Illuminating Consultation Cases

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Case 1

(Contributed by Rebecca Swain MD)

- 9 cm tan-yellow whorled mass
- Located in rectus abdominis muscle
- Deep to a C-section scar from 20 years ago
- Did not grossly involve the peritoneum
- Excised

Case 1

- 44 year old woman with a mass in the rectus muscle.
- Biopsy performed, reviewed at UCSF.
- Immunostains evaluated:
  - Positive: Pankeratin, keratin AE1/AE3, CK7
  - Negative: CK20, TTF-1, ER, CD34, CD31, S100, INI1 (positive stain, negative result)
- Diagnosis: Carcinoma, likely metastatic, pancreaticobiliary, gyn, skin adnexal
Tumors and Masses of the Abdominal Wall
(From Current Diagnosis and Treatment: Surgery)

- Hernia
- Lipoma
- Hemangioma
- Endometriosis
- Fibromatosis (desmoid tumor)
- Malignant tumor – most are metastatic, lung and pancreas are the most common primary sites
Summary

- Young woman
- Tumor in the anterior abdominal wall
- Pan keratin and CK7 positive
- No internal primary site identified
- Related to a C-section scar
- PO Day 1 serum hCG = 27 IU/L, PO Day 3 serum hCG = 9 IU/L

Immunohistochemistry of Trophoblastic Tumors

General trophoblastic markers: HSD3B1, CD10, inhibin, CK18, pankeratin

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Best Marker</th>
<th>MIB1 Rate</th>
</tr>
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<tbody>
<tr>
<td>Choriocarcinoma</td>
<td>hCG</td>
<td>+ +++</td>
</tr>
<tr>
<td>ETT</td>
<td>p63</td>
<td>+ or ++</td>
</tr>
<tr>
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Inhibin

Case 1

Another Case

HCG

HPL

p63
Description of 14 Cases of A New Type of Trophoblastic Tumor


Epithelioid Trophoblastic Tumor

- Patient age 15-66 (average 36)
- Antecedent pregnancy:
  - Normal delivery 68%
  - Spontaneous abortion 16%
  - Hydatidiform mole 16%
- Interval 1-25y (average 6.2)
- Presentation: amenorrhea or abnormal bleeding – can be misdiagnosed as ectopic
- Some patients present with extrauterine tumors – lung or other sites
- Low levels of HCG

Diagnosis

Epithelioid
Trophoblastic Tumor

Ki-67
Epithelioid Trophoblastic Tumor

- DNA genotyping reveals paternal alleles that are not present in adjacent maternal tissues ➔ trophoblastic origin
- Conflicting data on Y-chromosome, but a recent study suggested that most ETT do not have Y chromosome material present (paternal X favored)

ETT Location of Primary Tumor

- Cervix or LUS 50%
- Corpus 30%
- Extrauterine 20%

• Moral: Can be easily mistaken for cervical cancer
**ETT Immunohistochemistry:**
- Scattered HPL, HCG, PLAP, Mel-CAM + cells.
- p63 +, HLA-G +
- MIB1 10-25%

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**ETT**

One of the original descriptions


Two lung tumors reported.
Epithelioid Trophoblastic Tumor

- Clinical behavior similar to PSTT
- Most have benign clinical evolution
- ~25% metastasize
- Serum HCG, although low, can be used to monitor treatment
- May not respond to standard GTD chemotherapy
- Hysterectomy is standard therapy
- Resection of metastases may help

Case 1 Key Points

- ETT is derived from intermediate trophoblasts of the chorion laeve
- Low levels of serum HCG
- Usually primary in the cervix or uterus
- Nodular, epithelioid appearance resembles a carcinoma
- Differential diagnosis
  - Squamous cell carcinoma of the cervix: CK5/6, p16, HPV testing; LMW CK, staining for trophoblastic markers, molecular genotyping
  - Placental site nodule: size, cellularity, low MI, low Ki-67
- Difficult to treat with chemotherapy, hysterectomy is usually performed
- Extrauterine primary tumors occur in the lungs, pelvis and elsewhere

Gestational Trophoblastic Neoplasia

- Persistent or invasive hydatidiform mole
- Choriocarcinoma
- Epithelioid Trophoblastic Tumor (ETT)
- Placental Site Trophoblastic Tumor (PSTT)
- Mixed Trophoblastic Tumor
Case 2
(Contributed by Dave Park)

- 41 year old G5P3
- Persistently elevated HCG in the range of 200-300 IU/L
- Underwent a D&C for suspected missed abortion.
Immunohistochemistry of Trophoblastic Tumors

General trophoblastic markers: HSD3B1, CD10, inhibin, CK18, pankeratin

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Summary

- Intrauterine
- Ill defined, invades the myometrium
- Polygonal cells, atypia, mitotic activity
- Low HCG and p63, extensive HPL
- Diagnosis: Placental site trophoblastic tumor (PSTT)
Trophoblastic Pseudotumor of the Uterus
An exaggerated form of “Syncytial Endometritis” Simulating a Malignant Tumor

Robert J Kurman, MD (MAJ, MC, USA), Robert E Scully, MD, and Henry J Norris, MD

Cancer 38:1214-1226, 1976


Proposed name Placental Site Trophoblastic Tumor

Placental Site Trophoblastic Tumor

PSTT

- Mean age about 31y, range 20 to 63y
- 60-70% follow an uneventful term pregnancy, the rest follow CHM or abortion
- Requirement for a paternal X chromosome; antecedent gestation female
- Time from previous pregnancy to PSTT diagnosis 1 week to 204m, median 12-18m
- Presentation is with vaginal bleeding, uterine enlargement
- Usually slight to moderate elevation of serum hCG
- About 85% of cases are in stage I at diagnosis

PSTT at NETDC

(Gynecol Oncol 82:415-419, 2001)

- 13 patients, average age lower 30’s
- Most antecedent pregnancies normal or abortion; hydatiform mole rare
- Average time from antecedent pregnancy to diagnosis ~16m (2w - 5y)
- Serum hCG slightly elevated (< 500 mIU/ml)
- Treatment usually by hysterectomy; 4 had pelvic metastases at diagnosis
- 43% had recurrences; all had received chemotherapy
Placental Site Trophoblastic Tumor – Gross Appearance

A tumor mass is almost always present

Ill defined edge, not sharply circumscribed
**PSTT Immunohistochemistry**

- **Positive**
  - Cytokeratin cocktail
  - LMW cytokeratin (CK18)
  - Inhibin
  - hPL (97% +, 56% strong +)
  - CD146 (MelCAM), HLA-G

- **Negative or weak**
  - hCG (almost always scattered + cells)
  - PLAP, p63
Differential Diagnosis

- **Squamous cell carcinoma**: Different appearance, different immunophenotype
- **Choriocarcinoma**: Different cell population, less proliferation, different HCG profile, different immunophenotype
- **ETT**: Related, but different cytology, different low power appearance, different immunophenotype

Differential Diagnosis

- **Exaggerated placental site reaction**
  - A benign expansion of the normal population of implantation site intermediate trophoblasts in the placental bed
  - High cellularity can mimic PSTT
  - No mass in EPS Reaction
  - Can be very cellular, but lacks cohesive masses of cells
  - Does not permeate and splay the myometrium
  - Minimal mitotic activity and Ki-67 immunoreactivity
  - Lack of a genetic association with PSTT – majority have a paternal Y chromosome
**PSTT Clues to the Diagnosis**

- Low levels of HCG
- Tumor mass present – check the ultrasound or other imaging
- Sheets of implantation site intermediate trophoblasts
- Invasion of myometrium by nests and sheets of intermediate trophoblasts
- Mitotic figures and increased MIB1 (~10%)
- HPL + many cells, HCG + few cells
- No chorionic villi

**PSTT Behavior**

- ~ 15% clinically malignant
- Primary treatment is surgical
- Response to chemotherapy variable
  - EMA/CO 71% respond, 38% have a complete response
- Unfavorable prognostic factors
  - Stage > I (extrauterine spread)
  - Mitotic index > 5 mf/10 hpf
  - Large tumor size, clear cells
  - Interval from antecedent pregnancy to diagnosis (> 2 y less favorable)

**Case 2 Key Points**

- PSTT is derived from implantation site trophoblastic cells
- Cohesive groups of IT form a mass and invade the myometrium, splaying the muscle bundles
- Intravascular tumor common
- No villi
- At least some mitotic activity
- hPL, Ki-67 are the most useful immunostains

**Diagram**

- Syncytiotrophoblast
- Choriocarcinoma
- Cytotrophoblast → Villous IT in trophoblastic columns
- Implantation site IT
  - p63+, HPL +++
- Chorionic-type IT
  - p63+++ , HPL +/-
- Exaggerated placental site
- Placental site trophoblastic tumor
- Placental site nodule
- Epithelioid trophoblastic tumor
Table 4. Immunohistochemical features of trophoblastic lesions of the uterus.

<table>
<thead>
<tr>
<th></th>
<th>CK18</th>
<th>HLAG</th>
<th>Inhibin</th>
<th>HCG</th>
<th>HPL</th>
<th>p63</th>
<th>PLAP</th>
<th>MIB1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSN</td>
<td>⭐</td>
<td>⭐</td>
<td>+/-</td>
<td>+/-</td>
<td>⭐</td>
<td>⭐</td>
<td>⭐</td>
<td>5%</td>
</tr>
<tr>
<td>ETT</td>
<td>⭐</td>
<td>⭐</td>
<td>+/-</td>
<td>+/-</td>
<td>⭐</td>
<td>+/-</td>
<td>⭐</td>
<td>20%</td>
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<tr>
<td>EPS</td>
<td>⭐</td>
<td>⭐</td>
<td>+/-</td>
<td>⭐</td>
<td>-</td>
<td>+/-</td>
<td>⭐</td>
<td>Near 0%</td>
</tr>
<tr>
<td>PSTT</td>
<td>⭐</td>
<td>⭐</td>
<td>+/-</td>
<td>⭐</td>
<td>-</td>
<td>+/-</td>
<td>⭐</td>
<td>10%</td>
</tr>
<tr>
<td>Chorio Ca</td>
<td>⭐</td>
<td>⭐</td>
<td>⭐</td>
<td>+/-</td>
<td>+/-</td>
<td>&gt;</td>
<td>&gt;</td>
<td>50%</td>
</tr>
</tbody>
</table>

Immunohistochemistry of Trophoblastic Proliferations

Case 3

- Sessile vulvar lesion from a 66 year old female
  - Is it verrucous carcinoma?
  - Is it invasive?
  - If it is invasive how deeply invasive is it?
  - Is further excision necessary?
  - Is lymph node sampling necessary?
Is it Verrucous Carcinoma?

What do you think?

What is Verrucous Carcinoma of the Vulva?

- A very well differentiated variant of squamous cell carcinoma
- Occurs in elderly women
- Locally aggressive with eventual formation of a large warty tumor
- Lymph node metastases are rare
- Treatment is by wide local excision; vulvectomy may be necessary; does not require lymph node dissection
- 5-year survival - unknown
Diagnostic Criteria for Verrucous Carcinoma

- Marked acanthosis, verrucous surface contour
- Large rounded bulbous rete ridges push into the underlying tissue
- Minimal pleomorphism
- Coarse chromatin, variable nucleoli
- Infrequent mitotic figures
- No koilocytosis
S = hyperplasia, sharp
B = hyperplasia, blunt
C = verrucous carcinoma

Not verrucous carcinoma!

Our case: Not verrucous carcinoma; well differentiated squamous cell carcinoma
Vulvar acanthosis with altered differentiation

“VAAD”


Despite the name “verrucous” carcinoma...
No good evidence of an association with HPV

Verrucous Carcinoma and HPV

- 27 cases initially classified as VC reviewed; after review 13 accepted
- 11 cases initially classified as VC of vulva/perineum
  - 5 accepted as VC – none had HPV
  - 4 reclassified as SCC – none had HPV
  - 2 reclassified as giant condylomas, 1 had HPV 6, 1 had HPV 11

Conclusions
- HPV unlikely to be causally related to VC
- Positive HPV test favors giant condyloma over VC

Mod Pathol 2012; 25:1354-1363
Differences Between Verrucous Carcinoma and Condyloma

- Verrucous carcinoma is usually large, condyloma is smaller
- Verrucous carcinoma shows pushing invasion into the underlying dermis, condyloma grows off the surface
- Usually more abnormal cytology in verrucous carcinoma
- No koilocytosis in verrucous carcinoma, characteristic of condyloma
- No HPV in verrucous carcinoma, HPV present in condyloma
Classification of Vulvar Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Type</th>
<th>HPV Associated</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratinizing SCC</td>
<td>Some, most HPV -</td>
<td>Most common</td>
</tr>
<tr>
<td>Basaloid SCC</td>
<td>Yes</td>
<td>Occasional</td>
</tr>
<tr>
<td>Warty or condylomatous SCC</td>
<td>Yes</td>
<td>Occasional</td>
</tr>
<tr>
<td>Verrucous SCC</td>
<td>No</td>
<td>Rare</td>
</tr>
</tbody>
</table>

VIN adjacent to thin vulvar SCC

<table>
<thead>
<tr>
<th>Type Ca</th>
<th>Classic VIN</th>
<th>Differentiated VIN</th>
<th>No VIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratinizing SCC-38</td>
<td>9</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Warty SCC-6</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Basaloid SCC-4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Age Pt.                     | 62          | 78                 | 75     |

More Questions?

- Is it invasive?
- What is the depth?
- Does the patient need more treatment?
Histologic Features Suggestive of Invasion

- Rete ridges are irregular in size, shape and distribution
- Rete ridges extend deeply into the dermis
- Complex budding or branching of the rete ridges
- Paradoxical keratinization deep in the rete ridges or in dermal nests
- Prong like buds of epithelium grow into the dermis
- Irregular, often angulated nests of atypical squamous cells in the dermis
- Too many (crowded) nests of cells, often irregularly distributed
- Single or small clusters of atypical cells in the dermis
- Cells in the dermis have vesicular nuclei, prominent nucleoli, eosinophilic cytoplasm – different from adjacent VIN
- Desmoplastic or edematous stroma around dermal nests
- Growth adjacent to or around thick walled blood vessels or nerves

Squamous Cell Carcinoma of the Vulva

Measurements of Invasion

Depth = From the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion

Superficially Invasive Squamous Cell Carcinoma of the Vulva (Stage IA)

- The term “microinvasive carcinoma” is not used in the vulva
- The category of stage IA is an attempt to define a group with a very low risk of lymph node metastasis
- Definition: ≤ 1 mm in depth and ≤ 2 cm diameter
- Lymphovascular invasion, growth pattern do not exclude tumors from this category
Staging of Vulvar Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Location</th>
<th>Size</th>
<th>Depth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage Ia</td>
<td>Confined to vulva</td>
<td>2 cm or less</td>
<td>1 mm or less</td>
</tr>
<tr>
<td>Stage Ib</td>
<td>Confined to vulva</td>
<td>&gt; 2 cm</td>
<td>Any tumor &gt; 1 mm, regardless of diameter</td>
</tr>
</tbody>
</table>

Depth of Invasion = 6.5 mm
Width = 13 mm
Length = 21 mm
1 mm from the deep margin
Our Case

- Stage Ib
- More treatment required
- Lymph node dissection or, possibly, sentinel lymph node biopsy
- ? Re-excision to get a wider margin

Squamous Cell Carcinoma of the Vulva

**Therapy and Results**

- Radical vulvectomy in the past
- Treatment now more conservative - wide excision, hemivulvectomy for lateralized tumors
- About 30% of patients have LN metastases, lymphadenectomy generally performed; role for SLN Bx
- Survival 75% overall, 90-100% stage I

Case 3 Key Points

- Must meet specific criteria to be diagnosed as verrucous carcinoma: very well differentiated, pushing invasion, rounded rete ridges
- Prongs, irregular nests, infiltrative patterns, higher grade exclude verrucous carcinoma regardless of the surface contour
- Depth of invasion and size are critical
- Any tumor that exceeds 1 mm in depth is likely to be treated with lymph node dissection
- Only stage Ia is treated conservatively