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Drug induced Autoimmune Hepatitis: An unfortunate case of herbal toxicity from Skullcap supplement.

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Abstract

BACKGROUND

The surge in traditional herbal dietary supplement (HDS) popularity has led to increased drug-induced liver injuries (DILI). Despite lacking evidence of efficacy and being prohibited from making medical claims, their acceptance has risen over sevenfold in the last two decades, with roughly 50% of US adults using these supplements monthly. An estimated 23,000 emergency room visits annually in the US are linked to HDS side effects. NIH-funded research suggests HDS contribute to 7-20% of DILI cases, with similar trends in Europe—Spain reporting 2% and Iceland up to 16%. Patients with acute liver failure from HDS undergo liver transplantation more frequently than those from prescription medicines. Describing a case of drug-induced autoimmune hepatitis due to Skullcap supplements, this association appears to be the first documented in literature.

CASE SUMMARY

A middle-aged Caucasian woman, previously healthy, presented with sudden jaundice. Four months earlier, her liver enzymes were normal. She mentioned recent use of Skullcap mushroom supplements. Tests for chronic liver disease were negative. The first liver biopsy indicated severe resolving drug-induced liver injury. Despite treatment, she was readmitted due to worsening jaundice. Follow-up tests raised concerns about

autoimmune hepatitis. A subsequent biopsy confirmed this diagnosis. The patient responded as expected to stopping the medication.

CONCLUSION

This scenario highlights an uncommon instance of drug-induced liver injury (DILI) caused by Skullcap supplements. It's crucial for hepatologists to recognize this connection due to the increasing prevalence of herbal supplements.

INTRODUCTION

The rise in popularity of traditional herbal dietary supplements (HDS) has caused an increase in incidence of drug induced liver injury (DILI). Herbs and botanicals along with their extracts and metabolites fall under the umbrella term "dietary supplements" in the United States.[1] Even though these agents generally lack proof of efficacy and that their manufacturers are not permitted to make medical claims, their acceptance in the society has increased over 7-fold in the last two decades.[2] Approximately, 50% of the adult population in the United States admits to having used a "dietary supplement" in the last month.[3] It is estimated that there are 23,000 emergency room visits in the United States each year secondary to the side effects of HDS.[4] The true incidence of liver injury secondary in the United States to HDS is difficult to estimate. The NIH funded Drug Induced Liver Injury Network (DILIN) estimates that approximately 7-20% all cases of DILI are secondary to HDS.[5] Which is akin to the data from Europe, with Spain reporting 2% of all DILI cases as secondary to HDS and Iceland reporting the rate as high as 16%.[6,7] In addition, patients presenting with acute liver failure secondary to HDS have been found to undergo liver transplantation more frequently than those with DILI from prescription medicines, (56.1 *vs* 31.9%, $p < 0.005$).[8] As such, awareness about the side effects of these medications and a comprehensive understanding of their outcomes is paramount. Here we describe a case of drug induced autoimmune hepatitis (DIAIH)

resulting from Skullcap supplements. To our understanding, this is the first such association described in literature

CASE PRESENTATION

Chief complaints

New onset Jaundice

History of present illness

A 62-year-old Caucasian female, with a history of Sjogren's disease presented with generalized fatigue, arthralgias, pruritus and new onset jaundice. She denied any prior history of liver disease, alcohol intake, intravenous or intranasal drug use, blood transfusions or needlestick injuries. She did however endorse taking Skullcap supplements over for 1-2 months due to long standing history of anxiety and insomnia.

History of past illness

Sjogren's syndrome

Anxiety

Insomnia

Personal and family history

Nonsmoker, No alcohol or illicit Drug use. No GI related malignancy or Liver disease in the family.

Physical examination

General: Age appropriate female in no distress

HEENT: Atraumatic, normocephalic; scleral icterus present, moist mucous membranes.

CVS: S1S2+ RRR

Lungs: symmetric chest rise seen

Abdomen: soft, non-distended, non-tender, BS present, no palpable hepatomegaly appreciated

Extremities: No edema or clubbing

Skin: Jaundiced

Neuro: Alert, Awake, oriented x 3. No gross neuro deficits appreciated

Laboratory examinations

Her initial labs on presentation that were pertinent: Alkaline Phosphatase (Alk Phos) 164 IU/L, AST 1091 IU/L, ALT 980 IU/L, Total Bilirubin (T bili) 9.5, INR 2.4

The R factor on initial calculation was 20.5, indicative of a primary hepatocellular injury pattern.

IgG was elevated at 2573 mg/dL

Testing for Hepatitis A, B, and C, CMV, EBV, and HSV were all negative including serology and quantitative testing.

ANA was positive given her history of Sjogren's disease.

Her baseline AST, ALT, Alk phos and bilirubin were within normal range 4 months before presentation.

Imaging examinations

MRCP done at admission did not show any signs obstruction or primary hepatic pathology.

Case Summary

Given her prior history of autoimmune disease and new onset hypergammaglobulinemia in the context of suspected DILI, a liver biopsy was pursued. The initial liver biopsy showed resolving centrilobular necrosis with predominant eosinophilic inflammation. Due to down trending liver enzymes over the next 72 h, the patient was discharged with outpatient follow-up. However, the patient was admitted a month later with worsening jaundice, acute kidney injury, and new onset ascites concerning for subacute liver failure. Her LFTs were Alk Phos 619 IU/L, AST 1222 IU/L, ALT 540 IU/L, and T bili 6.6 mg/dL. Infectious workup was negative. Over the next few days, transaminases down trended but the T bili continued to rise, peaking at 11.8 mg/dL. Paracentesis showed a serum ascites albumin gradient of 1.4 which was consistent with portal hypertension. A repeat

liver biopsy was pursued which showed extensive plasma cells consistent with drug-induced autoimmune hepatitis (figure2). Unfortunately, the patient's course was complicated by the development of spontaneous bacterial peritonitis, GI bleed and acute tubular necrosis necessitating dialysis. As such, she was never challenged with steroids. Due to her worsening status, she was listed for a simultaneous liver kidney transplantation. However, the patient finally did improve following a long and protracted course with resolution of jaundice (figure1) but remained on hemodialysis.

FINAL DIAGNOSIS

DILI causing autoimmune Hepatitis

TREATMENT

Cessation of culprit drug

OUTCOME AND FOLLOW-UP

Resolution of Jaundice

DISCUSSION

The last three decades have heralded an increased use of herbal medicinal products with up to 25% of the adult American population admitting to their use at some point.[9] These products are not regulated by the FDA and their side effect profile remains largely unknown. Skullcap is a plant native to North America (*Scutellaria lateriflora*), which has been used for centuries to treat anxiety, digestive disorders, and menstrual disorders. Skullcap extracts contain large quantities of flavonoids like scutellarin and baicalin which account for its sedative and antispasmodic activities.[10] However, Skullcap has been associated with a mixed hepatocellular and cholestatic pattern of liver injury.

Additionally, majority of cases of DILI from Skullcap are attributed to Chinese Skullcap (*Scutellaria baicalensis)*, while the association of North American Skullcap with DILI is not

as robust.[11] In our case, as is evident form the biopsy and the corresponding serology, the patient did have DIAIH.

C*astiella* et al. have postulated a-5-fold classification for drug induced autoimmune liver disease.[12] Type 1, AIH with DILI: Reactivation of pre-existing AIH after the introduction of a new drug. Type 2, Drug induced Autoimmune Hepatitis (DI AIH): New onset AIH resulting from DILI. This results from an immune mediated reaction in a genetically primed individual, resulting in the necessitation of immunosuppressive treatment. Type 3, Immune Mediated DILI (IM DILI): acute or chronic liver injury that resolves upon cessation of the drug. DILI is often accompanied by a myriad of other features including fever, eosinophilia, lymphadenopathy, and rash. Individuals usually respond well to treatment and achieve sustained omission without relapse. Type 4, mixed autoimmune type: Mixed features of DI-AIH and IM-DILI. Individuals have a complete response to treatment, but relapse cannot be evaluated due to sustained immunosuppression for non-hepatological reasons. Lastly, type 5 encompasses individuals with DILI and positive autoimmune antibodies. The significance of these antibodies remains uncertain.

CONCLUSION

This case outlines a rare presentation of DILI from Skullcap supplements. Hepatologists must be aware of this association as the popularity of herbal supplements continues to rise.

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