Educational Case

Educational Case: Evaluating a patient with cirrhosis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.[1]

Primary objective

Objective HB1.6: Cirrhosis. Classify types of cirrhosis, in terms of etiology, pathogenesis, morphologic pattern (gross and microscopic), and their relationship to neoplasia.

Competency 2: Organ system pathology; Topic: Hepatobiliary (HB); Learning goal 1: Hepatitis.

Secondary objectives

Objective HB3.4: Radiology of cirrhosis. Identify the major space occupying lesions that may be seen on radiographic imaging of the normal and cirrhotic liver, and discuss the complications of cirrhosis.

Competency 2: Organ system pathology; Topic: Hepatobiliary (HB); Learning goal 3: Hepatic neoplasms.

Objective CHEM1.4: Liver and gastrointestinal disease. Discuss the clinical presentation and the pathophysiologic bases of liver and gastrointestinal diseases including the efficient use of laboratory tests to make a definitive diagnosis and manage the disease.

Competency 3: Diagnostic medicine and therapeutic pathology; Topic: Chemistry (CHEM); Learning goal 1: Pathogenesis, diagnosis, and treatment of common disorders.

Patient presentation

A 56-year-old man accompanied by his wife presents to the clinic with chief concern of vague abdominal pain for the past two weeks. The patient has also experienced progressive shortness of breath, bloating, and fatigue during this time frame. His medical history is significant for obesity and lifestyle-controlled diabetes mellitus. Surgical history is significant for repair of a femoral fracture following a motor vehicle accident in 1990, which required a blood transfusion. The patient is unsure of his vaccination status. He takes no medications other than over-the-counter acetaminophen for a recent cold. He works as a marketing executive and recently traveled to several European and Southeast Asian countries on business. He does not report using tobacco products or illicit drugs. The patient states that he drinks occasionally, at which point his wife informs the physician that he consumes a six-pack of beer after work each day and more on the weekends.

Diagnostic findings, Part 1

Vital signs include a temperature of 97 °F, a heart rate of 87 beats per min, a respiratory rate of 18 breaths per min, an oxygen saturation of 94%, and a blood pressure of 137/86 mm Hg. Physical examination shows an uncomfortable-appearing male in no acute distress. The cardiac exam demonstrates regular rate and rhythm, with no rubs, or gallops. Lung auscultation demonstrates bilateral basilar crackles. Abdominal examination reveals a soft, protuberant abdomen with shifting dullness to percussion. There is pitting edema present to the mid-tibia bilaterally, with multiple bruises on the lower extremities.

Questions/discussion points, Part 1

What is the differential diagnosis for this patient's history and physical examination findings?

The differential diagnosis for abdominal pain with associated peripheral edema, fatigue, and shortness of breath is broad and includes heart failure, liver failure, renal failure, nephrotic syndrome, malnutrition,

malabsorption, myxedema, lymphatic obstruction, and trauma.[2] The patient has specific risk factors for heart failure (obesity, diabetes mellitus, high alcohol consumption), liver disease (obesity, high alcohol consumption, hepatitis risk from travel or transfusion, and acetaminophen use), coagulopathy (bruises), and renal failure (diabetes mellitus).

Diagnostic findings, Part 2

Given the patient's broad differential, a comprehensive work-up is initiated including an electrocardiogram (EKG), B-type natriuretic peptide (BNP), complete blood count (CBC), coagulation panel, and complete metabolic panel (CMP). EKG findings are within normal limits, and the remaining laboratory results are displayed in Tables 1–3.

Questions/discussion points, Part 2

How do this patient's laboratory results help to differentiate between causes of coagulopathy?

The patient's elevated prothrombin time (PT), activated thromboplastin time (aPTT), and international normalized ratio (INR) are significant and suggestive of coagulopathy. These measurements are used to evaluate the integrity of the patient's clotting cascade.[2,3] PT is a measurement of clotting speed via the extrinsic or tissue factor and common pathways.[2,3] PT is used to assess the activity of clotting factors VII, V, X, II, and fibrinogen and can be prolonged if these are deficient or if there is an inhibitor. Deficiency could occur in the case of vitamin K deficiency, warfarin therapy, liver disease, and disseminated intravascular coagulation.[2,3] INR is a calculated standardization of the PT, used similarly to PT for assessment of extrinsic and common pathway clotting time and for monitoring the effects of warfarin pharmacotherapy.[2] aPTT measures the clotting time of the intrinsic and common pathways of the clotting cascade and is elevated in the setting of deficiencies in factors XII, XI, IX, VIII, V, X, II, or fibrinogen. aPTT can be elevated in some types of von Willebrand disease due to stabilization of factor VIII, antiphospholipid syndrome, in the presence of inhibitors, and in disseminated intravascular coagulation (DIC), severe vitamin K deficiency, or liver disease.[2] aPTT is also used in monitoring the effects of heparin pharmacotherapy.[2] Notably, vitamin K deficiency, DIC, and liver disease affect both PT and aPTT.[2] The presence of coagulopathy affecting both arms of the clotting cascade as reflected by the abnormal PT and aPTT measurements should be considered in context of the synthetic function of the liver.

The patient's CBC is also significant for low red blood cell count (RBC), low hemoglobin and hematocrit (Hgb and Hct, respectively), an elevated mean corpuscular volume (MCV), and an elevated red cell distribution width (RDW), all of which suggest megaloblastic anemia. Megaloblastic anemia can occur secondary to a micronutrient vitamin

Table 1
Complete blood cell count with differential.

	Value	Reference range
White blood cell count (WBC) (/mm^3)	5300	4500–11,000
Red blood cell count (RBC) (million/mm^3)	3.6	4.3–5.9
Hemoglobin (Hgb) (g/dL)	11.6	13.5–17.5
Hematocrit (Hct) (%)	35	41–53
Mean corpuscular volume (MCV) (μm^3)	112	80–100
Mean corpuscular hemoglobin (MCH) (pg/cell)	33	25.4–34.6
Mean corpuscular hemoglobin concentration (% Hb/cell)	34	31–36
Red cell distribution width (RDW) (%)	18	12.2–16.1
Platelets (/mm^3)	180,000	150,000–400,000
Neutrophils (%)	60	54–62
Bands (%)	3	3–5
Eosinophils (%)	1	1–3
Basophils (%)	0.35	0–0.75
Lymphocytes (%)	28	25–33
Monocytes (%)	5	3–7

Table 2
Coagulation panel.

	Value	Reference range
Prothrombin time (PT) (sec)	22	11–15
Activated partial thromboplastin time (aPTT) (sec)	51	25–40
International normalized ratio (INR)	1.8	< 1.1

B_{12} or folate deficiency.[4–6] In patients who consume large quantities of alcohol to the exclusion of more nutritious food may develop nutrient deficiencies. Folate and vitamin B_{12} deficiencies impair hematopoiesis and primarily cause a decrease in number of RBCs. More severe cases can cause a significant decrease in WBCs and platelets as well, resulting in a pancytopenia.[4] It is likely that megaloblastic anemia is contributing to this patient's symptoms of fatigue and shortness of breath.

How do this patient's laboratory results help to differentiate between causes of liver disease?

CMP demonstrates low total protein and low albumin, both of which are indicators of the synthetic capacity of hepatocytes.[7,8] The major contributors to the total protein measurement are globulin and albumin fractions.[7] The globulin fraction includes enzymes, including clotting factors produced by hepatocytes, as well as immunoglobulins produced by plasma cells, and the albumin fraction consists exclusively of albumin produced by hepatocytes.[7] Damage to hepatocytes that results in decreased synthetic capacity is thus revealed by decreased albumin and total proteins measurements in the setting of coagulopathy.[7,8] Hepatocyte integrity can be further assessed with the measurement of serum levels of hepatocellular enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and should be considered in relation to biliary excretory function measured with alkaline phosphatase (ALP) and bilirubin levels.[8]

This patient's metabolic laboratory studies demonstrate a hepatocellular pattern of liver injury as suggested by markedly elevated hepatocellular enzymes AST and ALT out of proportion to an also elevated ALP.[8–10] A cholestatic pattern of liver injury would be more likely if the ALP was elevated out of proportion to the AST and ALT, accompanied by a more severe hyperbilirubinemia. This pattern would warrant further consideration of biliary obstructive and non-hepatic etiologies.[8–10] The hepatocellular pattern of liver injury can be further characterized by the AST:ALT ratio, which is > 1 in this case.[8,9] The AST:ALT ratio should be < 1 in a normal person without elevations, and elevated values with an AST:ALT ratio > 1 are strongly suggestive of alcoholic liver disease, due to a variety of reasons related to alcohol metabolism in hepatocytes.[9] Hepatocellular patterns of liver injury closer to an AST:ALT ratio of < 1 are more suggestive of metabolic-associated fatty liver disease (MAFLD).[9,11] AST and ALT levels can decline in chronic liver disease as the severity progresses to end-stage liver disease and hepatocyte death

Table 3
Complete metabolic panel with B-type natriuretic peptide.

	Value	Reference range
Sodium (mEq/L)	130	136–145
Potassium (mEq/L)	4.0	3.5–5.0
Chloride (mEq/L)	95	95–105
Bicarbonate (mEq/L)	28	22–28
Urea nitrogen (mg/dL)	7	7–18
Creatinine, serum (mg/dL)	0.6	0.6–1.2
Glucose (mg/dL)	123	80–140
Proteins, total (g/dL)	4.6	6.0–7.8
Albumin (g/dL)	2.4	3.5–5.5
Bilirubin, total (mg/dL)	1.2	0.1–1.0
Alkaline phosphatase (ALP) (U/L)	74	20–70
Aspartate aminotransferase (AST) (U/L)	142	8–20
Alanine aminotransferase (ALT) (U/L)	108	8–20
B-type Natriuretic peptide (BNP) (pg/mL)	165	<100

removes the source of these enzymes.[12]

How do this patient's laboratory studies help to differentiate between causes of hyponatremia?

The patient's CMP is also significant for low sodium, which in the context of physical exam findings of peripheral edema and shifting dullness to abdominal percussion indicating ascites, are suggestive of a hypervolemic state. This is consistent with hypervolemic hyponatremia, in which inappropriate water retention results in a dilutional hyponatremia, often secondary to renal failure, nephrotic syndrome, congestive heart failure, or cirrhosis.[13–15] In cirrhotic patients, the lack of oncotic pressure secondary to hypoalbuminemia results in a volume shift from intravascular spaces to extracellular compartments, as demonstrated by this patient's ascites and peripheral edema.[14,16,17] It is also significant that the patient's brain natriuretic peptide (BNP) is above normal limits. BNP is a hormone released in response to the increased cardiac ventricular wall stress experienced in a state of increased ventricular blood volume. It stimulates natriuresis, diuresis, and systemic vasodilation, while inhibiting the renin–angiotensin–aldosterone system to decrease blood pressure and increase cardiac ejection fraction.[18,19] This patient's slightly elevated BNP is evidence of hypervolemia, but is significantly less than would be expected in decompensated heart failure.[20–22] Thus, heart failure is unlikely to be the underlying etiology for this patient's hypervolemic hyponatremia. Renal failure is also made less likely by the patient's low creatinine, which is removed by the kidney and elevated in the setting of acute kidney injury and renal failure.[8,23] Creatinine is generated through the metabolism of creatine by hepatocytes, so chronic liver disease and loss of hepatocyte synthetic function is commonly associated with lower levels of creatinine.[16,24]

Diagnostic findings, Part 3

It is concluded that the patient's symptoms are likely due to a hepatic disease process, and he is given a preliminary diagnosis of cryptogenic liver failure, with alcoholic liver disease as the most likely etiology. The remainder of the differential for liver disease includes the following: viral hepatitis, autoimmune hepatitis, drug- and toxin-induced liver injuries, metabolic-associated fatty liver disease, hemochromatosis, Wilson disease, and α1-antitrypsin deficiency.[8] Appropriate laboratory tests and an abdominal ultrasound with sonoelastography are ordered. The results are displayed Tables 4–6.[25–28]

Questions/discussion points, Part 3

How do this patient's additional laboratory results narrow the differential diagnosis?

The results of the hepatitis panel are significant for positivity for hepatitis B surface antibody (HBsAb) and negativity for the remainder of the tested antigens and antibodies. HBsAb positivity suggests previous exposure to the hepatitis B surface glycoproteins, which occurs during vaccination or infection.[29] During infection by the hepatitis B virus (HBV), the host's immune system is also exposed to the hepatitis B core proteins (HBc) and mounts an immune response that results in hepatitis B

Table 4
Hepatitis panel.

Hepatitis A IgM antibody (HA Ab-IgM)	Not detected
Hepatitis A IgG antibody (HA Ab-IgG)	Not detected
Hepatitis B surface antigen (HBsAg)	Not detected
Hepatitis B surface antibody (HBsAb)	Detected
Hepatitis B IgM core antibody (HBcAb-IgM)	Not detected
Hepatitis B IgG core antibody (HBcAb-IgG)	Not detected
Hepatitis B type e antigen (HBeAg)	Not detected
Hepatitis C antibodies (HC Ab)	Not detected

Table 5
Ultrasonography findings.

Abdominal ultrasound	○ Mild hepatomegaly
	○ Nodular liver surface with heterogenous echotexture
	○ Segmental hypertrophy of the caudate lobe
	○ Segmental atrophy of right lobe
	○ Diffusely increased echogenicity of hepatic parenchyma compared to right renal cortex
	○ Enlarged portal vein with slow venous flow
	○ Enlarged splenic vein
	○ Mild splenomegaly
	○ Ascites

IgM core antibody (HBcAb-IgM) positivity during acute infection. This is followed by hepatitis B IgG core antibody (HBcAb-IgG) positivity later in the disease course and following resolution.[29] Hepatitis B type e antigen (HBeAg) detection is associated with a high level of active viral replication resulting in increased infectivity.[29] Detectable HBsAb with undetectable levels of other HBV antigens and antibodies suggests that the patient was successfully vaccinated against HBV and is unlikely to have been infected previously.[29] Undetectable levels of hepatitis A IgM, IgG, and hepatitis C antibodies (HA Ab-IgM, -IgG and, HC Ab, respectively) suggests that the patient has neither been nor is currently infected with the hepatitis A or C viruses.[29] Thus the patient's current presentation is unlikely to be related to a viral hepatitis.

What focal and diffuse liver lesions can be demonstrated with ultrasonography?

Abdominal ultrasound is a commonly utilized tool for detecting and characterizing lesions of the liver.[30] Normal liver parenchyma is echogenic with a homogenously porous appearance and visibly branching vasculature.[30] Abnormal ultrasonographic findings can be indicative of focal and diffuse liver disease depending on the morphologic pattern.[27,30] A hepatic cyst, the most common and often incidentally found space-occupying lesion of the liver, can be visualized as a round anechoic space with a variable degree of septation depending on lesion complexity.[30,31] A hepatic abscess secondary to infectious etiology can have a variable presentation on ultrasonography including but not limited to septations, debris, and the presence of gas demonstrated as bubbles or an air-fluid level.[32] Hemangiomas are the most common benign liver tumor and appear as well-defined hyperechoic lesions with vascular activity visible with use of color-Doppler.[33] Focal nodular hyperplasia (FNH) is the second most common benign liver tumor and is thought to result from a hyperplastic response to an arteriovenous malformation.[34] Ultrasonographic features of FNH are variable, but approximately 20% of cases demonstrate a central scar with disruption of surrounding vasculature.[35] A hepatocellular adenoma is a benign neoplasm of the liver associated with oral contraceptive use that is usually asymptomatic unless the neoplasm ruptures and bleeds.[36] This neoplasm is often characterized on ultrasonography as a solitary, well-circumscribed mass of variable echogenicity.[37]

Diffuse liver disease includes etiologies such as the various viral and immune hepatitides, storage diseases, hepatic steatosis, fibrosis, and cirrhosis.[38] Ultrasonography findings are often non-specific in the case of diffuse liver disease, and biopsy is usually required to differentiate between the various etiologies.[38] In cases of acute hepatitis, the most common finding is hepatomegaly with diffusely decreased echogenicity.[38] Chronic hepatitis can be demonstrated by the presence of focal or diffuse hepatic steatosis and fibrosis developed in response to prolonged periods

Table 6
Sonoelastography.

	Value	Reference range
Sonoelastography (kPa)	22.3	4.1–5.5

of parenchymal damage and regeneration.[38] Diffuse hepatic steatosis can also occur in cases of alcohol abuse, metabolic-associated steatohepatitis, chronic hepatitis, glycogen storage diseases, and various drug therapies.[39] Heterogenous or coarsened hepatic echotexture on ultrasonography is evidence of a loss of parenchymal uniformity as seen in cases of cirrhosis, metabolic storage diseases, and chronic hepatitis.[40,41] Surface nodularity can be a useful finding in differentiating cirrhosis from other forms of diffuse liver disease, as metastatic tumor nodules are the only other notable disease process that demonstrates this ultrasonographic finding.[38]

A feared complication of diffuse liver disease, hepatocellular carcinoma (HCC) is the most common primary liver cancer in adults and can present as a focal, multifocal, or diffuse lesions on ultrasonography.[27,38] Over 80% of new cases of HCC occur in the setting of cirrhosis.[42] Thus cirrhotic patients are currently recommended to undergo biannual abdominal ultrasonography as a non-invasive and cost-effective screening modality.[42] In addition to cirrhosis, risk factors for HCC include any disease process which results in chronic hepatic injury, such as the immune and viral hepatitides, alcohol consumption, storage diseases, and metabolic-associated steatohepatitis.[43,44] Focal HCC lesions tend to be hypoechoic compared to surrounding hepatic parenchyma. As focal HCC lesions grow, they become increasingly heterogenous and echogenic, demonstrating features of fat accumulation, necrosis, and calcification, or development of a central scar that can be misinterpreted as FNH.[38] Advanced HCC usually presents in patients with underlying diffuse liver disease as multifocal lesions with variable echogenicity, and can appear similar to metastases on imaging.[38,43,44] HCC foci developing within regenerative nodules demonstrate a nodule-in-nodule appearance on magnetic resonance imaging.[45] Diffuse or infiltrative HCC presents with scattered hepatic nodularity, rather than distinct masses, that is difficult to differentiate from cirrhosis based on advanced imaging alone.[46]

How do this patient's ultrasonography findings affect the differential diagnosis?

Abdominal ultrasound findings of mild hepatosplenomegaly, liver surface nodularity with heterogenous echotexture, and segmental hypertrophy and atrophy are consistent with cirrhosis.[26] Abnormal blood flow resultant from the disruption of normal hepatic cellular architecture results in segmental hypertrophy of the caudate lobe and lateral segments of the left lobe, with concurrent segmental atrophy of the right lobe and medial segments of the left lobe.[47] Nodule formation occurs secondary to fibrotic and regenerative processes involving both stromal and parenchymal hepatocytes, and is seen as the nodular surface and heterogenous texture on this patient's abdominal ultrasound.[8,47] Diffusely increased echogenicity of the hepatic parenchyma when compared to the right kidney is indicative of abnormal accumulation of lipids within hepatocytes, that occurs in response to chronic disease processes.[38] Hepatic echogenicity is normally similar to or greater than that of the renal cortex, which serves as a standard of comparison in determination of lipid accumulation.[38] Additional findings of an enlarged splenic vein and ascites are suggestive of portal hypertension and hypoalbuminemic edema, both of which are complications of cirrhosis.[26] Sonoelastography utilizes sonography and the application of mechanical pressure to evaluate tissue stiffness and elasticity, and it has been demonstrated to have a high negative predictive value when ruling out cirrhosis.[48] Stiffness and elasticity are measured in kilopascals (kPa), with increasing values correlating to higher stages of fibrosis.[48,49] Sonoelastography values over 10 kPa suggest advanced chronic liver disease, over 12.5 kPa suggest cirrhosis, and those exceeding 21 kPa suggest clinically significant portal hypertension.[49,50] This patient's sonoelastography findings suggest the presence of cirrhosis with clinically significant portal hypertension, which is further supported by previous physical exam, laboratory, and ultrasound findings. Despite recent and improved non-invasive modalities for assessment of liver fibrosis and cirrhosis, liver biopsy remains the gold standard for identification and classification of cirrhosis.[49]

Diagnostic findings, Part 4

An ultrasound-guided liver biopsy is performed, and the results are in Figs. 1–3.

Questions/discussion points, Part 4

### What is the cellular architecture of the liver?

Hepatic micro-architecture is structured in terms of 1- to 2-mm diameter lobules composed of portal triads of hepatic arteries, portal veins, and bile ducts, surrounding plates of hepatocytes which radiate towards a central vein at the center.[8,51] Hepatocytic trabeculae are separated by intervening sinusoidal spaces in which a mixture of portal venous and hepatic arterial blood flows from the portal tract to the central vein.[8,51] Alternatively, the micro-architecture can be classified into acini made of three zones according to distance from the portal tract, which correlate to their respective degrees of oxygenation.[8,51,52] The area adjacent to the portal tract is zone 1, which is the most well-oxygenated region, the intermediate zone between the portal tract and the central vein is zone 2, and the area adjacent to the central vein is zone 3, which is the least oxygenated.[8,51] Non-parenchymal cells of the liver include liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), and hepatic stellate cells (HSCs).[8,51,52] Fenestrated LSECs separate the sinusoidal spaces from the space of Disse which is occupied by hepatocytic microvilli responsible for transportation of nutrients from sinusoidal blood to the hepatocytes.[8,51] KCs are phagocytic monocytes present on the luminal aspect of LSECs.[8,51,52] HSCs occupy the space of Disse and are the primary mediators of hepatic fibrosis.[8,51,52] Bile canaliculi border hepatocytes and drain ultimately into the terminal bile ducts of the portal tracts.[8,51,52]

What is the process of hepatocyte damage?

Irreversible injury to hepatocytes results in either apoptotic or necrotic cell death.[8,52] The former commonly occurs secondary to viral, autoimmune, or drug- and toxin-induced hepatitides, and the latter often occurs secondary to ischemic and hypoxic injury.[8,52] Hepatocyte apoptosis is a form of cell death whereby caspase cascades are activated,
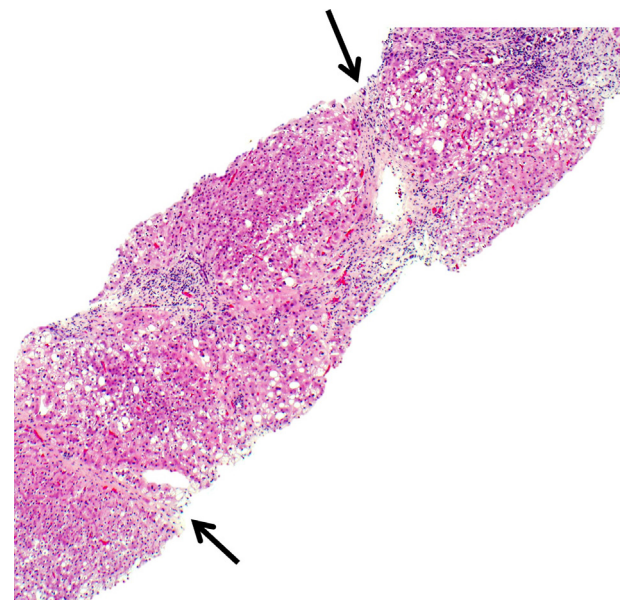

Fig. 1. Liver biopsy. At low power, the liver biopsy shows steatosis throughout, and inflammation (upper right and middle left). Bands of fibrosis are visible at low power (arrows). H&E, 40x.
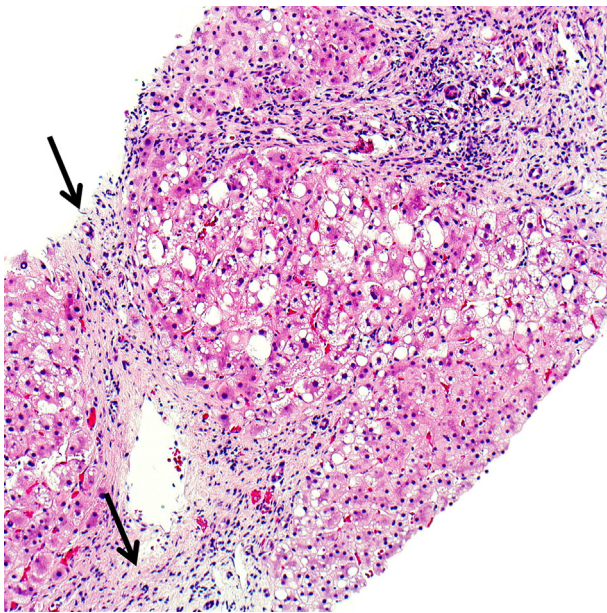
Fig. 2. Liver biopsy. At higher power, bands of fibrosis surrounding a nodule are seen (arrows). The hepatocytes contain numerous clear fat droplets, and there is predominantly lymphocytic portal inflammation in the upper right. H&E, 200x

initiating an organized process of pyknosis, karyorrhexis, and cellular fragmentation into acidophil bodies, which appear intensely eosinophilic on staining.[8] Hepatocyte necrosis occurs when a hepatocyte is unable to maintain osmotic regulation, so it swells, and ruptures, releasing cytoplasmic contents, including pro-inflammatory cytokines, into the extracellular compartment.[8] Confluent necrosis is a phenomenon in which areas of necrosis are localized to one or more lobular acinar zones. Hepatocyte drop-out begins near the central vein in zone 3, where oxygenation is at its lowest within the acinus, and extends contiguously toward the penetrating hepatic vessels through zone 2 and zone 1. When necrosis involves multiple adjacent acini of multiple lobules it is
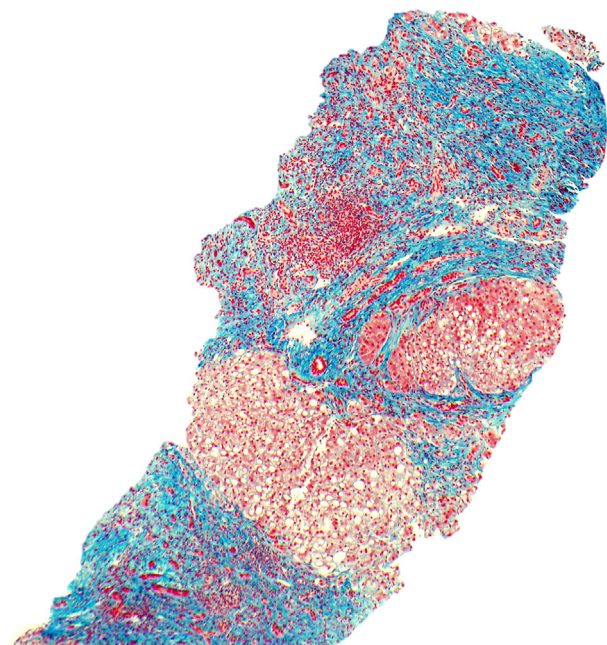
Fig. 3. Liver biopsy. Trichrome stain highlights in blue, the circumferential bands of fibrosis surrounding regenerative nodules. Trichrome stain, 100x.

described as bridging necrosis.[8] Confluent and bridging necrosis are the result of acute or severe chronic hepatocyte injury.[8]

What is the response to hepatocyte apoptosis and necrosis?

KCs lining fenestrated LSECs are activated in response to hepatocyte injury.[8,17,52] KCs contribute to the cellular response to hepatocyte damage by producing the following cytokines: platelet-derived growth factor (PDGF), tumor necrosis factor alpha (TNF-a), endothelin-1 (ET-1), monocyte chemoattractant protein-1 (MCP-1), and transforming growth factor beta (TGF-b). PDGF and TNF-alpha stimulate HSC proliferation and activation of previously quiescent HSCs. ET-1 stimulates vasoconstriction, TGF-b stimulates fibrogenesis, and MCP-1 and PDGF stimulate chemotaxis of activated HSCs to the site of injury.[8,17,52] KCs further contribute to the activation of previously quiescent HSCs by degrading collagen type IV in the space of Disse. Additionally, KCs phagocytize hepatocyte apoptotic bodies and produce pro-apoptotic ligands, such as Fas.[8,17,52] The net effects of KC activation and function include hepatocyte dysfunction and death, HSC activation and chemotaxis, and stimulation of fibrogenesis.[8,17,52]

Quiescent vitamin A-rich HSCs located in the space of Disse function as lipid-storing cells until they become active and convert to myofibroblasts.[8,17,52] Sources of activation include cytokines and chemokines produced by KCs and other non-parenchymal cells, pro-inflammatory cytokines associated with chronic inflammation, direct stimulation by toxins, and disruption of the extracellular matrix.[8] Myofibroblasts are highly fibrogenic and contribute significantly to the generation of types I and III collagen, which form fibrolysis-resistant collagen bundles through cross-linking and deposition of extracellular matrix within the space of Disse.[53] In a state of chronic liver disease, fibrogenesis is perpetuated and fibrous septa formed at the sites of parenchymal loss begin to surround regenerating hepatocytes, distorting the microarchitecture of the hepatic lobules and producing the nodularity of cirrhosis.[1,3,8] Fibrosis and fibrolysis are concurrent bidirectional processes, with active liver disease favoring the former and remitting liver disease favoring the latter.[8,17,52] Regression of cirrhotic nodularity with reversal of fibrotic scar formation has been demonstrated in cases where the insulting factor is removed before permanent microarchitectural change takes place.[54] Vascular architecture is also disrupted by this remodeling process, resulting in intralobular vascular shunts within the fibrous septa.[8,17,52]

What are the types of cirrhosis and how can they be differentiated on histopathology?

Cirrhosis can be classified based on both the morphologic findings and the underlying etiology.[55] Morphological categories are separated into the following: micronodular, macronodular, and mixed.[55] In micronodular cirrhosis, nodules are uniform and less than 3 mm in diameter.[51] They are irregular and more than 3 mm in diameter in macronodular cirrhosis, and varied sizes with features of both in mixed cirrhosis.[51] Mixed cirrhosis is often an intermediate through which micronodular cirrhosis progresses to macronodular cirrhosis.[55] A micronodular pattern of cirrhosis can be seen in cases of cirrhosis secondary to alcoholic liver disease, hemochromatosis, and hepatic venous and biliary outflow obstructions.[55] Macronodular cirrhosis is more commonly seen in cases of chronic viral hepatitis, primary biliary cholangitis, Wilson disease, and α-1 antitrypsin deficiency.[8,55] Etiologies of cirrhosis can also be classified based on their pattern of hepatocyte damage and subsequent fibrosis.[55] For example, cirrhosis secondary to alcoholic liver disease and MAFLD demonstrate an initial centrilobular and perivenular pattern of fibrosis that advances toward the periportal acinar zones with progression of disease. Other etiologies of chronic liver disease that result in cirrhosis, including viral hepatitides, autoimmune hepatitis, chronic cholestatic disease, and metabolic and storage diseases, can be distinguished by a predominance of periportal fibrosis.[56]

What are the histopathologic features of alcoholic liver disease?

Alcoholic liver disease is characterized by macrovesicular steatosis most prominent in acinar zone 3, or the perivenular area, continuing outward through acinar zones 2 and 1 in increasingly severe disease states.[57] Alcohol-metabolizing cytochromes are present in disproportionate amounts in the centrilobular hepatocytes when compared to the periportal hepatocytes.[56] Metabolism of alcohol and byproduct formation place additional stress on these centrilobular hepatocytes and are responsible for the hepatocellular ballooning pattern of hepatocellular injury seen on histopathological evaluation of alcoholic liver disease.[56] Hepatocellular ballooning and subsequent necrosis constitutes the primary mechanism of injury in alcoholic liver disease, which progresses to a micronodular cirrhosis with perivenular and pericellular fibrosis, visible as blue-stained collagen on Masson trichrome stain.[56] Mallory-Denk bodies are damaged filamentous inclusions in hepatocytes observable on hematoxylin and eosin (H&E) and chromotrope aniline stains in chronic liver disease, including alcoholic liver disease and cirrhosis.[56] The presence of centrilobular fibrosis accompanied by obliteration of the central vein, and perivenular necrosis with Mallory-Denk bodies constitutes sclerosing hyaline necrosis, a histopathological finding consistent with alcoholic cirrhosis.[58] Megamitochondria may also be seen on H&E stain in cases of alcoholic cirrhosis.[57] Metabolic-associated fatty liver disease demonstrates a similar histopathological pattern to that of alcoholic liver disease. Notable differences that exist between MAFLD and alcoholic liver disease include more significant steatosis in the former than the latter and more significant inflammation in latter than the former.[59] While also present in MAFLD, perivenular fibrosis tends to be more significant in alcoholic liver disease.[59] This patient's liver biopsy findings are consistent with alcoholic cirrhosis.

How does the pathophysiology of cirrhosis explain its clinical presentation and complications?

The symptomatic presentation of cirrhosis and its complications occurs secondary to increased intrahepatic vascular resistance, loss of synthetic and metabolic functions of hepatocytes, and prolonged regenerative processes.[60] Prolonged hepatocyte injury and subsequent fibrogenesis results in increased formation of collagen in the space of Disse and the loss of endothelial fenestration, a process which is referred to as sinusoidal capillarization.[60] Vascular reorganization is accompanied by fibrotic expansion of the portal tract and fibrosis of the central vein which results in portal hypertension.[60] Decreased synthetic capacity of the liver due to loss of functional hepatocytes results in diminished nitric oxide production and contributes to increased intrahepatic vascular resistance and portal hypertension.[61] This leads to the development of intrahepatic portal-systemic shunts that results in collateral circulation which bypasses normal liver flow.[17,52,60] While these shunts help to reduce portal hypertension, they enlarge over time and result in many serious and often life-threatening complications of cirrhosis.[17,52,60] Esophageal varices, a major complication of portal hypertension and vascular congestion, are abnormally enlarged veins in the esophagus that pose a significant bleeding risk to cirrhotic patients.[61]

Intrahepatic shunting also leads to decreased metabolism of ammonia by functional hepatocytes and subsequently increased bioavailable ammonia in systemic circulation.[17,52,60] Increased flow of nitrogen-rich blood to the brain leads to the development of hepatic encephalopathy, a neuropsychiatric condition characterized by memory impairment, asterixis, myoclonus, and personality and behavioral changes.[62] Increased blood flow from portal-systemic shunting further contributes to the development of hepatopulmonary and hepatorenal syndromes.[17,52,60] In hepatopulmonary syndrome, pulmonary capillary dilation causes a ventilation–perfusion mismatch presenting with dyspnea, platypnea, and hypoxemia, such as in this patient's case.[63] Hepatorenal syndrome occurs when splanchnic vasodilation secondary to intrahepatic shunting leads to renal hypoperfusion and subsequent activation of the renin-angiotensin-aldosterone system, ultimately progressing to renal failure.[64,65] Vascular congestion secondary to portal hypertension and shunting also contributes to the development of splenomegaly and caput medusa, two prominent physical exam findings in cirrhotic patients.[60]

Both portal hypertension and the decreased synthesis of albumin by hepatocytes contribute to the formation of ascites, the accumulation of protein-rich fluid in the abdominal cavity.[60] Ascites is a common finding in cirrhotic patients and can become complicated by infection resulting in spontaneous bacterial peritonitis.[66] This commonly presents with fever and altered mental status which can be accompanied by chills, abdominal pain, nausea, and vomiting.[66] Loss of hepatocytes contributes to decreased metabolic function, including bilirubin and estradiol metabolism. Reduced excretion of bilirubin results in intrahepatic cholestasis and jaundice, and reduced estradiol metabolism leads to hyperestrogenism and its effect of palmar erythema, gynecomastia, and spider angiomata, which are most prevalent on the upper trunk and face.[60]

What are the next steps in management for this patient?

Management of this patient begins with determination of whether the cirrhosis is compensated or decompensated.[67] Compensated cirrhosis is an early asymptomatic stage of the disease process without complications of portal hypertension and liver dysfunction.[67] Decompensated cirrhosis is an acute deterioration in liver function with the presence of complications, and it can be precipitated by many etiologies such as medications, infections, hypovolemia, electrolyte imbalance, and alcohol use.[68,69] In this patient, the presence of complications suggests decompensated cirrhosis.[68] In the absence of life-threatening complications, such as variceal hemorrhage, management is directed toward symptomatic treatment, initiation of relevant surveillance programs, risk reduction, and patient education.[68] The presence of new-onset ascites warrants a diagnostic paracentesis with analysis of cell count, total protein, albumin, and bacterial culture with sensitivity testing.[69] Cirrhotic patients are effectively immunosuppressed and frequently decompensate due to infections such as spontaneous bacterial peritonitis.[68] In the absence of a known prior episode of spontaneous bacterial peritonitis, results from the diagnostic paracentesis will be used to determine if the patient requires oral antibiotic prophylaxis.[69] Reduction of ascites is accomplished with salt restriction and diuretic pharmacotherapy such as spironolactone with or without loop diuretics.[68,69] Hepatic encephalopathy, which is not present in this patient, is managed with the administration of lactulose with or without rifaximin to encourage stooling and elimination of nitrogen from the systemic circulation.[69]

Health surveillance for this patient will include regular screenings for HCC and esophageal varices.[44,61,69] Screening for HCC is recommended every six months for cirrhotic patients and is performed via right upper quadrant ultrasonography.[69] Screening for esophageal varices via endoscopic gastroduodenoscopy (EGD) is indicated in newly diagnosed compensated cirrhosis, unless sonoelastography demonstrates a liver stiffness of at least 20 kPa and CBC demonstrates a platelet count of at least 150,000.[70] If no varices are detected on initial screening, EGD is repeated every three years in the absence of ongoing liver injury and every two years in the presence of ongoing liver injury.[70] For patients with decompensated cirrhosis, EGD is recommended at the time of diagnosis followed by repeat screening every year.[71] If present, esophageal varices are risk-stratified based on size and count. Primary prevention of variceal hemorrhage includes nonselective beta blockers and/or endoscopic band ligation depending on risk.[69] Acute variceal hemorrhage is a life-threatening emergency managed with vasoconstrictors, endoscopic band ligation, balloon tamponade, and surgical intervention.[72] Placement of a transjugular intrahepatic portosystemic shunt (TIPS) can be performed as a salvage treatment to reduce portal hypertension and variceal hemorrhage risk, but its use must be considered alongside potentially worsening hepatic encephalopathy secondary to increased intrahepatic shunting.[72]

The model for end-stage liver disease (MELD) and Child–Pugh scores are two clinically useful calculations that use patient laboratory values and symptom severity to stratify risk and estimate disease severity in cirrhotic patients.[73] The MELD score is commonly used in transplant allocation.[74] Due to the progressive nature of chronic liver disease, liver transplant remains the definitive treatment option for advanced cirrhosis.[74] This patient's initial laboratory work-up demonstrates a MELD score of 20 and an estimated three-month mortality of 19.6%.[73] Patient education is an important intervention in the management of cirrhosis and includes counselling on alcohol reduction or abstinence, signs and symptoms of serious complications, and the importance of continued surveillance and long-term follow up.[67]

Teaching points

- Cirrhosis is characterized by hepatic fibrosis, prolonged hepatocellular regeneration, and disruption of hepatic microarchitecture that occurs secondary to chronic liver diseases. It is commonly classified by morphology or etiology.
- Morphologic classifications include both macroscopic and microscopic patterns. Macroscopic patterns include micronodular, macronodular, and mixed types of cirrhosis. Microscopic patterns vary by etiology but can be categorized as biliary and nonbiliary types of cirrhosis.
- Etiologies of cirrhosis include infectious (predominately viral) and autoimmune hepatitides, storage disorders, alcoholic and metabolic-associated steatohepatitides, and biliary dysfunction.
- The loss of hepatocytes results in decreased metabolic and synthetic capacity of the liver leading to coagulopathies, jaundice, hepatic encephalopathy, hyperestrogenism, hypoalbuminemia, and ascites, which can be further complicated by spontaneous bacterial peritonitis.
- Fibrosis and vascular reorganization in cirrhosis results in the development of portal hypertension and subsequent intrahepatic shunting leading to complications including hepatic encephalopathy, hepatopulmonary syndrome, hepatorenal syndrome, and esophageal varices.
- Loss of hepatic parenchyma in the setting of cirrhosis is demonstrated by elevated liver enzymes (specifically AST ALT, ALP) in acute liver disease and declining levels in end-stage chronic liver disease. Interpretation of hepatocellular and cholestatic patterns of liver enzyme elevations can be used to differentiate liver disease etiology and direct further management.
- Various identifiable patterns of AST, ALT, and ALP elevation are suggestive of different types of liver injury. A normal AST:ALT ratio is < 1 whereas an AST:ALT ratio > 1 is highly suggestive of liver injury. Predominant elevations of AST and ALT with or without notable ALP elevation suggest a hepatocellular pattern of liver injury. A hepatocellular pattern with an AST:ALT ratio >1 is strongly suggestive of an alcoholic etiology of liver damage while a ratio of < 1 suggests metabolic-associated fatty liver disease. Predominantly elevated ALP with or without significant AST and/or ALT elevations suggests a cholestatic pattern of liver injury.
- Ultrasonography and sonoelastography are the most commonly used imaging modalities in the characterization of liver disease and cirrhosis. Ultrasonography characterizes hepatic parenchyma and can differentiate etiologies of focal and diffuse liver disease. Sonoelastography measures the stiffness and elasticity of hepatic tissue to determine the extent of hepatic fibrosis and can be used to risk stratify related complications.
- Ultrasonographic evidence of cirrhosis includes heterogenous echotexture, nodularity, hepatosplenomegaly, segmental hypertrophy and atrophy, and vascular abnormalities.
- Normal liver parenchyma appears homogenous and porous with an echogenic texture that is similar to that of the renal cortex. Abnormal ultrasonographic findings vary depending on the etiology of focal or diffuse liver disease.

- Prolonged hepatocyte regeneration in the setting of chronic liver disease significantly increases the risk of developing hepatocellular carcinoma in cirrhotic patients.

Authors' note

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