CLINICAL VIGNETTE

Jaundice and Abnormal Liver Chemistries After a Food Recall

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Case

A 36-year-old female presented to the emergency department with two days of jaundice. The patient reported eating Thai food for dinner and noted onset of cramping epigastric pain a few hours later. Her pain persisted and spread to her right upper quadrant. She presented to an outside emergency room with severe abdominal pain and dysuria and was diagnosed with gastroesophageal reflux and a urinary tract infection (UTI). Labs were remarkable for elevated liver chemistries. Outside hospital imaging showed subtle periportal edema, a nonspecific finding which could be seen with aggressive fluid resuscitation, hepatic edema, or hepatitis, as well as a possible small hemangioma. Other labs at the outside hospital included negative H. pylori test, urinalysis suggestive of a UTI, elevated direct bilirubin, alkaline phosphatase (AP), alanine transaminase (ALT), and aspartate transaminase (AST). She was prescribed 5 days oftrimethoprim-sulfamethoxazole for her UTI as well as pantoprazole for the presumed GERD.

After her visit to the outside emergency room, her abdominal pain improved and had resolved when she presented to our hospital. However, she noted pruritus and full body jaundice. Her urine was amber colored despite drinking a lot of water to hydrate of her UTI. She denied pale stools, fevers, chills, or reflux. She was free of nausea or vomiting, dysuria, hematuria, or myalgias. There was no recent travel or other sick contacts.

Surgical history was notable for a childhood exploratory laparotomy after a skiing accident. Medications included an oral contraceptive pill for years, a daily multivitamin, biotin, lysine, vitamin B12, folate, and occasional melatonin. Her alcohol intake was minimal, and she denied intravenous drug use. She denied any other herbal supplement use and no family history of autoimmune disease or liver disease.

She had no lymphadenopathy, hepatosplenomegaly, asterixis, and her abdomen was nontender. Computed tomography of her abdomen and pelvis was unremarkable other than a moderate stool burden.

Admission labs were notable for downtrending AST and ALT, increasing AP and bilirubin. On physical exam, she was noticeably jaundiced with scleral icterus.

There was no biliary or pancreatic duct dilatation. Initial testing for autoimmune hepatitis, primary biliary cirrhosis, and hemochromatosis were negative. Gastroenterology was consulted, and noted that the patient had eaten a recently recalled prepackaged vegetarian lentil and leek crumble meal a few days prior to her symptom onset. Her hepatitis panel was negative, total IgG was normal, and cytomegalovirus (CMV) and Epstein-Barr virus (EBV) PCR were negative. Magnetic resonance cholangiopancreatography (MCRP) did not show obstruction.

The patient remained hemodynamically stable with no mental status changes during her admission. She was discharged on ursodiol for pruritus, which she was able to discontinue. At her follow up, liver chemistries continued to improve. At follow up with Hepatology, and additional testing was obtained, including alpha-1-antitrypsin deficiency and testing for Wilson's disease, which were unremarkable. Given her normal serologic evaluation, it was thought that her symptoms and laboratory abnormalities were due to acute ingestion, likely from the recalled pre-packaged vegetarian meal. At two-month follow up visit, her liver chemistries had normalized and she was doing well.

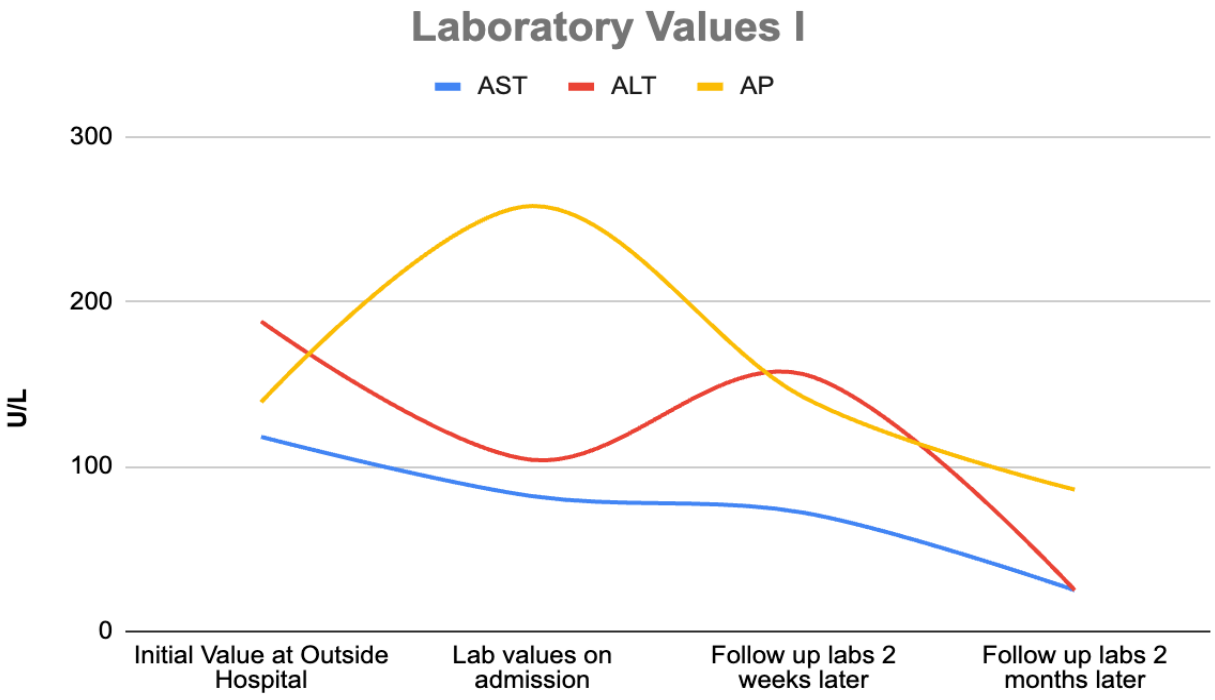
Labs/Diagnostics

Table I. Laboratory Values of Liver Enzymes

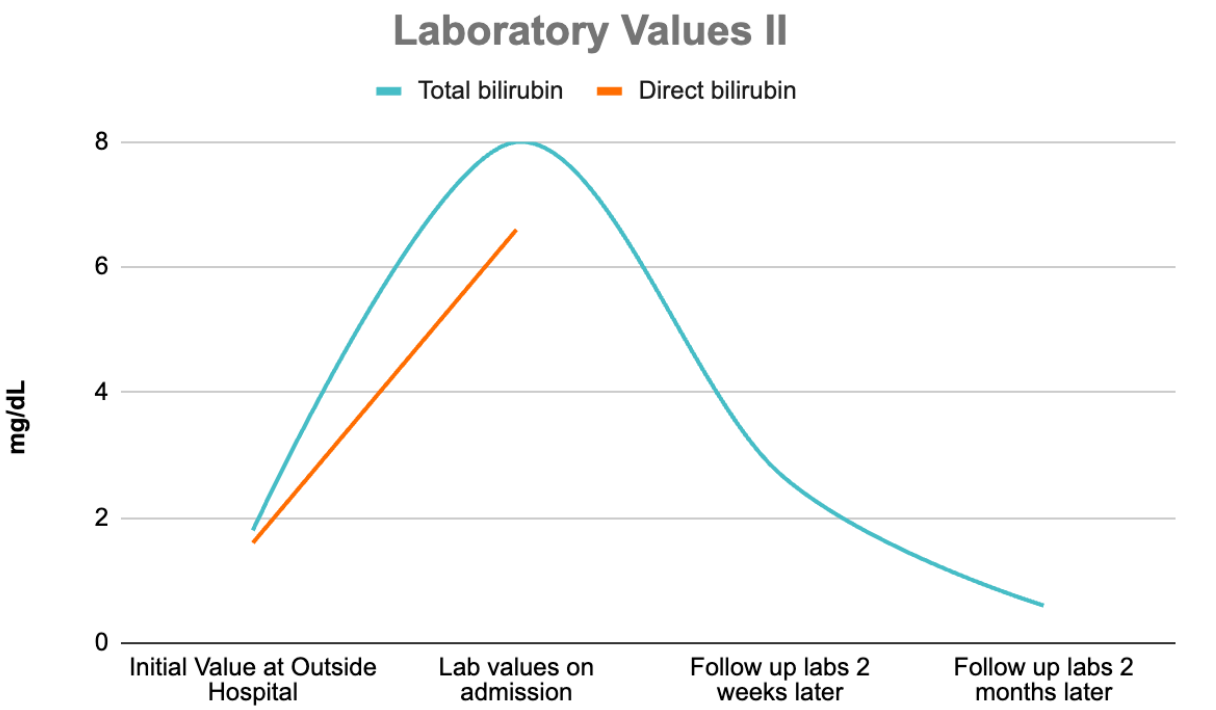
Lab	Initial Value at Outside Hospital	Lab values on admission	Follow up labs 2 weeks later	Follow up labs 2 months later	Normal Range
AST	118	82	72	25	13 - 62 U/L
ALT	188	104	156	25	8 - 70 U/L
AP	139	258	142	86	37 - 113 U/L
Total bilirubin	1.8	8.0	2.7	0.6	0.1 - 1.2 mg/dL
Direct bilirubin	1.6	6.6	n/a	n/a	</= 0.3 mg/dL

***AST: aspartate transaminase, ALT: alanine transaminase, AP: alkaline phosphatase
***The normal range for the laboratory values at patient's outside hospital have different ranges that includes the following: AST (0-32 U/L), ALT (0-33 U/L), AP (35-104 U/L), total bilirubin (0.0-1.2 mg/dL), direct bilirubin (0.0-0.3 mg/dL)

Graph I. Laboratory Values of Liver Enzymes



Graph II. Laboratory Values of Liver Enzymes



Discussion

Liver chemistries are commonly ordered. Comprehensive metabolic panels include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and bilirubin. Derangements of these labs, though not true measures of hepatic function, often indicate hepatocellular or cholestatic injury. AST is found in several organs, including the liver, cardiac muscle, skeletal muscle, kidney, and brain, and therefore is not specific to the liver. ALT, on the other hand, is more specific to the liver, though it is also present in smaller amounts in organs such as cardiac muscle, skeletal muscle, and kidney. Both aminotransferases are enzymes that help transfer amino acids to alpha-ketoglutarate as part of the body's production of energy.[1] AP is found primarily in the liver and bone, though other sources include the placenta, intestine, and kidney. Its function varies depending on where it is found. In the bone, it plays a role in skeletal mineralization.[2] Pregnant individuals can present with elevated AP due to increased production of the enzyme by the placenta. In general, AP levels tend to rise with biliary obstruction due to increased synthesis of the enzyme. Gamma-glutamyl transpeptidase (GGT) can help differentiate between liver and bone disease when AP is elevated. GGT is elevated in liver disease, but not in bone disease.[1] Bilirubin is the byproduct of erythrocyte breakdown. Its conjugated form made in the liver is converted by bacteria in the colon to urobilinogen, which is excreted in urine and stool. When bile flow is obstructed, urobilinogen is unable to be excreted in stool and excess conjugated bilirubin instead enters the circulation to be excreted in the urine, causing the characteristic clay-colored stool and dark urine.[1] Elevated conjugated, or direct, bilirubin can indicate hepatocellular dysfunction or cholestasis.

Though the differential for the etiology of elevated liver chemistries is broad, a thorough history and physical exam can help clarify the cause of the lab abnormalities. Specifically, asking about IV drug use, new sexual partners, and recent travel, as these can predispose patients to infectious hepatitis. History of alcohol use could point to alcoholic hepatitis. Several medications, including over the counter medications and supplements, have been implicated in liver injury. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) produced LiverTox, a database for medications and supplements that have been linked to hepatotoxicity. In our case, none of the supplements the patient reported using have been linked to hepatotoxicity.[3] A thorough physical exam can also aid in diagnosis. Right upper quadrant tenderness may indicate acute hepatitis or a gallbladder or biliary pathology.[4] Physical exam signs of cirrhosis include jaundice, palmar erythema, spider angiomas, gynecomastia, abdominal distention and a fluid wave. Physical exam findings of heart failure, such as lower extremity edema or jugular venous distension, can suggest congestive hepatopathy. It is also important to evaluate the chronicity of changes in liver chemistries. Acute liver failure can be diagnosed in patients without preexisting liver disease who have severe elevations in liver chemistries for

a duration of less than 26 weeks, INR greater than 1.5, and encephalopathy.[5]

A useful framework for interpreting elevations in liver enzymes include organizing them as hepatocellular, cholestatic, or mixed patterns. Calculating the R-ratio can help categorize the pattern of liver injury. The R-ratio is calculated using the following formula: R = (ALT/ALT ULN)/(AP/AP ULN). An R ratio greater than 5 signifies hepatocellular injury, a ratio less than 2 signifies cholestatic pattern of liver injury, and a ratio of 2-5 signifies a mixed pattern. In our patient, the R ratio suggested a mixed pattern of liver injury.

The differential for a hepatocellular pattern of liver injury include infectious etiologies, such as hepatitis, HSV, EBV, and CMV; autoimmune conditions; genetic disorders including Wilson's disease, hemochromatosis, and alpha-1-antitrypsin deficiency; drug or toxin-induced; and ischemia. This patient had a negative infectious workup, and her testing for auto-immune and genetic disorders was negative. Furthermore, she reported minimal alcohol use, no drug use, and no supplement or medications associated with hepatotoxicity.

The differential for a cholestatic pattern of liver injury include biliary disease such as gallstone-related disease, autoimmune conditions such as primary biliary cirrhosis and primary sclerosing cholangitis, and malignancy.[3] Imaging in our patient was unremarkable, and the patient was otherwise healthy with no suspicion for autoimmune or genetic etiologies.

Finally, the differential for a mixed pattern of liver injury, as seen in our patient, most commonly includes medications with common culprits including antiepileptic drugs, antibiotics, and toxins. However, this mixed pattern can also be seen in other conditions such as alcoholic hepatitis, viral hepatitis, auto-immune hepatitis, ischemia, and extrahepatic obstruction.

The only notable aspect of our patient's history was the timing of her symptom onset and ingestion of a few key meals, with the likely cause elucidated in the context of similar reports across the nation.

Conclusion

In this case, the patient underwent extensive evaluation for infectious, autoimmune, structural, and genetic causes, which were unrevealing. Ultimately, a particular detail in the history played a key part in her diagnosis, underscoring the importance of a thorough history and value of revisiting the patient interview.

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