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CASE REPORT

Acute liver injury induced by weight-loss herbal supplements

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Abstract

We report three cases of patients with acute liver injury induced by weight-loss herbal supplements. One patient took Hydroxycut while the other two took Herbalife supplements. Liver biopsies for all patients demonstrated findings consistent with drug-induced acute liver injury. To our knowledge, we are the first institute to report acute liver injury from both of these two types of weight-loss herbal supplements together as a case series. The series emphasizes the importance of taking a cautious approach when consuming herbal supplements for the purpose of weight loss.

Key words: Hydroxycut; Herbalife; Hepatotoxicity; Herbal; Weight-loss

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INTRODUCTION

We have seen a significant increase in the popularity and usage of over the counter herbal supplements over the past few years[1]. Unfortunately, the majority of these herbal supplements are not regulated by drug administrations worldwide. Many herbal supplements contain compounds that carry potentially severe side effects including hepatotoxicity. We report three cases of acute liver injury induced by weight-loss herbal supplements. Hydroxycut (MuscleTech, Mississauga, Ontario, Canada) (case 1) and Herbalife (Herbalife, Los Angeles, USA) (cases 2 and 3) supplements were the suspected culprits of acute liver injury. Hydroxycut is a popular dietary supplement consisting of a variety of herbal mixtures that claims to enhance the weight loss process[2]. Acute liver injury associated with Hydroxycut use has been previously reported, but only one case had liver biopsy data showing cholestasis and portal inflammation[3-6]. Similarly, Herbalife weight-loss dietary products are popular supplements consisting of a variety of herbal mixtures that claim to facilitate weight reduction[7]. Cases of acute liver injury after consumption of Herbalife products have been previously reported, with two patients developing fulminant liver failure requiring

liver transplantation. The first patient survived while the second died[8-11]. In all of our cases, we were able to demonstrate drug-induced acute liver injury on liver biopsy specimens.

CASE REPORT

Case 1

A 31-year-old woman presented to our hospital complaining of 2-wk history of fatigue, jaundice, and nausea. She denied any prior medical or surgical conditions, family history of liver disease, and acetaminophen or prescription medication use. She further denied history of blood transfusion, tattoo, alcohol use, or recreational drug use. She had been taking Hydroxycut for one year to enhance her weight loss. She had been taking the recommended dose of 2 tablets twice a day.

The patient was afebrile with normal hemodynamics upon presentation. Her physical examination was remarkable for generalized jaundice, scleral icterus, and mild upper quadrant tenderness to palpation without rebound or guarding. Initial laboratory studies were significant for serum aspartate aminotransferase (AST) level of 1407 U/L (normal range 15-41), serum alanine aminotransferase (ALT) level of 1278 U/L (normal range 7-35), serum alkaline phosphatase of 256 U/L (normal range 38-126), serum total bilirubin (TB) of 7.1 mg/dL (normal range 0.2-1.2), and international normalized ratio (INR) of 1.3 I/U (normal range 0.8-1.2). Given these findings, patient was admitted to the hospital for a higher level of care.

Standard blood tests were negative for hepatitis A, B, C, E, Ebstein Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody, alpha-1-antitrypsin deficiency, and anti-mitochondrial antibody. Serum acetaminophen and urine toxicity screens were negative. Serum ceruloplasmin, ferritin, iron studies, and immunoglobulins were all within the normal range. Right upper quadrant ultrasound showed diffuse echogenicity of the liver. Liver biopsy was performed and showed multi-lobular necrosis consistent with acute toxic necrosis and fulminant hepatitis (Figure 1).

The patient's liver function tests peaked 4 d after admission with serum AST level of 1613 U/L, ALT level of 1227 U/L, serum alkaline phosphatase of 268 U/L, serum TB of 10.5 mg/dL, and INR staying at 1.3 I/U. She did not develop evidence of hypoglycemia or portal-systemic encephalopathy. Her jaundice and scleral icterus resolved over the following 2-wk. Her liver tests gradually improved within the following few months.

Case 2

A 37-year-old woman presented to our hospital with a 1-mo history of diffuse abdominal pain, mild nausea, and painless jaundice. She denied any past medical or surgical history, family history of liver disease, or any alcohol or illicit substance abuse. She admitted that she had been taking Herbalife dietary supplements for the past 3-mo in an attempt to lose weight. Her Herbalife regimen consisted of the Formula One Nutritional Shake Mix, the Multivitamin Complex, the Cell Activator, the Cell-U-Loss, the Herbal Concentrate Original, and the Total Control formula.

The patient was afebrile with normal vital signs on presentation. Her physical exam was noticeable for bilateral scleral icterus and generalized jaundice. Her abdominal exam revealed a non-tender, non-distended abdomen with no stigmata of liver disease. Initial laboratory studies were significant for an AST level of 2199 U/L, serum ALT level of 2068 U/L, serum alkaline phosphatase of 185 U/L, and TB of 15.3 mg/dL. All other laboratory values, including amylase, lipase, and INR, were within normal limits. Given these lab abnormalities, the patient was admitted to the hospital for further work-up.

Standard blood tests were negative for hepatitis A, B, C, E, EBV, CMV, HIV, antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody, alpha-1-antitrypsin deficiency, and anti-mitochondrial antibody. Serum acetaminophen and urine toxicity screens were negative. Serum ceruloplasmin, ferritin, iron studies, and immunoglobulins were all within normal range. A computerized tomography (CT) scan of the abdomen and pelvis with intravenous (IV) contrast showed multiple low-density lesions in the liver measuring up to 8-mm. A liver biopsy revealed acute necrotizing hepatitis both centrolobular and periportal, consistent with a drug-induced etiology (Figure 2). However, her liver biopsy specimens also showed evidence of bridging fibrosis, which suggest some degree of chronic liver disease but with drug-induced injury in addition.

The patient was treated supportively with fluids and nutrition. Her liver tests steadily declined from the day of admission and on hospital day 8 (day of discharge) her liver tests revealed a AST level of 1788 U/L, ALT level of 1501 U/L, and serum alkaline phosphatase of 183 U/L. The only laboratory value to increase was the patient's serum TB, which was at 29.9 mg/dL on discharge. The patient did not develop encephalopathy, hypoglycemia, or any other complications. The patient was followed for several months, throughout which her symptoms continued to improve.

At her 2-mo follow-up, the patient's icterus and jaundice had resolved completely. Her labs at this time showed a serum AST level of 51 U/L, serum ALT level of 43 U/L, serum alkaline phosphatase of 65 U/L, and serum TB of 1.1 mg/dL.

Case 3

A 53-year-old previously healthy woman presented with a 3-wk history of painless jaundice and pruritus. She denied any family history of liver disease, or any alcohol or illicit substance abuse. She had not been taking any new prescribed medications. On further questioning about over-the-counter supplements she divulged a 4-mo history of consuming various Herbalife weight loss products in the form of shakes, teas and pills.

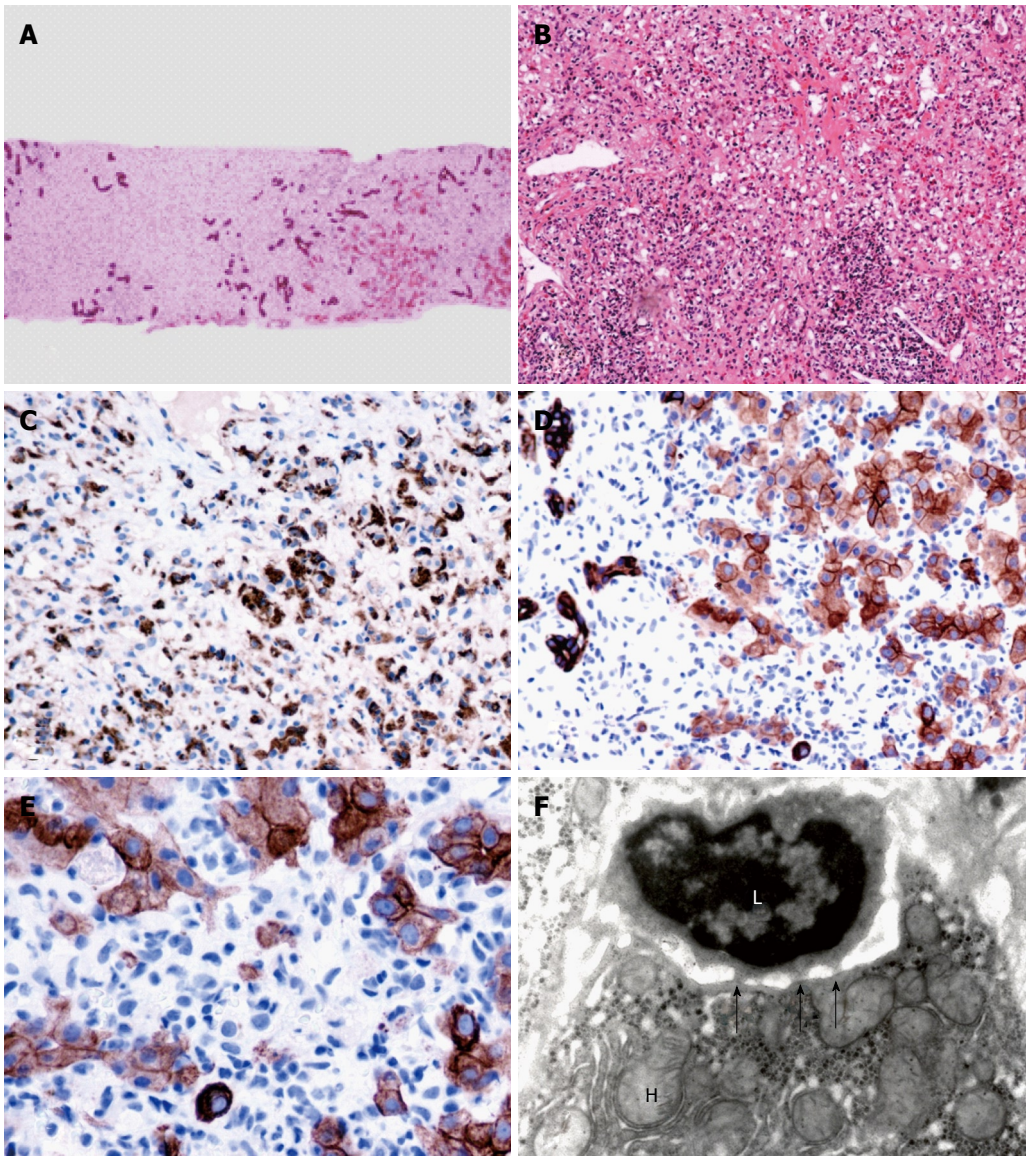

Figure 1 Liver biopsy showed extensive patchy areas of multilobular necrosis with only bile ducts remaining, extensive ductal metaplasia, severe lymphocytic and macrophages in filtration of portal tracts and lobular parenchyma and patchy plasma cell infiltrates. Histological changes were consistent with acute troxis necrosis and fulminant hepatitis. A: Liver lobules showing massive necrosis with only bile ducts remaining (hematoxiline and eosin stain × 52); B: Lymphocytic infiltration of portal tract and lobular parenchyma (hematoxiline and eosin stain × 130); C: Liver lobular necrosis with macrophages cleaning the debris (CD68 stain × 130); D: Ductal metaplasia. Lymphocytic infiltration in the sinusoids (CAM5.2 stain × 260); E: High power, lymphocytes destroying hepatocytes (CAM5.2 stain × 520); F: Lymphocyte "eating" hepatocytes in a liver parenchyma (troxis necrosis), arrow showing immunological synapses (Electron microscopy × 15000).

On physical exam the patient's vital signs were within normal limits. On general inspection she had scleral icterus and jaundice, with evidence of excoriations. A 2-cm palpable liver edge could be appreciated, that was tender to touch. There were no other signs of chronic liver disease. Initial laboratory values revealed a hepatocellular pattern of injury, with an AST of 1282 U/L, ALT of 983 U/L, and alkaline phosphatase of 292 U/L, with a TB of 18.2 mg/dL. An ultrasound showed borderline hepatomegaly of 17-cm.

Standard blood tests for hepatitis A, B, C, E, EBV, CMV, HIV, antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody, alpha-1-antitrypsin deficiency, and anti-mitochondrial antibody were negative. Serum acetaminophen and urine toxicity screens were negative. Serum ceruloplasmin, ferritin, iron studies, and immunoglobulins were all within normal range.

Liver biopsy was performed and showed cholestasis, consistent with drug induced hepatitis (Figure 3). 2-mo after complete abstinence from the Herbalife supplements her jaundice resolved, as did her liver tests.

DISCUSSION

Acute liver injury induced by over the counter weight-loss herbal supplement Hydroxycut and Herbalife products have been reported previously[3-6,8-11]. These case reports were limited by the fact that liver biopsies were performed in only a few patients, confirming clinical suspicions histologically. In terms of our patients, all three had liver biopsy performed and all showed some common morphological features including diffuse lymphocytic infiltration of sinusoids and portal tracts, ductal metaplasia and toxic necrosis. Some variations of morphological features could be explained by predominance of intrinsic or idiosyncratic mechanisms of hepatic injury, individual patient response to the affecting drug and duration of injury. The patients' liver biopsy specimens were stained with periodic acid-Schiff (PAS) stain with diastase. No hyaline globules were identified in any of the three cases. The absence of histological findings and the fact that our patients had no history of chronic obstructive pulmonary disease excluded diagnosis of alpha-1-antitripsin deficiency in all three

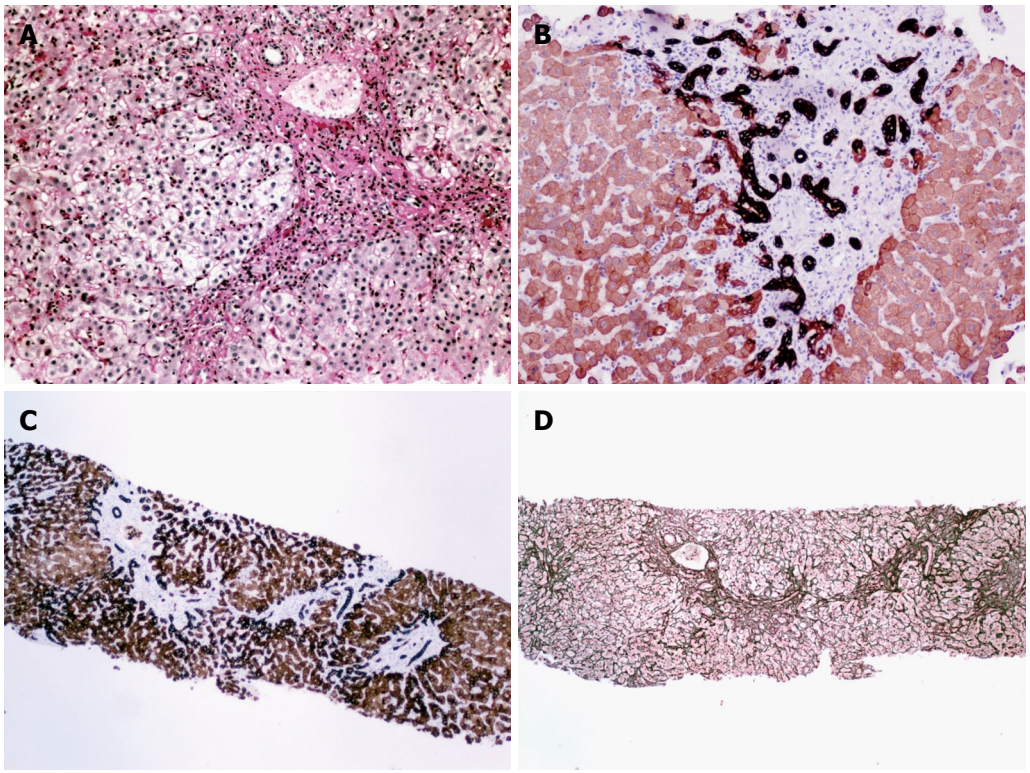

Figure 2 Liver biopsy was performed and showed pe riportal bridging fibrosis, ductal metaplasia, cholestasis, moderate intralobular lymphocytic infiltration, and troxis necrosis and ap optosis consistent with dr ug-induced hepatitis on top chronic liver disease. A: Li ver showing periportal fibro sis and cholestasis (periodic acid-Schiff stain × 130); B: Portal tract showing duc tal metaplasia and peripor tal fibrosis (AE1/AE3 stain × 260); C: Portal - portal bridging fibrosis (CAM5.2 stain × 52); D: Portal - portal bridging fibrosis (Reticu lin stain × 52).

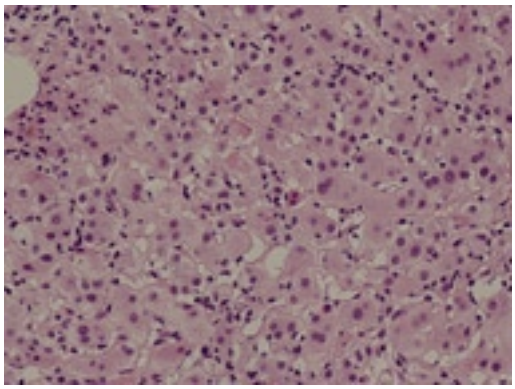

Figure 3 A liver biopsy revealed acute hepatitis characterized by hepatocellular injury, with periportal fibrosis, cholestasis, ductal metaplasia and diffuse intralobular and periportal troxis necrosis consistent with a drug-induced etiology. Intralobular lymphocytic infiltration. Arrow showing apoptosis of hepatocytes (hematoxiline and eosin stain × 260).

cases. Prussian blue and copper stains did not reveal excessive iron or copper depositions in the hepatocytes and Kupffer cells.

Only one previous case of Hydroxycut-induced acute liver injury had reported findings on liver biopsy. Although the most likely explanation for the mechanism of liver injury caused by these herbal products is idiosyncratic reaction, one of the ingredients in Hydroxycut, green tea extract (*Camellia sinensis*), has been linked with acute liver injury in other over the counter weight-loss herbal supplements[12-20]. In fact, the weight-loss herbal supplement Exolise (Arkopharma, Carros, France), which also contained *C. sinensis*, was withdrawn from the market because it was linked to multiple cases of liver injury[13]. Furthermore, several cases of hepatotoxicity were associated with another herbal weight-loss supplement, Cuur (Scandinavian Clinical Nutrition, Sweden), which also contains the ethanolic dry extract of green tea (*C. sinensis*)[15]. Rechallenging patients with the same product led to hepatotoxicity, confirming the role of *C. sinensis*[12,16]. In all reported cases of acute liver injury induced by Hydroxycut, patients' liver function tests recovered over time following cessation of the product. However, there have been cases of liver failure caused by green tea extract *C. sinensis,* requiring orthotopic liver transplantation[13,16].

The liver biopsy obtained in our patient who took Hydroxycut showed multi-lobular necrosis consistent with acute toxic necrosis and fulminant hepatitis. These findings are similar to the findings in patients with liver injury associated with green tea extract *C. sinensis*, where prominent necrosis with inflammatory reaction is the hallmark presentation[15,16].

The exact mechanism of hepatotoxicity induced by Hydroxycut is unknown. However, as this product contains green tea extract *C. sinensis*, it is possible that this may play a role in acute liver injury caused by Hydroxycut. Prior investigation into the mechanism of hepatotoxicity by green tea extract was inconclusive[21]. Others have hypothesized that a possible allergic reaction to the green tea extract, contamination during the production of the extract or a metabolic idiosyncrasy are possible mechanisms of liver injury in these patients[16].

Both of our patients took several Herbalife weight-loss herbal products concurrently, similar to most of the previously reported cases of hepatotoxicity due to Herbalife products[8-11]. Therefore, it is difficult to identify the exact ingredient or mechanism that causes the liver injury, as in the previously documented cases[8-11]. In a previously reported case, one investigator was able to isolate contami-

nation with *Bacillus subtilis*, in which the bacterial supernatant caused dose-dependent increase of LDH leakage in HepG2 cells[8]. Although not commonly known as a human pathogen, *B. subtiliis* has been reported to cause food poisonings and a case of cholangitis in an immunocompromised patient[22-23]. Investigators have also suggested that another explanation for hepatotoxicity due to Herbalife products could be secondary to locally restricted contamination with chemicals such as softeners, preservatives, flavor enhancers, pesticides, or heavy metals either intentionally added during the production process or contained in the unrefined raw herb extracts[24].

To date, Herbalife has refused to provide detailed analyses of their products' composition and ingredients[25]. This contamination hypothesis could also explain the different patterns of pathology seen on liver biopsy specimens previously observed in patients with hepatotoxicity from Herbalife products as both predominantly cholestatic injury pattern and acute hepatitis pattern have been reported[8-11]. Our patients had findings consistent with acute hepatitis due to drug-induced liver injury on their liver biopsy specimens.

Due to the obesity epidemic, the usage of weight-loss herbal supplements has flourished. Green tea extract is one of the key components in many of the over-the-counter weight-loss herbal supplements. Although significant liver injury induced by herbal supplements taken for weight loss purposes is a rare event, we cannot ignore the fact that there have been multiple reported cases in the medical literature of hepatotoxicity associated with weight-loss herbal supplements including Hydroxycut and Herbalife products. Even though our patients successfully recovered from the adverse reactions, we must bear in mind that the hospitalization and medical care of these patients were associated with significant cost and healthcare resource utilization, while there is no evidence that herbal supplements can help with weight-loss[26]. We must also consider the impact on patients with underlying chronic liver disease, in whom herbal weight loss medications could cause worsening in their synthetic function and even fulminant failure. In May of 2009, the US Food and Drug Administration warned consumers to immediately stop using Hydroxycut products, citing linkage to liver damage in one patient who died due to liver failure[27]. However, Hydroxycut products are currently still available in many parts of the world. Likewise, Herbalife products are widely available globally. Therefore, it is these authors' view that closer monitoring of patients taking weight-loss herbal supplements as well as tighter regulation from government drug agencies is warranted. Furthermore, our cases once again demonstrated the importance of questioning patients regarding the usage of herbal or nutritional supplements at the time of evaluation.

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