Vulvar Diseases
Recognizing and Treating
Vulvar Intraepithelial Neoplasia

Hope K. Haefner, MD
Co-Director, The University of Michigan
Center for Vulvar Diseases
haefner@umich.edu

Learning Objectives
After this presentation the participant will:

- Gain tips on vulvoscopy and diagnosis of VIN
- Understand the use of anal cytology and anoscopy in the VIN population
- Evaluate treatments for VIN
**Disclosures/Conflicts of Interest**

- Hope K. Haefner, MD is on an advisory board for Merck Co., Inc.
- Multiple medications in vulvovaginal care are “off-label”

<table>
<thead>
<tr>
<th>ISSVD 1986</th>
<th>ISSVD 2004</th>
<th>LAST 2012</th>
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<tbody>
<tr>
<td>VIN 1</td>
<td>Flat condyloma or HPV effect</td>
<td>LSIL</td>
</tr>
<tr>
<td>VIN 2</td>
<td>VIN, usual type a.VIN, warty type</td>
<td>HSIL</td>
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<tr>
<td>VIN 3</td>
<td>b.VIN, basaloid type c.VIN, mixed (warty/basaloid) type</td>
<td></td>
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<tr>
<td>Differentiated VIN</td>
<td>VIN, differentiated type</td>
<td></td>
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<tr>
<td>Little or no oncogenic potential (low risk)</td>
<td>Significant oncogenic potential (high risk)</td>
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<td></td>
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<tr>
<td>• HPV 6, 11, 42, 43, 44</td>
<td>• HPV 16, 18, 31, 33, 35, 51 and 52</td>
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<tr>
<td>• Usually present as raised, acuminate, verrucous lesions but may also be flat non-pigmented papillomas</td>
<td>• Almost always flat warts</td>
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<tr>
<td>• 2/3 of external genital warts</td>
<td>• 1/3 of external genital warts</td>
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</table>
Other Means of Magnification

Bausch and Lomb
2 x magnification
Part 81-33-05
www.opticsplanet.net

Colposcopic Techniques

- 3% to 5% acetic acid
- Soak initially for 3-5 minutes
- Use copious amounts
- Reapply often
- Avoid using in presence of breaks in epithelium or inflammation
Clinical Pitfalls of Vulvar Colposcopy

- Acetowhitening is nonspecific
- Marked acetowhite changes in up to 65% of normal women
- Normal anatomic variants – like vestibular micropapillae – often confused with HPV colposcopically and histologically
### Increasing Incidence of HSIL (VIN)

- Heightened awareness of neoplasia
- Increased tendency to perform biopsies
- Commonly associated with other lower genital tract neoplasias (anus, vagina, cervix) and/or carcinomas
- More women are being diagnosed at a younger age

### Risk Factors for HSIL VIN

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<thead>
<tr>
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<th>Immunosuppression</th>
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<tr>
<td>History of HPV (vulva, vagina, cervix)</td>
<td>Pregnancy</td>
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<tr>
<td>Early age of onset of sexual intercourse</td>
<td>HIV</td>
</tr>
<tr>
<td>Multiple lifetime sexual partners</td>
<td>Autoimmune connective tissue disorders</td>
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<tr>
<td>Cigarette smoking</td>
<td>Diabetes</td>
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<tr>
<td></td>
<td>Transplant recipient</td>
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<td>Chronic hepatitis</td>
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<td>Chemotherapy</td>
</tr>
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</table>
Symptoms

- Most - completely asymptomatic
- Itching or burning
- Irritation
- Dyspareunia

Signs

No typical gross appearance
Gray-white
HSIL (VIN) warty

T Wright, MD

Brown
Brown

Red Can be Confused with Lichen Planus or Nonsquamous VIN (Paget)
• HSIL (VIN) has a variety of patterns and over a variety of specific areas on the vulva

Concerning Colposcopic Features of HSIL (VIN)

• Areas of ulceration
• Focal nodules
• Atypical vessels
VIN Differentiated

Histopathology of HSIL (VIN)

Associations with cancer:

- HSIL 5 - 20%
- Differentiated VIN > 95%
Anesthesia
- 1% lidocaine
- 27-30 gauge needle to inject 1-3 cc's of anesthetic agent
- Inject subepidermally

Biopsy
- Keyes punch
  - 3-5 mm diameter dermatologic instruments (usually 4 mm)
  - Fine suture (3.0 or 4.0 Vicryl Rapide) vs. Monsel’s/Silver nitrate

Cervical biopsy instruments that can also be used for vulvar biopsy

- Baby Tischler
- Baby Kevorkian
Exaggerated lithotomy position

Reprinted with permission of the ASCCP
Knee-Shoulder Position

Left lateral or Sim’s position
Anal Cytology: Technique

Use moistened Dacron swab or Cytobrush
Insert into canal until resistance is not met (above ano-squamocolumnar junction)
   - Above anal verge to distal rectum (3-4 cm)
Rotate/apply pressure to walls of canal while removing sampling device (bends)
   slowly (count to 10)
Notify Pathology (Cytology) Department
Anal Intraepithelial Neoplasia (AIN 2,3)
Management of Vulvar Intraepithelial Neoplasia
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**HSIL (Vulvar Intraepithelial Neoplasia)**

**Natural history if untreated:**

HSIL can regress, persist, progress

One long-term follow-up study

*7 of 8 untreated VIN 3 developed CA (took 7-18 years to progress)*

*Jones, RW Obst. Gynecol. (1994)*
HSIL

Acceptable treatment modalities:

- Surgical excision
- Laser ablation
- Electrosurgical excision
- Possibly - treatment with imiquimod

Question 1
I treat VIN (HPV related) with

a. Topical therapy
b. Laser therapy
c. Wide local excision
d. A combination of all of the above
Margins and Depth

Vulvar Intraepithelial Neoplasia

• Margins
• Depth
  • Hair bearing areas to 2.7 mm
  • Non-hair bearing = 0.1 to 1.9 mm
    (average = 0.5 +/- 0.2 mm)
VIN III Recurs After Treatment  
(mean follow-up 39 months)

No statistically significant differences between groups

Recurrence Rate

- Vulvectomy
- Partial Vulvectomy
- Local Excision
- Laser Vaporization

Gynecologic Oncology. 2005; 97: 645-651

Treatments

Recent double blind, randomized studies with topical imiquimod (use same dosing as for condyloma)

Topical imiquimod can reverse vulvar intraepithelial neoplasia:

A randomised, double-blinded study
Ole Mathiesen, Sanne K. Buus, Marie Cramers
Gynecologic Oncology 107 (2007) 219–222
Other Treatments

Treatment of Usual VIN:
Targeted Medical Therapy with Imiquimod

Imiquimod (Aldara™, 3M Pharmaceuticals), is currently FDA-approved for treatment of external genital and perianal warts (1997), non hypertrrophic actinic keratoses in immunocompetent individuals (2004), and superficial basal cell carcinoma (2004). Off label use for HSIL of the vulva.

Adapted from Journal of Investigative Dermatology. 2006; 126:1338–1347
Veregen® Dosage and Administration

- Apply tid to all external genital and perianal warts
  - Use about 0.5 cm strand of ointment per wart
  - Ensure complete coverage (thin layer over disease)
  - Not necessary to wash off the ointment from the treated area
- Treat until complete clearance of all warts or up to 16 weeks

Veregen® is not for ophthalmic, oral, intravaginal, or intra-anal use.

Targeted Medical Therapy with Cidofovir

Cidofovir: a nucleotide analogue of dCTP

- Inhibits viral DNA polymerase at drug concentrations 100-fold lower than concentrations that inhibit cellular DNA polymerase.
- Effects against HPV diseases cannot be explained by this mechanism (since HPV does not encode viral DNA polymerase and uses the cell's DNA replication machinery.)

HPV-associated HSIL: Risk of Progressive Disease

- Untreated HSIL (VIN 2,3) → significant invasive potential
  - particularly in women over 30(1)

- Untreated VIN progression to invasive cancer ≥10% per year
  - Only about 2% for CIN 3(2)

- Lifetime risk of invasive vulvar cancer after treatment for HSIL (VIN 2,3) = 3% to 4%
  - Only 0.3% to 0.4% for CIN 3.(1)

HGSIL Progression to SCC\(^{(1)}\)
(from PALGA, the Nationwide Netherlands Database of Histo- and Cytopathology)

- Progression to SCC over 14 years, treated patients
  - 5.7% of 1826 patients with HPV-associated VIN
  - 32.8% of 67 patients with VIN differentiated
- Median time from VIN dx to SCC dx
  - 41.4 mos for HPV-associated VIN
  - 22.8 mos for VIN differentiated


VIN differentiated

T Wright, MD
**Differentiated VIN** is diagnosed infrequently compared to HSIL (**Usual VIN**)

(Usual VIN 96%)

Differentiated VIN 4%

(of solitary lesions)

European Journal of Cancer. 2009;45: 851-856

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**Vin Differentiated**

Acceptable treatment modality:

Surgical excision
Treating Differentiated VIN

The cancer risk with differentiated VIN justifies treatment by surgical excision (e.g. partial vulvectomy) to definitively exclude invasive disease.

Follow-up

- Recommended that patients receive close follow-up
Stop Smoking!
Non-Squamous Types

- Paget disease
- Melanoma in situ

A 79 y.o. G2P2 complains of a vulvar sore and itching that started 1 year ago. A biopsy is performed.
Question 2
What is Your Diagnosis?

a. Lichen planus
b. VIN
c. Lichen sclerosus
d. Paget’s disease
Question 3
Which treatment do you recommend as her initial therapy?

a. Triamcinolone acetonide ointment
b. Laser therapy
c. Wide local excision
d. Radical vulvectomy

d

Question 4
What is the rate of Paget disease of the vulva being associated with an underlying adenocarcinoma?

a. 1% - 25%
b. 26% - 50%
c. 51% - 75%
d. 76% - 100%
Paget Disease

- Multifocal
- Eczematoid, weeping
- Brick red
- Scales
- Eczematoid plaque
- Sharply demarcated

Differentiating Paget From Other Conditions

- Positive mucin as well as immunoperoxidase CEA staining can be used to differentiate Paget disease from melanoma
  - Paget (mucin and CEA positive)
  - Melanoma (mucin and CEA negative)
Paget’s Disease

+immunoperoxidase CEA

+mucin

Photo courtesy of R. Lieberman, MD

Melanoma

Photo is courtesy of R. Lieberman, MD
Paget Disease

- Occurs most commonly on the nipple and areola, where its presence signifies an underlying adenocarcinoma of the breast
- Apocrine gland origin
- Red velvety area with white islands of hyperkeratosis and at times may be pinkish and eczematoid

Paget Disease

Workup

- History and PE
  - Symptoms include itching, burning (soreness)
  - Signs include velvety appearance and bleeding
- Papanicolaou smear
- Mammogram
- Cystoscopy
- Colonoscopy
Paget Disease Treatment

- Wide local excision (how far?)

Recurrence

- Laser
- Excision
- Topical treatments
A 29 y.o. G4P4 is referred to you by a dermatologist for pigmentation on her vulva. A biopsy has revealed a compound nevus with slight atypia.
Question 5
What treatment do you recommend?

a. Wide local excision(s)
b. Laser
c. Radical vulvectomy
d. No treatment. Observation only.
Is there a Need for **Skin Grafts** with Squamous and Nonsquamous VIN?

Close Follow-up Long Term for HSIL, as Well as Nonsquamous SiL
www.asccp.org

- Diagnosis of Precancerous Vulvar Abnormalities
- Management of Precancerous Vulvar Abnormalities

Online CME Series