

SYMPTOMS TO DIAGNOSIS

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Elevated aminotransferases in a 62-year-old woman

A 62-YEAR-OLD WOMAN made an appointment to see her primary care physician after returning from a trip to Malaysia. She had experienced a few days of constant right-upper-quadrant abdominal pain while traveling home. The pain had worsened with taking deep breaths and was not instigated by food intake. She also had nausea. By the time of her appointment, 4 weeks after the episode, the symptoms had resolved. She reported no hematochezia, melena, shortness of breath, chest pain, muscle weakness, jaundice, weight loss, or loss of appetite.

The patient had no history of tobacco, alcohol, or illicit drug use. Her medical history included gastroesophageal reflux disease and Sjögren syndrome, diagnosed 10 years earlier based on positive SS-A and SS-B antibody tests, along with symptoms of dry eyes and dry mouth. Her only medications were artificial tears and omeprazole. She also took a multivitamin, a vitamin C supplement, and flaxseed oil. Both parents had hypertension, and her father had type 2 diabetes. She had no history of surgery.

INITIAL EVALUATION AND MANAGEMENT

At the primary care visit, the patient's temperature was 97.6°F (36.4°C), heart rate 72 beats per minute, blood pressure 104/62 mm Hg, respiratory rate 18 breaths per minute, weight 64 kg (141 lbs), and body mass index 25.4 kg/m². She was comfortable, alert, and oriented. Her lungs were clear to auscultation, with no wheezing or crackles. Heart rate and rhythm

were regular with no extra heart sounds or murmurs. She had no pain on palpation of her abdomen, and there was no organomegaly.

Laboratory test results

Notable results of blood testing as part of the routine examination were as follows:

- White blood cell count $3.7 \times 10^9/L$ (reference range 4.5–10.8)
- Hemoglobin 13 g/dL (12.3–15.3)
- Hematocrit 39% (38–48)
- Mean corpuscular volume 90 fL (80–100)
- Platelet count $277 \times 10^9/L$ (130–400)
- Alkaline phosphatase 58 U/L (40–129)
- Aspartate aminotransferase (AST) 213 U/L (0–32)
- Alanine aminotransferase (ALT) 120 U/L (0–33)
- Total bilirubin 0.8 mg/dL (0.1–1.2)
- Gamma-glutamyl transferase 91 U/L (28–100)
- Lipase 14 U/L (5–36)
- Right-upper-quadrant ultrasonography: normal-appearing liver.

DIFFERENTIAL DIAGNOSIS

1 Which of the following initial considerations might explain this patient's elevated aminotransferase levels?

- ☐ Alcohol use
- ☐ Nonalcoholic fatty liver disease (NAFLD)
- ☐ Autoimmune hepatitis
- ☐ Viral hepatitis

Alcohol-related liver disease

Both AST and ALT can be elevated in alcoholic liver disease, although levels are often less than 300 U/L and rarely exceed 500 U/L.¹ The ratio of serum AST to ALT (the De Ritis ratio) can help differentiate var-

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ious causes of liver disease.^{2,3} The ratio in patients with alcoholic liver disease, ranging from cirrhosis to alcoholic hepatitis (which results from chronic, heavy consumption of alcohol), is typically greater than 1.5.¹ The increase in AST relative to ALT with heavy alcohol users is attributed to both of the following:

- Vitamin B6 depletion, which reduces activity of ALT to a greater extent than that of AST
- Mitochondrial damage resulting from alcohol and leading to release of AST.²

Our patient's AST was higher than her ALT, but she denied alcohol use, and her gamma-glutamyl transferase, typically elevated in alcohol-related liver disease, was normal.² Unless she was drinking surreptitiously, alcohol-related liver disease is unlikely to explain her aminotransferase elevations.

Nonalcoholic fatty liver disease

NAFLD is increasingly common, reflecting the rising prevalence of obesity. In patients with obesity, excess adipose tissue is deposited in the liver, leading to oxidation of fatty acids, subsequent inflammation (non-alcoholic steatohepatitis), and eventually cirrhosis in some patients.⁴ Patients who have obesity with other features of metabolic syndrome such as type 2 diabetes or dyslipidemia are at risk for this condition.⁴ In patients with NAFLD, AST and ALT can be normal or elevated to a mild to moderate degree. The AST-ALT ratio is commonly less than 1 but can increase to greater than 1 in the presence of advanced fibrosis.⁵ Our patient had no risk factors for NAFLD such as obesity, diabetes, or hyperlipidemia.

Autoimmune hepatitis

Autoimmune hepatitis, caused by an unregulated immunologic attack on hepatocytes, can present as acute liver failure or chronic indolent disease.⁶ The condition has a predilection toward females and can occur at any age.⁶ At one end of the spectrum, patients can be asymptomatic with mild elevation in aminotransferases (< 5 times the upper limit of normal).⁶ At the other end of the spectrum, patients can present with acute liver failure, with aminotransferases reaching levels greater than 1,000 U/L.⁷

Autoimmune hepatitis is associated with several other autoimmune conditions, including Sjögren syndrome, which this patient had.⁸ It should remain in the differential diagnosis. Immunoglobulin G (IgG) levels and anti-smooth muscle antibody titers can help diagnose autoimmune hepatitis if 2 of 3 of the following features are present:

- ALT greater than 5 times the upper limit of normal
- IgG greater than 2 times the upper limit of normal, or positive anti-smooth muscle antibody titer
- Moderate to severe interface hepatitis (ie, inflammation of the parenchyma near the portal tracts) seen on histology.⁹

Viral hepatitis

Viral hepatitis should be considered as a possible cause of aminotransferase elevation because of the patient's recent travel to Asia, where hepatitis B is the most common viral cause of hepatitis.¹⁰ Hepatitis A and C can also cause hepatocellular injury. In acute viral hepatitis, aminotransferases can rise to several thousand units per liter,¹¹ while in chronic hepatitis C, aminotransferases may increase to a milder degree or even be normal.¹² Our patient had recently experienced an episode of right-upper-quadrant abdominal pain, associated with nausea, which can be a symptom of acute viral hepatitis.

Given her recent travel to Malaysia, the patient should undergo testing for hepatitis viruses as follows:

- For **hepatitis A**, the screening test is the anti-hepatitis A IgM antibody test¹³
- For **hepatitis B**, surface antigen denotes active infection, whereas surface antibody corresponds with cured infection or prior immunization¹⁴; anti-core IgM, which is positive in active infection, marks the window phase when the surface antigen is no longer present but the surface antibody has not yet developed¹⁴
- For **hepatitis C**, screening is done by obtaining the hepatitis C antibody, followed by hepatitis C virus RNA if positive.¹⁵

FURTHER TESTING

The patient was referred to the hepatology clinic. She remained symptom-free, but her laboratory test abnormalities persisted. An evaluation for causes of liver disease was obtained, with the following results:

- Alkaline phosphatase 63 U/L (35–104)
- AST 245 U/L (0–32)
- ALT 141 U/L (0–33)
- Total bilirubin 0.4 mg/dL (< 1.2)
- Alpha-1 antitrypsin 118 mg/dL (90–200)
- Antinuclear antibody greater than 1:2,560 (< 1:40; diffuse cytoplasmic pattern)
- Antimitochondrial antibody negative
- Anti-smooth muscle antibody negative
- IgG 2,000 mg/dL (700–1,600)
- Hepatitis A IgM nonreactive
- Hepatitis B core antibody nonreactive

- Hepatitis B surface antigen nonreactive
- Hepatitis C antibody nonreactive.

In view of her high-titer antinuclear antibody and elevated IgG level, she underwent liver biopsy to evaluate for autoimmune hepatitis. The biopsy showed normal hepatic parenchyma.

NEXT STEPS: CONSIDER NONHEPATIC PROCESSES

At the follow-up visit to discuss her liver biopsy results, the patient remained asymptomatic, but her aminotransferase levels were still elevated. Given the absence of any significant findings on liver biopsy, nonhepatic sources of aminotransferase elevation were considered.

2 Which nonhepatic processes could cause her elevated aminotransferases?

- ☐ Myocardial infarction
- ☐ Myopathy from medications, inflammation, or thyroid disorders
- ☐ Muscular dystrophy such as adult myotonic dystrophy
- ☐ Hemolysis

The possibility that elevations in aminotransferases reflect a disorder outside the liver should be considered routinely in the differential diagnosis. Nonhepatic causes of AST-dominant aminotransferase elevation include myositis,¹⁶ strenuous exercise,¹⁶ myocardial infarction,¹⁷ hemolysis,¹⁸ renal infarction,¹⁹ and pulmonary embolism.²⁰ AST and ALT are enzymes. AST catalyzes the reversible transfer of an amino group from aspartate to alpha-ketoglutarate to create oxaloacetate, and ALT catalyzes an amino group from alanine to alpha-ketoglutarate to create pyruvate. Glutamate is a byproduct of these processes.²¹ Both AST and ALT serve as metabolic links between carbohydrate and protein metabolism and are involved in aerobic glycolysis.² Because these enzymes are abundant in hepatocytes, they are regarded as “liver enzymes,” but AST and ALT are found in extrahepatic tissues, including the heart, skeletal muscle, kidney, and red blood cells.²²

Myocardial infarction

In myocardial infarction, myocytes die and release their contents, including troponin, a marker used to diagnose acute coronary syndrome.²³ While undergoing necrosis, cardiac myocytes also transiently release AST and, to a lesser extent, ALT.¹⁷ The patient in our case did not have cardiovascular symptoms, so myocardial infarction is unlikely to be implicated in her aminotransferase elevation.

Myopathy

Myopathy, or muscular disease, can result from inflammation, adverse drug reactions, or thyroid disease, among other causes.²⁴ Myositis, or inflammation of the muscle, often leads to weakness.²⁴ Types of myositis include dermatomyositis and immune-mediated necrotizing myopathy (IMNM).²⁴ Dermatomyositis can cause muscle weakness with characteristic rashes, and IMNM often causes severe proximal weakness.^{16,24}

Regardless of the type of myopathy or myositis, levels of creatine kinase (CK) and aldolase rise when myocytes are damaged.²⁴ Aminotransferases, normal constituents of skeletal myocytes, are also released, with AST superseding ALT.²⁵ Acute muscle injury usually causes AST-ALT ratios close to or greater than 4, whereas in chronic myopathies including myositis the elevation of AST and ALT may be more symmetrical because of the shorter half-life of AST.²⁵ Of note, aldolase is not specific to myocytes; as a component of the glycolytic pathway, it is present in significant amounts in hepatocytes. Thus, serum aldolase elevations do not necessarily indicate muscle damage.

Some medications cause myopathy by altering mitochondria or myofibrillar proteins and generate an immune response or change the balance of electrolytes (eg, hypokalemia, hyperkalemia, or hypermagnesemia).²⁶

In patients with significant hypothyroidism, myopathy is related to alterations in glycogenolytic and oxidative metabolism or changes in the contractile proteins; CK and other muscle enzyme elevations are common.²⁷

Our patient did not initially complain of muscle weakness. Myopathy related to omeprazole (which the patient took), although described in the literature, is rare,²⁸ and she did not exhibit signs or symptoms of thyroid disease. Still, given her AST-predominant aminotransferase elevation, subclinical myopathy should be investigated.

Muscular dystrophy

Muscular dystrophies cause progressive weakness and a loss of muscle mass. As with myopathies, muscle damage from dystrophy can result in the release of ALT and AST.²⁹ Myotonic dystrophy is the most common dystrophy seen in adults and is characterized by myopathy and variable myalgias and myotonia, or the inability to relax muscles. Our patient did not exhibit these features.

Hemolysis

AST and ALT normally reside in red blood cells.²² When these cells undergo lysis for any reason, the

result is aminotransferase elevation, with AST being predominant.¹⁸ Our patient had no signs or symptoms of anemia on presentation.

RHEUMATOLOGY REFERRAL

Despite the patient's lack of symptoms of IMNM and her negative liver biopsy, her aminotransferase elevations required further investigation. The results of CK testing showed an elevation of 5,857 U/L (26–192). High levels of CK are a specific marker for muscle damage, and aldolase and lactate dehydrogenase can also be elevated due to injury outside the muscle.³⁰ Given the patient's elevated CK level, she was referred for rheumatologic evaluation. By the time of her evaluation, she had developed bilateral proximal arm weakness and, later, proximal leg weakness.

On rheumatology evaluation, electromyography and nerve conduction testing were consistent with a mildly active diffuse myopathic process. Left quadriceps biopsy study showed scattered muscle fibers undergoing necrosis or regeneration, and immunofluorescence testing demonstrated myosin heavy chain class I isoforms following the pattern of myonecrosis and regeneration.

SUSPECTED DIAGNOSIS: IMMUNE-MEDIATED NECROTIZING MYOPATHY

3 What features can be associated with IMNM?

- ☐ Muscle weakness
- ☐ Interstitial lung disease
- ☐ Malignancy
- ☐ Skin findings

IMNM is characterized by severe proximal muscle weakness and myofiber necrosis with minimal inflammatory cell infiltrate; proximal muscle weakness is the main clinical feature.³¹ There are 3 subtypes, and patients can be antibody-negative or, in 10% of cases, can have 1 of 2 antibodies: anti-signal recognition particle (SRP) or anti-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR).^{30–33}

Interstitial lung disease is associated with anti-SRP myositis in 10% to 20% of patients and with anti-HMGCR myositis in 5% of patients.^{31–34} In these 2 subtypes of IMNM, skin and extramuscular manifestations are uncommon, occurring in fewer than 10% of patients.^{31–34}

Of the 3 subtypes of IMNM, antibody-negative IMNM has the strongest association with cancer.³⁵ Other inflammatory myopathies, most notably der-

matomyositis, also have strong associations with malignancy, particularly in older individuals.³⁶ In comparison, anti-HMGCR IMNM has a weak association with cancer but a strong association with the use of statins, and anti-SRP IMNM has no association with cancers.³⁵

The diagnostic workup for CK elevation with suspected inflammatory myopathy includes electromyography, select immune serologic testing, careful skin examination, consideration to assess for interstitial lung disease with non-contrast computed tomography of the chest, and muscle biopsy of clinically affected muscle.³³ In patients with immune-mediated myopathy, those with IMNM often have higher CK levels. Muscle enzyme elevation can precede the development of weakness.³³ There are several causes of asymptomatic “CK-emia,” including endocrine disturbances, electrolyte abnormalities, strenuous exercise, and medications.³⁷ Unexplained CK-emia is not uncommon. Electromyography can also assist in ensuring that a patient has a myopathy rather than a neuropathy.

4 What are the next steps in the evaluation?

- ☐ Steroid therapy
- ☐ Methotrexate therapy
- ☐ Computed tomography and cancer screening
- ☐ Test for anti-HMGCR

Oral corticosteroids can be given for mild to moderate proximal weakness, starting with prednisone 1 mg/kg/day. If symptoms are severe, as when weakness is debilitating and interferes with quality of life, intravenous steroids can be given for 3 to 5 days.³³

Methotrexate is typically started after several months of steroid therapy. (Many rheumatologists and neuromuscular neurologists initiate therapy with several drugs from the outset—in an effort to limit the use of high-dose corticosteroids, as high doses are often required to control myositis—especially if used as monotherapy.) Intravenous immunoglobulin in high doses or rituximab can be given for severe or refractory disease and may need to be continued for 2 years after disease control is achieved. Concurrently, oral corticosteroids should be weaned to the clinical minimally effective dose.³²

Computed tomography in cancer screening

IMNM can manifest as a paraneoplastic condition.³³ There are no evidence-based guidelines regarding cancer screening, but computed tomography of the chest, abdomen, and pelvis and age-appropriate cancer

screenings are recommended for patients with INMN to rule out malignancy.³³ If the patient has pulmonary symptoms, pulmonary function testing and high-resolution computed tomography can elucidate whether there is concomitant interstitial lung disease.³³ Computed tomography of the chest, abdomen, and pelvis in our patient demonstrated no concerning lesions.

Anti-HMGCR antibodies

INMN can result from statin use, a possibility that can be confirmed by testing for serum anti-HMGCR antibodies. About 89% of patients over age 50 with this antibody present have been exposed to statins, but patients can form antibodies without a history of statin use.³⁸ Our patient had never been prescribed statins, and her antibody level was nondetectable.

PATIENT OUTCOME

Our patient received both methotrexate and prednisone. She was tapered off prednisone after 3

years and was transitioned to monotherapy with mycophenolate.³² Her AST and ALT levels downtrended. INMN has a worse prognosis than other types of myopathy. After examination of her chart at the time of this review, she was found to have resumed her medications, and her AST and ALT were still mildly elevated, although she was still asymptomatic.

TAKE-HOME POINTS

- Elevated AST and ALT can be a marker of damage to tissues other than liver, particularly muscle, and especially when AST is higher than ALT.
- INMN can cause muscle enzyme elevations before the onset of recognized muscle weakness.

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