Evaluating Patients With Mildly Elevated Transaminase Levels

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Case Study: S.B. is a 52-year-old woman with recurrent stage IV ovarian cancer. She initially presented three and a half years ago with complaints of abdominal pain, increased abdominal girth, and abdominal bloating. A CA-125 blood test was elevated, and a computed tomography scan of the abdomen and pelvis revealed bilateral ovarian masses highly suspicious for malignancy. She was taken to surgery for a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and suboptimal tumor reduction. Pathology revealed poorly differentiated papillary serous ovarian cancer. Metastatic disease was noted in the rectosigmoid area and vaginal apex. Postoperatively, she received six cycles of paclitaxel and carboplatin. At completion, her CA-125 normalized and imaging studies showed no evidence of disease. However, within three months, her CA-125 was elevated and a palpable mass at the vaginal apex was proven by biopsy to be recurrent disease.

S.B. presented to a cancer center for further treatment recommendations. She received vaginal radiation and then enrolled in a clinical trial and received carboplatin, sargramostim (granulocyte macrophage–colony-stimulating factor [GM-CSF]), and interferon gamma-1b. After five cycles of chemotherapy, S.B.’s serum alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) were mildly elevated (less than five times the upper limit of normal) and she had vague complaints of right-side abdominal soreness. Her treatment was delayed for two weeks, and she ultimately was removed from the clinical trial and placed on single-agent carboplatin. S.B. now presents to the clinic for a chemotherapy appointment and is complaining of weight gain, fatigue, and persistent right-side abdominal soreness. Physical examination reveals mild tenderness in her right upper quadrant but no hepatosplenomegaly. Laboratory evaluation reveals persistent, mildly elevated transaminase levels, as well as elevated serum lipids. S.B.’s medical history is significant for hypertension, hypothyroidism, and sarcoidosis. She denies any history of substance abuse, including alcohol and drugs. She denies tobacco use. Her family history is unremarkable.

Abnormal laboratory results noted during routine follow-ups or screening visits can be perplexing to healthcare providers. Clinicians are responsible for interpreting and addressing abnormal results to provide superior and cost-effective health care. All laboratory tests have a range of normal values, defined as the average value in a group of healthy individuals plus or minus two standard deviations. Five percent of individuals have laboratory values that fall either 2.5% above or 2.5% below the limits of normal (Pratt & Kaplan, 2000). Normal laboratory values vary according to a number of physiologic factors, such as age, gender, blood group, and postprandial states, as well as other contributing factors, such as pregnancy (Green & Flamm, 2002). Therefore, providers must be aware of such factors with all patients. Serum liver enzymes can be elevated in as many as 6% of the American population in the absence of any real liver pathology (Green & Flamm).

Many healthcare providers order serum liver enzymes as part of routine physical examination. Serum liver studies often are called “liver function tests”; however, standard liver chemistries do not measure how a liver actually is functioning. The tests can detect hepatocellular injury, intra- or extrahepatic cholesterol, infiltrating diseases of the liver, impairment of hepatic synthesis, and alterations in liver metabolism (Green & Flamm, 2002).
The transaminases, AST and ALT, are enzymes responsible for key hepatic metabolic processes. Both are released into the bloodstream in the presence of hepatocellular injury or death. ALT is found predominantly in the liver, whereas AST also is abundant in the heart, skeletal muscle, and blood (Green & Flamm, 2002). Transaminase measurements lack sensitivity and specificity in detecting chronic liver injury. Patients with cirrhosis often have normal or only slightly elevated transaminase levels because low levels of the enzymes are released with chronic injury. Specificity also is reduced because the enzymes are present in skeletal muscle and can rise in response to muscle injury or severe exertion (Johnston, 1999).

Alkaline phosphatase is an enzyme synthesized by the liver, bone, intestines, and placenta. Elevations of alkaline phosphatase are seen in a variety of conditions, including cholestasis, biliary abnormalities (e.g., bile duct obstruction), pregnancy, bone disease, medication reactions, and acute hepatitis. Primary biliary cirrhosis and primary sclerosing cholangitis are conditions in which the microscopic intrahepatic and large extrahepatic bile ducts become fibrotic or narrowed, respectively (Askey, 2006). Infiltrative diseases of the liver parenchyma, such as sarcoidosis, granulomatous diseases, and liver metastasis also cause elevations in alkaline phosphatase. Patients with these diseases typically have minimal or no rise in serum ALT or AST (Green & Flamm, 2002).

Serum albumin and prothrombin, usually seen in conjunction with international normalized ratio (INR), are proteins made by the liver. Although measurements of serum albumin and prothrombin do not evaluate liver function specifically, they are used to assess the severity of liver damage and liver function in patients with acute or chronic liver disease (Askey, 2006).

Serum levels of enzymes 5'-nucleotidase and γ-glutamyltransferase (GGT) are used in conjunction with alkaline phosphatase to confirm liver-related disorders. When an elevation of serum 5'-nucleotidase or GGT is associated with an elevation of serum alkaline phosphatase, the liver is identified as the etiology of the disease (Green & Flamm, 2002).

Bilirubin is a byproduct of the breakdown of red blood cells. The conjugation process from indirect to direct bilirubin is via the splenic and portal veins to the liver, where bilirubin is conjugated, becomes water soluble, and is transported rapidly into bile. Elevated direct bilirubin indicates cholestasis, and alkaline phosphatase and GGT also are elevated. Many healthy people have mildly elevated indirect bilirubin; however, almost no detectable conjugated bilirubin is present in the serum of people with normal hepatic function.

Clinical Evaluation

Repeating laboratory testing is an important step in the evaluation process; repetition will confirm an abnormality and prevent the anxiety and cost associated with unnecessary workups. Remember, however, that normal repeat laboratory results do not exclude the possibility that liver disease is present. For example, patients with hepatitis C may have transaminase levels that fluctuate between normal and abnormal (Giannini, Testa, & Savarino, 2005; Green & Flamm, 2002).

A mild or minimal transaminase elevation, defined as less than five times the upper limit of normal, is the most common laboratory abnormality in routine clinical practice (Giannini et al., 2005). Many factors can contribute to transaminase elevations (see Figure 1); therefore, obtaining a thorough history is vital. A history should include symptoms, concomitant medical conditions, illicit drug use (e.g., anabolic steroids, cocaine, ecstasy), occupational exposures, alcohol use, family history, and current medications. The presence of other illnesses, such as thyroid disease, heart disease, muscle disease, or diabetes, should be assessed because such conditions can cause or contribute to transaminase elevations.

All medication use, including prescriptions, herbal remedies, over-the-counter drugs, and vitamins, should be assessed (American Gastroenterological Association, 2002). Common medications associated with elevated transaminase levels are listed in Figure 2. Consider a patient’s current cancer therapy. Many antineoplastic drugs, such as docetaxel, gefitinib, gemcitabine, imatinib mesylate, interferons, interleukin-2, irinotecan, methotrexate, oxaliplatin, and others, may cause a rise in liver enzymes. The elevation often is transient and resolves with discontinuation of therapy (Battiato & Wheeler, 2005; Camp-Sorrell, 2005).

Hepatic steatosis or steatohepatitis (fatty liver infiltration), with or without associated inflammation, may be the most common cause of mild transaminase elevation. Nonalcoholic fatty liver disease (NAFLD) refers to a wide spectrum of disease, ranging from simple fatty liver (steatosis), which usually is benign, to steatosis with inflammation and hepatocyte necrosis (nonalcoholic steatohepatitis [NASH]) to cirrhosis (Adams & Talwalkar, 2006; Bayard, Holt, & Boroughs, 2006).

NAFLD is a major cause of liver disease, affecting approximately 30% of adults and 20% of children in the United States (McCullough, 2006). Patients often have characteristics associated with metabolic syndrome, such as obesity, diabetes, hyperlipidemia, hypertension, and insulin resistance, so the disease should be considered when those risk factors are present (Adams & Angulo, 2006; Marchesini et al., 2003). Secondary factors that may cause NAFLD include exposure to toxins, medications, total parenteral nutrition, gastric bypass surgery, and others (Bayard et al., 2006).

NAFLD is a diagnosis of exclusion and requires evidence of fatty infiltration in the absence of excessive alcohol ingestion. Excess alcohol consumption also can cause mild transaminase elevations. Alcohol-related injury includes hepatic steatosis, hepatitis, and cirrhosis. The histologic similarities between NAFLD and alcoholic liver disease may be difficult to
distinguish. Likewise, NASH resembles alcoholic steatohepatitis.

Therefore, healthcare professionals should assess alcohol use accurately. Question patients about the quantity of alcohol they consume and the length of time that they have been drinking. Verify patients’ stated alcohol consumption by asking family members. Most reports define excessive alcohol consumption as greater than seven drinks per week (70 g of total alcohol) for women and greater than 14 drinks per week (140 g alcohol) for men (Adams & Talwalkar, 2006; Liou & Kowdley, 2006).

Alcohol abuse should be considered in patients presenting with a high AST:ALT ratio. ALT is more specific to the liver and, therefore, usually rises more than AST in response to liver injury or steatosis. One exception is with alcoholic hepatitis, when AST:ALT usually is greater than 2:1. In fact, the higher the AST:ALT ratio, the greater the likelihood that alcohol is contributing to the abnormal elevation (Johnston, 1999).

Chronic viral hepatitis is another common cause of elevated transaminase levels. Patients should be questioned about risk factors such as IV or intranasal drug use, a history of blood transfusions, exposure to nonsterile needles (e.g., body piercing, tattoos), and sexual exposures. Because of the high prevalence of hepatitis infections, testing should be considered for all patients, including those with no reported risk factors.

Several uncommon illnesses also are known to cause mild transaminase elevations. Autoimmune hepatitis is more prevalent in women and should be considered in patients with a history of autoimmune thyroiditis and connective tissue disorders (Green & Flamm, 2002).

Hereditary hemochromatosis (iron overload) is an autosomal recessive condition characterized by pathologic deposition of iron. Wilson disease (copper overload), another autosomal recessive condition, has associated neuropsychiatric symptoms along with copper deposition in hepatic tissue.

Patients should be questioned about specific symptoms, although most patients with mildly elevated transaminase levels are asymptomatic. The most common symptom is nonspecific right upper-quadrant discomfort. Other symptoms may include fatigue, weight loss or gain, easy bruising, and fluid retention (Adams & Talwalkar, 2006).

Physical Examination

A thorough physical examination should be performed, with a focus on the abdomen. Assess for pain upon palpation of the liver and spleen, organomegaly, jaundice, bruising, collateral veins, ascites, and generalized edema. An abnormal liver may feel firm or hard and blunt on percussion. Irregularity of liver contour suggests an abnormality, and further workup is warranted (Bickley, 1999).

Diagnostic Workup

Decisions regarding the order of appropriate tests should be based on each patient. Additional testing, which includes extensive serologic, radiologic, and pathologic evaluation, can be costly. The whole clinical picture must be evaluated carefully. The likelihood that a patient actually has liver disease as well as the possible cause should be considered. Although altered liver chemistries may not indicate disease, prompt diagnosis and therapy can help to prevent the progression of end-stage liver disease.

Laboratory evaluation begins with a complete blood count (CBC) with differential and platelets, prothrombin time (PT), and serum albumin. Alkaline phosphatase and bilirubin also should be ordered initially to assess for hepatic cholestasis, although they often are normal in patients with hepatic injury. Thyroxine (T4) and thyroid-stimulating hormone should be checked to exclude thyroid disease as a contributing factor.

No blood test is available to confirm the diagnosis of NAFLD (Green & Flamm, 2002). However, serologic evaluation is important to rule out other common causes of mild transaminase elevation. Serology should be ordered to rule out acute and chronic hepatitis. Order a hepatitis B surface antigen (also called HbsAg), hepatitis B core immunoglobulin M (i.e., IgM) antibody, and hepatitis C (HCV) antibody. If hepatitis C infection is suspected and the HCV antibody is negative, HCV-RNA measurement may establish the diagnosis.

Patients without common explanations for transaminase elevations can be evaluated for rare causes. Order serum ferritin, iron, and total iron-binding capacity (TIBC) to assess for hemochromatosis. Wilson disease can be identified via assessment of serum ceruloplasmin, serum copper, and 24-hour urine for copper. Patients with suspected autoimmune hepatitis should have autoantibodies tested: antinuclear, anti-smooth-muscle, and anti-liver-kidney microsomes (Giannini et al., 2005).

Radiologic imaging can be used to visualize the hepatic parenchyma and is most valuable in identifying mass lesions, cholestasis, and extrahepatic conditions. Elective radiologic testing may confirm the presence of hepatic steatosis. Ultrasound, computed tomography, and magnetic resonance imaging are options. Ultrasound is the least expensive and easily available in most facilities; however, it is less sensitive in detecting minimal steatosis (Adams & Talwalkar, 2006).

The need for liver biopsy should be decided on an individual basis. Biopsy may be considered for patients with chronic transaminase elevations (longer than six months) and for those in whom diagnosis is uncertain. The gold standard for the diagnosis of NAFLD is liver biopsy (Adams & Angulo, 2006; Cortez-Pinto, de Moura, & Day, 2006). Imaging studies cannot distinguish steatosis from steatohepatitis or stage the degree of liver fibrosis. Biopsy can confirm diagnosis, assess degree of inflammation and presence of fibrosis or cirrhosis, and provide prognostic information.
Treatment Options

Treatment is based on identified etiology of disease. If initial serologic testing is negative and a patient is asymptomatic, lifestyle modifications may be recommended with clinical follow-up and repeated measurement of serum transaminase levels at specified intervals. Lifestyle modifications alone, such as abstaining from alcohol consumption, controlling diabetes and hyperlipidemia, losing weight, and stopping or changing potentially hepatotoxic medications and supplements, may correct abnormalities. Patients should discontinue all nonessential medications.

The most important treatment strategy is to remove or treat the identified cause of disease, which is important to prevent disease progression. Simple nonalcoholic fatty livers are benign; however, NAFLD and NASH can be progressive and may result in end-stage liver disease. Recommended lifestyle changes are diet modification (reduction in saturated fat, trans fat, and cholesterol), weight loss (to body mass index less than 25 kg/m²) if indicated, exercise (at least 30 minutes of moderate-intensity activity on most days), and limited alcohol intake. Diabetes and hypercholesterolemia, if present, should be managed optimally (Clark, 2006; Giboney, 2005; Solga et al., 2004). The first step in treatment should focus on weight loss, followed by pharmacologic treatment of insulin resistance. Both approaches will help to prevent progression of NAFLD and NASH (Cortez-Pinto et al., 2006).

Metabolic syndrome can predispose people to NAFLD and NASH. Management of this syndrome includes pharmacotherapy. Metformin, rosiglitazone (Avandia®, GlaxoSmithKline), and statin medications reduce elevated liver enzymes and improve hepatic steatosis. Statins may cause transaminase elevations. Close monitoring is warranted, and discontinuation of particular medications may be necessary (Bayard et al., 2006).

Case Study Follow-Up

S.B.’s workup included serologic screening (TIBC, serum iron, T4, CBC, PT, and partial thromboplastin time). Her infectious disease panel for hepatitis was nonreactive. Additional laboratory testing, anti-nuclear antibody, anti-smooth-muscle antibody, and anti-mitochondrial antibody were performed to rule out an autoimmune process. All of the tests were negative. Her remaining laboratory work was significant for elevated serum cholesterol. A computed tomography scan of her abdomen and pelvis was negative except for mild fatty liver infiltration.

A liver biopsy was performed to exclude the possibility of sarcoidosis. Pathology showed perportal and lobular hepatitis, moderate to severe macrovascular steatosis, and periporal fibrosis with some focal bile duct injury. No iron deposition or metastatic tumor was identified. The overall impression was NASH, although the liver fibrosis may have been drug induced. The component of drug toxicity most likely was related to the protocol therapy.

Lifestyle changes were recommended. S.B. received nutrition counseling and was advised to begin a regular exercise program. She also was placed on oralatorvastatin calcium (Lipitor®, Pfizer Inc.) 20 mg daily. During that time, she continued therapy for recurrent ovarian cancer with single-agent carboplatin. Her ALT and AST returned to normal in about seven months.

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References