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CASE REPORTS

Helpful or Harmful? A Case Report of Nutritional Supplements Causing Drug-Induced Liver Injury

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INTRODUCTION

Herbal supplement-induced liver injury represents a growing concern in the body of drug-induced liver injury (DILI) literature, with recent studies in mainland China, Iceland, and the United States reporting estimated rates of herb/dietary supplement-induced liver injury (HILI) between 1.16-6.38 per 100,000 (Björnsson et al., 2013; Shen et al., 2019; Vega et al., 2017). Notably, a recent 2020 study demonstrated an increasing prevalence of hepatotoxicity secondary to herbal and dietary supplements in the US and worldwide (Zheng et al., 2020). Recognizing the hepatotoxicity of various supplements is crucial, given the increasing usage of dietary and herbal supplements and the lack of regulation of herbal supplements in the United States.

HRP-AID is marketed as a twice-daily "immune system booster" to reduce the intensity and frequency of cold sore outbreaks. The product ingredients include 200 mg ascorbic acid, 20 mcg cholecalciferol, 20 mg a-tocopherol, 10 mg pyridoxine HCl, 50 mcg methylcobalamin, 25 mg zinc citrate, 70 mcg selenium, 250 mg L-lysine, 50 mg Astralagus extract (Astragalus membranaceus), 50 mg Echinacea (Echinacea purpurea), 50 mg garlic powder (Allium salivum), 50 mg natural caffeine (coffee arabica), 50 mg olive leaf extract Oleuropin 20% (Olea Europaea), 50 mg oregano powder (Thymus captatus), 50 mg of elderberry extract (Sambucus nigra) and 50 mg Red Panax ginseng extract (Panax ginseng). A literature review demonstrates that this is the first reported case of DILI secondary to *HRP-AID* supplementation.

CASE PRESENTATION

A 27-year-old woman with a past medical history of genital herpes presented with three days of acute onset abdominal pain, nausea, vomiting, generalized weakness, and jaundice. Further history revealed that she is a Liberian immigrant who immigrated to the United States nine years prior to work as a healthcare aide. She noted no history of prior liver disease or family history of liver disease, cirrhosis, hepatic malignancy, or any recent travel or sick contacts at home, socially, or work. However, she reported that her partner, who frequently travels to Liberia, had a history of "a liver ailment" treated a few years prior. The patient also denied a history of any prior blood transfusions, tattoos, or intranasal or intravenous drug use. Her social history was notable for drinking one glass of wine weekly.

Upon further questioning, the patient revealed that she takes no prescribed medications. She takes 1-2 ferrous sulfate pills when fatigued, particularly after menses. Furthermore, daily over the past month, she noted that she had been using two tablets of Prodigy Life *HRP-AID* supplements and lemon balm tea (100% *Melissa Officinalis*).

The patient's lab work was notable for significant abnormalities with AST 6597, ALT > 5000, alkaline phosphatase of 92, total bilirubin of 17.1, direct bilirubin of 9.3, INR of 2.7, ferritin > 7000, and a MELD-Na score of 29. The patient underwent a CT abdomen, abdominal ultrasound, and MRCP. These imaging studies revealed normal hepatic echogenicity with no acute abnormalities. These studies indicated acute hepatic inflammation. The patient was admitted to the intensive care unit for further management and treated with intravenous N-acetylcysteine and oral Vitamin K.

The patient's total and direct bilirubin levels peaked at 52.2 and 46 before down-trending to 30.6 & 28.2, respectively. The autoimmune panel was negative for antinuclear, anti-smooth muscle, mitochondrial M2, liver kidney microsomal antibodies, alpha-1 antitrypsin, ceruloplasmin, and celiac panel. The infectious workup was positive for hepatitis B surface antigen, hepatitis B

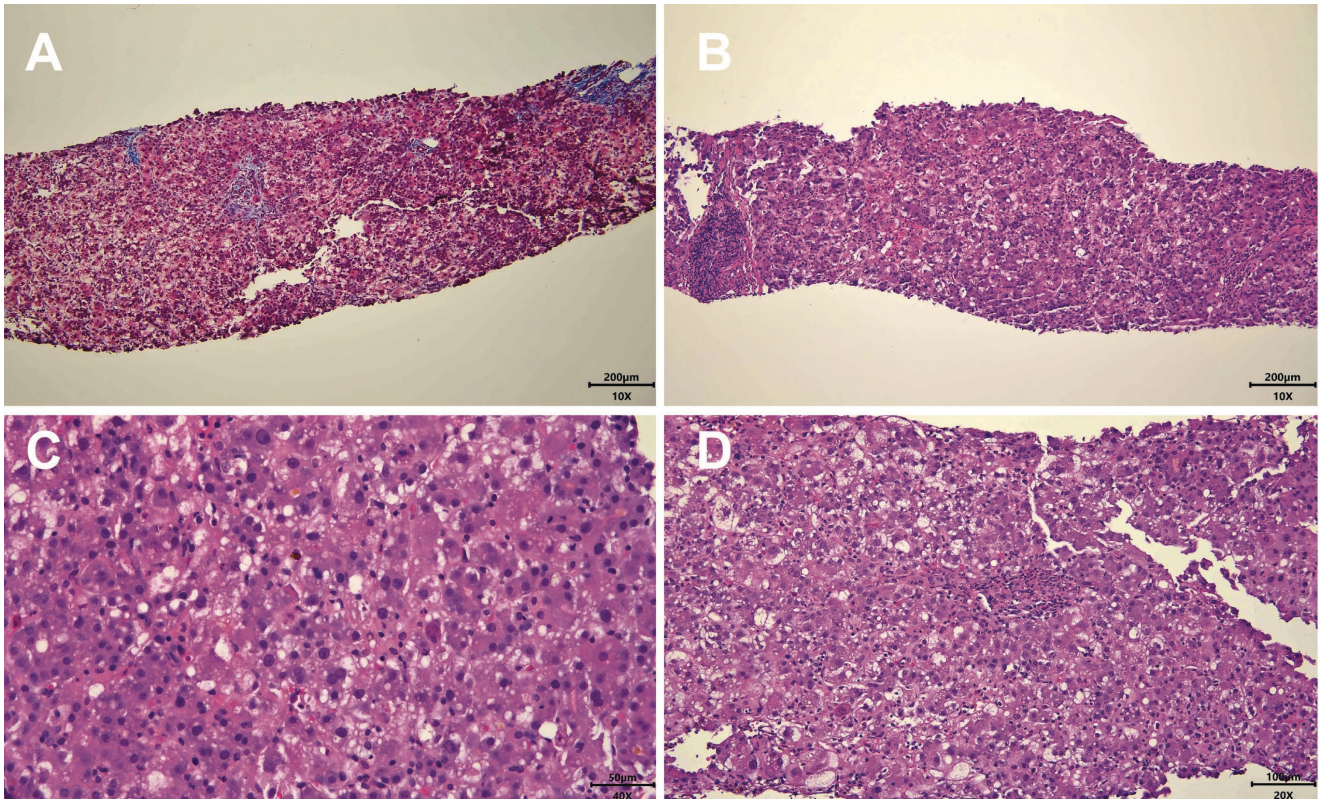

Figure 1: Liver biopsy pathology slides demonstrating acute hepatitis pattern of injury, likely suggestive of DILI. **A**) Trichome stain with no significant increase in fibrosis, ruling out chronic liver disease, **B**) 10x view illustrating moderate portal and lobular inflammation, **C**) 40x view of lobules with enhanced visualization of acidophil bodies present, **D**) 20x view highlighting lobular activity with cholestasis and scattered acidophil bodies.

core antigen, hepatitis Be antibody, and a hepatitis B viral PCR load of 21.9. The hepatitis B surface antibody was negative, indicating a chronic hepatitis B infection. Hepatitis A, C, D, and E were negative, ruling out possible acute co-infection or superinfection. Entacavir was initiated for the treatment of chronic hepatitis B. A liver biopsy was negative for fibrosis but showed evidence of acute hepatitis with moderate lobular inflammation, cholestasis, and lobular disarray with acidophil bodies suggestive of DILI.

Unfortunately, one month after discharge from the hospital, the patient was readmitted after she was evaluated at an outpatient visit. She was persistently nauseous with jaundice on physical exam. The patient had remained abstinent from herbal supplements. Labs on admission were notable for AST 2534, ALT 2244, ALP 196, total bilirubin 10.5, INR 1.3. A liver transplant workup was completed during this admission. She underwent a repeat liver biopsy, which was definitively conclusive for DILI. She was discharged from the hospital as her labs and symptoms improved with supportive care.

DISCUSSION

Here, we present the first case of DILI secondary to *HRP-AID*. The Roussel Uclaf Causality Assessment Method (RUCAM) score, a metric utilized to determine the probability of causality between a particular agent and resultant liver injury (Hao et al., 2014), was five, correlating to "possible" causality.

The mechanism of action between *HRP-AID* supplementation and liver injury is unclear. An obfuscating factor is that the supplement contains various components. Some ingredients are associated with liver injury in the literature. There have been reports of jaundice and liver injury resembling copper and iron overdose secondary to zinc toxicity, usually in supplement overuse ("StatPearls," 2022). Similarly, echinacea is a rare cause of clinically apparent liver injury (Xu et al., 2021). Case reports have described episodes of hepatitis and jaundice but with complete rapid recovery after stopping the supplement (Lawrenson et al., 2014). Ginseng has been associated with liver injury, mainly when used with other potentially

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hepatotoxic medications due to its effect on cytochrome P450 enzymes (Laube & Liu, 2019; Mateo-Carrasco et al., 2012), although there have been reports of isolated ginseng-associated liver injury (Lin et al., 2018). Many of these agents may have contributed to the patient's liver injury. There is a possible role for synergism between several potentially hepatotoxic agents.

This patient's liver injury was attributable to using *HRP-AID* supplements after ruling out other causes of acute liver injury. Chronic hepatitis B infection was unlikely to be causing the level of acute liver inflammation seen on the biopsy, given the patient's low viral load (Seto et al., 2018). Similarly, the patient's concurrent use of lemon balm was an unlikely cause of the patient's significant liver injury. No case reports of lemon balm-related liver injury exist in the current literature; lemon balm is hepatoprotective in animal models of liver disease (Kim et al., 2020). Thus, it was reasonable to assume that the patient's liver injury was attributable to her usage of *HRP-AID* supplements.

In conclusion, our *HRP-AID* supplementation-induced liver injury case expands on the growing knowledge of the causes of DILI. This case highlights the importance of obtaining a comprehensive social history, including herbal and dietary supplements. Clinicians should maintain a high suspicion for DILI secondary to alternative causes, including supplementation use, after ruling out common causes of acute liver injury. Clinicians must familiarize themselves with potential hepatotoxic supplements, remembering that drug-induced liver injury may occur secondary to several potentially hepatotoxic substances taken concurrently.

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Author contributions:

A. Bhasin & P. Chun wrote the manuscript, reviewed the literature, and are the article guarantors. J. Bilello wrote the manuscript and reviewed the literature. D. Halegoua revised the manuscript. M. Ambelil provided the pathology slides and analysis.

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