GOBLET CELL CARCINOID

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Dr. Hanlin Wang declares he has no conflict(s) of interest to disclose.
2010 WHO Classification of Neuroendocrine Neoplasms of the Appendix

- Neuroendocrine tumor (NET)
  - NET G1 (carcinoid)
  - NET G2
- Neuroendocrine carcinoma (NEC)
  - Large cell NEC
  - Small cell NEC
- Mixed adenoneuroendocrine carcinoma
- EC cell, serotonin-producing NET
- L cell, glucagon-like peptide-producing and PP/PYY-producing NETs
- Goblet cell carcinoid (GCC)
- Tubular carcinoid
Tubular Carcinoid of the Appendix

- Always small (<1 cm)
- Found at the tip or distal half
- Primarily in the submucosa but may involve the muscularis propria, and rarely the subserosa
- Discrete small tubules and/or short solid cords
- Abundant fibrotic stroma
Tubular Carcinoid of the Appendix

- Cuboidal to low columnar cells with no cytologic atypia
- May have inspissated mucin in the lumens
- No mitotic figures
- Never recur or metastasize
- Not confused with metastatic adenocarcinoma
Goblet Cell Carcinoid

• A unique neoplasm with glandular and endocrine differentiation
• Almost exclusively seen in the appendix
  • Rarely seen in the stomach, small bowel and colon
• Synonyms
  • Adenocarcinoid
  • Mucinous carcinoid
  • Microglandular carcinoma
  • Crypt cell carcinoma
  • Amphicrine neoplasm
  • Mucin-producing neuroendocrine tumor/carcinoma
Goblet Cell Carcinoid

- Found in 0.3-0.9% of appendectomies
- Mean age: 59 years (18-89 years)
  - ~20 years older than that for classic carcinoid of the appendix
- Affecting males and females equally
- Initial presentation
  - Acute appendicitis in most cases
  - Lower abdominal palpable mass
Goblet Cell Carcinoid

- Rarely forms a mass lesion
- Usually infiltrates the appendiceal wall circumferentially in a concentric manner
- Lacks desmoplastic reaction
Typically spares the mucosa, but may show focal connection with the base of crypts.

No adenomatous change in the mucosa.
Small tight clusters, nests or cords of tumor cells, typically without overt luminal formation.
Small extracellular mucin pools
Minimal nuclear atypia
<table>
<thead>
<tr>
<th>Marker</th>
<th>GCC</th>
<th>Classic Carcinoid</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CK7</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>CK20</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CDX2</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>CD56</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Beta-catenin (nuclear)</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>p53</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Ki67</td>
<td>intermediate</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>MUC1</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>MUC2</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>MSI</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Chromogranin
GCC with A Component of Adenocarcinoma

- Mixed adenoneuroendocrine carcinoma
  - Mixed carcinoid-adenocarcinoma
  - Mixed goblet cell carcinoid-adenocarcinoma
- Adenocarcinoma ex goblet cell carcinoid
  - Signet-ring cell type
  - Poorly differentiated carcinoma type
Goblet Cell Carcinoids and Related Tumors of the Vermiform Appendix


ALLEN P. BURKE, M.D. (MAJ, USAF, MC), LESLIE H. SOBIN, M.D., BIRGITTE H. FEDERSPIEL, M.D., KRIS M. SHEKITKA, M.D. (LTCol, USAF, MC), AND ELSON B. HELWIG, M.D.

Goblet cell carcinoid
- N=25
- Negative appendectomy or right hemicolecotomy margins
- Average follow-up: 19 months
- No metastasis or death

Mixed carcinoid-adenocarcinoma*
- N=10
- Average follow-up: 16 months
- 8 died of metastatic carcinoma
- 1 alive with disease
- 1 alive without disease following radiation therapy

*Carcinomatous growth patterns included fused or cribriform glands, single file structures, infiltrating signet-ring cells or sheets of solid cells; accounting for >50% of the tumor volume
<table>
<thead>
<tr>
<th>Pathologic Classification of Goblet Cell Carcinoid Tumors</th>
<th>Morphologic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical GCC (group A)</td>
<td>Well-defined goblet cells arranged in clusters or cohesive linear pattern</td>
</tr>
<tr>
<td></td>
<td>Minimal cytologic atypia</td>
</tr>
<tr>
<td></td>
<td>Minimal to no desmoplasia</td>
</tr>
<tr>
<td></td>
<td>Minimal architectural distortion of the appendiceal wall</td>
</tr>
<tr>
<td></td>
<td>Degenerative change with extracellular mucin is acceptable</td>
</tr>
<tr>
<td>Adenocarcinoma ex GCC, signet ring cell type (group B)</td>
<td>Goblet cells or signet ring cells arranged in irregular large clusters, but lack of confluent sheets of cells</td>
</tr>
<tr>
<td></td>
<td>Discohesive single file or single cell infiltrating pattern</td>
</tr>
<tr>
<td></td>
<td>Significant cytologic atypia</td>
</tr>
<tr>
<td></td>
<td>Desmoplasia and associated destruction of the appendiceal wall</td>
</tr>
<tr>
<td>Adenocarcinoma ex GCC, poorly differentiated carcinoma type (group C)</td>
<td>At least focal evidence of goblet cell morphology</td>
</tr>
<tr>
<td></td>
<td>A component (&gt; 1 low power field or 1 mm²) not otherwise distinguishable from a poorly differentiated adenocarcinoma, which may appear as either (a) gland forming, (b) confluent sheets of signet ring cells, or (c) undifferentiated carcinoma</td>
</tr>
</tbody>
</table>
Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma type

Adenocarcinoma ex GCC
Signet-ring cell type

- Large irregular clusters
- Lack confluent sheets

Adenocarcinoma ex GCC
Signet-ring cell type

- Discohesive single cell and single file infiltration
- Architectural distortion of the appendiceal wall and desmoplastic reaction

Adenocarcinoma ex GCC
Signet-ring cell type

- Marked nuclear atypia with hyperchromatic nuclei

TABLE 9. Mean Survival Time and Survival Status of All Cases of GCC by Subtype

<table>
<thead>
<tr>
<th>FU Months</th>
<th>Mean Survival (mo)</th>
<th>NED (%)</th>
<th>AWD (%)</th>
<th>DOD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All GCCs</td>
<td>49 ± 5 (8-191)</td>
<td>43 ± 7</td>
<td>28/61 (46)</td>
<td>19/61 (31)</td>
</tr>
<tr>
<td>Group A</td>
<td>66 ± 8 (13-191)</td>
<td>119 (1 case)</td>
<td>24/28 (86)</td>
<td>3/28 (11)</td>
</tr>
<tr>
<td>Group B</td>
<td>35 ± 5 (8-95)</td>
<td>43 ± 6</td>
<td>4/26 (15)</td>
<td>15/26 (58)</td>
</tr>
<tr>
<td>Group C</td>
<td>29 ± 5 (16-59)</td>
<td>31 ± 6</td>
<td>0 (0)</td>
<td>1/7 (14)</td>
</tr>
</tbody>
</table>

*Patients dying from disease only.
AWD indicates alive with disease; DOD, died of disease; FU, follow up; GCC, goblet cell carcinoma; NED, no evidence of disease.

TABLE 10. Prognosis of Stage IV GCCs Compared with Stage IV Primary Adenocarcinoma of the Appendix

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. Cases (%)</th>
<th>DOD (%)</th>
<th>3-y DSS (%)</th>
<th>5-y DSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All GCCs</td>
<td>40/63 (63)</td>
<td>14/40 (35)</td>
<td>17/24 (71)</td>
<td>8/19 (42)</td>
</tr>
<tr>
<td>Group A</td>
<td>10/30 (33)</td>
<td>1/10 (10)</td>
<td>7/7 (100)</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Group B</td>
<td>23/26 (88)</td>
<td>7/23 (30)</td>
<td>9/11 (82)</td>
<td>3/8 (38)</td>
</tr>
<tr>
<td>Group C</td>
<td>7/7 (100)</td>
<td>6/7 (86)</td>
<td>1/6 (17)</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>19/28 (68)</td>
<td>11/19 (61)</td>
<td>4/13 (31)</td>
<td>0/11 (0)</td>
</tr>
</tbody>
</table>

DOD indicates died of disease (stage IV only); DSS, disease-specific survival (stage IV only); GCC, goblet cell carcinoma.
Group 1: GCC or GCC with <25% adenocarcinoma
Group 2: GCC with 25-50% adenocarcinoma
Group 3: GCC with >50% adenocarcinoma
Group 4: Adenocarcinoma without GCC component

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<table>
<thead>
<tr>
<th>Group</th>
<th>Stage; N (%)</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>1 (n=23)</td>
<td>20 (87)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>2 (n=27)</td>
<td>18 (67)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>3 (n=24)</td>
<td>7 (29)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>4 (n=68)</td>
<td>13 (19)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

Definition of Adenocarcinoma

• Individual dyshesive cells
• Solid sheets of cells
• Infiltrative cords of cells (not within muscularis propria) or larger cords incompatible with GCC
• Complex glandular architecture (irregular, angulated, cribriform, tufting)
• Clusters of cells simulating GCC but with increased cytologic or architectural atypia beyond typical GCC nests (enlarged or irregular nests/glands, increased cytologic atypia, increased mitotic activity)
• Destructive invasion or desmoplasia

Group 3 (>50%)

Solid sheets of goblet/signet-ring cells

Infiltrating single cells

Group 2 (25-50%)
- An area of poorly differentiated signet-ring cell adenocarcinoma in a GCC

Simplified 2-Tier Histologic Grading System

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytologic atypia <em>a</em></td>
<td>At least 1 focus &gt;1 mm² in size*</td>
<td>0: Absent</td>
</tr>
<tr>
<td></td>
<td>High nuclear-to-cytoplasmic ratio with reduction in or loss of intracytoplasmic mucin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nuclei are enlarged and hyperchromatic with irregular nuclear shape and contours</td>
<td></td>
</tr>
<tr>
<td>Stromal desmoplasia</td>
<td>Dense fibrous connective tissue surrounding tumor cell clusters or individual tumor cells</td>
<td>0: Absent</td>
</tr>
<tr>
<td></td>
<td>Replaces surrounding smooth muscle of the muscularis propria **</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Results in distortion of the normal appendiceal architecture</td>
<td></td>
</tr>
<tr>
<td>Solid growth pattern</td>
<td>At least 1 focus &gt;1 mm² in size ***</td>
<td>0: Absent</td>
</tr>
<tr>
<td></td>
<td>Loss of distinct cell cluster architecture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cells tightly packed together with no or minimal intervening stroma</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>Sum of above points</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low grade: 0-1/3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High grade: 2-3/3</td>
<td></td>
</tr>
</tbody>
</table>

*Four contiguous high power fields (x400) with a 0.55-mm field diameter are used to assess a 1 mm² area. At least one cytologically atypical tumor cell is required to be in each high power field.

**Desmoplasia of the submucosa or subserosal fat or serosal adhesions are insufficient.

***Spatially separate small foci of solid growth pattern, which aggregate to a total of 1 mm², are insufficient.

Cytologic atypia: enlarged hyperchromatic nuclei, irregular nuclear contour, variable loss of cytoplasmic mucin

Peritumoral stromal desmoplasia that replaces the smooth muscle of the appendiceal wall

Recognition of Adenocarcinoma in GCC

Histologic Features
- Complex glandular architecture
- Loss of clustered architecture
  - Infiltrating individual discohesive cells
  - Solid sheets or irregular large clusters of cells
- Significant cytologic atypia
- Desmoplasia

Tumor Volume
- >50% (Burke, 1990)
- >One low power field or 1 mm² for Tang’s group C (2008)
- Partial or near complete loss of GCC clustered architecture for Tang’s group B (2008)
  - >30% (WHO, 2010)
  - >25% and >50% (Taggart, 2015)
- > 1 mm² (Lee, 2015)
Poorly differentiated adenocarcinoma with focal glandular formation
Solid sheets of goblet/signet-ring cells

Irregular large clusters of goblet/signet-ring cells

Desmoplasia
Infiltrating individual goblet/signet-ring cells with cytologic atypia

Solid cords with cytologic atypia and loss of intracytoplasmic mucin

Infiltrating individual goblet/signet-ring cells with cytologic atypia
Cytologic atypia with mitoses

Desmoplasia
Goblet Cell Carcinoid Staging and Management

• Staged as adenocarcinoma of the appendix
• Ki-67 labeling index is not required for grading
• Treatment options are primarily based on tumor stage and the presence or absence of adenocarcinoma
Management of Goblet Cell Carcinoid

• Appendectomy alone
  • Stage I (pT1 or pT2) pure GCC with negative margin
  • Comorbidities that do not allow further surgical intervention
  • Lifelong surveillance for metastasis

• Right hemicolectomy
  • Higher stage (pT3 or pT4) disease
  • Positive appendectomy margin
  • Presence of adenocarcinoma
  • Perforated appendix

• Cytoreductive surgery and intraperitoneal chemotherapy
  • Peritoneal spread

• Systemic chemotherapy
  • Stages III and IV disease
  • Recurrent disease

• Prophylactic oophorectomy, particularly for postmenopausal women
  • Candidates for right hemicolectomy and/or chemotherapy

Shenoy S. World J Gastrointest Surg 2016;8:660-9
Summary

- GCC is a unique clinicopathologic entity that is frequently associated with adenocarcinoma
- Histologic identification and quantification of adenocarcinoma is important in determining prognosis and thus in guiding clinical management
- The entire appendectomy specimen should be histologically examined when a GCC case is encountered; and the margin status should be reported
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