A 55-year-old woman is being evaluated for persistently elevated liver enzymes. She has no signs or symptoms of any liver disease, including jaundice, scleral icterus, and hepatosplenomegaly. Two months before presentation, she was incidentally noted to have aminotransferase values elevated to 3 times the upper limit of normal. At this time, aspartate transaminase (AST) was 256 U/L (8 to 43 U/L) and alanine transaminase (ALT) was 386 U/L (7 to 45 U/L). Five weeks later, aminotransferase determinations were repeated, and levels had increased further (AST, 422 U/L; ALT, 616 U/L). Previous liver test results were normal.

Her past medical history was significant for the following: poorly controlled diabetes mellitus type 2, class 3 obesity, migraine headaches, alcohol use disorder in prolonged remission, urge incontinence, chronic back spasms, and bipolar disorder. Relevant medications she had received in the past 5 months included insulin, topiramate, tolterodine, cyclobenzaprine, and amitriptyline, and she had intermittently taken trimethoprim-sulfamethoxazole and nitrofurantoin for recurrent urinary tract infections. She denied use of alcohol for many years, illicit substances, recent travel, or acetaminophen. She lives in Minnesota. No family members have a history of liver disease.

At presentation, vital signs are as follows: temperature, 37.4°C; respiratory rate, 14 breaths/min; blood pressure, 126/69 mm Hg; oxygen saturation on room air, 94%; and pulse, 94 beats/min. On examination, she was alert and oriented to person, place, and time; she was in no apparent distress and was appropriately engaged in conversation. Eye examination found scleral icterus. Lungs were clear to auscultation bilaterally. On cardiovascular examination, rate and rhythm were normal, with S1/S2 heard without murmurs or extremity edema. Abdominal examination revealed obese non-tender abdomen without hepatosplenomegaly or shifting dullness. Last, neurologic examination findings were grossly normal without asterixis. Laboratory values were notable for the following (reference ranges provided parenthetically): hemoglobin, 12.1 g/dL (11.6 to 15.0 g/dL); white blood cell count, 5.4 × 10^9/L (3.4 to 9.6 × 10^9/L); platelet count, 163 × 10^9/L (157 to 371 × 10^9/L); international normalized ratio (INR), 1.1 (0.9 to 1.1); sodium, 137 mmol/L (135 to 145 mmol/L); creatinine, 0.99 mg/dL (0.59 to 1.04 mg/dL); glucose, 283 mg/dL (70 to 140 mg/dL); albumin, 3.8 g/dL (3.5 to 5.0 g/dL); alkaline phosphatase, 327 U/L (35 to 104 U/L); AST, 936 U/L (8 to 43 U/L); ALT, 1038 U/L (7 to 45 U/L); total bilirubin, 3.7 mg/dL (≤1.2 mg/dL); and direct bilirubin, 3.1 mg/dL (0.0 to 0.3 mg/dL).

1. What term best describes her current presentation?
   a. Compensated cirrhosis
   b. Decompensated cirrhosis
   c. Acute liver failure
   d. Chronic hepatitis
   e. Acute hepatitis

Historically, liver biopsy has been considered the “gold standard” for diagnosis of cirrhosis. In the current era, liver biopsy is rarely needed for this indication. Rather, clinicians can use other noninvasive tools to establish a diagnosis of cirrhosis. For example, a large meta-analysis has reported that the features most accurate in predicting cirrhosis in adults are ascites, spider
angiomas, platelet count below 160,000/mm³, and Bonacini cirrhosis discriminant score greater than 7. The Bonacini cirrhosis discriminant score is calculated by giving points for the following parameters: platelets, ALT/AST ratio, and INR. An online calculator for the Bonacini cirrhosis discriminant score can be found at https://www.merckmanuals.com/medical-calculators/CirrhosisProbability_MC.htm. Abdominal imaging can also illustrate a cirrhotic-appearing liver (including but not limited to nodular appearance, atrophic right lobe, hypertrophic left lobe, splenomegaly, portosystemic shunts, and varices) and manifestations of portal hypertension, and liver stiffness (a surrogate for liver fibrosis) can be measured by elastography. Our patient did not have these features suggestive of cirrhosis. Patients who have complications of cirrhosis, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome, are considered to have decompensated cirrhosis; these complications were absent in our patient. Acute liver failure is defined by acute liver injury with hepatic encephalopathy and impaired synthetic function (INR ≥1.5), generally without preexisting liver disease. Our patient’s INR was 1.1, and she did not have hepatic encephalopathy. Hepatitis represents nonspecific liver inflammation and can be classified as chronic (present for at least 6 months) or acute (onset less than 6 months), which was seen in our patient.

Because she was clinically stable and asymptomatic, we continued supportive measures and next steps in diagnostics.

2. Which is the most appropriate next diagnostic test?
   a. Endoscopic retrograde cholangiopancreatography
   b. Liver ultrasound
   c. Ceruloplasmin determination
   d. Liver biopsy
   e. Hepatitis E IgG

   The pattern of any liver injury can be characterized as hepatocellular, cholestatic, or mixed by calculating the R factor:

   \[ \text{R factor} = \frac{\text{patient’s ALT}/\text{upper limit of normal ALT}}{\text{patient’s alkaline phosphatase}/\text{upper limit of normal alkaline phosphatase}} \]

   An R factor greater than 5, 2 to 5, and less than 2 is consistent with hepatocellular, mixed, and cholestatic pattern of injury, respectively. Our patient’s liver test results are most consistent with hepatocellular-predominant injury.

   A subacute or chronic biliary obstruction typically leads to a cholestatic-predominant pattern of liver test abnormalities. Other features of biliary obstruction, such as ductal dilation, are often noted on imaging, and patients may experience complications stemming from a biliary obstruction, such as pain or cholangitis. These features were absent in our patient, and therefore endoscopic retrograde cholangiopancreatography would not be recommended. Nonalcoholic fatty liver disease (NAFLD) is the leading cause of mild transaminase elevations in the United States and is becoming more prevalent. Ultrasound of the liver is a sensitive test for NAFLD and would be the next best step in evaluation for our patient. A low serum ceruloplasmin level alone has a low positive predictive value for Wilson disease, and the level can be normal and elevated in those with Wilson disease as it is also an acute phase reactant. Moreover, Wilson disease is rare and more frequently detected in children and young adults. It is also often associated with a low alkaline phosphatase level, which was not seen in our patient. Hence, assessing a serum ceruloplasmin level would be low yield in this situation. Liver biopsy is invasive and would not be considered in initial evaluation of acute hepatitis. If autoimmune hepatitis (AIH) is suggested by bloodwork or as discussed before in the diagnosis of cirrhosis, it is recommended that this diagnosis be confirmed. Hepatitis E virus can cause acute hepatitis. However, this is uncommon in North America. Moreover, anti–hepatitis E IgG may be absent in the acute phase of an infection. Hence, this is not the correct answer.

   For our patient, ultrasound examination of the liver was completed, which showed hepatic steatosis without ductal dilation.
and a normal spleen size. Additional testing was also performed. This included the following negative test results: hepatitis A IgM, hepatitis C antibody, hepatitis B core IgM and hepatitis B surface antigen, acetaminophen level, and antinuclear antibodies. However, an elevated IgG level of 2780 mg/dL (767 to 1590 mg/dL) was found, and smooth muscle antibody titer was positive (1:320). Liver biopsy was performed. This revealed a dense lymphoplasmacytic inflammation (moderate in activity) in the portal tracts with interface activity and patchy areas of hepatocyte necrosis. Mild macrovesicular steatosis was also present. The interlobular bile ducts were uninjured. Trichome stain was negative for fibrosis.

3. What is the most likely diagnosis?
   a. NAFLD
   b. Alcoholic hepatitis
   c. Classic AIH
   d. Drug-induced liver injury (DILI)
   e. Lymphoma

Nonalcoholic fatty liver disease is common and may affect 20% to 30% of adults in the United States. Our patient has metabolic risk factors for fatty liver disease and evidence of hepatic steatosis consistent with NAFLD. It can be associated with either normal levels or long-term elevations of aminotransferases (typically less than 4 times the upper limit of normal, or less than 250 to 300 U/L). Whereas our patient had hepatic steatosis and metabolic risk factors for NAFLD, the acuity and degree of liver enzyme elevation in our patient would not be explained by NAFLD alone. Alcohol-associated liver disease is a clinical spectrum that can be associated with hepatic steatosis with normal liver test results, short- and long-term elevations in liver enzymes (typically in a hepatocellular injury—predominant pattern), cirrhosis with or without decompensation, and acute alcoholic hepatitis. Characteristically, AST is often 1.5 to 2 times higher than ALT. However, AST elevations greater than 400 U/L are atypical, and alcohol-associated disease alone should not cause transaminase elevations as high as what is noted in our patient. Classic AIH can cause a corticosteroid-responsive hepatocellular-predominant liver enzyme elevation (either short or long term). In AIH, liver test results can range from being normal (so-called burned out AIH) to marked aminotransferase elevations that rarely exceed 5000 U/L. There is no single diagnostic test for AIH, and other causes of hepatitis should be excluded. Elevations in gamma globulin and elevations in autoantibodies (antinuclear, smooth muscle, liver kidney microsomal) may also be present. However, these autoantibodies may also be found in other populations (eg, 20% of patients with NAFLD have an elevated smooth muscle antibody titer). A liver biopsy is generally recommended in considering a diagnosis of AIH. This may show lymphoplasmacytic inflammation with interface activity (as seen in our patient), which is suggestive of AIH but not pathognomonic. Frequently, hepatic fibrosis is also present. The absence of hepatic fibrosis and her medication history caused us to consider alternative causes beyond classic AIH; DILI may cause short- or long-term elevations in liver enzymes (either hepatocellular- or cholestatic-predominant pattern). Some medications have been classically associated with drug-induced AIH or autoimmune DILI (AI-DILI). Like classic AIH, AI-DILI may have elevations in autoantibodies and lymphoplasmacytic interface activity on liver histologic evaluation. In contrast, AI-DILI has a temporal relationship with a medication; hepatic fibrosis is often absent on the liver biopsy specimen (as seen here), and it should not recur after a limited course of treatment and avoidance of the offending agent. Our patient did not have other manifestations that would suggest a hematologic malignant neoplasm, and when lymphoma infiltrates the liver, it is typically associated with a cholestatic pattern of liver enzyme elevation.

Our patient continued to be asymptomatic. It was then crucial to identify the offending agent to prevent future occurrences.
4. Which of her recent medications is the most likely cause of her presentation?
   a. Nitrofurantoin
   b. Divalproex
   c. Amitriptyline
   d. Topiramate
   e. Trimethoprim-sulfamethoxazole

   Nitrofurantoin is classically associated with Al-DILI. Liver injury is typically noted within 3 months of drug exposure (although a latency period of more than 1 year has been reported). The other medication options are not associated with Al-DILI. For our patient, we believed the likely offending agent was nitrofurantoin, and we advised lifelong avoidance.

5. In addition to advising avoidance of the offending agent, how would you approach treatment at this time?
   a. Close observation
   b. N-Acetylcysteine IV
   c. Methylprednisolone IV
   d. Azathioprine
   e. Budesonide

   The severe hepatitis would justify medical therapy in addition to holding of the offending medical agent. N-Acetylcysteine is used for the treatment of acetaminophen toxicity and can also be considered in acute liver failure secondary to nonacetaminophen DILI. Either oral or intravenous (IV) administration of corticosteroids is the appropriate treatment option to help induce remission in the acute setting for Al-DILI. Azathioprine can be used to help maintain remission and to minimize corticosteroid exposure in those with classic AIH but not Al-DILI. Budesonide has a high first-pass metabolism with minimal systemic absorption and is associated with fewer glucocorticoid-related adverse effects. However, there are limited data to support its use in severe Al-DILI, and it is not recommended for severe cases of classic AIH.

   With her Al-DILI diagnosis, we decided to hospitalize the patient and to initiate IV administration of methylprednisolone. We decided to hospitalize her for the IV administration of corticosteroids because she had poorly controlled diabetes mellitus (hemoglobin A1c at admission was 10.5%), and we were concerned for hyperglycemia with corticosteroid initiation; and she has a history of bipolar disorder, among other psychiatric illnesses, and although these illnesses were stable, we wanted to observe her during corticosteroid initiation in case this were to change. She received 5 days of IV administration of methylprednisolone. We chose IV administration of corticosteroids rather than oral administration because of the extent of her elevated transaminases. The medication was well tolerated and resulted in improvement in aminotransferase levels. She was discharged on oral prednisone with a taper guided by her biochemical response. Ultimately, her liver test results normalized, and she remains off corticosteroids.

DISCUSSION

It is important to recognize DILI because it carries substantial morbidity and mortality. Whereas acetaminophen is often implicated in acute DILI in the United States, nonacetaminophen idiosyncratic DILI is increasingly important and is the focus of this case and our discussion. Nonacetaminophen DILI has an estimated annual incidence of between 10 and 15 per 10,000 to 100,000 persons exposed to prescription medications and accounts for 10% of all cases of acute hepatitis. The Drug-Induced Liver Injury Network’s 2015 report showed a 16% mortality of DILI in patients with prior liver disease and 5.0% in those without. The possibility of DILI should be considered among individuals presenting with abnormal liver test results. A detailed history is key. On occasion, medication exposures may occur without the patient’s knowledge (eg, prophylactic antibiotics given during a medical procedure). Antimicrobials are the most common offending agent (45%), followed by herbal and dietary supplements (16%) and cardiovascular medications (10%). In order of most to least common, the top 5 antimicrobial agents associated with DILI are amoxicillin-clavulanate, isoniazid, nitrofurantoin, trimethoprim-
sulfamethoxazole, and minocycline. However, the list of possible offending medications is much longer, and a helpful clinical tool is the National Institutes of Health DILI database, LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK547852/).

Drug-induced liver injury has a wide clinical spectrum. Patients are often asymptomatic and have mild elevations in liver enzymes (either short or long term, hepatocellular- or cholestatic-predominant pattern of injury). Less commonly, systemic manifestations (rash, fever, myocarditis, myositis) occur as exemplified by drug reaction, eosinophilia, and systemic symptoms (DRESS syndrome). In the United States, DILI is the leading cause of acute liver failure, which is associated with a high mortality. Indeed, Hy’s law, based on observations by Dr Hyman Zimmerman in the 1990s, suggests that in patients who have drug-induced hepatocellular injury with jaundice and no other explanation, the mortality is 10%.

Last, as found here, select medications can also mimic chronic liver diseases such as AIH or AI-DILI.

It can be difficult to distinguish between classic AIH and AI-DILI. Classic AIH is diagnosed by a combination of laboratory tests, history, histologic features on liver biopsy, and exclusion of other causes. The presence or absence of autoantibodies (eg, smooth muscle antibody) alone is not adequately sensitive or specific for classic AIH, and they may be present in either condition. However, acuity of onset, lack of concurrent autoimmune disease, hypersensitivity symptoms (fever, rash, eosinophilia), absence of fibrosis on liver biopsy specimen that otherwise has features suggestive of classic AIH, lack of relapse after offending drug withdrawal (in the case of our patient, withdrawal of nitrofurantoin), and temporal relationship with a medication generally suggest AI-DILI. On occasion, the diagnosis of AIH vs AI-DILI can be made only by monitoring the patient’s response and lack of symptom relapse after drug removal. Examples of commonly prescribed medications strongly associated with AI-DILI include nitrofurantoin, minocycline, hydralazine, and anti–tumor necrosis factor α agents. Atorvastatin, rosuvastatin, isoniazid, and propylthiouracil also have an association with AI-DILI. A comprehensive list of medications known to cause AI-DILI has been expertly reviewed by Leise et al. Checkpoint inhibitors (eg, ipilimumab and pembrolizumab) are increasingly used and can also lead to immune-related adverse events including hepatitis, which is usually corticosteroid responsive. Checkpoint inhibitor–induced hepatitis is not considered to be AI-DILI as the mechanism of hepatocellular injury is restoration of cytotoxic T-cell activity, which is the primary function of these medications.

Distinguishing classic AIH from AI-DILI is important because treatment and prognosis differ. Therapy for classic AIH involves induction of remission with corticosteroids and use of azathioprine to help maintain remission. Withdrawal of immunosuppression will typically lead to disease recurrence among those with classic AIH, and disease flairs are associated with adverse outcomes. Treatment of AI-DILI involves withdrawal of the offending agent. In contrast to most other forms of DILI, many patients with AI-DILI benefit from corticosteroids, particularly when any of the following are present: symptoms, severe inflammation (particularly if the aminotransferase elevations are more than 3-fold and the bilirubin level is more than 2-fold), and lack of improvement after the offending agent is stopped. Corticosteroids are tapered on the basis of the patient’s biochemical response, and resolution typically takes 1 to 3 months. Recurrent liver enzyme elevations after corticosteroid withdrawal would suggest classic AIH and the need for prolonged immunosuppressive therapy; AI-DILI has an excellent prognosis with transplant-free survival approaching 100%. In contrast, the 10-year survival for classic AIH is approximately 90%, with a 7% to 40% chance of progression to cirrhosis.

Our patient had features of NAFLD but presented with severe acute hepatitis secondary to nitrofurantoin-induced AI-DILI. An accurate medication history is critical.
during the investigation of patients presenting with elevated liver enzymes. Recognition of DILI is important because withdrawal of the offending agent is crucial to its management; AI-DILI is a corticosteroid-responsive subtype of DILI that is classically caused by several commonly prescribed medications, including nitrofurantoin.

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**REFERENCES**


**CORRECT ANSWERS:** 1. e. 2. b. 3. d. 4. a. 5. c.