Disorders Associated with Vulvar Pain

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Current Vulvovaginal Updates
Disclosures
Hope K. Haefner, MD

- Previously on the advisory board of Merck Co., Inc.
- Discussing iphone apps, but I have not received and will not receive any income from the apps
- Topical steroids that are used for various vulvovaginal conditions are not FDA approved for the vulva and vagina, however, they are the current first line treatment

Learning Objectives

At the conclusion of this presentation, you (participants) should be able to:

- Understand the current terminology for vulvar pain
- Formulate a differential diagnosis of disorders associated with vulvar pain
- Familiarize yourself with a variety of treatments for these painful conditions
Written Information Available:

University of Michigan Center for Vulvar Diseases

Then, click on Information on Vulvar Diseases

http://obgyn.med.umich.edu/patient-care/womens-health-library/vulvar-diseases
Vulvar Pain Terminology
2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia

A. Vulvar pain caused by a specific disorder*
  • Infectious (e.g., recurrent candidiasis, herpes)
  • Inflammatory (e.g., lichen sclerosus, lichen planus, immunobullous disorders)
  • Neoplastic (e.g., Paget disease, squamous cell carcinoma)
  • Neurologic (e.g., postherpetic neuralgia, nerve compression or injury, neuroma)
  • Trauma (e.g., female genital cutting, obstetric)
  • Iatrogenic (e.g., postoperative, chemotherapy, radiation)
  • Hormonal deficiencies (e.g., genitourinary syndrome of menopause [vulvovaginal atrophy], lactational amenorrhea)

B. Vulvodynia—Vulvar pain of at least 3 months’ duration, without clear identifiable cause, which may have potential associated factors

The following are the descriptors:
  • Localized (e.g., vestibulodynia, clitorodynia) or Generalized or Mixed (Localized and Generalized)
  • Provoked (e.g., insertional, contact) or Spontaneous or Mixed (Provoked and Spontaneous)
  • Onset (primary or secondary)
  • Temporal pattern (intermittent, persistent, constant, immediate, delayed)

* Women may have both
2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia

Appendix:
Potential Factors Associated with Vulvodynia*

- Comorbidities and other pain syndromes (e.g., painful bladder syndrome, fibromyalgia, irritable bowel syndrome, temporomandibular disorder; level of evidence 2)
- Genetics (level of evidence 2)
- Hormonal factors (e.g., pharmacologically induced; level of evidence 2)
- Inflammation (level of evidence 2)
- Musculoskeletal (e.g., pelvic muscle overactivity, myofascial, biomechanical; level of evidence 2)
- Neurologic mechanisms
  - Central (spine, brain; level of evidence 2)
  - Peripheral: neuroproliferation (level of evidence 2)
- Psychosocial factors (e.g., mood, interpersonal, coping, role, sexual function; level of evidence 2)
- Structural defects (e.g., perineal descent; level of evidence 3)

* The factors are ranked by alphabetical order.

2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia

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* Women may have both
A 21 y.o. G0 presents with a history of chronic immunosuppression secondary to autoimmune hepatitis. She has noted vulvar changes for one year. She complains of vulvar pain and occasional vulvar bleeding.
The histologic images shown represent which vulvar condition(s)?

A. 1 HSIL of the vulva and 2 condyloma
B. 1 and 2 both condyloma
C. 1 and 2 both molluscum contagiosum
D. 1 condyloma and 2 HSIL of the vulva

Lower Anogenital Squamous Terminology (LAST)
<table>
<thead>
<tr>
<th>ISSVD 1986</th>
<th>ISSVD 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIN 1</td>
<td>Flat condyloma or HPV effect</td>
</tr>
</tbody>
</table>
| VIN 2     | VIN, usual type  
a. VIN, warty type  
b. VIN, basaloid type  
c. VIN, mixed (warty/basaloid) type |
| VIN 3     |  |
| Differentiated VIN | VIN, differentiated type |

Treatment for condyloma HSIL in this patient should be:

A. Laser  
B. Wide local excision (WLE)  
C. A combination of laser and WLE  
D. No treatment. Observation only.
<table>
<thead>
<tr>
<th>ISSVD 1986</th>
<th>ISSVD 2004</th>
<th>LAST 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIN 1</td>
<td>Flat condyloma or HPV effect</td>
<td></td>
</tr>
<tr>
<td>VIN 2</td>
<td>VIN, usual type a.VIN, warty type b.VIN, basaloid type c.VIN, mixed (warty/basaloid) type</td>
<td><strong>Low Grade</strong> <strong>High Grade</strong></td>
</tr>
<tr>
<td>VIN 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiated VIN</td>
<td>VIN, differentiated type</td>
<td></td>
</tr>
</tbody>
</table>
2015 ISSVD Terminology of Vulvar Squamous Intraepithelial Lesions

- Low grade squamous intraepithelial lesion (Flat condyloma or HPV effect)
- High grade squamous intraepithelial lesion (VIN usual type)
- Intraepithelial neoplasia, differentiated-type

Lichen Sclerosus and VIN Differentiated V-to-Y Flaps
V-to-Y Flaps

V-to-Y Flaps
Question

I see patients with chronic vaginitis

- Yes
- No

Question

I like to see patients with chronic vaginitis

- Yes
- No
A Healthy Vagina May Contain:

A. Proteus, Klebsiella and E. coli
B. Candida albicans
C. Both
D. Neither

The Normal Vagina

- Complex ecosystem of variable organisms
- Predominance of Lactobacilli (facultative gram + bacteria) maintain low pH between 3.5-4.5
- Suppress pathogenic bacteria
- 60% produce hydrogen peroxide which protects against pathogens
- Staph, strep, enterococci, E.coli, Proteus, Klebsiella, anaerobes, candida albicans in 20-70% of healthy asymptomatic women
pH and Wet Mount

<table>
<thead>
<tr>
<th>pH (3.0-4.5)</th>
<th>WBC</th>
<th>Paras-</th>
<th>Features</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Few or none</td>
<td>no</td>
<td>NL lactobacilli</td>
<td>Creamy, mucous, white</td>
</tr>
<tr>
<td>Yeast</td>
<td>no</td>
<td>no</td>
<td>Hyphae Spores (400x)</td>
<td>Curdy</td>
</tr>
<tr>
<td>Bacterial Vaginosis (Amsel Criteria)</td>
<td>&gt;5.0</td>
<td>No to small</td>
<td>no</td>
<td>Clue Cell</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>&gt;5.0</td>
<td>yes</td>
<td>maybe</td>
<td>Motile trich</td>
</tr>
<tr>
<td>DIV</td>
<td>&gt;5.0</td>
<td>yes</td>
<td>yes</td>
<td>Mixed bacteria, absent or reduced lacto</td>
</tr>
<tr>
<td>Atrophic Vaginitis</td>
<td>&gt;5.0</td>
<td>likely</td>
<td>yes</td>
<td>Scant cells, few bacteria</td>
</tr>
</tbody>
</table>
A 49y.o. G4P2 presents with chronic vulvar pruritus and a painful vulvar irritation. Her vaginal pH is 4.0. She has had 3 other identical episodes this year.
Culture Positive for Candida Glabrata

- Low vaginal virulence
- Rarely causes symptoms, even when identified by culture
  - 50% of the time non-albicans yeast is an innocent bystander and is not causing the patient’s symptoms
    Nyirjesy 2016
- Exclude other co-existent causes of symptoms and only then treat for C. glabrata

What treatment do you recommend for her symptomatic Candida glabrata?

A. Oral fluconazole
B. Boric acid per vagina
C. Intravaginal metronidazole
D. Terconazole
Other Antifungals
Boric Acid

- Puratronic, 99.99995% (metals basic)
- Formula
  \[ \text{H}_3\text{BO}_3 \]
- Formula Weight
  \( 61.83 \)
- Form
  Crystalline Powder
- Melting Point
  \( 170.9^\circ \)
- Merck Number
  11,1336
**Boric Acid Capsule or Suppository**
**PER VAGINA**

Fill 0-gel capsule halfway (600 mg)
For treatment of acute infection; insert *per vagina* qhs x 14 days

For prevention of recurrence; insert *per vagina* twice weekly

**KEEP AWAY FROM CHILDREN**
**CONTRAINDICATED IN PREGNANCY**

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**Before Treatment**
After Treatment

Does she qualify for the diagnosis of having recurrent Candida infections?

A. Yes
B. No
Yeast/Candida iphone App

Contributors

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There are limited data on some of the treatment regimens. The compounded medications generally are suggestions to consider when other agents are not working. The compounded medications are generally used for resistant strains of Candida.
Treatment by Type

Yeast Culture/Speciation Results

Candida albicans
Candida glabrata
Candida parapsilosis
Candida tropicalis
Candida lusitaniae
Trichosporon
Saccharomyces cerevisiae
Candida kefyr
Candida dubliniensis

There are limited data on some of the treatment regimens. The compounded medications generally are suggestions to consider when other agents are not working. The compounded medications are generally used for resistant strains of Candida.
Miconazole 7 day cream 2% (100 mg per dose)
- One applicatorful per vagina nightly for 7 nights

Miconazole 7 day cream 2% (100 mg per dose) plus miconazole nitrate cream 2%
- One applicatorful per vagina nightly for 7 nights
- Miconazole nitrate 2% cream to the vulva twice a day for up to 14 days

Miconazole 3 day cream, suppository, ovule 4% (200 mg per dose)
- One applicatorful, suppository or ovule per vagina nightly for 3 nights

Miconazole 3 day cream, suppository, ovule 4% (200 mg per dose) plus miconazole nitrate cream 2%
- One applicatorful, suppository or ovule per vagina nightly for 3 nights
- Miconazole nitrate 2% cream to the vulva twice a day for up to 14 days

Miconazole 1 day insert (ovule) (1200 mg per dose) plus miconazole nitrate cream 2%
- One insert (ovule) per vagina for one day or night
- Miconazole nitrate cream 2% cream to the vulva twice a day for up to 14 days

Miconazole nitrate topical 2% cream to the vulva twice a day for up to 14 days

For some recurrent infections, consider using Miconazole 2% vaginal cream: 1 applicatorful per vagina nightly for 14 nights, followed by 1 applicatorful twice weekly for up to six months.

Compounded

Boric acid suppositories
In pregnancy, boric acid is not to be used, instead use maintenance creams for recurrent yeast.

Vaginal boric acid suppositories 600 mg per vagina for 14 nights; If recurrent, consider suppression after re-treatment with twice weekly boric acid 600 mg per vagina.

Boric acid capsules can be FATAL if swallowed/taken orally.
Skin Abscess

Antibiotic therapy as adjunctive therapy to I and D for
- Abscess greater than or equal to 2 cm
- Extensive surrounding cellulitis
- Multiple lesions
- Signs of comorbidity
- Immunosuppression
- Systemic infection
- Methicillin-resistant Staph
  - Trimethoprim-sulfamethoxazole
Painful Skin Abscess
An Unfortunate Patient

- 55 y.o. female admitted for nausea, vomiting, diarrhea, elevated bili
- Hospitalized for 3 wks bone marrow transplant complications (AML)
- Developed vulvar pain 3 days ago when lesions first developed. No significant change in size of lesions over 3 days. Afebrile.
Your Diagnosis Is? Part A

A. Rhizopus infection
B. Hematoma secondary to hematologic disorder
C. Malignant melanoma
D. Hidradenitis suppurativa
Your Diagnosis Is? Part B

A. Rhizopus infection
B. Hematoma secondary to hematologic disorder
C. Malignant melanoma
D. Hidradenitis suppurativa
Rhizopus

- Mucormycosis (sometimes called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes
- Fungi live in soil and in association with decaying organic matter, such as leaves, compost piles, or rotten wood
- Examples of the types of fungi that most commonly cause mucormycosis are: *Rhizopus* species, *Mucor* species, *Cunninghamella bertholletiae*, *Apophysomyces* species, and *Lichtheimia* (formerly *Absidia*) species
Rhizopus

- 13/1500 transplant patients developed this infection in study from 1993
- Surgical resection for cure
- Antifungals-liposomal amphotericin B
- Dressing changes/amphotericin B
A 64 y.o. G4P4 was recently diagnosed with lichen sclerosus (no biopsy performed). She was started on clobetasol propionate. She calls complaining of vulvar pain.
Your Diagnosis Is?

A. Lichen planus
B. Pemphigoid
C. Lichen sclerosus with herpes infection
D. Invasive squamous cell carcinoma
How many different types of herpes viruses exist that affect humans with disease?

A. 2
B. 4
C. 8
D. 80

http://en.wikipedia.org/wiki/Herpesviridae

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Subfamily</th>
<th>Target cell</th>
<th>Latency</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2</td>
<td>HSV</td>
<td>Alphaherpesvirinae</td>
<td>mucoepithelia</td>
<td>neuron</td>
<td>contact</td>
</tr>
<tr>
<td>3</td>
<td>VZV</td>
<td>Alphaherpesvirinae</td>
<td>mucoepithelia</td>
<td>neuron</td>
<td>contact or respiratory</td>
</tr>
<tr>
<td>4</td>
<td>CMV</td>
<td>Betaherpesvirinae</td>
<td>epithelia, monocytes, lymphocytes</td>
<td>monocytes</td>
<td>contact</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>congenital transplantation</td>
</tr>
<tr>
<td>5</td>
<td>EBV</td>
<td>Gammaherpesvir.</td>
<td>B lymphocyte</td>
<td>B lymphocyte</td>
<td>saliva</td>
</tr>
<tr>
<td>6,7</td>
<td>HLV</td>
<td>Betaherpesvirinae</td>
<td>T lymphocyte</td>
<td>T lymphocyte</td>
<td>Respiratory</td>
</tr>
<tr>
<td>8</td>
<td>KSHV</td>
<td>Gammaherpesvir.</td>
<td>Endothelial cells</td>
<td>Unknown</td>
<td>body fluids</td>
</tr>
</tbody>
</table>

http://en.wikipedia.org/wiki/Herpesviridae
What percent of people with herpes are unaware that they are infected?

A. 10-20%
B. 21 – 40%
C. 50- 70%
D. Over 80%

Herpes and Infertility

A new study has found that the little-known member of the human herpes virus family called HHV-6A infects the lining of the uterus in 43% of women with unexplained infertility but cannot be found in uterine lining of fertile women. The study was conducted by investigators at the University of Ferrara, Italy.
A 19 year old woman presents with vulvar erosions (majority perianal and buttock) and ulcers increasing for weeks. The itchy/painful lesions started around the vulva and anal area. She is now consumed with itching and discomfort and nothing works.
• Biopsy - lichen simplex chronicus and secondary impetiginized excoriations. Rebiopsy - ulceration with mixed inflammation.

• Symptoms are relieved with Sitz baths and a compounded cream - amitriptyline, baclofen, cyclobenzaprine, diclofenac, gabapentin, ketamine, and lidocaine.

• She is suicidal, depressed and co-dependent on her mother.

Your Diagnosis Is?

A. Contact dermatitis
B. Herpes simplex in immunosuppressed
C. Crohn’s disease
D. Behcet’s disease
Severe primary irritant contact dermatitis

Due to topical compound

- 7 tubes a day
15 year-old girl had sudden onset of dysuria and severe vulvar burning/pain. She was feeling tired.

She has a cough, a low grade fever and malaise.

Her doctor diagnosed acute HSV and started her on acyclovir and she presents to see you three days later.
Your Diagnosis Is?

A. Aphthous ulcers
B. Atypical herpes simplex virus
C. Drug rash
D. Trauma – abuse
Vulvar Aphthous Ulcers
Canker sores on the vulva
Acute painful ulcer(s) of sudden onset
Common as acute reactive ulcers in younger patients - often missed
Synonyms:
Ulcus vulvae acutum
Lipschütz ulcers
Reactive nonsexually related acute genital ulcers*

Vulvar Aphthous Ulcers
“Canker Sores” on the Vulva

Average age is 14 (9-19) years
Sudden onset
Usually multiple, painful, well demarcated punched-out ulcers
Size: most <1 cm; can be 1-3 cm
Prodrome - flu-like with mild fever, headache, malaise
Duration 1-3 weeks, can last months
One episode, less common recurrent
Past history of oral aphthae – canker sores
Rarely Behcet’s in North America

Aphthae

**Acute (more common)**
- Usually a prodrome - fever, headache, malaise, GI upset
- EBV, Mycoplasma pneumoniae, viral upper respiratory infection or gastroenteritis, influenza, Strep, CMV

**Recurrent / Complex** (recurrent oral and genital aphthae)

- Inflammatory Bowel disease - Crohn’s, Ulcerative colitis, Celiac disease
- Behcet’s disease
- Medications – cytotoxic, NSAIDs
- Myeloproliferative disease, cyclic neutropenia, lymphopenia
- HIV

**Syndromes** – rare
- PFAPA – periodic fever, aphthae, pharyngitis, adenitis
- MAGIC – mouth and genital ulcers with inflamed cartilage
Evaluation Vulvar Aphthae

Thorough history and physical – eye, oral, genital

Lab tests –
- CBC, diff
- Serology for HSV, HIV, EBV, syphilis, CMV, *Mycoplasma pneumoniae*
- Influenza – swab PCR
- HSV - swab for PCR
- For Strep -throat swab  and antistreptolysin O titer
- Tests as indicated for - RARE- paratyphoid and typhoid (stool, blood culture), TB enterocolitis, Yersinia

GI investigations –
for inflammatory bowel disease and celiac disease

Diagnosis of exclusion – etiology often not found

Vulvar Aphthae – Therapy

Pain control – topical, systemic
Prednisone 40 mg po q am x 5 days, then 20 mg po q am x 10 days
- ultra potent topical corticosteroid

Educate -Most often a one-time event, can recur

If not controlled:
- Intralesional triamcinolone (Kenalog 10) 5-10 mg/ml
- Doxycycline 50-100 mg bid
- colchicine 0.6 mg bid-tid if tolerated
- dapsone 50-150 mg per day
- dapsone + colchicine
- pentoxifylline 400 mg tid
- cyclosporine 100 mg 1-3/d
- thalidomide 100-150 mg per day
61-year-old G3P3 presents with constant vulvar drainage and pain
If you could only look at one other area of her body, where would you look?

A. Eyes  
B. Colon  
C. Axilla  
D. Mouth
What is this?

A. Squamous cell carcinoma
B. Epithelial inclusion cyst
C. Pyogenic granuloma
D. Paget’s disease
A 62 y.o. G2P2 presents with complaints of vulvar pain. Only able to urinate twice daily. Vulvar biopsy on three occasions spongiosis with hyperkeratosis and hypergranulosis with squamous atypia and underlying chronic inflammation.

Crohn’s disease?

Most recent biopsy in done 5 mos previously.
Part 1
Would you re-biopsy?

A. Yes
B. No

As you examine her, she mentions she can only urinate twice a day. You touch the medial aspect of the vestibule on her right and it is hard and firm.

Would you do a biopsy?

A. Yes
B. No
Histopathology reveals:

A. Adenocarcinoma  
B. Lichen planus with HSIL  
C. Squamous cell carcinoma  
D. Lichen sclerosus with HSIL

Invasive squamous cell carcinoma; depth of invasion is at least 4mm. Carcinoma extends to multiple specimen edges on all three biopsies.
Take home messages:
  Don’t forget to listen to your patients with pain, and touch areas of pain.
  Don’t hesitate to re-biopsy if the results are not consistent with the whole picture.

Summary

When patients do not respond to therapy
  – Reconsider the diagnosis
  – Check for infection - fungal, bacterial, HSV
  – Consider contact dermatitis to a medication, over washing, etc.
  – Evaluate for pre-cancer or cancer
If in Doubt, Cut it Out