The Role of Chromosomal Translocations in the Molecular Pathology of Sarcomas

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Overview of translocations in bone and soft tissue sarcomas

Importance of chromosomal translocations – consistency and specificity
Role in biology, diagnosis, and therapy

Translocations in alveolar rhabdomyosarcoma (RMS)
Common 2;13 translocation – generating PAX3-FKHR fusion
Single breakpoints – single fusion size
Variant 1;13 translocation – generating PAX7-FKHR fusion

Translocations in Ewing’s sarcoma
Common 11;22 translocation – generating EWS-FLI1 fusion
Breakpoint variability – generating variable sized fusions
Protein products – ETS transcription factor (FLI1) and RNA binding protein (EWS)
Variant translocations involving other ETS proteins with EWS or related FUS protein
Additional translocations in Ewing sarcoma-like tumors

EWS protein and related RNA binding proteins
Fusions involving EWS and transcription factor-encoding genes in other sarcomas
TET family of RNA binding proteins – multiple regions of homology
Additional fusions involving genes related to EWS in sarcomas
Exception – TCF12-CHN fusion in myxoid chondrosarcoma
Fusion protein function and specificity – relationship of fusion protein to target cell
Expanding story of EWS-ATF1 and related fusions – same fusion in different tumors
Clear cell sarcoma and angiomatoid fibrous histiocytoma
Other gene fusions associated with divergent tumor types

Methodologies for detection of chromosomal translocations
Considerations for use of established technologies (Southern, PCR, FISH)
Immunohistochemistry – strategy to detect fusion protein (example: DSRCT)
Available antibodies to detect fusion proteins - application to various tumors
Microarray analysis of fusion-positive sarcomas
Identification of downstream target genes and other cellular features
Example - Expression profiling of fusion positive and negative RMS
Use of microarray data to identify IHC markers for fusion-positive ARMS

Clinical utility of detection of chromosomal translocations
Differential diagnosis
Prognosis
Major Points:

- These fusion genes are useful reagents in the differential diagnosis of bone and soft tissue sarcomas.

- The detection of these fusion products is complex because of multiple breakpoints and variant partners, and thus a negative result must be interpreted cautiously.

- The fusion of EWS or related genes to one of multiple transcription factor-encoding genes in many of these sarcomas complicates the use of EWS reagents in the differential diagnosis of these sarcomas. These fusions also raise an essential issue of the relationship of these aberrant fusion proteins to the specific tumor phenotype and target cell.

- Several examples have been found in which a fusion gene is associated with two or more completely unrelated tumor types, and thus these gene fusions are not absolutely specific for a single lineage.

- For several translocation-associated sarcomas, antibodies to the C-terminal fusion partner have been shown to be useful markers of the presence of the fusion protein.

- Microarray-based strategies to elucidate genes associated with these fusion-positive tumors and downstream targets of these fusion proteins are generating useful markers for differential diagnosis and prognosis of these tumors.

- A small number of studies have been performed to address the clinical significance of these fusion genes as minimal disease markers. In studies of Ewing's sarcoma, potential utility has been found in the predictive value of minimal disseminated disease in bone marrow but not in the predictive value of minimal disease in peripheral blood stem cell collections.

References:

Barr FG: Gene fusions involving PAX and FOX family members in alveolar rhabdomyosarcoma, Oncogene 2001, 20:5736-5746
Davicioni E, Finckenstein FG, Shahbazian V, Buckley JD, Triche TJ, Anderson MJ: Identification of a PAX-FKHR gene expression signature that defines molecular classes and determines the prognosis of alveolar rhabdomyosarcomas, Cancer Res 2006, 66:6936-6946
Molecular Insights Into the Morphological Heterogeneity of Ovarian Carcinomas – Does Histological Type Matter?

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Major Histological Types of Ovarian Carcinomas

- Serous (>50%)
- Mucinous (<10%)
- Endometrioid (10-20%)
- Clear cell (<10%)

Treatment Guidelines for Ovarian Carcinoma

- Standard therapy is surgical debulking followed by chemotherapy (carboplatin + paclitaxel)
- In contrast to endometrial carcinoma, Rx is NOT histotype dependent
- Treatment of recurrent/drug-resistant disease remains a major challenge

On the horizon...

- “Personalized” medicine using drugs that target specific molecular defects in tumor cells
- Ovarian carcinomas have characteristic genetic alterations, but the frequency with which a given gene is mutated varies substantially with:
  - Histologic type
  - Tumor grade
- What role will pathologists play in determining the specific molecular defects in ovarian cancer cells?

Major Types of Ovarian Carcinoma: Characteristic Genetic Alterations (Selected)

- Serous (p53)
- Mucinous (K-RAS)
- Endometrioid (CTNNB1, PTEN, K-RAS, p53)
- Clear cell (?)

What are we learning about ovarian cancer?
Gene Expression Profiling of Ovarian Carcinomas

- Affymetrix oligonucleotide microarrays
- U133A array: approximately 22,000 probe sets (14,500 genes)
- Tissue samples: 4 normal ovaries, 99 primary ovarian carcinomas
  - 41 serous
  - 37 endometrioid
  - 13 mucinous
  - 8 clear cell

Principal Component Analysis

- Identifies a set of statistically independent projections, or components, of the expression data
- The first PC captures the greatest fraction of the overall variance in tumor gene expression compared to any other projection
- The second PC captures the greatest fraction of variance subject to being independent of the first PC
- Using any 2 PCs a pair of coordinates can be determined for each sample: tumors falling close together have more similar gene expression than tumors further apart

Ovarian Endometrioid Adenocarcinoma (OEA) Tumor Progression Model

- Ovarian carcinomas arise through a multi-step process in which clonal selection acts on cells with somatic mutations and altered gene expression to allow outgrowth of progeny with increasingly aggressive growth properties
- The genes mutated in cancer frequently encode proteins that function in conserved signaling pathways
Wnt/β-catenin/Tcf Pathway Defects
Ovarian Endometrioid Adenocarcinomas (OEAs)

- 72 primary OEAs collected (CHTN, UM, Kumamoto U.)
- Majority (60) from CHTN-GOG bank
- All OEAs evaluated for mutations in CTNNB1 (β-caten) exon 3

Results
- Missense mutations found in 18 OEAs (25%)
- OEAs with CTNNB1 mutations show nuclear accumulation of β-caten by immunohistochemical staining

TOV-112D (β-caten) OSE

Wnt pathway intact

Grade 1 Grade 2 or 3
Wnt pathway defect 13 6 19
Wnt pathway intact 5 42 53
18 54 72

p = 1.2 X 10^-4
(Fisher’s exact)

Stage 1 or 2 Stage 3 or 4
Wnt pathway defect 19 0 19
Wnt pathway intact 25 28 53
44 28 72

p = 1.5 X 10^-4

Mutational analysis of PTEN (n=72) and corresponding mutations of CTNNB1 and K-RAS in OEAs

Modified from : DA Altomare and JR Testa (Oncogene, 2005)
Correlation of PTEN and/or PIK3CA mutation with Wnt/β-catenin/Tcf pathway defects in OEAs

<table>
<thead>
<tr>
<th>PTEN or PIK3CA mutation</th>
<th>Wnt/β-catenin/Tcf pathway DEFECTIVE</th>
<th>Wnt/β-catenin/Tcf pathway INTACT</th>
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<tbody>
<tr>
<td>Wild type PTEN and PIK3CA</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>50</td>
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<td></td>
<td>19</td>
<td>53</td>
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p=.0024 two-sided Fisher’s exact test

p53 is a Sensor of Various Stresses

The Majority Of TP53 Mutations Are Missense Mutations

Missense Mutations are Clustered in the DNA-binding Domain

TP53 Mutations in OEAs: Exons 5-8

- 32 mutations identified (n=72)
  - 81% missense
  - Remainder nonsense or frameshift
- 5 additional tumors showed intense and diffuse nuclear accumulation of p53 protein
  - Presumptive missense mutations outside of region sequenced
p53 Mutations in OEAs: Association with High Tumor Grade and Stage

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2 or 3</th>
<th>p = .0009</th>
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</thead>
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<td>Mutant p53</td>
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<td>34</td>
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<tr>
<td>Wild type p53</td>
<td>18</td>
<td>54</td>
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</table>

<table>
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<tr>
<th>Stage 1 or 2</th>
<th>Stage 3 or 4</th>
<th>p = 3 × 10⁻⁴</th>
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<tr>
<td>Mutant p53</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>Wild type p53</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>28</td>
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</table>

First two principal components for 99 tumors, all probe-sets, log-transformed data

Conclusions

- The findings support subdivision of ovarian endometrioid adenocarcinomas into two subgroups
  - Low grade OEAs are characterized by frequent Wnt/β-Cat/Tcf and PI3K/Pten pathway defects, infrequent p53 mutations, favorable outcome
  - High grade OEAs are characterized by frequent p53 mutations, infrequent Wnt/β-Cat/Tcf and PI3K/Pten pathway defects, poorer outcome

- High grade OEAs have a similar gene expression profile to ovarian serous carcinomas (both have frequent p53 mutations)
Developing Models of Ovarian Cancer in Mice

OEA-like Tumors Arise in the Setting of APC and PTEN Inactivation in the Ovarian Surface Epithelium

APC-/PTEN- OEA-like Murine Tumors: Inhibition by Rapamycin

Bioluminescence Imaging Strategy for Mouse Model of Ovarian Cancer

- Obtain ROSA26 (lox-stop-lox luciferase) mice (Kaelin and colleagues)
- Generate APCloxP/loxP/PTENloxP/loxP/ROSA26i-L-S-LucB mice
- Inject ovarian bursa with AdCre, monitor tumor progression and response to drugs in vivo
Bioluminescence Imaging

What can pathologists do to help...?

- Current morphological classification provides useful information - classification schemes continuing to evolve
- Within a given histotype, specific molecular alterations are associated with tumor grade
- Immunostaining for signaling pathway components, properly interpreted, can substitute for selected mutational analyses
  - Nuclear accumulation of β-catenin (vs. membranous)
  - Loss of Pten (increased pAkt, pS6)
  - Nuclear accumulation of p53
The molecular genetics of endometrial cancer

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Department of Pathology and Laboratory Medicine
Weill Medical College of Cornell University

Introduction
• Classification of endometrial carcinoma
• Morphologic shortcomings of light microscopy
• Molecular genetics of endometrial carcinoma
• Application of genetic studies to diagnostics
• Remaining important diagnostic issues
• Mouse model to further explore diagnostic and treatment possibilities

Type I vs. II (Bokhman 1983)

Type I
• Unopposed estrogen (hyperplasia)
• Pre- and perimenopausal (mean age 59 years)
• Low to moderate grade, minimal myometrial invasion
• Good prognosis

Type II
• Lack of unopposed estrogen (atrophy)
• Postmenopausal (mean age in late 60s)
• High grade, often with metastases
• Poor prognosis (cause a disproportionate number of deaths)

Endometrial Tumorigenesis

Estrogen

Ni epithelium

Atrophy

EIC

Serous Ca

Endometrial Hyperplasia

Endometrial Tumorigenesis

Uterine Endometrioid Carcinoma (UEC)
**Molecular Genetics**

- **PTEN mutational analysis**
  Exon specific PCR with direct sequencing
- **Microsatellite Instability**
  7 anonymous loci
- **KRAS mutational analysis**
  Oligonucleotide hybridization
- **TP53 mutational analysis**
  Exon specific PCR with direct sequencing

**Comparison of molecular genetic alterations between UEC and USC**

<table>
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<tr>
<th></th>
<th>UEC</th>
<th>USC</th>
<th>p-value*</th>
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<tr>
<td><strong>PTEN</strong></td>
<td>62%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>28%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>K-ras</strong></td>
<td>26%</td>
<td>2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>p53</strong></td>
<td>17%</td>
<td>93%</td>
<td>&lt;0.001</td>
</tr>
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</table>

* 2-sided Fisher’s exact test

**Clinical Utility of Molecular Markers**

- **PTEN** antibodies
- **MI** May identify some HNPCC families
- **K-ras** Studies on prognosis are conflicting
- **P53** Associated with a poor prognosis, immunostaining is used diagnostically

**Molecular genetic alterations**

- Supports the notion of two major types of endometrial carcinoma
- Provides some insight into the pathogenesis
  - Early and late changes?
  - Relationship to one another?
  - Relationship to hormonal influence?
Endometrial Intraepithelial Carcinoma

Endometrial Tumorigenesis

Fundamental Questions

- Are mutations in PTEN sufficient for the development of CAH or UEC?
- What is the relationship of PTEN mutations and MI in the development of CAH and UEC?
**Mouse model of UEC**

**Pten Knockout Mouse**
- **PTEN** most commonly mutated gene in UEC
- Deletion of exon 5 (contains phosphatase domain)
- Genetic background: C57B6/129sJ
- Homozygous deletion: Embryonic lethal
- Heterozygous deletion: Variety of abnormalities including endometrial neoplasia

**Morphologic variants of mouse carcinomas**

- **Mucinous**
- **Squamous**

**Immunohistochemical Analysis of Endometrial Lesions**

**PTEN**

**P-AKT**

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>% of mice with lesions</th>
<th>No. (%) of mice with invasive carcinomas</th>
<th>No. of lesions per mouse (mean±SD)</th>
<th>LOH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>71.4%</td>
<td>0</td>
<td>1.14±0.34</td>
<td>NA</td>
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<tr>
<td>24</td>
<td>88.9%</td>
<td>0</td>
<td>9.78±3.94</td>
<td>30</td>
</tr>
<tr>
<td>32</td>
<td>100%</td>
<td>0</td>
<td>18.36±8.37</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>100%</td>
<td>2 (25%)</td>
<td>28.75±15.34</td>
<td>60</td>
</tr>
</tbody>
</table>

**Histologic analysis of Pten+/+ / Mlh1/-/- Mice**

16 weeks

- **Multifocal CAH**

14 weeks

- **Invasive carcinoma**
ENDOMETRIAL LESIONS IN 14-18 WEEK MICE

<table>
<thead>
<tr>
<th>Pten genotype</th>
<th>Mlh1 genotype</th>
<th>No. (%) of mice with lesions</th>
<th>No. (%) of mice with invasive carcinoma</th>
<th>No. of lesions per mouse (mean ± SD)</th>
<th>Size of lesion (mm²)</th>
<th>LOH (%)</th>
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</thead>
<tbody>
<tr>
<td>+/+</td>
<td>+/+</td>
<td>7</td>
<td>5 (71.4)</td>
<td>0.64 ± 0.09</td>
<td>0.09</td>
<td>NA</td>
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<tr>
<td>+/-</td>
<td>+/-</td>
<td>7</td>
<td>5 (71.4)</td>
<td>0.64 ± 0.09</td>
<td>0.09</td>
<td>NA</td>
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<tr>
<td>+/-</td>
<td>-/-</td>
<td>6</td>
<td>3 (50)</td>
<td>1.07 ± 0.20</td>
<td>0.10</td>
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<tr>
<td>+/-</td>
<td>-/-</td>
<td>5</td>
<td>5 (100)</td>
<td>1.34 ± 0.19</td>
<td>2.39</td>
<td>60</td>
</tr>
<tr>
<td>+/-</td>
<td>-/-</td>
<td>5</td>
<td>5 (100)</td>
<td>1.34 ± 0.19</td>
<td>2.39</td>
<td>60</td>
</tr>
</tbody>
</table>

**MI and Pten LOH**

**LOH of Pten and additional loci on chromosome 19**

**Deletion in Exon 5 in a Pten+/-/Mlh1-/- CAH**

**Conclusions**

- Mouse model mimics the human disease.
- Pten loss leads to hyperplasia but is not sufficient for invasion.
- DNA mismatch repair deficiency accelerates the phenotype, maybe in part due to increased mutation in the wild type allele of Pten (human disease).
- Objective markers of invasion would have clinical utility (mouse model).
Objective Markers of Invasion

- Use the mouse model to identify markers of invasion.
- Gene expression profiles of CAH vs carcinoma using Affymetrix Mouse Genome 430A
- Arrays were analyzed for differentially expressed genes between 8 CAH and 4 invasive carcinomas and specifically analyzed for those showing significant increased expression in carcinoma.
- Interesting candidates were confirmed by RT-PCR

RT-PCR of Ovgp1

OGP Immunohistochemistry on human tissue

PIK3CA Mutations

- PIK3CA mutations recently identified in endometrioid carcinoma
- PIK3CA is the catalytic subunit of PI3K an enzyme with activity that directly opposes the action of PTEN
- We recently investigated the status of PIK3CA in 44 cases of UEC and CAH 29 cases of CAH
- Mutations were found in 2(7%) of CAH and 17(39%) of UEC
- In contrast PTEN mutations were found in 14(48%) of CAH and 25(57%) of UEC
- PIK3CA mutation may be a marker of invasion

Endometrial Tumorigenesis

1. Complex hyperplasia vs Complex atypical hyperplasia
   - Profiling 3% vs 25% risk of carcinoma
2. Complex atypical hyperplasia vs Carcinoma
   - Hormone Rx vs TAH in younger women
3. Complex atypical hyperplasia vs EIC
   - TAH vs TAH with staging
4. UEC vs USC
   - TAH with limited staging vs staging and chemoRx
Relationship of Hormones and Genetics

- UEC has been associated with the use of estrogen
- Association of tamoxifen and endometrial cancer remains controversial
- Recent studies have shown that AKT phosphorylates ER alpha in a ligand independent manner
- What is the relationship between between PTEN and estrogen pathway

Alterations in hormone status

- CD1 Pten het No rx 26 weeks
- CD1 wt ovx/estrogen 26 weeks
- CD1 Pten het ovx 26 weeks
- CD1 Pten het estrogen 26 weeks
- CD1 wt ovx/estrogen 24 weeks

Conclusions

- Loss of Pten can lead to hyperplasia in the absence of estrogen
- Development of endometrial carcinoma is accelerated by estrogen treatment
- ER alpha is not required for Pten related tumor development and lack of ER alpha may be associated with a more aggressive phenotype
- Relevance to hormonal therapy for women with PTEN mutation positive endometrial carcinoma?

Summary

- Molecular genetics support the dualistic categorization of endometrial carcinoma
- PTEN plays a central role in the endometrial tumorigenesis and the absence of mismatch repair accelerates the process
- Objective markers of invasion (OGP and PIK3CA) may have an impact on management of women with CAH
- The relationship of PTEN mutations and hormones may change the approach to hormonal therapy

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Molecular Characterization of Neoplasms of the Pancreas

March 2, 2008

Ralph H. Hruban, M.D.
Professor of Pathology and Oncology
The Sol Goldman Pancreatic Cancer Research Center
The Johns Hopkins Medical Institutions

Disclosure

• Dr. Hruban has the potential to receive milestone payments and royalties from Anza Therapeutics as a result of the mesothelin invention

“If you've seen one Redwood, you've seen them all”

Ronald Reagan
(3/12/1966)
As paraphrased by Jerry Brown

Examples

1. Medullary carcinoma and microsatellite instability
2. Undifferentiated carcinomas and E-cadherin loss
3. Beta-catenin gene mutations in solid-pseudopapillary neoplasms
4. KRAS2 gene mutations in undifferentiated carcinomas with osteoclast-like giant cells
5. Chromosome 11p loss in pancreatoblastoma
6. PIK3CA and STK11 gene mutations in Intraductal Papillary Mucinous Neoplasms
Medullary Carcinoma


Poorly differentiated, Syncytial growth pattern, Pushing boarders

Microsatellite Instability (MSI)

1. MSI status has prognostic value - median survival for MSI cases of 62 months, versus 10 months (hazard ratio = 5.6; P = 0.007)

2. MSI status may have therapeutic implications - Fluorouracil (5FU)-based adjuvant chemotherapy benefits patients with stage II or stage III colon cancer with microsatellite-stable tumors but not those with tumors exhibiting high-frequency microsatellite instability

Nakata et al., Clin Cancer Res. 2002; 8: 2536-40.

3. Has implications for other family members
   - The medullary phenotype is highly associated with a family history of cancer in first-degree relatives (P < 0.001).


Microsatellite Stable
Microsatellite Unstable

hMLH1

Medullary Carcinoma

- Microsatellite Instability
- Medullary

Good Prognosis, Not 5-FU, Family Hx

Undifferentiated Carcinoma

- A malignant epithelial neoplasm with a significant component showing no glandular structures or other features to indicate a definite direction of differentiation
- Mean survival of 5.2 months after diagnosis

E-cadherin Expression

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Proportion of cancers with E-cadherin loss</th>
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<tbody>
<tr>
<td>Noncohesive carcinomas</td>
<td></td>
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<tr>
<td>Undifferentiated carcinomas</td>
<td>14/15 (93%)</td>
</tr>
<tr>
<td>- Anaplastic</td>
<td>6/6 (100%)</td>
</tr>
<tr>
<td>- UCOCGC</td>
<td>8/14 (58%)</td>
</tr>
<tr>
<td>Overall</td>
<td>22/28 (79%)</td>
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<tr>
<td>Cohesive carcinomas</td>
<td></td>
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<tr>
<td>Ductal adenocarcinoma</td>
<td>2/7 (29%)</td>
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<tr>
<td>- Moderate</td>
<td>01/02 (50%)</td>
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<tr>
<td>- Poor</td>
<td>01/01 (100%)</td>
</tr>
<tr>
<td>Overall</td>
<td>02/03 (67%)</td>
</tr>
</tbody>
</table>

| Overall                     | 14/15 (93%)                               |
| Noncohesive carcinomas      | 6/6 (100%)                                |
| Overall                     | 22/28 (79%)                               |

p<0.001

Winter and Iacobuzio, Clinical Cancer Research
Survival in Relation to E-cadherin Status in Resection Specimens

Undifferentiated Carcinomas

Loss of E-cadherin
Non-cohesive
Poor Prognosis

Undifferentiated Carcinoma with Osteoclast-like Giant Cells

- Malignant epithelial neoplasm composed of large benign appearing multinucleated giant cells admixed with atypical neoplasic mononuclear cells
- Highly aggressive neoplasms with a mean survival of <12 months

Macrophage
Cytokeratin

p53

KRAS2 Gene Mutations in the Components of an UCOCGC

<table>
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<tr>
<th></th>
<th>WT</th>
<th>Cys</th>
<th>Ser</th>
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Case 1

Osteoclast-like Giant Cell Tumors are undifferentiated carcinomas that arise directly from intraductal epithelial precursors – “Undifferentiated Carcinomas with Osteoclast-like Giant Cells”

Biopsy of an ampullary lesion was initially interpreted as reactive, but KRAS2 gene sequencing revealed a codon 12 mutation. A resection was performed revealing an UCOCGC of the pancreas. Immunolabeling for p16 showed loss of expression in the mononuclear cells and retained expression in the giant cells.

Undifferentiated Carcinoma with Osteoclast-Like Giant Cells

KRAS2 gene mutation → Epithelial with Reactive Giant Cells

Poor Prognosis

Solid-Pseudopapillary Neoplasm
Solid-Pseudopapillary Neoplasms

- Clinically, the vast majority occur in young women (20’s), with a female to male ratio of 10-20:1
- Grossly well demarcated masses. On cross section, they are cystic and solid with areas of hemorrhage and necrosis

Solid-Pseudopapillary Neoplasms

- >90% have β-catenin mutations
- KRAS2 wild-type
- 15% TP53 mutations
- 0% DPC4, p16

Abraham et al., American Journal of Pathology. 2002;160:1361-1369
Solid-Pseudopapillary Neoplasm

- Has therapeutic implications-
  Surgical resection, even the surgical resection of metastases is the treatment of choice

Pancreatoblastoma

Solid-Pseudopapillary Neoplasm

Loss of β-catenin → Non-cohesive

Great Prognosis
Pancreatoblastoma

- Malignant neoplasms showing multiple lines of differentiation including acinar differentiation and squamoid nests
- Endocrine and ductal differentiation may also be seen
- Occur primarily in children (1-15 years)- Previously called infantile pancreatic carcinoma
Genetic Alteration in Pancreatoblastomas

- Associated with Beckwith-Wiedemann Syndrome
- 86% LOH on 11p*

Similar to other infantile embryonal tumors such as hepatoblastomas
- Hepatoblastoma
- Nephroblastoma
- Pleuropulmonary blastoma

Pancreatoblastoma

LOH on 11p

Squamoid nests and acinar cells

Unified with other Primitive Neoplasms

Am J Pathol 159:1619
Unique Genetic Changes

- **PIK3CA**: Four mis-sense PIK3CA gene mutations in 36 IPMNs (11%)
- **STK11/LKB1**: Sequence analysis of a pancreatic cancer from a patient with PJS revealed loss of the wild-type allele of the STK11/LKB1 gene
- **STK11/LKB1**: Inactivation of STK11/LKB1, by homozygous deletions or somatic sequence mutations coupled with loss of heterozygosity, was also demonstrated in 4-6% of 127 sporadic pancreatic and biliary adenocarcinomas.


Screening implications

ENDOSCOPIC ULTRASONOGRAPHY (EUS)

- High frequency US + endoscopy
- Screened 109 patients with PJS or a strong family history of pancreatic cancer

Canto et al, Clin Gastroenterol Hepatol. 2006; 4:766-81

Peutz-Jeghers Syndrome

47 y.o. W/F with 1.5 cm lesion

CT
EUS
IPMN with Carcinoma-In-Situ

Almost half of the reduction in breast cancer mortality over the last 25 years has come from mammography


MORPHOLOGY

Molecular

PROGNOSIS

TREATMENT

Selected References