agents and sulfa drugs are more often implicated in such cases.

Recurrent mucosal erythema multiforme may follow clinical or subclinical herpes simplex attack and can be easily diagnosed clinically. Usually similar lesions are present on oral mucosa also.

HIV-associated aphthous ulcers are typically large, painful, and recurrent. Patients are generally severely immunocompromised with thirty-seven percent have coexistent oral ulcers. It can persist for weeks or months, becoming necrotic and causing disabling pain. Local destruction by nonhealing ulcers can be severe, with formation of a recto-vaginal fistula reported. Such cases can be excluded by history and HIV testing.

**Treatment**

The goals of treatment are to provide pain relief, improve healing, and prevent scarring. Supportive measures and good wound care alone may be sufficient in mild cases, characterized by mildly symptomatic, superficial genital erosions. Topical potent corticosteroids and pain control measures are indicated in patients with moderately severe AGU (ie, pain tolerable but uncomfortable, ulceration without necrosis). Systemic corticosteroids may be required in patients with severely painful, multiple, or necrotic ulcers.

Strong reassurance is very important in young...
non-sexually active girls. Patient and parent should be reassured that ulcers are not infectious, communicable, or sexually transmitted.\textsuperscript{2,11,19} Initial pain control measures should include topical xylocaine 2% jelly, sitz baths, and oral non-steroidal anti-inflammatory drugs. Adequate pain control may require narcotics in severe cases.\textsuperscript{11,19} Twice daily sitz baths in plain, warm water are the best method for gentle cleansing and debridement of necrotic tissues. Cleansing with a handheld shower head is a good alternative. Soaps and other topical over-the-counter agents are not tolerated and should be discouraged because of their irritant or allergic potential.\textsuperscript{11}

The mainstay of topical therapy for NSAGU is ultra-potent or potent topical corticosteroids. Theses potent topical corticosteroids do not cause side effects in the 2 weeks or less that is adequate to settle acute flare-ups. Topical steriods should be used in their ointment form to reduce exposure to irritant or allergic components of creams, gels, or foams.\textsuperscript{2,11,19}

Topical sucralfate suspension (cytoprotective and healing agent) and topical amlexanox paste (Aphthasol) may be used also as for oral aphthae.\textsuperscript{11,38,39} Amlexanox is an anti-inflammatory immunomodulator agent without local immunosuppressive effect, and with efficacy equal to clobetasol ointment for the treatment of oral aphthae.\textsuperscript{39}

External dysuria can be severe. Voiding under water in a bathtub and use of topical anesthetic and barrier agents before micturition are helpful solutions. Some patients required hospitalization for pain control with intravenous opioid medications and placement of a urinary catheter.\textsuperscript{11,19}

Despite the theoretical risk of exacerbating a recent or current infection, systemic corticosteroids may be required in patients with severely painful, multiple, or necrotic ulcers. Daily prednisolone was started at 10 to 25 mg for patients with moderate ulcers and at 40 to 50 mg for patients with severe cases. This was weaned once the ulcers had healed. A maximum of 16 days of treatment with oral prednisone was required in most patients. Patients who required longer duration to complete resolution (>6 weeks) should be biopsied and referred for colonoscopy to rule out Crohn’s disease.\textsuperscript{11,19} In cases associated with ulcer necrosis or secondary cellulitis, broad spectrum systemic antibiotics such as a cephalosporin may be indicated.\textsuperscript{2,11,19}

Some authors advice long-term doxycycline prophylaxis for patients with a history of recurrences. It is thought that its action may be related to its anti-inflammatory effect. Usual dose given for prophylaxis of vulvar aphthae is 50 to 100 mg per day for several months or even years. This dose should be reduced once patients have been asymptomatic for 6 months and the dose is tailored for each patient according to response.\textsuperscript{19}

**Follow-up and Prognosis**

It is important that women with AGU receive ongoing weekly follow-up until the ulcer(s) has re-epithelialized and pain has resolved. The ulcers heal spontaneously regardless of treatment, usually without scarring. Mean time to healing is reported as 16-21 days (range 5-52 days).\textsuperscript{1,2,17} This time frame permits repetition of laboratory studies, i.e., convalescent serologies for EBV or CMV. Evidence of seroconversion can support the diagnosis of an acute infection, and these women may be at lower risk of recurrence of AGU. However, these laboratory investigations are rarely requested in private practice as it is
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costly and does not affect the treatment strategy.\textsuperscript{1,2}
After the ulcer has healed, yearly follow-up is necessary to rule out progression to systemic disease such as inflammatory bowel disease or Behçet’s disease.\textsuperscript{2} In two case series, 23-33% of women experienced a recurrence within one year. Recurrent cases may be considered to have complex aphthosis. Six per cent were ultimately diagnosed with Behçet’s disease.\textsuperscript{1,17} In the series from Brazil, 20% of women with non-HSV AGU met criteria for Behçet’s disease.\textsuperscript{40}

CONCLUSIONS
NSAGU is a rare benign condition in vulvar dermatology which may be very painful with marked emotional distress especially among nonsexually active peripubetal girls. It is often misdiagnosed, over-investigated, and under-reported. Recognition of NSAGU is important so that patients receive appropriate and timely treatment and prognostic counseling, involving their parents as needed. Awareness of this condition is very important to avoid misdiagnosis and wrong treatment as sexually transmitted HSV infection. An accurate diagnosis of NSAGU will also prevent invasive investigations and subspecialty consultation and provide reassurance to the patients and their families. More than 70% of NSAGU are idiopathic. The remaining cases may be related to a preceding systemic illness or caused by direct cytotoxic infection. Contrary to the common belief, the association of NSAGU with EBV is rare. Women and their families should be reassured on three main points: (i) NSAGU are not sexually transmitted; (ii) ulcers heal spontaneously; and (iii) most patients have no recurrence and no long-term sequelae. No formal treatment guide-

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