A 25-year-old man presented to his primary care physician with generalized malaise. His symptoms started around 2 months earlier with progressive fatigue, nausea, decreased appetite, and weight loss (15 lb in 2 months). He denied having fever, chills, night sweats, abdominal pain, diarrhea, melena, or hematochezia.

His medical history was remarkable only for depression, well controlled with sertraline (Zoloft), which he started taking 3 years ago. He was not taking any other prescribed, over-the-counter, or herbal medications.

He had no family history of cancer or liver disease. He did not smoke and rarely drank alcohol. He had never used recreational drugs. He was sexually active with one female partner, used condoms for protection, and had never been diagnosed with a sexually transmitted disease. He had not traveled recently and had not been exposed to any pet.

On physical examination, the patient was alert and oriented. He was afebrile, his heart rate was 90 beats per minute and regular, his respiratory rate was 18 breaths per minute, and his blood pressure was 125/77 mm Hg. Auscultation of the chest was clear. His heart sounds were normal, and there was no murmur, gallop, or rub. His right upper quadrant was mildly tender, and his liver was palpably enlarged. He had no peripheral edema, clubbing, rash, telangiectasia, or other skin changes. Examination of the joints revealed no warmth, swelling, or erythema.

The patient’s laboratory values on admission are shown in Table 1. Of note, his serum alkaline phosphatase level was 1,307 U/L (reference range 40–150 U/L).

Table 1

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULTS</th>
<th>NORMAL RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>142 mmol/L</td>
<td>132–148</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.8 mmol/L</td>
<td>3.5–5.0</td>
</tr>
<tr>
<td>Chloride</td>
<td>109 mmol/L</td>
<td>98–111</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>19 mmol/L</td>
<td>23–32</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>21 mg/dL</td>
<td>8–25</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 mg/dL</td>
<td>0.7–1.4</td>
</tr>
<tr>
<td>Glucose</td>
<td>87 mg/dL</td>
<td>65–100</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>14.1 g/dL</td>
<td>12–16</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>55.5%</td>
<td>39–51</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>19.5 ×10^9/L</td>
<td>4–11</td>
</tr>
<tr>
<td>Platelet count</td>
<td>316 × 10^9/L</td>
<td>150–400</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>46 U/L</td>
<td>5–45</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>123 U/L</td>
<td>7–40</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1,307 U/L</td>
<td>40–150</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase</td>
<td>110 U/L</td>
<td>0–51</td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>2.0 mg/dL</td>
<td>0–1.5</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.3 g/dL</td>
<td>3.5–5</td>
</tr>
<tr>
<td>Activated partial</td>
<td>27.1 seconds</td>
<td>24.6–34.0</td>
</tr>
<tr>
<td>thromboplastin time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>10.1 seconds</td>
<td>9.9–13</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>0.9</td>
<td>0.9–1.1</td>
</tr>
</tbody>
</table>

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ELEVATED ALKALINE PHOSPHATASE

Approach to elevated alkaline phosphatase

- Abnormal liver function test* or elevated gamma-glutamyltransferase (GGT)
- Normal liver function test* and normal GGT

- Elevated alkaline phosphatase
  - Liver ultrasonography
  - Liver biopsy
  - Endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, or both

- Normal
  - Mass in the liver
  - Other imaging tests
  - Check medication list
  - Alfa fetoprotein
  - Autoantibodies
  - Check for intrahepatic causes

- Dilation of the ducts

FIGURE 1

LIVER TESTS CAN NARROW THE DIAGNOSIS

The most commonly used laboratory tests of the liver can be classified into those that measure either:
- **Liver synthetic function** (eg, the serum albumin and bilirubin concentrations and the prothrombin time) or
- **Liver damage**, as reflected by the serum concentrations of the enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and gamma-glutamyltransferase (GGT).1,2

ALT and AST are normally concentrated in the hepatocytes and thus, when present in the serum in elevated concentrations, are markers of liver cell injury. The serum levels of these enzymes start to increase within a few hours of liver cell injury as they leak out of the cells via the damaged cell membrane. AST is less liver-specific than ALT, since AST levels can be elevated not only in liver injury but also in muscle, cardiac, and red blood cell injury.3,4

Alkaline phosphatase is actually a heterogeneous group of enzymes found mainly in liver and bone cells. Hepatic alkaline phosphatase is concentrated near the biliary canalicular membrane of the hepatocyte. Accordingly, increased levels of hepatic alkaline phosphatase are mainly seen in liver diseases that predominantly affect the biliary system.5

GGT is also concentrated in hepatic biliary epithelial cells, and thus GGT elevation is another marker of hepatobiliary disease. In fact, measuring the GGT level can help to determine whether an isolated elevation of alkaline phosphatase is due to liver injury.2,3

Accordingly, liver diseases can be classified into two broad categories:
- **Hepatocellular injury**, in which the primary injury occurs to the hepatocytes
- **Cholestatic injury**, in which the primary injury is to the bile ducts.

In the former, elevated levels of ALT and AST predominate, while in the latter, elevated alkaline phosphatase is the main finding.1

WHAT TEST NEXT FOR OUR PATIENT?

What is the next most appropriate diagnostic step for our patient?

□ Liver biopsy
□ Ultrasonography of the liver
□ Computed tomography (CT) of the liver
□ Observation

Our patient has an elevated GGT level, which suggests that his elevated alkaline phosphatase is of hepatic rather than bony origin. Moreover, a serum alkaline phosphatase level that is elevated out of proportion to the aminotransferase levels reflects cholestatic liver injury.
Cholestatic liver diseases can be classified into two broad categories based on whether the injury affects the microscopic intrahepatic bile ducts (intrahepatic cholestasis) or extrahepatic large bile duct (extrahepatic cholestasis). The simplest diagnostic test to differentiate between the two is ultrasonography, which can identify extrahepatic biliary obstruction fairly well. Therefore, the diagnostic workup of cholestatic liver injury should start with ultrasonography of the liver to differentiate between intrahepatic and extrahepatic processes (Figure 1).

### Common causes of cholestatic liver disease

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>CLINICAL CLUES</th>
<th>DIAGNOSTIC TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>More common in males, young age, association with ulcerative colitis</td>
<td>Endoscopic retrograde cholangiopancreatography (ERCP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Magnetic resonance cholangiopancreatography (MRCP)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>More common in women, middle age, history of pruritus and fatigue</td>
<td>Antinuclear antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antimitochondrial antibodies</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>Jaundice, abdominal pain</td>
<td>Ultrasonography, ERCP, MRCP</td>
</tr>
<tr>
<td>Infiltrative diseases</td>
<td>History of amyloidosis, sarcoidosis, malignancy</td>
<td>Ultrasonography, computed tomography</td>
</tr>
<tr>
<td>Amyloidosis, sarcoidosis, lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication-induced</td>
<td>Medication history and timing</td>
<td>Discontinuation of the medication</td>
</tr>
<tr>
<td>Outflow obstruction</td>
<td>Dyspnea, edema, jaundice, abdominal pain, ascites</td>
<td>Echocardiography, ultrasonography, computed tomography, magnetic resonance imaging</td>
</tr>
</tbody>
</table>

**CAUSES OF CHOLESTATIC LIVER DISEASE**

**TABLE 2** lists the common causes of cholestatic liver disease.

**Viral hepatitis**

Viral hepatitis most often produces a hepatocellular pattern of injury (ie, AST and ALT elevations predominate). However, in rare cases it can cause a cholestatic pattern of injury.

Our patient subsequently had serologic tests for viral hepatitis, including hepatitis A, B, and C, and the results were negative.

**Autoimmune liver disease**

The three most common forms of autoimmune liver disease are autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis.

**Autoimmune hepatitis** is characterized by high serum ALT and AST levels, whereas primary biliary cirrhosis and primary sclerosing cholangitis are associated with predominant elevations of alkaline phosphatase, since they are cholestatic disorders.

Our patient's alkaline phosphatase level was much higher than his ALT and AST levels, making the latter two diseases more likely.

**Primary biliary cirrhosis** (and autoimm-
mune hepatitis) are associated with auto-
antibodies in the serum, such as antinuclear antibody, smooth muscle antibody, and anti-
mitochondrial antibody.

Our patient subsequently was tested for 
these antibodies, and the results were nega-
tive.

Primary sclerosing cholangitis usually af-
facts the extrahepatic biliary system. Thus, if 
it is present, abnormalities should be seen on 
imaging.

As mentioned previously, no dilated intra-
hepatic or extrahepatic biliary ducts were seen 
on ultrasonography in our patient. Moreover, 
primary sclerosing cholangitis is associated 
with inflammatory bowel disease, particularly 
ulcerative colitis, which our patient did not have.

Drug-induced liver injury
Drug-induced liver injury is a common cause 
of cholestatic liver disease. However, our pa-
tient was not taking any prescribed, over-the-
counter, or herbal medications. Additionally, 
he denied heavy alcohol use.

Infiltrative disorders
Infiltrative disorders such as amyloidosis, sar-
coidosis, or lymphoma should be considered 
in the differential diagnosis of cholestatic liver 
disease. A clue to a possible infiltrative process 
is a markedly elevated level of alkaline phos-
phatase with a mildly increased serum biliru-
bin concentration, both of which our patient 
had.

• AFTER ULTRASONOGRAPHY,
WHAT IS THE NEXT STEP?

Which of the following is the next most 
appropriate diagnostic test for our patient?

□ Endoscopic retrograde 
cholangiopancreatography (ERCP)
□ Magnetic resonance 
cholangiopancreatography (MRCP)
□ Liver biopsy
□ CT of the abdomen

Figure 1 shows a proposed algorithm for evalu-
ating increased alkaline phosphatase levels.

If there is no biliary duct dilation on ultra-
sonography, then abnormal levels of alkaline 
phosphatase most likely represent an intrahe-
patic pattern of cholestatic liver injury. There-
fore, additional imaging with CT or magnetic 
resonance imaging is of limited diagnostic 
value. ERCP is used today for therapy rather 
than diagnosis, so its use is limited to patients 
known to have dilated biliary ducts on imaging. Liver biopsy, however, can provide useful 
findings.

Case continued: He undergoes biopsy
Our patient underwent transjugular liver bi-
opsy. During the procedure, transjugular ve-
nography showed stenosis in the right, middle, 
and left hepatic veins and the hepatic portion 
of the inferior vena cava, consistent with 
Budd-Chiari syndrome.

The liver biopsy specimen was positive for 
extensive deposition of slight eosinophilic and 
amorphous material in a sinusoidal pattern in 
the liver parenchyma, as well as in the portal 
tracts, with markedly atrophic hepatocytes. 
Congo red birefringence confirmed the diag-
nosis of amyloidosis. The immunohistochemi-
cal phenotype was positive for kappa light 
chains, which is diagnostic for primary-type 
amyloidosis, also called amyloidosis of light 
chain composition, or AL.

Bone marrow aspiration and bone mar-
row biopsy were performed and showed 22% 
plasma cells, well above the normal range (0–2%), consistent with the diagnosis of multiple 
myeloma.

• BUDD-CHIARI SYNDROME:
A CHALLENGING DIAGNOSIS

Budd-Chiari syndrome is a rare condition 
characterized by obstruction of venous out-
flow from the liver at a site that may vary from 
the small hepatic veins up to the inferior vena 
cava or even the right atrium.5,6 Obstruction 
of hepatic venous outflow leads to sinusoidal 
congestion and hypoxic damage of the hepato-
cyes.7 Hypoxia and necrosis of the hepa-
tocytes result in the release of free radicals. 
Cirrhosis can eventually occur secondary to 
ischemic necrosis of hepatocytes and hepatic 
fibrosis.8

The estimated incidence of this syndrome 
is 1 in 2.5 million persons per year.7 It is more 
prevalent in women and young adults.8

ERCP is now 
used for 
therapy 
rather than 
diagnosis
Heterogeneous in its causes and manifestations

In about 75% of patients with Budd-Chiari syndrome, a hereditary or acquired hematologic abnormality or thrombotic diathesis can be found.8–10 Some of the major causes are summarized in Table 3. The most common causes are hematologic diseases, especially myeloproliferative disorders.7,8,11

Budd-Chiari syndrome is also heterogeneous in its manifestations, which depend on the extent of the occlusion, on the acuteness of the obstruction, and on whether venous collateral circulation has developed to decompress the liver sinusoids.9,12,13 Therefore, on the basis of its clinical manifestations, it can be classified as fulminant, acute, subacute, or chronic.12–16

The fulminant form presents with hepatic encephalopathy within 8 weeks after the development of jaundice. The subacute form, which is the most common, has a more insidious onset in which hepatic sinusoids are decompressed by portal and hepatic venous collateral circulation. The patient usually presents with abdominal pain, ascites, hepatomegaly, nausea, vomiting, and mild jaundice. Finally the chronic form presents as complications of cirrhosis.12–16

Imaging plays an important role in diagnosing Budd-Chiari syndrome

Imaging plays an important role in detecting and classifying Budd-Chiari syndrome.

Duplex ultrasonography is useful for detecting this syndrome and has a sensitivity and specificity of 85%.9

CT and magnetic resonance imaging can also help in the diagnosis by showing thrombosis, obstruction, or occlusion in the hepatic vein or the inferior vena cava.5

Venography is the gold standard for diagnosis. However, it should be performed only if noninvasive tests are negative or nondiagnostic and there is a high clinical suspicion.

---

**TABLE 3**

Some of the major causes of Budd-Chiari syndrome

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>CLINICAL CLUES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myeloproliferative disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>Increased hematocrit and hemoglobin with normal oxygen saturation</td>
</tr>
<tr>
<td>Essential thrombocytopenia</td>
<td>Increased number of platelets</td>
</tr>
<tr>
<td>Primary myelofibrosis</td>
<td>Pancytopenia, teardrop red blood cells</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>Leukocytosis, Philadelphia chromosome</td>
</tr>
<tr>
<td><strong>Paroxysmal nocturnal hemoglobinuria</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hereditary coagulopathy</strong></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>Family history</td>
</tr>
<tr>
<td>Protein C or S deficiency</td>
<td>History of venous thrombosis</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td></td>
</tr>
<tr>
<td><strong>Connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Behçet disease</td>
<td>Recurrent oral aphthous ulceration, recurrent genital ulcers</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>History of venous or arterial thrombosis</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
</tr>
<tr>
<td><strong>Nephrotic syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Proteinuria, edema, hyperlipidemia</td>
<td></td>
</tr>
</tbody>
</table>
of this disease. Budd-Chiari syndrome has a characteristic pattern on venography known as “spider web,” which is due to the formation of venous collaterals to bypass the occluded hepatic veins.

Liver biopsy is not necessarily required to confirm the diagnosis of Budd-Chiari syndrome, but it can help in diagnosing the acute or subacute forms and also in ruling out other causes. Histologic findings can include centrilobular congestion, loss of hepatocytes, hemorrhage, and fibrosis. Regenerative nodules are found in about 25% of patients.

TREATING BUDD-CHIARI SYNDROME

The primary goal of treatment is to prevent further extension of the venous thrombosis in the hepatic veins, in their collaterals, and in the intrahepatic and extrahepatic portal venous system. Resolution of hepatic congestion improves liver perfusion and preserves function of the hepatocytes.

Anticoagulation is recommended in the early stages. Heparin therapy should be initiated and subsequently switched to warfarin with the goal of achieving an international normalized ratio of the prothrombin time of 2.0 to 2.5. Thrombolysis is effective in the acute form. Recanalization, including percutaneous or transhepatic angioplasty of localized segments of the narrowed hepatic veins or inferior vena cava, has long-term patency rates of 80% to 90%. If thrombolytic therapy and angioplasty are unsuccessful, a transjugular intrahepatic portosystemic shunt or a surgical procedure (side-to-side portocaval shunt, central splenorenal shunt, or mesocaval shunt) should be considered.

Liver transplantation is another treatment option in those with fulminant Budd-Chiari syndrome or advanced liver cirrhosis.

PROGNOSIS HAS IMPROVED

The prognosis of Budd-Chiari syndrome has improved, thanks to both earlier diagnosis and new treatments. The 1-year survival rate, which was about 60% before 1985, has increased to more than 80% in recent cohort studies.

Studies have shown that the Child-Pugh score, which is based on a combination of serum albumin, bilirubin, prothrombin time, encephalopathy, and ascites, can be considered as an independent prognostic factor. A lower Child-Pugh score and a younger age are associated with a good prognosis. (The Child-Pugh score cannot be applied to our patient because he does not have cirrhosis.)

What happened to our patient?

Our patient was started on anticoagulation for his Budd-Chiari syndrome and on bortezomib (Velcade) and dexamethasone for his multiple myeloma. He achieved remarkable improvement in his liver function tests. Follow-up duplex ultrasonography 1 month after discharge revealed that the stenosis in the hepatic veins had resolved. He is following up with the oncology clinic for management of his multiple myeloma.

REFERENCES

ELEVATED ALKALINE PHOSPHATASE


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