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Concurrent severe hepatotoxicity and agranulocytosis induced by Polygonum multiflorum: A case report

ADRs of Polygonum multiflorum

You-lin Shao, Chun-Ming Ma, Jian-Ming Wu, Feng-Cai Guo, Suo-Cai Zhang
Abstract

BACKGROUND
Various types of drug-induced liver injury are induced by Polygonum multiflorum (PM); however, it rarely causes neutropenia. Herein, we report a case of a 65-year-old woman with concurrent severe hepatotoxicity and agranulocytosis induced by PM.

CASE SUMMARY
A 65-year-old woman reported with severe hepatotoxicity and agranulocytosis 17 days after ingestion of PM. The results of the Roussel Uclaf Causality Assessment Method demonstrated a highly probable relationship between hepatotoxicity and PM, with a total score of 10. The Naranjo algorithm results indicated that agranulocytosis had a probable relationship with PM, with an overall score of 6. Granulocyte colony-stimulating factor (for once), steroids, compound glycyrrhizin, and polyene phosphatidylcholine therapy was initiated. After 15 days of treatment, there was a gradual improvement in liver biochemistry, leukocytes, and neutrophils levels.

CONCLUSION
Concurrent hepatotoxicity and agranulocytosis are rare and critical adverse drug reactions of PM, which should be highly valued.

Key Words: Polygonum multiflorum; Hepatotoxicity; Agranulocytosis; Case report

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Core Tip: Polygonum multiflorum (PM) is a common traditional Chinese medicine and is commonly used as a dietary supplement. However, severe idiosyncratic hepatotoxicity in certain individuals has been reported. Moreover, if idiosyncratic
agranulocytosis occurs simultaneously, it may be fatal. Roussel Uclaf Causality Assessment Method scale and Naranjo algorithm are useful tools for the assessment of drug-induced liver injury and adverse drug reactions, respectively. Early discontinuation can prevent disease progression, facilitating recovery. The combination therapy of glucocorticoids, anti-inflammatory medications, and liver protection is beneficial for idiosyncratic drug reactions.

INTRODUCTION

As a commonly used traditional Chinese medicine, Polygonum multiflorum (PM) is used to treat various diseases through medicinal or dietary supplementation[1]. Unfortunately, PM is the most common cause of herbal medicine-related DILI[2]. PM-induced liver injury was first reported in Hong Kong in 1996[3]. Since then, PM hepatotoxicity has attracted attention worldwide[4]. Although concurrent hepatotoxicity and neutropenia induced by chemotherapy have been presented frequently[5], the neutropenia caused by PM has rarely been reported. Moreover, the simultaneous occurrence of these two complications owing to the use of PM has not been reported to date. This study aimed to present a case of concurrent hepatotoxicity and agranulocytosis induced by PM to emphasize the importance of timely diagnosis and treatment of these complications.

CASE PRESENTATION

Chief complaints

A 65-year-old woman was admitted with a history of yellowish pigmentation of skin or whites of the eyes for 10 days on March 4, 2022.

History of present illness

On recording history, owing to insomnia and dreaminess, she reported a 17-day history of consecutive use of PM (30 g/day) from February 11, 2022. She had fatigue, loss of appetite, and jaundice; however, she had no nausea and vomiting, abdominal pain, and
fever. There was no history of trauma, surgery, drug and alcohol abuse, and blood transfusions, without recent travel history or family history of liver or blood system disorders.

**History of past illness**
Nine years ago, she suffered drug-induced liver injury caused by taking Traditional Chinese medicine. After three weeks of treatment, her liver function returned to normal and was maintained until this episode (the last liver function test was on October 12, 2021).

**Personal and family history**
There was no history of trauma, surgery, drug and alcohol abuse, and blood transfusions, without recent travel history or family history of liver or blood system disorders.

**Physical examination**
Her vital signs were stable. Skin and scleral jaundice were evident. Auscultation of both lungs and heart was clear, with regular heart rate and rhythm. No abdominal tenderness or rebound tenderness was noted, with a negative Murphy’s sign and mild percussion in the liver area. No flapping tremor was detected.

**Laboratory examinations**
Liver function tests revealed severe acute liver injury. Complete blood count revealed agranulocytosis (erythrocyte $4.07 \times 10^9$ cells/L, platelets $159 \times 10^9$ cells/L, leukocytes $1.17 \times 10^9$ cells/L, and absolute neutrophil count $0.02 \times 10^9$ cells/L). Other possible causes of liver damage were ruled out by checking HBV surface antigen, hepatitis A, C, D, E virus antibodies, Epstein-Barr virus antibodies, cytomegalovirus antibodies, autoimmune liver disease antibodies, immunoglobulins, thyroid function, ceruloplasmin, etc. The results are summarized in Table 1.
*Imaging examinations*

The patient’s liver ultrasound showed normal echotexture and liver outline and non-dilated intrahepatic and extrahepatic bile ducts.

*Pathologic evaluation*

Cytological evaluation of bone marrow puncture revealed a myeloid/erythroid ratio of 0.16, and the erythrocyte and myeloid series cells were 47% and 7.5% of all nucleated cells, indicating severe agranulocytosis (Figure 1 and Table 2).

**FINAL DIAGNOSIS**

The updated Roussel Uclaf Causality Assessment Method (RUCAM)\(^6\) was used to assess whether PM was associated with acute liver injury in this patient. The results of RUCAM demonstrated a highly probable relationship between liver injury and PM, with a total score of 10 (RUCAM scores: \(\geq 9 = \text{highly probable}, 6-8 = \text{probable}, 3-5 = \text{possible}, 1-2 = \text{unlikely}; \leq 0 = \text{excluded}\)). The hepatocellular injury was noted with an R-value of 22.44. Owing to the use of PM before the disease onset, the Naranjo algorithm\(^7\) was used to score for PM. The result indicated that agranulocytosis had a probable relationship with PM, and the overall score was 6 (Naranjo scores: 9-10 = definitely), 5-8 = probable, 1-4 = possible, score \(\leq 1 = \text{doubtful}\).

**TREATMENT**

PM intake was discontinued three days before admission, and treatment was initiated immediately after admission. The following treatments were administered: granulocyte colony-stimulating factor (300 \(\mu g/\text{day}\), subcutaneous injection) for once, hydrocortisone sodium succinate (200 mg/\text{day}, 5 days → 100 mg/\text{day}, 5 days, intravenous infusion), compound glycyrrhizin (100 mL/day) and polyene phosphatidylcholine (465 mg/day) for 15 days by intravenous drip.
OUTCOME AND FOLLOW-UP

Her liver biochemistry, leukocytes, and neutrophils levels improved gradually (Figure 2). Following this, the patient was discharged on day 15 after admission, and her liver biochemistry and granulocytes returned to normal on day 45. To avoid the recurrence of adverse drug reactions (ADRs), the patient was advised to avoid taking PM again.

DISCUSSION

The present case report is unique as the co-occurrence of drug-induced liver injury (DILI), and agranulocytosis caused by PM has been poorly characterized. RUCAM is an established scoring tool used to assess the likelihood of DILI. The RUCAM score of 10 may be interpreted as the PM being a “highly probable” cause of the patient’s hepatocellular injury. In contrast, the Naranjo algorithm is a scoring tool used to assess the likelihood of ADRs. The Naranjo score of 6 may be interpreted as PM being a “probable” cause of the patient’s agranulocytosis.

Unpredictable immune-mediated adverse reactions to drugs or their reactive metabolites are known as idiosyncratic drug reactions. Idiosyncratic ADR can generally occur at any dose within the normal therapeutic range. Idiosyncratic ADRs are extremely rare (1 in 10,000 ~ 1 in 100,000). Life-threatening idiosyncratic ADRs include DILI, serious myelosuppression, and cutaneous reactions[8]. DILI is the most common among these[9].

Idiosyncratic drug reactions owing to traditional Chinese drugs and dietary supplements are a major cause of DILI in China. PM is widely used in traditional Chinese medicine and dietary supplements; however, is a major contributor to herbal DILI[10, 11]. PM-induced hepatotoxicity occurs only in certain individuals[12]. PM can induce various types of DILI, such as 59.7%, 15.4%, and 24.9% of hepatocellular, cholestatic, and mixed types, respectively[13]. Despite a significant rise in the number of liver injuries caused by PM, such injuries occur only in a small proportion of individuals ingesting PM and are associated with idiosyncratic hepatotoxicity[14]. Hepatotoxicity does not occur in the majority of patients taking recommended
therapeutic doses of PM, suggesting that an idiosyncratic response may be the primary mechanism of PM-induced DILI\cite{14}. The following are the mechanisms of PM-related DILI\cite{14}: (1) cholestasis, leading to lipid peroxidation causing liver damage; (2) affecting drug transport or metabolism through the CYP450 enzyme system; (3) causing mitochondrial dysfunction through oxidative stress causing liver damage; and (4) genetic susceptibility\cite{15}. In the present case, liver function gradually improved after the administration of glucocorticoids, compound glycyrrhizin, and polyene phosphatidyicholine was used to suppress inflammation and protect the liver. Although no pharmacological therapy for DILI has been adequately tested in randomized clinical trials, corticosteroids may be beneficial\cite{9, 16}. Compound glycyrrhizin is a safe and effective treatment for patients with DILI\cite{17}.

In addition to hepatotoxicity, agranulocytosis is another common adverse drug reaction\cite{18}. In blood, absolute neutrophil count $<1.5 \times 10^9$ cells/L was defined as neutropenia and $<0.5 \times 10^9$ cells/L as agranulocytosis. Individuals with absolute neutrophil count $<0.1 \times 10^9$ cells/L had a significantly increased risk of morbidity and death owing to infection\cite{18}. The clinical manifestations of idiosyncratic drug-induced agranulocytosis range from asymptomatic to various infections, and serious infections are often life-threatening\cite{5}. There is approximately 5% mortality associated with idiosyncratic drug-induced neutropenia\cite{19}. Poor prognosis is associated with individuals aged $\geq$65 years, absolute neutrophil count $<0.1 \times 10^9$ cells/L, severe infection, and comorbidities\cite{20}. At present, the mechanism of PM-induced granulocytopenia is unknown, which is speculated to be related to idiosyncratic ADR. The most likely immune mechanisms for idiosyncratic drug-induced neutropenia are the hapten hypothesis and the danger signal hypothesis, which are related to the class I and II HLA genes\cite{18}. In general, drug hepatotoxicity and hematological toxicity occur independently, and the co-occurrence of the two is rare, among which the mostly reported were antithyroid drugs\cite{21, 22}, clozapine\cite{23}, methotrexate\cite{24}, and fusidic acid\cite{25}. Regardless of the hepatotoxicity or hematologic toxicity of the drug, the primary treatment is immediate withdrawal. Despite the lack of prospective controlled
randomized trials, two-thirds of reported cases of drug-related neutropenia received G-CSF\cite{26}. G-CSF at 300 \( \mu g \)/day helped reduce the time to recovery of blood counts without causing any major toxicity or adverse effects\cite{27}. Our patient was a 65-year-old woman with a minimum neutrophil count of \( 0.02 \times 10^9 \) cells/L. Fortunately, after receiving a dose of 300 \( \mu g \) of G-CSF, her leukocyte and neutrophil counts improved rapidly, and she did not develop any infection even without antibiotics.

**CONCLUSION**

To the best of our knowledge, this is the first case report of concurrent hepatotoxicity and agranulocytosis with PM. It is a sudden, insidious disease that progresses rapidly and needs attention. Early discontinuation can prevent disease progression and facilitate recovery. The early elevation of granulocytes is essential to avoid infection; combination therapy of glucocorticoids, anti-inflammatory drugs, and protection of the liver is beneficial for idiosyncratic drug reactions.


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