

Liver Damage due to Hypervitaminosis

Alexander M. Sy, MD¹, Smriti R. Kumar, MD², Jonathan Steinberg, MD², Monica Tulia Garcia-Buitrago, MD³, and Leopoldo Ramon Arosemena Benitez, MD¹

¹Division of Hepatology and Liver Transplantation, University of Miami Leonard M. Miller School of Medicine, Miami, Florida

²Department of Medicine, Jackson Memorial Hospital/University of Miami Leonard M. Miller School of Medicine, Miami, Florida

³Department of Pathology, University of Miami Leonard M. Miller School of Medicine, Miami, Florida

ABSTRACT

Dietary supplements are unregulated medications that can lead to serious liver injury. Despite this, many people take vitamin supplements believing they are safe because they do not require prescriptions. We are reporting a case of an African American man who took large doses of vitamin supplements leading to noncirrhotic portal hypertension. The case highlights the importance of detailed history taking to diagnose and treat patients properly.

INTRODUCTION

Many people take vitamin supplements believing they are safe because they do not require prescriptions. However, these dietary supplements are unregulated medications that can lead to serious liver injury. We are reporting a case of hypervitaminosis A leading to noncirrhotic portal hypertension, highlighting the importance of detailed history taking.

CASE REPORT

A 47-year-old African American man complained of gradual abdominal distention, leg edema, and progressive dyspnea on exertion leading to orthopnea 2 weeks before admission. He denied alcohol use but admitted a recent intake of Ginkgo biloba and other supplements targeting memory, circulation, and sexual function enhancement. He was tachycardic on admission. Physical examination was negative for jaundice. He was cachectic with muscle wasting. Right lung examination revealed pleural effusion. The abdominal examination was positive for ascites and hepatomegaly. Splenomegaly and other stigmata of chronic liver disease were absent. There was bilateral pitting edema up to his leg. The neurologic examination was normal. Tests showed total bilirubin 1.0 mg/dL, aspartate aminotransferase 80 IU/L, alanine aminotransferase 58 IU/L, alkaline phosphatase 83 IU/L, serum albumin 2.9 g/dL, and prothrombin time 16.2 seconds. The rest of his laboratory test results were normal. The thoracic x-ray confirmed large right pleural effusion and smaller left pleural effusion. A liver sonogram with Doppler revealed a normal liver, patent vascular structures with no obstruction, and moderate ascites. Ascitic fluid was negative for infection. Serum albumin-ascitic fluid gradient was 1.7 with total protein (TP) 4.8 g/dL. He was started on furosemide 40 mg intravenous injection twice a day and spironolactone 100 mg twice a day. Transthoracic echocardiogram revealed a thickened pericardium concerning for constrictive pericarditis; however, cardiac catheterization was normal. Autoimmune, metabolic, and viral etiologies of chronic liver disease were all ruled out.

On further questioning, the patient disclosed that he had been chronically taking large doses, up to 30 days' worth per day of niacin, vitamin C, vitamin B12, calcium, zinc, vitamin B6, magnesium, vitamin D3, vitamin E, vitamin B complex, vitamin A, and Ginkgo biloba. His brother died from complications of acquired immune deficiency syndrome, and he believed that he was infected with human immunodeficiency virus and taking large doses of vitamins will boost his immune system and prevent him from developing the disease. His human immunodeficiency virus testing was nonreactive and tests for magnesium, vitamin A, vitamin B12, and alpha-tocopherol levels were normal. The patient's wife reports no unusual behavior before starting mega doses of supplements. Psychiatry diagnosed him compulsive disorder with a delusional fixation on dietary supplements. Transjugular liver biopsy was subsequently performed and revealed a wedge portal venous pressure of 23 mm Hg with a hepatic venous pressure gradient of 15 mm

Hg. The net right atrial pressure was 0 (3/−3), ruling out cardiac etiology of his ascites. The core biopsy showed a liver parenchyma with hypertrophy and hyperplasia of stellate (Ito) cells, which demonstrated scalloped or crescent-shaped nuclei and cytoplasmic fat vacuoles (Figure 1). A few glycogenated nuclei, mild lymphocytic portal infiltrate, and centrilobular sinusoidal dilation were also identified. The trichrome stain showed perisinusoidal, perivenular, and periportal fibrosis (Figure 2). The histological findings were consistent with stellate cell lipidosis, compatible with hypervitaminosis A. He had multiple admissions for recurrent ascites and hepatic hydrothorax, leading to the placement of transjugular intrahepatic portosystemic shunt. Despite repeated counseling, he continued to take mega doses of vitamin A. Unfortunately, his condition continued to deteriorate with worsening ascites, hepatic hydrothorax, encephalopathy, and spontaneous bacterial peritonitis. He was not considered a transplant candidate because of the underlying psychiatric disorder. He died 8 months after his initial presentation.

DISCUSSION

Vitamin A is a lipid-soluble compound of the retinoic acid family that is mainly stored in the hepatic stellate (Ito) cells and is important for normal vision, immune system, and reproduction. It is an over-the-counter vitamin supplement that is also naturally present in plants and animals. The animal source and supplements, known as preformed vitamin A, are the active form and when taken in excess can lead to toxicity as compared to the plant source, also known as provitamin A carotenoids. The latter has to be converted to the active form, which is regulated by the body in a complex process. It is recommended that for adult male and female to consume 900 and 700 μg retinol daily, respectively, to avoid deficiency and toxicity.¹

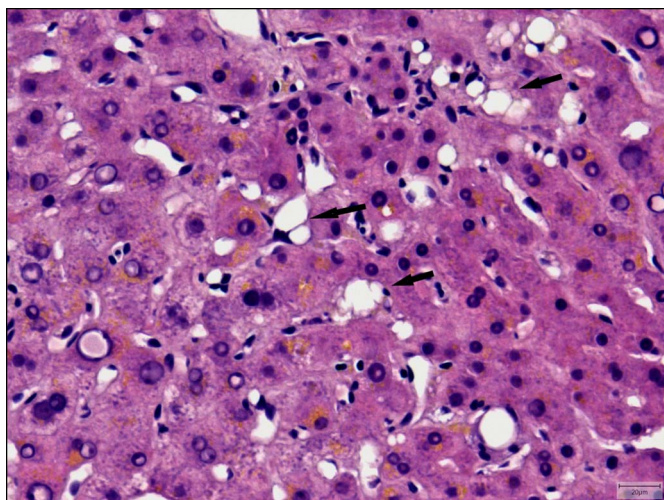


Figure 1. Vacuolated Ito cells (arrows) (hematoxylin and eosin stain, 40 \times magnification).

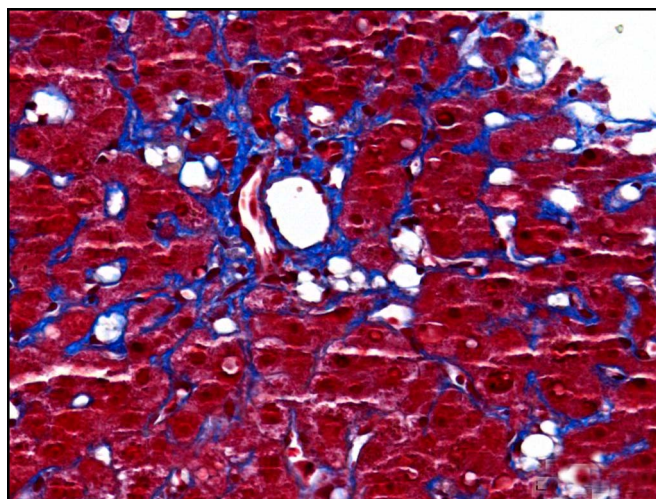


Figure 2. Pericellular perisinusoidal fibrosis (trichrome stain, 40 \times magnification).

Vitamin A deficiency is rarely seen in the United States. In resource-rich countries where vitamin A consumption is generally adequate, supplementing for disease prevention is commonly not recommended.² Paradoxically, almost 50% of US adults report taking 1 or more dietary supplements, some of which carry risks of serious hepatotoxicity such as vitamin A.³ Vitamin A toxicity, also known as hypervitaminosis A, is because of chronic ingestion of large amounts of the synthetic form.⁴ It can present acutely or chronically and can be potentiated by alcohol use.⁵ Acute toxicity presents with non-specific findings, whereas chronic toxicity can present with dermatologic, skeletal, and neurologic symptoms. Chronic toxicity can also lead to liver injury, although a single ingestion of more than 500,000 IU has been reported to provoke noncirrhotic portal hypertension.⁶ Neuropsychiatric changes as a consequence of toxicity have been reported.⁷ It was proposed that toxic levels of unbound retinyl esters can elicit neuropsychiatric effects, including depression, psychosis, and impulsivity, symptoms exhibited by our patient.⁸

Histologically, hypervitaminosis A causes hepatocyte injury, necrosis, stellate cell hyperplasia, and subsequent fibrosis resulting in perisinusoidal, pericentrilobular, and periportal scarring causing sinusoidal dilatation and obstruction thus impairing hepatic venous outflow and consequently leading to noncirrhotic portal hypertension. A rare case of intrahepatic cholestasis had also been reported.⁹ The plasma retinol concentration is not a reliable estimate of the vitamin A requirement because of its insensitive relationship between liver concentration, and there is no noninvasive marker available for the assessment of vitamin A excess.¹⁰

In portal hypertension, ascitic fluid shows high serum albumin-ascitic fluid gradient and low TP content. In our case, the TP is elevated at 4.8 g/dL suggesting cardiac congestion; however, this was not supported by cardiac catheterization and pressure

measurement. Thus, it was postulated that the elevated TP may be part of the toxicity.

The cornerstones of therapy are discontinuation of supplements and refraining from ingestion of vitamin A-rich foods because there is no known antidote. Usually, portal hypertension resolves within months to years after discontinuation of the supplement. However, in some cases, the liver injury progresses to cirrhosis, even requiring transplantation.^{10,11}

Hypervitaminosis A is a rare, although well-described, cause of liver damage. This case highlighted the importance of obtaining a complete history of dietary supplement intake when evaluating patients mimicking signs and symptoms of cirrhosis.

DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. AM Sy is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received February 24, 2020; Accepted May 21, 2020

REFERENCES

1. Dietary reference intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. *Institute of Medicine (US) Panel on Micronutrients*. Washington, DC: National Academies Press (US), 2001.
2. Moyer VA; US Preventive Services Task Force. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: US preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2014;160(8):558–64.
3. Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. *Hepatology*. 2014;60:1399–408.
4. Biesalski HK. Comparative assessment of the toxicology of vitamin A and retinoids in man. *Toxicology*. 1989;57(2):117.
5. Leo MA, Lieber CS. Alcohol, vitamin A, and beta-carotene: Adverse interactions, including hepatotoxicity and carcinogenicity. *Am J Clin Nutr*. 1999;69(6):1071–85.
6. Beste LA, Moseley RH, Saint S, Cornia PB. Clinical problem-solving. Too Much of a good thing. *N Engl J Med*. 2016;374(9):873–8.
7. O'Donnell J. Polar hysteria: An expression of hypervitaminosis A. *Am J Ther*. 2004;11(6):507–16.
8. Mawson A. Mefloquine use, psychosis, and violence: A retinoid toxicity hypothesis. *Med Sci Monitor*. 2013;19:579–83.
9. Ramanathan VS, Hensley G, French S, et al. Hypervitaminosis A inducing intra-hepatic cholestasis: A rare case report. *Exp Mol Pathol*. 2010;88(2):324–5.
10. García-Muñoz P, Bernal-Bellido C, Marchal-Santiago A, et al. Liver cirrhosis from chronic hypervitaminosis A resulting in a liver transplantation: A case report. *Transpl Proc*. 2019;51(1):90–1.
11. Jorens PG, Michielsen PP, Pelckmans PA, et al. Vitamin A abuse: Development of cirrhosis despite cessation of vitamin A. A six-year clinical and histopathologic follow-up. *Liver*. 1992;12(6):381–6.

Copyright: © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of The American College of Gastroenterology. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work, provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.