Case 6

Case 6 – Clinical Summary

Female, age 55
- Liver resection.
- Large multiloculated cyst 18 cm maximum dimension in left lobe.
Case 6 – Histological Findings

- Multiloculated cystic neoplasm
- Mucinous epithelium showing varying degrees of dysplasia, focally high-grade
- Ovarian-like subepithelial mesenchymal stroma
- Occasional foci of invasive adenocarcinoma
Case 6 – Diagnosis

- Hepatobiliary cystadenoma with foci of invasive carcinoma (cystadenocarcinoma)
- Mucinous cystic neoplasm with foci of invasive carcinoma (mucinous cystadenocarcinoma)
- MCN terminology used in WHO 2010 Classification

Case 6 – Discussion Points

1. Is hepatobiliary cystadenoma the hepatic counterpart of mucinous cystic neoplasms arising in pancreas?
   - Both tumours have female preponderance (> 95% of cases)
   - Histological features similar (including ovarian-like stroma)
   - Similar pathogenetic mechanisms postulated (to account for ovarian-like stroma)
     - Epithelial cells covering embryonic gonads in early foetal life lie close to developing embryonic foregut derived from ectopic ovarian tissue

2. Is the presence of a mesenchymal an essential pre-requisite to make a diagnosis of hepatobiliary cystadenoma?
   - Some pancreatic pathologists suggest that mucinous cystic neoplasms can only be diagnosed if an ovarian-like stroma is present
     - Mainly done to aid in the distinction from other cystic lesions (especially intraductal papillary mucinous neoplasm, IPMN)
     - Intraductal papillary neoplasm (IPN) of bile duct can also present as a cystic lesion in liver
   - This approach would mean that hepatobiliary cystadenomas could only be diagnosed in women

3. What is the risk of malignant transformation?
   - No prospective studies
   - Detection of focal malignant change requires extensive sampling
     - 39/158 (25%) had foci of malignancy or were classified as cystadenocarcinoma (range 0-42%)
     - Wide range in reported prevalence may reflect differences in diagnostic criteria
   - Mucinous cystic neoplasms in pancreas
     - 7 - 36% have areas of invasive carcinoma
     - Size (>4cm) and presence of solid areas correlate with malignancy

Case 7 - Clinical Summary

Male, age 67
- Extended right hemi-hepatectomy for hilar lesion causing obstructive jaundice.
- Slide submitted is from extrahepatic segment of bile duct.
- Macroscopy showed thickened segment of bile duct 2cm long, extending from hilum towards junction with cystic duct
Case 7 – Histological Findings & Diagnosis

**Histological Findings**
- Malignant glands invading full thickness of bile duct wall
- Foci of perineural and vascular invasion
- Occasional foci of intramucosal carcinoma
- Tumour present at resection margin

**Diagnosis**
- Hilar Cholangiocarcinoma

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<table>
<thead>
<tr>
<th>Site of origin</th>
<th>Hilar / perihilar</th>
<th>Peripheral (perihepatic)</th>
</tr>
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<tbody>
<tr>
<td>Growth Pattern</td>
<td>Perihedral</td>
<td>Mass-forming</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Chronic inflammatory bile-duct disease</td>
<td>Chronic inflammatory bile-duct disease</td>
</tr>
<tr>
<td></td>
<td>e.g. PSC, hepatitis, parasitic diseases</td>
<td>Also chronic parenchymal liver disease (e.g. HCV, AIDS, NASH)</td>
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<tr>
<td>Premalignant lesion</td>
<td>Biliary intra-epithelial neoplasia (Bil-IN)</td>
<td>Less clearly defined</td>
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<tr>
<td>Histology</td>
<td>Adenocarcinoma</td>
<td>Mostly adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>May overlap features from pure HCC or pure CC</td>
<td></td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Biliary obstruction</td>
<td>Liver mass</td>
</tr>
<tr>
<td>Problem with histological assessment</td>
<td>Distinction from inflammatory causes of bile duct structure (including IgG4-associated disease)</td>
<td>Distinction from other hepatic neoplasms (primary or metastatic)</td>
</tr>
</tbody>
</table>

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Case 7 – Discussion Points

1. Macroscopic Classification of Cholangiocarcinoma

2. Hilar Cholangiocarcinoma versus Inflammatory Stricture

**Features supporting a diagnosis of malignancy**
- Subtle nuclear atypia, mitoses
- Infiltrative growth pattern (including perineural invasion)
- Immunohistochemistry
  - KL1
  - EMA/K7 (to identify individual cells in inflamed stroma)
  - (bcl-2, p53, k-ras)
- Other approaches (mainly used for brush cytology specimens)
  - digital image analysis (DIA) to assess aneuploidy
  - fluorescence in-situ hybridization (FISH) to assess chromosomal abnormalities

3. Assessment of Perineural/Vascular Invasion

- Typically present in outer wall of bile duct
- Often extends beyond macroscopically visible tumour
  - Important mechanism for tumour recurrence following resection
- Isolated malignant glands may be present some distance from periphery of main lesion identified macroscopically
- Importance in assessment of margins from resection specimens
Case 8 - Clinical Summary

Female, age 25
- Liver transplantation.
- Multiple nodules 1-6 cm diameter composed of firm white tissue throughout liver.
- Previous biopsy elsewhere reported as showing fibrosis - cause
Case 8

**Diagnosis**
Epithelioid haemangioendothelioma
Lymph node metastasis

1. **Characteristic “zonation”** (Dietze 1989)
   - highest cellularity at periphery
     - “tectorial” growth pattern along sinusoids
     - intravascular “sprouts”
   - obliteration of sinusoids and vessels leads to increasing fibrosis centrally
     - myxoid stroma, scanty tumour cells
Epithelioid Haemangioendothelioma - Discussion Points

2. Usually multifocal
   • > 80% of cases, both lobes
     – Implications for surgical resection
     – Liver transplantation as treatment option
   • Extrahepatic disease in 30-40% of cases
     – Lung commonest site
     – Other sites include lymph nodes, peritoneum, spleen & bone (Mehrabi 2006)
     – Metastatic disease, Multifocal primary sites
   • Recent molecular studies have shown identical WWTR1-CAMTA1 fusion product in different nodules from 2 patients with multifocal hepatic EHE (Errani 2012)
     – Suggests metastatic implants from same neoplastic clone

Epithelioid haemangioendothelioma - Discussion Points

3. Differential Diagnosis
   – Other neoplasms (esp sclerosing carcinoma)
   – Reactive conditions with fibrosis (including Budd-Chiari syndrome)
   • Overall 60-80% incorrect initial diagnosis (Makhlouf 1999, Mehrabi 2006)
     – Most common cholangiocarcinoma (29%), angiosarcoma (10%), HCC (6%), metastatic carcinoma (6%), sclerosing haemangioma (6%)

Epithelioid haemangioendothelioma - Discussion Points

4. Behaviour unpredictable
   – Low grade malignancy (40-50% 5 year survival)
   – High cellularity associated with poor outcome (Makhlouf 1999)
   – Size & number of nodules, number of segments involved also prognostic (Grotz 2010)

Case 9 - Clinical Summary

Case 9

Male, age 37
• Liver transplantation
• Multiple haemorrhagic nodules throughout the liver

Further Clinical Information
• Presented Dec 1988 with signs of decompensated liver disease (suspected ALD)
• Liver biopsy (at referring hospital) – extensive fibrosis (“pattern not typical of alcoholic cirrhosis”)
• Review of liver biopsy – occasional atypical endothelial cells ? angiosarcoma
• Repeat liver biopsy – vasoformative neoplasm, in keeping with angiosarcoma
• Liver transplantation, March 1989
Case 9 – Diagnosis

Hepatic Angiosarcoma

Case 9 – Discussion Points

1. **Broad spectrum of changes**
   - May reflect different stages in evolution
   - Problems with liver biopsy diagnosis
     - Subtle intrasinusoidal changes in early lesions (“tectorial growth pattern”)
     - Fibrous stroma may replace/obscure neoplastic cells (may be mistaken as a reactive/fibrotic process)

2. **“Bland” cytology versus aggressive clinical course**
   - Even areas with early lesions (lack of mitoses) have high Ki 67 labelling index

3. **Aetiology – role of occupational/environmental factors?**

Angiosarcoma – Aetiological Factors

- **Recognised Risk Factors (long latent period, up to 50 years)**
  - Vinyl chloride monomer
    - Incidence declining, no new cases in Europe in people first exposed after 1972
  - Thorotrast
  - Arsenical compounds
  - Radiation
  - Organophosphates (e.g. pesticides)
  - Androgenic/anabolic steroids

Most cases (>80%) no obvious cause identified

Case 10 - Clinical Summary

Female, age 28
- Lesion 2.5cm diameter in left lobe
- Liver resection
Case 10 - Histological Findings

- Complex lesion containing adipose tissue, blood vessels, spindle cells and epithelioid cells
- Epithelioid cells focally have trabecular arrangement
- Irregular margins
- Immunostaining positive for HMB 45, Mel-A and SMA

Case 10 – Diagnosis

**Hepatic Angiomyolipoma**

Case 10 – Discussion Points

1. Histiogenesis
2. Heterogenous morphological patterns
3. Potential for malignant behaviour

Angiomyolipoma - Histiogenesis

- Part of the spectrum of perivascular epithelioid cell neoplasms (PEComas) - derived from perivascular epithelioid cells (Rao, Histopathology 2013)

- Members of PEComa family include:
  - Angiomyolipoma (AML) of kidney and liver (liver = 2nd commonest site)
  - Clear cell sugar tumour (CCST) of lung
  - Lymphangioleiomyomatosis
  - Lymphangiomma
  - Clear cell myomelanocytic tumor (skin, falciform ligament/ligamentum teres)
  - Non-specified PEComas (soft tissue, visceral organs, bone, skin)

- Variable association with tuberous sclerosis (“tuberous sclerosis complex”)
  - Hepatic AML rarely associated (unlike renal AML)
Angiomyolipoma – Heterogeneous Histological Appearances

Most lesions contain a mixture of 3 main components

1. Mature adipose tissue
2. Blood vessels – often tortuous and thick-walled
3. Smooth muscle: spindle cell or epithelioid (most specific & diagnostic)

- May be classified as lipomatous, angiomatous, myomatous if one component predominates (>80%) or otherwise as mixed (Nonomura 2012)

Problems with histological diagnosis

- Cases with a predominance of one pattern may be mistaken as lipoma, vascular lesion or smooth muscle neoplasm
- Problems with needle biopsy diagnosis (sampling variability)
- Most hepatic AML (65%) have a predominantly myomatous pattern (Nonomura 2012)
  - Epithelioid smooth muscle components may have a trabecular pattern and can mimic hepatocellular neoplasms (adenoma or HCC)
  - 25/48 (52%) surgically resected cases of AML had pre-operative diagnosis of HCC (Nonomura 2012)

Epithelioid Angiomyolipoma versus Liver Cell Adenoma / HCC

Immunohistochemistry

Antigens expressed by AML (and not by liver cell neoplasms)
- SMA
- HMB 45, Melanoma-associated antigen
- Other: CD 117, S100 (focal), cathepsin K (Rao 2013)

Antigens expressed by liver cell neoplasms (and not by AML)
- Hep Par 1
- Cytokeratin

Angiomyolipoma – Potential for Malignant Behaviour

- Great majority behave in a benign fashion
- Cytological atypia and infiltrative margins commonly present, but do not indicate malignancy

- 4 cases of malignant AML reviewed by Nguyen (Nguyen 2008)
  - 3 metastasized, one death from aggressive local disease
  - Generally larger than benign hepatic AML (all > 10cm)
  - All 4 had foci of coagulative necrosis
  - No other distinguishing features