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A unique case of autoimmune hepatitis: Can dietary weight-loss supplements act as toxin-induced precipitants?

Madeline Sterling, Sarang Kim

ABSTRACT

Introduction: Dietary and weight loss supplements have been shown to cause acute hepatitis through toxic liver injury. Herein, we present a case of a woman who was found to have both acute hepatitis and autoimmune hepatitis (AIH) in the setting of ingesting a popular weight loss supplement, Hydroxycut®. Case Report: A 29-year-old female without significant past medical history presented to our hospital with three weeks of abdominal pain, decreased appetite and jaundice. She intentionally lost 15 pounds in the last four months using two weight loss supplements, Hydroxycut and Herbalife. Initial lab work at her primary care physician's office revealed AST of 2409 U/L, ALT of 2000 U/L, TBili of 15.1 md/dL. She was advised to go to the emergency room given her physician's concern for liver injury. In the hospital, her vital signs were within normal limits (WNL) and her physical exam revealed jaundice, scleral icterus and mild epigastric tenderness, without encephalopathy. After other etiologies of acute hepatitis were ruled out, autoimmune panels were ordered which revealed an elevated ANA at 1:1280, A-SMA 1:10, normal AMA and LKM1 titers. An US-guided liver biopsy showed findings consistent with both acute hepatocyte necrosis secondary to toxin exposure and ongoing autoimmune hepatitis (AIH). She was started on prednisone and AZT for AIH and her transaminases, hyperbilirubinemia and jaundice improved. She was counseled on the dangers of herbal supplements. Conclusion: This case offers new insight into the conceptualization of AIH and the ability of weight-loss supplements to act as precipitants of both acute and chronic hepatitis. In the context of the obesity epidemic, more attention should be given to these dietary aids and their adverse effects.

Keywords: Autoimmune hepatitis, Herbal supplements, Hydroxycut, Liver injury, Public health, Toxicology, Weight loss supplements, Women's health

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INTRODUCTION

The use of herbal supplements and dietary weight loss aids has been steadily increasing. Although obese

and overweight women are the most frequent users, a significant percentage of normal weight women use dietary aids [1] and often do not disclose using them to physicians [2]. Without regulation by the FDA, these products are available for purchase without sufficient characterization, labeling of their components or safety testing [3]. Over the last decade, research has demonstrated that dietary and weight-loss supplements are capable of causing acute hepatitis secondary to drug induced liver injury (DILI) [4]. To date, it remains unclear whether such agents have the potential to induce autoimmune hepatitis and sustained liver damage.

In this report, we present a case of a woman who was diagnosed with both acute and autoimmune hepatitis (AIH) in the setting of ingesting dietary weight loss supplements for a sustained period of time. Here we review the patient's clinical presentation, diagnosis and treatment. We also suggest a new framework with which to conceptualize AIH in the context of dietary supplement use.

CASE REPORT

A 29-year-old female presented to our hospital complaining of three weeks of abdominal pain, decreased appetite and jaundice. She reported that her bowel movements were gray-white and her urine had been darker for two weeks. She denied fevers, chills or unintentional weight loss, pruritus, rashes or bleeding. Her last menstrual period was two weeks prior and she was not taking an oral-contraceptive pill. She saw her primary care physician (PCP) two days prior to admission because of jaundiced skin. She admits to having intentionally lost 15 pounds in the last four months and having used an herbal supplement, Hydroxycut®, for one month, last taken three months prior. At her PCP, initial lab work revealed AST of 2409 U/L, ALT of 2000 U/L, total bilirubin of 15.1 mg/dL and alkaline phosphatase 154 U/L. Lipid and Thyroid panels were within normal limits (WNL). The patient denied prior medical or surgical conditions, family history of Inflammatory bowel disease (IBD), hepatobiliary or autoimmune illnesses. She is from Mexico and emigrated with her family nine years ago to New Jersey, without recent travel. She denied recent infections, sick exposures, previous hepatitis infections, blood transfusions, or ingestion of prescribed medications.

The patient was afebrile with normal hemodynamics upon presentation. Her physical was remarkable for scleral icterus, jaundice, and mid-epigastric tenderness to palpation without rebound, guarding, murphy or psoas signs, hepatosplenomegaly or asterixis. Her laboratory examination was significant for AST 2270 U/L, ALT 1972 U/L, total bilirubin 25.7 mg/dL and direct bilirubin 15.7 mg/dL with INR 1.5 I/U. Given these findings, the patient was admitted and monitored closely; she was given vitamin K. Diagnostic evaluation was negative for hepatitis A, B, C, CMV and EBV. Autoimmune panels revealed elevated ANA at 1:1280, A-SMA of 1:10, negative AMA and negative ALK; gamma globulins were found to be 1.5 times the upper limit of normal (ULN). Her ceruloplasmin and iron studies were within normal limits. During her hospital course, the patient remained clinically stable and without encephalopathy. Transaminases and bilirubin decreased but remained elevated (AST 1375 U/L ALT 1149 U/L and total bilirubin 19.1 mg/dL, direct 10.4 mg/dL), prompting further evaluation with a diagnostic procedure.

An US-guided liver biopsy was performed. Two cores of parenchyma show evidence of acute and chronic disease processes. Ballooning hepatocytes and Mallory hyaline are suggestive of toxin-induced necrosis (Figure 1). Chronic active hepatitis evidenced by portal plasma cell infiltration (Figure 2), bridging necrosis and marked intrahepatic cholestasis (Figure 3) point to autoimmune hepatitis.

Following discharge, the patient was seen by university gastroenterologist, who started her on 30 mg prednisone and 50 mg AZT regimen. After six months of treatment, the patient's transaminases stabilized to AST 50 U/L and ALT of 74 U/L.

DISCUSSION

Autoimmune hepatitis (AIH) is characterized by unresolved inflammation of the liver of unknown etiology and is thought to result from a complex interaction of genetic predisposition, immunomodulatory mediators and environmental triggers [5]. It is considered a separate disease entity from acute livery injury, which is associated with various herbal preparations including ma huang (*Ephedra*), Jin Bu Huan, germander, chaparral, pennyroyal, kava, the nutritional supplement Herbalife® and the weight-loss aid Hydroxycut® [6].

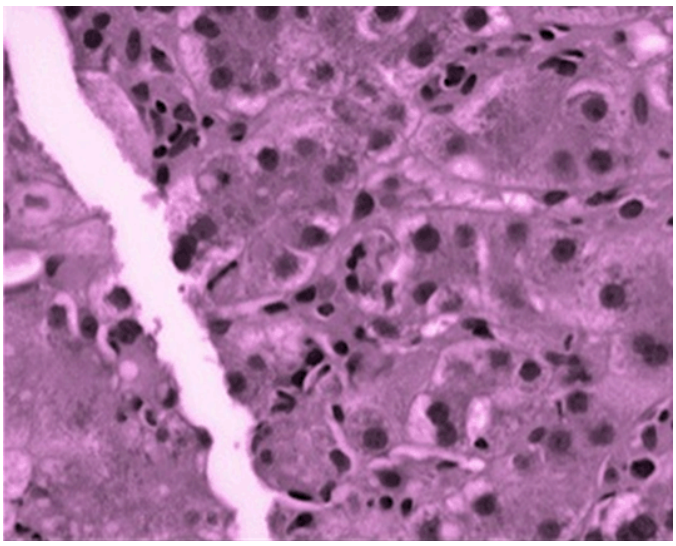

Figure 1: Ballooning hepatocytes with Mallory hyaline inclusions, suggested of acute toxic hepatitis (H&E stain, x400).

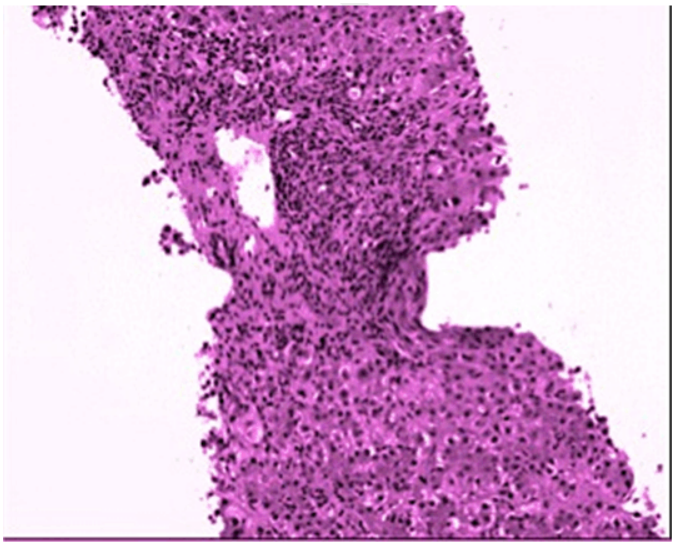

Figure 2: Portal plasma cell infiltration, focal bridging necrosis and ductile reactive fibrosis (H&E stain, x40).

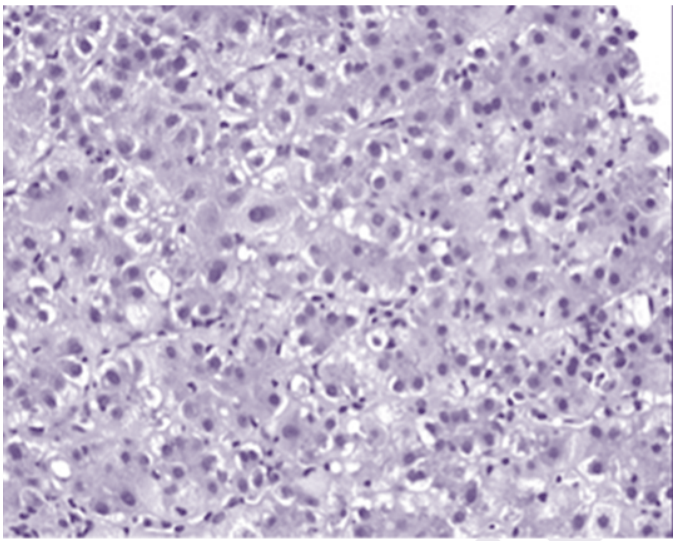

Figure 3: Intrahepatic cholestasis in AIH (magnification x100).

Although the patient initially reported using Hydroxycut® and Herbalife® for one month and three months respectively prior to admission, she later admitted to using them more frequently (almost daily for three months total) up to the time of admission. The patient's transaminases, hyperbilirubinemia with intrahepatic cholestasis and INR of 1.5 are consistent with sustained use of these supplements. The hepatotoxic components of these agents most likely to cause injury are Cambogia, *Camellia sinensis* and Chromium, which are found in several other weight-loss aids on the market such as thermo cut and *Garcinia* extreme [7, 8]. The classic features of acute hepatitis secondary to toxin exposure by the agents are seen on liver biopsy. Ballooning and apoptotic hepatocytes with Mallory hyaline inclusions can be visualized. Intrahepatic and canalicular cholestasis also suggest toxic injury.

Although the acute presentation, history of substance use and histologic features are consistent with drug toxicity, the patient's serologic studies and biopsy results also suggest drug-induced autoimmune hepatitis as an additional diagnosis. Although the onset of AIH is usually insidious, a fulminant presentation has been seen [9], especially after ruling out chronic viral hepatitis, non-alcoholic fatty liver disease, hereditary liver diseases, primary biliary cirrhosis and primary sclerosing cholangitis.

This patient had elevated antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) consistent with AIH; antibodies to liver/kidney microsomal type 1 (anti-LMK1) were absent, but these are rarely seen in US adults with AIH, only occurring in 4% of cases. Her liver biopsy demonstrates characteristic histologic features of AIH, including interface hepatitis, portal plasma cell infiltration, bridging fibrosis and lobular cholestasis [10]. Consistent with AIH treatment guidelines, the patient was placed on a regimen of prednisone and azathioprine and her transaminases improved with time.

This patient's clinical and pathological diagnoses suggest that both acute toxic hepatitis and an acute presentation of autoimmune hepatitis were present. The lobular inflammation and bridging fibrosis superimposed on portal and periportal hepatitis is consistent with an acute flare of subclinical disease.

Several prescribed medications have been shown to cause autoimmune hepatitis including minocycline, nitrofurantoin, methyldopa, NSAIDS, and hydralazine [11]. In recent years, herbal agents (black cohosh, greater celandine and dai-saiko-to) have been shown to inflict immune-histologic features on liver biopsy [12]. Few reports, however, have considered weight loss supplements to act as precipitants of autoimmune disease, apart from their ability to inflict toxin-induced hepatitis. Given this patient's dual diagnosis of acute hepatitis and autoimmune hepatitis, it is important to consider the long-term and chronic effects that dietary supplements can have.

There is much to be learned regarding the mechanism by which a subset of herbal and dietary supplements can induce autoimmune hepatitis. It has been suggested that in a genetically susceptible individual, the drug is recognized as a neo-antigen and the host goes on to produce antibodies to the agent and autoantibodies to itself [13]. Through a chain like mechanism, acting much like a drug-hapten model, a necroinflammatory process ensues in the liver and autoimmune disease results. This case highlights the variability in which such a disease process comes to clinical attention. Although a diagnosis of AIH was made, we are unable to speculate how long the patient was suffering from AIH. The dietary agent(s) may have triggered autoimmune disease much like they trigger acute hepatitis. Or, the agents may have brought an ongoing, subclinical illness to clinical attention.

CONCLUSION

This case highlights the need for physicians and healthcare providers to be aware of such products and their dangers. Over the last five years, research has found weight loss supplements to cause severe hepatic toxicity. In recent years, certain weight loss supplements - including Hydroxycut - have been recalled by the FDA due to their association with hepatic toxicity. In patients with underlying chronic or autoimmune diseases, the effects of herbal and weight loss supplements may be even more significant. Further clinical and epidemiologic research is needed to ascertain the mechanism by which they cause damage and the prevalence and effects of their use among susceptible population.

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Author Contributions

Madeline Sterling – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Sarang Kim – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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