

Hepatotoxicity due to Trimethoprim-Sulfamethoxazole: Jaundice in a 56 year old Woman

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Case Presentation

History

A 56-year old woman presented complaining of yellow skin. After ultrasound-guided drainage of a 6 x 5 cm liver abscess 1 month before, she had been sent home on a 1 month course of trimethoprim-sulfamethoxazole DS twice daily after wound culture showed *Klebsiella pneumoniae*. She did well for 25 days, until developing fevers to 102, nausea, vomiting, anorexia and pruritis 5 days prior to presentation, with jaundice on the day prior to presentation. She had no other past medical history, had no known allergies to medications, and took no other medications or herbals. She denied tobacco, alcohol, or drug use, had never received blood products, had immigrated to the US from Japan 20 years ago, and had not traveled for many years.

Clinical Data

- General: Thin woman in no distress.
- Vital signs: Temp 97.3 degrees F, Blood pressure 106/64, Heart rate 64, Respiratory rate 20.
- Skin: Jaundiced. No tattoos. Light urticarial rash on shoulders.
- Head/Neck: Sclera icteric. Mucous membranes moist. No jugular venous distension.
- Lungs: No crackles, wheezes, or rhonchi.
- Cardiac: Regular rate and rhythm. No murmurs, rubs, or gallops.
- Abdomen: Soft, nontender, nondistended. No hepatosplenomegaly, spider angiomas, or palmar erythema.
- Extremities: No edema or clubbing.
- Neuro: Alert and oriented. No asterixis.

Laboratory/Radiological Data

- Total bilirubin 12.7, direct bilirubin 8.4, AST 316, ALT 359, Alk Phos 614, lipase 50
- INR 0.88, albumin 3.4
- WBC 5.7 with 70% neutrophils, 15% lymphocytes, 8% monocytes, and 7% eosinophils
- Hb 11.1, and Cr 0.7.
- Hepatitis serologies, acetaminophen level, ANA, anti-smooth muscle, and anti-mitochondrial antibodies were negative.
- CT scan showed significant resolution of the liver abscess, normal CBD diameter, and no other abnormalities.

Clinical Course

- This patient was presumed to have trimethoprim-sulfamethoxazole hepatotoxicity
- Her symptoms and lab abnormalities resolved slowly over the next few weeks after discontinuation.

Discussion

General

- Drug-related hepatotoxicity is defined as injury to the liver that is associated with impaired liver function caused by exposure to a drug or another noninfectious agent.
- Common, accounting for approximately one half of cases of fulminant hepatic failure worldwide.

Classifications

- Drug-related hepatotoxic events can be classified as unpredictable or predictable.
 - Trimethoprim-sulfamethoxazole hepatotoxicity is defined as an unpredictable event, having a low incidence, being unrelated to dose, and having a variable latency period ranging from a few days to 1 year.
 - Predictable hepatotoxic events, typified by acetaminophen hepatotoxicity, have a high incidence, occur within a few days of exposure, and are dose related.
- Can be further classified by patterns of liver injury, defined as hepatocellular, cholestatic, or mixed.
 - Trimethoprim-sulfamethoxazole traditionally creates a mixed pattern, as was the case in this patient.
 - Mixed pattern is often caused by hypersensitivity injury and can be associated with fever, rash, and eosinophilia.
 - This patient showed signs and symptoms of hypersensitivity injury, namely fevers and urticarial rash.
 - Liver biopsy specimens in hypersensitivity injury often show eosinophilic infiltrates or granulomas (see figure 1).

Diagnosis

- Can be difficult to make with certainty.
- Other causes of liver injury must be ruled out, including viral, alcohol-induced, or autoimmune hepatitis, biliary tract disorders, or hemodynamic injury (see figure 2).

Management

- The cornerstone of treatment is withdrawal of all suspected drugs.
- With the exception of N-acetylcysteine for acetaminophen toxicity, no other specific antidotes have been identified.
- Ursodiol and corticosteroids have been used, but no controlled trials have validated these interventions.
- If coagulopathy or encephalopathy is present, the patient should be promptly transferred to a liver transplant center.

Prognosis

- Prognosis is poorer for hepatocellular than for cholestatic drug hepatotoxicity, and Hy's Law indicates that drug-induced "clinically apparent" hepatocellular jaundice carries at least a 10% mortality rate.

References

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 Lee, W.H. Drug-Induced Hepatotoxicity. *N Engl J Med* 2003; 349:474-485.
 Berg PA, Daniel PT. Co-trimoxazole-induced hepatic injury--an analysis of cases with hypersensitivity-like reactions. *Infection*. 1987;15 Suppl 5:S259-64.

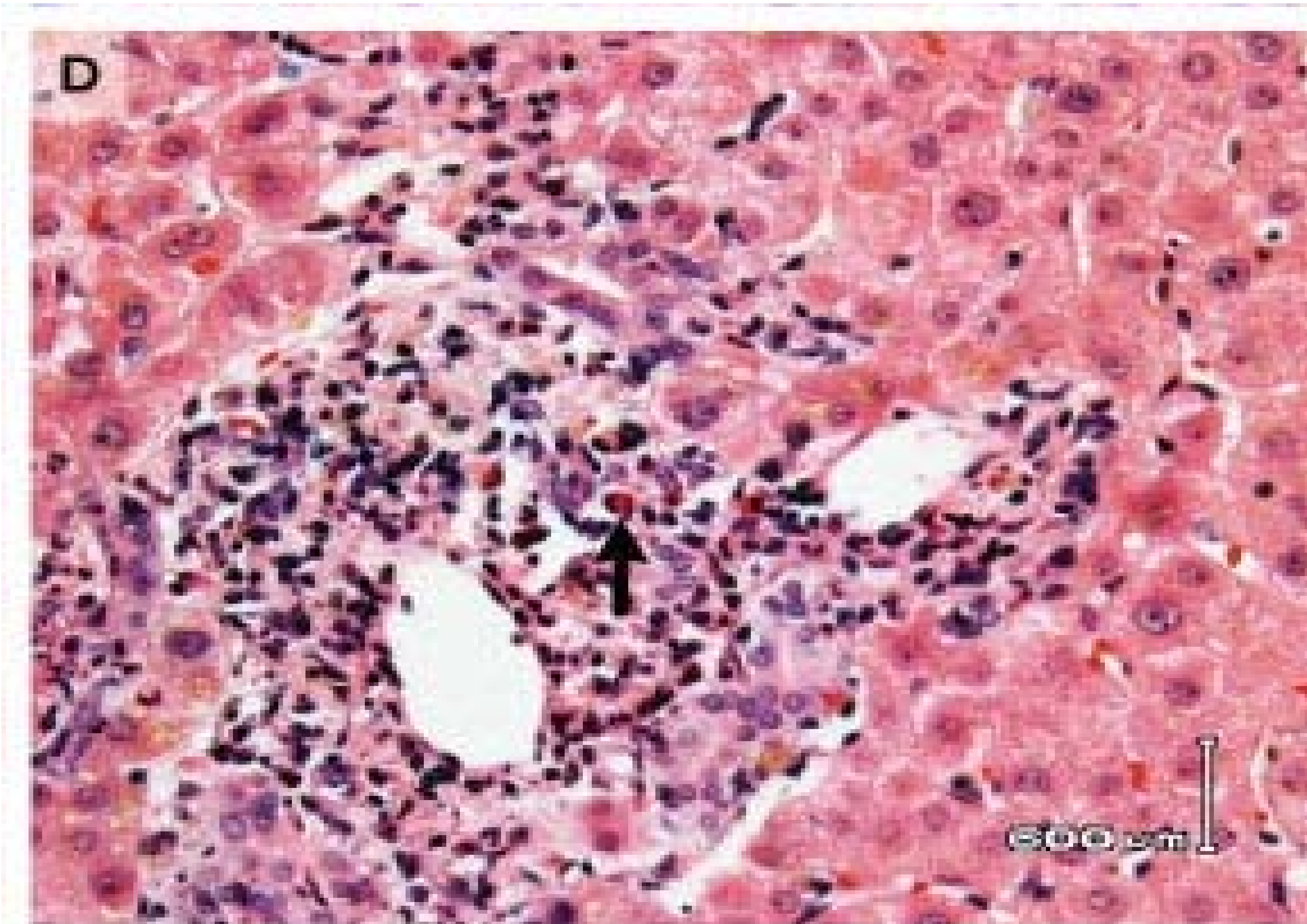


Figure 1. Hypersensitivity injury: eosinophilic infiltrate in portal triad (arrow)--often noted in trimethoprim-sulfamethoxazole hepatotoxicity. (not this patient)

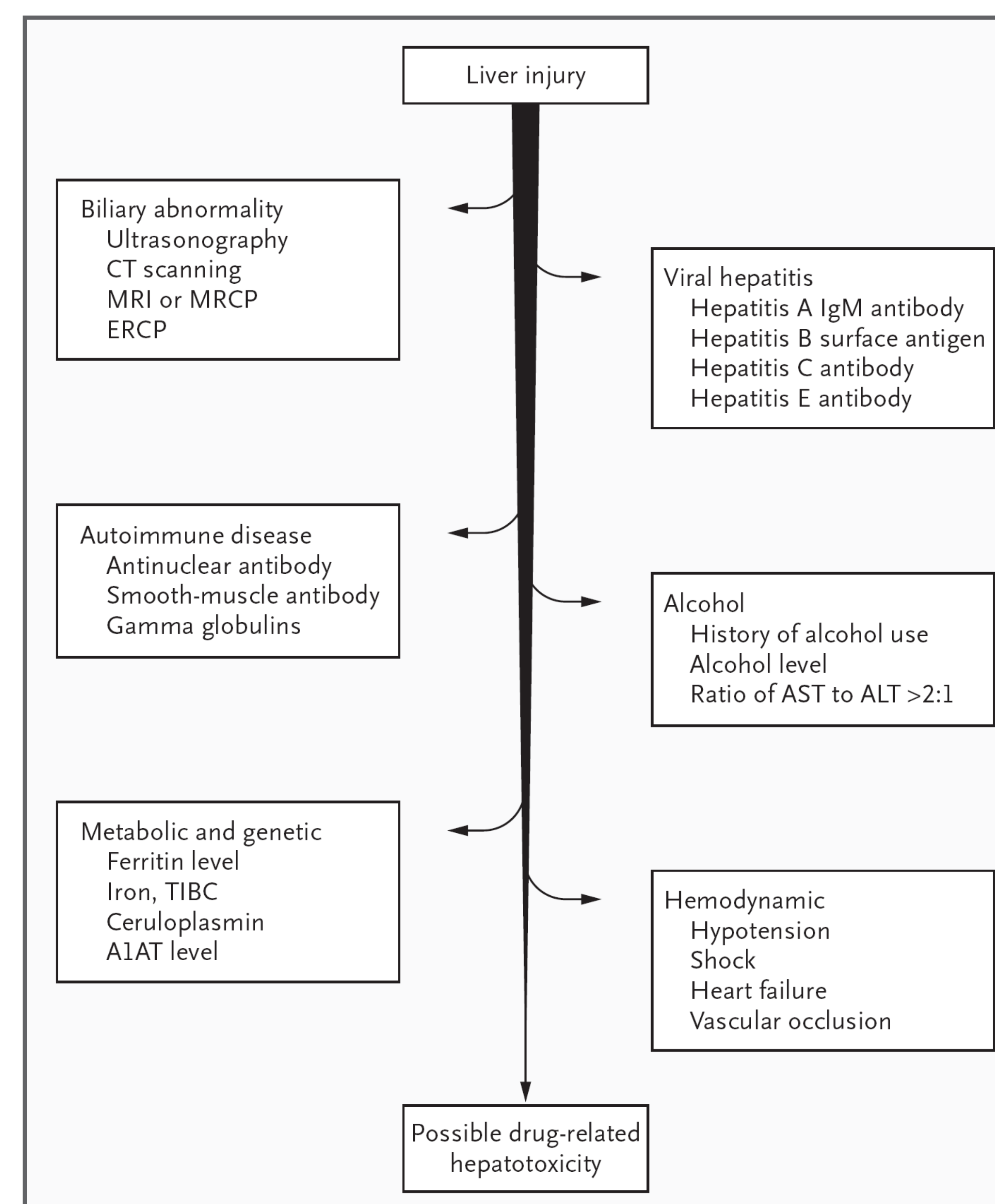


Figure 2: Diagnosis of drug-related hepatotoxicity