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Case 4-2023: A 56-Year-Old Man with Abnormal Results on Liver Testing

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PRESENTATION OF CASE

Dr. Esperance A. Schaefer: A 56-year-old man with a history of alcohol and opioid use was evaluated in the gastroenterology clinic of this hospital because of abnormal results on liver testing.

Three years before the current presentation, the patient had elevated levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase on routine testing performed by his primary care physician. At that time, he reported that testing for hepatitis C virus (HCV) antibodies had been positive in the past. The HCV RNA level was undetectable; other laboratory test results are shown in Table 1. Cessation of alcohol use was advised. Two years before the current presentation, the levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase had decreased; additional laboratory test results obtained at that time are shown in Table 1.

Seven months before the current presentation, the patient was evaluated in the emergency department of another hospital because of pain and swelling in the left wrist that had lasted for 3 weeks. The temporal temperature was 36.6°C. The volar aspect of the left wrist was erythematous and swollen, as was the left knee. Tests for Lyme disease antibodies and rheumatoid factor were negative. Radiographs showed subcutaneous edema of the left knee but no fracture, dislocation, or evidence of advanced arthropathy of the left knee or wrist. A 10-day course of prednisone was prescribed for presumed inflammatory arthritis. The joint swelling and pain resolved.

Six months before the current presentation, the patient was evaluated in the same emergency department because of a painful rash. The temporal temperature was 36.3°C. The distal left forearm was erythematous and had scattered small subcutaneous nodules. Laboratory evaluation revealed pancytopenia, coagulopathy, and elevated levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. Blood levels of electrolytes, glucose, and uric acid were normal, as were the results of kidney-function tests; other laboratory test results are shown in Table 1. A plain radiograph of the left wrist showed soft-tissue

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Table 1. Laboratory Data.

Variable	Reference Range, Adults, Other Hospital	3 Yr before Current Presentation, Other Hospital	2 Yr before Current Presentation, Other Hospital	6 Mo before Current Presentation, Other Hospital	3 Mo before Current Presentation, Other Hospital	Reference Range, Adults, This Hospital*	On Current Presentation, This Hospital
Alanine aminotransferase (U/liter)	10–50	926	75	92	96	10–55	72
Aspartate aminotransferase (U/liter)	15–41	1254	116	130	167	10–40	108
Alkaline phosphatase (U/liter)	32–100	1152	479	585	456	45–115	427
γ-Glutamyltransferase (U/liter)	8–61	—	—	362	—	8–61	419
Total bilirubin (mg/dl)†	0.0–1.2	8.3	—	2.9	3.4	0.0–1.0	3.3
Direct bilirubin (mg/dl)†	0.0–0.2	—	—	1.3	1.4	0.0–0.4	1.6
Hemoglobin (g/dl)	13.5–17.5	—	—	12.4	14.3	13.5–17.5	12.4
Hematocrit (%)	41.0–53.0	—	—	40.2	44.9	41.0–53.0	38.5
White-cell count (per μl)	4000–11,000	—	—	4220	2860	4500–11,000	2230
Platelet count (per μl)	150,000–450,000	—	—	61,000	59,000	150,000–400,000	43,000
Prothrombin time (sec)	12.1–14.7	—	—	14.8	16.6	11.5–14.5	15.5
Prothrombin-time international normalized ratio	0.9–1.1	—	—	1.2	1.4	0.9–1.1	1.2
Partial-thromboplastin time (sec)	23.0–34.0	—	—	25.1	—	22.0–36.0	31.5
Antinuclear antibody	—	—	—	—	—	<1:160	<1:160
Antimitochondrial antibody	—	—	—	—	—	1:20	1:5120
$Alpha_1$-antitrypsin (mg/dl)	—	—	—	—	—	100–190	155
Ceruloplasmin (mg/dl)	—	—	—	—	—	19.0–31.0	32.8
HIV types 1 and 2 antibody and antigen	—	—	—	—	—	Negative	Negative
IgG (mg/dl)	—	—	—	—	—	700–1600	2105
IgA (mg/dl)	—	—	—	—	—	66–436	363
IgM (mg/dl)	—	—	—	—	—	43–279	874
Serum protein electrophoresis	—	—	—	—	—	No abnormal bands	No abnormal bands
High-sensitivity troponin T (ng/liter)	—	—	—	—	—	0–14	<6
N-terminal pro–B-type natriuretic peptide (pg/ml)	—	—	—	—	—	<900	177

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
† To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

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edema but no abnormalities of the bone. A second course of prednisone was prescribed, and the patient was referred to a dermatologist and a gastroenterologist for consultation.

Two weeks later, the patient was evaluated by a dermatologist affiliated with the other hospital. He had multiple tan macules on the face and trunk, angiomas, and reddish-purple papules (some >1 cm in diameter) on the left forearm. A biopsy of a papule on the left forearm was performed. Histopathological examination of the biopsy specimen revealed nonspecific suppurative and granulomatous dermatitis. No microorganisms were identified, and culture of the biopsy specimen was negative.

Four months before the current presentation, the patient was evaluated by a gastroenterologist affiliated with the other hospital. He had spider angiomas and fullness of the left upper quadrant. On a serum-based test for liver fibrosis (FibroTest), he had a score of 0.96 (with scores of 0.00 to 0.21 indicating no fibrosis and scores of 0.74 to 1.00 indicating severe fibrosis). Imaging studies were obtained.

Dr. William R. Bradley: Magnetic resonance cholangiopancreatography (MRCP) revealed a nodular hepatic contour with patchy perfusion but no focal hepatic lesions (Fig. 1A). Splenomegaly, portal vein thrombosis with cavernous transformation, and perigastric, paraesophageal, and splenorenal collateral vessels were also identified (Fig. 1B and 1C). There was no dilatation of the intrahepatic bile ducts; the common bile duct measured 8 mm in diameter (Fig. 1D).

Dr. Schaefer: Three months before the current evaluation, esophagogastroduodenoscopy and colonoscopy were performed. Grade 2 esophageal varices were identified and banded. Eight days later, the patient was admitted to a second hospital because of new confusion, lethargy, delayed and slurred speech, and visual hallucinations. The blood ammonia level was 99 μmol per liter (169 μg per deciliter; reference range, 11 to 60 μmol per liter [19 to 102 μg per deciliter]). Urinalysis was normal; other laboratory test results are shown in Table 1. A chest radiograph was normal. Abdominal ultrasound images showed persistent splenomegaly and heterogeneous liver echotexture without ascites. A computed tomographic scan of the head, obtained without the administration of intravenous contrast material, was normal. An electrocardiogram showed sinus bradycardia, a pattern consistent with incomplete right bundle-branch block, downsloping ST-segment depressions in the precordium, and a prolonged corrected QT interval. Treatment with lactulose was initiated for a working diagnosis of hepatic encephalopathy. Confusion resolved, and the patient was discharged home on the second hospital day with arrangements made for additional cardiac testing after discharge.

One month before the current evaluation, an echocardiogram showed normal left ventricular size and function, mild right ventricular dilatation, moderate tricuspid regurgitation with right atrial dilatation, and an estimated right ventricular systolic pressure of 71 mm Hg. Perfusion images obtained during vasodilator stress testing showed no evidence of inducible left ventricular ischemia. The patient was referred to the gastroenterology clinic of this hospital for additional evaluation.

In the gastroenterology clinic, the patient reported chronic dyspnea with exertion. He had no orthopnea, chest pain, or palpitations. He had consumed six beers daily for approximately 30 years but had not consumed alcohol during the previous 18 months. Three years before the current presentation, the patient had received a diagnosis of dyslipidemia, with a blood low-density lipoprotein cholesterol level of 337 mg per deciliter (8.7 mmol per liter; reference range, 70 to 129 mg per deciliter [1.8 to 3.3 mmol per liter]) and a total cholesterol level of 380 mg per deciliter (9.8 mmol per liter; reference range, 155 to 199 mg per deciliter [4.0 to 5.1 mmol per liter]). He had a history of opioid use disorder, including intravenous opioids; the disorder had been in remission with the use of buprenorphine–naloxone. Other medical history included depression, insomnia, and multiple knee surgeries. In addition to buprenorphine–naloxone, medications included lactulose, omeprazole, and trazodone. Penicillin had caused a rash. He had worked as a laborer but was disabled and no longer working. He had smoked two cigarettes daily for 30 years. His family history included stroke in his father, diabetes in his mother, and rheumatoid arthritis in his sister.

On examination, the heart rate was 73 beats per minute, the blood pressure 99/65 mm Hg, and the oxygen saturation 97% while the patient was breathing ambient air. The weight was 69.9 kg

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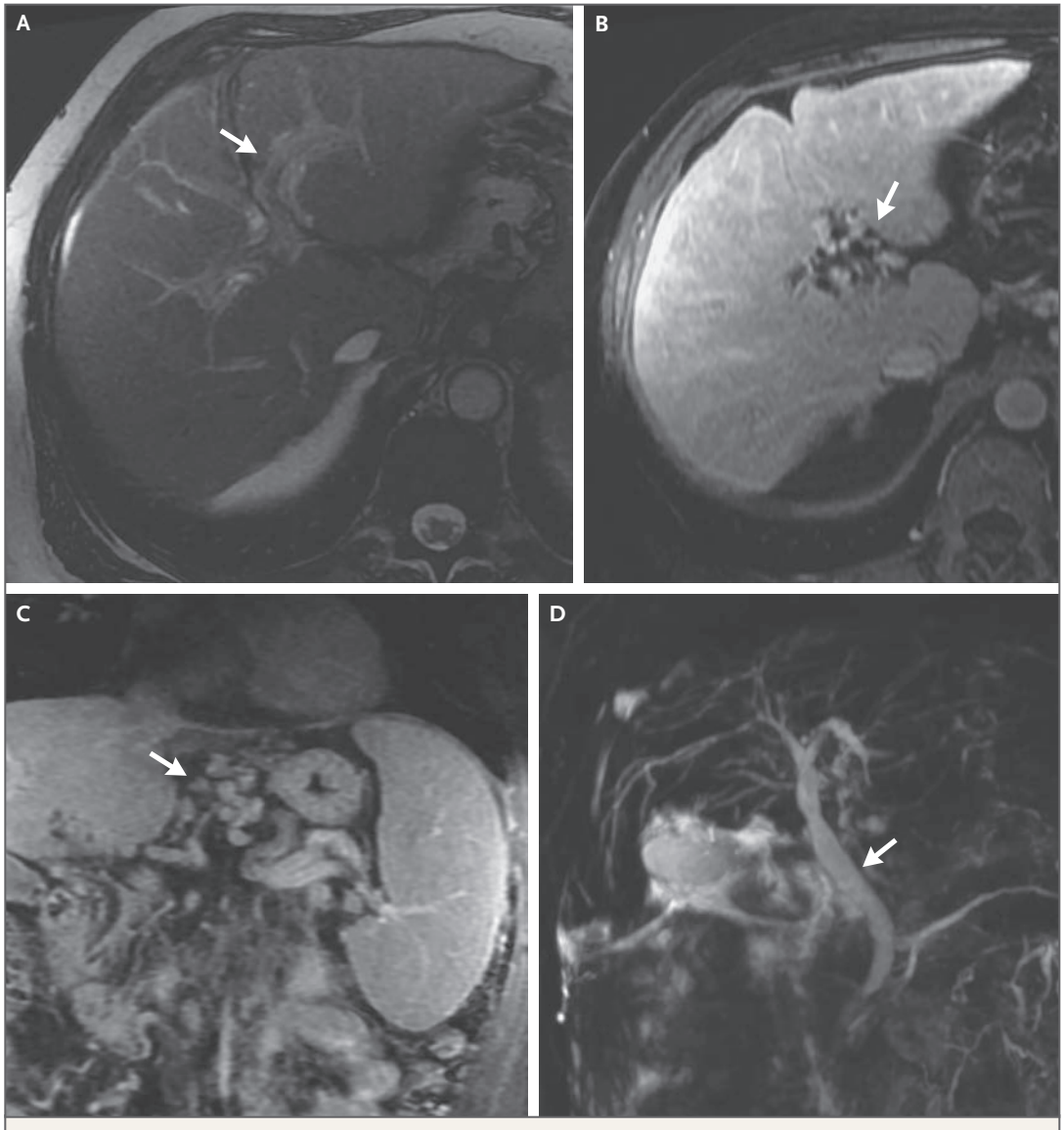

Figure 1. MRCP Images.

Magnetic resonance cholangiopancreatography (MRCP) was performed with the administration of intravenous contrast material 4 months before the current presentation. An axial T2-weighted image (Panel A) shows a periportal hyperintense signal (arrow), hypertrophy of the caudate lobe of the liver, and hepatic surface nodularity. An axial T1-weighted image (Panel B) shows cavernous transformation of the portal vein (arrow). A coronal T1-weighted image (Panel C) shows evidence of portal hypertension, including splenomegaly and upper abdominal collateral vessels (arrow). A coronal maximum-intensity-projection image (Panel D) shows mild irregularity of the intrahepatic bile ducts and prominence of the common bile duct (arrow), which measures 8 mm in diameter.

and the body-mass index (the weight in kilograms divided by the square of the height in meters) 24.9. He was alert and oriented; asterixis was present. The lung fields were clear, and there was a grade 2/6 holosystolic murmur at the left sternal border. Abdominal examination revealed a palpable hard mass in the epigastrium, a finding that indicated a probable firm caudate lobe of the liver. The knees had healed surgical scars, and there was no edema in the legs. A few spider angiomas were present on the chest. The remainder of the examination was normal. Laboratory test results are shown in Table 1. Serologic testing was negative for antinuclear

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antibodies and was positive for antimitochondrial antibodies, with a titer of 1:5120.

Additional diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Irun Bhan: This 56-year-old man presented for an outpatient evaluation in the gastroenterology clinic because of abnormal results on liver testing. He reported a history of prolonged daily alcohol consumption, and he had previously reported a positive test for HCV antibodies. Results of laboratory tests for liver function had been abnormal for at least 3 years, as evidenced by previous testing performed by his primary care physician. More recently, thrombocytopenia and splenomegaly had developed. Imaging had revealed a nodular hepatic contour, which is consistent with cirrhosis, as well as evidence of portal hypertension, including splenomegaly, collateral vessels, and chronic portal vein thrombosis. The patient had been admitted to another hospital with altered mental status associated with hyperammonemia, which had resolved with the administration of lactulose; this episode had been consistent with hepatic encephalopathy. Physical examination at this hospital revealed spider angiomas and a firm liver edge, findings that are consistent with cirrhosis.[1] The first step in evaluating this patient is to consider potential causes of chronic liver disease.

HCV Infection

The patient had reported a positive test for HCV antibodies. Laboratory testing confirmed the presence of HCV antibodies; this finding could be consistent with previous infection. The HCV RNA level was undetectable; this finding rules out active HCV infection. Given the absence of previous treatment, it is possible that he had spontaneous resolution of acute HCV infection, which occurs in 20 to 50% of patients who are infected with HCV.[2,3] Alternatively, he could have had a false positive HCV antibody test. The data do not support a history of chronic HCV infection, and a previous HCV infection is unlikely to explain his chronic liver injury. The inaccurate attribution of HCV positivity can adversely affect patient care by inhibiting the search for other causes of liver disease.

Alcohol Consumption

The patient had consumed six servings of alcohol daily for approximately 30 years, which places him at risk for alcohol-induced liver disease.[4] Although decades of alcohol consumption could explain his chronic liver disease, certain features of this patient's presentation require further examination. The elevated levels of alanine aminotransferase and aspartate aminotransferase obtained 3 years before the current presentation were too high to be due to alcohol-induced hepatitis. In addition, more recent laboratory testing revealed a markedly cholestatic pattern of liver injury, which is suggestive of a process that damages the biliary epithelium or impairs bile outflow (or both), rather than alcohol-induced liver injury. The R factor — the ratio of the elevation in the alanine aminotransferase level to the elevation in the alkaline phosphatase level — is used to determine whether a pattern on biochemical testing is indicative of hepatocellular injury or cholestatic injury. An R factor of less than 2 indicates a cholestatic pattern[5]; this patient had an R factor of 0.4.

Cholestatic Pattern of Liver Injury

In this patient, the cholestatic pattern of liver injury is unlikely to be caused by an infiltrative disease such as cancer, amyloidosis, or infection, but these diseases cannot be ruled out without a liver biopsy. There is no convincing evidence that biliary obstruction is causing the cholestatic pattern of liver injury. MRCP revealed mild irregularity of the intrahepatic bile ducts, but this finding can be observed in the context of chronic liver disease. The common bile duct was considered to be dilated, given the patient's age, but this abnormality could be a consequence of chronic opioid use and associated increased pressure in the sphincter of Oddi, which would not cause clinically significant liver disease.[6] Echocardiography revealed elevation of the estimated right ventricular systolic pressure, but the patient did not have longstanding clinical manifestations of heart failure, so congestive hepatopathy is unlikely to be the primary cause of liver disease. The marked elevation of the alkaline phosphatase level and the positive test for antimitochondrial antibodies in this patient are most consistent with primary biliary cholangitis.

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PRIMARY BILIARY CHOLANGITIS

Primary biliary cholangitis (previously called primary biliary cirrhosis) is an autoimmune disease that is characterized by T-cell–mediated destruction of the small intrahepatic bile ducts. Diagnosis is based on the presence of at least two of three criteria: biochemical evidence of cholestasis, with elevation of the alkaline phosphatase level, usually to a level that is more than 1.5 times the upper limit of the normal range; the presence of antimitochondrial antibodies; and histologic evidence of nonsuppurative cholangitis and destruction of the interlobular bile ducts.[7] This patient met the first two criteria. Although other conditions, such as congestive hepatopathy and cirrhosis, can increase the alkaline phosphatase level, the degree of elevation of the alkaline phosphatase level and the high titer of antimitochondrial antibodies in this patient support a diagnosis of primary biliary cholangitis.

Several other findings on laboratory testing and physical examination in this patient also support a diagnosis of primary biliary cholangitis. An increased IgM level and hypercholesterolemia are both associated with primary biliary cholangitis; hypercholesterolemia is present in 50 to 75% of patients with this disease.[8,9] The tan macules that were observed on physical examination in this patient could be xanthomas associated with hypercholesterolemia. Biopsy of the purple papules on his forearm revealed granulomatous dermatitis, a nonspecific finding that is associated with systemic inflammatory disorders, which could be related to primary biliary cholangitis.[10] Finally, his arthralgias are a nonspecific finding that could be due to rheumatoid-factor–negative nonerosive synovitis associated with primary biliary cholangitis.[11]

In patients with primary biliary cholangitis, the alkaline phosphatase level generally rises slowly to a plateau and remains relatively stable.[12] In this patient, the alkaline phosphatase level obtained 3 months before the current presentation was lower than the level obtained 6 months before the current presentation; this decrease was temporally associated with prednisone treatment. Glucocorticoids are not routinely administered in patients with primary biliary cholangitis, but some patients may have a response to such treatment, particularly those with an inflammatory subtype of the disease.[13,14]

OVERLAP SYNDROMES

Overlap syndromes between primary biliary cholangitis and other immune-mediated diseases have been recognized. In this patient, the granulomatous dermopathy and possible response to prednisone suggest the possibility of an overlap syndrome between primary biliary cholangitis and sarcoidosis.[15] Although a positive test for antimitochondrial antibodies is highly specific for primary biliary cholangitis, this result has also been reported in patients who have sarcoidosis and do not have primary biliary cholangitis.[16] However, abdominal imaging in this patient did not reveal any findings that were suggestive of sarcoidosis. The particularly high levels of alanine aminotransferase and aspartate aminotransferase obtained 3 years before the current presentation suggest the possibility of an overlap syndrome between primary biliary cholangitis and autoimmune hepatitis. Results of tests for autoantibodies (e.g., anti–smooth muscle antibodies) that would support the diagnosis of autoimmune hepatitis are not available.

PORTAL HYPERTENSION

This patient had findings on physical examination and imaging that were suggestive of underlying cirrhosis with associated portal hypertension. However, patients with primary biliary cholangitis can have presinusoidal portal hypertension (and related complications) before the development of cirrhosis. Such presinusoidal portal hypertension can be due to injury of the portal tracts. It can also be due to the development of nodular regenerative hyperplasia, which is characterized by alternating patches of regenerative and atrophic hepatocytes.[17,18]

PORTOPULMONARY HYPERTENSION

The elevation of the estimated right ventricular systolic pressure on echocardiography is suggestive of pulmonary hypertension. It would be important to further evaluate the patient for pulmonary hypertension and its cause by performing right heart catheterization. Portopulmonary hypertension — pulmonary arterial hypertension that occurs in the presence of portal

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hypertension and in the absence of other causes — would be my greatest concern. Portopulmonary hypertension is associated with mortality that is higher than the risk predicted by the Model for End-Stage Liver Disease (MELD) score, the measure used to determine status on the waiting list for deceased-donor transplantation in the United States, so affected patients may be eligible for a MELD exception score that raises their status on the waiting list.[19] However, moderate and severe portopulmonary hypertension is associated with increased perioperative mortality and must be treated before proceeding with transplantation.[20] I suspect that the diagnostic test in this case was a liver biopsy to confirm the diagnosis of primary biliary cholangitis and assess the underlying stage of liver disease.

CLINICAL IMPRESSION

Dr. Schaefer: The combination of a high titer of antimitochondrial antibodies and a cholestatic pattern of liver injury suggested a diagnosis of primary biliary cholangitis. However, the elevated right ventricular systolic pressure on echocardiography increased the likelihood of superimposed congestive hepatopathy. Although several elements of this patient's presentation were suggestive of cirrhosis, he could have had noncirrhotic portal hypertension. A transjugular liver biopsy with hemodynamic evaluation was performed.

CLINICAL DIAGNOSIS

Primary biliary cholangitis.

DR. IRUN BHAN'S DIAGNOSIS

Primary biliary cholangitis.

PATHOLOGICAL DISCUSSION

Dr. Bailey Hutchison: Hematoxylin and eosin staining of the liver-biopsy specimen revealed lobules that did not have pathologically significant inflammation, hepatocyte injury, or steatosis. The lobules were vaguely nodular and showed a juxtaposition of mildly hyperplastic trabeculae and mildly atrophic trabeculae with sinusoidal dilatation. Reticulin staining highlighted the vague nodularity of mildly hyperplastic and mildly atrophic hepatic plates; these changes are consistent with mild nodular regenerative hyperplasia. However, given the mild nature of these findings, correlation with clinical findings is necessary to establish a diagnosis of nodular regenerative hyperplasia.

The portal tracts were variably expanded and contained moderate lymphoplasmacytic inflammatory infiltrates (Fig. 2A). These inflammatory cells trickled outward into the limiting plate of hepatocytes, but there was no associated hepatocyte damage that would be suggestive of interface activity. Trichrome staining highlighted the expanded portal tracts but did not show definitive portal–portal bridging (Fig. 2B). The portal tracts were ductopenic, with many portal tracts missing a native bile duct that corresponded to the present artery and vein (Fig. 2C). Several of these portal tracts had a prominent ductular reaction (Fig. 2D). These findings were highlighted on immunohistochemical staining for cytokeratin 7 (Fig. 2E) and cytokeratin 19. Copper staining was positive for copper accumulation in periportal hepatocytes (Fig. 2F). Taken together, the overall morphologic findings are diagnostic of a chronic cholestatic process.

There were no florid duct lesions, which would be diagnostic of primary biliary cholangitis. However, the histologic evidence of chronic cholangiopathy, together with the patient's clinical presentation and laboratory findings, is consistent with a diagnosis of primary biliary cholangitis. The presence of ductular proliferation and ductopenia in the absence of established fibrotic bridging is consistent with stage 2 of 4 primary biliary cholangitis, on the basis of the Scheuer staging system.[21] There was no definitive histologic evidence of chronic HCV infection, alcoholic cirrhosis, or nonalcoholic fatty liver disease.

PATHOLOGICAL DIAGNOSIS

Primary biliary cholangitis.

DISCUSSION OF MANAGEMENT

Dr. Schaefer: Patients who receive a diagnosis of primary biliary cholangitis are typically women in the fifth or sixth decade of life who present with an elevated alkaline phosphatase level. The most common symptoms are fatigue and pruri-

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tus, but the disease may be asymptomatic.[22] Primary biliary cholangitis is more likely to occur in women than in men (5:1). Men tend to be older and to have a higher bilirubin level at the time of diagnosis than women. In addition, men are less likely than women to have a favorable response to ursodeoxycholic acid, which is the first-line therapy for primary biliary cholangitis.[23] Treatment with ursodeoxycholic acid results in normalization of the alkaline phosphatase level (defined as a level <1.5 times the upper limit of the normal range), the γ-glutamyltransferase level, and the alanine aminotransferase level in approximately 60% of patients by 2 years, and the treatment has been associated with significant increases in 5-year and 10-year survival.[24,25] After this patient's biopsy results confirmed the diagnosis of primary biliary cholangitis, treatment with ursodeoxycholic acid was initiated.

Primary biliary cholangitis may progress to cirrhosis and its attendant complications, including portal hypertension, particularly in patients who do not have an adequate response to treatment. This patient had clinical evidence of portal hypertension, including esophageal varices, upper abdominal collateral vessels, and splenomegaly, but he did not have evidence of cirrhosis on liver biopsy. The hemodynamic evaluation performed during the transjugular liver biopsy revealed a hepatic venous pressure gradient of 5 mm Hg (reference range, 1 to 5). However, splenorenal collateral vessels were present, and shunting through these collaterals can result in a lower gradient. Before the development of cirrhosis, primary biliary cholangitis may lead to presinusoidal portal hypertension with a normal hepatic venous pressure gradient, which can be due to either injury of the portal tracts or nodular regenerative hyperplasia that causes compression of the portal venules. In this patient, the irregular hepatic plates seen on reticulin staining could be suggestive of evolving nodular regenerative hyperplasia.[26,27] His clinical presentation with varices, collateral vessels, and splenomegaly but no cirrhosis was consistent with noncirrhotic portal hypertension.

The elevation of the estimated right ventricular systolic pressure on echocardiography was suggestive of portopulmonary hypertension. The patient was referred for evaluation in the pulmonary hypertension clinic affiliated with this hospital.

Dr. Josanna M. Rodriguez-Lopez: In patients with liver disease, pulmonary hypertension may be caused by several mechanisms. These might include genetic abnormalities, altered concentrations of vasodilating and vasoconstricting mediators, a hyperdynamic state, and fluid overload. A rare but severe form of pulmonary hypertension is pulmonary arterial hypertension. Pulmonary arterial hypertension is a pulmonary vascular disease that is caused by a proliferative vasculopathy involving cellular proliferation, vasoconstriction, fibrosis, and thrombosis. It is characterized by elevated pulmonary arterial pressure and increased pulmonary vascular resistance, which result in right heart failure.

Portopulmonary hypertension is pulmonary arterial hypertension that occurs in the presence of portal hypertension and in the absence of an alternative cause. Portopulmonary hypertension is a subtype of pulmonary arterial hypertension and therefore is a subtype of World Health Organization group 1 pulmonary hypertension. It is a known complication of liver disease that is present in 4.5 to 8.5% of patients who are evaluated for liver transplantation.[28,29]

In this patient, right heart catheterization revealed severe precapillary pulmonary hypertension, with an elevated mean pulmonary arterial pressure (55 mm Hg; reference value, <20), a normal pulmonary capillary wedge pressure (12 mm Hg; reference value, ≤15), and an elevated pulmonary vascular resistance (8.5 Wood units; reference value, <3). There was no alternative cause for pulmonary arterial hypertension, so a diagnosis of portopulmonary hypertension was made.

The definitive treatment for portopulmonary hypertension is liver transplantation. However, uncontrolled portopulmonary hypertension has been associated with poor outcomes and high mortality among patients undergoing liver transplantation.[30] Guidelines recommend treatment with medications that are specific for pulmonary arterial hypertension before liver transplantation in patients with a mean pulmonary arterial pressure of more than 35 mm Hg, with the aim of lowering the pressure to less than 35 mm Hg and normalizing the pulmonary vascular resistance and right ventricular function.[31,32] Support for the treatment of portopulmonary hypertension with medications that are specific for pulmonary arterial hypertension has mostly been

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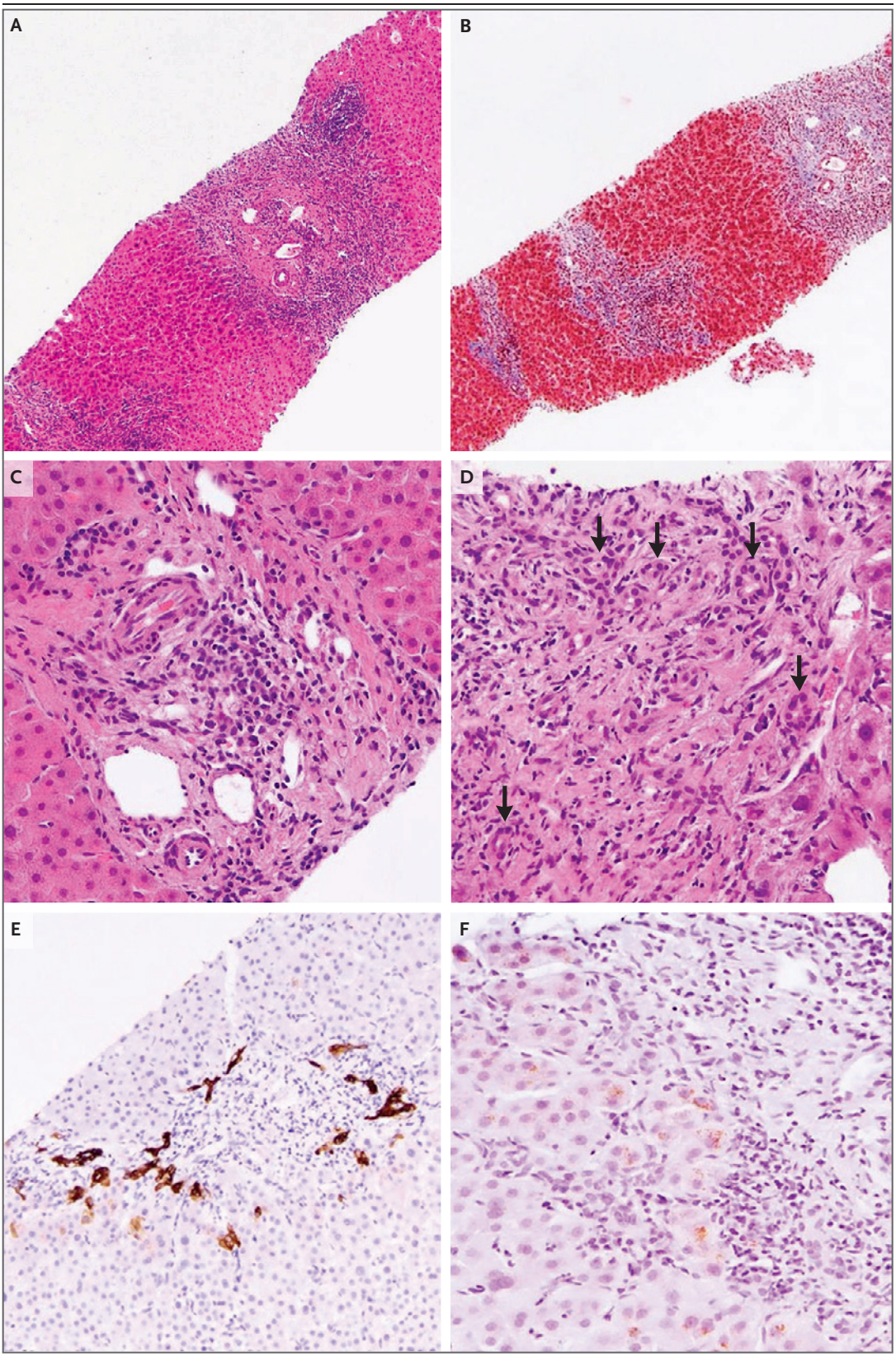

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Figure 2 (facing page). Liver-Biopsy Specimen.
Hematoxylin and eosin staining shows expanded portal tracts and portal inflammation (Panel A), but trichrome staining shows no definitive evidence of portal–portal bridging (Panel B). At higher magnification of the portal tracts, hematoxylin and eosin staining shows the loss of native bile ducts (Panel C) and ductular proliferation (Panel D, arrows). Immunohistochemical staining of a representative portal tract for cytokeratin 7 shows no native bile duct and highlights ductular proliferation (Panel E). Copper staining is positive for copper deposition (Panel F). These findings are indicative of a chronic cholestatic disease process.

extrapolated from studies involving patients with other subtypes of pulmonary arterial hypertension, although limited studies involving patients with portopulmonary hypertension have shown similar benefits.[33,34] In this patient, treatment with sildenafil was initiated. Repeat right heart catheterization revealed a clinically significant decrease in pulmonary arterial hypertension, but the mean pulmonary arterial pressure remained higher than 35 mm Hg. Therefore, treatment with inhaled treprostinil was initiated.

Dr. Schaefer: After 1 year of treatment, the patient underwent right heart catheterization, which revealed a mean pulmonary arterial pressure of 21 mm Hg. Liver transplantation is considered to be the definitive treatment for primary biliary cholangitis with severe liver disease, as well as for portopulmonary hypertension. Given the increased risks associated with liver transplantation in patients with pulmonary arterial hypertension, close collaboration with the anesthesiologist was an important part of the evaluation for liver transplantation.

Dr. Jerome C. Crowley: Liver transplantation is one of the most physiologically stressful surgical procedures, and anesthetic management requires an understanding of the implications of liver dysfunction as well as the effects of the surgery on the patient. In this patient with concurrent pulmonary hypertension, each phase of the liver-transplantation procedure presents additional challenges.

The dissection phase involves the initial exploratory laparotomy and removal of the native liver. In this phase, the management of volume status is critical, given the potential for clinically significant blood loss. This patient is at risk for clinically significant blood loss related to either dilatation of the venous collateral vessels due to portal hypertension or thrombocytopenia due to decreased production and splenic sequestration of platelets. Coagulation test results can be difficult to interpret in the presence of liver dysfunction, and viscoelastic hemostatic assays may be useful in determining the risk of coagulopathic bleeding. The management of volume status can be even more challenging in the context of pulmonary hypertension and right ventricular dysfunction, and close monitoring with pulmonary artery catheterization and transesophageal echocardiography is indicated.

Reperfusion of the allograft is associated with substantial physiological consequences. These include a change in temperature associated with cold preservation before implantation, acidosis from anaerobic metabolism in the new graft, elaboration of inflammatory mediators in response to reperfusion injury, hyperkalemia, and potential thromboembolism from altered coagulopathy and multiple vascular anastomoses. This combination precipitates systemic vasodilation, bradycardia, negative inotropy, and arrythmias. All these effects can be injurious to a healthy heart, but in a patient with pulmonary hypertension and right ventricular dysfunction, they can be catastrophic. Preemptive pharmacologic therapy and temporary mechanical circulatory support, including venoarterial extracorporeal membrane oxygenation, may be used to prevent or treat these derangements, if needed. In the neohepatic phase of surgery, monitoring for right ventricular dysfunction and worsening tricuspid regurgitation is indicated.

Dr. Schaefer: At the time that the patient was added to the waiting list for liver transplantation, his MELD score was 11 (with scores ranging from 6 to 40 and higher scores indicating more severe liver disease). He was granted a MELD exception with an initial MELD score of 28. He is still awaiting transplantation.

FINAL DIAGNOSIS

Primary biliary cholangitis with portopulmonary hypertension.

This case was presented at the Medicine Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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