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CASE REPORT

Hepatology

Herbal and dietary supplement induced liver injury leading to hepatitis-associated severe aplastic anemia: A case report

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Abstract

Herbal and dietary supplements (HDS) are a common etiology of drug induced liver injury and, specifically, Herbalife® supplements have been implicated. Hepatitis associated aplastic anemia (HAAA) is a rare and potentially fatal complication after acute hepatitis characterized by pancytopenia. While there have been rare cases of HDS leading to HAAA, no cases of Herbalife® induced liver injury leading to HAAA have been reported from this specific HDS. We report a unique case of severe aplastic anemia developing after sub-fulminant liver failure associated with chronic HDS use. This case illustrates the importance of warning the public about HDS as their use continues to increase. It is not only important to recognize HDS as etiology, but also for healthcare providers to carefully monitor these patients after resolution of liver injury for the development of HAAA.

KEYWORDS

drug induced liver injury, herbal and dietary supplements, Herbalife®, liver failure

1 | INTRODUCTION

Diagnosis of drug induced liver injury (DILI) is challenging due to varied presentations including hepatocellular, cholestatic, or mixed.[1] Idiosyncratic DILI occurs with agents that infrequently cause liver damage and in an unpredictable manner.[1] Herbal and dietary supplements (HDS) have been shown to cause idiosyncratic DILI and account for 15.5% of DILI cases in the United States.[1,2] Specifically, Herbalife® supplements as consumed by the patient in this case report, which are HDS marketed to support balanced nutrition and weight loss, have been implicated in HDS induced liver injury, and there are few reports of liver failure due to HDS (Table S2).[3–6]

Hepatitis-associated aplastic anemia (HAAA) is a rare complication after acute hepatitis characterized by pancytopenia. It is often fatal without prompt treatment with bone marrow transplantation, which is standard of care, or immunosuppression. HAAA is responsible for approximately 5% of all cases of acquired severe aplastic anemia.[7] Frequently the etiology of the initial liver disease remains unknown but can be seen after infectious liver injury.[7,8] Rare cases of HAAA after

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug induced liver injury; GGT, gamma-glutamyl transferase; HAAA, hepatitis-associated aplastic anemia; hATG, horse anti-thymocyte globulin; HDS, herbal and dietary supplements; INR, international normalized ratio.

acute hepatitis from HDS have been reported, although not specifically associated with this HDS.[8,9] This report highlights the need for healthcare providers to maintain a high index of suspicion for DILI secondary to HDS use in patients with liver injury, and to diligently follow-up for complications such as HAAA even after discontinuation of HDS.

2 | CASE REPORT

We present the case of a 13-year-old male with subfulminant liver failure who subsequently developed severe aplastic anemia. He presented with 1 week of abdominal pain, fatigue, poor appetite, transient nausea and vomiting, and 1 day of jaundice. On admission his laboratory data was consistent with hepatitis, cholestasis, and mild coagulopathy (Figure 1). He was transferred to a pediatric hospital with hepatology subspecialty care on day 4 of admission. Abdominal ultrasound demonstrated gallbladder wall and periportal edema). Although his clinical symptoms improved, his liver inflammation and function continued to worsen on the day of his transfer (Figure 1).

Liver biopsy demonstrated mixed portal and lobular inflammation including eosinophils and rare plasma cells as well as lobular disarray and hepatocellular necrosis, consistent with acute hepatitis without features of underlying chronic or metabolic liver diseases (Figure 2A,B). He had an extensive laboratory evaluation for infectious, metabolic, and autoimmune etiologies which were all negative (Table S1). Due to continued increase in alanine aminotransferase and conjugated bilirubin, and concern for possible bacterial cholangitis given neutrophils on liver biopsy, a brief trial of piperacillin/tazobactam was initiated without improvement. A trial of methylprednisolone was initiated for indeterminant hepatitis with significant improvement in conjugated bilirubin and liver enzymes. On day 20 of admission, the family revealed that he had consumed this specific Herbalife Formula 1® daily for 5 months before admission, as well as intermittent consumption of the Herbalife Protein drink mix®. HDS induced liver injury was the presumed etiology of his liver injury given otherwise negative work up. He was discharged on day 22 of admission with improving laboratory values (Figure 1).

After discharge he was slowly weaned off oral steroids, with normalization of conjugated bilirubin 4 weeks after discharge. Repeat liver biopsy for rising liver enzymes, 3 months after the first, showed significant interval improvement with only mild residual inflammation (Figure 2C) and without residual fibrosis (Figure 2D).

During routine hepatology follow up, 71 days from initial presentation, his platelet and white blood cell counts were first noted to drop (Figure 1). Hematology/oncology was consulted, and bone marrow biopsy was performed 106 days from initial presentation due to continued dropping blood counts with neutropenia and lymphopenia concerning for bone marrow failure vs infection. Bone marrow biopsy demonstrated markedly hypocellular bone marrow (5%–10%) with panhypoplasia, without evidence of dysplasia or blasts (Figure 3A). Fanconi anemia and dyskeratosis congenita were ruled out. He was diagnosed with severe HAAA (Figure 1). Since he did not have any matched sibling donors for bone marrow transplant, he received immunosuppressive therapy with horse anti-thymocyte globulin (hATG) and oral cyclosporine (Figure 1). A second bone marrow biopsy performed 3 months after initial aplastic anemia treatment demonstrated normalization of marrow (Figure 3B). He had a complete response to immunosuppressive therapies by 5 months and is currently being weaned off oral cyclosporine. Two years from initial presentation, he continues to be

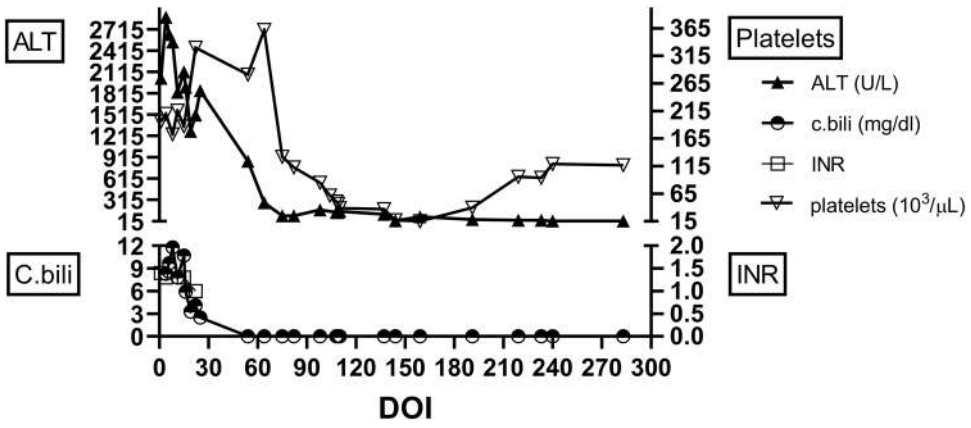

FIGURE 1 Laboratory value trend from initial admission including conjugated bilirubin (c. bili), international normalized ratio (INR), alanine aminotransferase (ALT), and platelets. Initial liver and bone marrow biopsies indicated. Initiation of treatment for hepatitis associated aplastic anemia (HAAA) on day 138. There was a second liver biopsy on day 107 and second bone marrow biopsy on day 233.

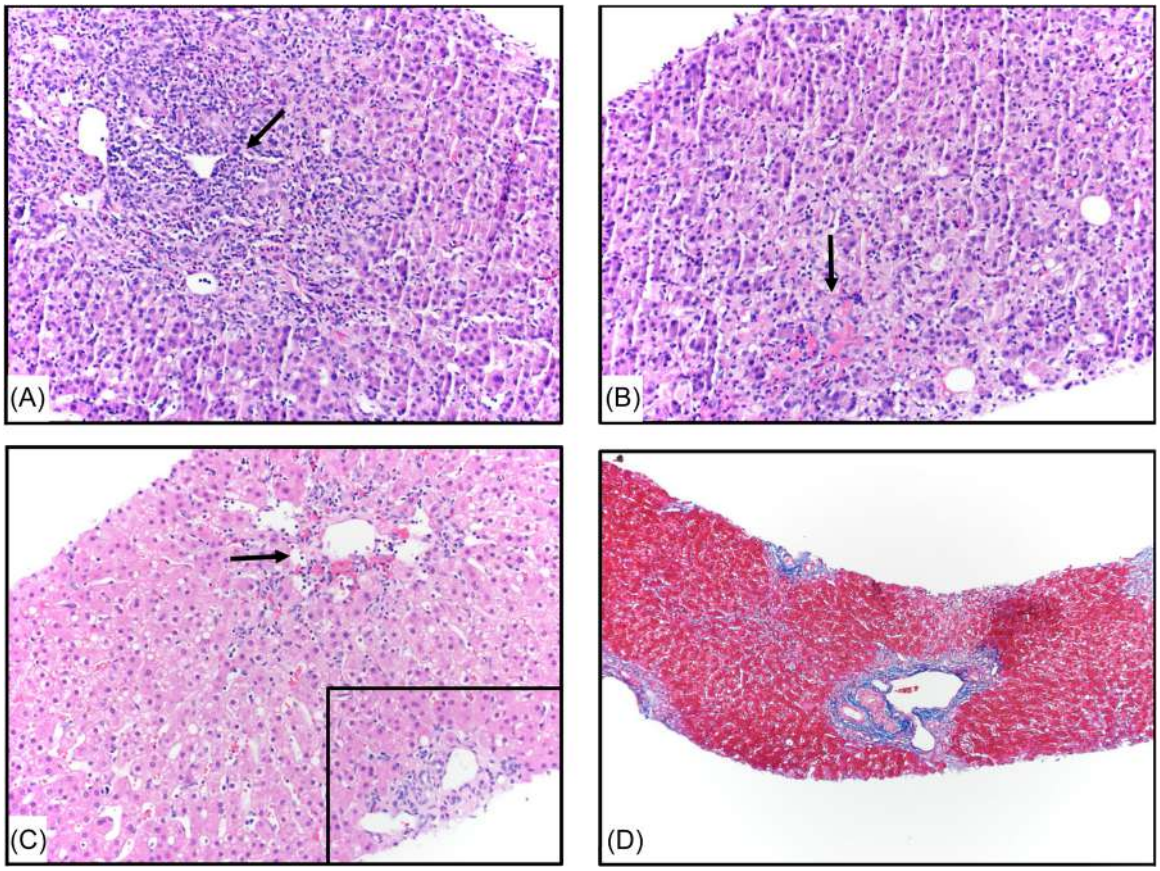

FIGURE 2 (A) Moderate/severe mixed inflammation, fewer lymphocytes and plasma cells involving the portal tracts (arrow). (B) Significant lobular disarray and hepatocellular necrosis. Multifocal zone 3 red cell extravasation and cell injury (arrow). (C) Mild zone 3 inflammation and injury (arrow). Majority of the portal tracts were unremarkable (inset). (D) No residual fibrosis.

clinically well with normal blood counts, aminotransferases, and conjugated bilirubin.

3 | DISCUSSION

The use of HDS globally continues to increase, with at least half of the US population reporting HDS use.[10] HDS use is a well-established etiology of DILI and the proportion of HDS induced liver injury cases worldwide has continued to increase over the years.[11] Specifically, these particular HDS supplements have been implicated in HDS induced liver injury in multiple studies.[3–5,12,13] This particular HDS is a brand of dietary supplements that contain multiple ingredients with varying formulations. In our patient, the diagnosis of sub-fulminant hepatic failure due to use of this particular HDS is supported by 3 main factors. There was no other etiology for his liver injury identified after extensive evaluation. The time course of his illness beginning 5 months after daily consumption of HDS is consistent with a previous study describing the average time to onset of symptoms in HDS induced livery injury.[5] Last, discontinuation of all HDS supplementation led to resolution of liver injury. In our patient, timing of developing cytopenias and subsequent HAAA diagnosis was consistent with other studies showing typical onset of HAAA 2–3 months from initial presentation with hepatitis.[7,14]

Our patient's recovery from sub-fulminant liver failure was complicated by development of HAAA.[7,14] Additionally, his age and sex place him in the highest prevalence category for the development of HAAA.[7,8] While it is not possible to prove causation by laboratory testing or biopsy that this is a case of HDS induced sub-fulminant hepatic failure associated with the development of HAAA from a particular HDS, we have described significant evidence based on previous studies to support this hypothesis. Furthermore, there are a few reports of HDS induced liver injury leading to HAAA (Table S2).[8,9]

As the use of HDS worldwide and specifically in the USA increases, cases of HDS induced liver injury will continue to become more common.[10,11] Knowledge of specific HDS, such as Herbalife® as described here, and the severity of the complications they may cause, including potential sub-fulminant liver failure and HAAA, will help to better equip pediatricians and gastroenterologists to take a comprehensive history

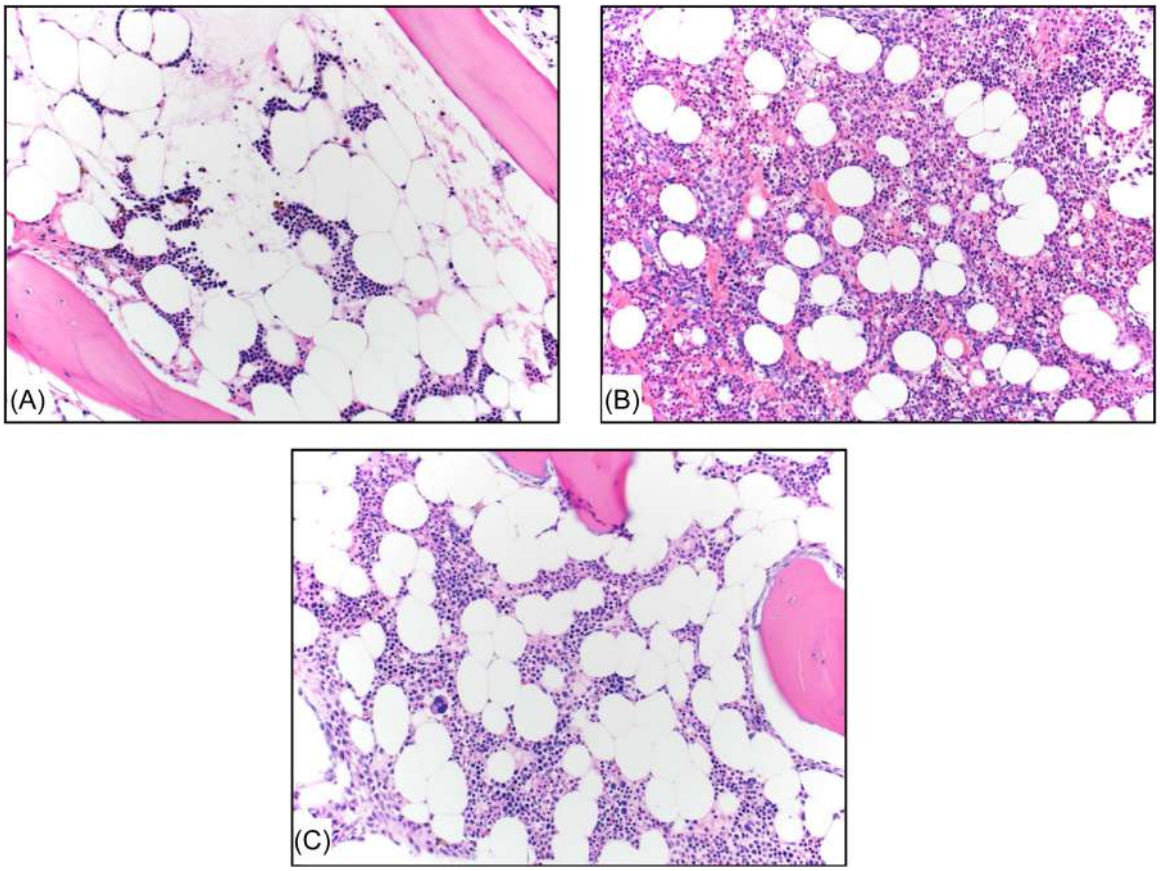

FIGURE 3 (A) Markedly hypocellular (5%–10%) marrow with panhypoplasia and relative erythroid predominance. (B) Normocellular marrow with trilineage hematopoiesis. (C) Hypocellular marrow (~30%) with trilineage hematopoiesis without any dysplastic features.

as well as to educate their patients about the potential risks associated with HDS. In addition, patients who have a history of HDS induced liver injury should be carefully monitored for the development of HAAA even after discontinuation of the supplement. HAAA is often fatal without prompt referral and treatment. This case report underscores the importance of continued surveillance and follow-up care for patients who have experienced HDS induced liver injury. While HDS induced liver injury due to Herbalife® consumption has been well documented, this case adds to the literature the first reported case of HAAA related to use of this specific HDS.

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CONFLICT OF INTEREST STATEMENT

Dr. Sanjiv Harpavat serves on a Data Safety Monitoring Board for a biliary atresia therapeutic trial, sponsored by Syneos Health. Dr. Rebecca Mercedes receives funding from the NIH T32 training grant number T32DK007664. All other authors declare no conflicts of interest relevant to this article to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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