Clinical Aspects of HPV Infection

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Disclosures/Conflicts of Interest

Hope K. Haefner, MD was previously on the advisory board of Merck Co., Inc.
Written Information Available:

University of Michigan Center for Vulvar Diseases (Google)

Then, click on Information on Vulvar Diseases

http://obgyn.med.umich.edu/patient-care/womens-health-library/vulvar-diseases
Learning Objectives

By the end of session, participants should be able to:

• Explore the epidemiology of HPV related disease
• Discuss the various locations of HPV related disease
• Formulate strategies to prevent and treat vulvar HPV related disease
US Estimated Cancer Statistics 2015

<table>
<thead>
<tr>
<th>Site</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>12,900</td>
<td>4,100</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>54,870</td>
<td>10,170</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,290</td>
<td>14,180</td>
</tr>
<tr>
<td>Vulva</td>
<td>5,150</td>
<td>1,080</td>
</tr>
<tr>
<td>Vagina</td>
<td>4,070</td>
<td>910</td>
</tr>
</tbody>
</table>


HPV

- non-enveloped double stranded DNA virus
- genome of 8000 base pairs encoding 2 protein types

Late proteins: L1 and L2 (from viral capsid) expressed only during initial infection

Involved in packaging of the virus

Early proteins: E1, 2, 4, 5, 6, 7 expressed throughout its life cycle

Regulate the replication of viral DNA
Anogenital HPV Infection

• Over 180 HPV types; approximately 40 infect the anogenital region
• Anogenital HPV are divided in two groups
  – Low risk: HPV 6,11
  – High risk: HPV 16,18 (31, 33, 35, 45, 51, 52, etc.)
• Many HPV infections are not associated with visible lesions; long latency is possible
• Incidence has been gradually rising over the last 50 years
• But it is now falling (however, only in younger individuals) due to vaccine protection

Phylogenetic Tree: Anogenital HPV Types

Development of HPV-Related Precancer and Cancer

- High-risk HPV is necessary but not sufficient
- Other risk factors for malignant progression:
  - Number of sexual partners
  - Younger age at first intercourse
  - Viral load
  - Poor cellular immune response
  - Type of epithelial cell infected
  - Cigarette smoking
  - Hormones
  - Genetics
  ...

<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>LSIL</td>
</tr>
<tr>
<td>VIN 2</td>
<td>VIN, usual type</td>
<td>HSIL</td>
</tr>
<tr>
<td></td>
<td>a.VIN, warty type</td>
<td></td>
</tr>
<tr>
<td>VIN 3</td>
<td>b.VIN, basaloid type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.VIN, mixed (warty/basaloid) type</td>
<td></td>
</tr>
<tr>
<td>Differentiated VIN</td>
<td>VIN, differentiated type</td>
<td></td>
</tr>
</tbody>
</table>
The 2015 International Society for the Study of Vulvovaginal Disease Terminology of Vulvar Squamous Intraepithelial Lesions

- Low grade squamous intraepithelial lesion of the vulva [Vulva LSIL] (Flat condyloma or HPV effect)
- High grade squamous intraepithelial lesion of the vulva [Vulvar HSIL] (VIN usual type)
- Vulvar Intraepithelial neoplasia [VIN], differentiated-type [DVIN]

LSIL (Condylomata)

Spiked (acuminate) warts were recognized as abnormalities of the genitalia in ancient Greece and Rome
HPV Types Causing Genital Warts

Low-risk HPV types

CDC STD Treatment Guidelines 2015
http://www.cdc.gov/std/tg2015

Recommended Regimens for External Anogenital Warts (i.e., penis, groin, scrotum, vulva, perineum, external anus, and perianus*)

Patient-Applied:
- **Imiquimod** 3.75% or 5% cream
- **Podofilox** 0.5% solution or gel
- **Sinecatechins** 15% ointment

Provider–Administered:
- Cryotherapy with liquid nitrogen or cryoprobe
- Surgical removal either by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery
- **Trichloroacetic acid** (TCA) or **bichloroacetic acid** (BCA) 80%–90% solution
Silk Touch Laser
Hand held device
Laser Fumes

- Mask protection
- CDC STD Treatment Guidelines


<table>
<thead>
<tr>
<th>Author/Citation</th>
<th>Study Design</th>
<th>Population, Sample Size, Methods</th>
<th>Outcome measures</th>
<th>Summary Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramson Arch Otolaryngol Head Neck Surg 1990</td>
<td>Cross-sectional</td>
<td>7 patients w/ laryngeal papilloma 1 had suction tip applied directly to papilloma 0 had tip held above during laser therapy and smoke collected into phosphate buffered saline collection trap 5/6 had suction tip placed onto papilloma and plaque collected</td>
<td>HPV detected via Southern blot</td>
<td>No HPV detected unless contact made directly with papilloma 2 samples had HPV DNA via Southern blot (not using sensitive techniques, laryngeal papilloma also with low copies of viral DNA congruent to HPV)</td>
</tr>
<tr>
<td>Andre J Am Acad Dermatol 1990</td>
<td>Case series</td>
<td>3 patients treated by CO2 laser for LGW Biopsies obtained from warts and Fumes collected in buffered saline. DNA extracted</td>
<td>Presence of HPV by blot hybridization</td>
<td>2/3 patients had HPV DNA detected in both the lesion and laser plume</td>
</tr>
<tr>
<td>Bregman Acta Derm Venereol 1994</td>
<td>Cross-sectional</td>
<td>15 physicians performing electrosurgery of LGW 11 physicians CO2 laser of EGW</td>
<td>Presence of HPV DNA 6, 11, 16, 18, or 33 via PCR pre- and post-procedure</td>
<td>No conjunctival HPV noted Post Electrosurgery Nasalabial: 2/19 to 6/19 post procedure Nasal: 0/19 to 2/19 post procedure</td>
</tr>
</tbody>
</table>
HSIL of the Vulva

Colposcopy


High-risk HPV types
Other Means of Magnification

Bausch and Lomb
2 x magnification
Part 81-33-05

www.opticsplanet.net
$29.79 US

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
Previously, an Increasing Incidence of HSIL of the vulva

- Heightened awareness of neoplasia
- Increased tendency to perform biopsies
- Commonly associated with other lower genital tract neoplasias (anus, vagina, cervix) and/or carcinomas
### Risk Factors for HSIL

<table>
<thead>
<tr>
<th>History of HPV (vulva, vagina, cervix)</th>
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<tbody>
<tr>
<td>Early age of onset of sexual intercourse</td>
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<tr>
<td>Multiple lifetime sexual partners</td>
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<tr>
<td>Cigarette smoking</td>
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### Immunosuppression

<table>
<thead>
<tr>
<th>Pregnancy</th>
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<tbody>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Autoimmune connective tissue disorders</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Transplant recipient</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
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<tr>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

### Symptoms

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

No typical gross appearance

Gray-white

HSIL (VIN) warty

T Wright, MD collection
Brown

Red Can be Confused with Lichen Planus or Nonsquamous VIN (Paget)
Concerning Colposcopic Features of Vulvar HSIL

• Areas of ulceration
• Focal nodules
• Atypical vessels

Vulvar biopsy

Anesthesia
• 1% lidocaine (sodium bicarb)
• 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
Tips
Management

VIN Management

**Surgical**
- Excision (hair bearing areas)
- Ablation - laser, cautery, CUSA (non hair bearing areas)

**Medical**
- Imiquimod – medical treatment of choice
- 5-FU – no longer used
- Interferon – systemic / topical - cumbersome
- Photodynamic therapy – systemic or topical
- Cidofovir – limited data
HSIL

Acceptable treatment modalities:
- Surgical excision (hair bearing areas)
  * Laser ablation (non hair bearing areas)
- Electrosurgical excision
  * Imiquimod
    * Ideal for clitoris/prepuce, urethra

Margins and Depth
Vulvar HSIL

- Margins
- Depth
  - Hair bearing areas to 2.7 mm
  - Non-hair bearing = 0.1 to 1.9 mm
    (average = 0.5 +/- 0.2 mm)
Silk Touch Laser
Hand held device
Recurs After Treatment
(mean follow-up 39 months)

No statistically significant differences between groups

0 10 20 30
Recurrence Rate
Vulvectomy Partial Vulvectomy Local Excision Laser Vaporization

Gynecologic Oncology. 2005; 97: 645-651

Treatment of Vulvar HSIL:
Targeted Medical Therapy with Imiquimod


Adapted from Journal of Investigative Dermatology. 2006; 126:1338–1347
Side Effects of Topical Imiquimod

- Skin irritation
- Erythema
- Erosion
- Edema
- Pain
- Pruritus
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.


Other Treatments (?Historical)

5 - fluorouracil (2003)

Cidofovir (2001)

Bleomycin (1980)
Concerns with Topical Therapy and Laser Therapy

Missing malignancy

VIN (VIN 3)
Invasion at time of diagnosis

- Chafe 1991: 19%
- Hording 1995: 17%
- Herod 1996: 16.4%
- Husseinzadeh 1999: 20.5%
- van Seters 2005 (review): 3.5%
**HSIL of the Vulva**

*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)*

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**HPV-associated HSIL: Risk of Progressive Disease**

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

- Untreated VIN progression to invasive cancer
  ≥10% per year

- Lifetime risk of invasive vulvar cancer after treatment for HSIL (VIN 2,3) = 3% to 6%

HGSIL Progression to SCC
(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


Stop Smoking!
**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

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**Anal Intraepithelial Neoplasia (AIN 2,3)**
FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV

For Immediate Release
December 10, 2014

The U.S. Food and Drug Administration today approved Gardasil 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) for the prevention of certain diseases caused by nine types of Human Papillomavirus (HPV). Covering nine HPV types, five more HPV types than Gardasil (previously approved by the FDA), Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers.

9-Valent HPV Vaccine

AAHS = Amorphous aluminum hydroxyphosphate sulfate adjuvant

“ORIGINAL TYPES”
6 11 16 18

“NEW TYPES”
31 33 45 52 58
The *Morbidity and Mortality Weekly Report* (MMWR) Series is prepared by CDC and is available free of charge in electronic format. To receive an electronic copy each week, visit [http://www.cdc.gov/mmwr/mmwrssubscribe.html](http://www.cdc.gov/mmwr/mmwrssubscribe.html)
Close Follow-up  Long Term for These Conditions