Vulvar Neoplasms: Benign and Malignant

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Forum 044
Vulvar Disease: What Do You Know? An Overview
VULVAR NEOPLASMS: Benign and Malignant

DISCLOSURES
NONE
What's important?

• 10% of all pigmented lesions occur on genital skin
• Vulvar melanoma-late diagnosis-less than 50% 5 yr survival
• Avg depth 4.0 mm
• 2% of melanomas in women arise on vulva
• Genital melanoma Females>Males, Greatest in caucasians
• Only 4% of dermatologists include vulvar exam on FSE
• Stirrups vs supine with feet on corners of table

MELANOMA

• Average age 60-70
• 6% arise in preexisting nevi
• Most common labia minora, clitoris
• 5 year survival less than 50% (due to depth at detection)
• Often multifocal, unlike other sites
• 25% amelanotic
• German study - anogenital melanoma deeper Breslow depth than female genital tract
• Remember perianal area!

GENITAL MELANOMAS

- Biopsy
  - New or non-resolving erythematous plaques as 25% of genital melanoma unpigmented
  - Multifocal sampling for large lesions
VULVAR MELANOMA

- Most common histology - acral lentiginous, then nodular
- BrafV600E mutations common in dysplastic nevi and common nevi of genital track (>90%) but not of vulvar melanomas
- Suggests that dysplastic nevi and common nevi are not melanoma precursor in genital tract
- C-Kit 28% (imatinib) (most common vulvar)
- NRAS 28% (most common vaginal)
- Recent study 9/13 vulvar melanomas as PD-L1 expression (nivolumab, pembrolizumab)
- Swedish study found decrease in rate (3% per yr over last 25yrs) of vulvar melanoma contrasted to increase in rate (6% per year) of cutaneous melanoma

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AMELANOTIC MELANOMA
ATYPICAL NEVI OF GENITAL TYPE AND MIS
NODULAR MELANOMA
VULVAR MELANOSIS

Women in 40s rather than 70s
Flat, asymmetric, tan to blue, black, irregular borders and size
Most common on Labia minora
  Mucous membranes and modified mucous membranes rather than keratinized skin of vulva
Indistinguishable from melanoma clinically
Maybe post inflammatory
Lichen sclerosus may be predisposing disease
Unusual in older women (Suspect Melanoma)
No increased risk of melanoma
MANAGEMENT OF VULVAR MELANOSIS

- Initial photographs
- Reassured if pt has lichen sclerosus
- Biopsy
- Follow up for clinical change
- Low threshold for biopsy for any clinical change as morphology not distinct in genital pigmented lesions
- Melanosis **NOT** premalignant
Two common distinct pathways

1. **Human Papilloma Virus (HPV) related**
   - young women
   - often multifocal
   - smokers
   - 20% burden of invasive SCC
   - better prognosis

2. **Non HPV related**
   - elderly women
   - often associated with lichen sclerosus
   - 80% burden of invasive SCC
A. Human Papilloma Virus (HPV) related

1. Low Grade Squamous Intraepithelial Lesion (LSIL) - (VIN1)
2. High Grade Squamous Intraepithelial Lesion (HSIL)-(VIN2/3)

- HSIL, VIN often thought to have low rate of progression to SCC 3%, this is in treated patients
- 10% risk of progression to SCC in untreated patients
LOW GRADE SQUAMOUS INTRAEPITHELIAL LESION (LSIL) - (VIN1)

HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) - (VIN2/3)

LSIL- condyloma effect

HSIL
VULVAR HSIL (HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION- HPV RELATED)

- 6.5 -10% of HSIL progresses to SCC
- 1% regresses without treatment (usually within 10 months)
- Regression associated with young age, pregnancy, the presence of multiple pigmented lesions
- ISSVD refrains from using Bowenoid papulosis as it is impossible to know histologically if lesion will progress or regress
VULVAR HSIL (VIN)

- High risk HPV types, 16 most frequent
- Stain with p16, Ki67 (mitotic index), absence of p53
PERIANAL HSIL (PIN)
TREATMENT OF HSIL (USUAL TYPE VIN)

- Treatment recommended for everyone
- Surgery with 5mm to 1cm without damage to clitoris, urethra, anus or other critical structures
- Ablative laser therapy with margin of 5mm to 1cm of normal skin (2mm deep), if hair bearing need to treat to base of follicles (down into subcutis)
- Imiquimod 5% 3x week for 12-20 weeks, non responsive lesions are excised, close clinical followup after treatment
  - 81% had complete or partial response
TREATMENTS HSIL

- Cidofovir 1% and 5FU are effective but have increased adverse effects
  - Cidofovir trial in HIV+ patients
- Photodynamic therapy
- Sinecatechins - clinical trials nly
HSIL RECURRENCE

- Risk of recurrent disease increased
  - Age > 50
  - Multifocal disease
  - Adjacent HPV or lichen sclerosus
  - Immunosuppression
  - + excision margins
  - Coexisting vaginal or cervical disease (VAIN or CIN)

Satmary W. Gynecologic onc. 2018;148:126-131 (dVIN and HSIL not differentiated)
Differentiated VIN (dVIN)

- Higher progression to SCC rate than HSIL (usual VIN)
- Elderly women
- Often associated with lichen sclerosus
- 1-3% of women with LS develop invasive SCC
- LS is present in 50% of women with SCC
- **More than 50%** of HPV unrelated SCC have adjacent dVIN
DVIN IN LICHEN SCLEROSUS

Rarely diagnosed except in excision specimens adjacent to invasive SCC
dVIN in Lichen Sclerosus
BASAL CELLS HYPERCHROMATIC
PARAKERATOSIS
DYSKERATOSIS
PROMINENT INTERCELLULAR
SPACES
LOSS OF GRANULAR LAYER
P53 STAINING MATCHES
ADJACENT TUMOR
DVIN

Enlarged vesicular nuclei

Macro nucleoli

Abundant eosinophilic cytoplasm
Invasive Squamous cell carcinoma (HPV related)

- **HPV related SCC**
  - younger women (under age 60)
  - 25% of invasive SCC HPV related
  - 76% of HPV related SCC is warty or basaloid
  - 33% well to moderately differentiated
- **p16+ and HPV+** hallmark of HPV related SCC (HPV16- 72%, HPV33- 6%, HPV18- 5%)
INVASIVE SCC (HPV RELATED)

- Incidence is increasing world wide mirroring increase in HPV prevalence
- Interval between HSIL (usual VIN) to invasive SCC, shortens with increasing age (50 months for 15-29 yrs, 25 months for age 70 yrs)
- No difference in time to progression to invasive SCC for multifocal vs unifocal disease
INVASIVE SQUAMOUS CELL CARCINOMA (HPV UNRELATED)

- **HPV unrelated** carcinomas, well to moderately differentiated SCC
  - p53 mutation is the hallmark of HPV independent SCC
  - 73% strong diffuse expression of p53 even above basal layer (mis sense mutation that leads to more stable protein)
  - 27% of dVIN and SCC have complete absence of p53 from nonsense mutation or deletion
  - **normal** p53 staining - patchy p53 in basal layer
- **More than 50% of HPV unrelated SCC have adjacent dVIN**
  - Complete excision recommended of all hyperplastic vulvar lesions adjacent to SCC so p53 staining can be compared in lesional and nonlesional skin
LICHEN SCLEROSUS AND INVASIVE SCC

• Poorly controlled lichen sclerosus has much greater risk of progression to invasive SCC
• 507 women - observed 7 yrs, superpotent topical steroids
  • 0 compliant pts, 7 partially compliant pts developed SCC
  • manifested as treatment resistant hyperkeratotic plaques and nodules
  • **Incomplete disease control only risk for invasive SCC**
• Even asymptomatic lichen sclerosus needs **continuous maintenance therapy**, such as mometasone furoate 0.1% (Lee A et al. Long-term management of adult vulvar lichen sclerosus: a prospective cohort study of 507 women. JAMA Dermatol. 2015;151(10):1061-7.)
• **Unknown** if lichen planus predisposes to vulvar SCC (Is vulvovaginal lichen planus associated with SCC? Day T et al. J of lower genital tract ds. 2018;22(2):159-165.)
• Looked at all non HPV SCC of of vulva
• 95% of excisions had ls next to it, other 5% had LS in subsequent biopsies
• No evidence of LP
SCC IN LICHEN SCLEROSUS

Treatment resistant hyperkeratotic plaque
SCC IN POORLY CONTROLLED LICHEN SCLEROSUS
SCC (HPV NON RELATED)

- Younger women (<50 yrs) more likely to have local disease
- Older women (>50) more likely to have regional disease or metastases
- Survival longer in younger women than older women even with same disease stage (5yr survival 87% <50 yrs, 53% > 50yrs)
- Local disease recurrence - Pathological margins
  - margins <3mm - local recurrence 17%
  - margins 3-8mm - local recurrence 25%
  - **margins >8mm** - local recurrence 22%
  - **margin distance did not** effect overall survival, only perineurial invasion influenced survival
Tumor size important prognostic indicator even with negative lymph nodes

- 2.1-3.99cm: 5yr OS 79%, 4-5.99cm: 78%, 6-7.99cm: 36%

- Prognosis significantly declines if size of tumor >6cm

- One positive LN did not affect survival

- Two or more positive nodes experienced greater than 5 times higher risk of death than node negative patients

- Extra-capsular growth in lymph node metastasis increased the risk of death 5.2 times.
• Re-excison of adjacent VIN (HSIL or dVIN) in vulvar SCC did not change disease free survival

• Perhaps due second primaries due to existing risk factors for SCC (HPV or Lichen sclerosus)

• Impact of re-excison of residual adjacent VIN and histological tumor free margin on survival in primary SCC of vulva. Gasimli K et al. Archives Gyn and OB. 2018;298:945-950.
VULVAR PAGETS DISEASE (EXTRAMAMMARY)

- Average age 64 yrs
- Vulva (labia) most common site of extramammary Pagets disease
- Erythematous to hyperkeratotic plaques
- Symptom - pruritus
- Multifocal
- Median size 6.5cm
- Only 30% associated with underlying neoplasm
- Recurrence very common
PAGETS DISEASE

- **Histology**
  - Pagets cells sit on top of basal layer
  - Large cells with ample cytoplasm
  - Vacuolated to clear cytoplasm
  - Prominent nuclei and nucleoli
  - PAS+
  - CEA+
  - EMA+
  - Cytokeratin 7+
EXTRAMAMMARY PAGETS DISEASE
OVERVIEW - TREATMENT OF PAGETS DISEASE

• Standard treatment - **wide local excision** (WLE) (2-3 cm margins) with XRT if LN+ (40-70% + resection margins)

• **Laser** - high rate of recurrence as may not reach adnexal extension

• **Photodynamic** (5 aminolevulinic acid) - high recurrence

• **Radiation** - appropriate dose unknown - 0-35% recur, skin complications

• **Imiquimod** - recurrence 19%?????
TREATMENT OF PAGET'S DISEASE

- Often do not recur (50% without further therapy) even with positive margins
- Could not predict invasive disease even with multiple scouting biopsies
- Recurrence most common in surgical scar from excision
- Increased recurrence if invasive disease present
- **No evidence** that microinvasive disease (invasion<1mm) decreases survival
- Risk of developing invasive disease is 8%
MOH’S SURGERY VS WIDE LOCAL EXCISION

- **MMS** 12% 5 yr recurrence rate as opposed to **50% WLE** recurrence rate, Wollina et al. Surgical treatment of extramammary Paget’s disease. Current Treatment Options in Oncol. 2018;19:27.

- **WLE** 2.5x higher recurrence rate even with negative margins than **MMS**, Long et al. A matter of margins: surgical and pathological risk factors for recurrence in extramammary Paget’s disease. Gynecologic oncology 2017;147:358-363.

- Damavandy A et al. CK7 immunostain during **MMS** decreases local recurrence from 26% to 3% (combined initial recurrent dx and disease with first treatment)
IMIQUIMOD ADVERSE EFFECTS

- Targets Toll like receptor 7 (TLR7) of dendritic and Langerhan cells
- Release INF, TNF, IL-12 which activates CD8+ cells
- Apoptosis of transformed cells

Application
- 5-7x week - 82% adverse effects causing frequency reduction
- 3-4x week - 2% adverse effects causing frequency reduction
- 1-2x week - 0% adverse effects causing frequency reduction

- Treatment duration 4 months
  - 73% CR
  - 27% PR or stable disease
  - 0% progression
IMIQUIMOD RESULTS

- Complete response versus Partial response
  - No difference in age
  - No difference in primary vs recurrent disease
  - No difference in tumor size
  - No difference in treatment duration
PAGETS THERAPY - TAKE HOME MESSAGE

- Surgery often mutilating with significant decrease in quality of life
- Recurrence rate for all therapies HIGH (perhaps less with MMS)
- Use imiquimod 3-4 x week as sole therapy
- If using surgery, consider imiquimod prior to surgery to decrease size of tumor
- Life long follow up
- Low threshold to biopsy for recurrent disease
TAKE HOME MESSAGES

• Many pigmented vulvar lesions are indistinguishable clinically
  • Low threshold for biopsy

• LONG TERM MONITORING ESSENTIAL
  • Lichen sclerosus
  • Vulvar melanosis
  • Pagets disease
TAKE HOME MESSAGES

- Lichen Sclerosus requires maintenance therapy to reduce risk of SCC
- Paget's disease and Lichen Sclerosus
  - Low threshold to biopsy - new or non-responsive areas
  - Baseline photographs
- Vulvar melanosis
  - Low threshold to biopsy - new or non-responsive areas
  - Baseline photographs
• THANKS TO DR. LYNNE MARGESSON, AND ISSVD LIBRARY FOR PHOTOS.

• References


