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Scotch pine-induced liver injury: A case report

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Abstract

Herbal medicines are widely used worldwide to treat minor ailments and prevent disease. Scotch pine (*Pinus sylvestris*) has many medicinal applications but is most well-known for its antiseptic properties and beneficial effects on the respiratory system. Herbal products can cause adverse side effects like liver injury, which is referred to as herb-induced liver damage (HILI). In this article, we present a patient who used Scotch pine to treat asthma and developed HILI. To the best of our knowledge, this is the first case of Scotch pine-related HILI described in the literature.

Keywords: Hepatotoxicity; liver injury; *Pinus sylvestris*.

Introduction

Herb-induced liver damage (HILI) is an unprecedented adverse reaction related to the intake of herbal products.[1] HILI has been increasingly reported on in recent years, attracting the attention of physicians, pharmaceutical companies, and regulatory groups.[2] Many plants have the potential to be hepatotoxic, as numerous case reports, case series, and literature reviews have shown.[3,4] However, the potential hepatotoxicity of multiple chemical compounds in any plant and incomplete diagnostic exclusion has made a clear clinical evaluation difficult.[5]

The gastroprotective,[6] anti-carcinogenic,[7] and hepatoprotective effects[8] of *Pinus sylvestris* have been demonstrated in most preclinical studies, but clinical studies are scarce. However, Parrott et al.[9] reviewed cholestatic patterns associated with Scotch pine,and the causality assessment in that report provided evidence of the hepatotoxic effect of *P. sylvestris*.

Case Report

A 71-year-old Turkish woman was admitted to an external center with complaints of upper right quadrant abdominal pain, weakness, and fatigue for 2 months. There was no radiating abdominal pain. She had a history of gastroesophageal reflux disease (GERD), asthma, and a cholecystectomy. There was no serious disease in the family history. She had been using pantoprazole intermittently for a long time due to GERD. A detailed anamnesis revealed that she had been using Scotch pine for about 3 months due to asthma. The patient used 200 mL of Scotch pine juice for 21 days a month. Lung auscultation revealed no additional features except for rhonchi on expiration and tenderness in the upper right quadrant of the abdomen. Liver function tests revealed alanine aminotransferase (ALT 253 IU/L), aspartate transaminase (AST 213 IU/L), total bilirubin (0.34 mg/dL), direct bilirubin (0.14 mg/dL), and alkaline phosphatase (ALP 464 IU/L) levels, as well as the international normalized ratio (INR 1.01 s). Viral (hepatitis A, hepatitis B, hepatitis C, Epstein–Barr virus, rubella virus, cytomegalovirus, and herpes virus) and autoimmune markers, including anti-liver kidney microsomal, anti-mitochondrial, anti-smooth muscle, and anti-nuclear antibodies, were all negative. Ceruloplasmin and serum concentrations of immunoglobulin were also within normal range. An abdominal sonogram showed normal liver dimensions and increased parenchymal echo consistent with grade I–II steatosis. Liver contours were regular. No solid or cystic lesion was found in the parenchyma. No gallbladder was observed (operated). The common bile duct and intrahepatic bile ducts were of normal width. The spleen was of normal size, and the parenchyma was homogenous. The pancreas was of normal size and echo structure in the parts where it could be observed. A liver biopsy was not performed because the patient did not give informed consent for the procedure. The type of liver injury in our case was assumed to be cholestatic liver injury (ALT >5N and R factor ≤2) with a Roussel Uclaf Causality Assessment Method score of 9. Highly probable HILI due to the use of *P. sylvestris* extract was considered, and intake was stopped immediately. After stopping *P. sylvestris* intake, the patient recovered rapidly, and liver enzyme levels returned to normal within 14 days. At the 3-month follow-up, the patient was taking pantoprazole intermittently, and no abnormality was found in liver function tests.

Discussion

Herbal drug treatments have been extensively and adequately used for numerous diseases and healthcare for thousands of years.[8] A prospective study from a German traditional Chinese medicine hospital to analyze the frequency of liver injury induced[10] found that only 488 (0.79%) of 61,516 patients were hospitalized because of liver injury as a result of using herbs or herbal products.

There are many different varieties of pine trees. Some species have not only hepatoprotective[9] but also hepatotoxic effects.[10] Parrott et al.[9] have shown that wood-derived stilbenes isolated from Scotch pine caused weak mixed-function oxidase induction in fish and rat liver cells. *P. sylvestris* also causes HILI, possibly through the same mechanism. To the best of our knowledge, our case is the first case of Scotch pine-induced liver injury described in the literature.

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Age, sex, daily doses, metabolism profile, and drug interactions are host-related risk factors for HILI.[11] This has been formally described in the literature and is probably related to the higher use of herbal products by women.[12,13] The frequency of liver injuries is higher in patients over 40 and increases with age (as with our patient), which has been highlighted in recent reports.[14,15]

There are no specific diagnostic procedures or standards for herb-induced hepatotoxicity. The diagnosis requires a thorough review of the patient's medical history, thoughtful analysis of the laboratory results, and histology. Teschke et al.[16] reported that although a liver biopsy may be useful in assessing liver damage, it is not necessary for the diagnosis. We did not perform a liver biopsy because the patient did not agree. Liver function improved substantially after stopping the intake of *P. sylvestris*. In addition, the absence of abnormalities in the patient's liver function tests despite prolonged intermittent pantoprazole use before *P. sylvestris* ingestion and the absence of any change at the 3-month follow-up despite pantoprazole use suggested liver injury due to *P. sylvestris* use. The mechanism by which pantoprazole causes liver damage is not well understood. Despite its widespread use, pantoprazole has only been linked to a few cases of liver damage. Elevations in serum ALT levels have occurred in <1% of patients in large-scale, long-term pantoprazole studies. Proton pump inhibitor (PPI)-induced clinically significant liver injury typically occurs within the first 4 weeks of treatment and is characterized by a pattern of acute hepatocellular injury that resolves quickly after discontinuation. The rapid recurrence of PPI-induced liver injury suggests hypersensitivity, but this could simply be due to altered metabolism or acute toxicity of a metabolic by-product.[17] It was therefore not suggestive of pantoprazole-induced liver injury in this case. Re-challenge is the most effective method to identify a causal factor. However, this is ethically unacceptable for obvious reasons. We chose not to challenge her again and advised her to stop using the herbal remedy altogether.

Our case report emphasized the importance of detailed history-taking that includes inquiring about the use of herbal supplements. The majority of cases of HILI are benign and become well when you stop using drugs. To stop the course of potentially fatal liver disease, it is crucial to identify the offending substance early and stop using it. It may be possible to avoid major adverse reactions by standardizing the labeling of herbal treatments with information about side effects and a warning against concurrent use with other pharmaceuticals and herbal supplements.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author have no conflict of interest to declare.

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