Drug-Induced Liver Disease

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Cover Illustration by Christine Armstrong
INTRODUCTION

Several hundred medicinal agents, chemicals, and herbal therapies can potentially cause hepatic injury. Regarded as “a penalty for progress” by Hans Popper 40 years ago, drug-induced liver disease (DILD) appears to be increasing in incidence, reflecting a growing number of new agents introduced into clinical use in the past several years as well as increased recognition of hepatotoxicity among older agents.

INCIDENCE

The frequency of DILD is 4% to 10% of all adverse drug reactions. A significantly higher percentage of acute hepatitis cases are the result of drug-induced liver injury, and drugs are responsible for more than 50% of all cases of fulminant hepatic failure in the United States. Most of these cases are due to acetaminophen, but numerous other agents are also responsible, most notably isoniazid (INH) and other antituberculosis drugs. DILD is responsible for 15% of all liver transplants performed in the United States; again, acetaminophen represents about half of these cases. It should not be surprising, therefore, that DILD is the most common reason that drugs are abandoned during clinical development phases or have restrictions placed on their use following marketing and is a leading reason for their removal from the marketplace.

In reports by Pillans and by Jmelnitzky et al, approximately 60% of cases of DILD involved female patients, consistent with the general notion that with a few exceptions (eg, amoxicillin-clavulanate), women are more susceptible to DILD. Table 1 lists patient-related factors that may enhance susceptibility to DILD.

AGENTS CAUSING DILD

Most medicinal agents that cause liver injury do so rarely, on an idiosyncratic basis. Only a few compounds are intrinsically hepatotoxic when taken in sufficient dosage; the prime example is acetaminophen. Agents causing unpredictable idiosyncratic injury can be divided into those associated with immunoallergic manifestations (eg, fever, rash, eosinophilia) and those not associated with such features (Table 2). The latter group are thought to act through reactive metabolites formed in the course of their use. Drugs acting through hypersensitivity mechanisms represented approximately 30% of cases reported by Jmelnitzky et al.

MORPHOLOGIC PATTERNS OF INJURY

DILD can take the form of any known hepatic disorders associated with other etiologies. The pathology can be broadly divided into acute hepatocellular or cholestatic injury and chronic liver disease, which can include chronic cholestasis mimicking primary biliary cirrhosis (PBC), chronic active hepatitis simulating autoimmune hepatitis, steatohepatitis, vascular diseases, and neoplastic lesions of the liver (Table 3). In the series by Jmelnitzky et al, approximately 90% of patients with drug-induced hepatotoxicity presented with acute forms of liver disease and the remainder presented with chronic liver disease. Among patients presenting with acute DILD, acute hepatocellular injury (including instances of acute liver failure) was seen in 41%, acute cholestatic hepatitis in 24%, bland cholestasis in 15.5%, and indeterminate acute injury in 10%. In their series, the average time for liver-associated enzymes (LAEs) to normalize after the drug was discontinued varied according to the type of acute injury but was considerably longer with cholestatic injury—4 weeks for acute hepatocellular injury, 12 weeks for bland cholestasis, and 16 weeks for cholestatic hepatitis. A similar time to recovery was noted by Galan et al. For drugs causing acute injury with complete recovery biochemically and clinically, it is expected that histologic recovery will also be complete. There are no unequivocal examples of acute hepatotoxins leading to subclinical injury after the agent has been withdrawn and enzymes have normalized.

Integral to the ability to recognize DILD is an understanding of the biochemical correlates of injury. In general, hepatocellular, cholestatic, and mixed patterns of injury may be recognized, all of which can be subdivided into acute and chronic injury patterns. Table 4 lists many of the disorders that are in the differential diagnosis of acute DILD, with associated laboratory findings.
ACUTE CHOLESTATIC INJURY

CASE PRESENTATION

A 58-year-old man is seen for new onset of jaundice. Two weeks earlier, he had completed a 10-day course of amoxicillin/clavulanate for suspected bronchitis. Soon after finishing the antibiotic, he noted fatigue, itching, mild right upper quadrant discomfort, and anorexia with weight loss of a few pounds. His urine also became dark, and he was referred for evaluation. He tells you that he drinks 3 or 4 beers on the weekends and has an occasional glass of wine or a cocktail with dinner. He quit smoking 8 years ago and has never had any form of hepatitis to his knowledge. He has not received any vaccinations against hepatitis A or B. He donated blood about 2 years ago but has not received any transfusions. He has never been denied any insurance coverage, and has no history of elevated LAEs or jaundice on prior physical examinations. He and his wife are fond of sushi and often eat raw oysters, but his wife has not been ill. His medications include pravastatin for the past 3 years, and losartan-hydrochlorothiazide for the past 2 years. He takes acetaminophen or ibuprofen for occasional headaches and to treat joint pains, and he takes fexofenadine on occasion for allergies. He takes a multivitamin every day but denies using any herbal agents. His past surgical history includes an appendectomy, tonsillectomy, right herniorrhaphy, and tennis elbow repair.

On physical examination, he is afebrile and in no acute distress, but has scleral icterus and mild right upper quadrant tenderness without noticeable hepatosplenomegaly. No asterixis is noted nor ecchymoses found, and there is no palmar erythema or edema.

His laboratory results return as follows: alkaline phosphatase, 670 U/L; alanine aminotransferase (ALT), 180 U/L; aspartate aminotransferase (AST), 150 U/L; total bilirubin, 6.2 mg/dL (4.0 mg/dL direct); albumin, 3.9 g/dL; total protein, 6.9 g/dL; γ-glutamyltranspeptidase (GGTP), 700 U/L; international normalized ratio (INR), 1.13. Results of a complete blood count (CBC) are normal with a hematocrit of 42%, platelet count of 190 × 10^9/mm³, and leukocyte count of 6.2 × 10^9/mm³ with 12% eosinophils.

- What is the differential diagnosis at this point?

DIFFERENTIAL DIAGNOSIS AND FURTHER WORK-UP

The new onset of jaundice requires an evaluation that will distinguish between acute hepatocellular and cholestatic causes. Hepatocellular injury is associated with viral hepatitis, autoimmune hepatitis, and other metabolic disorders as well as drug and toxin exposures, including alcohol injury. Cholestatic causes are subdivided into those causing intrahepatic cholestasis from drugs or infiltrative processes versus those causing extrahepatic biliary obstruction (eg, gallstones, pancreatic cancer). In this patient with jaundice and right upper quadrant pain, extrahepatic biliary obstruction certainly should be on the list of differential diagnoses along with acute hepatitis A, given his fondness for raw seafood. However, the elevated alkaline phosphatase and GGTP, along with more modest elevations in aminotransferases, suggests a cholestatic process (Table 4). The presence of pruritus and eosinophilia suggests an allergic cause.

An abdominal ultrasound was ordered, revealing a normal-sized liver with no ductal dilatation, a normal gallbladder without gallstones, and normal-appearing pancreas. A normal imaging study such as this in the

Table 1. Patient Risk Factors for DILD

<table>
<thead>
<tr>
<th>Patient Factor</th>
<th>Drug Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Halothane, INH, amoxicillin-clavulanate</td>
</tr>
<tr>
<td>Older</td>
<td>Salicylates, valproate</td>
</tr>
<tr>
<td>Younger</td>
<td>Amoxicillin-clavulanate</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Most drugs other than amoxicillin-clavulanate</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>Halothane</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>Methotrexate</td>
</tr>
<tr>
<td><strong>JRA, SLE</strong></td>
<td>Salicylates</td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
<td>IV tetracycline, allopurinol</td>
</tr>
<tr>
<td><strong>HIV/AIDS</strong></td>
<td>Dapsone, TMP-SMX</td>
</tr>
<tr>
<td>Chronic hepatitis B, C</td>
<td>HAART, anti-TB drugs</td>
</tr>
<tr>
<td>Other preexisting liver disease</td>
<td>Niacin, MTX, pemoline, tolcapone</td>
</tr>
<tr>
<td><strong>Fasting, malnutrition</strong></td>
<td>APAP, methimazole</td>
</tr>
<tr>
<td>(reduced glutathione)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoalbuminemia</strong></td>
<td>MTX, INH</td>
</tr>
<tr>
<td><strong>Deficiency of epoxide</strong></td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td><strong>hydrolase</strong></td>
<td></td>
</tr>
<tr>
<td>**Deficiency of N-acetyltrans-</td>
<td>Sulfonamides, INH</td>
</tr>
<tr>
<td><strong>ferase-2</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Reduced levels of IL-10, IL-4</strong></td>
<td>Diclofenac</td>
</tr>
</tbody>
</table>

Data from Zimmerman, Larrey and Pageaux, Aithal et al, Schlienger and Shear, Lewis. APAP = acetaminophen; DILD = drug-induced liver disease; HAART = highly active antiretroviral treatment; IL = interleukin; JRA = juvenile rheumatoid arthritis; INH = isoniazid; IV = intravenous; MTX = methotrexate; SLE = systemic lupus erythematosus; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole.
presence of jaundice generally excludes extrahepatic biliary obstruction, allowing one to focus on intrahepatic causes of cholestasis, including drug-induced lesions. In some cases, however, acute drug-induced cholestasis can produce a syndrome that mimics acute acalculous cholecystitis, and patients have been brought to the operating room when the diagnosis of a drug-induced syndrome was unsuspected.10

In the case patient, amoxicillin-clavulanate would be a prime suspect given the fact that it is one of the most commonly used antimicrobial agents leading to cholestatic jaundice.10,11,22 Liver injury related to amoxicillin-clavulanate typically affects middle-aged men more than women and is often associated with features of hypersensitivity including fever, rash, and eosinophilia.

Further testing in the case patient excluded PBC (a negative test for anti-mitochondrial antibody). Normal findings on a magnetic resonance cholangiopancreatography excluded sclerosing cholangitis. When performed, a liver biopsy shows classic features of a cholestatic hepatitis associated with amoxicillin-clavulanate injury and serves to exclude infiltrative causes, such as sarcoidosis, tuberculosis (TB), or fungal infections (if no granulomas are seen and the appropriate acid-fast bacilli and fungal stains are negative). The decision to perform a liver biopsy should be individualized and is usually recommended only when the diagnosis is in doubt or the recovery is slow in order to exclude chronic injury.

CLINICAL COURSE

The prognosis of drug-induced acute cholestatic injury is usually quite good, with resolution of the injury over a period of several weeks. Prolonged cholestasis has been described with several agents; in these cases, recovery can take up to 1 year.10,11 An increasing number of agents (including amoxicillin-clavulanate) are recognized as causing a chronic cholestatic picture that resembles PBC with destruction of the bile ducts, known as vanishing bile duct syndrome.23 Table 5 lists many of the agents associated with this condition. The clinical features that help to distinguish drug-induced causes of the vanishing bile duct syndrome from PBC are given in Table 6.

In this patient, the cholestatic injury slowly resolved over the next several weeks, and his biochemical abnormalities had normalized by the time they were rechecked 4 months later. The liver injury associated with amoxicillin-clavulanate can occur even after the drug has been stopped for as many as 6 or 7 weeks. In this case, the injury began shortly after treatment ended, consistent with this short delay. For most other medications associated with liver injury, however, acute injury occurs while the drugs are being taken.

Table 2. Features that Distinguish Intrinsic from Idiosyncratic Hepatotoxicity

<table>
<thead>
<tr>
<th>Feature</th>
<th>Intrinsic Toxicity</th>
<th>Idiosyncratic Toxicity</th>
<th>Aberrant Metabolism</th>
<th>Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Direct/indirect physiochemical destruction</td>
<td>Toxic reactive metabolite</td>
<td>Immune-mediated</td>
<td></td>
</tr>
<tr>
<td>Risk of injury</td>
<td>Very high (predictable)</td>
<td>Low (unpredictable)</td>
<td>Low (unpredictable)</td>
<td></td>
</tr>
<tr>
<td>Latency</td>
<td>Hours (acute)</td>
<td>Weeks–months (variable)</td>
<td>1–5 weeks (fixed)</td>
<td></td>
</tr>
<tr>
<td>Animal model</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Dose-dependency</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Positive response to rechallenge</td>
<td>N/A</td>
<td>Possibly (delayed)</td>
<td>Expected (prompt)</td>
<td></td>
</tr>
<tr>
<td>Injury pattern</td>
<td>Usually necrosis</td>
<td>Broad spectrum</td>
<td>Broad spectrum, granulomas</td>
<td></td>
</tr>
<tr>
<td>Clinical features</td>
<td>Fulminant hepatitis</td>
<td>Elevated LAEs, acute hepatitis, fulminant hepatic failure</td>
<td>Fever, rash, eosinophilia, arthralgias</td>
<td></td>
</tr>
<tr>
<td>Mortality rate</td>
<td>High*</td>
<td>Variable*</td>
<td>Variable*</td>
<td></td>
</tr>
<tr>
<td>Examples</td>
<td>APAP, salicylates, nicotinic acid</td>
<td>INH, diclofenac, troglitazone, ketoconazole</td>
<td>Sulfonamides, ticrynafen, sulindac, valproate, phenytoin, halothane</td>
<td></td>
</tr>
</tbody>
</table>

APAP = acetaminophen; INH = isoniazid; LAEs = liver-associated enzymes; N/A = not applicable.

*Hepatocellular jaundice is associated with a case-fatality rate or need for liver transplant of 10% or higher.
of post-traumatic seizures, she is started on prophylaxis with phenytoin. Approximately 6 weeks later, the patient develops a syndrome of fever, a diffuse maculo-papular skin rash, and lymphadenopathy, which brings her to medical attention. LAEs are as follows: ALT, 550 U/L; AST, 490 U/L; alkaline phosphatase, 180 U/L; INR, 1.2. Her CBC shows a hematocrit of 39%, leukocyte count of 15.0 × 10^3/mm^3; the differential count shows an increased percentage of lymphocytes, including some atypical lymphocytes.

On physical examination, the patient looks ill and has mild scleral icterus. Diffuse lymphadenopathy and splenomegaly are noted.

**How should the work-up and further management of this patient proceed?**

**DIFFERENTIAL DIAGNOSIS AND FURTHER WORK-UP**

In any case of suspected acute drug-induced injury, the suspected drug should be discontinued immediately.
as was done in this case. This measure is generally sufficient to prevent further progression of the injury, although in some cases of immune-mediated toxicity, various aspects of the injury can continue. The clinical features of this case do not suggest acute viral hepatitis A, B, or C, which are rarely associated with a rash or lymphadenopathy. In addition, the aminotransferase levels are generally significantly higher in viral hepatitis (typically in the thousands). Because this patient received multiple blood transfusions after her accident, post-transfusion hepatitis cannot be entirely excluded, although the risk of blood-borne infection is extremely low at present. Nevertheless, the appropriate serologic tests should be obtained, including tests for acute hepatitis A (anti-HAV IgM), acute hepatitis B (hepatitis B surface antigen [HBsAg] and anti-HBV core antigen IgM), and acute hepatitis C (HCV RNA), as well as mononucleosis. In the case patient, the serologic results exclude the usual causes of viral hepatitis, and a negative test for mononucleosis also rules out that possibility.

CLINICAL COURSE

Phenytoin is a leading cause of hypersensitivity-related acute hepatocellular injury. The characteristic combination of symptoms, which includes fever, rash, hepatic involvement, and an atypical lymphocytosis, is now called the anticonvulsant or antiepileptic hypersensitivity syndrome. This syndrome occurs in approximately 1 in 3000 patients, generally within the first 2 to 8 weeks after starting therapy. The pathogenesis of the syndrome has been postulated to include a genetic-based inhibition of epoxide hydrolase leading to the inability to

<table>
<thead>
<tr>
<th>Injury Pattern</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST &lt; 300 U/L, ALT &lt; 100 U/L, elevated GGTP</td>
<td>Alcoholic injury</td>
</tr>
<tr>
<td>ALT ≥ AST with values &lt; 1000 U/L</td>
<td>Multiple nonalcoholic causes (viral, drug, nonalcoholic steatohepatitis)</td>
</tr>
<tr>
<td>AST ≥ or ≤ ALT (values &gt;1000 U/L)</td>
<td>Acute hepatocellular injury of various causes (viral, drug, ischemic)</td>
</tr>
<tr>
<td>With LDH:ALT ratio &gt; 1</td>
<td>Acute ischemia</td>
</tr>
<tr>
<td>With LDH:ALT ratio &lt; 1</td>
<td>Viral or drug cause</td>
</tr>
<tr>
<td>Rapid resolution in the presence of gallstones and absence of other causes (≥ increased Alk phos)</td>
<td>Transient gallstone obstruction</td>
</tr>
<tr>
<td>With elevated CPK, LDH</td>
<td>Muscle injury</td>
</tr>
<tr>
<td>AST or ALT values &gt; 7500 U/L</td>
<td>Acute hepatocellular injury usually limited to toxins (APAP, mushrooms) or ischemia (“shock liver”) (Drugs rarely cause ALT &gt; 2000 U/L)</td>
</tr>
</tbody>
</table>

**Table 4. Biochemical Patterns in the Differential Diagnosis of Acute Drug-Induced Liver Disease**

**Acute Hepatocellular Injury**

(Resembles extrahepatic obstruction–like illness with jaundice but bile ducts not dilated)

<table>
<thead>
<tr>
<th>Injury Pattern</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alk phos &gt; 3−10 × ULN; AST/ALT &gt; 2 &lt; 10 × ULN; elevated GGTP</td>
<td>Intrahepatic hepatocanalicular cholestasis (so-called cholestatic hepatitis) (eg, amoxicillin-clavulanate, erythromycin, chlorpromazine)</td>
</tr>
<tr>
<td>Alk phos 1−3 × ULN; AST/ALT 1−8 × ULN</td>
<td>Androgens, estrogens, TPN, sepsis</td>
</tr>
<tr>
<td>Indirect</td>
<td>Drugs (eg, rifampin, novobiocin)</td>
</tr>
<tr>
<td></td>
<td>Gilbert’s syndrome (total bilirubin &lt; 5–6 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Hemolysis (total bilirubin &lt; 5–6 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>Resorbing hematoma</td>
</tr>
<tr>
<td></td>
<td>Multiple transfusions</td>
</tr>
<tr>
<td>Direct</td>
<td>Drugs: anabolic steroids*</td>
</tr>
<tr>
<td></td>
<td>Postoperative cholestasis</td>
</tr>
<tr>
<td></td>
<td>GVHD</td>
</tr>
<tr>
<td></td>
<td>Rotor’s syndrome, Dubin-Johnson syndrome</td>
</tr>
</tbody>
</table>

*Usually associated with elevations in Alk phos and/or aminotransferases.
detoxify arene oxide metabolites according to Shear and colleagues. However, the genetic basis for most DILD has not been established.

Phenytoin has been associated with a significant case fatality rate (up to 50%); in this case, however, the patient makes a gradual recovery over the next few months after the drug is discontinued. Other agents that have been associated with acute hepatocellular injury due to hypersensitivity are listed in Table 2.

**ACUTE HEPATOCELLULAR INJURY: METABOLIC IDIOSYNCRASY–RELATED**

**CASE PRESENTATION**

A 47-year-old Central American woman is started on INH chemoprophylaxis for the finding of a positive purified protein derivative test. Results of baseline LAE testing are normal, as is a chest radiograph, and she is otherwise healthy. She is told to return to the public health clinic on a monthly basis to report any hepatitis-like symptoms but decides to return to her native El Salvador for an extended visit just after starting therapy. She returns 4 months later. She has been taking INH daily and complains of feeling poorly for the past few weeks, with anorexia and fatigue. Laboratory studies reveal an ALT level of 1240 U/L; AST, 1135 U/L; bilirubin (total), 13.6 mg/dL; albumin, 2.7 g/dL; total protein, 5.3 g/dL; and an INR of 1.9. CBC reveals the following: hematocrit, 35%; mean corpuscular volume, 79 µm³; platelet count, 140 × 10³/mm³; with a normal leukocyte count and differential. She is clearly jaundiced on examination, without asterixis. She has mild right upper quadrant tenderness with a palpable liver edge. There is no ascites and no skin rash. She has taken a few ibuprofen caplets over the past few days for a headache but is not taking other medications besides the INH and a multivitamin. She does not know whether she has ever had viral hepatitis but delivered 2 children in the United States, 9 and 12 years ago, and was never informed of any liver problems. An obstetrical ultrasound revealed gallstones, but she has not had any prior biliary symptoms. Her children have been vaccinated for hepatitis B.

**DIFFERENTIAL DIAGNOSIS AND FURTHER WORK-UP**

The differential diagnosis of an acute viral hepatitis–like illness includes the usual viral causes, and in this case, the INH, which should be immediately discontinued. Acute hepatitis A and B are both suspect, but acute hepatitis C is unusual in the absence of a known parenteral exposure or blood transfusion. Rarely, the temporary occlusion of a bile duct followed by the passage of a gallstone is associated with an enzyme pattern reflecting hepatitis rather than extrahepatic biliary obstruction. Autoimmune hepatitis can present as an acute hepatitis, but the absence of hyperglobulinemia in this case makes this diagnosis less likely, pending the results of autoantibody testing.

An abdominal ultrasound shows a few small gallstones without ductal dilation or changes of cholecystitis, and the liver has an inhomogeneous echogenicity...
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that does not reflect fatty infiltration. Results of sero-
logic testing are as follows: HAV-IgM negative, HBsAg
negative, anti-HCV negative, antinuclear antibody neg-
ative. Serum ferritin level is 975 ng/mL.

• What do these test results rule out, and what addi-
tional tests are required?

The serologic test results in this patient rule out
acute hepatitis A and B, even without a negative anti-
core HBV IgM (because HBsAg is absent). Diagnosis of
acute hepatitis C requires a viral load test because the
antibody may not form for several months after an
acute infection. Acute cholecystitis seems unlikely,
based on the abdominal ultrasound, as does autoim-
mune disease.

The most likely cause of the case patient’s liver injury
is the INH. INH-related liver dysfunction characteristical-
ly occurs within 2 to 8 months after starting treatment.25
Patients older than 30 years are at increased risk, as are
those with underlying chronic viral hepatitis B or C.26
Monthly ALT and clinical symptom monitoring should
be performed during INH therapy under current guide-
lines27 as symptoms alone are nonspecific and once
symptoms or jaundice are present, significant hepatic
dysfunction has already occurred. Modest elevations in
ALT values (to < 3 times the upper limit of normal) are
seen in 10% to 20% of patients, but these abnormalities
often regress or normalize on continued treatment.25
ALT values that rise above 200 U/L should prompt
immediate discontinuation of the drug as there is a risk
of severe hepatic injury at that level, including liver fail-
ure in 1% to 4% of patients. Indeed, INH is one of the
leading causes of non–acetaminophen-related acute
liver failure3,7 as is pyrazinamide, which has been
removed from the Center for Disease Control and Pre-
vention’s list of prophylactic anti-TB agents due to its
high risk of severe hepatotoxicity.28

CLINICAL COURSE

Because this patient does not demonstrate enceph-
alopathy and her LAE levels and INR begin to normal-
ize on conservative management over the next few
weeks, her prognosis for recovery is excellent. Because
the reduction in bilirubin often lags behind the fall in
aminotransferases after acute hepatocellular injury, how-
ever, jaundice may persist. Should a patient not steadily
improve clinically and biochemically, early referral to a
liver transplant center is essential. Falling ALT and AST
values in the setting of developing or worsening enceph-
alopathy, jaundice, coagulopathy, and/or renal failure
are harbingers of irreversible liver failure.

AUTOIMMUNE HEPATITIS

CASE PRESENTATION

A 19-year-old student is started on minocycline
100 mg daily for severe acne. Fifteen months later, she
presents with several weeks of arthralgias in multiple
joints, low grade fevers, malaise, fatigue, nausea, right up-
per quadrant discomfort, and dark urine. The student
health service physician thought she may have mono-
nucleosis, but the heterophile test returned as negative.
In the meantime, she continued to feel poorly with wors-
ening polyarthralgias, anorexia, nausea, and jaundice.
She has no history of blood transfusions or herbal drug
use. LAEs are as follows: ALT, 520 U/L; AST, 350 U/L;
alkaline phosphatase, 110 U/L; bilirubin, 4.3 mg/dL.
Serologic results are negative for HBsAg, anti-HCV, and
HAV-IgM. Her antinuclear antibody (ANA) titer is 1:320
(homogeneous pattern) and she is anti–smooth muscle
antibody negative. CBC results were normal, including
the differential, and her INR was 1.2.

• What is the differential diagnosis in this case?

DIFFERENTIAL DIAGNOSIS

Viral hepatitis may present with the constitutional
symptoms described in this case but is excluded by the
negative serology. Most drugs are not considered a likely
cause of acute hepatotoxicity when they have been
taken for more than 9 to 12 months without evidence of
liver injury. However, minocycline is one of a number of
agents that have been implicated in causing chronic
hepatitis with autoimmune features that may occur after
extended use19 (Table 7). Three separate clinical presen-
tations have been observed with minocycline: a relatively
rare, rapid onset, serum sickness–like illness associated
with fever, myalgias, arthralgias, and rash occurring after
a mean of 15 days following administration; a more
common hypersensitivity syndrome with exfoliative der-
matitis and eosinophilia that occurs with 3 to 4 weeks of
exposure; and, the most common presentation, a chronic,
drug-induced lupus–like syndrome with jaundice,
malaise, polyarthralgia, fever, and the presence of auto-
antibodies (usually ANA) that appears after a year or
more of minocycline administration.29–31 On liver biop-
sy, typical autoimmune features are seen, including a
dense portal lymphoplasmacytic infiltrate with a marked
interface hepatitis. Women younger than 40 years are
most susceptible, with a latent period that is approxi-
mately half as long as that reported in men.
**CLINICAL COURSE**

Most cases of minocycline-related hepatic injury resolve after the drug is discontinued. Corticosteroid or other immunosuppressive therapy is required in patients with severe symptoms or in whom the hepatitis fails to improve after the drug is stopped.31 In the present case, minocycline was stopped and prednisone 40 mg daily was started and she became asymptomatic 2 weeks later. LAE levels were markedly decreased 6 weeks later. A steroid taper was instituted, and the prednisone was stopped after 3 months when the LAEs normalized. Although a sustained remission is likely, re-institution of immunosuppressive therapy would be needed should the syndrome recur off prednisone.19

**STEATOHEPATITIS**

**CASE PRESENTATION**

A 52-year-old woman was placed on tamoxifen 2 years ago following a lumpectomy and chemotherapy for breast carcinoma. She is referred for evaluation of ALT and AST values that have been mildly elevated for the past 2 years but have recently started to elevate further. She admits to regularly drinking wine with dinner for several years and takes a number of vitamins, including E, C, B complex, and thiamine. She takes small doses of acetaminophen or ibuprofen as needed for occasional headaches. Her recent laboratory tests show an ALT level of 122 U/L, AST of 84 U/L, total bilirubin of 0.8 mg/dL, and alkaline phosphatase of 78 U/L. Results of her CBC are normal as is the INR. Ultrasound reveals an enlarged liver with echogenicity consistent with fatty infiltration. No focal liver lesions are seen, and the rest of the examination results are normal. Her family physician has advised her to cease drinking all alcohol and to avoid acetaminophen.

- Has the patient been given sound advice regarding alcohol and acetaminophen ingestion?

**DIFFERENTIAL DIAGNOSIS AND FURTHER WORK-UP**

Alcohol-related liver injury is one of the most common causes of acute and chronic hepatic disease and is associated with a very characteristic biochemical injury pattern: the AST is always 2 to 3 times higher than the ALT and, in contrast to other causes of liver disease, there are strict upper limits to the elevations—300 U/L for AST and 100 U/L for ALT. Values that do not conform to these levels and to a AST:ALT ratio of 2:1 or 3:1 can be reliably excluded as being due to alcohol alone, and other causes should be sought. Other examples of drugs causing steatohepatitis are listed in Table 3. In the case patient, tamoxifen-related fatty liver is likely, based on the ratio of ALT to AST and on the ultrasound findings. The normal alkaline phosphatase level helps exclude hepatic or bony metastases.

**CLINICAL COURSE AND LONG-TERM MANAGEMENT**

Although the case patient has nonalcoholic steatohepatitis, there is no evidence that small doses of acetaminophen or ibuprofen are harmful in this setting. Indeed, most potential hepatotoxins are not any more likely to cause liver injury in patients with underlying liver disease than in those without.35 Regular ingestion of alcohol is generally admonished in any form of liver disease, although an occasional alcoholic beverage can be permitted. However, the risk of drug-induced steatosis and steatohepatitis from agents such as methotrexate and tamoxifen may be even higher in the setting of regular alcohol use.1,15

Although fibrosis can occur with prolonged use of tamoxifen, the injury is usually reversible after the

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**Table 7. Categories of Drug-Induced Autoimmune Chronic Hepatitis**

<table>
<thead>
<tr>
<th>Causative Drugs</th>
<th>Serology</th>
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</thead>
<tbody>
<tr>
<td><strong>I: Syndrome resembling autoimmune hepatitis type 1</strong></td>
<td></td>
</tr>
<tr>
<td>Clomethacin</td>
<td>ASMA, Anti-DNA</td>
</tr>
<tr>
<td>Methyl dopa</td>
<td>ANA (16%), ASMA (35%)</td>
</tr>
<tr>
<td>Minocycline</td>
<td>ANA, Anti-DNA</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>ANA (80%), ASMA (72%)</td>
</tr>
<tr>
<td>Oxyphenisatin</td>
<td>ANA (67%), ASMA (67%)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>ANA</td>
</tr>
<tr>
<td><strong>II: Syndrome resembling autoimmune hepatitis type 2 or acute hepatitis</strong></td>
<td></td>
</tr>
<tr>
<td>Dihyralazine</td>
<td>Anti-CYP1A2</td>
</tr>
<tr>
<td>Tienilic acid (ticrynafen)</td>
<td>Anti-CYP2C9</td>
</tr>
<tr>
<td>Halothane</td>
<td>Anti-carboxyesterase</td>
</tr>
<tr>
<td></td>
<td>Anti–protein disulfide isomerase</td>
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<tr>
<td>Iproniazid</td>
<td>AMA6</td>
</tr>
<tr>
<td><strong>III: Syndrome with histology of chronic hepatitis but no serologic markers</strong></td>
<td></td>
</tr>
<tr>
<td>Etretinate</td>
<td>—</td>
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<tr>
<td>Lisinopril</td>
<td>—</td>
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<tr>
<td>Sulphonamide</td>
<td>—</td>
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<tr>
<td>Trazodone</td>
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</tbody>
</table>


AMA6 = antimicrosomal antibody-6; ANA = antinuclear antibodies; ASMA = anti–smooth muscle antibodies.
Prevalence of Subclinical Liver Enzyme Elevations

**Table 8. Prevalence of Subclinical Liver Enzyme Elevations for Various Drugs**

<table>
<thead>
<tr>
<th>Prevalence (%)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–50</td>
<td>Tacrine</td>
</tr>
<tr>
<td>20–25</td>
<td>Chlorpromazine, triacetyloleandomycin, phenytoin, amidarone, perhexiline, papaverine, cispalatin, nicotinic acid, valproic acid, 6-mercaptopurine</td>
</tr>
<tr>
<td>10–20</td>
<td>Isoniazid, ketoconazole, androgens, erythromycin estolate, etretinate, ximelagatan</td>
</tr>
<tr>
<td>5–10</td>
<td>Penicillamine, chenodeoxycholate, fluycytosine, disulfiram, most nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>Stacins, salicylates, gold salts, sulfonamides, dantrolene, sulfonylureas, quinidine, thiabendazole, ticarcillin, ethionamide, tricyclic antidepressants</td>
</tr>
</tbody>
</table>


...drug is discontinued. In many instances, tamoxifen can be continued despite mild elevations in AST and ALT if the benefits appear to outweigh the risks, so long as the LAEs remain nonprogressive and asymptomatic and hepatic synthetic function remains normal. Liver biopsy is helpful in determining whether hepatic injury (ie, fibrosis) is progressing in cases in which the drug needs to be continued.

**SUBCLINICAL AMINOTRANSFERASE ELEVATIONS**

**CASE PRESENTATION**

A 58-year-old man is started on lovastatin for hypercholesterolemia. He is approximately 25 lb overweight and has prediabetes that is diet controlled. He often has a cocktail after work, wine with dinner, and beer on the weekends. His baseline LAE levels are normal, and he is instructed by his primary care physician to return in 4 to 8 weeks for follow-up. His repeat laboratory tests show a modest reduction in low-density lipoprotein cholesterol, but his ALT level has risen from 32 U/L pretreatment to 58 U/L (normal < 40 U/L). His AST level remains high-normal, at 36 U/L. Three weeks later, his ALT is 64 U/L and his AST is 42 U/L. His bilirubin, alkaline phosphatase, and CBC remain normal. He is asymptomatic but is referred for evaluation.

**DIFFERENTIAL DIAGNOSIS AND FURTHER WORK-UP**

Many drugs are associated with so-called “drug tolerance”—mild to moderate, clinically asymptomatic elevations in aminotransferases that do not appear to progress despite continuing the drug (Table 8). In some instances, the elevations normalize on therapy. Although the actual mechanism of tolerance is not known, it is thought to involve the release of cytokines or other substances that prevent more severe hepatotoxicity from occurring as many of these agents also are rarely associated with instances of fulminant liver failure (eg, INH, nicotinic acid, disulfiram, ketoconazole).

In general, when faced with new-onset mild LAE elevations in the absence of signs of acute hepatitis or other symptoms, it is important to know whether any drugs being prescribed are associated with either liver disease or subclinical LAE elevations and to determine whether any other cause can be identified. A decision also needs to be made regarding continuing or stopping the drug in question.

The author’s approach in the case patient would be to determine the trend of the LAE elevations along with obtaining an INR, platelet count, and albumin and globulin levels to help determine the presence or absence of hepatic synthetic impairment. A physical examination looking for signs of chronic liver disease (ie, cirrhosis, portal hypertension) and an abdominal ultrasound to look for hepatic steatosis or other abnormalities offer additional diagnostic clues (especially in a case such as this, in which the differential diagnosis includes alcoholic liver disease or nonalcoholic steatohepatitis as part of the metabolic syndrome). Obtaining baseline serology for chronic hepatitis C (anti-HCV) and B (HBsAg) is not unreasonable because they may be present in the absence of LAE elevations. As the patient does not appear to have rapidly rising ALT or AST levels, there is no reason at this point to look for acute viral hepatitis.

Tests for other metabolic and autoimmune causes of liver disease (eg, hemochromatosis, autoimmune hepatitis, Wilson’s disease, α1-antitrypsin deficiency, celiac sprue) are often included in an initial assessment of patients with subclinical LAE elevations as part of a “shotgun” approach to making a diagnosis, but these tests should be more carefully considered. For example, Wilson’s disease presenting after age 40 years is unusual, and the absence of any antecedent abnormal LAE test results makes hemochromatosis, autoimmune hepatitis, and α1-antitrypsin deficiency unlikely. Similarly, the de novo appearance of mild LAE elevations without any prior history of malabsorption, diarrhea, or iron deficiency anemia puts celiac disease extremely low on the list. The fact that his ALT level is higher than the AST level excludes alcohol as the cause.

**CLINICAL COURSE**

In the present case, the abdominal ultrasound is
reported as showing changes consistent with mild fatty infiltration of the liver, and serology results for hepatitis B and C are negative. He is told to limit his alcohol intake and repeat the LAE tests in 1 month while continuing the lovastatin. One month later, his ALT and AST levels are down to 45 U/L and 29 U/L respectively, although steatohapatitis as part of the metabolic syndrome has not been entirely excluded. He is told to return in another 4 to 6 weeks. On that occasion, he continues to be asymptomatic, his cholesterol is significantly improved, and the LAE results continue to normalize, confirming that this is likely an example of drug tolerance to the lovastatin.

- How long should LAE monitoring be continued in patients with drug-related subclinical LAE elevations?

The question of how best to monitor ALT and other markers of liver function in a patient with a risk of developing severe DILD has not been fully answered. Serial monitoring is a controversial recommendation because physicians are often reluctant to burden patients with the inconvenience and added cost of performing serial biochemical tests in the absence of data that prove such monitoring can effectively prevent acute drug-induced liver failure. It may seem clinically prudent to monitor ALT; the US Food and Drug Administration recommends such monitoring in the labeling of many drugs, and a working group of the American Association for the Study of Liver Diseases recommends monitoring as one means to prevent acute liver failure. Nevertheless, there are few—if any—studies that can be cited as demonstrating the unequivocal effectiveness of such measures. Theoretically, it should be possible to identify patients with progressively rising ALT levels and thus stop the offending drug in time to prevent further progression of liver injury, but even with recognized hepatotoxins, compliance with monitoring is often unacceptably low.

When monitoring is implemented, the frequency of testing should take into account the time that it usually takes to develop irreversible liver failure from a drug. In general, monthly lab tests are recommended; testing at less frequent intervals is often the equivalent of no monitoring at all. The predicted frequency and severity of developing acute drug-induced liver failure should also be taken into account. For example, the risk of developing fulminant hepatic failure from INH, pyrazinamide, and several other hepatotoxins is substantially greater than the risk of injury that drugs such as statins are thought to pose. Indeed, monitoring ALT values during statin therapy is not widely applied and even in the presence of stable underlying liver disease may not be necessary in all cases. Perhaps a simple finger-stick test for ALT (akin to home glucose monitoring) would improve compliance and cost-effectiveness of biochemical monitoring, if and when such a test becomes available. For now, clinical judgment and vigilance regarding the prevention of DILD using the tools at our disposal remain of paramount importance.

### PRINCIPLES OF CAUSALITY ASSESSMENT IN DILD

The ability to confidently diagnose DILD implies that the latency period, biochemical injury pattern, clinical features, and histologic appearance (if a liver biopsy has been done) are consistent with known reports of hepatotoxicity previously described with the agent and that all other reasonably possible causes have been excluded. When no other reports can be found, especially for a drug that has been marketed for a considerable period, it is even more important that all confounding factors be eliminated. The index of suspicion is necessarily lower for newly approved or marketed drugs in which the frequency and spectrum of hepatic injury have not yet been defined.

In the absence of acute drug allergy–associated features (eg, fever, rash, eosinophilia), acute hepatic injury from a drug acting through a toxic metabolite after only 1 or 2 doses or after the drug had been taken without problems for more than 12 months is rare. The presence of underlying liver disease (eg, hepatitis B or C) is a potential risk factor for hepatotoxicity for a relatively limited number of drug classes (notably highly active antiretroviral treatment and anti-TB agents). For most other drugs, no added risk of liver injury is anticipated. In some cases, however, the underlying chronic liver disease may make diagnosing acute (or chronic) DILD more difficult.

The most frequently used diagnostic test to determine causality of acute hepatic injury is known as a positive de-challenge—the finding that elevated LAEs decline and return to normal (usually within a few months) after the suspected offending drug is discontinued. Readministration of the suspected drug is rarely done after a positive de-challenge because of the risk of precipitating an even more rapid, more serious hepatic reaction, especially if there is any possibility that immunologic mechanisms are responsible. In the absence of any alternative therapies and under close clinical scrutiny, attempts at rechallenge should be conducted to determine if the drug is, in fact, responsible. However, the response in such circumstances may be equivocal because the results of rechallenge from drugs acting through metabolic idiosyncrasy are often quite variable and of limited clinical value. Because it is often not possible to predict
which patient may go on to develop fulminating hepatic failure, the best rule of thumb when faced with a possible diagnosis of acute DILD is to stop the drug immediately if the patient has any associated hepatic symptoms or jaundice or if the ALT exceeds 5 times the upper limit of normal. The risk of fatal necrosis or need for emergency liver transplant from acute hepatocellular injury with jaundice is at least 10%, and the prevention of irreversible hepatitis should always be the main goal of management.

REFERENCES