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CASE REPORT | LIVER

Unexpected Drug-Induced Liver Injury Associated With MenoFit: A Synbiotic Menopause Supplement

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ABSTRACT

MenoFit is a widely available over-the-counter synbiotic supplement, which is marketed for use in relieving menopausal symptoms. So far, there is no published data on liver injury because of its use. We present the first reported case of MenoFit-induced liver injury in a patient who presented with 1 week of jaundice and abnormal liver biochemical tests in the absence of other risk factors and negative comprehensive workup for known etiologies of liver disease.

KEYWORDS: drug-induced liver injury; DILI; dietary supplements; menopause

INTRODUCTION

The use of herbal and dietary supplements (HDSs) is widespread on a global scale. In the United States, this market has grown from approximately $10 billion in 1994 to more than $35 billion in 2014.[1] According to the Drug-Induced Liver Injury Network (DILIN) registry, these products are responsible for nearly 20% of liver injury in adults,[2] and according to the World Health Organization, this is now the fifth most common cause of liver disease-associated death.[3] Regulation of these products in the United States is minimal, with HDS not requiring Food and Drug Administration (FDA) approval before 1994. For newer HDS, although manufacturers are responsible for ensuring safety, still no FDA approval is required because they are for drug products.[4] MenoFit, an over-the-counter synbiotic supplement commonly used for menopause symptoms relief, includes a proprietary blend of 28-ingredient formulation of probiotics, herbs, vitamins, and minerals.[5] MenoFit is produced by MenoLabs, with claims to significantly reduce hot flashes, mood swings, headaches, cramps, allergy symptoms, anxiousness, sleeplessness, and promote weight loss. To date, there is no published data on liver injury because of its use, and drug-induced liver injury (DILI) because of MenoFit has not yet been reported on LiverTox: An Online Resource for Information on DILI.[6] Therefore, to our knowledge, we present the first case of MenoFit-induced DILI.

CASE REPORT

A 47-year-old Hispanic woman with obesity was admitted for an evaluation of epigastric pain, weakness, fatigue, nausea, jaundice, and abnormal liver biochemical tests for 1 week. Approximately 2 months earlier, she had started taking 1 capsule of MenoFit daily without any prescription, and her last dose was the day before her presentation. She admitted the long-term use of daily vitamin A, C, magnesium, and ginger but denied using other medications or HDS and reported no alcohol or recreational substance use. Physical examination was unremarkable except for scleral icterus and jaundice, with normal mental status. Initial laboratory results indicated abnormal liver biochemical tests—(hepatocellular pattern), and a comprehensive workup was negative for viral, autoimmune, or genetic causes (Table 1). Abdominal magnetic resonance imaging showed a heterogeneous liver with a smooth contour, borderline splenomegaly, and a 10-mm dilation of the common bile duct without choledocholithiasis, most likely because of previous cholecystectomy. The patient underwent a transjugular liver biopsy, which showed hepatocellular damage, with marked portal and lobular inflammation and early bridging necroinflammatory activity (Figure 1). All portal tracts were expanded by a mixed inflammatory infiltrate, including lymphocytes, neutrophils, eosinophils, and occasional plasma cells, with focal interface hepatitis.

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Table 1. Laboratory values during and after hospitalization

Laboratory test (reference with units)	Day of presentation	Day 5 after presentation	2 months later
White blood cell (3,500–10,500 cells/mm^3)	3,700		
Hemoglobin (11.2–15.7 g/dL)	12.9		
Platelets (150,000–450,000 cells/mm^3)	178,000		
Blood urea nitrogen (7–21 mg/dL)	10		
Creatinine (0.57–1.25 mg/dL)	0.72		
Alkaline phosphatase (40–150 U/L)	159	184	109
Aspartate aminotransferase (5–34 U/L)	1,671	2,190	134
Alanine aminotransferase (6–55 U/L)	2,104	2,564	164
Total bilirubin (0.2–1.2 mg/dL)	5.8	8.6	0.7
Direct bilirubin (0.1–0.5 mg/dL)	4		0.3
International normalized ratio (0.9–1.1)	1.23	1.3	
Albumin (3.5–5.0 g/dL)	3.7		
Hepatitis A, B, C, E	Negative		
Cytomegalovirus viral load	Negative		
Epstein-Barr virus viral load	Negative		
HIV 1 and 2	Negative		
Adenovirus viral load	Negative		
Influenza A/B PCR	Negative		
COVID-19 PCR	Negative		
Urine drug screen	Negative		
Serum alcohol level (<10 mg/dL)	<10 mg/dL		
Acetaminophen/salicylate level	Undetectable		
Antinuclear antibody	1:160		
Antismooth muscle antibody	Negative		
Antimitochondrial antibody	Negative		
Immunoglobulin G (540–1,822 mg/dL)	1,338		
Serum iron (40–160 μg/dL)	288		
Total iron binding capacity (250–450 μg/dL)	298		
Iron saturation (20%–55%)	97%		
Ferritin (5–275 ng/mL)	2,757		
Hemochromatosis gene (HFE) mutation	Negative		
Ceruloplasmin (18–53 mg/dL)	29		
Alpha-1-antitrypsin (90–200 mg/dL)	190.5		
Urine pregnancy test	Negative		
Blood cultures	Negative		

Perivenular hepatocytic dropout was noted (zone 3), with numerous inflammatory cells (Figure 1). The hepatic lobules showed numerous foci of inflammation and individual apoptotic hepatocytes (Figure 1). No significant cholestasis, steatosis, Mallory Denk bodies, or ballooning degeneration were seen. Trichrome stain showed no evidence of established fibrosis (Figure 1). These findings, along with the timing of the new supplement, were consistent with DILI. MenoFit was discontinued on admission. Her hospital course was complicated by elevated liver tests, peaking on days 4–5 (Table 1, Figure 2). Owing to worsening liver tests and severe histologic hepatocellular damage, a diagnosis of immunoallergic DILI was made, and intravenous methylprednisolone was started on day 5, resulting in significant improvement of liver tests. She was discharged on a prednisone taper for 6 weeks. The patient was instructed to abstain from taking any supplements. Two weeks after discontinuing prednisone (almost 2 months after discontinuing MenoFit), the liver tests continued to improve (Table 1, Figure 2). Liver tests beyond day 61 were not available; therefore, we cannot confirm whether they subsequently normalized.

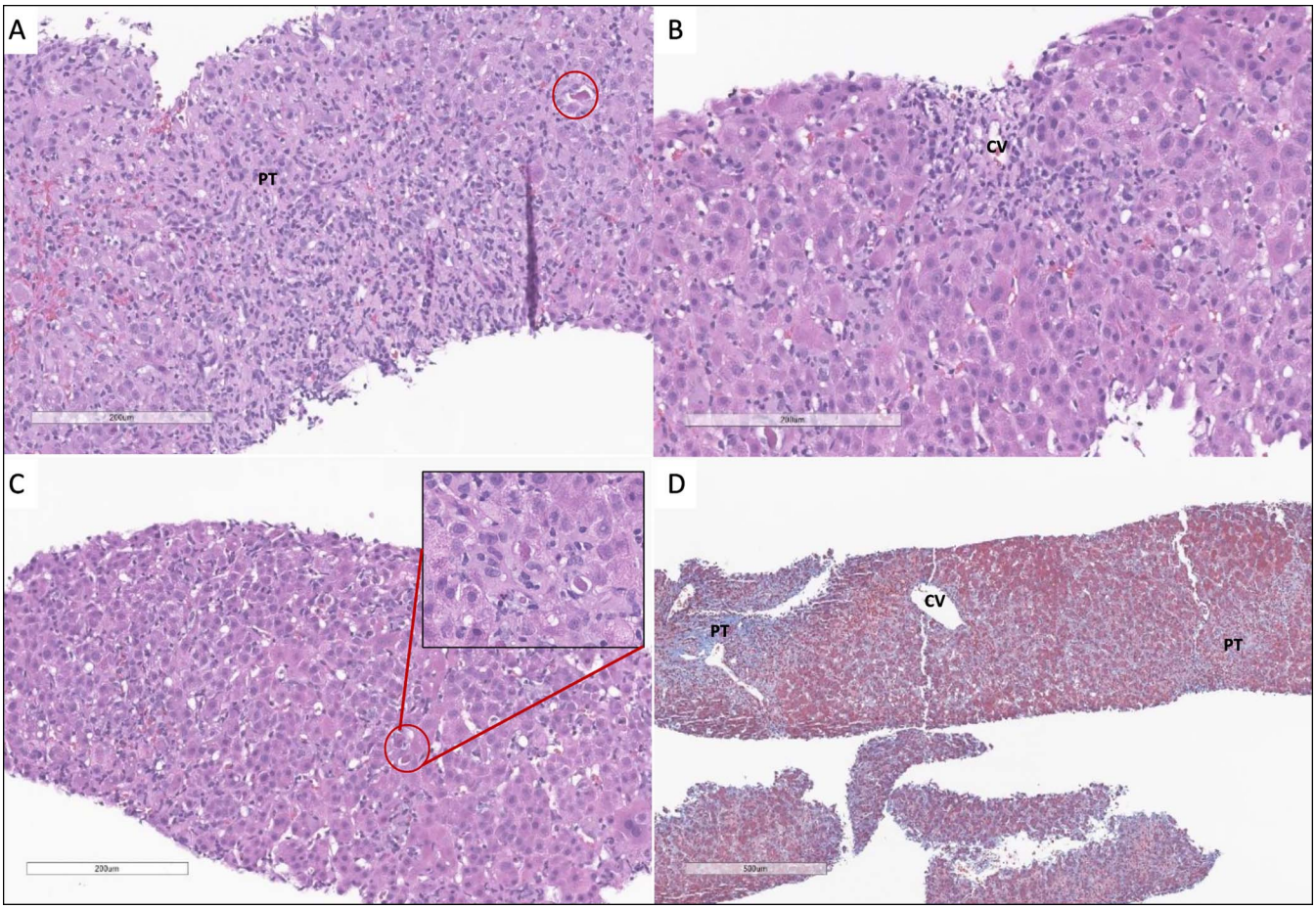

Figure 1. Histological findings. (A) PT are markedly expanded by a mixed inflammatory infiltrate, composed of lymphocytes, numerous eosinophils, neutrophils, and rare plasma cells. Extensive bile ductular proliferation is noted, with acute cholangiolitis. Interface hepatitis is noted. Individual necrotic hepatocytes (apoptotic bodies) are noted adjacent to the PT (red circle) (hematoxylin and eosin, 10×). (B) Hepatocytic dropout and marked inflammation is noted around the CV (zone 3). The adjacent sinusoids are packed with lymphocytes and histiocytes (hematoxylin and eosin, 10×). (C) The hepatic lobules show diffuse inflammatory activity, with lymphocytes and histiocytes present in the sinusoids. Individual necrotic hepatocytes (apoptotic bodies) are seen (magnified view). (D) Minimal fibrosis is noted in the PT, with no periportal or bridging fibrosis. Very early necroinflammatory bridging is noted between PT and CV (light blue in color) (Masson trichrome stain, 4×). CV, central veins; PT, portal tracts.

DISCUSSION

There has been an increasing incidence of DILI secondary to HDS, particularly in multiingredient supplements or those that have been adulterated. The incidence of DILI varies depending on the drug, ranging from 1 in 10,000 to 100,000.[7,8] According to LiverTox, more than 1,200 agents have been described to cause DILI. A study by Lu et al[9] found that the average duration of DILI was 16.2 days in a sample of 424 patients with DILI with various patterns of liver biochemical abnormality. HDS are regulated by the FDA more similarly to foods than drugs, and therefore, the rigorous premarket assessments of safety and effectiveness applied to medications are often not implemented for HDS. Consequently, case reports and other such scholarly projects have been crucial in identifying DILI caused by HDS.[10]

DILI has been shown to be associated with oxidative stress leading to hepatocyte inflammation and eventual necrosis. Recently, the concept of gut-liver axis has been implicated in mediating DILI.[3] Bacteria may produce metabolites that may compete with drugs over the metabolizing process, either decreasing the metabolism and eventual accumulation of drugs (example: p-cresol) or having synergistic toxicity with the drug (example: 1-phenyl-1,2-propanedione). Herbal medications may affect intestinal microbiota that often digest herbal supplements or could serve as a medium to transport compounds that are not absorbed by the intestinal tract. MenoFit formula includes a long list of probiotic and prebiotic blends, herbal extracts, and nutritional supplements. It is unclear if 1 or more ingredients in it are hepatotoxic.

The diagnosis of DILI is typically made clinically after ruling out alternate causes of liver injury and assessing the temporal relationship between medication initiation and liver injury. According to a DILIN prospective study, DILI diagnostic criteria include total bilirubin $\geq$2.5 mg/dL, INR >1.5, and any elevation in aminotransferases (aspartate aminotransferase or

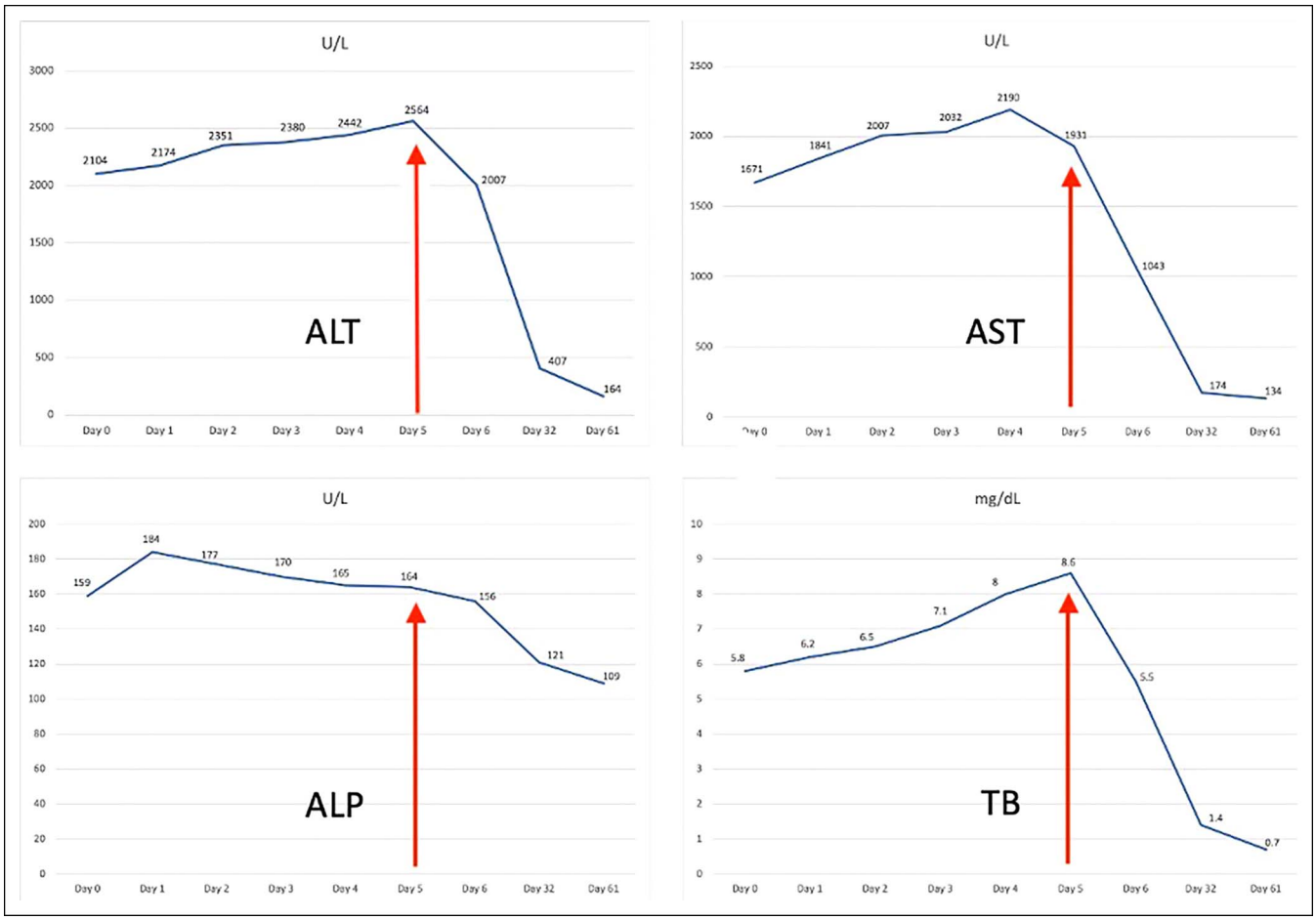

Figure 2. Laboratory trends during and after hospitalization. Red arrows indicate the initiation of methylprednisolone on day 5. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin.

alanine aminotransferase) or alkaline phosphatase.[11,12] Liver biopsy should be considered if symptoms persist long after the suspected medication has been discontinued, the patient has an atypical presentation, or there is suspicion of an alternative diagnosis such as autoimmune hepatitis.[13] However, it should be noted that only 50% of the patients enrolled in DILIN prospective study underwent liver biopsies.[14] There are no strict guidelines regarding when a liver biopsy is necessary for the diagnosis of DILI.[15]

The first step in management of DILI is to discontinue the culprit agent.[16] Certain drugs implicated in DILI, such as acetaminophen, have specific treatment regimens involving N-acetylcysteine or activated charcoal. Corticosteroid therapy may be considered if hypersensitivity reactions or autoimmune hepatitis-like features are present. However, it should be noted that although corticosteroids have demonstrated improved outcomes in some cases of DILI, the observational nature of much of the published literature makes it difficult to make definitive statements about their role in treating DILI.[17]

In the case described, given the significant improvement in liver tests on discontinuing the supplement and initiating steroids, the diagnosis of DILI was established. However, given the lack of long-term follow-up and lack of demonstration of normalization of liver tests, a suspicion of chronic DILI could not be ruled out.

With the increasing prevalence of HDS use in modern society, hepatologists are at the vanguard of the battle against DILI, and it is through our documentation of novel causes of DILI that we can better equip our colleagues to care for their patients. We hope that our case of MenoFit-associated DILI will spark further research into this topic and bolster our understanding of its underlying pathophysiology.

DISCLOSURES

Author contributions: A. Dadlani wrote the abstract, introduction, case presentation, Table 1, and Figure 2 and is the article guarantor. A. Anudu wrote the discussion. EC Marginean provided the biopsy slides and report and edited and reviewed the manuscript.

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