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Diagnosis and Management of Drug-Induced Liver Injury After the Use of *Polygonum multiflorum*

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ABSTRACT

Polygonum multiflorum, a species of flowering plant in the buckwheat family, is widely used in alternative medicine. However, a growing body of literature has implicated *P. multiflorum* as a cause of drug-induced liver injury. We report a case of successful treatment of a drug-induced liver injury after consumption of an herbal tea containing *P. multiflorum*.

INTRODUCTION

Polygonum multiflorum, a species of flowering plant in the buckwheat family, is widely used in alternative medicine. However, a growing body of literature has implicated *P. multiflorum* as a cause of drug-induced liver injury (DILI). We report a case of successful treatment of DILI with corticosteroids after consumption of an herbal tea containing *P. multiflorum*.

CASE REPORT

A 48-year-old woman presented to the emergency department with 2 days of pruritus and nausea. Three weeks before her presentation, she had traveled to Mexico. She reported no recent contact with animals or time spent outdoors. However, she began drinking Lipid Metabolic Management Tea containing *P. multiflorum* at least twice daily while in Mexico, with ongoing tea use for an additional week on returning to the United States. Her medical history was significant for constipation, abdominal pain, and cholecystectomy, and her regular medications included acetaminophen (no more than 800 mg daily), docusate, polyethylene glycol, and senna.

Examination was unremarkable other than scleral icterus; she had normal vital signs and no rash, hepatosplenomegaly, abdominal tenderness, or stigmata of chronic liver disease. Notable laboratory findings included alanine aminotransferase (ALT, U/L): 1769; aspartate aminotransferase (AST, U/L): 1,029; alkaline phosphatase (ALP, U/L): 218; total bilirubin (TBILI, mg/dL): 6.7; international normalized ratio: 1.1; and acetaminophen: <1 mg/dL. Right upper quadrant abdominal ultrasound with Doppler and computed tomography were unremarkable.

Serology and immunoglobulin testing for hepatitis A, B, C, and E; human immunodeficiency virus; Epstein-Barr virus; cytomegalovirus; smooth muscle antibodies; antinuclear antibodies; and antibodies to liver-kidney microsome type 1 were negative, and immunoglobulin G level was nonelevated (964). Ceruloplasmin and ferritin studies were within normal limits. Urine toxicology screening was negative. After 5 days of observation, the patient's pruritus and nausea were controlled, she showed no evidence of encephalopathy or coagulopathy, and her liver tests improved (ALT: 1,596; AST: 720; ALP: 237; and TBILI: 2.9). She was discharged home with close follow-up.

Five days later, repeat laboratory testing showed increased liver tests: ALT: 2,518; AST: 1,492; ALP: 265; and TBILI: 4.6. The patient was readmitted for an expedited liver biopsy. Her biopsy was reviewed by a subspecialized liver pathologist and demonstrated active hepatitis with moderate lymphocyte predominant portal and lobular lymphocytic inflammation with spotty necrosis and pericentral

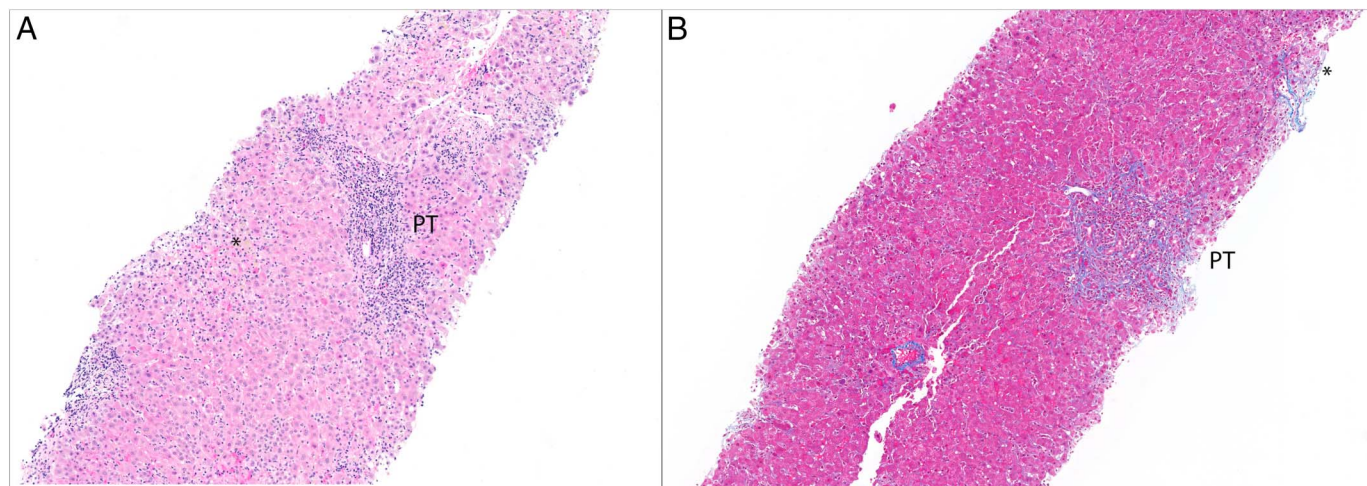


Figure 1. (A) Liver core biopsy tissue with PT lymphocytic inflammation, lobular lymphocytic inflammation, and pericentral dropout (*) and spotty necrosis (hematoxylin and eosin stain, 100× magnification). (B) There is no PT fibrosis, although pale staining of pericentral dropout is noted (*) on trichrome stain (100× magnification). PT, portal tract.

confluent dropout with pigmented macrophages, which raised primary consideration for infection, drug/herbal induced liver injury, or autoimmune hepatitis, although autoimmune hepatitis was not specifically suggested by histologic findings (Figure 1). The patient received 3 days of Solu-Medrol (500 mg on day 1, 250 mg on day 2, and 125 mg on day 3) with significant transaminase improvement, after which she was then transitioned to 80 mg oral prednisone daily and then 60 mg prednisone the following day. On day 5 of readmission, her laboratory test results were as follows: ALT: 961; AST of 146; ALP: 173; and TBILI: 2.0. Given the improvement, she was discharged and prescribed 40 mg prednisone daily with a weekly taper of 10 mg. At an outpatient appointment 7 weeks later, the patient had the following laboratory results: ALT: 23; AST of 19; ALP: 60; and TBILI: 0.7.

DISCUSSION

P. multiflorum has long been used by alternative medicine practitioners in crude and processed forms for many purposes, including alopecia, hyperlipidemia, constipation, and, paradoxically, hepatoprotection.¹ However, increasing evidence suggests that *P. multiflorum* can cause DILI, with consequences ranging from self-resolving acute liver injury to fulminant hepatic failure and even death.²⁻⁴

Despite the growing evidence demonstrating the hepatotoxicity of *P. multiflorum*, the mechanisms by which it and its metabolites harm the liver remain unclear. In our case report, we present a hepatic injury induced by a patient's consumption of *P. multiflorum* (M&V causality score > 15, definite), which differs in its natural history from previous case reports, including lack of improvement until corticosteroid therapy was initiated.^{3,5} This is significant because it draws attention to the heterogeneous presentations in patients with *P. multiflorum*-associated DILI and raises the question of whether poor clinical

outcomes can be attributed to a direct toxic effect on the liver or a potential immune response.

To the best of our knowledge, this is the first case report demonstrating successful treatment of *P. multiflorum* DILI with corticosteroids. Our patient was treated with pulse steroids and immediately demonstrated a steep reduction in her transaminases, as shown in Figure 1. Subsequent treatment with prednisone as an outpatient allowed for a good clinical trajectory, yet we acknowledge there is uncertainty regarding the need for and long-term outcome associated with immunosuppression in DILI. We also advise any immunomodulating treatment in *P. multiflorum*-associated DILI be initiated after other causes of acute liver injury have been excluded (eg, viral), and there is histologic evidence of DILI.

This case also highlights the potential toxicity of herbal preparations and the absence of regulatory oversight of their ingredients. This lack of regulation permits no standardization of the formulation and production of these products, and their multitude and idiosyncratic toxidromes create a diagnostic challenge for any clinician. Previous research has shown that *P. multiflorum*'s toxicity depends on its extraction and preparation, with crude extracts having more potency.¹ Therefore, in addition to asking the frequency and dosage of herbal supplements that patients consume, clinicians must inquire how they consume them. In the case of our patient, she was drinking an herbal tea containing *P. multiflorum* for weight loss and management of hyperlipidemia, with subsequent acute liver injury developing within weeks after the initial consumption. Fortunately, the patient came to clinical attention before developing signs of acute liver failure and improved after discontinuation of the herbal tea and treatment with corticosteroids.

In conclusion, we caution the public in consuming unregulated herbal or dietary supplements given their potential hepatotoxicity

and recommend clinicians elicit a thorough medication history that accounts for any of these products. Furthermore, given the breadth of these supplements and the multitude of their clinical presentations, we recommend clinicians maintain an appropriate diagnostic threshold for DILI. Finally, we encourage the clinical use of evidence-based resources such as LiverTox, which provides freely available information on the diagnosis, treatment, and prevention of numerous causes of DILI.⁶

DISCLOSURES

Author contributions: All authors have approved the final draft submitted. A. Zahir: conceptualization, data curation, writing (original draft), and writing (review and editing). M. Li: conceptualization, supervision, and writing (review and editing). RM Gill: pathologic diagnosis, photomicrographs, and writing (review and editing). D. Brandman: supervision and writing (review and editing). M. Li is guarantor of the article.

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Informed consent was obtained for this case report.

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