The Latest on the Ampulla: How to Stay out of Trouble

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## Agenda

### The Latest on the Ampulla: How to Stay out of Trouble

1. **Ampulla Anatomy**

2. **Endoscopic ampullary biopsy limitations**
   - Small size, cautery artifact, ulcerated, reactive epithelial changes

3. **Helpful tips**
   - EUS/ERCP/Cytology correlation
   - Check base of ulcer
   - Small atypical glands: deepers & IHC

4. Two case studies and two quizzes

5. **Summary**
Definition

• **Ampulla**
  - A cavity or the dilated end of a duct

• **Ampulla of Vater**
  - AKA hepatopancreatic ampulla
  - Confluence of PD & CBD
  - Located at major duodenal papilla
  - Most common site dysplasia/ca (SB)
  - Hybrid/mixed epithelium
    - Staining for both CK7 and CK20 common
    - Intestinal CDX2/MUC2+, MUC1-
    - Pancreatobiliary CDX2/MUC2-, MUC1+

Figure from Adsay etc. *Am J Surg Pathol* 2012; 36: 1592-1608
Endoscopic Ampullary Biopsy Limitations

- Small size
- Fragmentation
- Crush artifact
- Cautery artifact
- Ulcerated, inflamed
- But high stakes!
Cautery Artifact vs. Adenoma

Apoptosis in Adenoma
# Reactive Epithelial Changes

- < 3 months of prior procedure
- High interobserver disagreement
  - $\kappa = 0.24$, no clinical data
  - $\kappa = 0.49$, given clinical data

<table>
<thead>
<tr>
<th></th>
<th>Reactive Atypia</th>
<th>Adenoma</th>
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</thead>
<tbody>
<tr>
<td>Adjacent ulcer, infl.</td>
<td>+</td>
<td>-/+</td>
</tr>
<tr>
<td>Surface Maturation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cytoplasmic Eosinophilia</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>Nuclear enlargement, macronucleoli</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>Nuclear elongation, stratification</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Epithelial apoptosis</td>
<td>Less</td>
<td>More</td>
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Allard etc. *Am J Surg Pathol* 2018; (42)1095-1100; Chap. 41 in *Surgical Pathology of the GI tract/liver/biliary tract/pancreas* 2009
Squamous Metaplasia

- Prior procedure/stent
- May involve underlying ampullary ductules
- Diagnostic pitfalls
  - Not HGD
  - Not invasion
Papillary/Reactive Hyperplasia

- Prior procedure/stent
- Adjacent to tumor
- Mimic adenoma, but show:
  - Retained maturation
  - Less nuclear elongation/stratification
  - More pink cytoplasm
  - May have macronucleoli
Papillary Hyperplasia
Ampullary Biopsy Evaluation
Tip#1. Correlation, Correlation, Correlation!

- Often limited bx material
- EUS/ERCP
  - Small vs. Large mass
  - ? Invasion (infiltrative borders, ulceration, firm texture, ductal dilatation)
- Cytology
- Bx high false negative rate
  - 16-60%
  - Acknowledge the limitations!!!
Tip#2. Ulcer - Check Deep Edge of Biopsy
Whipple Resection: Ampullary Adenocarcinoma
Eroded mucosa with underlying cholangiocarcinoma
Tip#3. Beware Small Atypical Glands at Ampulla

Could be invasive carcinoma from:

• Pancreas
• Ampulla
• Distal Bile Duct
Tip#3. Small Atypical Glands: Deepers May Help

Adenocarcinoma: irregular haphazard glands, 4x anisonucleosis, stromal desmoplasia, single cell infiltration, atypical mitoses
Tip#3. Small Atypical Glands: IHC May Help

Adenocarcinoma with pancreaticobiliary differentiation:

- *CK7/19/MUC1+
- *CK20/CDX2/MUC2-
- P53 ++ or null
- SMAD4/DPC4-

*CK stains may be variable
Tip#4. Colonization of Ampullary Epithelium by Underlying Carcinoma

- Invasive pancreatic or cholangiocarcinoma grow along basement membrane of ampullary epithelium
  - Simulating adenoma
- IHC shows PB (not intestinal) differentiation

Photo from Adsay and Basturk. Chap. 41. Tumors of major and minor ampulla; in book Surgical Pathology of the GI tract/liver/biliary tract/pancreas 2009, pp1126
IHC: Invasive Pancreatic Ca Colonizing Ampulla

Photos from Chap 18. Preinvasive neoplastic lesions of the vaterian system; in AFIP Fascicle 23: Tumors of the gallbladder, extrahepatic bile ducts, and Vaterian system 2015, pp456-457
Quiz 1

Ampullary biopsy, what’s your diagnosis?

A. Squamous metaplasia
B. High-grade dysplasia
C. Low-grade dysplasia
D. Carcinoma colonization of ampullary epithelium
Ampullary biopsy, what's your diagnosis?

A. Squamous metaplasia
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Quiz 1 Answer

A. Squamous metaplasia  
B. High-grade dysplasia  
C. Low-grade dysplasia  
D. Carcinoma colonization of ampullary epithelium

Cholangiocarcinoma of DBD
Summary Ampullary Biopsy Evaluation

- Complex anatomy & histomorphology
- Correlation ERCP/EUS/Cytology
- Reactive changes post instrumentation
- Ulcer – ? tumor, check deep edge
- Abnormal epithelium – ? colonization by carcinoma
- Small atypical glands – Get deepers & IHC
Ampullary Biopsy

Case Study
Case 1

- 81 y.o. F jaundice
- EUS: Distal biliary stricture and ampullary mass
- Endoscopic ampullectomy
Case 1. Ampullary Biopsy Diagnosis

- Fragments of ampullary adenoma with focal necrosis, see note.
- Adjacent small intestinal mucosa with ulcer and acute inflammation.

Note: Focal necrosis, prominent nuclear changes, atypical cells and glands were seen in fibrotic tissue fragments. Deeper sections obtained show similar findings with no definitive evidence of invasion. Caution should be exercised as the fragmented superficial biopsy material may not be representative of the clinically concerning lesion, an invasive carcinoma cannot be completely excluded. Correlate with clinical and radiologic findings and rebiopsy are recommended if clinically indicated. The slides have been reviewed by Dr. XXX.
Case 1. Whipple Resection

Intra-Ampullary Papillary-Tubular Neoplasm (IAPN) with associated invasive carcinoma
Intra-Ampullary Papillary-Tubular Neoplasm

- Preinvasive, intra-ampullary, exophytic
  - Minimal/no involvement of BD, PD, or duodenal papilla
  - Analogous to ITPN of pancreas/BD
- 75% has invasive carcinoma on resection
  - Invasion subtle - hidden in crevices underneath polypoid areas
  - Missed by biopsy
- Biologically indolent
  - Even when invasive significantly better prognosis than invasive ampullary ca unaccompanied by IAPNs
Case 1. Summary

- **Ampullary mucosal biopsy:**
  - Fragments of adenoma with ulcer, necrosis (*careful note*)
- **Pancreaticoduodenectomy:**
  - Small foci of invasive adenocarcinoma, arising in IAPN
  - pT2N1
- **Discordance due to limitation of mucosal bx**
Case 2

- 63 y.o. M painless jaundice
- ERCP: CBD dilation, stent placed
- EUS: 2.9 cm lesion biopsied
Case 2. Ampullary Biopsy Diagnosis

- Ampullary mucosa with no diagnostic abnormality, see note.

Note: An AE1/3 is negative for an infiltrating process. Deeper sections are examined. If the lesion remains clinically concerning, repeat sampling is a consideration.
Case 2. Whipple Resection

Low-grade GIST, duodenum
Case 2. Summary

Retrospectively stained Bx
• One fragment DOG1+
• NOT MM – too thick
• NOT MP – superficial Bx
Quiz 2

- 44 y.o. male
- EUS: 1.2 cm ampullary mass
- Biopsied
What’s your diagnosis?
A. Adenocarcinoma
B. GIST
C. Pancreatic heterotopia
D. Neuroendocrine tumor
What's your diagnosis?

A. Adenocarcinoma
B. GST
C. Pancreatic heterotopia
D. Neuroendocrine tumor
Quiz 2 Answer

What’s your diagnosis?
A. Adenocarcinoma
B. GIST
C. Pancreatic heterotopia
D. Neuroendocrine tumor
# Ampullary Neoplasms: Other Than Adenoma/Adenocarcinoma

<table>
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<tr>
<th>Epithelial</th>
<th>Mesenchymal</th>
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<tbody>
<tr>
<td>Neuroendocrine Neoplasms</td>
<td>GIST</td>
</tr>
<tr>
<td>• Somatostatinoma</td>
<td>Lipoma</td>
</tr>
<tr>
<td>• Gangliocytic Paraganglioma</td>
<td>Neurofibroma, ganglioneuroma</td>
</tr>
<tr>
<td>MiNEN</td>
<td>Rhabdomyosarcoma, Kaposi sarcoma</td>
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Ampullary NEN with Distinctive Features

Somatostatinoma

Gangliocytic paraganglioma

Photo courtesy of Dr. Christina Arnold, Ohio State University
Pearls from Ampullary Bx Case Studies

• Recognize other tumors near ampulla – GIST, NEN, etc
  - Keep broad differentials more than adenoma/adenocarcinoma

• Write careful note to ampullary mass bx diagnosis
  - Acknowledge limitations (fragmentation, crush/cautery artifacts, prior procedure changes)
  - May not be representative of the entire lesion
  - Deepers, IHC, show around
  - Ask for clinical correlation
References

- Obeng et al. The utility of immunohistochemistry aids diagnosis of colonization of duodenal mucosa by invasive ampullary adenocarcinoma. USCAP 2019 abstract
- Reid MD etc. Ampullary carcinoma is often of mixed or hybrid histologic type: an analysis of reproducibility and clinical relevance of classification as pancreatobiliary versus intestinal in 232 cases. Mod Pathol 2016; 29: 1575-1585.
- Gaspar JP etc. Approach to the endoscopic resection of duodenal lesions. World J Gastroenterol 2016; 22(2):600-617
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