Granulocyte-colony-stimulating factors such as filgrastim are currently used for multiple indications, one of which is administration to healthy donors for allogeneic stem cell collection. So far, filgrastim has not been described as a cause of drug-induced liver injury. We report a case of drug-induced liver injury secondary to filgrastim use in a 54-year-old healthy donor. The patient presented with an upsurge of liver enzymes a week from the drug administration with a rapid downtrend over the next few weeks. We wish to highlight the possibility of a similar idiosyncratic adverse drug reaction in other healthy individuals.

INTRODUCTION

Granulocyte-colony-stimulating factors (G-CSFs) such as filgrastim have seen a recent increase in their use for numerous indications. One indication is mobilization of hematopoietic progenitor cells for collection from healthy donor before allogeneic stem cell transplant. In this case, the medication is administered to healthy individuals. These drugs have not been previously reported to be a potential cause of drug-induced liver injury (DILI). We present a case where a previously healthy patient presented with marked elevation of liver-associated enzymes 6 days after administration of filgrastim.

CASE REPORT

A 54-year-old Hispanic woman with a medical history of hypertension, hyperlipidemia, prediabetes, and obesity but no history of liver disease or cancer, elevated liver enzymes, risk factors for liver disease, presented for an acute elevation of liver function tests (LFTs) from previous levels within normal laboratory range. She was the matched related donor of her 31-year-old daughter with dedicator of cytokinesis 8 (DOCK8) deficiency, a rare, autosomal recessive form of hyperimmunoglobulin E syndrome, who was planned for hematopoietic stem cell transplantation. She was asymptomatic. The patient was a non-drinker with no family history of liver disease. She had an abdominal ultrasound 1 year before, indicated for nonspecific abdominal pain that showed no abnormalities. The patient had been on most of her medications for the last 5 years except for her blood pressure medications, which were hydrochlorothiazide-losartan combination pill that she had been taking for 3 weeks. She took no over-the-counter medications. She completed a course of stem cell mobilization from the marrow to peripheral blood with daily doses of 960 μg of filgrastim per standard protocol for 6 days and apheresis for collection on the day before the rise in LFTs.

Physical examination was unremarkable. Two days before receiving filgrastim, her LFTs were within normal range whereas on day 7, her alkaline phosphatase (ALP) rose to 534 U/L, alanine transaminase to 320 U/L, aspartate transaminase to 452 U/L, gamma-glutamyltransferase to 568 U/L, and lactate dehydrogenase to 658 U/L, and her platelet count decreased to 165 K/µL with a total bilirubin of 0.6 mg/dL and an International Normalized Ratio (INR) of 1.10 (Figure 1). All other liver workups including viral
hepatitis, autoimmune, hereditary, and toxic etiologies were negative. Her abdominal ultrasound showed an enlarged liver (15.7 cm) with increased hepatic echogenicity, suggestive of mild hepatic steatosis, subsequently ruling out common features of obstruction of biliary tract and viral hepatitis as the cause of elevated liver enzymes. She never received filgrastim again. The patient was able to undergo successful apheresis and uncomplicated peripheral blood progenitor cell collection. After 12 days from filgrastim cessation, the LFTs improved to ALP 275 U/L, alanine transaminase 43 U/L, aspartate transaminase 19 U/L, gamma-glutamyltransferase 421 U/L, and lactate dehydrogenase 225 U/L, with a total bilirubin of 0.4 mg/dL. Forty-one days later, the liver chemistries normalized. The patient continued to be on a stable dose of hydrochlorothiazide-losartan combination pill and reported no changes in weight.

**DISCUSSION**

G-CSFs are known to cause various adverse events in healthy volunteers such as bone pain, pyrexia, and rash and less commonly, splenic rupture, acute respiratory distress syndrome, vascular events, and exacerbation of autoimmune or inflammatory conditions. Little is known about DILI from G-CSFs. Liver injury has only rarely been associated with filgrastim in the past, although it has never been reported in a healthy individual. This patient was an otherwise healthy hematopoietic stem cell donor who received filgrastim for mobilization of hematopoietic progenitor cells and presented with acute elevation of previously normal LFTs that normalized after stopping the exposure. The concurrence of filgrastim administration and acute rise in transaminases and ALP, followed by rapid down trending with drug withdrawal (Figure 1), suggests possible DILI secondary to the drug. To define the pattern of liver injury and determine the causality of the injury from filgrastim, we calculated the R value and the Roussel Uclaf Causality Assessment Method (RUCAM). Both R value and RUCAM are a part of the American College of Gastroenterology guidelines for DILI assessment. The R value was 1.8 (cholestatic) initially, but it increased to 4.63 (mixed) in repeat evaluation on the same day and 6 (hepatocellular) on the following day. The RUCAM score was calculated to be 8, which in the absence of rechallenge, alcohol, pregnancy, or age above 55 years was the maximum possible score for the patient, indicating the causality relationship as “highly likely.” As per the current guidelines for the management of DILI, the culprit agent was withdrawn with normalization of the liver enzymes. The patient’s antihypertensive medications were unlikely to be a source of patient’s liver injury because both the drugs are rarely associated with hepatotoxicity and the patient was on a stable dose of hydrochlorothiazide-losartan combination pill before the episode, during it, and continued on the same dose afterward as well, with no effect on liver enzymes.

Figure 1. Trend of liver function tests. Day 0 is the first day of administration of filgrastim. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase.

This is the first case where exogenous filgrastim was associated with elevated liver chemistries in a healthy individual. The relationship between G-CSFs and their effects on liver are complex and not well understood, with conflicting literature describing some beneficial role in patients with liver failure by improving function and prolonging survival. Interestingly, liver injury has been reported previously in patients with endogenous G-CSF secreting tumors in the past. Suzuki et al reported 3 common pathologic changes: focal necrosis with neutrophil infiltration in the centrilobular zones, fibrous change, and enlargement of the portal area associated with neutrophil infiltration and intrahepatic cholestasis, all of which were reproduced in vitro except for cholestasis. G-CSF–induced lipopolysaccharide sensitization was studied in rats and was suggested as a possible mechanism of liver injury. The patient presented in a cholestatic pattern and progressed to mixed and hepatocellular patterns consecutively with rapid resolution after withdrawal. It is important to be aware of the hepatotoxic effects of these drugs as they are commonly administered to individuals with no liver disease history and this might be an underreported adverse drug reaction.

**DISCLOSURES**

Author contributions: D. Sharma wrote the manuscript. BL Da clinically evaluated the patient. A. Vittal, D. Kapuria, and T. Heller edited the manuscript. G. Ben Yakov is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received October 12, 2018; Accepted April 24, 2019

**REFERENCES**

1. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline update. J Clin Oncol. 2015;33(28):3199–212.
2. Crawford J, Becker PS, Armitage JO, et al. Myeloid growth factors, version 2.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2017;15(12):1520–41.

3. Food and Drug Administration. Filgrastim label information (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103353s5188.pdf). Accessed on June 13, 2018.

4. Su HC. Dedicator of cytokinesis 8 (DOCK8) deficiency. *Curr Opin Allergy Clin Immunol.* 2010;10(6):515–20.

5. Anderlini P. Effects and safety of granulocyte colony-stimulating factor in healthy volunteers. *Curr Opin Hematol.* 2009;16(1):35–40.

6. Buntzel J, Kuttner K. Hepatic-injury due to G-CSF application. *Onkologie.* 1995;18(1):54–6.

7. Danan G, Benichou C. Causality assessment of adverse reactions to drugs-I. A novel method based on the conclusions of international consensus meeting: Application to drug-induced liver injuries. *J Clin Epidemiol.* 1995;46:1323–30.

8. Chalasani NP, Hayashi PH, Bonkovsky HL, et al. Diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol.* 2014;109:950–66.

9. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs-II. An original model for validation of drug causality assessment methods: Case reports with positive rechallenge. *J Clin Epidemiol* 1993;46:1331–6.

10. U.S. National Library of Medicine; National Library of Medicine; National Institute of Health. 2018. (https://livertox.nlm.nih.gov/). Accessed on June 13, 2018.

11. Simonetto DA, Shah VH, Kamath PS. Improving survival in ACLF: Growing evidence for use of G-CSF. *Hepatol Int.* 2017;11(6):473–5.

12. Suzuki A, Takahashi T, Okuno Y, et al. Liver damage in patients with colony-stimulating factor-producing tumors. *Am J Med.* 1993;94(2):125–32.

13. Liu A, Fang H, Wei W, et al. G-CSF pretreatment aggravates LPS-associated microcirculatory dysfunction and acute liver injury after partial hepatectomy in rats. *Histochem Cell Biol.* 2014;142:667–76.

Copyright: © 2019 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.