Isoniazid Hepatotoxicity with Clinical and Histopathology Correlate

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Abstract. A fifteen-year-old girl was treated with isoniazid (INH) for latent tuberculosis infection (LTBI), and subsequently developed epigastric pain, vomiting, and jaundice after three months of treatment. Acute fulminant hepatic failure was diagnosed. INH was stopped, and she received N-acetyl cysteine and Vitamin K. Liver biopsy showed moderate to severe lymphocytic and plasmacytic portal and lobular inflammation, prominent ductal proliferation, moderate cholestasis (predominantly hepatocellular and canalicular), hepatocellular damage, and stage 3 bridging fibrosis. She was treated with steroids and azathioprine for probable autoimmune hepatitis (AIH). She received six months of rifampicin treatment for LTBI. Liver biopsy two years later showed mild portal inflammation, predominantly lymphocytic, mild portal fibrosis without bridging, irregular bile ducts without cholestasis, and no significant hepatocellular damage; overall the later biopsy demonstrated significant improvement. This case illustrates overlapping morphologic presentation in INH hepatotoxicity with hepatocellular injury and plasma cell infiltrate (due to probable AIH), as well as cholestatic features. Although her follow-up liver biopsy indicated lymphocytic inflammation, she is now asymptomatic with normal hepatic transaminases.

Key Words: Latent tuberculosis, hepatitis, interferon gamma release assay, INH toxicity.

Introduction

Isoniazid (INH) hepatotoxicity is a well-known entity but uncommon in children. Current recommendations from the American Thoracic Society do not include routine testing for liver transaminases prior to starting INH except in conditions like chronic liver disease, alcoholism, and HIV. It is also known that up to three quarters of patients on INH with elevated transaminases are asymptomatic. Here we report the case of a teenage girl taking INH for latent tuberculosis infection (LTBI) who developed acute liver failure. Liver biopsy showed findings consistent with autoimmune hepatitis, which to our knowledge is the first report of this type of hepatic damage induced by INH. The patient was successfully treated with prednisone and azathioprine along with discontinuation of INH. In addition, treatment of LTBI was completed with Rifampin.

Case Report

A 15-year-old Vietnamese girl was admitted with a three-day history of nausea, vomiting (non-bilious, non-bloody), right upper quadrant abdominal pain, general fatigue, and jaundice. She had been taking isoniazid (INH) for 3.5 months for LTBI. She had had the BCG vaccination as an infant in Vietnam. She reported no past medical or family history of liver disease. She denied taking any other medications or drinking alcohol. Clinically, the patient appeared jaundiced, tired, and had abdominal tenderness to superficial and deep palpation in the right upper quadrant. The liver was enlarged 2cm below the right costal margin. She had laboratory evidence of acute hepatitis that included ALT 1638U/L, AST 1300U/L, alkaline...
phosphatase 277U/L, bilirubin total 19.3mg/dl, bilirubin direct 10.2mg/dl, ammonia 95µMol/L, PT 18.7, PTT 42.8, INR 1.77, globulin 3.7gm/dl, albumin 2.8gm/dl, and immunoglobulin IgG 1540mg/dl. She had no mental status changes. After three days of Vitamin K, the coagulation studies improved but remained high. She then received five days of N-acetyl cysteine, and her coagulopathy improved. The workup for hepatitis included negative viral serology, normal ceruloplasmin, normal alpha 1-antitrypsin, and a positive antinuclear antibody (ANA≥640, actin smooth muscle antibody 35 {moderate to strongly positive >30}). Liver biopsy showed moderate to severe lymphocytic and plasmacytic portal and lobular inflammation, prominent ductal proliferation, moderate cholestasis (predominantly hepatocellular and canalicular), fibrosis with bridging consistent with stage 3 fibrosis (Figure 1), and was negative for iron and fungal stains, herpes simplex virus, cytomegalovirus, and adenovirus on immunohistochemical stains. Liver biopsy was also negative for AFB and granuloma. She received five days of N-acetyl cysteine and high-dose corticosteroids. The coagulopathy corrected in 17 days, and the liver transaminases normalized within a month. Azathioprine was started, and the steroids were slowly weaned over 1 month. Of additional concern were a history of a positive tuberculin skin test, BCG vaccination, and the risk of progression to TB disease while taking immunosuppressive therapy. A positive interferon gamma release assay (IGRA) confirmed LTBI, and 6 months of Rifampin was completed without problems.

Liver biopsy was repeated two years from the onset of hepatitis and showed a significant decrease in the number of plasma cells and overall amount of inflammation in the portal areas, as well as a decrease in the amount of fibrosis with no hepatocellular damage (Figure 2). There was mild portal inflammation (predominantly lymphocytic), mild portal fibrosis without bridging, and irregularity of bile ducts without cholestasis. Liver biopsy was negative for iron stain and accumulation of PAS positive diastase resistant material in hepatocytes. Liver function tests were normal at the time of repeat biopsy. Azathioprine was stopped, and follow-up liver function tests have been normal.

Discussion

Nine months of INH is recommended as treatment for LTBI, including regular clinical evaluation monitoring for side effects [1]. Routine liver function tests are not indicated unless patients are at risk for hepatitis or have symptoms of toxicity. Isoniazid is well tolerated in children, with an estimated incidence of liver failure of 3.2/100,000 children taking INH [2]. The risk of hepatotoxicity increases with age and presence of other cofactors like age >35 years, alcohol consumption, HIV, and hepatitis B and C infection [3,4].

Our patient developed acute fulminant hepatic failure while on isoniazid treatment. The history of...
INH treatment and the negative work up for other possible etiologies was consistent for INH-induced hepatotoxicity. The presence of autoimmune serologic markers [antinuclear (ANA) and smooth muscle antibodies (SMA)], negative viral hepatitis panel, and liver biopsy findings mimicked autoimmune hepatitis. Drug-induced hepatitis is difficult to distinguish from autoimmune hepatitis on the basis of morphology alone. However, based on the revised scoring system of the International Autoimmune Hepatitis Group [5,6,7,8] this patient probably had AIH (Table 1).

INH was the most likely trigger for hepatitis and subsequent acute liver failure in this patient. INH is reported to cause a cytotoxic liver injury with acute or sub-acute hepatic necrosis, typically non-zonal and panacinar injury. INH-induced hepatotoxicity can be idiosyncratic and not due to the result of a hypersensitivity or allergic reaction [9]. INH is also known to cause drug-induced chronic hepatitis (type IV - chronic toxicity without active necro-inflammatory disease) [10], isolated high transaminases, cytotoxic liver injury, positive ANA without liver injury, and liver injury with eosinophil infiltrate, but less is known about INH-induced AIH.

Some drugs may trigger the production of antibodies that are considered serologic markers of autoimmune response. This response is not consistent in all cases and occasionally these markers are associated with drug-induced acute liver damage [11].

Table 1. Revised international classification of AIH scoring for this patient.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
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<tbody>
<tr>
<td>Female sex</td>
<td>+2</td>
</tr>
<tr>
<td>ALP:AST &lt; 1.5</td>
<td>+2</td>
</tr>
<tr>
<td>IgG or serum globulins &gt; normal</td>
<td>0</td>
</tr>
<tr>
<td>ANA, SMA or LKM1 antibody</td>
<td>+3</td>
</tr>
<tr>
<td>AMA (antimitochondrial antibody)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis viral markers negative</td>
<td>+3</td>
</tr>
<tr>
<td>Drug history present</td>
<td>-4</td>
</tr>
<tr>
<td>Average alcohol intake &lt; 25gms/day</td>
<td>+2</td>
</tr>
<tr>
<td>Liver histology – interface hepatitis</td>
<td>+3</td>
</tr>
<tr>
<td>Other autoimmune disorder</td>
<td>0</td>
</tr>
<tr>
<td>HLA</td>
<td>n/a</td>
</tr>
<tr>
<td>Response to therapy</td>
<td>+2</td>
</tr>
<tr>
<td><strong>Patient’s Total Score</strong></td>
<td><strong>13</strong></td>
</tr>
<tr>
<td>Probable diagnosis</td>
<td>10-15</td>
</tr>
<tr>
<td>Definite diagnosis</td>
<td>&gt;15</td>
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There is no established diagnostic criteria for drug-induced autoimmune hepatitis. However, based upon similarity to idiopathic autoimmune hepatitis the following are important elements in the diagnosis: time to onset of two months or more, rash, arthralgia or extrahepatic manifestations, hepatocellular pattern of serum enzyme elevations, presence of an autoantibody in titers of 1:80 or greater (ANA, SMA or anti-LKM), raised immunoglobulin (IgG>1800 mg/dL) or total globulin levels (>3.0 grams/dL), and exposure to an agent that is typically associated with drug-induced autoimmune hepatitis, i.e., nitrofurantoin, methyl-dopa, minocycline, hydralazine, alpha interferon, beta interferon, or cholesterol lowering agents.

The liver biopsy showed features of chronic
hepatitis with interface hepatitis and prominence of plasma cells. There was a prompt response to corticosteroid therapy and ultimate resolution upon stopping the medication. In many cases, resolution can be slow and require corticosteroid therapy for several months. The above criterion fits this case except for hypegammaglobulinemia [12].

A CDC passive surveillance study of INH associated liver injury among persons on treatment for LTBI reported 17 cases of severe liver injury in 15 adults and 2 children between 2004-2008 [13]. Although rare, clinicians and patients should be aware of the potential adverse effects of INH. IGRA tests might be preferred over the tuberculin skin test in BCG vaccinated patients due to the higher specificity. The IGRA can confirm LTBI and avoid unnecessary treatment in patients with false-positive tuberculin skin test reactions [14].

In conclusion, this case illustrates INH toxicity that manifested as acute liver failure and responded to steroids/immunosuppression. The clinical course, serology, and changes in histology with treatment are valuable information for understanding drug-induced liver injury in children. Drug-induced liver injury mimics any pattern of primary liver disease and is not often reported in pediatrics. Histology is yet to differentiate drug-induced liver disease, especially in children.

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References