Vulvar Aphthous Ulcers

Clinical Presentation: Aphthous ulcers are "canker sores" on the vulva. They are more common in the mouth than on the vulva. They can occur once, return as recurrent lesions, or persist for a period of time as chronic lesions. They can vary in size and can be single or multiple.

Classification: There are two types of aphthous ulcers, simple and complex.

- Simple aphthous ulcers can be acute or recurrent.
- Complex aphthous ulcers can be recurrent or chronic on the vulva, and they can also occur in combination with oral aphthous ulcers. Complex aphthae are further divided into 'Primary' (idiopathic) and 'Secondary' (associated with underlying systemic diseases or syndromes).

<u>Simple Aphthous Ulcers:</u>

Synonyms: *(These are all simple aphthous ulcers)*

Ulcus vulvae acutum
Lipschütz ulcers
Sutton's Ulcer
Reactive nonsexually related acute genital ulcers
Nonsexually acquired genital ulceration (NSAGU).

Characteristics: Simple acute vulvar aphthous ulcers are more common than complex aphthae. They may be a one-time occurrence, or in one-third of cases they may recur with a few episodes per year.

- *Age*: incidence ranges from age 1-79, but the average age is 29 years, and most are under 25 years of age.
- *Onset of symptoms*: sudden.
- *Size*: most are 1-3 cm in diameter and 1-2 mm deep. Often multiple ulcers are seen.
- *Prodrome*: flu-like with mild fever, headache, malaise. There is not always a prodrome, especially with recurrent cases in older patients.

- *Clinical Course:* Early lesions can develop a necrotic, gray or gray-black eschar, with variable swelling and severe pain. Under the eschar lies an ulcer base with a yellow adherent exudate, which then can evolve into a deep punched out ulcer. Surprisingly, these lesions can heal with little or no scarring, although they are frequently accompanied by significant dysuria and labial swelling while active.
- *Location:* These ulcers can occur on hair bearing and mucosal skin and are most commonly found on the medial aspect of the labia minora. The ulcers are often symmetric with bilateral "kissing lesions".
- *Duration:* 1-3 weeks (however at times, they can last for months).

Diagnosis: Aphthous ulcers are a diagnosis of exclusion. Biopsies are non-specific, and blood work is often non-contributory. It has been suggested that aphthae develop as a hypersensitivity reaction to a virus or bacterial infection. This results in the deposition of immune complexes, triggering complement activation, vasculitis with micro-thrombi, tissue ischemia, necrosis, and ultimately ulcers.

Associations: In approximately 30% of cases simple vulvar aphthous ulcers are associated with viral or bacterial infections. The most common associated virus is EBV. A few reported cases have been associated with cytomegalovirus and mycoplasma pneumonia, and there are individual reports of other infections. A number of cases have recently been associated with coronavirus of 2019 (COVID-19) and COVID-19 immunization. Commonly associated infections include:

- Epstein-Barr Virus
- Mycoplasma pneumoniae
- Viral respiratory infections (parvovirus, influenza, paramyxovirus)
- Gastroenteritis (salmonella)
- Toxoplasmosis gondii
- Streptococcus
- Mumps
- Cytomegalovirus (CMV)
- Lyme disease
- COVID-19 and COVID-19 immunization
- Zika
- Chikungunya

Example: Epstein-Barr Virus associated with simple vulvar aphthous ulcers. Epstein-Barr virus (EBV) is a member of the herpes virus family (human herpesvirus 4). Most people get infected with EBV at some point in their lives. About 90% of adults have antibodies that show that they have a current or past EBV infection. EBV spreads most commonly through bodily fluids, primarily saliva. EBV can cause infectious mononucleosis and other illnesses. Symptoms and signs of EBV infection include fever, inflamed throat, swollen lymph nodes in the neck, enlarged spleen, swollen liver, rash, and fatigue.

Patients with vulvar aphthous ulcers are often unaware of the EBV infection, and usually have a prodrome with fever, malaise, and lymphadenopathy.

EBV infection can be confirmed with a blood test to detect antibodies including:

1. Epstein-Barr Virus VCA Antibody (IgM)
2. Epstein-Barr Virus VCA Antibody (IgG)
3. Epstein-Barr Virus Nuclear Antigen (EBNA) Antibody (IgG)

For more information, see http://www.cdc.gov/epstein-barr/laboratory-testing.html

Information on the other associated infections can be found in the references at the end of this article.

Complex Aphthous Ulcers:

Characteristics: Complex aphthous ulcers are less common than simple vulvar aphthous ulcers. They can be almost constant, with one or more ulcers being present. They can also be recurrent vulvar ulcers, and may be seen with or without oral ulcers. Oral and genital ulcers can occur at different times.

- *Size*: most < 1cm; can be 1-3 cm. They tend to be larger and deeper than simple vulvar aphthae.
- *Prodrome*: often none.
- *Clinical course*: The ulcers can be episodic or continuous with a yellow fibrinous base evolving into a deep punched-out lesion, accompanied by variable swelling and pain. Complex aphthae can heal with scarring. Multiple ulcers are typically seen.

- *Duration*: The duration of lesions can be weeks or months.

Classification of Complex Vulvar Aphthous Ulcers:

- *Primary Idiopathic Complex Aphthosis:* continuous and/or recurrent vulvar aphthous ulcers which arise spontaneously or without an obvious underlying cause. The diagnosis is made by exclusion of other conditions understanding that, at times, the primary disease may not be obvious yet (such as Crohn disease).
- *Secondary Complex Aphthosis:* describes vulvar aphthous ulcers that arise in conjunction with some systemic diseases, certain hematologic conditions, or other recognized syndromes.
    - *Systemic diseases* causing complex aphthous vulvar ulcers:
        - Inflammatory Bowel Disease: Crohn Disease and Ulcerative Colitis
        - Behçet's Disease
        - Immunodeficiency:
            - *HIV*: Vulvar ulcers associated with HIV are usually caused by secondary infections (herpes simplex virus, syphilis, cytomegalovirus, and other sexually transmitted infections). However, it is possible for patients with HIV to develop non-infectious aphthous ulcers associated with immunodeficiency alone. These HIV-associated aphthous ulcers were more commonly reported at the beginning of the AIDS epidemic. Typically, they were large, painful, and recurrent complex aphthous ulcers associated with very low CD4 counts and AIDS. One third of these patients had coexisting oral ulcers. Severe ulcers, at times, developed into rectovaginal fistulae.
            - *T-cell and B-cell lymphopenia*, a severe combined hereditary immunodeficiency found in Athabascan-speaking North American First Nation peoples, can be associated with oral and genital ulcerations as a presenting feature. Treatment is by bone marrow transplantation.

    - *Hematologic abnormalities* associated with complex vulvar aphthae:

- Cyclic neutropenia: This is a rare pediatric disorder with 3 to 6 days of neutropenia every three weeks. With flares there can be oral and genital aphthous ulcers plus infections (see reference). Women with neutropenia from other hematologic conditions may also present with recurrent or chronic complex vulvar and oral aphthae. (Dr. Lynette Margesson's personal experience)
- Myeloproliferative disease: Myelodysplastic syndrome with trisomy 8 can be associated with recurrent oral and genital complex aphthae that can recur every 2 to 4 weeks. (see reference).
- Lymphopenia due to leukemia or lymphoma: Acute myeloid leukemia can be associated with chronic, complex vulvar ulcers plus oral erosions and ulcers. The ulcers maybe the presenting finding. There may be weakness and fatigue from anemia and infections from leukopenia. (See reference).
  Leukemia cutis may develop vulvar ulceration, but this is rare and not strictly speaking an aphthous ulcer.

- *Syndromes* which include complex vulvar aphthous ulcers:
  - Mouth and Genital Ulcers Inflamed Cartilage Syndrome (MAGIC Syndrome): This is a very rare syndrome that presents in women and men with oral and genital aphthous ulcers. It shares features of Behçet's disease and relapsing polychondritis. There can be pustular lesions, uveitis, relapsing polychondritis, vasculitis and involvement of joints and the gastrointestinal tract.
  - Periodic Fever, Aphthosis, Pharyngitis and Adenitis Syndrome (PFAPA Syndrome): This is a rare pediatric syndrome starting in children 1 to 4 years old. It is characterized by recurrent or irregularly periodic fevers every 2 to 8 weeks. Oral and genital aphthous ulcers can flare with febrile episodes, pharyngitis, adenitis and abdominal pain (See references).

Work-up of Aphthous Ulcers: Aphthous ulcers are a diagnosis of exclusion. The etiology is seldom found.
Physical examination should include the oral cavity, vulvovaginal skin, and ocular mucosa.

Laboratory Testing for herpes simplex virus and syphilis should be performed as indicated. Do a CBC and test for infection, as indicated. Testing is mainly for the conditions associated with complex aphthous ulcers.
Pathology: No biopsy is required for acute ulcers. Consider a biopsy for chronic or persistent ulcers. Always biopsy if indurated tissue or other findings suspicious for malignancy are present. Biopsies may also be indicated to rule out inflammatory bowel disease, myeloproliferative diseases, and rarely, HIV.

Treatment of Simple and Complex Aphthous Ulcers: Treatment depends on the severity of symptoms. If mild, comfort measures, topical steroids and adequate pain management may be all that is needed. More symptomatic disease often requires immunosuppression with systemic steroids.

- Local therapy – Sitz baths, tub soaks or gentle, handheld showers with plain water only.
- Topical Pain Control- 5% lidocaine ointment or 4% lidocaine aqueous gel, applied 3-4 times a day as needed or until healed.
- Oral pain control – Nonsteroidal anti-inflammatory drugs (NSAID) if mild to moderate pain, opioids for 2-4 days if severe pain.
- Herpes prophylaxis- If not sure if the herpes virus is present, obtain relevant testing and place the patient on appropriate antiviral meds (acyclovir, valacyclovir, famciclovir) until test reports are available.
- Anti-inflammatory therapy:
    - Topical treatments:
      Apply clobetasol 0.05% ointment or halobetasol 0.05% ointment twice daily.
    - Oral treatments:
      Prednisone 40 – 60 mg each morning with food until pain resolves (3-7 days), then 20 to 30 mg each morning for 3-7 additional days.
      OR:
      Methylprednisolone (Medrol) 4-8mg orally two to three times daily for 3-7 days, then 2-4 mg two to three times daily for 3-7days. Take these medications with food.
      OR:
      Colchicine 0.6mg orally twice daily, (1mg per day is used for simple acute aphthous ulcers in Europe) until lesions resolve.

- Intralesional treatments:
  Triamcinolone 10 mg/ml intralesionally (Kenalog 10) diluted with saline for injection mixed 1:1. Use no more than 0.25 to 0.5 ml per lesion.

Treatment of complex aphthous ulcers: Complex aphthous vulvar ulcers can be more difficult to treat because of the chronic and/or recurrent nature of the lesions. Treatment choices are based on the patient's profile and possible underlying conditions. Systemic treatments will be needed to heal the chronic ulcer(s), reduce recurrences, and induce remission. More than one medication may be needed. Start with 10-14 days of prednisone (see above), then add doxycycline or colchicine and/or dapsone as below:

- To suppress recurrent or complex aphthous ulcers - doxycycline 50-100 mg a day
- Other medications used to suppress recurrences of complex vulvar aphthae include:
  -Colchicine 0.6 mg two to three times daily (dose limited by diarrhea)
  -Colchicine 1mg per day until lesions resolve (used instead of prednisone for simple acute aphthous ulcers in Europe)
  -Dapsone 50-150 mg/day
  -Combining dapsone with colchicine
  -Cyclosporine 100 mg two to three times daily (max 4mg/kg/d)
  - Thalidomide 100-150 mg per day. In order to prescribe Thalidomide in the United States, you must be enrolled in the THALOMID REMS.
  https://www.thalomidrems.com/prescribe.html
  - phosphodiesterase inhibitor - apremilast
  - Tumor necrosis factor alpha inhibitors, such as etanercept and adalimumab, are used at times

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EBV, CMV, Mycoplasma, Parvovirus B19
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