Painless Jaundice

Chaitan K. Narsule, M.D.
Goals of Discussion

• Bilirubin and the diagnostic evaluation of jaundice

• Cholangiocarcinoma

• Pancreatic cancer
Bilirubin and the Diagnostic Evaluation of Jaundice
About Bilirubin

- Normal breakdown product of hemoglobin when red blood cells are broken down by the reticuloendothelial system

- Insoluble unconjugated bilirubin is transported to liver bound to albumin
About Bilirubin

- Transported across the sinusoidal membrane of the hepatocyte into the cytoplasm

- Uridine diphosphate-glucuronyl transferase conjugates the insoluble unconjugated bilirubin with glucuronic acid
About Bilirubin

- Water-soluble bilirubin monoglucuronide and bilirubin diglucuronide are created.
- Conjugated bilirubin is actively secreted into the bile canaliculus.
About Bilirubin

- In terminal ileum and colon, bilirubin is converted to urobilinogen
  - 10-20% of the urobilinogen is reabsorbed into the portal circulation
  - This urobilinogen is either to be re-excreted into the bile or excreted by the kidneys into the urine
About Bilirubin

- Normal serum bilirubin = 0.5 - 1.3 mg/dL
- Jaundice: clinically apparent staining of tissues by bilirubin when levels exceed 2.0 mg/dL
- “Tea colored” urine is one of the first changes reported by patients
Evaluating Jaundice

• DDx parallels the metabolism of bilirubin

• Can be divided into two sets of disorders:
  – MEDICAL: increased production, decreased hepatocyte transport or conjugation, impaired excretion of bilirubin
  – SURGICAL: impaired delivery of bilirubin into the intestine
## Differential Diagnosis of Jaundice

<table>
<thead>
<tr>
<th>Abnormality in Bilirubin Metabolism</th>
<th>Predominant Hyperbilirubinemia</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased production</td>
<td>Unconjugated</td>
<td>Multiple transfusions, transfusion reaction, sepsis, burns, congenital hemoglobinopathies, hemolysis</td>
</tr>
<tr>
<td>Impaired hepatocyte uptake or conjugation</td>
<td>Unconjugated</td>
<td>Gilbert’s disease, Crigler-Najjar syndrome, neonatal jaundice, viral hepatitis, drug inhibition, sepsis</td>
</tr>
<tr>
<td>Impaired transport and excretion</td>
<td>Conjugated</td>
<td>Dubin-Johnson syndrome, Rotor’s syndrome, cirrhosis, amyloidosis, cancer, hepatitis (viral, drug induced, or alcoholic), pregnancy</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>Conjugated</td>
<td>Choledocholithiasis, benign stricture, periampullary cancer, cholangiocarcinoma, chronic pancreatitis, primary sclerosing cholangitis</td>
</tr>
</tbody>
</table>
Evaluating Jaundice

- Laboratory tests
  - Direct (conjugated) and indirect (unconjugated) bilirubin
  - Alkaline phosphatase
  - Transaminases
  - Amylase
  - CBC
Evaluating Jaundice

• Radiologic evaluation
  – confirmation of clinically suspected biliary obstruction by demonstrating intrahepatic and/or extrahepatic duct dilation
  – identification of site and cause of the obstruction
  – selection of the appropriate treatment modality for managing the jaundice
Evaluating Jaundice

- **Ultrasound**
  - often the initial screening test
  - extrahepatic (>10 mm) or intrahepatic (>4 mm) dilation suggests biliary obstruction
  - can identify gallstones, liver metastases, and occasionally masses of the liver and pancreas
Evaluating Jaundice

- **CT Scan**
  - sensitive in identifying biliary dilation
  - less sensitive than US in identifying gallstones
  - more accurate than US in identifying site and cause of extrahepatic biliary obstruction
  - Spiral CT can provide additional info regarding vascular involvement in patients with periampullary tumors
Evaluating Jaundice

- Therefore, for INITIAL radiographic evaluation:
  - if biliary obstruction from GALLSTONES is expected, use ULTRASOUND first
  - if biliary obstruction from TUMOR is expected, use CT scan first
Evaluating Jaundice

• Cholangiography
  – MR cholangiography (MRC)
    • non-invasive, provides anatomic detail regarding site of obstruction
  – Endoscopic retrograde cholangiography (ERC)
    • invasive
    • 2-5% risk of complications
    • may not be feasible in patients with altered gastroduodenal anatomy
Managing Jaundice

- **Endoscopic Retrograde Cholangiography (ERC)**
  - can clear retained CBD stones 85-90% of the time
  - allows for stent placement for internal decompression of biliary tract
Managing Jaundice

- Percutaneous Transhepatic Cholangiography (PTC)
  - favored in patients with more proximal bile duct obstruction involving or proximal to the hepatic duct bifurcation
  - stents can be passed across an obstructing lesion into the duodenum to permit internal drainage
  - serial dilation of stent tract permits passage of choledochoscopy into biliary tree for direct visualization, biopsy, or management of obstructing lesions or stones
Cholangiocarcinoma
Cholangiocarcinoma

- Uncommon tumor
- Can be present anywhere along the intrahepatic or extrahepatic biliary tree
- Most common location: hepatic duct bifurcation (60-80% of all cases)
- Most present with painless jaundice
Cholangiocarcinoma

- Incidence
  - 2,500 to 3,000 new cases each year in the US
  - 1 in 100,000 people per year
  - Equal frequency in men and women
  - Incidence increases with age
Cholangiocarcinoma

- Risk factors ("stasis, stones, infection")
  - primary sclerosing cholangitis
    - extrahepatic, occurring in 5th decade of life
  - choledochal cysts
    - risk increases steadily with age
  - hepatolithiasis
    - 5-10% risk of cholangiocarcinoma
  - liver flukes, thorotrast, dietary nitrosamines, exposure to dioxin
Cholangiocarcinoma

• Staging and Classification
  – intrahepatic
    • treated with hepatectomy
  – perihilar
    • treated with resection of BD w/hepatic resection
  – distal
    • treated with pancreatoduodenectomy
Cholangiocarcinoma

- Perihilar cholangiocarcinoma (Bismuth anatomic classification)
  - Type I tumor
    - confined to common hepatic duct
  - Type II tumor
    - involve bifurcation without involvement of secondary intrahepatic ducts
Cholangiocarcinoma

- Perihilar cholangiocarcinoma (Bismuth anatomic classification)
  - Type IIIa and IIIb tumors
    - extend to either right (IIIa) or left (IIIb) secondary intrahepatic ducts
  - Type IV tumor
    - involve the secondary hepatic ducts on both sides
## TABLE 52-9 -- TNM Staging for Extrahepatic Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1 N0 M0  Limited to bile duct</td>
</tr>
<tr>
<td>IB</td>
<td>T2 N0 M0  Invade periductal tissues</td>
</tr>
<tr>
<td>IIA</td>
<td>T3 N0 M0  Locally advanced w/o LN metastases</td>
</tr>
<tr>
<td>IIB</td>
<td>T1 N1 M0  Locally advanced with regional LN metastases</td>
</tr>
<tr>
<td></td>
<td>T2 N1 M0</td>
</tr>
<tr>
<td></td>
<td>T3 N1 M0</td>
</tr>
<tr>
<td>III</td>
<td>T4 Any N M0  Locally advanced and unresectable</td>
</tr>
<tr>
<td>IV</td>
<td>Any T Any N M1  With distant metastases</td>
</tr>
</tbody>
</table>

Cholangiocarcinoma

• Clinical presentation
  – Jaundice in >90% of patients with perihilar or distal tumors
  – Patients with intrahepatic cholangiocarcinoma are rarely jaundiced until late in disease
  – Pruritis, fever, mild abdominal pain, fatigue, anorexia, weight loss
Cholangiocarcinoma

• Diagnosis
  – Total serum bilirubin >10 mg/dL
  – Elevated levels of alkaline phosphatase
  – Serum CA 19-9 may be elevated
Cholangiocarcinoma

- Diagnosis (cont’d)
  - CT for evaluation
    - intrahepatic tumors easily visualized
    - perihilar and distal tumors often difficult to identify
    - trends
      - hilar tumors: dilated intrahepatic biliary tree, normal extrahepatic biliary tree and gallbladder
      - distal tumors: dilated intrahepatic and extrahepatic biliary tree and dilated gallbladder
Cholangiocarcinoma

• Diagnosis (cont’d)
  – Cholangiography (ERC or PTC)
    • most proximal extent of tumor is the most important feature in determining resectability in patients with perihilar tumors
    • MRC has diagnostic accuracy comparable to ERC and PTC
Cholangiocarcinoma

• Management
  – Curative treatment = complete resection
  – Intrahepatic tumor: partial hepatectomy
  – Perihilar tumor
    • If involving the hepatic duct bifurcation or proximal common hepatic duct (Bismuth I or II): hepaticojejunostomy
    • If involving the right or left hepatic duct (Bismuth IIIa or IIIb): right or left hepatic lobectomy
Hepaticojejunostomy at bifurcation of hepatic duct
Left hepatic lobectomy for Bismuth Type IIIb perihilar cholangiocarcinoma
Cholangiocarcinoma

• Management (cont’d)
  – Distal tumor: **pancreatoduodenectomy**
  – Nonoperative palliation for unresectable tumor
    • Percutaneous biliary drainage for perihilar tumors
    • Endoscopic drainage for distal tumor
Cholangiocarcinoma

• Management (cont’d)

– For exploratory laparotomy and unresectable tumor:

  • extensive metastatic disease: biliary stent placement + cholecystectomy

  • locally advanced, unresectable perihilar tumors: cholecystectomy, Roux-en-Y hepaticojejunostomy proximal to tumor, and gastrojejunostomy
Cholangiocarcinoma

- Chemotherapy has not been shown to improve survival in resected or unresected cholangiocarcinoma
- No prospective RCTs have been reported on the efficacy of external beam radiotherapy.
Pancreatic Cancer
Pancreatic Cancer

- Affects 25,000 to 35,000 people in the US each year
- 4th or 5th leading cause of cancer-related death in the US
- Increased frequency in men > women, blacks > whites
- 80% of cases occur between 60 - 80 years of age
Pancreatic Cancer

• **Risk factors**
  – Hx of hereditary or chronic pancreatitis
  – Cigarette smoking
  – Occupational exposure to carcinogens

  – **NOT** coffee drinking, which was once considered a risk factor
Pancreatic Cancer

• Pathology
  – ductal adenocarcinoma: 80-90% of all pancreatic neoplasms
  – 70% arise in pancreatic head of uncinate process
  – grossly, are hard, irregular, gritty masses that are poorly demarcated and yellow-gray
  – at time of Dx, usually > 3cm in diameter with distant metastasis
Pancreatic Cancer

• Pathology (cont’d)
  – degree of differentiation, mitotic index, and amount of mucous vary considerably
  – halo of chronic pancreatitis frequently surrounds tumor
  – perineural growth with invasion into neighboring nervous plexuses can cause abdominal and back pain
Pancreatic Cancer

- Pathology (cont’d)
  - other types of pancreatic cancer
    - mucinous noncystic carcinoma
    - signet ring cell carcinoma
    - adenosquamous carcinoma
    - anaplastic carcinoma
    - giant cell carcinoma
    - sarcomatoid carcinoma
    - acinar cell carcinoma
    - pancreatoblastoma
    - leiomyosarcoma, liposarcoma, plasmacytoma, lymphoma
Pancreatic Cancer

• Molecular Biology - Three types of genetic abnormalities
  – Activation of growth-promoting oncogenes (e.g. K-ras, ~90%)
  – Mutations that result in inactivation of tumor suppressor genes (e.g. p53, ~75%; p14, SMAD)
  – Excessive expression of growth factors and their receptors (e.g. EGF, HER2, HER3, HER4)
  – THEORY: Pancreatic cancer evolves in a step-wise fashion due to accumulation of multiple gene abnormalities
Pancreatic Cancer

- Hereditary Pancreatic Cancer Syndromes
  - Pancreatic cancer incidence is increased in families with:
    - Hereditary nonpolyposis colon cancer (HNPCC)
    - Familial breast cancer (with BRCA2 mutation)
    - Peutz-Jeghers syndrome
    - Ataxia-telangiectasia
    - Familial atypical multiple mole melanoma (FAMMM)
    - Hereditary pancreatitis
**Pancreatic Cancer**

- **Signs and Symptoms**
  - in head or uncinate process of pancreas:

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Infrequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (92%)</td>
<td>Nausea (37%)</td>
</tr>
<tr>
<td>Pain (72%)</td>
<td>Weakness (35%)</td>
</tr>
<tr>
<td>Jaundice (82%)</td>
<td>Pruritus (24%)</td>
</tr>
<tr>
<td>Dark urine (63%)</td>
<td>Vomiting (37%)</td>
</tr>
<tr>
<td>Light stools (62%)</td>
<td>Unexplained pancreatitis, steatorrhea, ascites</td>
</tr>
<tr>
<td>Anorexia (64%)</td>
<td></td>
</tr>
</tbody>
</table>
## Pancreatic Cancer

### Signs and Symptoms (cont’d)

- in neck, body, or tail of pancreas:

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Infrequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (100%)</td>
<td>Jaundice (7%)</td>
</tr>
<tr>
<td>Pain (97%)</td>
<td>Dark urine (5%)</td>
</tr>
<tr>
<td>Weakness (43%)</td>
<td>Light stool (6%)</td>
</tr>
<tr>
<td>Nausea (45%)</td>
<td>Pruritus (4%)</td>
</tr>
<tr>
<td>Anorexia (33%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting (37%)</td>
<td></td>
</tr>
</tbody>
</table>
Pancreatic Cancer

• Signs and Symptoms (cont’d)
  – New onset diabetes (due to factor inhibiting insulin release or inducing peripheral insulin resistance)
  – Trousseau’s syndrome (unexplained migratory thrombophlebitis)
  – Courvoisier’s sign: palpable gallbladder due to bile duct obstruction by tumor
Pancreatic Cancer

• Signs and Symptoms (cont’d)
  – Signs of metastatic spread
    • Sister Mary Joseph’s node: subumbilical deposit
    • Blummer’s shelf: pelvic peritoneal deposit
    • Virchow’s node: left supraclavicular LAD
    • Malignant ascities (caused by peritoneal carcinomatosis)
Pancreatic Cancer

• Blood tests
  – elevated bilirubin and alkaline phosphatase
  – CEA*
  – CA 19-9*
    • if > 37 U/mL, sensitivity = 86%, specificity = 87%
    • also elevated in other causes of jaundice (e.g. cholangitis)

* if extremely elevated, indicates unresectable and/or metastatic disease
Pancreatic Cancer

• Imaging studies
  – Ultrasound
    • can determine presence of pancreatic mass (cystic vs. solid) or stones
  – Triple phase CT of pancreas
    • IV contrast CT with images of arterial, parenchymal and venous phase of contrast perfusion of pancreas
    • tumor appears as hypodense mass with poorly demarcated edges, +/- dilated pancreatic duct
    • specificity = 95%, sensitivity > 95% for tumors > 2cm
Abdominal CT demonstrating mass at head of pancreas
Pancreatic Cancer

- **ERCP**
  - can identify stones and lesions, define location of bile duct obstruction, identify ampullary and periampullary lesions
  - however, malignant lesions may not be excluded by ERCP, necessitating resection anyway
  - double duct sign (superimposable bile duct and pancreatic duct strictures with proximal duct dilation) is suggestive of pancreatic head cancer
Two examples of double-duct sign
Pancreatic Cancer

• Role of biopsy
  – for unresectable tumors
    • Percutaneous CT or US guided bx
    • Endoscopic transduodenal biopsy
  – for resectable tumors
    • Bx not recommended as positive result confirms need for resection, and negative result is inconclusive
    • without preop bx, 5-10% of resected lesions will be benign
Pancreatic Cancer

- Staging - TNM system
  - T1: confined to pancreas, < 2 cm diameter
  - T2: confined to pancreas, > 2 cm diameter
  - T3: extend beyond pancreas, no arterial (celiac/SMA) involvement, +/- portal/SMV involvement, potentially resectable
Pancreatic Cancer

• Staging - TNM system (cont’d)
  – T4: extend beyond pancreas, arterial involvement, not resectable
  – N1: positive regional nodes
  – M1: distant metastasis
Pancreatic Cancer

Stage 1 and 2 cancers are amenable to resection.
Stage 3 and 4 cancers are considered to be unresectable.
Stage 3 survival = 8-12 months. Stage 4 survival = 3-6 months.

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Status</th>
<th>N Status</th>
<th>M Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II B</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Pancreatic Cancer

• Utility of staging laparoscopy
  – Deemed controversial for head tumors as radiographic imaging can, in most cases, delineate resectable from non-resectable cases
  – Bilioenteric/gastroenteric bypass still beneficial for patients with unappreciated vascular involvement by tumor
  – Laparoscopy may be useful for body/tail lesions, where there is little role for bypass
Pancreatic Cancer

• Resection of Head and Uncinate Process Tumors
  – tumors account for 70% of pancreatic tumors
  – resected by pancreatoduodenectomy +/- preservation of pylorus and proximal duodenum
  • also with cholecystectomy, hepaticojejunostomy, and gastrojejunostomy or duodenojejunostomy
Pancreatic Cancer

- Complications of pancreatoduodenectomy
  - mortality 2-4%
  - anastomotic leaks, intra-abdominal abscesses
  - leakage from pancreatic anastomosis (pancreatic fistula) ~ 15-20% of patients

  • incidence/duration of pancreatic fistula is not reduced by somatostatin analogues (octreotide)
Pancreatic Cancer

• Complications of pancreatoduodenectomy
  – delayed gastric emptying (15-40%)
    • questionably due to removal of cells (along with duodenum) which secrete motilin
    • erythromycin is useful in treating condition, which resolves with time
  – pancreatic malabsorption and steatorrhea due to exocrine insufficiency, or obstruction of pancreatic-jejunal anastomosis
    • Tx with exogenously administered pancreatic enzymes
Pancreatic Cancer

- Long term results of pancreatoduodenectomy for ductal CA
  - Overall 5-yr survival: 10-15%
    - Resection with negative margins: 26%
    - Resection with positive margins: 8%
  - Dependent on tumor diameter, diploid/aneuploid DNA content, and lymph node status
Pancreatic Cancer

- Resection of body and tail tumors
  - distal pancreatectomy +/- splenectomy for malignant tumors
  - 10% of such tumors are resectable
  - overall 5-yr survival: 8-14%

- Complications
  - subphrenic abscess (5-10%), pancreatic duct leak (20%)
    - if pancreatic fistula forms, amount of output (NOT time of closure) is altered by somatostatin analogues
Pancreatic Cancer

• Palliative Non-surgical Treatment
  – establishing diagnosis & relieving symptoms of jaundice, gastric outlet obstruction, and pain
  • percutaneous CT or US guided bx
  • percutaneous/endoscopic biliary decompression
  • endoscopic placement of endoluminal stents in duodenum
  • narcotic medications, percutaneous radiographically guided celiac plexus nerve block
Pancreatic Cancer

• Palliative Surgical Management
  – for pts undergoing laparotomy for dz found to be unresectable
  – biliary tract decompression: cholecystojejunostomy or choledochojejunostomy
  – gastrojejunostomy for duodenal compression (25% of patients)
  – Celiac plexus nerve block w/50% ethanol soln
Pancreatic Cancer

- A final word about chemoradiation therapy…
  - best results achieved with radiation therapy combined with either 5-fluorouracil or gemcitabine
  - Gastrointestinal Tumor Study Group (GITSG): combination of 5-fluorouracil with radiation therapy could increase the 2-yr survival rate for patients with tumor-free resection margins from 18% to 43%
The End

This presentation can be downloaded at:
www.chaitannarsule.com/surgery/