Common diagnostic problems in gallbladder pathology

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Case in discussion

- 62, F
- Underwent cholecystectomy with the diagnosis of chronic cholecystitis and cholelithiasis

A. Reparative atypia
B. AUS (undetermined significance LGD vs reactive)
C. Low-grade dysplasia
D. High-grade dysplasia / CIS
E. Invasive adenocarcinoma
Case – Our diagnoses

• 2003: Low-grade dysplasia
  – Note: Concern for HGD
• 2011 (3 years into seeing hundreds of HGD and invasive GBC): Reactive atypia
• 2014: International consensus meeting in Santiago, Chile: ~ 30% of experts: Dyspl; 70%: reactive

Focal epithelial atypia (FEA)/ (possible) Low-grade dysplasia

Focal EA of healing erosion

Focal EA of healing erosion

7/12: Reactive
2/12: LGD
3/12: HGD/CIS

• Crescendo maturation
• Columnar cytology
• Striking cellular stratification but smooth band
• Accentuated intercellular spaces
• Nuclear molding (Apply Barrett criteria)
Focal EA with surface columnar (goblet) cells

- Mitotic activity (brisk)
- Despite crowding and basophilia, overall relatively pale chromatin and small basophilic nucleoli

Focal EA with surface columnar cells:

- Pseudostratified but with polarization
- Uniform slender nuclei with even chromatin
Approach to **focal epithelial atypia (FEA)** w DDx of LGD or regenerative

- **Take 4 more blocks (with multiple fragments)**
  - Be especially alert if also goblet cells
- **If no convincing HGD, then it does not matter:**
  - “Low grade dysplasia is of no known clinical significance in GB, provided that HGD/invasion have been ruled out extensive/total sampling”

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**Case in discussion**

- 62, F
- Underwent cholecystectomy with the diagnosis of chronic cholecystitis and choledolithiasis
What is your diagnosis?

A. Reparative atypia
B. Metaplasia
C. Low-grade dysplasia
D. High-grade dysplasia / CIS
E. Invasive adenocarcinoma

Case – Our Diagnosis

- High-grade dysplasia/Carcinoma in-situ of gallbladder, extensive, with no definitive invasive carcinoma.

Note: The GB was submitted entirely* for microscopic examination.

HGD/CIS = BiiIN-3
GB Dysplasia

- **Incidence:** Parallels GB cancer-risk geography
- **Clinical significance:** Estimated ~ 20,000 cases seen in surg path (~ 1 mil cholecystectomies in the US)

10/12: LGD
1/12: Reactive
1/12: HGD/CIS

High-grade dysplasia / CIS
Extensive severe surface atypia: HGD/CIS

SURFACE involved by diffuse atypia despite acute injury

Different cytologic patterns (cell lineages) of GB dysplasia

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Biliary Cuboidal</td>
<td>(70%)</td>
</tr>
<tr>
<td>Biliary Pencillate</td>
<td>(13%)</td>
</tr>
<tr>
<td>Intestinal</td>
<td>(6%)</td>
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<tr>
<td>Gastric/mucinous</td>
<td>(10%)</td>
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12/12 observers called HGD/CIS in the international consensus conference

Columnar cell examples (intestinal or pencillate cell types) are more monotonous
Diagnostic issue #1:
Reactive atypia vs HGD/CIS

Macro-nuclei and macro-nucleoli: HGD

Acidophilic atypia of acute injury (hemorrhage)

Diagnostic issue #2:
Low vs High-grade?

Approach to “atypia, suspect HGD”

- Sample GB extensively
- HGD is wild-fire (usually involves most of the intact epithelium)
- Stay in low power
  - Real HGD usually shows its face in low power
<table>
<thead>
<tr>
<th></th>
<th>SEER database (“CIS”)</th>
<th>Our cohort (HGD/CIS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>686</td>
<td>125</td>
</tr>
<tr>
<td>1-yr</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>3-yr</td>
<td>89</td>
<td>93</td>
</tr>
<tr>
<td>5-yr</td>
<td>87</td>
<td>90</td>
</tr>
<tr>
<td>10-yr</td>
<td>79</td>
<td>86</td>
</tr>
<tr>
<td>% deaths documented to be due to GB/biliary cancers</td>
<td>6.8</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Few early deaths → Missed carcinomas due to undersampling

Deaths in long-term follow-up: Field-defect/field-effect (“marker” disease) for biliary cancers

HGD / CIS
or
Early invasive carcinoma?
What is your diagnostic T-stage?

A. No HGD/CIS
B. Tis (HGD/CIS)
C. T1a (lamina propria invasion)
D. T1b (muscularis inv)
E. T2 (crossing muscularis)

Correct answer:
US pathologists: B (Tis)
Asian and S. Am: D (T1b)

Santiago international consensus conference:
• Of the US-CIS cases (19 cases that had been classified as HGD/CIS-only/non-invasive by consensus of 6 US pathologists), > 50% were called T1 (invasive) by most Asian and South American Pathologists (24-86%)
Non-invasive (Tis) OR invasive (T1a/b) ?

Pseudo-invasive appearance of HGD/CIS
(Illustration: Virtual, by Photoshop pasting)

Peculiar aspect of GB histology (different than GI organs)

In such cases ....

1. PERFORM TOTAL SAMPLING to R/O T2
In such cases ....

1. **PERFORM TOTAL SAMPLING to R/O T2**

2. Remember, ~70% of “early” and 50% of “advanced” GBC is clinically/grossly unapparent (i.e., “I checked the gross carefully there is nothing there” simply does NOT work for GB)

IF T2 is ruled out confidently, then you can refer to the “Early Gallbladder Cancer” data

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![Image](image-url)


- **Even minimal/superficial T2 carcinomas have good prognosis** IF DEEPER CARCINOMA IS R/0’D BY TOTAL SAMPLING

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Roa et al., *Virchows Archives*, 2013 Nov: 651
Conclusions

• FEA (focal epithelial atypia)/LGD? warrants additional sampling (4 blocks or more); LGD is believed to be clinically insignificant
• HGD/CIS is significant
  – It is often extensive and overtly recognizable by the time of cholecystectomy
  – HGD/CIS is very difficult to (and may not have to be) distinguished from T1 carcinoma; *should be sampled extensively* to rule out T2 carcinoma
• If T2 (peri-muscular invasion) has been ruled out by total sampling, early GBC (Tis/T1) have a very good prognosis; but some cases (~5%), experience biliary tract cancer in long term follow up

Case in discussion

• 76, F
• Underwent cholecystectomy with the diagnosis of chronic cholecystitis
• Grossly, the gallbladder wall had transformed into a relatively thin uniform sclerotic band

Hyalinizing cholecystitis ("incomplete porcelain")
Case - Diagnosis

Invasive adenocarcinoma arising in hyalinizing cholecystitis (Ca in “incomplete porcelain GB”)

Porcelain GB

Textbooks / Medical Schools (since 1880’s):
- Porcelain = Extensively calcified
- Very high incidence of carcinoma
  - Cancer risk of up to 40 X
  - 60% of PGBs develop carcinoma
• **Radiology studies in 2000’s : Totally different picture**
  – “Porcelain (diffusely calcified) GB” is exceedingly uncommon
    – 44 in 25K (Stephen et al)
    – 15 in 10K (Towfigh et al)
  – Carcinoma is very uncommon in diffusely calcific porcelain GB
    • 2 cases and 0 cases in those studies
  – If it occurs, it occurs in cases with “mucosal-punctate calcifications” rather than those with diffuse mural

Pathologic analysis:
• >4K cholecystectomies analyzed systematically
• Targeted search

Results:
- 10 diffusely calcific (complete PGB); NONE had ca
- **106 cases of Hyalinizing Cholecystitis**
  - with minimal (65%) or no calcifications
  - 38 had invasive carcinoma;
    - Odds-ratio 4.6
    - < Half had calcifications

Any epithelium in the COMPLETELY hyalinized GB is suspect carcinoma because:
1. Epithelium is often denuded in hyalinizing cholecystitis
2. Aschoff-Rokitansky is very uncommon in HC

If present, CIS in hyalinizing cholecystitis is denuding, clinging or micropapillary types
Carcinoma arising in hyalinizing cholecystitis

“Minimal deviation adenocarcinomas” of GB (“adenoma malignum” pattern)

Extremely well-diff adenoca (“adenoma malignum”): ~3% of GBCs

1. Open round lumen formation; 2. Irregular contours; 3. Granular debris in the lumen
Those with round monotonous nuclei typically show prominent cherry-red nucleoli.

Subserosal/sub-hepatic band formation mimicking Luschka ducts.

Grooved cell variant: Nuclear grooves but no nucleoli.

Columnar cell variant.
Benign glandular proliferations of GB that mimic invasive adenocarcinoma
Sub-hepatic/sub-serosal ducts: “Luschka’s ducts”
Rokitansky-Aschoff Sinuses

Carcinoma

BENIGN- ARs  CARCINOMA
Conclusion

- GB carcinomas **can be very subtle** (similar to any part of the pancreatobiliary tract):
- The **context is important**
  - In hyalinizing cholecystitis ("porcelain"), any gland located in the completely hyalinized segment of the GB ought to be considered suspect for carcinoma
- In order to recognize minimal deviation adenocarcinomas, it is important to appreciate the morphologic repertoire of benign GB
  - Minimal deviation carcinomas can be recognized from their mimickers by a **constellation of findings based on their diversion from the normal structures**
“That’s why it’s called ‘same-day surgery’—
I take out your gall bladder and then play 18 holes of golf.”