GOBLET CELL CARCINOID
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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 carcinoid
  - 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

Goblet Cell Carcinoid

- Typically spares the mucosa, but may show focal connection with the base of crypts
- Small tight clusters, nests or cords of tumor cells, typically without overt luminal formation

Goblet or signet-ring cell morphology
Small extracellular mucin pools

Minimal nuclear atypia

Immunophenotypical and Molecular Features of GCC in Comparison with Classic Carcinoid and Conventional Adenocarcinoma

<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</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>BRAF</td>
<td>mutation</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>MSI</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

GCC with A Component of Adenocarcinoma

- Mixed adenoendocrine carcinoma
  - Mixed carcinoid-adenocarcinoma
  - Mixed goblet cell carcinoid-adenocarcinoma
  - Adenocarcinoma ex goblet cell carcinoid
  - Signet-ring cell type
  - Poorly differentiated carcinoma type

Goblet cell carcinoid

- N=25
- Negative appendectomy or right hemicolectomy 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

Goblet cell carcinoid and Related Tumors of the Vermiform Appendix


*Carcinomatous growth patterns included fused or cribiform glands, single file structures, infiltrating signet-ring cells or sheets of solid cells, accounting for >50% of the tumor volume.

### Table 4. Pathologic Classification of Goblet Cell Carcinoid Tumors

<table>
<thead>
<tr>
<th>Morphologic Criteria</th>
<th>Typical GCC (group A)</th>
<th>Atypical GCC (group B)</th>
<th>Adenocarcinoma ex GCC (signet ring cell type)</th>
<th>Adenocarcinoma ex GCC, poorly differentiated carcinoma type (group C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gland-forming</td>
<td>Well-defined goblet cells arranged in clusters or cohesive linear patterns</td>
<td>Dilated tubules, loss of normal goblet cells</td>
<td>Confluent sheets of signet-ring cells</td>
<td>At least focal evidence of goblet cell differentiation</td>
</tr>
<tr>
<td>Minimal differentiation</td>
<td>Minimal cystic changes</td>
<td>Distinctive signet-ring cell morphology</td>
<td>Single cell or single file infiltration</td>
<td>Architectural distortion of the appendiceal wall and desmoplastic reaction</td>
</tr>
</tbody>
</table>

Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma type

- Large irregular clusters
- Lack confluent sheets

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>GCC Type</th>
<th>5-Year Survival (%)</th>
<th>10-Year Survival (%)</th>
<th>15-Year Survival (%)</th>
<th>20-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCC A</td>
<td>90 (91)</td>
<td>60 (60)</td>
<td>50 (50)</td>
<td>40 (40)</td>
</tr>
<tr>
<td>GCC B</td>
<td>70 (70)</td>
<td>40 (40)</td>
<td>30 (30)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>GCC C</td>
<td>50 (50)</td>
<td>30 (30)</td>
<td>20 (20)</td>
<td>10 (10)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>GCC Type</th>
<th>Number of Cases</th>
<th>3-Year Disease-Free Survival (%)</th>
<th>5-Year Disease-Free Survival (%)</th>
<th>7-Year Disease-Free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad-GCC A</td>
<td>40 (41)</td>
<td>30 (31)</td>
<td>20 (21)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Ad-GCC B</td>
<td>30 (31)</td>
<td>20 (21)</td>
<td>10 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ad-GCC C</td>
<td>20 (21)</td>
<td>10 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>30 (31)</td>
<td>20 (21)</td>
<td>10 (11)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

DOD indicates 50% disease-free survival; DCS indicates disease-specific survival.
Table 1: Stage VIII Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Stage N (%)</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>II 20 (87)</td>
<td>1 1 1 1 (4) 1 (4)</td>
</tr>
<tr>
<td>2</td>
<td>II 28 (87)</td>
<td>1 1 2 (10) 1 1 (4)</td>
</tr>
<tr>
<td>3</td>
<td>II 24 (96)</td>
<td>1 1 16 (67) 0 1</td>
</tr>
<tr>
<td>4</td>
<td>II 38 (91)</td>
<td>1 1 13 (22) 1 1</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


Simplified 2-Tier Histologic Grading System

- 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.

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)
- > 1 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)
Infiltrating individual goblet/signet-ring cells with cytologic atypia

Solid cords with cytologic atypia and loss of intracytoplasmic mucin

Cytologic atypia with mitoses

Desmoplasia

Infiltrating individual goblet/signet-ring cells with cytologic atypia

Goblet or Signet Ring Cells

**That is the Question**

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


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
  • Concomitant surgery and intraoperative 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

**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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