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Drug-induced Liver Injury Due to a Horse Chestnut Dietary Supplement

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ABSTRACT

Drug-induced liver injury (DILI) is the most common cause of acute liver failure in the Western world. In recent years, natural herbal and dietary supplements have become widely available to the general public and have increased in popularity. Reports of idiosyncratic liver injury caused by such supplements have also increased over the last decade.

Horse chestnut is a herb used in dietary supplements primarily for complications of venous insufficiency. Clinically significant acute liver injury has been very rarely associated with its use. We present the case of a 70-year-old man with idiosyncratic horse chestnut-induced liver injury.

LEARNING POINTS

- Idiosyncratic drug-induced liver injury is one of the most challenging liver disorders.
- Herbs and natural dietary supplements are widely popular and should be considered when evaluating liver injury of unknown origin.
- Patients may not consider herbs and supplements to be drugs with the potential to cause adverse effects, requiring a more careful medication history.

KEYWORDS

Horse chestnut, drug-induced liver injury, dietary supplement

INTRODUCTION

Drug-induced liver injury (DILI) is defined as liver injury or disease caused by medications, herbs or other toxic substances. It remains the most common cause of acute liver failure in the Western world. Data from prospective registries have reported an increase in idiosyncratic DILI caused by herbal and dietary supplements over the last decade [1].

Horse chestnut is a herb prepared from the leaves or seeds of the horse chestnut tree (*Aesculus hippocastanum*), used in dietary supplements for decades. It is primarily used for complications of venous insufficiency, including varicose veins, ankle swelling and leg cramps, but also haemorrhoids and phlebitis. Extracts of horse chestnut seeds are also used for diarrhoea, fever and urinary hesitancy, and applied topically for muscle and joint aches due to arthritis or trauma [2, 3].

To our knowledge, there are only three case reports of acute liver injury associated with horse chestnut products [4–6].

CASE DESCRIPTION

A 70-year-old man with a medical history of chronic venous insufficiency, hypertension and allergic rhinitis was admitted to hospital having noticed jaundice over the previous 3 days, as well as acholia and choluria. His usual medications were irbesartan with hydrochlorothiazide

and desloratadine. He initially denied herbal supplement use, recent changes to medication, tobacco or alcohol consumption or recreational drug use, and reported no recent travel.

Physical examination revealed scleral icterus, and jaundice with no pruritus. There were no palpable lymph nodes or hepatomegaly. Laboratory tests on admission revealed aspartate transaminase 275 U/l, alanine transaminase 550 U/l, alkaline phosphatase 348 U/l, gamma-glutamyl transferase 1451 U/l, total bilirubin 11.2 mg/dl and direct bilirubin 8.23 mg/dl. Coagulation laboratory test results were within reference values. Serological markers for human immunodeficiency virus and hepatitis viruses A, B and C were negative. A polymerase chain reaction test for cytomegalovirus was negative. Epstein-Barr virus antibody to viral capsid antigen was negative for immunoglobulin M and positive for immunoglobulin G.

Ceruloplasmin, serum iron, iron saturation and thyroid-stimulating hormone were within normal limits. Anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-liver-kidney microsomal antibody and anti-soluble liver antigen antibody were all negative.

Abdominal ultrasound found no evidence of cholelithiasis, biliary ductal obstruction, hepatomegaly or hepatic parenchymal disease. Endoscopic ultrasound and magnetic resonance cholangiopancreatography corroborated previous findings and found no evidence of pancreatic duct obstruction or pancreatic parenchymal disease.

Liver enzymes were routinely repeated and continuously elevated, with total bilirubin reaching a maximum value of 22 mg/dl and direct bilirubin reaching 15.8 mg/dl.

During the entire aetiological investigation, both the patient and his family were extensively queried on several occasions about additional drug or herb history. Only after imaging tests were performed and bilirubin levels maintained a steady rise did the patient's wife remember that 1 month previously he had started a dietary supplement for his chronic venous insufficiency, taken until about a week before admission. The dietary supplement (Venenkraft) was then provided to the medical staff and found to be made from horse chestnut extract. After review of all previous negative medical examinations and relevant literature, a diagnosis of drug-induced liver injury due to consumption of a horse chestnut dietary supplement was established.

Soon afterwards, liver enzymes and bilirubin values started to progressively decrease and icterus, stool and urine alterations resolved. The patient was then discharged and told to stop taking any previous or new herbal supplements. During follow-up, liver enzymes and bilirubin values continued to decrease at a slow rate, eventually reaching normal levels.

DISCUSSION

A review of the literature showed that in the very few reports of liver toxicity attributed to horse chestnut extracts, injury became clinically apparent between 4 and 8 weeks after starting the herb and was associated with either hepatocellular or mixed patterns of serum enzyme elevations.

The first report found describes a 37-year-old man who received a single injection of a horse chestnut extract (Venoplant) after a fracture of the left humerus and presented 60 days later with jaundice and pruritus, moderate elevation of liver enzymes, hyperbilirubinemia and a liver biopsy consistent with drug-induced hepatic injury [4].

The second report describes a 69-year-old woman with acholia, choluria, conjunctival icterus and pruritus after 6 weeks of daily self-treatment with horse chestnut extract tablets (Venencapsan), with abnormal liver enzymes and hyperbilirubinemia. The patient improved but after restarting the herbal tablets was admitted with jaundice [5].

The third case is reported in a multicentre study and describes a 69-year-old woman who developed jaundice 4 weeks after starting a horse chestnut tablet, presenting with elevated liver enzymes and hyperbilirubinemia [6].

All case reports, including our own, describe a benign, self-limited and slowly resolving course with no reports of acute liver failure or other complications. In the first report, a single dose resulted in liver injury and in all cases the cause is thought to be idiosyncratic.Natural dietary supplements have increased in popularity throughout the last few years and have become widely available to the general public, prompting physicians to consider them when evaluating a case of suspected liver injury of unknown origin. In addition, our case shows that even when suspected, the patients themselves may not consider herbs and supplements to be drugs with the potential to cause harmful effects, requiring a more careful medication history and patient education.

The diagnostic challenge of the case, the rarity of available reports and the widespread popularity of natural dietary supplements prompted the authors to present this report.

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