Precancer and Cancerous Vulvar Disease

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Disclosures

*I have no conflicts of interest to disclose.*

Vulvar Disease

- Lichen Sclerosus and Planus
- Vulvar Condyloma and Dysplasia
  - HIV infected
- Extramammary Paget’s Disease
- Vulvar Cancer
  - Sentinel node biopsy
  - Vulvar Melanoma

Vulvar Lichen Planus

- Women 50-60 years
- May be related to aberrant cell mediated immunity to skin antigens
  - Papular or erosive lesions that can lead to sexual or urinary impairment
- Vaginal involvement in up to 70%
- Relationship to malignancy uncertain
- Paucity of data for evidence based recommendations
Management of Lichen Planus

- Association with beta-blockers, ACE inhibitors, lithium, HCTZ
- Topical steroid ointment (e.g. clobetasol, halobetasol)
  - Nightly application for 2-3 months
  - 71% complete response
  - 1-3 times weekly for maintenance with mid or low potency steroid
    (2.5% hydrocortisone)
  - Prednisone 40-60 mg PO QD tapered over 4-6 week course as alternative
- Small case series for tacrolimus 0.1% ointment
  - Up to twice a day for 12 weeks
  - Long term safety not established
- Nighttime sedation to decrease scratching

Lichen Sclerosus

- Occurs in anogenital region in 85-98%
- Two peaks of onset in prepubertal girls and postmenopausal women
- Associated factors
  - Trauma, Injury
  - Autoimmune diseases in 22%
    - Antibody formation to extracellular matrix protein 1 in 75%
    - Increased number of CD1 Langerhans cells in epidermis
  - Low estrogen states but no association with contraceptive use or HRT

1 Chan I et al, Clin Exp Dermatol 2004

Vulvar Lichen Sclerosus

- Risk of squamous cell carcinoma <5%
  - More liberal biopsy, excision and use of steroids may lead to risk reduction
- Treatment options
  - Topical steroid ointments (e.g. clobetasol, halobetasol)
    - 95% complete or partial relief of symptoms
    - 6-12 weeks of treatment
    - Maintenance 1-3 times/week
  - Good hygiene
  - Estrogen if labial fusion or epidermal thinning
  - Surveillance every 3-6 months if no treatment
Management of Recalcitrant Lichen Sclerosus

- Intralesional triamcinolone (5-20 mg) monthly for 3 months
- Retinoids
  - Acitretin 20-30 mg PO for 16 weeks effective
  - Mindful of side effects including elevated liver enzymes, hypertriglyceridemia, xerosis, chelitis
- Topical tacrolimus (0.03% cream)
- Topical oxatomide may relieve pruritus through antihistamine effect
- Limited role of ablative and excisional procedures

Vulvar Condyoma

- HPV 6/11 account for ~90%
- Disease recurrence in 20-30%
- Treatment for symptom control
  - No evidence that eradication eliminates HPV infectivity
  - No high quality evidence that any treatment significantly superior
  - Laser better for large or multifocal lesions but scarring in 28%
  - Intralesional interferon injection 2-3 times per week for recalcitrant lesions

Medical Management of Condyoma

- Trichloroacetic acid (TCA)
  - No systemic absorption and preferred in pregnancy
  - Weekly application for 4-6 weeks leads to 70% clearance
  - Thick large lesions may not respond secondary to poor penetration
- Imiquimod
  - Increases local interferon production and reduce HPV virus load
  - 40-50% complete response
- Sinecatechin (Veregen – green tea extract)
  - Two randomized trials with 10-15% ointment applied 3 times daily for up to 16 weeks
  - 57% clearance vs 35% for placebo

Condyoma in HIV Infected

- Incidence 33% in HIV positive versus 9% in seronegative
- Imiquimod may be more effective
  - 1/3 on antiretroviral therapy (HAART) treated with imiquimod achieve total clearance
Vulvar Intraepithelial Neoplasia (VIN)
- Increasing incidence worldwide, particularly in young women who account for 75% of cases
  - VIN3 2.86 per 100,000 women
- Subtypes
  - Basaloid (thickened, flat) or warty
  - Differentiated, associated with lichen sclerosus (5%)
- 90% HPV positive
  - Multifocal and multicentric associated with HPV 16, 18, 31

Imiquimod in Vulvar Dysplasia
- Topical immune response modifier
  - Stimulation of local cytokines and cell mediated immunity
  - Not recommended in pregnancy (Category C)
- 2 randomized trials & 8 observational studies (n=162)
  - 51% complete response
  - 25% partial response
  - 16% recurrence rate
- Typical course 16 weeks
  - 2/3 reduce to 2-3 times per week secondary to inflammation, erythema, erosion

Other Medical Therapies in Vulvar Dysplasia
- Topical 5-FU Cream
  - Chemical desquamation with response rate as high as 75%
  - Poorly tolerated because of burning pain, ulcerations, inflammation
- Investigational therapies
  - Photodynamic therapy
  - Cidofovir (antiviral)
  - Retinyl acetate gel
- HPV vaccination
  - Prophylactic use could prevent 2/3 VIN, VAIN, perianal disease

VIN in HIV-Infected Women
- 4-8% with VIN progress to cancer over 1-8 years in systematic review of 3322 patients
  - Carcinoma developed at incompletely treated site at median of 2.4 years
  - Incidence & severity of dysplasia correlates with worsening immunosuppression
  - Recurrence with laser may be higher than in those not infected (28% vs 17%)
- 1/3 develop recurrent VIN
  - Risk factors include multifocal disease, larger lesion size, positive margins (32-50% vs 11-17%), tobacco use

1 Mahto M et al, Int J STD AIDS 2010
1 Van Seters M et al, Gynecol Oncol 2005
Precancerous & Cancerous Vulvar Disease

Surveillance in HIV-Infected Women

- Two prospective studies (n=507)
  - 1.3% of HIV infected women developed VIN at median of 3.2 years
  - 1.6% developed VAIN at 6 year follow-up
- HAART decreases incidence of recurrence by a third
- HPV vaccination may offer some benefit but distribution of subtypes different
  - Pre-existing lower genital neoplasia not contraindication
  - In 5455 healthy women 16-24
    - Quadrivalent vaccine led to fewer cases VIN2-3 (0.1% vs 0.2%) but not sufficiently powered
- Recommend follow-up Q6 months for 5 years

Conley LJ et al, Lancet 2002
Jamieson DJ et al, Obstet Gynecol 2006

Paget’s Disease of the Vulva

- Average age 70
- Lesions multifocal
- Invasive adenocarcinoma present in 4-17%
  - HPV 16/33 account for 55.5%
  - 22% associated with cervical neoplasia
- Synchronous neoplasms in 20-30%
  - Breast, rectum, bladder, urethra, cervix, ovary

Insinga RP et al, Cancer Epidemiol Biomarkers Prev 2008

Treatment Outcomes of Vulvar Paget’s Disease

- Largest series of 43 patients
  - Median follow-up 54 months
  - Median OS 124.5 months but 70.8 months if invasive adenocarcinoma
- Surgical excision in 81.4%
  - Positive margin in 47.0%
  - Recommend gross margin 2-3 cm
  - Frozen section does not decrease risk of positive permanent margin
- Radiotherapy to 60 Gy in 18.6%
  - Recurrence in 34.3%
  - Repeat surgery 75.0%

Cai Y et al, Gynecol Oncol 2013

Risk for Recurrence in Vulvar Paget’s

- Microscopic positive margins in 40-70%
  - Moh’s surgery may lower recurrence (12.5% vs 33.3%)
- Adjuvant radiotherapy
  - Deep dermal invasion
  - Node metastasis
  - Positive margins
- Local recurrence in 15-61%
  - Risk factors include positive surgical margin, dermal invasion, and adnexal involvement

Lee KY et al, Dermatol Surg 2009
Imiquimod in Paget’s Disease of the Vulva

- Largest case series of 6 patients\(^1\)
  - Clinical resolution
    - 50% primary disease
    - 73% recurrent disease
- 29 documented cases in literature
  - Length of treatment not standardized
  - 5% Imiquimod therapy viable alternative to surgical excision

\(^1\)Sanderson P et al, J Obstet Gynecol 2013

Vulvar Cancer

- 4700 new cases, 990 deaths
  - Rate of invasive disease remains stable over last 2 decades
  - Incidence of in situ doubled
  - Falling mean age of diagnosis
- HPV responsible for 60% of vulvar malignancies
  - HPV 16/33 account for 55.5%\(^1\)
  - Associated with cervical neoplasia in 22%
- 5% lesions multifocal

\(^1\)Insinga RP et al, Cancer Epidemiol Biomarkers Prev 2008

Histologic Types

- Squamous cell (90%)
  - Keratinizing, simplex type in older women and not HPV related
  - Classic, warty associated with HPV 16,18,33
- Melanoma (5-10%)
- Basal cell (2%)
  - High incidence of antecedent or concomitant malignancy
- Sarcoma (1-2%)
  - Poor prognosticators include size >5 cm, high mitotic rate, infiltrating margin
- Extramammary Paget’ (<1%)
- Bartholin gland adenocarcinoma
  - 55% develop recurrent disease with 67% 5 year survival

Risk Factors

- Cigarette smoking
- Vulvar dystrophy (e.g. lichen sclerosus)
- Cervical dysplasia
- HPV infection
- Immunodeficiency
- Northern European Ancestry
Assessment of Inguinal Node Metastases

- 10% of superficially invasive tumors (1-3 mm) with node metastasis at diagnosis
- <3 positive nodes associated with lower risk of hematogenous spread
- 100% of sentinel nodes lie over or medial to femoral vessels
  - Superficial 85%
  - Deep 15%

Pretreatment Evaluation

- Palpation of inguinal nodes inaccurate
  - False negative & positive rate 20%
- Proximity to midline and size of lesion (>2 cm) should be noted
- Assessment of lower extremity edema and vascular integrity
- 5% with metastatic disease at presentation
- PET/CT and MRI helpful

Surgical Excision

- Resection with 1 cm clinical margin and dissection down to perineal membrane (deep fascia)
  - Shrinkage after fixation about 20%
  - Local rate of recurrence lower if tissue margin at least 8 mm\(^1\)
    - 50% recurrent rate if >8 mm
    - Consider re-excision or radiation
- Tumors extending to proximal urethra, vagina and bladder and rectal mucosa benefit from chemoradiation followed by selective resection
- Debulking of bulky groin nodes prior to chemoradiation preferable

Inguinofemoral Lymphadenectomy (LND)

- 16-24% of normal nodes with occult metastases
- 24-41% of clinically enlarged nodes with negative histology
  - Likely due to infection, necrosis
- Stage IA tumors do not require LND (1% risk of metastasis)
- Early stage, lateral disease with <3% risk of contralateral groin metastases\(^1\)
  - Contralateral LND performed if positive nodes on intraoperative frozen section
- High morbidity
  - Wound complications 20-40%
  - Lower extremity lymphedema 30-70%

\(^1\)Heaps JM et al, Gynecol Oncol 1990

\(^1\)Stehman FB et al, Obstet Gynecol 1992
Feasibility of Sentinel Node Biopsy

- GROINS V Trial\(^1\)
  - Multi-institutional trial in Netherlands
  - 403 women
  - Squamous cell tumor <4 cm
  - False negative predictive value 2.3%
  - Complications higher if complete lymphadenectomy
    - Wound breakdown (11.7\% vs 34.0\%)
    - Cellulitis (4.5\% vs 21.3\%)
    - Lymphedema (1.9\% vs 25.2\%)
  - Prognosis poorer if sentinel node metastasis larger (>2 mm)\(^2\)

Sentinel Node Biopsy & Lymphatic Mapping

- GOG 173\(^1\)
  - 453 women with squamous cell carcinoma
  - Primary tumor 2-6 cm
    - >2 cm from midline
  - 10 year accrual period
    - Intradermal injection of blue dye (95\% sensitivity) +/- technetium (97\% sensitivity)
    - Learning curve of surgeons
  - Sentinel node detected 91.7\%
  - False negative predictive value 3.7\%
    - 2.0\% if tumor < 4 cm
    - 7.4\% if tumor >4 cm

Radiation Therapy

- Primary radiation 60-70 Gy in non-surgical patients
  - Less toxicity compared to lymphadenectomy but higher recurrence rate and lower disease specific survival
  - Chemoradiation preferred, extrapolating from locally advanced cervical cancer data
- Consider adjuvant radiation in high risk tumors (45-50 Gy)
  - Size>4 cm
  - Lymphovascular space invasion
  - Positive surgical margins
  - Node involvement
- Improvement in survival with adjuvant RT compared to pelvic lymphadenectomy (59\% vs 31\%)\(^1\)

Primary Chemoradiation

- Administer cisplatin or concurrent 5-FU with cisplatin or mitomycin C
  - No prospective trials comparing RT alone to chemoradiation
- Chemoradiation preferred based on experience in cervical and anal cancers
  - Radiosensitizing chemotherapy superior to radiation alone in anal cancers
- Total radiation 10-20\% less when given with chemosensitization

\(^1\)Van der Zee AG et al, JCO 2008
\(^2\)Oonk MH et al, Lancet 2010
\(^1\)Kunos C et al, Obstet Gynecol 2009
Survival Prognosticators

- Nodal involvement most significant
  - 70-93% 5 year OS with negative nodes
  - 25-41% with positive nodes
- Stage
- Lymphovascular space invasion
- Older age

Recurrent Disease

- Majority of relapses in first year
  - 10% recur > 5 years from initial treatment
- Cervical or vaginal cytology recommended annually
- Sites of recurrence
  - Vulva 53%
  - Groin 19%
  - Pelvis 6%
  - Distant 8%
- Platinum based chemotherapy for metastatic disease

Survival with Recurrence

<table>
<thead>
<tr>
<th>Disease Site</th>
<th>Five Year Survival</th>
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<tbody>
<tr>
<td>Vulva</td>
<td>60%</td>
</tr>
<tr>
<td>Inguinal &amp; pelvic</td>
<td>27%</td>
</tr>
<tr>
<td>Distant</td>
<td>15%</td>
</tr>
<tr>
<td>Multiple sites</td>
<td>14%</td>
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1. Maggino T et al, Cancer 2000

Vulvar Melanoma

- 10% of all vulvar malignancies but <1% of all melanomas
  - Tumor size (<3 vs >3 cm) predicts prognosis
  - Median age 68
- Surgical excision
  - 1 cm margins if <1 mm thick
  - 2 cm for thicker lesions
- Evaluation of sentinel nodes feasible
  - Bilateral lymphadenectomy may not confer benefit
- Radiation may be used for localized control but no improvement in survival
Systemic Therapy in Vulvar Melanoma

- **Immunotherapy**
  - Interferon alpha
  - Anti-CLA4 monoclonal antibody (Ipilimumab)
  - Cisplatin based chemotherapy with interferon alpha and/or interleukin 2

- **Mutation status**
  - BRAF driver mutation at V600 site (10%)
    - Vemurafenib, dabrafenib
  - KIT mutation (25%)
    - Imatinib

Overall Prognosis by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Five Year Survival</th>
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<tbody>
<tr>
<td>0</td>
<td>77%</td>
</tr>
<tr>
<td>I (Localized)</td>
<td>70%</td>
</tr>
<tr>
<td>II (Anus, Upper Vagina, Urethra)</td>
<td>50%</td>
</tr>
<tr>
<td>III (Nodes)</td>
<td>48%</td>
</tr>
<tr>
<td>IV Distant Mets</td>
<td>24%</td>
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Conclusions

- Topical steroid ointments with maintenance therapy remain the mainstay of management of lichen sclerosus and lichen planus
- Imiquimod may be beneficial in vulvar dysplasia, condyloma, and Paget’s disease
- Sentinel node biopsy is a feasible alternative in select vulvar cancer patients