Case 27

A 73-year-old Caucasian woman presented with hematemesis. She had been diagnosed with cryptogenic cirrhosis several years previously but her disease was well compensated. She was seen at a local hospital and underwent esophagogastroduodenoscopy (EGD) that demonstrated no signs of esophageal varices but a large mass in the fundus and some nodular changes in the stomach. The concern was for a gastric malignancy. She is transfused and sent to you for further investigation.

Her other medical problems included hypertension for which she takes a diuretic. She denies prior surgery and does not drink alcohol or abuse drugs.

Her physical exam reveals a comfortable lady with stable vital signs. She is not icteric and her abdomen is soft and nontender. Her spleen is just palpable.

Laboratory Parameters When She is Seen After Transfer

- Hb 11.6 g/dl
- Platelets 94,000/μl
- INR 1.3
- Creatinine 0.8 mg/dl
- Tbili 1.0 mg/dl
- AST 71 iu/l
- ALT 23 iu/l
- ALP 48 iu/l
- Albumin 2.8 g/dl

During the night she develops further hematemesis. She is moved to intensive care and adequately resuscitated.

Questions

1. What is the differential diagnosis?
2. Which test(s) are indicated?
3. What is the best management scenario?
Fig. 27.1  CT scan

Fig. 27.2  EGD image
Answer: Large Fundal Varices

The CT scan (with i.v. contrast, Fig. 27.1) demonstrates large varices filling in the proximal stomach which are confirmed on the EGD image (Fig. 27.2). The liver has a nodular contour consistent with cirrhosis and there is minimal ascites. The endoscopic image has the scope in a retroflexed position and shows a mass in the fundus which could be confused with a tumor.

The differential diagnosis is essentially all causes of GI bleeding, but these should be separated into portal hypertensive and non-portal hypertensive causes in a patient with known cirrhosis. The latter will include ulcer disease, malignancy, and a Dieulafoy lesion, while the former includes variceal bleeding (esophageal or gastric) and severe portal hypertensive gastropathy.

The laboratory values suggest well-compensated disease but this does not exclude significant portal hypertension.

The initial work up should include an imaging study such as a CT scan or ultrasound scan (USS) (with Doppler). The latter is important to document the patency of the portal vein. However, after adequate resuscitation, repeat EGD is required. Pharmacological therapy with intravenous octreotide should be standard in patients with suspected portal hypertensive bleeding and should be started prior to the EGD, and antibiotics have also been shown to reduce mortality in this situation.

The patient has isolated gastric varices and several red spots are seen on the EGD image which are indicative of recent bleeding. Endoscopic treatment of isolated gastric varices is of limited benefit, although cyanoacrylate has shown some promise (but is not available in the United States). Band ligation of such large varices would be inadvisable but could be tried if the varices were smaller (which is a judgment call).

If the portal vein is open, the patient should undergo transjugular intrahepatic portosystemic shunting (TIPS) which controls bleeding in the majority of cases. Hence, it is important to document portal vein patency prior to EGD if possible since this will influence how aggressive you should be with endoscopic treatment.

References

1. Garcia-Tsao G, Sanyal AJ, Grace ND et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46:922–38.
2. Chau TN, Patch D, Chan YW et al. “Salvage” transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. Gastroenterology 1998;114:981–7.
Case 28

A 54-year-old man presents for liver transplant evaluation. He has a history of cirrhosis secondary to hepatitis C and alcohol. His liver disease has been complicated by ascites and encephalopathy and he has small varices although no history of GI bleeding.

His past medical history is unremarkable without evidence of diabetes, heart or lung disease, or prior surgeries. Medications include diuretics and lactulose.

He has a remote history of drug use and quit drinking over a year ago when he first developed ascites. He is married with grown up children and is still working in a local hardware store. His family history is unremarkable.

His review of symptoms is significant for mild abdominal discomfort and ankle edema. He has some mild shortness of breath and has noticed decreased exercise tolerance over the last year and he has had to take a lighter schedule at work.

On exam he is alert and oriented. His vital signs are normal with BP 120/75, pulse 106 and regular and he is afebrile. His respiratory rate is 22 per min. He has significant palmar erythema and multiple spider nevi on his face, anterior and posterior upper trunk. There is no scleral icterus.

Cardiovascular system reveals normal heart sounds and an added sound immediately after the second heart sound. Chest reveals clear lung fields. He is more comfortable lying flat. He has a liver edge palpable 2–3 cm below the right costal margin but no splenomegaly. There is dullness in the flanks and +ankle edema.

**Laboratory Studies**

- Hb 12.3 g/dl
- Platelets 73,000/μl
- WBC $6.2 \times 10^3/\mu l$
- INR 1.3
- Creatinine 1.1 mg/dl
- Tbili 1.4 mg/dl
- AST 37 iu/l
- ALT 34 iu/l
- GGTP 83 iu/l
- ALP 89 iu/l
- Albumin 2.6 g/dl
- Chest X-ray normal
Questions

1. As well as the standard work up for liver transplant are there any other tests you would consider?
2. What is the significance of his cardiac exam?
3. How is the diagnosis confirmed?
4. What is the prognosis after transplant and what is it based on?
O₂ saturation on room air 91%

pH 7.42
PaO₂ 54 mmHg
PaCO₂ 28 mmHg

Aa gradient (on room air)
= (150 − 5/4(PaCO₂)) − PaO₂
= 61 mmHg
Answer: Hepatopulmonary Syndrome

This patient’s $O_2$ saturation on room air in the absence of lung or heart disease is suggestive of hepatopulmonary syndrome (HPS) which is a diagnosis that is frequently undetected. Patients undergoing liver transplant evaluation should have an arterial blood gas.

HPS is defined by an increased alveolar–arterial gradient on room air with evidence of intrapulmonary vascular abnormalities or dilatations (IPVDs) occurring in patients with liver disease and in the absence of intrinsic lung disease. IPVDs are thought to arise due to poor clearance or excess production of pulmonary vasodilators and inhibition of circulating vasoconstrictors by the cirrhotic liver likely mediated through nitric oxide. The resultant dilation of the pulmonary vasculature leads to a large right to left shunt, which is not a true anatomical shunt as it partially responds to increased FiO$_2$.

The prevalence of HPS varies but it is thought to be 5–50% in cirrhotic patients. HPS can also occur in non-cirrhotic portal hypertension and occasionally acute liver disease. Mild abnormalities are very common. If the PaO$_2$ is less than 60 mmHg, this is very suggestive of HPS in patients with cirrhosis and no underlying cardiopulmonary disease.

HPS typically presents with dyspnea but often is initially asymptomatic and underdiagnosed. There does not appear to be a correlation between severity of liver disease and degree of hypoxemia although HPS is an independent predictor of death in patients with cirrhosis.

This patient’s cardiac exam shows evidence of a hyperdynamic circulation and in HPS there is usually an elevated cardiac output, decreased systemic and pulmonary vascular resistance, and decreased arterial-mixed venous oxygen content difference. As HPS progresses it can lead to decreased oxygenation induced by changes in posture such as platypnea – increase in dyspnea when sitting or standing upright and relieved by lying down or orthodeoxia – desaturation in the upright position relieved in a recumbent position.

The reason it is important to make a diagnosis of HPS is that it negatively impacts outcome after liver transplantation, particularly with a PaO$_2$ less than 60 mmHg.

The diagnosis can be confirmed in several ways. Contrast-enhanced echocardiography is used to document the presence of IPVDs. This can be performed with dye (indocyanine green) or agitated saline producing bubbles (bubble echo). In the absence of shunts, the dye/bubbles should only be seen in the right heart as the dye/bubbles do not clear the pulmonary capillary circulation. With a right to left shunt, the dye/bubbles will be seen in the left heart, within 3 heartbeats for an intracardiac shunt and 3–6 heartbeats for an intrapulmonary shunt.

Other methods for the detection of shunting include technetium labeled macroaggregated albumin (MAA) scanning. The labeled MAA should not traverse the pulmonary capillary bed but will be seen in the kidneys or brain, if intracardiac or intrapulmonary shunting is present. Pulmonary angiography should be reserved for cases where the diagnosis is still not certain after contrast echocardiography or MAA scan.
Routine chest imaging is typically normal in HPS. Lung function assessments can be abnormal although in a non-specific pattern. The diffusion capacity for carbon monoxide (DLCO) is usually decreased. Arterial blood gases in HPS are abnormal. A PaO<sub>2</sub> of less than 80 mmHg on room air is usual and the Aa gradient is usually greater than 20 mmHg.

The shunt fraction gives an estimate of the degree of shunting and requires measuring the PaO<sub>2</sub> while breathing 100% O<sub>2</sub> for 20 min. The formula is:

\[
\frac{Qs}{Qt} = \frac{([PAO_2 - PaO_2] \times 0.003)}{[([PAO_2 - PaO_2] \times 0.003)+5]}
\]

where Qs is the shunt flow and Qt is the total flow and PAO<sub>2</sub> is the alveolar partial pressure of oxygen and PaO<sub>2</sub> is the arterial partial pressure of oxygen.

The normal shunt fraction is 5%. Anything above 20–30% increases the risk of poor outcome after transplantation.

The only effective treatment for HPS is liver transplantation. Case reports detail the use of various agents including somatostatin analogues, methylene blue and indomethacin and are usually unsuccessful. TIPS has also been tried with limited improvement.

Several case series have documented good outcome after liver transplantation in selected patients with HPS. Although survival is not at levels seen in patients without HPS, the survival benefit of transplant is significant. Resolution of HPS after transplant is variable and can be seen after a few days or up to a year.

Most patients will need a model for end stage liver disease (MELD) exception as biological MELD scores are seldom at a level where transplant is likely, particularly in patients with blood type A or O.

References

1. Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. Lancet 2004;363:1461.
2. Krowka MJ, Mandell MS, Ramsay MA et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. Liver Transpl 2004;10:174.
Case 29

A 51-year-old man presents to the emergency room complaining of difficulty swallowing for the last few hours. He has a history of alcoholic cirrhosis and continues to drink. His liver disease has been complicated by variceal bleeding in the past and he has undergone band ligation of grade II esophageal varices, the last being 3 months ago but did not follow-up for a repeat session. He also has ascites controlled on diuretics and some mild encephalopathy.

According to his girlfriend who is with him he has been otherwise well without fever, abdominal pain or weight loss. He was out with a group of friends at a local bar drinking heavily when he first noted the symptoms but he is still intoxicated and difficult to comprehend.

His exam demonstrates normal vital signs. He is alert but mildly confused. There are no localizing neurological signs and his abdomen is mildly distended with normal bowel sounds. He has mild ankle edema.

Laboratory Studies

Hb 10.6 g/dl
Platelets 58,000/μl
INR 1.7
Creatinine 1.4 mg/dl
Tbili 3.3 mg/dl
AST 48 iu/l
ALT 17 iu/l
Albumin 2.4 g/dl

Questions

1. Is an endoscopy indicated or should he undergo imaging with oral contrast first?
2. If yes-how should the patient be sedated?
Fig. 29.1  EGD image

Fig. 29.2  EGD image
Case 27–65

**Answer: Esophageal Stricture Secondary to Band Ligation**

This man is not doing himself any favors. He has decompensated cirrhosis and yet continues to drink. He has developed dysphagia and the sudden onset is suggestive of a food bolus impaction. A contrast study in this situation would be inadvisable due to the risk of aspiration. This will also be an issue in terms of sedating the patient if an EGD is planned.

The patient actually underwent EGD under general anesthesia, since we were concerned about airway protection in the event of a bolus impaction, but also given his inebriated state. In general, anesthesiologists I have worked with would much prefer to intubate a patient like this rather than use moderate sedation. This patient may have proved particularly difficult to sedate using midazolam. Propofol would be an option but the airway would not be protected. There is some literature comparing moderate sedation with general anesthesia in this situation that suggests no real difference in outcome, but I would caution against sedation without airway protection in such a patient.

The images show a food bolus (Fig. 29.1; he was eating chicken wings with the beer) that was easily removed but there was an underlying stricture as seen in Fig. 29.2 with the arrow pointing to a pressure ulcer. The stricture was from repeated banding, which is actually surprisingly uncommon. Reviewing the literature on many studies of banding, strictures are very uncommon, particularly compared to sclerotherapy.

The patient still had varices proximal to the stricture and underwent dilation using a 10 mm pneumatic balloon with some relief. He was instructed to chew thoroughly and drink plenty of fluid with meals (not alcohol!). There is no literature on the best way to dilate such a stricture but we felt it was safer to use a balloon and avoid the proximal varices rather than Savary or Maloney push dilators.

**References**

1. Schmitz RJ, Sharma P, Badr AS et al. Incidence and management of esophageal stricture formation, ulcer bleeding, perforation, and massive hematoma formation from sclerotherapy versus band ligation. Am J Gastroenterol 2001;96:437–41.
2. Villanueva C, Miñana J, Ortiz J et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med 2001;345:647–55.
Case 30

A 52-year-old man presents to your clinic for follow-up. He has a history of cirrhosis secondary to hepatitis C and alcohol but has been abstinent for several years. His hepatitis C was treated in the past with pegylated interferon but he did not respond.

His disease has been well compensated without ascites or encephalopathy, although he has small varices on endoscopy. It has been over a year since his last visit.

He has no past medical history and is only taking some milk thistle. He is not working and continues to smoke. He has a remote history of intravenous drug use.

On exam, his vital signs demonstrate weight 205 pounds, BP 120/70, pulse 65 and he is afebrile. He has mild palmar erythema, no scleral icterus and normal cardiovascular and respiratory systems.

Abdominal exam demonstrates a palpable liver edge and a spleen tip but no ascites and no ankle edema. He has no asterixis.

Laboratory Studies

Hb 12.5 g/dl
Platelets 64,000/μl
INR 1.5
Creatinine 1.2 mg/dl
Tbili 1.9 mg/dl
AST 47 iu/l
ALT 34 iu/l
ALP 112 iu/l
Albumin 2.7 g/dl
AFP 12ng/ml

Questions

1. What options, if any are available to this patient?
2. Is he a candidate for liver transplant?
Fig. 30.1  CT scan

Fig. 30.2  CT scan
Answer: Multifocal Hepatocellular Carcinoma

This gentleman has developed at least three lesions in the liver. The largest is hypervascular and is shown in the first image. It measures 4 cm in diameter. Two smaller lesions are seen in the lower image and appear not to enhance but still are suspicious for hepatocellular carcinoma (HCC). The liver has a nodular contour and the spleen is enlarged consistent with cirrhosis and portal hypertension.

The approach to HCC is well described in American Association for the Study of Liver Diseases (AASLD) guidelines (referenced below). The important points to remember are that biopsy is seldom required to make a diagnosis. Any hypervascular lesion in a cirrhotic liver is considered to be HCC until proven otherwise and biopsy runs the risk of seeding the needle track with HCC cells. I have seen a case of recurrent HCC in the abdominal wall of a patient after liver transplant that had had a liver biopsy a year prior to transplant.

The size and number of lesions are important. A seminal paper published in the 1990s established the Milan criteria that determined that patients with a single lesion less than 5 cm, or three lesions less than 3 cm without vascular invasion or metastases, had good 4-year survival after liver transplant, compared to patients transplanted beyond these criteria. Based on this, the current MELD organ allocation system in the USA allows for an exception of 22 points if the patient’s actual MELD score is lower than this (which is invariably the case) in patients who have a T2 tumor (so within Milan criteria but also a single lesion needs to be greater than 2 cm in diameter).

Other studies have suggested that the Milan criteria are too strict and lesions up to 6.5 cm should be considered for transplant (the UCSF criteria) and some regions in the USA would provide a MELD exception for lesions this size.

The options for this patient are limited. He could get chemoembolization or radiofrequency ablation of the larger lesion. Systemic chemotherapy is rarely effective for HCC.

A live donor liver transplant is still an option for this patient since he would not need a MELD exception for a deceased donor organ. However, it should be made clear to the patient and the donor that there is a very significant risk of HCC recurrence.

References

1. Mazzaferro V, Regalia E, Doci R et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
2. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–36.
Case 31

A 46-year-old male presents to the ER with pain and abdominal distension. He has a history of alcoholic cirrhosis that has been complicated by ascites, encephalopathy and the presence of esophageal varices on endoscopy although he denies any bleeding.

For the last 24 h, he has experienced increasing abdominal pain, mainly peri-umbilical with nausea and vomiting. He has had no fever.

He is currently on a small dose of diuretics, lactulose, and nadolol.

He still smokes but quit drinking about a year ago. His ex-wife is with him but his social situation is poor as he lives alone and has recently lost his job. He has no children.

On exam, he has mild tachycardia but normal blood pressure. He is afebrile. He has mild scleral icterus.

His cardiovascular and respiratory systems are normal. His abdomen is distended with a fluid thrill but is tympanitic with increased bowel sounds. He has a 4–5 cm umbilical hernia that is tender and can be reduced with difficulty.

Laboratory Studies

Hb 12.4 g/dl
Platelets 59,000/μl
INR 1.6
WBC 13.5 × 10^9/μl
Tbili 3.1 mg/dl
AST 48 iu/l
ALT 32 iu/l
ALP 89 iu/l
Albumin 2.8 g/dl
Creatinine 2.4 mg/dl

Plain abdominal films show small bowel with air–fluid levels and a decompressed colon.

Questions

1. Does this patient need any further testing?
2. What is important to calculate?
3. Should this patient undergo surgery?
4. What if the hernia becomes strangulated, does this change the decision?
Calculated MELD score: 24
Answer: Risk Assessment in Cirrhotic Patients Undergoing Surgery

This is a common scenario in a busy hospital. A patient with liver disease who has a condition that likely needs surgery, in this case small bowel obstruction from his umbilical hernia.

He really does not need any other investigation but he needs nasogastric suction, intravenous fluids and analgesia as required and hopefully he will improve with these conservative measures. The problem will arise if he does not improve or if the clinical situation deteriorates such as strangulation of the hernia.

In general, elective surgery should be avoided in patients with decompensated liver disease. Several predictive models exist to determine the risk of morbidity and mortality after surgery in such patients, but the risk depends on the severity of liver disease and also the type and urgency of the surgery. This patient has a Child–Pugh score of 10 or 11 making him a Child’s C and his MELD score is given as 24. He is at very high risk of decompensation and surgery should be avoided if at all possible. However, if he worsens and has a potentially fatal disorder (strangulated hernia would count), then he needs to be operated on.

Several studies have quantified the risk depending on the type or surgery and its urgency. In cirrhotic patients undergoing abdominal surgery, Child’s class A, B, and C correspond to postoperative mortality of 10, 30, and 80%, respectively. The Child–Pugh score is somewhat subjective and in recent years, the MELD score has been used to assess mortality in liver patients. The MELD score incorporates three biochemical measurements into a complex logarithmic formula – the total bilirubin concentration, serum creatinine, and the international normalized ration (INR). Patient scores range from 6 to 40, with 6 reflecting “early” disease and 40 “severe” disease. The largest study of almost 800 cirrhotic patients undergoing major digestive, orthopedic, or cardiac surgery demonstrated that the MELD score correlated with short-term and long-term mortality extending out to 20 years. For each point increase in the MELD score above 8, there was a 14% increase in 30-day and 90-day mortality. The type of surgery is important but all emergent surgery increases the risk.

Unfortunately, it is all too common to see a patient in the liver clinic who was referred for decompensated liver disease who states that they were completely well until they underwent elective surgery several months ago, or worse still, someone is transferred from another institution as an inpatient and had a recent umbilical hernia repair and now is draining ascites from the wound and has developed hepatorenal syndrome (HRS).

The reasons for worsening of liver disease after surgery are unclear but may reflect circulatory changes brought on by surgery or anesthesia resulting in impaired hepatic vascular flow.
References

1. Malik SM, Ahmad J. Preoperative risk assessment for patients with liver disease. Med Clin North Am 2009;93:917–29.
2. Teh SH, Nagorney DM, Stevens SR et al. Risk factors for mortality after surgery in patients with cirrhosis Gastroenterology 2007;132:1609–1611.
Case 32

A 30-year-old Filipino woman presents with a 4-month history of progressive fatigue, jaundice, severe, generalized pruritus, dark urine, and pale stool. She has no history of abdominal pain, nausea, vomiting, no prior history of jaundice or viral hepatitis. She takes no medications and there is no family history of liver disease. She has had a prior cholecystectomy.

Physical examination reveals excoriations on skin from scratching. She has marked scleral icterus, no hepatosplenomegaly or ascites. No cutaneous stigmata of chronic liver disease.

Lab Results

Total bilirubin 19 mg/dl  
Direct bilirubin 13.7 mg/dl  
ALP 1833 iu/l  
GGTP 1756 iu/l  
ALT 194 iu/l  
AST 216 iu/l  
Albumin 3.2 g/dl  
Prothrombin time 21 seconds

Ultrasound shows mild hepatomegaly. There is no biliary ductal dilation, patent hepatic vessels, absent gall bladder, no splenomegaly or ascites.

Questions

1. How would one classify the pattern of this patient’s jaundice and abnormal liver enzyme elevation?  
2. What is the differential diagnosis?  
3. What additional diagnostic procedure should be performed?
Fig. 32.1  Liver biopsy H&E ×200

Fig. 32.2  Liver biopsy H&E ×400
Answer: Idiopathic Adulthood Ductopenia

This patient has cholestatic jaundice and more specifically *intrahepatic* cholestasis by virtue of the fact that the ultrasound does not demonstrate biliary ductal dilation.

Additional blood tests showed negative ANA, ASMA, and AMA. Her serum ACE level was normal and quantitative immunoglobulins revealed normal IgG and IgM levels.

Due to concern for a biliary process despite the negative ultrasound, she underwent an ERCP but the cholangiogram was normal without evidence of biliary duct beading or strictures.

The images show her liver biopsy. The first is at low power (Fig. 32.1) demonstrating brownish deposits, consistent with severe chronic cholestasis. There is also an absence of interlobular bile ducts in the portal area.

At higher power (Fig. 32.2), a portal tract is seen and confirms the absence of bile ducts and the presence of a mild chronic inflammatory infiltrate, including lymphocytes, neutrophils, and plasma cells.

The differential diagnosis is lengthy and includes:

- Primary biliary cirrhosis (PBC)
- Small duct primary sclerosing cholangitis (PSC)
- Autoimmune cholangitis
- Drug-induced cholestasis
- Ischemic bile duct damage
- Benign recurrent intrahepatic cholestasis
- Cholestasis of pregnancy
- Infectious cholangiopathy
- Total parenteral nutrition
- Sepsis-related cholestasis
- Chronic liver allograft rejection
- Graft versus host disease
- Infiltrative disorders: sarcoidosis, amyloid, cystic fibrosis, lymphoma
- Idiopathic adulthood ductopenia

As can be seen, all autoimmune serologies were negative and many of the other possible diagnoses were excluded as they were not clinically applicable.

A liver biopsy confirmed extreme paucity of bile ducts and a diagnosis of *idiopathic adulthood ductopenia* was made. The patient underwent successful orthotopic liver transplantation.

This condition was first described by Jurgen Ludwig in 1988, is similar to the infantile condition, Alagille’s syndrome and has an obscure natural history. Orthotopic liver transplantation is the only effective treatment. It is diagnosed in an adult patient with biochemical cholestasis, biopsy evidence of ductopenia (loss of interlobular or septal bile ducts in at least 50% of portal tracts). The diagnosis also requires a negative AMA, normal cholangiogram, no history of infantile cholestasis, no exposure to drugs or toxins that could produce cholangitis and no evidence of sarcoidosis or malignancy.
References

1. Ludwig J, Wiesner RH, La Russo NF. Idiopathic adulthood ductopenia: a cause of chronic cholestatic liver disease and biliary cirrhosis. J Hepatol 1988;7:193–9.
2. Sherlock S. The syndrome of disappearing intrahepatic bile ducts. Lancet 1987;2:493–6.
Case 33

A 47-year-old male presents with several episodes of hematemesis and melena. He has a history of cirrhosis secondary to alcohol and hepatitis C, which has been complicated in the past by multiple admissions for variceal hemorrhage, encephalopathy, and ascites. He continues to drink alcohol and has been very noncompliant in terms of follow-up.

He has previously undergone band ligation of esophageal varices and a TIPS was placed 2 years ago. He has also undergone coil embolization of gastric varices and several revisions of his TIPS, the last being several months ago.

He has not taken any prescribed medication for more than a month after his prescriptions ran out.

Exam demonstrates a disheveled looking man with a BP of 120/80 and pulse 104 beats per minute, regular.

He is alert and oriented and his abdomen is mildly distended. Melena is noted on rectal exam.

Laboratory Parameters

Hb 7.6 g/dl  
Platelets 62,000/μl  
INR 1.5  
Creatinine 0.8 mg/dl  
Tbili 2.5 mg/dl  
AST 88 iu/l  
ALT 48 iu/l  
GGTP 495 iu/l

After adequate resuscitation, he undergoes upper GI endoscopy that demonstrates small esophageal varices but large varices in the cardia with red wale signs but no active bleeding. Imaging a month ago had shown a patent TIPS and a significant splenorenal shunt.

Question

1. What treatment options are available for this patient (in the USA)?
Fig. 33.1  Angiogram pre-treatment

Fig. 33.2  Angiogram post-treatment
Answer: Balloon Occluded Retrograde Transvenous Obliteration of Varices

This gentleman continues to bleed despite aggressive treatment. He has undergone endoscopic therapy and also TIPS and then an attempt at coil embolization of gastric varices with access through the TIPS. His endoscopy shows gastric varices with stigmata of recent bleeding and he has a low hemoglobin. His continued drinking and poor compliance mean that he is not a good transplant candidate.

His options are limited, particularly in the USA, where cyanoacrylate is not available outside of a study setting.

One potential solution that is increasingly used in Asia is balloon occluded retrograde transvenous obliteration (BRTO). This procedure involves passing a catheter into the inferior vena cava through the femoral vein. The catheter is passed into the left renal vein and then the splenic vein through a splenorenal shunt. The gastric varices can be identified coming off the splenic vein and a balloon is inflated and foam or coils can be deployed to prevent retrograde flow.

In Figs. 33.1 and 33.2, previously place coils can be seen. A catheter is visible with a balloon inflated and filling of large gastric varices is readily apparent. Figure 33.2 was taken 20 min after the injection of a foam sclerosant into the varices and markedly reduced flow is seen.

The patient did well for several months after this but expired from other complications of his liver disease.

There is limited data comparing BRTO with other modalities of treatment. One study compared BRTO to cyanoacrylate injection and found similar initial success rates but noted increased rebleeding with injection therapy.

Complications of BRTO include balloon rupture such that sclerosant can leak into the systemic circulation and can cause pulmonary embolism or recurrent gastric variceal bleeding due to the sclerosant not obliterating the varices. In addition, there is some data that the portosystemic pressure gradient can rise following BRTO with concomitant worsening of esophageal varices.

References

1. Hong CH, Kim HJ, Park JH et al. Treatment of patients with gastric variceal hemorrhage: endoscopic N-butyl-2-cyanoacrylate injection versus balloon-occluded retrograde transvenous obliteration. J Gastroenterol Hepatol 2009;24:372–8.
2. Park SJ, Chung JW, Kim HC et al. The prevalence, risk factors, and clinical outcome of balloon rupture in balloon-occluded retrograde transvenous obliteration of gastric varices. J Vasc Interv Radiol 2010;21:503–7.
Case 34

A 28-year-old woman is admitted to the ICU with a 2-week history of abdominal pain, nausea, vomiting, generalized malaise, and fevers to 103°F. There is no history of bleeding or confusion. There is no relevant prior medical problems and no history of prescription or over the counter/herbal medications, including no acetaminophen. She denies recent travel or sick contacts. There is no history of alcohol, drugs, tattoos, or blood transfusions.

Physical examination reveals a young woman with mild icterus, no oral mucocutaneous lesions, no stigmata of chronic liver disease. Vital signs show she is febrile to 102°F, blood pressure 110/60, HR 95.

Her abdomen has mild diffuse tenderness with no guarding or rebound. No hepatosplenomegaly or ascites is appreciated. She is alert and oriented without asterixis.

Admission Lab Results

Total bilirubin 2.9 mg/dl
AST 20,300 iu/l
ALT 14,050 iu/l
ALP 93 iu/l
GGTP 250 iu/l
Albumin 3.0 g/dl
INR 10.6 (PT 117 s)
WBC 23.2 (25% bands)
Platelets 55 × 10⁹
Hgb 13.4 g/dl
Creatinine 0.7 mg/dl

Questions

1. What is this patient’s clinical diagnosis?
2. What is the differential diagnosis for her elevated LFT’s?
3. How should she be managed?
Fig. 34.1  Liver biopsy H&E ×100

Fig. 34.2  Liver biopsy H&E ×250
Fig. 34.3  Liver biopsy immunostain
Answer: Acute Herpes Simplex Virus (HSV) Hepatitis

The clinical diagnosis is that of “acute severe hepatitis”. The liver enzymes are indicative of a marked hepatocellular or necroinflammatory injury pattern.

By definition, the patient does not yet fulfill criteria for “fulminant hepatic failure” as she has no clinical encephalopathy. The original description of fulminant hepatic failure by Trey and Davidson in 1970 was that of the onset of altered mental status (hepatic encephalopathy) within 8 weeks of initial symptoms in an otherwise healthy individual without preexisting liver disease.

The differential diagnosis for acute, severe hepatitis includes:

- Acetaminophen overdose
- Autoimmune hepatitis
- Viral hepatitis (hepatitis A, B, E, HSV, CMV, EBV)
- Drug-induced
- Ischemic hepatitis (shock liver)
- Wilson’s disease

The patient is at high risk of progressing to fulminant hepatic failure and should be managed in a liver transplant center and monitored closely for the development of hepatic encephalopathy, which could indicate the presence of cerebral edema. Frequent neurologic checks are required.

Hospital course: within 18 h of admission, the patient had a rapid deterioration in her clinical condition with the development of grade 4 encephalopathy requiring intubation, ARDS requiring mechanical ventilation, acute renal failure, pancreatitis (amylase 9,600, lipase 8,300), DIC, gastrointestinal bleeding, and severe acidosis.

The patient ultimately died despite aggressive medical care.

A postmortem examination revealed massive, hemorrhagic hepatic necrosis involving 99% of the parenchyma as seen in Fig. 34.1. There were intranuclear inclusions (arrowed in Fig. 34.2) and an immunostain was positive for herpes simplex virus (Fig. 34.3). Serologies yielded a (+) HSV-1 IgM antibody.

HSV-1 and HSV-2 produce a wide variety of illnesses including mucocutaneous infections, CNS infections, and occasional infections of visceral organs (which could be life threatening). HSV hepatitis is a rare disease in adults, but does have a high mortality, especially if not diagnosed early. The disease can occur in immunocompetent patients, often characterized by the absence of mucocutaneous involvement.

Other clues to the diagnosis:

- High fevers
- Marked liver transaminase elevation
- Relatively low total bilirubin level
- Leukopenia (although not seen in the case presented here)

When suspected, IV acyclovir should be administered immediately. Liver transplant ought to be considered in patients where medical management fails to improve the disease course.
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Case 35

A 58-year-old woman was admitted with a 2-week history of progressive jaundice, dark urine, acholic stool, and abdominal distension. She had been in her usual state of health until 6 weeks previously. There was no personal or family history of liver disease, no risk factors for viral hepatitis, no history of alcohol use. Medical history was significant for locally invasive infiltrating ductal Ca of the left breast 6 years previously (estrogen receptor (ER) positive, progesterone receptor (PR) negative), for which she underwent mastectomy with axillary node clearance followed by adjuvant chemotherapy and tamoxifen.

Physical examination revealed scleral icterus, mild hepatomegaly with a liver edge three fingers below right costal margin, no splenomegaly and moderate ascites. There were no cutaneous stigmata of chronic liver disease and no asterixis.

Lab Results

- Total bilirubin 6.8 mg/dl
- Direct bilirubin 4.0 mg/dl
- AST 250 iu/l
- ALT 100 iu/l
- ALP 260 iu/l
- GGTP 451 iu/l
- Albumin 2.4 g/dl
- INR 1.5
- Plt 95,000/μl
- Hb 13.5 g/dl

Questions

1. How would you evaluate this patient further for the etiology of her liver disease?
2. What is the differential diagnosis for the radiographic appearance shown?
Fig. 35.1  CT scan

Fig. 35.2  Autopsied liver
Fig. 35.3  Immunohistochemical stain
Answer: Metastatic Breast Cancer Leading to Pseudocirrhosis

The triphasic CT scan of the abdomen reveals a nodular contour of the liver with heterogeneous attenuation consistent with cirrhosis as well as moderate ascites, but no biliary ductal dilation or splenomegaly.

At first glance, this case appears to be that of decompensated cirrhosis. The patient presents with features of liver failure: jaundice, hypoalbuminemia, prolonged INR, and a cirrhotic appearing liver with evidence of portal hypertension (ascites).

The puzzling issues are that she has no clear risk factors for chronic liver disease, the onset of liver failure has been rather rapid, and she does carry a history of prior malignancy.

Further work-up included:
Serologies for viral, autoimmune, and metabolic etiologies of cirrhosis: all negative.
CEA 250 ng/ml (normal < 5): markedly elevated, raising suspicion of metastatic breast cancer. Ascitic fluid analysis showed a high serum-ascites albumin gradient (SAAG) >1.1 (indicating portal hypertension) and negative cytology.

18F-FDG-labeled PET-CT scan (Fig. 35.1): inhomogeneous uptake consistent with cirrhosis but no focal areas of increased uptake to suggest FDG-avid malignancy.

A liver biopsy was planned; however, the patient had a massive variceal bleed that could not be controlled endoscopically. An emergent TIPS reduced the hepatic portal venous pressure gradient from 30 to 9 mmHg. Despite this, the patient later died and an autopsy revealed the cause of death to be related to the massive variceal hemorrhage and diffuse pulmonary alveolar damage.

The autopsy also revealed grossly evident tumor infiltration of the liver by metastatic tumor (pale, confluent areas in Fig. 35.2). Histopathology (Fig. 35.3) shows diffuse liver infiltration by a poorly differentiated, highly desmoplastic adenocarcinoma. Immunohistochemical stains were positive for CEA and ER, but negative for PR.

The differential diagnosis for a nodular-appearing liver on CT imaging includes: cirrhosis, nodular regenerative hyperplasia (NRH), and “pseudocirrhosis”, where the hepatic histology shows evidence of extensive fibrosis, representing a profound desmoplastic response to the infiltrating tumor. This case is an example of “pseudo-cirrhosis.” The only way to differentiate these three entities is via liver biopsy.

It is interesting that the PET-CT did not unequivocally demonstrate metastatic breast cancer in our patient’s liver. In one study, this radiologic modality has a 93% sensitivity, 79% specificity, 82% positive predictive value, and 92% negative predictive value.
References

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Case 36

A 52-year-old Caucasian male presents to his primary care physician with a 1-week history of fatigue, malaise, and anorexia. Over the last 2 days, he has noticed darkening of his urine and lightening in the color of his stools. He denies any fevers or chills, abdominal pain or pruritus. Remainder of review of symptoms is negative. He has a medical history significant for noninsulin-dependent diabetes. He has been on metformin and pioglitazone for over 3 years and is on no over the counter or herbal medications. He has not been on any recent antibiotics. He is married with three healthy children and works full time as an automotive mechanic. He drinks 6–8 beers on weekends and has no history of illicit drug use. His father died at the age of 59 from a sudden heart attack.

Physical exam is notable for a middle aged male in no apparent distress. He is afebrile with a heart rate of 98 beats per minute. His BMI is 29.5 kg/m². He is jaundiced with scleral icterus. Abdominal exam is soft and nontender without hepatosplenomegaly. He has no lymphadenopathy. He is mentating well and has no asterixis. There are no stigmata to suggest chronic liver disease.

Laboratory Parameters

Tbili 8.5 mg/dl
Direct 6 mg/dl
AST 1696 iu/l
ALT 3310 iu/l
ALP 155 iu/l
GGTP 229 iu/l

Normal renal function and hemogram
INR 1.4

Questions

1. What is the differential diagnosis?
2. What test(s) should you order?
3. What are potential treatment options?
HBs Ag: +
anti HBs: negative
anti HBe Total: +
anti HBe IgM: +
HBe Ag +
HBe Ab –
HBV DNA: 3,511,928 iu/ml
Answer: De Novo Acute Hepatitis B Infection

The liver enzyme abnormalities in this case are primarily hepatocellular in nature. The extreme elevations in transaminases with marked elevation in bilirubin narrow the differential diagnosis to a handful of disease entities, including: acute viral, autoimmune hepatitis, and drug-induced liver injury. Although the degree of injury would be categorized as “severe” based on the elevation in liver function tests and bilirubin, the patient does not fulfill criteria for acute liver failure as there is no evidence of encephalopathy or coagulopathy. In addition to supportive care and careful monitoring for evidence of impending liver failure, laboratory testing should be sent for hepatitis A, B, C and an autoimmune panel. A right upper quadrant ultrasound would be reasonable to ensure no evidence of underlying chronic liver disease.

The patient’s serologies indicate acute hepatitis B infection. The first detectable viral marker is HBsAg followed by hepatitis B e antigen (HBeAg) and HBV DNA. Titors may be high during the incubation period, but HBV DNA and HBeAg levels begin to fall at the onset of illness and may be undetectable at the time of peak clinical illness. Core antigen does not appear in blood, but antibody to this antigen (anti-HBc) is detectable with the onset of clinical symptoms. The positive IgM antibody is the hallmark of an acute hepatitis B infection.

The Center for Diseases Control estimate between 140 and 320,000 cases of acute hepatitis B yearly in the USA. About 30% of patients develop symptoms with nearly 15,000 requiring hospitalization. Symptoms usually develop 2–4 months following exposure to the virus. Transmission of the virus is predominantly via sexual contact, percutaneous exposure (IVDU), or vertical transmission (mother to child). As is the case in the patient above, a significant number of times the etiology of transmission is never determined. The highest concentration of the virus is found in blood, semen, vaginal discharge, breast milk, and saliva. The time period between exposure and onset of symptoms is referred to the “incubation period.” The most common symptoms are fatigue, anorexia, abdominal pain, and jaundice. As opposed to hepatitis A infection, fever is uncommon in HBV.

AST and ALT levels increase to between 500 and 5,000 iu/l and fall after the acute phase. Serum bilirubin seldom increases above 10 mg/dl. Alkaline phosphatase and prothrombin time are usually normal or mildly elevated.

The virus is spontaneously cleared in 95% of adults with acute infection, with the remainder of individuals developing chronic infection. This is in contrast to neonates and children infected with hepatitis B where a majority will develop chronic infection. Because of the natural history and spontaneous clearance, treatment is almost never needed in adults with acute hepatitis B infection. Although some small studies suggest that antivirals such as lamivudine may prevent the progression of severe infection to fulminant status and because of their excellent safety profile may be considered in rare, severe cases. Acute liver failure develops in 0.5–2% and is associated with fatality in up to 93% of cases without liver transplantation.
From 1990 to 2002, the incidence of reported cases of acute hepatitis B declined by 67% secondary to routine vaccination in children and adolescents. The incidence, however, has increased by 5% in men above the age of 19, 20% in men above the age of 40, and 30% in women above the age of 40. The highest incidence is seen in African Americans and Hispanics.

The gentleman in this case was discharged on hospital day 4 when his enzymes began a downward trend. Recommendations were given to the patient and his family to avoid sharing of razor blades and toothbrushes. His spouse was vaccinated against HBV.

The patient was seen in follow-up and at 4 months he developed complete normalization of his enzymes and seroconversion with the appearance of surface antibody:

- HBsAg −, anti HBs 290 miu/ml, anti HBcore total +, anti HBcore IgM −, HBeAg −, HBeAb +, HBV DNA undetectable.

References

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Case 27–65

A 53-year-old man presents to the emergency room with hematemesis. He has a history of cryptogenic cirrhosis and has been evaluated for liver transplant in the past but was felt to be early based on a low MELD score.

His wife is with him and states that he was feeling fine up until a few hours ago when he started complaining of some abdominal discomfort. There has been no fever or chills and as far as she is aware, his bowels have been moving normally without blood or change in stool color. His appetite has been good and there has been no weight loss.

His liver disease has been well compensated in the past and his only medication includes a small dose of beta-blocker.

He does not smoke or drink and works fulltime.

In the ER, he looks comfortable but anxious. His vital signs are BP 110–75, pulse 64 and he is afebrile.

He has a few spider nevi but no scleral icterus. His heart and lungs are normal. Abdominal examination demonstrates an enlarged liver and spleen but no ascites or ankle edema. While being examined, he has another episode of hematemesis with what appears to be a very large amount of fresh blood and clots.

Initial Laboratory Studies

Hb 7.4 g/dl  
Platelets 56,000/μl  
INR 1.5  
Tbili 1.9 mg/dl  
AST 38 iu/l  
ALT 32 iu/l  
ALP 101 iu/l  
GGT 49 iu/l  
Albumin 2.9 g/dl  
Creatinine 0.8 mg/dl

He is emergently intubated, resuscitated and transferred to the intensive care unit and started on a somatostatin analogue, and antibiotics. Endoscopy shows actively bleeding large esophageal varices and a large amount of fresh blood and clot in the stomach obscuring the fundus. Despite several attempts at endoscopic treatment, the bleeding cannot be controlled.

Questions

1. What is/are the next option(s)?
2. What imaging is required in the ICU?
Fig. 37.1 Angiogram

Fig. 37.2 Angiogram
Fig. 37.3  Angiogram
Answer: Transjugular Intrahepatic Portosystemic Shunt (TIPS)
as Salvage Therapy for Variceal Bleeding

This gentleman has a life-threatening problem. He has actively bleeding esophageal varices that cannot be controlled despite pharmacological therapy with a somatostatin analogue (in the USA this would typically be octreotide) and endoscopic therapy. In addition, he may have bleeding gastric varices but the fundus is obscured. Endoscopic treatment of bleeding esophageal varices is successful 80–90% of the time, but this figure is not nearly as high with gastric variceal bleeding.

The definition of failure of endoscopic therapy is controversial but most authorities would agree that inability to stop bleeding with two endoscopies within 14 days is reasonable. This patient has failed endoscopic therapy since he continues to bleed even after the first procedure. An appropriate intervention for short-term cessation of bleeding at this time would be balloon tamponade. Several balloons are available including the Sengstaken-Blakemore tube (which has gastric and esophageal balloons and a single gastric suction port), the Minnesota tube (a Sengstaken-Blakemore tube with an esophageal suction port as well), and the Linton-Nachlas tube (which has a single gastric balloon). These can be used for 12–24 h to control ongoing bleeding. At some point, the patient should get a bedside ultrasound to ensure that the portal vein is patent.

Figures 37.1–37.3 show insertion of a TIPS which involves the creation of a low-resistance connection between the hepatic vein and the intrahepatic portion of the portal vein by an interventional radiologist. The connection is kept patent by the deployment of an expandable metal stent across it, so that some of the portal venous blood flow is shunted to the systemic circulation, thereby decreasing portal pressure and decreasing variceal bleeding. Several studies have shown that TIPS is very effective for refractory variceal hemorrhage. The TIPS is formed by passing a needle catheter via the transjugular route into the hepatic vein and wedging it there. The needle is then extruded into the liver parenchyma and attempts are made to find a branch of the intrahepatic portion of the portal vein. Figure 37.1 shows the catheter in place in the portal vein. A series of balloon catheters are then used to dilate the tract from the hepatic vein to the portal vein (Fig. 37.2) and the stent, which is typically a 10-mm diameter covered wire mesh device, is inserted (Fig. 37.3).

To assess the response, pressures are measured. In this patient, the pre-TIPS angiogram demonstrated hepatofugal flow from the portal system into a prominent paraumbilical vein and left coronary vein (top right of first image). The wedged pressure in the hepatic vein was 40 mmHg (a measure of portal pressure) and the free hepatic vein pressure was 16 mmHg giving a portosystemic gradient of 24 mmHg pre-TIPS consistent with portal hypertension. After the TIPS, the gradient dropped to 9 mmHg and the post-TIPS angiogram demonstrated flow through the TIPS shunt with decreased filling of the paraumbilical vein and left coronary vein.

The main complication of TIPS is the development of portosystemic encephalopathy (PSE), which occurs 30% of the time and can be debilitating. We typically will start the patient on lactulose prior to TIPS. Very occasionally, a TIPS needs to be deliberately occluded due to severe PSE (usually in elderly patients). Regular imaging is suggested after TIPS with Doppler sonography to ensure patency, although newer covered stents have lower stenosis rates.
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4. Chau TN, Patch D, Chan YW et al. “Salvage” transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. Gastroenterology 1998;114:981–7.
Case 38

A 31-year-old Caucasian female nurse of Spanish/Portuguese descent was evaluated by her primary care physician for complaints of fatigue and lower extremity paresthesiae. A thyroid mass was palpated on exam that prompted a biopsy revealing papillary thyroid cancer. Her only other medical history is heterozygosity for factor V Leiden deficiency without prior thrombus, for which she is maintained on 81 mg of aspirin daily. The patient was employed full time as a nurse; however, she was no longer able to work due to her current symptoms. She is separated and has one healthy 7-year-old son. She previously smoked 1/2 pack of cigarettes per day, drinks seldomly, and has no history of illicit drug use. She has two tattoos, the first obtained 12 years ago. Her mother died at the age of 37 from sudden cardiac death, which was thought to be related to heart failure. Several other family members on her mother’s side have had early death from a variety of diseases and all had the same fatigue and paresthesiae, and were thin (with some suggestion of a bulimia type eating disorder due to constant vomiting). Review of systems is positive for constipation, light headedness, and blurred vision from her right eye. The patient undergoes thyroidectomy and removal of 2.2 cm papillary thyroid cancer with no evidence of vascular invasion or lymph node metastases. She is treated successfully with postoperative radiation.

She is referred to the liver clinic by her oncologist because of abnormal liver tests in a mixed pattern.

Physical exam is notable for a healthy young female with a BMI of 25.8 kg/m². Her supine blood pressure is 118/62 with a heart rate of 62, upon standing she does complain of light headedness and her repeat blood pressure is 88/42 with a heart rate of 96. She has no stigmata to suggest chronic liver disease. Her abdominal exam is normal.

She has normal renal function and hemogram.

Questions

1. What is the diagnosis?
2. Is liver transplantation a viable option?
3. How would the diagnosis of thyroid cancer affect her status as a candidate?
Fig. 38.1  Rectal biopsy H&E ×100
Answer: Familial Amyloidosis and Liver Transplantation

This patient has familial amyloid polyneuropathy (FAP). FAP is an autosomal dominant multisystemic fatal disorder, characterized by a progressive peripheral neuropathy and autonomic neuropathy with neural and systemic amyloid deposits. The disease is caused by a mutant gene on chromosome 18. The amyloid protein in type 1 FAP (the most common form) is the variant transthyretin in which methionine is a substitute for valine at position 30 (TTR Met 30). More than 90% of TTR Met 30 is produced by the liver.

Amyloidosis is a generic term that refers to the extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins, many of which circulate as a constituent of plasma. There are at least 25 different human protein precursors of amyloid fibrils known.

As in this particular case, a majority of patients with FAP present with peripheral polyneuropathy: pain, sensory loss, and motor disability. Gastrointestinal dysfunction may also develop, including constipation, diarrhea, and sometimes fecal incontinence. A rectal biopsy can show amyloid, particularly on a congo red stain, but can also be seen on a standard H&E stain as shown in Fig. 38.1 with the amorphous pink material between the smooth muscle fibers in the muscularis mucosa. Difficulty in gastric emptying with nausea and vomiting are also frequent. Cardiovascular symptoms range from orthostatic hypotension to different arrhythmias and first and second degree atrioventricular block. Kidney involvement typically manifests as proteinuria with the reduction of the glomerular filtration rate and decreased creatinine clearance.

Although cases of FAP type 1 may be found all over the world, the most important clusters are in Portugal and Sweden. Frequently, the disease is present in either the father or the mother and there are also other family members affected.

Since more than 90% of TTR Met 30 is produced within the liver, it is expected that liver transplantation will stop disease progression and that TTR Met 30 will clear from the serum. The first orthotopic liver transplantation for FAP patients was performed in 1990. Since 1995, over 1,500 liver transplantations for FAP have been performed, on average 110 patients with FAP are transplanted per year (http://www.fapwtr.org/ram1.htm).

It is now established that liver transplantation for symptomatic patients with FAP is an acceptable treatment for the disease and at the current time the only way to halt disease progression. Key points which have been gained from the experience with transplantation in these patients include:

1. The earlier the transplant after the onset of symptoms the better the outcome.
2. Caution should be warranted before listing patients with longstanding disease (greater than 6 years) as many of these patients will not have regression of their signs and symptoms.
3. Consideration should be given to combined heart–liver transplantation in those patients with orthostatic hypotension and cardiac arrhythmias
4. A complete screening of renal function should be performed and combined liver–kidney transplantation should be considered in patients with moderate-to-severe kidney involvement.
5. Domino transplant seems to be a safe way to increase donor offers and so far there is no evidence of FAP de novo in the recipient.

At the present time, there is no consensus on the optimum window of time between presumed cure of various extrahepatic malignancies and liver transplantation, and each case needs to be taken individually. As recommended in the current AASLD guidelines on liver transplantation, close consultation was obtained with oncology before listing this patient for liver transplantation.

The patient in this case received a living donor liver transplant from her 27-year-old sister who tested negative for FAP. The patient’s liver upon explant showed intact architecture with predominantly portal-based amyloid deposits and was used in a domino fashion to transplant a 67-year-old woman with HCV cirrhosis and HCC.

References

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Case 39

A 25-year-old Caucasian female is admitted to the hospital with a 2-week history of right upper quadrant pain, bloating, nausea, vomiting, and malaise. She endorses chills, but no fevers and has noticed that her urine has become “cola colored.” The patient is single and is sexually active in a monogamous relationship. She has three tattoos and a prior stint with IV heroin; however, she has been clean for several years. She has been drinking a moderate amount of alcohol for the last 7 years, and very heavy amounts for the last 1 year, consuming 5–7 mixed drinks including vodka daily. Her last drink was 2 days prior to admission. She also smokes one-half pack of cigarettes per day. She has been told in the past that she has hepatitis C, although she has never been treated. She has no other significant medical history. She takes a daily oral contraceptive pill. Her parents and younger brother are in good health.

Physical exam reveals a young female who is profoundly jaundiced with deep scleral icterus. Temperature is 100.2°F with a heart rate of 106 beats per minute; her BMI is 26.2 kg/m². She is in no distress and answers questions appropriately although she is lethargic and drifts to sleep several times during your exam. Her abdomen is distended and she has pain to palpation in the right upper quadrant. Her liver is palpable 5 cm below her right costal margin. A hepatic bruit is auscultated in the right upper quadrant. She has no splenomegaly, but shifting dullness is positive. She has 1+ pitting edema bilaterally, palmar erythema but no asterixis.

Laboratory Data Are Notable for

- WBC 18,000 with 91% Neutrophils
- Hg 12 g/dl; MCV 109 fL
- Platelets 155,000/μl
- PT 20 seconds (normal 8–10); INR 2.2
- Tbili 14.5 mg/dl (conjugated 11)
- AST 202 iu/l
- ALT 81 iu/l
- AP 120 iu/l
- GGTP 685 iu/l
- Albumin 3.3 g/dl
- Normal electrolytes and renal function
- HCV Ab +
- PCR undetectable

Questions

1. What is the differential diagnosis?
2. How would you characterize the severity and prognosis of the patient’s illness?
3. What treatment if any would you recommend?
Hounsfield units:
Liver 16
Spleen 42

Fig. 39.1  CT scan
**Answer: Severe Acute Alcoholic Hepatitis**

This young patient has the hallmark clinical features of severe acute alcoholic hepatitis: low-grade fever, jaundice, tender hepatomegaly, leukocytosis, and moderate elevation of AST compared to ALT. Other physical exam findings may include a hepatic bruit, which is reported in >50% of cases and if heard is pathognomonic for the disease. Approximately 25–30% of patients with alcoholic hepatitis present with manifestations of portal hypertension (ascites, varices, encephalopathy), which may be a consequence of advanced fibrosis and cirrhosis or the result of transient portal venous obstruction from hepatic swelling. Up to 50% of patients presenting with acute alcoholic hepatitis will have underlying cirrhosis.

The spectrum of alcoholic liver disease ranges from asymptomatic fatty liver to alcoholic hepatitis to decompensated cirrhosis. Fatty liver or hepatic steatosis is the most common form of alcoholic liver disease and is reversible with abstinence from alcohol intake. Its first clinical manifestation is typically asymptomatic hepatomegaly. As a consequence of preferential alcohol oxidation, the liver develops fatty deposition. Alcoholic fatty liver is rarely diagnosed clinically because most patients are asymptomatic and do not seek medical attention. However, up to 90% of alcoholics have steatosis. Fatty liver can occur within hours after a large alcohol binge. It represents a direct effect of ethanol and can occur despite an adequate nutritional state. The CT scan image (Fig. 39.1), in this case, reveals an enlarged fatty liver (Hounsfield units of the liver are much lower when compared with the spleen; i.e., the liver is less dense, correlating with severe fatty infiltration).

The diagnosis of acute alcoholic hepatitis can almost always be made on clinical grounds and rarely is a liver biopsy needed. In the rare case, where the diagnosis is uncertain a liver biopsy may be obtained revealing hepatocellular disarray; polymorphonuclear cell infiltration in the parenchyma; Mallory’s hyaline bodies (seen in approximately one-third of cases), which are clumps of intermediary cytokeratin filaments due to tubulin–acetaldehyde adducts; and some degree of steatosis, cholestasis, fibrosis, and necrosis. The presence of neutrophils is a hallmark of alcoholic hepatitis and is unusual in chronic viral hepatitis.

Alcohol is metabolized primarily through the liver. Once alcohol is ingested and absorbed through the gut, it is metabolized by both gastric and hepatic alcohol dehydrogenase to acetaldehyde. Acetaldehyde is in turn oxidized by the liver using aldehyde dehydrogenase and the microsomal ethanol-oxidizing system, cytochrome P450 2E1 (CYP2E1).

Heavy alcohol consumption is considered >20 g/day in women and >80 g/day in men. The incidence of cirrhosis is significantly increased in men who consume >40–60 g/day. Approximately 20% of men drinking >12 beers/day will go on to develop cirrhosis in 10 years.

It is estimated that 30% of patients with alcoholic hepatitis are infected with HCV.

A high prevalence (25–65%) of hepatitis C virus infection has been recognized in alcoholics. Such patients tend to have more severe disease, decreased survival, and an increased risk of HCC.
There are several characteristic laboratory abnormalities in patients with alcoholic liver disease, but no lab test in particular is diagnostic. The most common pattern of LFT abnormality is a disproportionate elevation of serum AST to ALT. This ratio is usually greater than 2, a value that is rarely seen in other forms of liver disease. The absolute value of serum AST and ALT are usually less than 500 iu/l (and typically less than 300). The unusual variant “alcoholic foamy degeneration” which is characterized by jaundice and hyperlipidemia can elevate AST as high as 700.

Other lab abnormalities include: marked elevation in GGTP, macrocytosis as a result of poor nutritional status and B12 and folate deficiencies; thrombocytopenia as a result of primary bone marrow hypoplasia or splenic sequestration due to splenomegaly from portal hypertension. Leukocytosis is a hallmark lab finding and correlates closely with the severity of the hepatic injury.

The presentation of alcoholic hepatitis can be dramatic and many times carries a grave prognosis. The prognosis of alcoholic liver disease depends upon its severity. Several predictive models have been proposed, which can also help to guide therapy. The Maddrey’s discriminant function is perhaps the most widely used. It takes into account the elevation in prothrombin time and Bilirubin: $4.6 \times (\text{patient’s PT} - \text{control PT}) + \text{total bilirubin}$. Scores $\geq 32$ are considered severe and warrant consideration for treatment. More recently, the MELD score has been used to prognosticate outcome, with a score of $>11$ considered severe disease.

Therapy is generally supportive and many times futile. Survival in patients admitted to an intensive care unit is approximately 5%. This is especially true when there is concomitant renal failure. In addition to strict abstinence, aggressive nutrition and supplementation, treatment of withdrawal, several studies have shown a role for steroids (prednisolone) or pentoxyfylline. Appropriate patients who have been abstinent for at least 6 months should be considered for liver transplantation.

The patient in the case presented was started on pentoxyfylline 400 mg po TID. Despite treatment, however, over the next several months, the patient deteriorated with the onset of ascites, renal failure, and eventually variceal bleeding requiring endoscopic band ligation. After 6 months of abstinence and formal alcohol rehab, the patient underwent successful liver transplantation. She was seen in the clinic 1 year after her transplant and is doing well and has remained abstinent from all drugs and alcohol.

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Case 40

A 33-year-old Caucasian male with a past medical history significant only for psoriasis, presents to a local emergency room with progressively worsening right flank pain over the last 1 month. He also reports some mild nausea and early satiety. He has unintentionally lost 7 pounds during this period. The remainder of his review of systems is negative. Specifically he denies any dysuria, fevers, or chills. The patient takes a proton pump inhibitor as required for reflux. He has undergone an appendectomy and left inguinal hernia repair over 20 years ago. He is married with one 8-year-old daughter. The patient works in a shipping yard. He smokes 1/2 pack of cigarettes for 15 years. He drinks socially. There is no history of blood transfusions or tattoos. He admits to experimenting with nasal cocaine in high school.

Physical exam is notable for a young gentleman who is slightly anxious, but otherwise appears well. His BMI is 26.7 kg/m². He has no stigmata to suggest chronic liver disease. The patient is tender in his right upper and lower quadrant. Liver edge is palpable 4 cm below the right costal margin. There is no splenomegaly. The remainder of the physical exam is normal.

Laboratory Data

Tbili 1.5 mg/dl
AST 22 iu/l
ALT 28 iu/l
AP 66 iu/l
GGTP 88 iu/l

Albumin 4.2 g/dl
INR 1

AFP 2 ng/ml
CEA 1.2 ng/ml
CA 19-9 0.8 iu/ml

UA: negative

Renal function, hemogram and electrolytes are all normal
Workup for chronic liver disease including HCV is negative

Questions

1. What is the differential diagnosis?
2. What additional testing if any would you recommend?
3. What treatment if any would you recommend?
Fig. 40.1  CT scan
**Answer: Fibrolamellar Hepatocellular Carcinoma**

This patient presented in this case is relatively young with no evidence to suggest chronic liver disease. Tumor markers are normal and CT scan shows a large heterogeneous mass with central scar in what otherwise appears to be normal liver parenchyma (Fig. 40.1). Although the differential would include typical HCC, focal nodular hyperplasia, metastatic tumor, hepatic abscess, and giant cavernous hemangioma, the most likely diagnosis given the clues would be fibrolamellar hepatocellular carcinoma (FLHCC).

FLHCC was first described in 1965 as a distinctive form of primary HCC. Controversy exists as to whether FLHCC is a distinct entity or a morphological variant of HCC. The two differ in many ways including patient demographics, risk factors, tumor markers, and prognosis.

The reported incidence of FLHCC seems to vary by geographical region. The incidence of FLHCC in the USA was reported to be 1–2% of the total HCC cases versus 5.8% of all liver cancers in a Mexican cohort.

More than 85% of all FLHCC cases occur in individuals aged <35 years with the average age being 25. This is in contrast to primary HCC where the mean age at diagnosis is between 50 and 65 years of age. Also in apposition to HCC where males are affected nearly 2:1 compared to females, FLHCC shows an equal frequency among gender.

The etiology of FLHCC is still unknown, although some reports have linked occult HBV and focal nodular hyperplasia and long-term oral contraceptive and estrogen use to the formation of FLHCC there is no solid evidence to suggest causality. In contrast to typical HCC, FLHCC generally occurs in patients without chronic liver disease and cirrhosis.

The diagnosis of FLHCC is made on the combination of clinical presentation, imaging studies, and negative tumor marker, however, pathological diagnosis remains the gold standard. Macroscopically, about 75% of cases have a prominent central scar. Microscopically, FLHCC usually consists of malignant hepatocytes that are well differentiated in a background of noncirrhotic liver. The pathological diagnosis of FLHCC is based upon the following: large tumor cells with deeply eosinophilic cytoplasm, the presence of macronucleoli and abundant fibrous stroma arranged in thin parallel lamellae around tumor cells and is clearly distinguishable from conventional HCC in the hands of an experienced pathologist.

At presentation, 70% of FLHCC patients have metastatic lymphadenopathy. Nearly half of patients develop distant metastasis.

Liver function tests are typically normal or only mildly elevated. Commonly used markers for HCC such as alpha fetoprotein are of little help in diagnosing FLHCC, as only a small proportion of patients show minor elevations.

On CT scan, tumors are typically sharply demarcated with a central scar, sometimes with calcification, usually occurring in an otherwise noncirrhotic, normal appearing liver. The lesion seen on CT scan is usually hypodense, which may show marked enhancement after contrast injection.
Overall, the key to successful management of FLHCC is early diagnosis. As is being considered for the patient in the current case, the cornerstone for treatment is surgical resection and lymph node dissection. The outcome of patients with FLHCC after surgical resection is usually good. A 50–75% cure rate has been reported after complete surgical resection. In cases in which partial hepatectomy is not technically feasible because of size or extension, liver transplantation should be considered. However, recurrence occurs in about half of patients within 3.5 years of transplant. If resection and liver transplantation are not options, chemotherapy or hepatic artery chemoembolization can be used as an alternative treatment approach.

References

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2. Ichikawa T, Federle MP, Grazioli L et al. Fibrolamellar hepatocellular carcinoma: imaging and pathologic findings in 31 recent cases. Radiology 1999;213:352–61.
Case 41

A 43-year-old Caucasian female with no significant past medical history was in her usual state of health until 1 week prior to presentation when she developed what she described as “flu-like symptoms,” including fever up to 102°F, anorexia, diarrhea, epigastric fullness and discomfort (mostly in her right quadrant), malaise, and myalgias. At the onset of her symptoms, the patient did take approximately 2 g of acetaminophen daily for three days. Her fevers subsided, but the remainder of her symptoms persisted which prompted a visit to her local emergency room. After admission into the hospital and administration of intravenous fluids, the patient states that she feels much better. She denies any cough, her urine appears darker than normal, but she denies any dysuria. The patient and her family returned from visiting her in-laws over the Christmas holiday in Monterrey, Mexico 2 weeks prior to the onset of her symptoms. None of her family members are ill. Her only surgical history is the removal of a benign ovarian cyst over 4 years ago. She takes a daily multivitamin, oral contraceptive (which she has been on since the age of 32) and as needed ibuprofen and acetaminophen. She denies any herbal medications or recent antibiotics. The patient works as an accountant at a pediatric hospital. She has been married for over 20 years now and has three young children all in good health. The patient occasionally drinks wine. There are no other habits or high risk behavior. The patient’s father died of colon cancer at the age of 81.

Physical examination is notable for a generally well-appearing, middle-aged female in no distress accompanied by her entire family. Temperature is 100.8°F and vital signs are stable. She has mild scleral icterus. She has no stigmata of chronic liver disease. Her lungs and heart are normal. Her abdomen is soft, although she is mildly tender in her right upper quadrant. Her liver edge is smooth and is palpable three fingerbreadths below her right costo vertebral angle. She has no shifting dullness, and extremities are without edema. She is mentating well and has no asterixis.

Laboratory Data

Tbili 3.0 mg/dl (direct 2.2); bilirubin peaked at 6.5 mg/dl
AST 2540 iu/l
ALT 3380 iu/l
ALP 125 iu/l
Amylase and Lipase normal
WBC 4,700 with 38% lymphocytes (3% atypical)
INR 1.2
Questions

1. What is the differential diagnosis?
2. What additional testing if any would you recommend?
3. What treatment if any would you recommend?
4. When can the patient safely return to work?
ANA, Smooth muscle Antibody, Immunoglobulins WNL
HBsAg –

Anti-HB core Total negative
HCV Ab –
Anti HAV Total Ab +
Anti HAV IgM Ab +
EBV IgG Ab +
EBV IgM Ab –

Right Upper Quadrant Ultrasound with Dopplers reveals:
Increased periportal echogenicity throughout the liver; no focal hepatic masses and no intrahepatic biliary dilation. Marked circumferential gallbladder wall thickening which almost completely obliterates the lumen of the gallbladder. No discrete shadowing stone is identified. Patent and appropriately directed flow within the hepatic vasculature.
Answer: Acute Hepatitis A Infection

This patient has an acute severe hepatitis but no evidence of coagulopathy or encephalopathy to categorize it as acute liver failure. The degree of hepatocellular injury and the onset of fever and diarrhea, in addition to the multiple risk factors (travel, work exposure) would place acute hepatitis A virus (HAV) at the top of the differential diagnosis. The presence of HAV IgM confirms the diagnosis.

HAV is a nonenveloped RNA virus in the hepatovirus genus of the picornavirus family. Hepatitis A has an incubation period of approximately 4 weeks. Its replication is limited to the liver, but the virus is also present in bile, stool, and blood during the late incubation period and acute preicteric phase of illness. Despite persistence of virus in the liver, viral shedding in feces, viremia, and infectivity diminish rapidly once jaundice is apparent.

HAV is transmitted almost exclusively by the fecal-oral route. Person-to-person spread of HAV is enhanced by poor personal hygiene and overcrowding: large outbreaks as well as sporadic cases have been traced to contaminated food, water, milk, frozen fruit, and shellfish.

In developing countries, exposure, infection, and subsequent immunity are almost universal in childhood. With improvements in personal hygiene and sanitation, the frequency of subclinical childhood HAV infection will continue to decline (Fig. 41.1). In turn, a susceptible cohort of adults emerges and the likelihood of clinically apparent and severe HAV infection may increase. Hepatitis A infection tends to be more symptomatic in adults. Travel to endemic areas is a common source of infection for adults of nonendemic areas.

Antibodies to HAV (anti-HAV) can be detected during acute illness when serum aminotransferase activity is elevated and fecal HAV shedding is still occurring. This early antibody response is predominantly of the IgM subclass and persists for several months. The detection of acute hepatitis A is made by demonstrating anti-HAV IgM. During convalescence, however, anti-HAV of the IgG subclass becomes the predominant antibody. IgG antibodies will remain detectable indefinitely and are thought by most experts to provide lifelong immunity to the host.

The incubation period for HAV ranges from 15 to 45 days (mean 4 weeks). The prodromal symptoms of acute viral hepatitis are generally systemic and quite variable. Constitutional symptoms of anorexia, nausea and vomiting, fatigue, malaise, arthralgias, myalgias, and headache may precede the onset of jaundice by 1–2 weeks. A low-grade fever (100–102°F) is often present in hepatitis A. With the onset of clinical jaundice, the constitutional symptoms usually diminish. A substantial proportion of patients with acute hepatitis A never become icteric. Patients may complain of abdominal discomfort as the result of tender hepatomegaly. Complete clinical and biochemical recovery is expected within 1–2 months in nearly all cases of hepatitis A.

The serum aminotransferases show variable increase during the prodromal phase and precede the rise in bilirubin level. The level of elevation in these enzymes does not correlate well with the severity of illness or degree of liver cell damage. Peak levels vary from 400 to 4,000 iu or more. These levels are usually reached at the time the patient is clinically jaundiced. The serum bilirubin may continue to rise despite falling aminotransferase levels. In most instances, the total bilirubin is equally divided between the conjugated and unconjugated fractions.
As in this case, virtually all previously healthy patients with hepatitis A recover completely from their illness with no clinical sequelae. The case fatality in hepatitis A is very low (approximately 0.1%) and almost always occurs in the setting of advanced age or underlying debilitating disease. A small proportion of patients with hepatitis A experience relapsing hepatitis weeks to months after apparent recovery from acute infection. Relapses are characterized by recurrence of symptoms, aminotransferase elevations, occasionally jaundice, and fecal excretion of HAV. Another unusual variant of acute hepatitis A is cholestatic hepatitis, characterized by protracted cholestatic jaundice and pruritus. Rarely, liver test abnormalities may persist for months or even up to a year. Even when these complications of hepatitis A occur, it remains a self-limiting disease and does not progress to chronic liver disease.

Physical isolation of patients with hepatitis A is rarely necessary except in the case of fecal incontinence. Because most patients hospitalized with hepatitis A excrete little if any HAV, the likelihood of transmission from these patients during their hospitalizations is low. Hospitalized patients may be discharged when there is substantial symptomatic improvement, a significant downward trend in the enzymes levels, and normalization of PT. Mild aminotransferase elevation should not be considered a contraindication to the gradual resumption of normal activity.

Fig. 41.1 Incidence of acute hepatitis A virus infection, by year – United States, 1989–2006

References

1. Brundage SC, Fitzpatrick AN. Hepatitis A. Am Fam Physician 2006;73:2162–8.
2. Jeong SH, Lee HS. Hepatitis A: clinical manifestations and management. Intervirology 2010;53:15–9.
Case 42

A 19-year-old white male with a past medical history significant for attention deficit-hyperactivity disorder (ADHD) presents to his local emergency room with a one day history of severe nausea and nonbloody emesis. The patient reported some abdominal discomfort and fatigue. Remainder of review of systems was negative, although the patient did report feeling depressed after a “big-time fight” with his girlfriend. The patient denied any suicidal or homicidal ideation. He had his tonsils and adenoids removed 3 years ago. His prescription medications include amphetamine and dextroamphetamine for ADHD and venlafaxine which he has recently started on for anxiety. He denied any recent antibiotics, herbal, or over-the-counter medications. The patient lives with his mother and is coping with the recent separation of his parents. He has a 9-year-old healthy sister. He denies alcohol, but he does smoke one pack of cigarettes per day and smokes marijuana on weekends. He denies any intravenous drug use. He has a tattoo of his girlfriend’s name which he obtained 1 year ago. His relationship with his girlfriend is monogamous, and he says he always uses protection. He has a family history significant for alcohol abuse and depression.

Physical examination is notable for a thin (BMI 19.1 kg/m²) somewhat ill-appearing Caucasian male. He is afebrile, heart rate is 101 per minute, and blood pressure is 142/66. He answers questions appropriately, and there is no asterixis. He has no stigmata of chronic liver disease. He is nonicteric. Cardiac and pulmonary exam are normal. His abdomen is soft; bowel sounds are normal, but he is mildly tender in right quadrant. There is no appreciable hepatosplenomegaly.

| Hospital day | Tbili (mg/dl) | AST (iu/l) | ALT (iu/l) | ALP (iu/l) | INR | BUN (mg/dl) | Cr (mg/dl) |
|--------------|--------------|-----------|-----------|-----------|-----|------------|-----------|
| 1            | 1.8          | 32850     | 24750     | 95        | 3.3 | 13         | 0.8       |
| 3            | 2.4          | 1290      | 4400      | 101       | 1.9 | 48         | 5.7       |
| 7            | 0.9          | 56        | 330       | 88        | 1.0 | 15         | 1.8       |

pH 7.27; lactate 2.9
WBC 9,400/μl
Amylase 350 iu/l, Lipase 780 iu/l
Acetaminophen level 12 (44 h after ingestion)
Right Upper Quadrant US with Dopplers
Normal liver, normal hepatic flow
Questions

1. What is the differential diagnosis?
2. How would you assess the degree of liver injury and what models can be used to help predict prognosis?
3. What treatment if any would you recommend?
Table 42.2  King’s college criteria for liver transplantation in acute liver failure secondary to acetaminophen

| Condition                                                                 |
|---------------------------------------------------------------------------|
| Arterial pH < 7.3 (irrespective of the grade of encephalopathy), or        |
| Grade III or IV encephalopathy, and                                       |
| Prothrombin time > 100 s, and                                             |
| Serum creatinine > 3.4 mg/dl                                              |
**Answer: Acute Hepatitis Secondary to Intentional Acetaminophen Ingestion**

Initially, this patient adamantly denied taking any excessive medications. When his liver tests returned and he was further questioned, he eventually admitted to ingesting a “fistful” of Tylenol®, estimated to be just over 16 g (50 × 325 mg tablets).

The massive elevations (nearly 1,000× upper limits of normal) and exclusively hepatocellular injury, elevated INR, and development of acute tubular necrosis all point towards acetaminophen toxicity as the cause of liver injury.

Acetaminophen (N-acetyl-p-aminophenol; APAP; paracetamol) is the most widely used analgesic-antipyretic in the United States. Although safe when taken at prescribed doses, overdose can cause severe and sometimes life-threatening hepatic injury. Acetaminophen has become the most common etiology of acute liver failure in the United States and accounts for more intentional and unintentional overdoses and overdose deaths each year in the US than any other pharmaceutical agent.

The maximum recommended dose in a 24 h period in adults is 4 g. Toxicity is likely to occur with a single ingestion >12 g over a 24 h period. Virtually all patients who ingest doses >350 mg/kg develop severe liver toxicity unless appropriately treated.

Acetaminophen is rapidly and completely absorbed from the intestinal tract. Serum concentrations peak between one-half and 2 h after an oral dose. At therapeutic doses, 90% of acetaminophen is metabolized in the liver to sulfate and glucuronide conjugates, which are then excreted in the urine. Approximately 2% is excreted in the urine unchanged. The remaining acetaminophen is metabolized via the hepatic cytochrome P450 mixed function oxidase pathway to a toxic, highly reactive intermediate N-acetyl-p-benzoquinoneimine (NAPQI). Appropriate acetaminophen doses produce a small amount of NAPQI which is rapidly conjugated with hepatic glutathione, forming nontoxic cysteine and mercaptate compounds that are excreted in the urine. However, with toxic doses of acetaminophen, the sulfation and glucuronidation pathways become saturated, and more acetaminophen is metabolized to NAPQI via cytochrome P450. When hepatic glutathione stores are depleted by approximately 75%, NAPQI begins to react with hepatocytes and leads to injury and necrosis. There is evidence that conditions that deplete stores of glutathione, such as malnutrition and a period of fasting may predispose patients to acetaminophen toxicity.

Clinical manifestations of acetaminophen poisoning are divided into four stages:

1. (0.5–24 h): nausea, vomiting, diaphoresis, pallor, lethargy, and malaise, though some patients may remain asymptomatic. Lab studies are typically normal.
2. (24–72 h): laboratory evidence of hepatotoxicity is seen in nearly all patients within 36 h; and occasionally nephrotoxicity; stage one symptoms may resolve and patient may appear to improve clinically; as stage two progresses patient may develop RUQ tenderness and liver enlargement and PT may elevate.
3. (72–96 h): LFTs peak from 72 to 96 h after ingestion. The systemic symptoms of stage 1 reappear in conjunction with jaundice and encephalopathy.
4. (4 days to 2 weeks): patients who survive stage III enter a recovery phase that is usually completed 1 week after ingestion.

Histological changes in the liver vary from cytolysis to centrilobular necrosis. The centrilobular region (zone III) is preferentially involved because it is the greatest area of concentration of CYP2E1 and therefore the site of maximal production of NAPQI. Histological recovery lags behind clinical recovery and may take up to 3 months.

Acute renal failure due primarily to acute tubular necrosis occurs in 25% of patients with significant hepatotoxicity and in more than 50% of those with frank hepatic failure.

All patients with a clear history of acetaminophen or suspected of overdose should undergo measurement of serum acetaminophen concentration. If any doubt exists about the time of ingestion, a serum concentration should be obtained immediately at the time of presentation. A serum concentration should also be obtained 4 h following the time of acute ingestion or presentation.

Management consists of supportive care, prevention of drug absorption, and, when appropriate, the administration of antidotes, namely, N-acetylcysteine (NAC).

Treatment with NAC is recommended for all patients with liver tenderness, elevations of aminotransferases, supratherapeutic serum acetaminophen concentrations (greater than 20 mcg/ml), and those with history of excessive ingestion, risk factors for toxicity, and acetaminophen concentrations >10 mcg/ml. If a patient has a detectable acetaminophen concentration but is without signs, symptoms, or risk factors for toxicity and without elevations of aminotransferases, then treatment is likely not necessary.

The outcome of acetaminophen intoxication is nearly always good if NAC is given in a timely fashion. No deaths have been reported in any of the large studies of acetaminophen overdose provided NAC was given within 10 h of ingestion, regardless of the initial serum acetaminophen concentration.

Several statistical models have been developed for predicting the outcome in patients with acute liver failure, including the MELD. Perhaps the most widely recognized of these models, however, is the King’s College Criteria (see table above). This model was developed in a cohort of over 500 patients who were managed between 1973 and 1985. Recommendations for liver transplantation were based upon the results. The predictors of outcome were stratified according to whether the ALF was caused by acetaminophen or “other” causes. The positive and negative predictive values of the Kings College Criteria for mortality in patients with acetaminophen-induced ALF (not including patients who were transplanted) are 88 and 65%, respectively.

The patient in this case was administered NAC as soon as his enzyme elevation was noted. His transaminases dramatically normalized, and although he developed oliguric renal failure secondary to ATN, he never required renal replacement therapy. He was eventually discharged to an inpatient psychiatric ward on hospital day 6.
References

1. Larson AM. Acetaminophen hepatotoxicity. Clin Liver Dis 2007;11:525–48.
2. Smilkstein AU, Knapp GL, Kulig KW et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). N Engl J Med 1988;319:1557–62.
3. O’Grady JG, Alexander GJ, Hayllar KM et al. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–45.
Case 43

A 43-year-old male presents to the emergency room with confusion and jaundice. He is a heavy drinker and has been drinking even more heavily recently following separation from his wife. He complains of abdominal discomfort and nausea. He has no other medical history. He has been laid off work recently due to his alcoholism.

He smokes and admits to drinking 20–30 beers on a daily basis and has been drinking vodka in addition over the last 2 weeks.

He is cirrhotic based on imaging from 2 years ago when he presented to the outpatient clinic with abnormal liver tests.

He is on no prescribed medication.

On examination, vital signs are stable. He is obviously confused with asterixis. He has palmar erythema, scleral icterus, and an enlarged liver and spleen. Skin reveals jaundice and multiple 5–10 mm lesions as shown in the photographs.

Laboratory Studies

Total bilirubin 25.6 mg/dl  
Direct bilirubin 19.7 mg/dl  
AST 154 iu/l  
ALT 47 iu/l  
ALP 135 iu/l  
GGTP 657 iu/l  
Albumin 2.2 g/dl  
INR 1.9

Questions

1. What is the relevance of the skin lesions – are they always pathological?  
2. How many lesions are considered significant?  
3. Is there a recognized distribution in patients with liver disease?  
4. Is the etiology of his liver disease relevant?
Answer: Spider Nevi (Angioma)

Figures 43.1–43.4 show the classic appearance of a spider nevus. There is a central arteriole and capillaries extending outwards. They blanch with pressure and then refill from centrally when the pressure is released.

They are seen in 10–15% of healthy children and young adults. They are commonly seen in pregnancy, and in women where there appears to be a relationship with the menstrual cycle, and in high output states such as thyrotoxicosis. In liver disease, they are common in cirrhosis, particularly if alcohol is the etiology.

The number is thought to be relevant with more than 5–7 indicative of pathology. The distribution follows that of the superior vena cava, so lesions are seen above the nipple line, face, shoulders, and upper extremities.

The pathogenesis is unclear but is related to dilation of existing vessels rather than neoproliferation.

Some studies have suggested that their presence together with other markers of liver disease is indicative of increased hepatic fibrosis in patients with chronic hepatitis C.

References

1. Khasnis A, Gokula RM. Spider nevus. J Postgrad Med 2002;48:307–9.
2. Li CP, Lee FY, Hwang SJ et al. Spider angiomas in patients with liver cirrhosis: role of alcoholism and impaired liver function. Scand J Gastroenterol 1999;34:520–3.
3. Romagnuolo J, Jhangri GS, Jewell LD et al. Predicting the liver histology in chronic hepatitis C: how good is the clinician? Am J Gastroenterol 2001; 96:3165–74.
Case 44

A 64-year-old woman presents to your outpatient office because of worsening ankle edema. She has a history of cirrhosis likely from significant alcohol use but quit drinking several years ago. Her liver disease has been complicated by encephalopathy, and she has mild portal hypertension based on imaging and endoscopy.

Her past medical history is significant for hypertension and a hysterectomy many years ago for a nonmalignant condition.

Her current medications include a thiazide diuretic and lactulose.

She is an ex-smoker but denies drug use. Her alcohol history is significant for daily drinking including spirits and beer up until 4 years ago.

She is widowed and comes to the appointment with an adult daughter.

Her family history is notable for several family members with alcoholic liver disease.

Her review of symptoms is significant for the ankle edema and some shortness of breath on exertion but no chest pain, weight loss, or abdominal distension. She does feel very fatigued.

On exam, she is alert and oriented. Her vital signs show BP 140/85, pulse 82 and regular, and she is afebrile. She has mild palmar erythema and a few spider nevi. There is no scleral icterus.

Cardiovascular system reveals normal heart sounds with a pansystolic murmur heard best at the left sternal edge, and chest reveals a few bibasilar crackles. Her abdomen is soft and nontender. The liver is palpable several cms below the right costal margin and she has a spleen tip in the left upper quadrant. There is some dullness in the flanks, and she has 2+ ankle edema.

Laboratory Studies

Hb 11.2 g/dl
Platelets 57,000/μl
INR 1.4
Creatinine 1.4 mg/dl
Tbili 1.9 mg/dl
AST 52 iu/l
ALT 39 iu/l
GGTP 120 iu/l
ALP 188 iu/l
Albumin 2.7 g/dl
Questions

1. What test(s) would you order?
2. How is the diagnosis confirmed?
3. What is/are the treatment option(s)?
4. Does this condition recur after transplant?
Dobutamine stress test

Right ventricular pressure 40 mmHg
**Answer: Portopulmonary Hypertension**

This lady has symptoms and signs suggestive of portopulmonary hypertension (PPHTN). This condition is defined by pulmonary arterial hypertension in the setting of portal hypertension in the absence of other causes of pulmonary hypertension.

The pulmonary symptoms typically include dyspnea on exertion, chest pain, fatigue, orthopnea, and syncope. Exam can demonstrate right ventricular overload with tricuspid incompetence (as in this case), worsening ascites, and dependent edema. Her laboratory studies also suggest some hepatic congestion.

The diagnosis cannot be made clinically but is suspected on echocardiography and confirmed by right heart catheterization. This lady should undergo a stress echocardiogram, which is a good screening test for pulmonary hypertension. The right ventricular pressure is elevated and should prompt referral to a cardiopulmonary specialist and right heart catheterization to make a diagnosis. Pulmonary artery hypertension is defined by a mean pulmonary artery pressure (MPAP) >25 mmHg at rest and a pulmonary capillary wedge pressure (PCWP) <15 mmHg.

The pathogenesis of PPHTN is unclear but may occur on the background of genetic susceptibility as there are cases of familial pulmonary hypertension related to dysfunction of the bone morphogenetic protein receptor type II. Some studies suggest that the underlying portal hypertension leads to porto-systemic collaterals and substances that normally would be metabolized in the liver mediate the pulmonary hypertension. Multiple cytokines and hormones have been implicated including serotonin, IL-1, vasoactive intestinal peptide, glucagon, endothelin-1, and thromboxane B2.

The hyperdynamic circulation seen in cirrhosis and chronic thromboembolism may also play a role. Pulmonary histology in PPHTN demonstrates in situ thrombosis, pulmonary arteriopathy, and vasoconstriction.

It is important to make a diagnosis of PPHTN as it negatively impacts outcome after liver transplantation, particularly with a MPAP >35 mmHg.

Treatment can be by liver transplantation, which has a good outcome in patients with a MPAP below 35 mmHg. Higher MPAP and increased peripheral vascular resistance (PVR) (>250 dynes s cm⁻⁵) are associated with significant mortality after transplantation, and MPAP >50 mmHg is an absolute contraindication to transplant.

The medical therapy of PPHTN has increased over the last few years and involves vasodilatory agents including epoprostenol (Flolan), sildenafil (Revatio), iloprost, and bosentan, best administered in the setting of a pulmonary hypertension clinic. The data is based on case series rather than randomized controlled trials, but the goal is to reduce MPAP and decrease PVR to acceptable levels for transplant. There is very limited data to demonstrate improved outcome after transplant in patients treated with these agents.

Several case series have documented good outcome after liver transplantation in selected patients with PPHTN. Although survival is not at levels seen in patients without PPHTN, the survival benefit of transplant is significant. Resolution of PPHTN after transplant is usual, and there is no evidence that it recurs.
References

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3. Krowka MJ, Mandell MS, Ramsay MA et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. Liver Transpl 2004;10:174.
Case 45

A 57-year-old Asian male presents to the emergency room with hematemesis. The patient has been recently diagnosed with non-small cell lung cancer. The cancer has not yet been treated. He is not known to have liver disease.

His current medications include aspirin and atenolol for hypertension.

The patient also reports a history of intermittent dysphagia to solid food for the last several weeks.

He is a heavy smoker with a 42 pack-year smoking history. He denies use of alcohol or drugs.

The patient is admitted to the intensive care unit and intubated for airway protection. He undergoes an emergent upper endoscopy which shows large masses starting right below the upper esophageal sphincter. The masses progressively became thinner distally.

Laboratory Parameters Show

WBC $9 \times 10^3$/uL
Hb 9.0 g/dl
Tbili 0.9 mg/dl
AST 34 U/l
ALT 45 U/l
Creatinine 1.2 mg/dl

Questions

1. What is the pathogenesis of these lesions?
2. What is the long-term prognosis?
Fig. 45.1  Upper esophagus at 20 cm from the incisors

Fig. 45.2  Mid esophagus distally
**Answer: Downhill Varices**

The EGD pictures (Figs. 45.1 and 45.2) demonstrate large esophageal varices extending from the upper esophagus to the mid esophagus. The varices become thinner and disappear in the mid to distal esophagus. Downhill varices are a result of obstruction of the superior vena cava (SVC). When the SVC is obstructed superior to the azygous vein, venous blood is redirected downhill as it flows through the esophageal veins into the azygous vein. This results in development of downhill varices in the upper to mid esophagus. The most common etiologies of downhill varices are malignancies such as lung cancers and mediastinal tumors. Other potential etiologies include mediastinal fibrosis, substernal goiter, and trauma from central intravenous line placement. The patient may also have other signs of SVC obstruction such as dyspnea, dysphagia, facial and arm swelling, plethora, and headache. Because malignancy is the most common etiology, the prognosis from bleeding is often poor.

Band ligation and sclerotherapy can be attempted, but data on their efficacy is limited and would be expected to cause significant discomfort this high in the esophagus.

**References**

1. Cotran RS, Kumar V, Collins T (eds). Robbins Pathologic Basis of Disease, 6th ed. Philadelphia, PA: WB Saunders; 1999, pp 845–901.
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3. Felson B, Lessure AP. “Downhill” varices of the esophagus. Dis Chest 1964;46:740–6.
Case 46

A 47-year-old man presents to your outpatient clinic for follow-up. He has a history of cirrhosis secondary to hepatitis C. He attempted treatment in the past but could not tolerate the side effects and developed worsening depression.

His disease has been well compensated with minimal ascites controlled on diuretics and no encephalopathy. He has grade 1 esophageal varices on endoscopy.

His past medical history is significant for hypertension and some mild depression. He works as a schoolteacher. He denies current tobacco or alcohol but has a remote history of intranasal cocaine use.

His current medications include paroxetine, furosemide 40 mg daily, spironolactone 100 mg daily, and metoprolol 25 mg daily.

On exam, his vital signs demonstrate weight 165 pounds, BP 135/75, and pulse 62, and he is afebrile. He has no scleral icterus and normal cardiovascular and respiratory systems.

Abdominal exam demonstrates a soft nontender abdomen without organomegaly and no ascites and no ankle edema. He has no asterixis.

Laboratory Studies

Hb 12.5 g/dl  
Platelets 64,000/μl  
INR 1.5  
Creatinine 1.2 mg/dl  
Tbili 1.9 mg/dl  
AST 47 iu/l  
ALT 34 iu/l  
ALP 112 iu/l  
Albumin 2.7 g/dl  
AFP 257 mcg/l

Questions

1. What options if any are available to this patient?  
2. What is the treatment that is illustrated, and has it worked?  
3. Is he a candidate for liver transplant?
Fig. 46.1  CT scan

Fig. 46.2  CT scan
Fig. 46.3 CT scan

Fig. 46.4 Follow up CT, after 2 months
Answer: Treatment of Solitary Hepatocellular Carcinoma (HCC)

This man has developed HCC, which is increasingly common in the United States in people with cirrhosis secondary to hepatitis C. Some studies suggest that the yearly incidence of HCC may be anywhere from 3 to 8% in patients with hepatitis C cirrhosis.

The MRI images (Figs. 46.1–46.3) show a 3 cm lesion in the posterior right lobe (arrowed in Fig. 46.1). Figure 46.2 shows the lesion after transarterial chemoembolization has been administered, and the third image (Fig. 46.3, CT) shows a radiofrequency ablation probe being placed into the lesion. The follow-up MRI 2 months later (Fig. 46.4) shows the treated lesion which did not enhance, suggesting successful treatment.

Multiple treatment modalities exist for HCC including:

- Surgical resection
- Liver transplantation
- Transarterial chemoembolization (TACE)
- Radiofrequency ablation (RFA)
- Percutaneous ethanol or acetic acid ablation
- Cryoablation
- Radiation therapy
- Systemic chemotherapy

The basic algorithm for management of HCC is shown in the first reference below, but essentially, the decision to use which treatment modality is based on center preference and also severity of underlying liver disease.

Resection is a good treatment option for HCC as it can be potentially curative. A single HCC confined to the liver without evidence of vascular invasion in a patient without portal hypertension, and well-preserved hepatic function would be an ideal candidate. Very good 5-year survival rates have been reported.

Liver transplant for HCC is discussed in another case.

TACE uses the fact that the majority of the blood supply to HCCs is derived from the hepatic artery so that eliminating hepatic arterial supply to the tumor should cause ischemia. In addition, chemotherapy can be given directly to the tumor. The chemotherapy is often given with lipiodol, which promotes intratumoral retention of chemotherapy drugs. After the chemotherapy has been delivered, the hepatic artery branch can be occluded in a variety of ways.

TACE is usually not curative but is used as a bridge to transplant for larger tumors, but there is limited data on its efficacy compared to other modalities.

RFA involves the application of radiofrequency thermal energy directly to the lesion. This causes the temperature of the tissue to rise, and when it reaches beyond 60°C, cells begin to die, resulting in a necrosis of tumor cells.

RFA is a reasonable option for patients who are not candidates for resection but typically only works well for lesions less than 4 cm. Again, it is often used as a bridge to transplant, but there is limited data for outcome after RFA compared to other treatments.
Reference

1. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–36.
Case 47

A 52-year-old man presents with bright red blood per rectum. He has a history of cirrhosis secondary to alcohol and is still drinking. His liver disease has been complicated by ascites, but he denies encephalopathy or spontaneous bacterial peritonitis (SBP). He has undergone endoscopy and colonoscopy in the last year at his local hospital and states that they were “OK”.

His bowels have been moving normally with a normal stool color up until yesterday when he noticed blood in the toilet bowl. He denies abdominal pain or fever.

Upon presentation to the emergency room he is witnessed to have further bleeding per rectum with bright red blood but also several large clots.

He has been taking diuretics but no other medications.

He is divorced, lives alone and is not working.

On exam, he looks comfortable and is alert and oriented.

Pulse is 110 beats per minute, regular, blood pressure 95/60

His abdomen is soft, and the flanks are dull. Extremities reveal mild ankle edema.

Rectal exam demonstrates dark red clots.

Laboratory Studies

Hb 9.3 g/dl
Platelets 35,000/μl
INR 1.8
BUN 21 mg/dl
Creatinine 1.7 mg/dl
Tbili 2.5 mg/dl
AST 89 iu/l
ALT 45 iu/l
Albumin 2.6 g/dl

Questions

1. What should you do next?
2. What are the treatment options for this condition?
Fig. 47.1  Endoscopic image

Fig. 47.2  CT scan of the pelvis
Answer: Rectal Varices

The endoscopic image (Fig. 47.1) demonstrates significant rectal varices seen on retroflexion (the black tube on the right is the scope). The CT image of the pelvis (Fig. 47.2) shows the varices around the distal rectum (arrowed). Scrolling up through the images showed a single vessel running all the way from the perirectal varices up to the splenic vein.

The differential diagnosis here is essentially all the causes of bright red blood per rectum including hemorrhoids, diverticular bleeding, arteriovenous malformations and tumor.

In a patient with portal hypertension, ectopic varices also have to be considered. An upper source of GI bleeding could be a possibility but is unlikely given the relatively well-maintained hemodynamics and hemoglobin.

The usual algorithm for lower GI bleeding includes resuscitation and then colonoscopy. The timing of the colonoscopy will depend on the degree of bleeding.

In this patient, there was significant bleeding, and we elected to proceed with colonoscopy after a rapid purgative preparation.

The rectal varices were immediately evident, and there was no evidence of any blood proximal to the rectum.

Treatment of rectal varices is based on very limited data. Banding or sclerotherapy does not appear to be effective. I have on one occasion used the gastric balloon of a Blakemore tube inserted into the rectum to control torrential bleeding from huge rectal varices. Unfortunately, the patient died after a prolonged intensive-care course.

There is anecdotal data that in bleeding ectopic varices – treatment with TIPS and/or embolisation by a radiologist can control bleeding. In this case, the bleeding stopped spontaneously, and we elected not to try a TIPS due to his elevated MELD score although the patient may have had some decompression based on the CT images showing a single vessel supplying the rectal varices from the splenic vein.

Reference

1. Vangeli M, Patch D, Terreni N et al. Bleeding ectopic varices – treatment with transjugular intrahepatic porto-systemic shunt (TIPS) and embolisation. J Hepatol 2004;41:560–6.
Case 48

A 25-year-old man presents with jaundice. He is otherwise asymptomatic but does admit to dark urine and pale stool. The jaundice has gradually worsened over the last few weeks and he is now complaining of itching. No one else has been sick, and he denies any foreign travel.

He denies fever or abdominal pain, and his appetite is good with a stable weight.

He has no other past medical history that he is aware of but knows he has had an abdominal surgery as an infant. He takes no medications.

He does not smoke or drink.

He is married with a young child. He works as a carpenter.

His family history is not available as he was adopted as a toddler. He is not aware of his birth parents and is not in contact with his foster parents.

On exam, he looks comfortable and is alert and oriented. He is obviously jaundiced.

Pulse is 70 beats per minute, regular, blood pressure 115/60, and he is afebrile.

His abdomen is soft and nontender. There is a midline scar in the epigastric area extending into the right upper quadrant. Extremities reveal no edema.

Laboratory Studies

Hb 14.2 g/dl
Platelets 74,000/μl
INR 1.5
Creatinine 1.1 mg/dl
Tbili 22.5 mg/dl (direct 19.1 mg/dl)
AST 109 iu/l
ALT 75 iu/l
ALP 457 iu/l
GGT 987 iu/l
Albumin 3.2 g/dl

Questions

1. What should you do next?
2. What are the treatment options for this condition?
Fig. 48.1  MRI abdomen

Fig. 48.2  Liver biopsy H&E ×100
Fig. 48.3  Liver biopsy H&E ×250
**Answer: Biliary Cirrhosis After Kasai Procedure for Extra-Hepatic Biliary Atresia as a Child**

This young man has an obstructive picture with jaundice and pale stool and dark urine. The differential diagnosis includes posthepatic causes of jaundice such as biliary obstruction from stones or tumor, or intrahepatic causes such as cholestatic liver disease. In this case, he states he had surgery as an infant. A cholecystectomy would be unusual at that age, but inadvertent damage to the biliary tree during such a procedure could lead to secondary biliary cirrhosis. Typically, this would occur after only a few years and not 20–25 years as in this case.

He does have some evidence of portal hypertension given the low platelet count but looks to be relatively well compensated.

The next best test would be imaging. The MRI (Fig. 48.1) shows evidence of biliary ductal dilation, and there are stones and sludge within the biliary tree (arrowed). On other cuts, it was evident that there was a biliary-enteric anastomosis, and the spleen is big consistent with portal hypertension.

This was actually a patient who had undergone a Kasai procedure (hepatoporto-enterostomy) for extra-hepatic biliary atresia (EHBA) at the age of 1 month. He has developed secondary biliary cirrhosis which is seen in the majority of cases.

This patient was being worked up for liver transplant, and we decided to obtain a tranjugular liver biopsy to assess the degree of liver damage since he had so much biliary obstruction. The low power image (Fig. 48.2) shows a cirrhotic nodule and at higher power (Fig. 48.3) the cholestasis is readily apparent.

EHBA has an incidence of approximately 1 in 10,000–20,000 births and is characterized by inflammation of the bile ducts leading to progressive obliteration of the extrahepatic biliary tract. The diagnosis of BA should ideally be made within the first month of life as multiple studies have demonstrated that the success of biliary drainage using the Kasai procedure is poor after 3 months of age.

The Kasai procedure attempts to restore bile flow from the liver to the proximal small bowel by using a roux-en-Y loop of bowel and a direct anastomosis to the capsule of the liver following excision of the biliary remnant and portal fibrous plate.

If the procedure is successful, the small patent bile ducts drain into the small bowel and relieve the biliary obstruction and prevent nutritional issues from cholestasis.

Biliary cirrhosis usually occurs within 5–10 years, and liver transplantation is required. The outcome after transplant is good with overall survival of approximately 70–80% long term survival. More recent case series have suggested better long-term outcome with early Kasai procedures and perhaps explains this patient’s later presentation.
References

1. Chardot C, Carton M, Spire-Bendelac N et al. Prognosis of biliary atresia in the era of liver transplantation: French national study from 1986 to 1996. Hepatology 1999;30:606–11.
2. Shinkai M, Ohhma Y, Take H et al. Long-term outcome of children with biliary atresia who were not transplanted after the Kasai operation: >20-year experience at a children’s hospital. J Pediatr Gastroenterol Nutr 2009;48:443–50.
Case 49

A 45-year-old male presents to the emergency room brought in by his family. He has become increasingly jaundiced over the last several days and is mildly confused. His wife states that he “drinks like a fish.” His last alcohol was yesterday.

He complains of some mild abdominal pain but otherwise denies fever or chills. His bowels move normally without blood, and he denies dysuria.

His past medical history is significant for diabetes and hypertension, but he has been off medication for several months after he lost his job and his medical insurance. He denies any over-the-counter medications.

His family history is notable for alcohol-related liver disease in his father and several male siblings.

Exam demonstrates an obese male, looking older than stated, with vital signs weight 257 pounds, BP 120/80, pulse 104 regular, and temperature 100°F.

He is not in distress but has mild asterixis. He is obviously icteric and has multiple spider nevi. He has temporal wasting. His heart and lungs are normal but his abdomen is distended with dilated abdominal veins. His liver is markedly enlarged and tender, but his spleen is impalpable. Extremities show ++ ankle edema, and his skin demonstrates jaundice.

Laboratory Studies

Hb 12.6 g/dl
Platelets 246,000/μl
WBC 15.3 × 10^3/μl
INR 2.3
Creatinine 4.3 mg/dl
Tbili 37.5 mg/dl
Direct bili 24.3 mg/dl
AST 210 iu/l
ALT 109 iu/l
GGTP 236 iu/l
ALP 128 iu/l
Albumin 2.5 g/dl

Ultrasound of abdomen

Heterogeneous liver, no ductal dilation, normal-looking kidneys, minimal ascites.

Questions

1. What else is required to make a definitive diagnosis?
2. What is the prognosis?
3. Are there any treatment options other than abstinence from alcohol?
Laboratory Studies 2 Weeks Ago

Hb 13.1 g/dl
Platelets 232,000/μl
WBC $6.7 \times 10^3/\mu l$
INR 1.6
Creatinine 1.4 mg/dl
Tbili 3.1 mg/dl

Current urine studies
Urine sodium <5 mEq
Urine protein <200 mg
Urinalysis – no red cells, no casts, no bacteria
Answer: Type I Hepatorenal Syndrome (HRS)

This man presents with classic alcoholic hepatitis, but it has been complicated by type 1 HRS. This is a diagnosis that is actually quite difficult to make (according to the international ascites club) since several other disorders need to be excluded.

There are two types of HRS which by definition occur in patients with cirrhosis, severe alcoholic hepatitis, or fulminant hepatic failure. Type I is defined as at least a 50% lowering of the creatinine clearance to a value below 20 ml/min in less than a 2 week period or at least a twofold increase in serum creatinine to a level >2.5 mg/dl (221 μmol/l). Hence, the lab values shown from 2 weeks ago would fulfill this criterion. Patients do not need to be oliguric although most are. Type II is defined as any renal insufficiency in a patient that has the above liver diseases but does not meet criteria for type I. In general, this is essentially similar to diuretic-resistant ascites.

The absolute definition of HRS is:

- Patient with liver disease/failure and portal hypertension.
- Plasma creatinine >1.5 mg/dl (133 μmol/l) that progresses over days to weeks.
- Absence of any other apparent cause for renal disease, including shock, ongoing bacterial infection, current or recent treatment with nephrotoxic drugs, and the absence of ultrasonographic evidence of obstruction or parenchymal renal disease.
- Urine red cell excretion <50 cells per high power field.
- Urine protein excretion <500 mg/day.
- Lack of improvement in renal function after volume expansion with intravenous albumin (1 g/kg of body weight per day up to 100 g/day) for at least two days and withdrawal of diuretics.

The pathogenesis is related to splanchnic arterial vasodilation in the setting of portal hypertension. This is thought to be mediated by increased production or activity of vasodilators such as nitric oxide, mainly in the splanchnic circulation. In patients with significant liver disease, the cardiac output increases and the systemic vascular resistance decreases despite activation of the renin-angiotensin and sympathetic nervous systems.

The glomerular filtration rate and sodium excretion (usually <10 mEq/day in advanced cirrhosis) decline in this setting along with a fall in mean arterial pressure, despite the intense renal vasoconstriction.

HRS is best considered a reversible form of renal dysfunction in patients with liver failure (cirrhosis or acute liver failure), and treatment aims at improving the vasodilation by using vasoconstrictors. However, the underlying liver disease needs to be taken care of, and this usually means patients with type I HRS need urgent liver transplant evaluation as long as there are no other contraindications.

In the United States, we would typically use a combination of octreotide and midodrine (with intravenous albumin) or norepinephrine as vasoconstrictors. In countries where it is unavailable, the potent vasoconstrictor terlipressin is used as it demonstrates a survival benefit in HRS.
In this patient, the prognosis is poor since his discriminant function is greater than 32. In addition, several studies have shown that the MELD score is also a good predictor of mortality in such patients, and his score is >40.

The cause of death in patients with alcoholic hepatitis is usually renal failure, and studies have shown that pentoxifylline is beneficial in this situation.

In this patient, after a trial of fluid, we would typically start him on pentoxifylline along with intravenous albumin.

**References**

1. Gines P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009;361:1279.
2. Salerno F, Gerbes A, Gines P et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56:1310.
Case 50

A 49-year-old female is admitted with a chief complaint of “I wasn’t feeling well”. The patient states she was in her usual state of health until 5 days prior to admission when she began to develop severe fatigue. The next day she began to develop nausea, bilious emesis, and darkening of her urine. The patient thought she had the flu and continued to work. Over the next two days, she began to develop right upper quadrant pain, anorexia, chills, and light headedness and finally presented to her local emergency room. She has a past medical history significant only for endometriosis. Over the last several days, she did take a few tablets of acetaminophen and ibuprofen, but otherwise takes no prescription medications, herbals nor has she had any recent antibiotic exposure. The patient lives with her husband of 25 years and their 15-year-old son. She works full-time as a bank teller. She has one tattoo which she obtained over 25 years ago. She has no habits, and there has been no recent travel. The patient’s father died at the age of 69 of a pulmonary embolism following an open cholecystectomy.

The patient’s husband is being followed in the liver clinic for chronic hepatitis B which was diagnosed over 15 years ago. He underwent a liver biopsy 3 years ago which revealed 1/6 fibrosis and minimal disease activity. The patient was seen in the liver clinic 1 year ago and was a symptomatic; however, his AST and ALT were 64 and 140 respectively. He was HBsAg +, sAb -, core total +, eAg negative, and eAb +. His viral load was 350,000 iu/ml and was being maintained on 10 mg of adefovir. Within the last 2 months, because of a lack of finances, the patient stopped taking his medication. He was last seen about 6 weeks ago complaining of fatigue. His lab work showed ALT 156 and ALT 320, and his DNA was 11,360,000 iu/ml. A resistance panel was performed, revealing the presence of a precore tag mutation. The patient was restarted on adefovir 10 mg in addition to 100 mg of lamivudine.

On physical exam, the patient was febrile at 100.5°F with a heart rate of 90 and blood pressure of 100/50. She was lethargic and confused with asterixis. She was jaundiced with scleral icterus. Cardiac and lung exam were normal. Abdomen was flat with hypoactive bowel sounds. She was very tender in her right upper quadrant. There was no evidence of hepatosplenomegaly. Extremities were without clubbing cyanosis or edema. There were no stigmata to suggest chronic liver disease.

Laboratory Data Revealed

Tbili 7.9 mg/dl (conjugated 4.8 mg/dl)
AST 6380 iu/l
ALT 7319 iu/l
ALP 218 iu/l

INR 4.9
pH 7.50, lactate 3.9
Hemogram, electrolytes, and renal function were all WNL
12 h after admission, repeat labs reveal:
   Tbili 12 mg/dl
   AST declined to 777 iu/l
   ALT 2500 iu/l
   INR to 11.5
   HBsAg: Non-reactive
   HBsAb: 233 miu/ml
   HBeAb +
   HBeAb IgM +
   HBcAb +
   HDV IgM –
   HBV DNA: 134,222 iu/ml (58,824 copies/ml)

Questions

1. Does this patient fulfill criteria for acute liver failure?
2. What is the patient’s prognosis?
3. What treatment if any would you recommend?
Fig. 50.1  Gross liver specimen

Fig. 50.2  Liver biopsy, H&E low power
**Answer: Acute Liver Failure Secondary to Acute De Novo Hepatitis B Virus**

The patient fulfills criteria for acute liver failure (ALF): the onset of coagulopathy and encephalopathy in a previous healthy individual. An important point for clinicians to realize is that although many patients with ALF will have elevated bilirubin levels, jaundice is not included in the formal definition. ALF is a rare condition with only approximately 2,000 cases per year in the United States. The most common cause of ALF in the US is acetaminophen toxicity. ALF secondary to HBV develops in less than one percent of patients infected with the virus.

Without liver transplantation, the fatality rate in patients with ALF from HBV is 93%. There are approximately 50 cases of ALF due to hepatitis B Virus (HBV) in the US each year. If detected in time, transplantation can be life-saving, with a 1 year survival of approximately 85%.

The injury in patients with severe hepatitis B infection is a consequence of the patient’s violent immune response. The patient’s viral serologies in this case provide a unique but telling tale into this immune response. It was during the process of fighting the infection and producing antibodies to the HBV that the patient became acutely ill. Unfortunately, the reaction and liver injury in this case was too far advanced for the patient to recover from. Antivirals would not reverse and would likely not stabilize the acute injury in this case. An argument could be made to administer antivirals to decrease the patient’s viral load pre LT in the hopes of decreasing the incidence of recurrent HBV post transplant.

Although the decision tree in patients with ALF secondary to HBV is somewhat easier given the high mortality, knowing when to “pull the plug” on a patient with ALF and send them for LT can be a difficult decision. The clinician must weigh the chances of the patient’s spontaneous recovery with the chances of progressive deterioration and multisystem organ failure. Many prognostic models have been proposed to help in this decision-making process.

To the untrained eye, the precipitous fall in the patient’s enzyme in the case above may be viewed as an improvement; however, in conjunction with the worsening coagulopathy, this is actually a sign of impending doom and is a consequence submassive hepatocellular necrosis. The gross pathology (Fig. 50.1) of the patients explant reveals a “shriveled” liver weighing only 525 g (normal weight of a female adult liver 1,200–1,400 g). Histology (Fig. 50.2) reveals lobular necrosis with hemorrhage involving over 90% of the liver. Almost no hepatocytes are recognized.

The patient’s husband in this case had an acute “flare” in his disease off of antiviral medications. The patient and her husband did have relations during this period. Transmission of HBV among adults is predominantly through sexual contact. HBV is a preventable disease, and all adults with potential exposure risk should be offered vaccination.
References

1. Lee HC. Acute liver failure related to hepatitis B virus. Hepatol Res 2008;38:S9–13.
2. Kim WR. Epidemiology of hepatitis B in the United States. Hepatology 2009;49:S28–34.
3. Wai CT, Fontana RJ, Polson J et al. Clinical outcome and virological characteristics of hepatitis B-related acute liver failure in the United States. J Viral Hepat 2005;12:192–8.
Case 51

A 55-year-old lady presents for elective outpatient endoscopy. She has a history of alcoholic cirrhosis that has been complicated by variceal bleeding 2 months ago when she was first diagnosed with liver disease. She underwent band ligation. She quit drinking at this time but previously had been drinking a bottle of vodka every few days. She developed encephalopathy while she was hospitalized with the bleeding but this is well controlled on lactulose. She has required a small dose of diuretics for ankle edema but has noticed some improvement in her overall condition with abstinence from alcohol.

She has no other medical problems.

Medications include nadolol, lactulose, furosemide, and aldactone. She is also taking a multivitamin and folate.

She is divorced and has no children. She has not worked for several years.

She is still smoking a packet of cigarettes daily but has no history of drug use.

She has a strong family history of alcoholism.

Her review of systems is significant for fatigue but is otherwise negative.

On exam she looks well and is alert and oriented.

Vital signs show BP 105/65, pulse 58, and she is afebrile.

There is mild scleral icterus and multiple spider nevi.

Heart reveals normal S1 and S2 without added sounds. Chest reveals lung fields.

His abdomen is soft and nontender with a spleen easily palpable. There is +ankle edema.

Laboratory Studies

Hb 9.6 g/dl
Platelets 42,000/μl
WBC 3.1 × 10³/μl
INR 1.8
Creatinine 1.4 mg/dl
Tbili 4.9 mg/dl
AST 89 iu/l
ALT 67 iu/l
GGTP 189 iu/l
ALP 139 iu/l
Albumin 2.4 g/dl

She undergoes endoscopy and representative images (Figs. 51.1 and 51.2) are shown.
Questions

1. Is there an advantage in treating her with band ligation in combination with a beta-blocker or is banding alone sufficient?
2. If she has to undergo TIPS, will this improve her survival?
3. Is she a candidate for shunt surgery?
Fig. 51.1  Endoscopic images

Fig. 51.2  Endoscopic images
Answer: Secondary Prophylaxis of Variceal Hemorrhage

This lady still has grade II esophageal varices with red wale signs at endoscopy (first image). She undergoes repeat band ligation as seen in the second image and likely will need further sessions to try and eradicate her varices.

There is a vast amount of literature on preventing rebleeding after an initial esophageal variceal bleed, and the American Association for the Study of Liver Diseases has published guidelines dealing with this topic.

The patient appears to be on an adequate dose of nadolol as evidenced by her pulse and blood pressure. Nonselective beta-blockers reduce the risk of a primary bleed, and several studies have shown that they reduce the risk of recurrent bleeding by about 40%. Ideally, the efficacy of beta-blockers should be measured by the reduction in hepatic venous pressure gradient, but this requires invasive testing, and most studies use a reduction of 25% in resting heart rate as a surrogate marker.

A combination of beta-blocker and endoscopic therapy with band ligation is better than either treatment alone in preventing rebleeding but does not reduce mortality compared to either treatment. Hence, patients who have experienced variceal bleeding should undergo band ligation until eradication of varices (we typically repeat an endoscopy every 6–8 weeks until varices are no longer present or too small to band) as well as beta-blocker treatment. If patients are intolerant to beta-blockers, band ligation alone is sufficient.

Transjugular porto-systemic shunting (TIPS) can be considered, particularly in patients with continued bleeding despite these measures. Studies comparing TIPS with endoscopic therapy for the prevention of variceal rebleeding found an advantage for TIPS, but this did not extend to a survival benefit and TIPS was associated with more complications such as encephalopathy, liver failure, and repeat intervention for TIPS dysfunction (although these studies were with uncoated TIPS stents).

As illustrated in another case, shunt surgery such as a distal splenorenal shunt is an option to prevent rebleeding but should be reserved for patients with well-maintained liver synthetic function which is not the case here. The ultimate treatment would be liver transplant, but this is contraindicated in patient with such short sobriety.

References

1. Hayes PC, Davis JM, Lewis JA, Bouchier IAD. Meta-analysis of value of propranolol in prevention of variceal hemorrhage. Lancet 1990;336:153.
2. Gonzalez R, Zamora J, Gomez-Camarero J et al. Meta-analysis: combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. Ann Intern Med 2008;149:109.
3. Jalan R, Forrest EH, Stanley AH et al. A randomized trial comparing transjugular intrahepatic portosystemic stent-shunt with variceal band ligation in the prevention of rebleeding from esophageal varices. Hepatology 1997;26:1115.
Case 52

A 25-year-old white female comes to the liver clinic to reestablish care. She initially presented to the children’s hospital at the age of 9 with hematemesis. She underwent urgent EGD revealing bleeding esophageal varices and was treated with endoscopic sclerotherapy. She never had recurrent bleeding and never followed-up afterwards. She has been recently diagnosed with a spontaneous left lower extremity blood clot and is found to have protein C deficiency. Before starting her on chronic anticoagulation, given her history of GIB, hematology recommends consultation with you.

The patient states she feels well. She has a history of anxiety and takes as needed benzodiazepines. Two years ago the patient underwent an uneventful laparoscopic cholecystectomy for symptomatic gallstones, an intraoperative liver biopsy revealed mild fibrosis and bile ductular proliferation. Although the patient doesn’t know details, she knows her mother is on lifelong warfarin for a history of blood clots. The patient lives with her fiancé and works as a cashier at a convenience store. She smokes one-half pack of cigarettes per day and drinks only on special occasions. There is no history of high-risk behavior.

On exam, she appears well and is not in distress. Her heart rate is 80 beats per minute, blood pressure 110/50; BMI is 27.7 kg/m². She has no evidence of scleral icterus or stigmata to suggest chronic liver disease. Her lungs and cardiac exam are normal. Abdominal exam reveals some dilated umbilical veins, no hepatomegaly, but a palpable spleen tip. No appreciable ascites. Her left leg has some mild erythema and trace edema.

An EGD was performed revealing mild-to-moderate portal hypertensive gastropathy (most notable in the fundus) and grade 1 esophageal varices but no evidence of gastric varices.

Laboratory Data Revealed

Tbili 1.8 mg/dl (conjugated 0.2)
AST 32 iu/l
ALT 17 iu/l
AP 94 iu/l
INR 1.1
Alb 3.7 g/dl

Electrolytes and renal function normal
Platelet count of 120,000, remainder of hemogram normal

Questions

1. How would you work up this patient?
2. What are your recommendations regarding anticoagulation?
Fig. 52.1  CT scan done (prior to surgery 2 years ago)

Fig. 52.2  CT scan done (prior to surgery 2 years ago)
Case 27–65

Answer: Hypercoaguable State Leading to Portal Vein Thrombosis, Cavernous Transformation and Portal Hypertension

This young lady has portal hypertension, but interestingly, this was first noted as a child, and hence, congenital causes have to be high on the differential diagnosis. The main possibilities include portal vein atresia or portal vein thrombosis. Cirrhosis is uncommon in young children and would be expected to worsen with time and yet this lady did well for many years. The first test to obtain would be an imaging study to look at the liver and hepatic vasculature. CT scan, MRI, or ultrasound all have a potential role.

Portal hypertension is defined by a hepatic venous pressure gradient (HVPG) greater than 5 mmHg. A variety of disorders can cause portal hypertension in the absence of cirrhosis, a condition referred to as “noncirrhotic portal hypertension.”

Portal hypertension has been categorized as prehepatic, intrahepatic, or posthepatic based upon the site of obstruction to flow. The clinical consequences of portal hypertension (ascites, varices, and encephalopathy) are similar regardless of the cause or site of obstruction.

Presinusoidal portal hypertension is caused by obstruction to flow through the portal venous system in the extrahepatic portion of the portal vein (extrahepatic presinusoidal portal hypertension; see image one above) or at the level of portal vein branches within the liver (intrahepatic presinusoidal portal hypertension).

The causes of portal vein thrombosis (PVT) vary with age. In adults, approximately 25% of patients with PVT have underlying cirrhosis, with the prevalence correlating with the severity of underlying liver disease. In children, the most common etiology of PVT is thrombophlebitis of the umbilical vein (omphalitis) and ultimately the portal vein. Omphalitis is a rare event in industrialized countries but is estimated to be as high as 6% in the developing world.

No apparent cause for portal vein thrombosis is evident in more than one-third of patients. Many of these patients probably have an underlying hypercoagulable state. The following hypercoagulable states have been identified in different studies comparing patients with portal vein thrombosis compared to various controls and should be tested for:

- Factor V Leiden
- Prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- MTFR gene mutation that raises homocysteine
- Myeloproliferative disorders, in some cases diagnosed only by the presence of a JAK2 617F mutation
- Increased factor VIII levels

Chronic portal vein thrombosis develops in patients whose thrombosis does not spontaneously resolve. This may either produce a chronic noncavernous thrombosed portal vein or cavernous transformation of the portal vein. Cavernous transformation
refers to the development of collateral blood vessels that bring blood in a hepatopedal manner from the region of obstruction. When seen in a transverse section, as on a CT scan, cavernous transformation gives the appearance of multiple caveolar orifices (white arrows in image two above). Image one above reveals abrupt “cut off” of the portal vein (arrow) at the confluence secondary to extensive thrombus.

More than 85–90% of patients with chronic portal vein thrombosis have esophageal varices, while 30–40% have concomitant gastric varices with bleeding occurring in 50–70% of patients. In contrast to variceal bleeding in patients with cirrhosis, the risks of developing liver failure, encephalopathy, and death are much lower in patients with portal vein thrombosis or other causes of extrahepatic portal vein obstruction without underlying cirrhosis.

Since the liver parenchyma is not directly involved in patients with portal vein thrombosis, a majority of patients have histologically normal livers.

There are few controlled data on which to base clinical decisions in patients with portal vein thrombosis. Thus, treatment should be determined by an individual patient’s clinical circumstances, the pathophysiology involved, and the available expertise. A surgical approach can be considered for patients with correctable anatomic abnormalities causing extrahepatic portal vein obstruction, provided there is no cirrhosis.

A 2009 guideline from the American Association for the Study of Liver Diseases recommends consideration of long-term anticoagulation in patients with chronic portal vein thrombosis without cirrhosis who have a permanent risk factor for venous thrombosis that cannot be corrected. In patients with gastroesophageal varices, anticoagulation should not be initiated until adequate prophylaxis for variceal bleeding has been instituted.

The young lady in this case was “cleared” to remain on anticoagulation. She was started on a nonselective beta blocker with titration to a heart rate of 55 beats per minute. Close follow-up was arranged in both the hematology and hepatology clinics given her prior history of noncompliance.

References

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Case 53

A 53-year-old white female with a past medical history significant for hypertension and hypercholesterolemia is brought to the emergency room with chest pain and syncope. The patient was “found down” in her kitchen by her 14-year-old son. She was diaphoretic, grasping for air, holding her chest, complaining of severe, crushing pain. Upon arrival, emergency medical service (EMS) documented her temperature as 99.1°F, heart rate 116, systolic blood pressure 82, and respiratory rate 22. Her oxygen saturation was 83% on room air. The patient’s only other medical history includes long standing hypothyroidism. She underwent a carpal tunnel release on her right hand 4 years ago. Her prescription medications include hydrochlorothiazide and synthroid. She stopped taking her cholesterol medication (rosuvastatin) months ago as she thought it was the cause of her “aching muscles.” She does suffer from chronic low back pain and takes as needed ibuprofen and acetaminophen. She took 3 g of acetaminophen two days prior to admission. Her husband notes that she has been complaining of intermittent chest discomfort for the last month. She was scheduled for an evaluation with her primary care physician next week. The patient lives with her husband of 28 years and their three healthy children. She works full-time as a school bus driver. She has a 20 pack year smoking history and currently smokes ten cigarettes per day. She averages between 6 and 8 beers per week. She has two tattoos, the first of which she obtained 25 years ago. Her father passed from pneumonia at the age of 59. He suffered from a debilitating stroke 1 year prior. Her mother died at the age of 66 from postoperative complications following an abdominal aortic aneurysm (AAA) repair. The patient’s 57-year-old brother has diabetes.

Physical exam is notable for an obese, middle-aged white female with a BMI of 33.7 kg/m². She is awake, but confused. She is diaphoretic and very anxious. Sclerae are nonicteric. JVP is measured at 13 cm. She has rales bilaterally, and an S3 is auscultated on cardiac exam. Her abdomen is soft and nontender. Bowel sounds are normal. Liver edge is smooth and palpable 2 cm below the right costo-vertebral angle. There is no appreciable splenomegaly. She has trace lower extremity edema. There are no stigmata suggestive of chronic liver disease.

An EKG reveals ST elevations in the anterior leads. Troponin I is 125.6 ng/ml. The remainder of initial laboratory data are shown below.

The patient is taken emergently for cardiac catheterization. Coronary angiography reveals high grade, three vessel disease. Right heart catheterization reveals pressures consistent with severe biventricular congestive heart failure. An intraaortic balloon pump is inserted, and the patient is taken emergently to the operating room for coronary artery bypass (CABG).

You are consulted on postoperative day 3 for a rising bilirubin. The primary team also asks you “when would it be safe to restart her statin?”
Laboratory Data

On admission

Na 141 mEq/l
BUN 39 mg/dl
Cr 2.6 mg/dl
WBC 15,400/μl
Hb 14 g/dl
Platelets 390,000/μl
Troponin I: 125.6 ng/ml
Tbili 0.8 mg/dl
AST 8690 iu/l
ALT 6888 iu/l
ALP 226 iu/l
INR 1.4
LDH 2480 iu/l

Post CABG day 3
BUN 8 mg/dl
Cr 1.4 mg/dl
Tbili 3.3 mg/dl (conjugated 1.9)
AST 874 iu/l
ALT 290 iu/l
ALP 118 iu/l

Questions

1. What is the differential for the abnormalities noted in liver function tests and the increasing bilirubin level?
2. What further testing would you recommend?
3. What treatment if any would you recommend?
4. When would it be safe to start a statin?
Answer: Ischemic/Hypoxic Liver Injury

There are only a handful of liver injuries which will cause transaminase levels to be in the tens of thousands initially and then drop in half the next day. Perhaps the most commonly encountered of these in the United States is ischemic liver injury. One study quoted a prevalence of 0.9% of all ICU admissions to suffer from ischemic liver injury.

The case presentation here is quite classic. The transaminase levels are remarkably high in the setting of shock (in this case cardiogenic); there is concomitant kidney injury (likely the result of acute tubular necrosis). The elevated LDH is also a clue and makes a viral etiology less likely. As the underlying insult resolves, the transaminase levels improve precipitously.

It is not uncommon for the consult in these cases to be called in several days after admission. The primary team is comforted by the rapid improvement in transaminase levels, but is concerned given the rising total bilirubin.

The term “ischemic hepatitis” was first coined in 1979 to refer to liver injury characterized histologically by centrilobular liver cell necrosis with a sharp increase in serum aminotransferase levels in the setting of cardiac failure.

The etiology of ischemic liver injury is a result of a reduction in hepatic perfusion leading to hepatic anoxia and necrosis. The degree of liver injury is proportional to the amount of liver rendered ischemic. The outcome is dependent upon restoration in hepatic blood flow and oxygen delivery. Global hypotension (as seen in shock/hypotension) typically leads to rapid recovery with no long-term effects, granted there is no significant underlying liver disease. Ischemia resulting from vascular occlusion or injury to the contrary can cause permanent injury and lead to fibrosis and ischemic cholangiopathy.

In one of the larger studies to evaluate this entity, over a 10-year period, 142 episodes of ischemic hepatitis were identified. Four main groups were identified: decompensated congestive heart failure, acute cardiac failure, exacerbated chronic respiratory failure, and toxic/septic shock. The hemodynamic mechanisms responsible for liver injury were different in the four groups. In congestive heart failure and acute heart failure, the hypoxia of the liver resulted from decreased hepatic blood flow due to left-sided heart failure and from venous congestion secondary to right-sided heart failure. In chronic respiratory failure, liver hypoxia was mainly due to profound hypoxemia. In toxic/septic shock, oxygen delivery to the liver was not decreased, but oxygen demands were increased. A “shock” state was present in only 55% of cases. We agree with the authors of this study that the commonly used term “shock liver” should be disregarded, and replaced with “hypoxic liver injury.”

The workup in cases like this should be determined on a case-by-case basis but in most instances should be limited and cost-efficient. A right upper quadrant ultrasound with Dopplers to rule out underlying liver disease and vascular occlusion should be performed. Viral serologies are not unreasonable. The bilirubin will typically “lag” behind the transaminase levels and will peak on days 3–5. Avoiding additional hepatic insults is important. Generally supportive care and improving the underlying...
cause of hypoxia will improve the liver injury. Liver failure is rare in these settings; when it does occur, it almost always occurs in the setting of severe cardiac disease or cirrhosis.

The use of statins in patients with liver disease is a commonly asked question of primary care physicians. Statins have become one of the most widely prescribed medications in the western world. Their beneficial effects in patients with cardiovascular disease are well established. They have an excellent safety profile. The most common clinical hepatic manifestation of statins is asymptomatic elevations in liver enzymes with an incidence of about 3%. In general, however, the incidence of liver enzymes elevations in statin-treated patients has not been consistently different than placebo. The risk of “significant” liver injury is extremely rare, and the risk of acute liver failure has been limited to a handful of case reports.

Understanding the beneficial effects a statin would have for the patient in this particular case, we recommend starting the medication after liver enzymes were closer to normal values. The patient’s enzymes returned to near normal after 2 weeks from her initial presentation. She was restarted on her statin medication and repeat enzymes 1 month later were completely normal. We recommend monitoring every 3–4 months for the first year. The patient has had no sequelae from her acute liver injury.

References

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Case 54

A 41-year-old lady presents with several weeks of right upper quadrant pain, abdominal distension, and shortness of breath. She denies any jaundice or change in urine or stool color.

She is otherwise well and has no other medical problems.
She takes no medications and denies over-the-counter or herbal supplements.
She is married and works as a secretary. She has two children who are alive and well.
She denies tobacco or alcohol and does not use illicit drugs.

There is no family history.

Exam shows a lady who is uncomfortable. Vital signs show BP 125/80, pulse 104, respiratory rate 26 per minute, and she is afebrile.

There is mild scleral icterus but no spider nevi or palmar erythema. She is alert and oriented. Heart reveals normal S1 and S2 without added sounds. Chest reveals decreased air entry at the right base with a stony dull percussion note and decreased fremitus.

Her abdomen is distended with a liver that is felt 6 cm below the right costal margin and is tender but not pulsatile. There is a fluid thrill but no dilated abdominal veins. She has 2+ ankle edema to the knees bilaterally.

Laboratory Studies

Hb 15.3 g/dl
Platelets 587,000/μl
WBC 16.6 × 10³/μl
INR 1.5
Creatinine 1.2 mg/dl
Tbili 3.4 mg/dl
AST 238 iu/l
ALT 206 iu/l
GGTP 349 iu/l
ALP 287 iu/l
Albumin 2.9 g/dl

Ultrasound shows ascites and chest x-ray shows a right pleural effusion

Questions

1. What are the other tests required to make a diagnosis?
2. What are the treatment options?
3. What is the long-term prognosis?
Fig. 54.1 Ultrasound

Fig. 54.2 Ultrasound
**Answer: Budd–Chiari Syndrome**

The ultrasound with Doppler (Figs. 54.1–54.4) shows echogenic material in the inferior vena cava (IVC) that is arrowed (Fig. 54.1), and all of the hepatic veins show no flow and are barely visible indicating complete thrombosis.

Budd–Chiari syndrome (BCS) is defined by obstruction of venous outflow from the liver. This is typically due to hepatic venous or inferior vena caval thrombosis.

This lady has a classic presentation with a relatively acute onset of tender hepatomegaly, ascites and lower extremity edema. In several large case series, most patients will present in this fashion or with chronic disease characterized by portal hypertension and cirrhosis. A few will have fulminant hepatic failure. BCS is more common in women and a quarter of patients will have an overt myeloproliferative disorder (typically polycythemia vera). This lady’s elevated hemoglobin and platelet count are very suggestive and subsequent work-up confirmed this was indeed the case.

Laboratory studies typically show a mixed picture of enzyme elevation and mild hyperbilirubinemia. If the disease is not treated encephalopathy and liver failure can ensue.

The diagnosis is typically made as in this case with Doppler imaging showing either thrombosis or lack of flow in the hepatic venous outflow tract. Ct scan or MRI can also be employed and the gold standard is venography. The differential diagnosis includes right heart failure and constrictive pericarditis so echocardiogram is a useful test, particularly as analysis of ascitic fluid can demonstrate a total protein >3.0 g/l, and the serum-ascites albumin concentration gradient can be >1.1 g/dl, as seen in patients with cardiac and pericardial disease.

Liver biopsy is not necessary to make a diagnosis but can be helpful for determining prognosis and for guiding therapy, since patients with advanced fibrosis or cirrhosis are unlikely to improve with revascularization.

Treatment can be medical, radiologic, or surgical depending on the acuity of presentation and severity of the obstruction but is also guided by local expertise. The goal is restore venous outflow and decompress the liver to prevent portal hypertension and its sequelae. It is important to complete a hypercoaguable work up and involve a hematologist in the care of these patients so as not to delay use of anticoagulation or anti-platelet agents. In patients with an acute presentation, direct thrombolytic therapy into the thrombosed vessels has had some success.

This patient was treated with diuretics with a good response and was started on heparin and aspirin while waiting for a diagnosis.

She later underwent a TIPS placement. Recent data would suggest that long-term survival after TIPS is 80%, equivalent to that seen with transplant. There are small case series illustrating the benefit of dilation or stent therapy without TIPS, but this runs the risk of restenosis or reocclusion. Because of the improvement in interventional radiology over the last 10–15 years, nontransplant surgery for BCS is very rarely employed.

Liver transplant is an excellent option for patients with evidence of cirrhosis and decompensation who are not candidates for TIPS. It also has the advantage of correcting
potential hematologic etiologies including protein C, protein S, or antithrombin III deficiencies. Several large case series have demonstrated 70–80% 5–10 year survival.

The American Association for the Study of Liver Diseases guidelines for BCS recommend:

- Correcting any underlying risk factor(s) for venous thrombosis.
- Start anticoagulation therapy immediately using low molecular weight heparin and switching to warfarin.
- Maintain permanent anticoagulation therapy unless contraindications/complications.
- Treat complications of portal hypertension.
- Treat venous obstruction amenable to percutaneous angioplasty/stenting in all symptomatic patients.
- Consider TIPS in patients without ongoing improvement on anticoagulation therapy (with or without angioplasty).
- Consider liver transplantation if TIPS insertion fails or does not improve the patient’s condition and in those with fulminant hepatic failure.
- Refer/confer care with a transplant center.

References

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3. De Leve LD, Valla D-C, Garcia-Tsao G. Vascular disorders of the liver. Hepatology 2009;49:1729–64.
Case 55

A 41-year-old man presents to the emergency room with ascites and lower extremity edema. He is not known to have liver disease and in fact was very healthy up until a motor vehicle accident 4 months ago where he was in the passenger seat and his car had a head-on collision with a minivan. Fortunately, he was wearing a seatbelt then and suffered only a fractured tibia that has healed well.

He has noticed increasing abdominal distension over the last few days and now cannot get his shoes on without difficulty. He denies GI bleeding or encephalopathy.

There has been no fever or chills, but he has noticed some shortness of breath.

He denies any prescribed or over the counter medication.

He does not smoke or drink and is married. He has no obvious risk factors for viral hepatitis and no family history of liver disease.

On exam, he looks well with vital signs showing BP 120/75, pulse 92, and he is afebrile. His BMI is 23 kg/m². There is no scleral icterus, but he has several spider nevi.

His heart exam is normal, and lungs reveal some decreased air entry at the right base. His abdomen is distended with dullness in the flanks. His liver is palpable just below the right costal margin, and the spleen is easily felt. He has ++ankle edema to the thighs.

Laboratory Studies

Hb 11.2 g/dl
Platelets 64,000/μl
INR 1.3
Tbili 2.1 mg/dl
AST 102 iu/l
ALT 95 iu/l
ALP 149 iu/l
Albumin 2.5 g/dl
Creatinine 1.3 mg/dl

Questions

1. Which is the likely diagnosis?
2. How is the diagnosis made?
3. What treatment options are available?
Fig. 55.1  CT image

Fig. 55.2  CT image
Fig. 55.3  Angiogram

Fig. 55.4  Angiogram
Fig. 55.5  Angiogram
Answer: Hepatic Arterio-Portal Fistula as a Cause of Portal Hypertension

This is a very interesting case that shows not all portal hypertension is due to increased resistance in portal venous flow. The usual classification of portal hypertension is based on the site of the obstruction – prehepatic, intrahepatic, or posthepatic. The normal portal system is under very low pressure and a gradient of <5 mmHg is typical. Clinical consequences arise when the pressure gradient between the portal and hepatic veins reaches 10–12 mmHg. Increases of portal blood flow can be significant in the postprandial state (from 700 to 1,500 ml/min) but due to the passive dilation of low resistance vessels in and around the liver, the portal pressure rises only marginally.

In this patient, the trauma of the motor vehicle accident has led to the formation of a fistula between the hepatic artery and portal vein. The portal blood flow increases dramatically in this situation, beyond the capacity of low resistance vessels to accommodate and portal hypertension ensues. It can also lead to significant fibrosis in the liver and cirrhosis.

The CT images (Figs. 55.1 and 55.2) show the arterial phase and the hepatic artery fills, but a connection can be seen to the portal vein which is seen filling in Fig. 55.2. The angiogram (Figs. 55.3–55.5) shows a catheter in the right hepatic artery and the portal vein can be seen filling rapidly (Fig. 55.3). The magnified second image (Fig. 55.4) shows the catheter in the fistula and coils are being placed, and the third image (Fig. 55.5) shows closure of the fistula without flow into the portal system.

Hepatic (or splenic) arterioportal fistula is a very rare cause of portal hypertension but illustrates the physiology of the portal system very well. It typically can occur after trauma or rupture of an arterial aneurysm, tumor invasion and has been reported as a complication of liver biopsy. Congential causes include hereditary hemorrhagic telangiectasia. There are reports in the older literature of surgical repair of fistulae, but most case reports and case series now detail successful radiologic treatment as in this case. Occasionally, liver transplantation is required.

References

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3. Korula J, Fried J, Weissman M et al. Fatal hemorrhage from an arterio-portal-peritoneal fistula after percutaneous liver biopsy. Gastroenterology 1989;96:244–6.
Case 56

A 31-year-old lady presents to the emergency room with hematemesis. She has a history of cirrhosis likely secondary to autoimmune disease that has been complicated in the past by several episodes of variceal bleeding but otherwise she denies ascites or encephalopathy. Her last endoscopy was 3 months ago and revealed grade I esophageal varices and small gastric varices. She has undergone multiple sessions of band ligation in the past and is maintained on secondary prophylaxis for variceal hemorrhage.

Her past medical history is significant for thyroid disease.
Her current medications include levothyroxine and nadolol.
She does not smoke or drink and is married without children and is working as a legal assistant.
The rest of her review of systems is negative.

On exam, she looks well with vital signs showing BP 110/60, pulse 62, and she is afebrile. There is no scleral icterus although she has several spider nevi. She is alert and oriented. Her heart and lungs are normal. Abdomen is soft and nontender with a spleen tip palpable but no ascites.

Laboratory Studies

Hb 10.7 g/dl
Platelets 75,000/μl
INR 1.2
Tbili 1.1 mg/dl
AST 45 iu/l
ALT 32 iu/l
ALP 87 iu/l
Albumin 3.5 g/dl
Creatinine 0.7 mg/dl

After adequate resuscitation and somatostatin, endoscopy is performed and reveals grade II esophageal varices with red wale signs and gastric varices in the fundus. Bands are placed on the esophageal varices.

Questions

1. Should this patient be referred for transplant?
2. Are there other options available?
Fig. 56.1 Ultrasound
Answer: Prevention of Recurrent Variceal Hemorrhage with Distal Splenorenal Shunt

This lady presents with another episode of variceal bleeding despite being on a beta-blocker and having undergone multiple endoscopies in the past. Her liver synthetic function is normal and she appears to be active and is still working. Liver transplant would fix the underlying portal hypertension, but she is early based on her MELD score, and most experts would not recommend this.

You could continue with the current strategy but she has bled again despite adequate medical therapy. TIPS would be a consideration in this patient. Another option would be surgical decompression.

In the 1980s, there were several trials comparing endoscopic therapy with portocaval shunting which showed similar efficacy, and this was in the days of sclerotherapy rather than band ligation. In addition, this type of surgery is complex and requires significant expertise and is only available in certain centers. Another study published in 1990 suggested that distal splenorenal shunt (DSRS) was superior to sclerotherapy in bleeding control but the sclerotherapy arm had improved survival, which was still apparent if sclerotherapy failed to control the bleeding and the patient needed salvage DSRS.

However, today a patient would undergo band ligation for esophageal varices rather than sclerotherapy, and TIPS would be a viable option.

A more recent study compared TIPS with DSRS and found that in Child’s A and B patients, the control of recurrent bleeding was similar, but the TIPS group needed more intervention for TIPS stenosis or dysfunction. This study was started in the era before covered TIPS which have lower stenosis rates.

The ultrasound image (Fig. 56.1) shows a patent DSRS (the “S”) between the splenic vein (“SV”) and renal vein (“RV”). Good flow is noted on the Doppler. This lady did well after DSRS and has not bled in the last 2 years. I have followed several other patients from the TIPS vs. DSRS trial that similarly have not bled in 10 years and are still early for transplant suggesting that in patients with well-preserved liver synthetic function and significant portal hypertension, DSRS is a viable alternative if the anatomy is amenable, and the center has the expertise to perform the procedure.

References

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Case 57

A 36-year-old man presents to your outpatient office with abdominal distension which has gradually worsened over several weeks. He denies fever, chills, weight loss, or abdominal pain. He denies GI bleeding or encephalopathy.

His only past medical history is knee surgery following his collegiate athletic career.

He takes occasional over the counter analgesics but takes no prescribed medication.

He is married and works in a local advertising agency. He has never been a heavy drinker and does not smoke or drink.

There is no family history of liver disease.

The rest of his review of systems is negative.

On exam he looks well and is alert and oriented.

Vital signs show BP 115/65, pulse 64 and he is afebrile.

There is no scleral icterus and no spider nevi.

Heart reveals normal S1 and S2 without added sounds. Chest reveals clear lung fields.

His abdomen is distended with a fluid thrill. Spleen is easily palpable, and there are dilated abdominal veins. There is a murmur heard best in the epigastric area which grows louder with a Valsalva manoeuvre and seems to diminish when pressure is applied over the umbilical area with the palm of the hand. He has +ankle edema bilaterally.

Laboratory Studies

Hb 14.1 g/dl
Platelets 73,000/μl
WBC 5.3 × 10³/μl
INR 1.1
Creatinine 1.3 mg/dl
Tbili 0.6 mg/dl
AST 18 iu/l
ALT 16 iu/l
GGTP 83 iu/l
ALP 96 iu/l
Albumin 3.1 g/dl

Questions

1. What is the sound that is heard over the epigastric area?
2. What makes the sound?
3. Does the patient need to have cirrhosis to produce this sound?
4. What might you see on ultrasound?
Fig. 57.1  Ultrasound
Answer: Cruveilhier–Baumgarten Disease or Syndrome

This patient obviously has portal hypertension. He has ascites, splenomegaly, and dilated abdominal veins, and the sound in the epigastric area is a venous hum. Some experts suggest that the direction of flow of blood in the dilated abdominal veins is indicative of either portal hypertension or vena caval obstruction, but the presence of valves can make it difficult to distinguish inferior flow (suggesting portal hypertension) or flow superiorly (vena caval obstruction).

The ultrasound image (Fig. 57.1) shows a liver that is echogenic in echotexture (smallest arrow), and on other images was markedly decreased in size, and nodular in contour. A large amount of abdominal ascites is present (large arrow) and there is a patent paraumbilical vein (long arrow). The venous hum results from collateral connections between the portal system and the remnant of the umbilical vein and should increase with the Valsalva and decrease with pressure over the umbilicus.

The term Cruveilhier–Baumgarten syndrome is based on a description by Cruveilhier in 1852 and then Baumgarten in 1908 and is characterized by portal hypertension, splenomegaly, and evidence of excessively prominent umbilical circulation – visible abdominal veins and a venous hum. The disease refers to these findings in a patient who has a patent umbilical vein, an atrophic liver but with little or no fibrosis on pathology, whereas the syndrome most commonly occurs in patients with cirrhosis.

There is some suggestion that the presence of the collaterals in this syndrome makes typical varices in the distal esophagus and proximal stomach smaller (and less likely to bleed).

The classic intrahepatic venous circulation found in the syndrome can be appreciated on Doppler sonography with hepatopetal flow in the segmental portal veins and heptofugal flow leaving the liver in a paraumbilical vein in the falciform ligament which joins veins in the anterior abdominal wall around the umbilicus (causing the venous hum).

References

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Case 58

A 37-year-old white male with a history of chronic lower back pain is admitted directly to the hospital from his scheduled pain clinic visit with new onset jaundice and abdominal distension. The patient has been experiencing increasing back pain for the last 2 weeks. He states that the pain is higher than his chronic back pain. He also has developed new onset lower extremity edema in the last week. The patient’s wife noticed some confusion and disorientation in the last several days. One day prior to admission, she noticed yellowing of his eyes. Review of systems is notable for nausea, constipation with intermittent rectal bleeding in the last month, dyspnea on exertion, and diaphoresis. One month prior, the patient and his wife were in South Carolina on vacation. There is no history of fevers, chills, sick contacts, or antibiotic use. The patient is a former police man and was involved in a work-related injury 3 years ago. Since then, he has been suffering with lower back pain. He is seen regularly in the chronic pain clinic and has been consistent with his physical therapy regimen. In the last several months, he has been able to wean to as needed narcotics, although in the last several weeks, his narcotic use had increased to hydrocodone/acetaminophen 7.5/750 up to 8 pills a day. He also has recently been diagnosed with depression and insomnia and was started on a low dose of amitriptyline. The patient lives with his wife of 4 years. He is monogamous and has never used illicit drugs. He drinks 10–14 beers per week. He does not smoke. He has no tattoos nor has he ever had any blood transfusion. He currently works at the department of motor vehicles. The patient’s sister was diagnosed with leukemia at the age of 24. She has been in remission for over 10 years.

Physical exam was notable for a lethargic, ill-appearing white male. Vital signs reveal: temperature 37.2°C, heart rate 110, Blood pressure 98/54, respiratory rate 22, saturation 92%, and BMI 31.7 kg/m². Sclerae were icteric. Other than tachycardia, cardiac and pulmonary exam were normal. Abdominal exam was notable for marked distension. Liver edge was palpable 8 cm below right costovertebral angle and was tender. There was no splenomegaly. Fluid wave was easily elicited. Pitting edema was noted from ankles to mid thigh. Rectal exam revealed moderate external hemorrhoids one of which was thrombosed and oozing a small amount of blood, no internal masses were palpated. There was no palpable adenopathy.

A diagnostic tap was performed: hematocrit 22%

A CT scan is performed (see Fig. 58.1). In addition, a note is made of an enhancing lesion in the sigmoid colon.

Laboratory Data

Na 135 mM/l
BUN 39 mg/dl
Creat 3.2 mg/dl
Arterial blood gas: pH 7.20, pCO2 19, pO2 226; lactate 14
WBC 24,000; 93% neutrophils
Hb 7.5 g/dl
Platelets 347,000/μl
Tbili 7.2 mg/dl
AST 2443 iu/l
ALT 2487 iu/l
ALP 500 iu/l
GGTP 2452 iu/l
LDH 2136 iu/l
CPK 800 iu/l
Uric Acid 16 mg/dl
Alb 3.4 g/dl, total protein 6.1 g/dl
NH3 94 μmol/l
PT 94 seconds, INR 11; PTT 48 seconds
Fe 92 ug/dl, TIBC 223 ug/dl, % Sat 41, Ferritin 2,900 ng/dl
Urine tox, acetaminophen level negative
HAV IgM –
HBsAg –, core total/IgM –, HBsAb –
HCV PCR –
CMV/HSV negative
EBV indicates past exposure
ANA, smooth muscle, LKAM, Immunoglob all normal
Ceruloplasmin 39 mg/dl, AIAT 269 mg/dl
AFP 9 ng/ml, CA 19-9 660 iu/ml, CEA 9 ng/ml

Questions

1. What is the differential diagnosis?
2. How do you account for the hematocrit level in the ascites fluid?
3. How would you make a definitive diagnosis in this case?
4. What treatment if any would you recommend?
Fig. 58.1  CT scan

Fig. 58.2  Liver biopsy
Fig. 58.3  Sigmoidoscopy
Answer: Metastatic Colon Cancer to the Liver presenting as Acute Liver Failure

This case fulfills criteria for acute liver failure (ALF): the rapid deterioration of liver function resulting in coagulopathy and alteration in the mental status of a previously healthy individual. The differential diagnosis in this case includes: acetaminophen/drug induced, viral, veno-occlusive, ischemic, and autoimmune hepatitis. All of these, however, can reasonably be ruled out with history, exam, blood work, and imaging. The extreme elevations in iron studies seen in many cases of acute severe hepatitis can cause some confusion to the unseasoned clinician; however, these constitute a manifestation of hepatocellular damage and likely have no prognostic value. Moreover, hereditary hemochromatosis should never be on the differential of acute liver failure.

The presence of massive hepatomegaly, cholestatic pattern to the liver function tests, and bloody tap in a relatively young person make an infiltrative or malignant process the most likely cause. Prior to histology, given the elevated LDH and high uric acid, lymphoma was at the top of our list of possible causes.

The patient’s hemodynamic instability was secondary to intrahepatic hemorrhage. The equivalent ascites and serum hematocrit measured from the diagnostic paracentesis, in conjunction with inappropriate response to multiple blood transfusions were evidence of active bleeding. The CT scan (Fig. 58.1, white arrow) showed an actively bleeding lesion in the periphery of the right lobe. The patient was sent emergently to angiography where embolization of a branch of the right hepatic artery was performed resulting in cessation of active bleeding.

Both a transjugular liver biopsy (performed prior to knowledge of a questionable sigmoid lesion was discovered on CT scan) and flexible sigmoidoscopy were performed. Liver biopsy (Fig. 58.2) revealed normal liver parenchyma with tumor thrombus noted within branches of the portal vein (white arrow). Sigmoidoscopy revealed a 5 cm, bleeding, partially obstructing mass in the recto-sigmoid junction (Fig. 58.3). Pathological evaluation and special stains confirmed a diagnosis of colon cancer with metastatic spread to the liver.

Hematological malignancies (leukemia and lymphoma) aside, metastatic spread of solid organ cancers to the liver presenting as ALF is a very rare phenomenon with only a handful of cases described in the literature. Given the unique blood supply of the liver, massive metastatic tumor burden in the liver is not an uncommon occurrence. So, why then did this patient develop acute liver failure? We hypothesize (given the presence of tumor only within the branches of the portal vein and not the hepatic parenchyma) that the tumor metastasis via the portal vein, in conjunction with the intraperitoneal hemorrhage, resulted in an ischemic liver injury; this in conjunction with massive tumor burden resulted in this patient’s liver failure.

In every case of ALF with prodromal symptoms or abnormal imaging, hepatic histology should be obtained by liver biopsy as soon as possible to diagnose infiltrative hepatic disease and avoid futile transplantation.

The unfortunate gentleman in this case developed anuric renal failure and worsening mental status. He was made comfort measures only and died 7 days after
admission. Microsatellite instability was performed on the pathology of the colon cancer and was negative. Screening colonoscopies were performed on the patient’s two sisters and were normal.

References

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2. Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. Gut 1998;42:576–80.
Case 59

You are called by the ER to come and see a 66-year-old lady who has presented with jaundice. She is from out of state and has been visiting family in the area for the last 2 weeks. No medical records are available.

She denies any fever, abdominal pain, change in urine or stool color, or pruritus. She does not speak English and relatives with her say that she has a history of alcoholic cirrhosis. She has a small scrap of paper with her that looks like a medication list and includes a small dose of furosemide and spironolactone, and she has been taking lactulose.

She was apparently diagnosed with a liver lesion 3 months ago based on surveillance imaging and has been undergoing treatment although it is unclear which type of treatment.

Her physical exam is notable for an elderly woman in no apparent distress. Her vital signs are normal, and she is afebrile. She is obviously icteric with multiple spider nevi, palmar erythema, and an easily palpable left lobe of liver and spleen tip. There is no obvious ascites or ankle edema.

Laboratory Studies

Hb 9.8 g/dl  
Platelets 58,000/μl  
WBC 4.1 × 10^3/μl  
INR 1.6  
Creatinine 1.1 mg/dl  
Tbili 12.5 mg/dl  
AST 67 iu/l  
ALT 48 iu/l  
GGTP 105 iu/l  
ALP 157 iu/l  
Albumin 2.4 g/dl  
AFP 2.4 ng/ml  
Blood ethanol level undetectable

Ultrasound – small shrunken liver, no biliary ductal dilation, ill-defined 6 cm heterogeneous mass in the left lobe.

Questions?

1. What is the differential diagnosis?
2. How would you manage this patient?
Fig. 59.1  CT scan
**Answer: Decompensation After Arterial Chemoembolization**

This unfortunate lady has developed worsening liver function manifested by jaundice several weeks after transarterial chemoembolization (TACE) for HCC. The CT scan (Fig. 59.1) shows a lesion that does not enhance after contrast compatible with a treated lesion (arrowed). The liver is cirrhotic, and ascites is apparent. No biliary dilation is seen to suggest obstruction.

The differential diagnosis includes anything that could cause decompensation in a cirrhotic patient such as infection, bleeding, acute alcohol, and medications. However, she looks well and has an undetectable alcohol level. Her enzymes argue against infection or a medication-induced effect. Her tumor could have recurred or perhaps she has developed another lesion at or near the hilum that is causing biliary obstruction but again her numbers and imaging do not correlate with this. The most likely explanation is worsening of her underlying liver disease due to TACE.

Since the bulk of blood supply to HCCs comes from the hepatic artery, the principle behind TACE is to embolize or infuse chemotherapy directly into a hepatic artery branch that supplies the tumor. It is not surprising that some adjacent liver tissue suffers some ischemic damage.

Indeed, some of the contraindications for TACE include situations where an added ischemic insult could push the patient into liver failure such as portal vein thrombosis, elevated bilirubin, high tumor volume, ascites, or high transaminases.

Several large studies and meta-analyses have examined the incidence of complications after TACE and found the most common adverse effect, occurring in 60–80%, is a self-limiting postembolization syndrome that causes pain, fever, and a rise in liver enzymes. The rate of liver failure after TACE depends on the pretreatment liver function but can be as high as 20% and can be irreversible in 2–3%.

**References**

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2. Marelli L, Stigliano R, Triantos C et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 2007;30:6.
3. Chan AO, Yuen MF, HuiCK et al. A prospective study regarding the complications of transcatheter intraarterial lipiodol chemoembolization in patients with hepatocellular carcinoma. Cancer 2002;94:1747.
Case 60

A 57-year-man presents to the emergency room with fatigue and just not feeling well. He has a history of cirrhosis likely secondary to fatty liver disease. His complications include ascites controlled on diuretics and mild encephalopathy. His last endoscopy was 2 years ago which showed mild portal hypertensive changes.

His other medical problems include diabetes controlled on insulin and a remote cholecystectomy.

He is married and is accompanied to the hospital by his wife. He is on disability but used to work as a chef.
He denies tobacco, alcohol, or drug use.
His father was an alcoholic.
The rest of his review of systems is pertinent for some shortness of breath on exertion but he denies blood in the stool, melena, abdominal pain, or weight loss.
He has had no fever or chills.
On exam, he looks tired but is alert and oriented.
Vital signs show BP 100/60, pulse 112 and he is afebrile.
There is mild scleral icterus and several spider nevi.
Heart reveals normal S1 and S2 without added sounds. Chest reveals lung fields.
His abdomen is obese but soft and non-tender with a palpable spleen tip.

Laboratory Studies

Hb 6.7 g/dl
MCV 72 fl (normal 80–95fl)
Platelets 59,000/μl
WBC 3.8 × 10³/μl
INR 1.3
Creatinine 1.1 mg/dl
Tbili 2.9 mg/dl
AST 68 iu/l
ALT 53 iu/l
GGTP 123 iu/l
ALP 118 iu/l
Albumin 2.6 g/dl
Stool hemoccult positive

After adequate resuscitation he undergoes upper GI endoscopy.
Questions

1. Is the severity of changes seen on endoscopy related to the degree of portal hypertension?
2. If this patient has esophageal varices that are banded/sclerosed, does this affect this condition?
3. What is the appropriate treatment?
Fig. 60.1 Endoscopic images

Fig. 60.2 Endoscopic images
**Answer: Portal Hypertensive Gastropathy**

The endoscopic images (Figs. 60.1 and 60.2) show portal hypertensive gastropathy (PHTG). The first image (Fig. 60.1) shows the gastric antrum where there is severe PHTG with hyperemic mucosa and diffuse oozing on contact with the scope. More proximally in the stomach, the second image demonstrates the “chickenwire” appearance of mild PHTG.

Severe PHTG in the antrum can be confused with gastric antral vascular ectasia (GAVE or watermelon stomach). The latter is characterized by ecstatic mucosal blood vessels and is also seen in patients with cirrhosis. It can present in a similar manner with microcytic anemia but can be treated with cautery or argon plasma coagulation.

PHTG typically is worse in the proximal stomach but can be present anywhere. Biopsy is usually not required to make a diagnosis. Increasing incidence or severity is not always the natural history in cirrhosis and the presence of PHTG is not related to age, sex, cause of cirrhosis, or grade of gastroesophageal varices. However, severe gastropathy is associated with an increase in portal venous pressure gradient and impaired liver metabolic activity. Interestingly, several studies have suggested that sclerotherapy or band ligation of esophageal varices increases the risk of developing portal hypertensive gastropathy.

As with causes of bleeding in portal hypertension, PHTG can be treated by trying to decrease portal pressure through non-selective beta blockers, TIPS, shunt surgery or ultimately by liver transplant. TIPS appears to work quite well for this condition, but in my experience most patients seem to do well with iron supplementation and beta-blockade.

This patient presents with anemia which is presumably from chronic blood loss as his esophageal varices were small (and variceal bleeding typically has a more dramatic presentation). Endoscopy shows severe distal PHTG. Treatment with oral iron and nadolol was started and appeared to decrease the transfusion requirement over the next 6–12 months.

**References**

1. Payen JL, Cales P, Voigt JJ et al. Severe portal hypertensive gastropathy and antral vascular ectasia are distinct entities in patients with cirrhosis. Gastroenterology 1995;108:138.
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5. Perez-Ayuso RM, Pique JM, Bosch J et al. Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis. Lancet 1991;337:1431.
Case 61

You are asked by the obstetric service to see a 31-year-old lady for abnormal liver enzymes and nonspecific symptoms. She is in week 37 of her first pregnancy. She had some problems with hyperemesis in the first trimester, but otherwise, the pregnancy has been normal. Her ALT yesterday was 67 iu/l.

She has no other medical problems. Medications include a prenatal vitamin. She does not smoke or drink. She is married and works as a secretary. There is no family history of liver disease.

Her review of symptoms is significant for some nausea and vomiting and upper abdominal pain. She has some loose stool over the last 24 h. She denies fever or chills. She has no pruritus.

You are busy in the clinic and send a fellow to see the patient. The fellow calls back several hours later with his assessment and with new laboratory studies.

The patient’s vital signs show a BP 145/95, pulse 100, and she is afebrile. She is able to answer questions appropriately, but her husband states that she looks sleepier than earlier today.

She has mild scleral icterus and palmar erythema. Cardiovascular system reveals normal heart sounds. Lungs are clear. Abdomen demonstrates a gravid uterus consistent with a 37 week pregnancy. There is right upper quadrant tenderness. Ankles reveal +ankle edema.

Laboratory Studies

Hb 9.7 g/dl  
Platelets 62,000/μl  
WBC 10.2 × 10³/μl  
INR 1.4  
Creatinine 1.4 mg/dl  
Tbili 3.1 mg/dl  
AST 367 iu/l  
ALT 359 iu/l  
GGTP 140 iu/l  
ALP 196 iu/l  
Albumin 2.8 g/dl  
Blood glucose 67 mg/dl

You urgently go over and see the patient and inform the primary service that she likely needs emergent delivery.
Questions

1. What is the characteristic appearance of the liver biopsy in this condition?
2. Is there a risk of this disease recurring in subsequent pregnancies?
Ultrasound: Normal-looking liver without biliary dilation
Liver biopsy: Pathology resident states the hepatocytes have a “foamy cytoplasm”
**Hepatology and Transplant Hepatology**

**Answer: Acute Fatty Liver of Pregnancy**

This clinical scenario probably occurs a few times a year at a tertiary care liver transplant center.

Liver disease in pregnancy can be separated into diseases that are unique to pregnancy, “normal” liver or biliary diseases occurring in a pregnant woman (viral hepatitis or gallstone disease), and pregnancy occurring in a patient with known liver disease (typically viral hepatitis or cirrhosis).

The approach to liver disease in pregnancy is guided by a few factors, namely, the trimester, the degree of liver enzyme elevation, the presence of itching, and the severity of disease.

Hyperemesis gravidarum occurs in the first trimester and presents with relatively mild elevation of liver enzymes and intractable nausea and vomiting. It can be confused with viral hepatitis. Intrahepatic cholestasis of pregnancy is a disorder of late pregnancy and presents with itching, cholestatic enzymes, and negative imaging for biliary dilation. It often recurs in subsequent pregnancies and is associated with fetal loss. Treatment is delivery. Acute fatty liver of pregnancy (AFLP), HELLP syndrome (hemolysis with a microangiopathic blood smear, elevated liver enzymes, and a low platelet count), and severe preeclampsia cause the most confusion in making a diagnosis since they can have a similar presentation.

This lady presents in the third trimester with nausea, vomiting, and abdominal pain, all of which are common in AFLP. Her laboratory studies show elevated transaminases and hypoglycemia, which together with her mental status, are concerning for significant liver dysfunction. The low platelet count might suggest HELLP, but disseminated intravascular coagulopathy is not infrequent in AFLP.

The pathogenesis of AFLP is not completely understood, but several studies have shown an association with one of the inherited defects in mitochondrial beta-oxidation of fatty acids, long-chain 3-hydroxyacyl CoA dehydrogenase deficiency (LCHAD). This suggests that some affected women and their fetuses might have an inherited enzyme deficiency in beta-oxidation that predisposes the mother to AFLP. LCHAD catalyzes one of the steps in the beta-oxidation of fatty acids in mitochondria (the formation of 3-ketoacyl-CoA from 3-hydroxyacyl-CoA), and deficiency leads to the accumulation of long-chain 3-hydroxyacyl metabolites produced by the fetus or placenta which is toxic to the maternal liver. Not all cases of AFLP have the enzyme deficiency.

The diagnosis of AFLP is based on an appropriate clinical presentation and supportive laboratory tests. Liver biopsy is not necessary and will be risky because of the coagulopathy. However, it is diagnostic, showing a characteristic microvesicular fatty infiltration of the hepatocytes. There is a foamy cytoplasm due to fat droplets surrounding centrally located nuclei, and there is sparing of a sharply defined rim of cells around the portal tracts.

Treatment is based on maternal support and emergent delivery. Maternal and fetal mortality has improved with better recognition of the disease but is still seen. Recurrence in subsequent pregnancies has been documented.
References

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2. Wilcken B, Leung KC, Hammond J et al. Pregnancy and fetal long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency. Lancet 1993;341:407–8.
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Case 62

A 57-year-old Caucasian male presents to the emergency room with hematemesis. His wife states that he has a history of chronic hepatitis C infection diagnosed 10 years ago. He was never treated and in fact has not seen a doctor for more than 6 years.

He has no other medical history and denies any prescribed or over-the-counter medications.

He has a remote history of intravenous drug use from age 19 to 25. He does not smoke or drink.

He has otherwise been well recently without abdominal pain or fever. He denies ascites or prior encephalopathy.

In the emergency room, the patient has another episode of hematemesis. His vital signs show him to be hypotensive with blood pressure 90/40 and heart rate 110. He is intubated for airway protection and resuscitated. An upper endoscopy is performed emergently.

Laboratory Parameters

WBC $7 \times 10^3/\mu$L
Hemoglobin 8.0 g/dl
Platelet $68 \times 10^3/\mu$l
PT 25 seconds
Tbili 1.8 mg/dl
AST 154 U/l
ALT 112 U/l
Creatinine 1.2 mg/dl

Questions

1. What are the appropriate management steps?
2. How effective is endoscopic therapy?
Fig. 62.1  Endoscopic images

Fig. 62.2  Endoscopic images
**Answer: Acute Variceal Bleeding**

The EGD pictures (Figs. 62.1 and 62.2) demonstrate a large amount of fresh blood in the fundus and a gastric varix spurting blood along the greater curvature (GOVII). A sclerotherapy needle is being used to inject a sclerosant into the varix and the bleeding stops. The patient has a known history of chronic hepatitis C infection. From his social history, it is likely that he had had the infection for more than 30 years, which increases the likelihood of advanced liver disease such as cirrhosis. About one-third of patients with varices experience variceal hemorrhage, and each episode of hemorrhage can have 20–30% mortality. In patients with acute variceal hemorrhage, diagnostic and therapeutic endoscopy should be done emergently once patients are hemodynamically stable. Intravenous octreotide and antibiotics should be started promptly when variceal hemorrhage is suspected. Type I gastric varices (GOV I) are found along the lesser curve (usually 2–5 cm in length) which are potentially treatable with endoscopic band ligation therapy. Type II (GOV II) are found along the greater curve extending toward the fundus of stomach. Isolated gastric varices are found in the fundus (IGV I) or other parts of the stomach (IGV II). Band ligation is ineffective in GOV II and IGV.

The AASLD guidelines for variceal hemorrhage recommend:

- Acute GI hemorrhage in cirrhotic patients is an emergency that requires prompt intravascular volume support and blood transfusions, being careful to maintain a hemoglobin of approximately 8 g/dl.
- Short-term (max. 7 days) antibiotic prophylaxis should be instituted in any patient with cirrhosis and GI hemorrhage with PO norfloxacin or IV ciprofloxacin.
- In patients with advanced cirrhosis, IV ceftriaxone (1 g/day) may be preferable, particularly in centers with a high prevalence of quinolone-resistant organisms.
- Pharmacological therapy (somatostatin or its analogues octreotide and vapreotide; terlipressin) should be initiated as soon as variceal hemorrhage is suspected and continued for 3–5 days after the diagnosis is confirmed.
- EGD, performed within 12 h, should be used to make the diagnosis and to treat variceal hemorrhage either with band ligation or sclerotherapy.
- TIPS is indicated in patients in whom hemorrhage from esophageal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy.
- Balloon tamponade should be used as a temporizing measure (max. 24 h) in patients with uncontrollable bleeding for whom a more definitive therapy (e.g., TIPS or endoscopic therapy is planned).
- For gastric varices, endoscopic variceal obturation using tissue adhesives such as cyanoacrylate is preferred, where available. Otherwise, EVL is an option.
- TIPS should be considered in patients in whom hemorrhage from fundal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy.

As well as cyanoacrylate (that is not available outside of a study in the United States), intravariceal thrombin injection has also been shown to be useful.
References

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Case 27–65

Case 63

A 52-year-old African American male presents with a 4-week history of progressively worsening abdominal pain and distension. Four weeks ago, he began to develop diffuse, crampy abdominal pain which he describes as sharp and jabbing with radiation to his upper chest and back. He also describes increasing abdominal distension and is no longer able to fit into his pants. Over the last 2 weeks, he has reported constant nausea, intermittent nonbloody emesis, and nonbloody diarrhea. His appetite is poor, and he has lost 15 pounds. He also is very short of breath and has developed a new dry cough. The patient has a history of poorly controlled diabetes and schizoaffective disorder and is on sertraline and quetiapine fumarate, although he admits to noncompliance. He has a history of hepatitis C diagnosed 8 years ago but never treated due to his psychiatric history. The patient currently lives with his girlfriend. He has seven children from previous relationships. He works as a construction worker but has been forced to quit given his recent illness. He has drunk most of his adult life, averaging between 6 and 10 beers per day in addition to a pint of rum. He does admit to drinking more heavily in the last month. His last drink was the day of admission. He has a 60 pack year smoking history and currently smokes 2 packs per day. He uses IV drugs in the form of heroin, and his last use was 1 week prior to admission. The patient is adopted and does not know details regarding the medical history of his biological family. On review of systems, he complains of chills, fatigue, light headedness, and darkening of his urine.

Physical exam is notable for an ill-, lethargic-appearing male with a BMI of 21.8 kg/m². He is afebrile, with a heart rate of 98, and a blood pressure of 106/48. Respiratory rate is 18 per minute and oxygen saturation is 91% on room air. He has temporal wasting and scleral icterus. His parotid glands are enlarged bilaterally. His mucous membranes are dry. He has decreased breath sounds one-third of the way up on his right side. Heart sounds are distant. His abdomen reveals dilated umbilical veins, a firm liver palpable 3 cm below the right costal margin. There is no audible hepatic bruit. He has full flanks and shifting dullness. He is tender diffusely. Extremities reveal multiple needle tracks and trace lower extremity edema. He has palmar erythema, Dupuytren’s contractures bilaterally and a few scattered spider nevi. He answers questions appropriately and is oriented but does have a liver flap.

Laboratory Data

WBC 25.0 × 10^3/μl with 19% bands
Hg 9 g/dl, MCV 111 f/l
Platelet count 71,000/μl
Tbili 7 mg/dl (conjugated 2.5 mg/dl)
AST 488 iu/l
ALT 200 iu/l
ALP 215 iu/l
GGTP 681 iu/l
Alb 2.3 g/dl

Serum NH3 77 µmol/l
INR 2.2 (PT 25 seconds)

HCV Ab +, Genotype 1
Viral load 1,344,990 iu/ml
HAV Total +
HBsAg −, HBc +, sAb +

Ascites tap: Alb < 1.0, TP < 1.5; WBC 125 × 103/μl with 58% Neutrophils
RBC 490K
Cytology: abundant RBCs, mesothelial cells, macrophages, neutrophils and lymphocytes; negative for malignant cells

Questions

1. What is the differential diagnosis?
2. What additional testing if any would you recommend?
3. What treatment if any would you recommend?
Case 27–65

AFP 28450 ng/ml

Fig. 63.1  CT scan abdomen

Fig. 63.2  CT scan abdomen
Answer: HCV/ETOH Cirrhosis with Superimposed Acute Alcoholic Hepatitis and Multifocal HCC

The acute deterioration in this patient can be accounted for by both the development of HCC with hepatic/portal vein thrombus and superimposed acute alcoholic hepatitis.

The symptoms of weight loss, night sweats, and new onset abdominal pain with radiation to the back are all concerning for malignancy. In the setting of a cirrhotic liver with classic characteristics (hypervascular lesion with washout in the portal venous phase) and marked elevation in AFP, a liver biopsy is not needed to establish the diagnosis of HCC.

Although markedly elevated in this case, and solidifying the diagnosis, AFP is a notoriously poor marker for screening of HCC. The sensitivity of AFP is 41–65%, with a specificity of 80 to 94%.

The acute onset of jaundice, elevated INR, WBC, 2:1 pattern of elevation of AST/ALT and marked elevation in GGT in the setting of excessive consumption of alcohol are consistent with acute alcoholic hepatitis. Acute alcoholic hepatitis occurs superimposed on cirrhosis in approximately 40% of individuals.

The epidemic of fatty liver disease aside, alcoholic liver disease and HCV are the two most common causes chronic liver disease in the country and many times coexist in the same individual. The combination of insults seems to work in synergy in both the progression of fibrosis and the development of HCC. A daily uptake of >80 g of alcohol alone increases HCC risk fivefold while the presence of HCV alone increases HCC 20-fold. The combination of both factors increases the risk of HCC development over 100-fold.

Men are far more likely to develop HCC. Although not completely understood, these differences in sex distribution are thought to be due to variation in viral hepatitis carrier states, exposure to environmental toxins, and the trophic effect of androgens. In addition, the incidence of HCC is greater in black Americans than white Americans. Other risk factors for HCC present in the case, but more controversial and less definitive in their association include smoking, diabetes, and the positive hepatitis B core antibody.

The differential for frankly bloody ascites include: traumatic tap, cirrhosis, or malignancy. Ascites is bloody in approximately 50% of patients with HCC.

The HCC in this case was multifocal with the largest lesion being 7 cm. The lesion was invading the right diaphragm and was actually abutting the right heart (see Fig. 63.2; black arrow: HCC, white arrow right ventricle). There was subocclusive thrombosis of the inferior vena cava, middle hepatic, right and main portal veins. Per the patient’s wishes, he was made palliative care, sent home on hospice and died 8 days after his presentation.
References

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2. Gupta S, Bent S, Kohlwes J. Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C. A systematic review and critical analysis. Ann Intern Med 2003;139:46–50.
Case 64

You are asked to see a 71-year-old man who is on the non-teaching service by the medical resident.

The patient has a history of cryptogenic cirrhosis complicated by ascites that was refractory to diuretics. He has been undergoing regular large volume paracentesis. There is no history of encephalopathy or GI bleeding although endoscopy 3 months ago had shown small esophageal varices.

He was admitted for observation following placement of a TIPS yesterday afternoon. The procedure was uncomplicated, and the initial hepatic venous pressure gradient was 22 mmHg and dropped to 5 mmHg following the TIPS.

This morning he is combative and was put in restraints by the covering housestaff.

On exam, he is confused and uncooperative. Vital signs show BP 135/80, pulse 92 regular, and he has a normal axillary temperature.

He has palmar erythema and several spider nevi. There is mild scleral icterus. He will not cooperate to look for asterixis.

Heart reveals normal S1 and S2 without added sounds. Chest reveals clear lung fields.

His abdomen is mildly distended with dull flanks. There is no tenderness, and bowel sounds are heard. There is +ankle edema bilaterally.

Laboratory Studies

Hb 11.5 g/dl
Platelets 61,000/μl
WBC 8.1 × 10³/μl
INR 1.8
BUN 32 mg/dl
Creatinine 1.8 mg/dl
Tbili 3.1 mg/dl
ALT 32 iu/l
Albumin 2.2 g/dl

Questions

1. What test(s) are required to make a diagnosis?
2. What treatment options are available apart from medical therapy?
3. If the current laboratory parameters were similar prior to TIPS, should the patient have undergone TIPS?
Venous ammonia: 16 µmol/l
MELD score: 23
Answer: Hepatic Encephalopathy Following TIPS

This elderly patient has developed altered mental status after placement of a TIPS, likely related to hepatic encephalopathy (HE).

This is a diagnosis that can be difficult to make since it is defined by a variety of neuropsychiatric abnormalities seen in patients with liver disease, after excluding other unrelated neurologic and/or metabolic abnormalities. The severity of HE can be graded from stages I through IV with stage I representing mild symptoms and stage IV coma. More recently, there have been attempts to reclassify HE to enable better clinical studies. This new system uses the following:

Type A – HE associated with acute liver failure
Type B – HE associated with porto-systemic bypass and no liver disease
Type C – HE associated with cirrhosis and portal hypertension and/or shunts.

Type C is subdivided into episodic, persistent and mild. This last subdivision of minimal HE has gained attention since the diagnosis is based on psychometric testing and patients have no signs or symptoms (stage 0), and several studies have suggested that these patients are at increased risk of accidents while driving.

The diagnosis of HE should be made clinically and does not require an ammonia level. Ammonia levels do not correlate well with the degree of HE and are difficult to measure accurately. Ammonia is produced in the gut from several sources including the breakdown of nitrogenous material by bacteria and also from glutamine in enterocytes. It enters the portal vein, and the liver metabolizes it back to glutamine or urea. In liver dysfunction, ammonia clearance is impaired, and shunting also occurs if there is portal hypertension.

Accurate measurement of venous (or preferably arterial) ammonia requires the sample to be placed on ice and analyzed quickly. The partial pressure of ammonia is a better test since it is in this state that ammonia crosses the blood brain barrier, but again is difficult to measure directly.

The pathogenesis of HE is still unclear but likely involves ammonia as well as other neurotransmitters such as gamma-aminobutyric acid (GABA) in the central nervous system.

After TIPS, HE is seen in up to 30% of patients and is more likely to occur in older patients, more severe liver disease and in patients with HE prior to the TIPS. Prior to being used to prioritize organ allocation for liver transplant in the US, the MELD score was developed to predict mortality after TIPS. A score of greater than 18 predicts poor outcome and this patient should not have undergone TIPS for this nonemergent indication.

The treatment of post-TIPS HE is the same as HE in other situations. Precipitating factors should be reversed if present such as constipation, GI bleeding, dehydration, electrolyte abnormalities, infections, and medications, and worsening hepatic function. Lactulose should be titrated to 3–4 soft bowel movements daily. Protein restriction is generally not recommended. Other agents used include neomycin, metronidazole, and zinc although the data for their efficacy is limited. Recently, oral rifaximin has been shown to be effective but is very expensive in the US. As a last resort, the TIPS can be occluded or downsized, but this will very likely cause the ascites to reaccumulate.
References

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Case 65

A 61-year-old lady is brought to the emergency room by her husband with several hours of confusion. She has a history of alcoholic liver disease that has been complicated in the past with encephalopathy. She has esophageal varices detected on endoscopy but no history of GI bleeding. Her ascites has been controlled on diuretics in the past, but she has not been seen for almost a year. Her last imaging was an ultrasound at that time that showed portal hypertension but no mass.

She is usually alert and oriented, and her husband states that he thinks she has been compliant with her lactulose and appeared to be well last night. There has been no nausea or vomiting. Her bowels have been moving normally without blood.

Her past medical history is significant for diabetes controlled on diet and depression.

Medications include lactulose, nadolol, and a multivitamin.

She lives with her husband and they have no children. She smokes a packet of cigarettes a day. She has not been evaluated for transplant because of continued alcohol use. Her husband confirms that she drinks a bottle of vodka every few days and several beers a night. There is no history of drug use and no family history of liver disease.

The rest of her review of systems is negative.

On exam, she is confused and appears disheveled. Vital signs show BP 105/60, pulse 68 regular and she has a low grade temperature of 100.1°F.

There is palmar erythema, scleral icterus and multiple spider nevi.

Heart reveals normal S1 and S2 without added sounds. Chest reveals clear lung fields.

Her abdomen is distended with a fluid thrill. Palpation of the upper abdomen elicits a grimace. Bowel sounds are sparse. Her liver and spleen are impalpable. She has +ankle edema bilaterally.

Laboratory Studies

Hb 10.4 g/dl
Platelets 41,000/μl
WBC 12.1 × 10³/μl (74% neutrophils)
INR 2.4
Sodium 122 mmol/l
Creatinine 1.3 mg/dl
Tbili 18.2 mg/dl
AST 159 iu/l
ALT 86 iu/l
GGTP 207 iu/l
ALP 175 iu/l
Albumin 2.3 g/dl
Questions

1. What should you do next?
2. What should you do straight after that?
3. Does she need albumin/octreotide/hypertonic saline?
Ascitic fluid tap

Blood tinged fluid

Cell count  50,000 red cells  
            700 white cells  
            60% polymorphonuclear

Gram stain  negative for any organisms

Albumin  0.9 g/dl

After 48 h

Ascitic fluid culture  no growth
Answer: Spontaneous Bacterial Peritonitis (SBP)

This lady presents with a relatively acute onset of change in mental status, low-grade fever, and ascites in the setting of ongoing alcohol use. She has not been seen for some time, and we are not told her baseline bilirubin. However, she is coagulopathic, has an elevated white-cell count with abdominal tenderness in the setting of jaundice. She very likely has hepatic encephalopathy, but the question is what is the etiology? The main differential diagnosis is between alcoholic hepatitis and SBP, but the development of HCC or another infection is also possible. Apart from SBP, which is defined as infection in the ascitic fluid without evidence of an intraabdominal surgically treatable source, the possibility of secondary bacterial peritonitis (from a ruptured viscus – gallbladder, colon, or peptic ulcer) should be considered and abdominal imaging is advisable.

The first test that should be performed is a diagnostic ascitic tap. Despite the thrombocytopenia and elevated INR, she does not need blood products prior to the tap. Several studies have documented that a tap in this situation is very safe and guidelines from the AASLD do not recommend prophylactic platelet or plasma/cryoprecipitate transfusion. Apart from the tap, blood cultures and a sepsis workup are warranted, and abdominal imaging with ultrasound would not be unreasonable.

The ascitic tap should be performed at the bedside, and antibiotics can be started while waiting for the result if the suspicion for SBP is high (as is the case in this patient). The diagnosis of SBP is made on a positive culture and an elevated absolute polymorphonuclear leucocyte (PMN) cell count of >250 cells/mm³. A small amount of the fluid should be sent for chemistry to determine the albumin content. In this case, the difference between the serum albumin and ascites albumin (serum ascites albumin gradient or SAAG) was 1.4 g/dl, indicative of portal hypertension. Another 10 ml should be inoculated into blood culture bottles at the bedside (rather than sent to the laboratory in a syringe since this reduces the sensitivity). The gram stain can be ordered but has a very low sensitivity in determining if bacteria are present.

The cell count should be available within 1–2 h. In this case, the tap was bloody and needs to be corrected by subtracting one PMN for every 250 red cells. The PMN count was 300, positive for SBP. The choice of antibiotic should cover gut organisms, as well as streptococcal species and the possibility of staphylococcal infection and a third generation cephalosporin such as cefotaxime 2 g intravenous every 8 h is reasonable, with 5–7 days of treatment usually sufficient. We also give intravenous albumin (1.5 g/kg of body weight on day 1 and 1 g/kg of body weight on day 3) on the basis of a study that showed very low mortality in SBP patients treated in this manner.

There are several SBP variants based on cell count and culture. In this patient, the ascitic fluid culture was negative, so she falls into the category of culture negative neutrocytic ascites, which may be related to poor culture technique. The opposite variant is monomicrobial, nonneutrocytic bacterascites where the culture is positive but the PMN count is <250. Both should be treated as SBP, particularly if the clinical setting is convincing. It is also possible to get polymicrobial bacterascites from trauma to the bowel during paracentesis.
Prophylaxis for SBP is also important in patients with prior episodes or in those with a low protein concentration (<1.5 g/dl) in the ascitic fluid. Daily norfloxacin 400 mg or double strength bactrim, or weekly ciprofloxacin 750 mg are acceptable dosing schedules.

References

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