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LETTER TO THE EDITOR

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CASE REPORT

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

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Abstract

BACKGROUND

Various types of drug-induced liver injury are induced by *Polygonum multiflorum* (PM); however, it rarely causes neutropenia. Herein, we report the 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 d 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), a steroid, compound glycyrrhizin, and polyene phosphatidylcholine therapy were initiated. After 15 d 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

Core Tip: *Polygonum multiflorum* 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.

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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 drug-induced liver injury (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], 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 paper presents 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 the skin or whites of the eyes for 10 d on March 4, 2022.

History of present illness

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

History of past illness

Nine years ago, the patient suffered drug-induced liver injury caused by taking traditional Chinese medicine. After 3 wk 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

The patient had no history of trauma, surgery, drug and alcohol abuse, or blood transfusions, without recent travel history or family history of liver or blood system disorders.

Physical examination

The patient's 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 (erythrocytes 4.07 × 10^9 cells/L, platelets 159 × 10^9 cells/L, leukocytes 1.17 × 10^9 cells/L, and absolute neutrophil count 0.02 × 10^9 cells/L). Other possible causes of liver damage were ruled out by checking hepatitis B virus surface antigen, hepatitis A, C, D, and 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 score: ≥ 9 = highly probable, 6–8 = probable, 3–5 = possible, 1–2 = unlikely; ≤ 0 = 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 score: 9–10 = definitely, 5–8 = probable, 1–4 = possible, score ≤ 1 = doubtful).

TREATMENT

PM intake was discontinued 3 d before admission, and treatment was initiated immediately after admission. The following treatments were administered: Granulocyte colony-stimulating factor (300 μg/d, subcutaneous injection) for once, hydrocortisone sodium succinate (200 mg/d, 5 d → 100 mg/d, 5 d, intravenous infusion), compound glycyrrhizin (100 mL/d), and polyene phosphatidylcholine (465 mg/d) for 15 d by intravenous drip.

OUTCOME AND FOLLOW-UP

The patient's 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 DILI and agranulocytosis caused by PM have been poorly characterized. RUCAM is an established scoring tool used to assess the likelihood of DILI. A 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. A 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 ADRs can generally occur at any dose within the normal therapeutic range. Idiosyncratic ADRs are extremely rare (1 in 10000 approximately 1 in 100000). 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, it 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[4]. Hepatotoxicity does not occur in the majority of patients taking recommended therapeutic doses of PM, suggesting that an idiosyncratic response may

Table 1 Relevant laboratory examination reports on admission

Parameter	Result	Normal range
Liver and kidney function		
Alanine aminotransferase	1442.8	7-40 U/L
Aspartate aminotransferase	1565	13-35 U/L
Alkaline Phosphatase	217	50-135 U/L
γ-glutamyl transferase	183.2	7-45 U/L
Total bilirubin	110	3.4-22 μmol/L
Direct bilirubin	91.1	1.7-10.3 μmol/L
Albumin	36.9	40-55 g/L
Globulin	22.3	20-40 g/L
Serum creatinine	43.6	35-80 μmol/L
Serum urea	4.74	2.9-8.2 mmol/L
Serum lipids		
Total cholesterol	3.67	3.4-5.8 mmol/L
Low-density lipoprotein cholesterol	0.6	0.78-2 mmol/L
High-density lipoprotein cholesterol	1.91	0-3.7 mmol/L
Triglycerides	1.88	0.56-1.7 mmol/L
Coagulation function		
Prothrombin Time	13.7	11.0-15.0 sec
Prothrombin activity	86.56	75%-160%
International normalized ratio	1.02	0.8-1.5
Complete blood count		
Leukocyte	1.17	4.5-10 × 10^9 cells/L
Neutrophils	0.02	1.8-6.3 × 10^9 cells/L
Eosinophils	0	0.02-0.52 × 10^9 cells/L
Basophils	0	0-0.06 × 10^9 cells/L
Lymphocytes	0.98	1.1-3.2 × 10^9 cells/L
Monocytes	0.17	0.1-0.6 × 10^9 cells/L
Erythrocyte	4.07	3.8-5.1 × 10^{12} cells/L
Platelet	159	125-350 × 10^9 cells/L
Inflammatory markers		
C-reactive protein	10.28	0-5 mg/L
Procalcitonin	0.192	0-0.05 ng/mL
Screening for causes of acute liver injury		
Autoimmune liver diseases		
Immunoglobulin A	1.4	0.72-4.29 g/L
Immunoglobulin G	13.3	8-17 g/L
Immunoglobulin G4	0.427	0.05-1.54 g/L
Immunoglobulin M	1.2	0.29-3.44 g/L
Anti-nuclear antibody	Negative	
Anti-smooth muscle antibody	Negative	
Anti-liver kidney microsome-1	Negative	

Anti-soluble liver antigen/liver pancreas antigen	Negative	
Anti-liver cytosol-1	Negative	
Anti-centromere antibody	Negative	
Anti-Mitochondrial-M2 antibody	Negative	
Anti-gp210 antibodies	Negative	
Anti-Sp100 antibodies	Negative	
Virology test		
Hepatitis A IgM	Negative	
Hepatitis B surface antigen	Negative	
Hepatitis B core antibody IgM	Negative	
Hepatitis C antibody	Negative	
Hepatitis E IgM	Negative	
Anti-CMV IgM	Negative	
Anti-EBV viral capsid antigen IgM	Negative	
Anti-EBV early antigen IgM	Negative	
COVID-19 RNA	Negative	
HBV DNA	< 100	< 100 IU/mL
Thyroid function		
Thyroid-stimulating hormone	0.8	0.56-5.91 uIU/mL
Free triiodothyronine	4.4	3.53-7.37 pmol/L
Free Thyroxine	14.68	7.98-16.02 pmol/L
Other		
Ceruloplasmin	0.36	0.16-0.45 g/L
Alpha-fetoprotein	2.9	0.0-9.0 ng/mL

IgM: Immunoglobulin M; COVID-19: Coronavirus disease 2019; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; HBV: Hepatitis B virus.

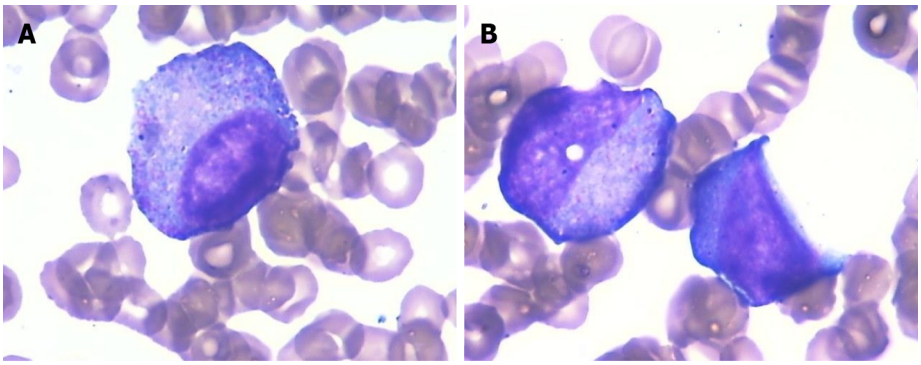

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Figure 1 Microscopic view of bone marrow aspirate showing severe agranulocytosis. A: A neutrophilic myelocyte; B: A neutrophilic myelocyte and a promyelocyte.

be the primary mechanism of PM-induced DILI[4]. The following are the mechanisms of PM-related DILI[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[15]. In the present case, liver function gradually improved after the administration of a glucocorticoid, compound glycyrrhizin, and polyene phosphatidylcholine was used to suppress inflammation and protect the liver. Although no pharmacological therapy for DILI has been adequately tested in randomized clinical trials, corticost-

Table 2 Histological description of bone marrow aspiration at admission (total number of 200 nucleated cells)

Cell type	%	Reference value range
Myeloblasts	1.5	0.31-0.97
Promyelocytes	1.5	1.51-1.63
Neutrophilic myelocytes	2.5	4.45-8.53
Neutrophilic metamyelocytes	2	5.93-9.87
Neutrophilic stab granulocytes	0	20.22-27.22
Neutrophilic segmented granulocytes	0	6.52-12.36
Eosinophils	0	0.15-0.61
Basophils	0	0.00-0.07
Pronormoblasts	0.5	0.27-0.87
Early erythroblasts	0.5	0.51-1.33
Polychromatic normoblasts	12.5	5.5-9.32
Orthochromatic normoblasts	33.5	8.39-13.11
Lymphocytes	42.5	15.71-29.82
Monocytes	2.5	2.12-3.88
Plasmacytes	0.5	0.29-1.13
Total	100	
Myeloid:erythroid ratio	0.16	2-4:1

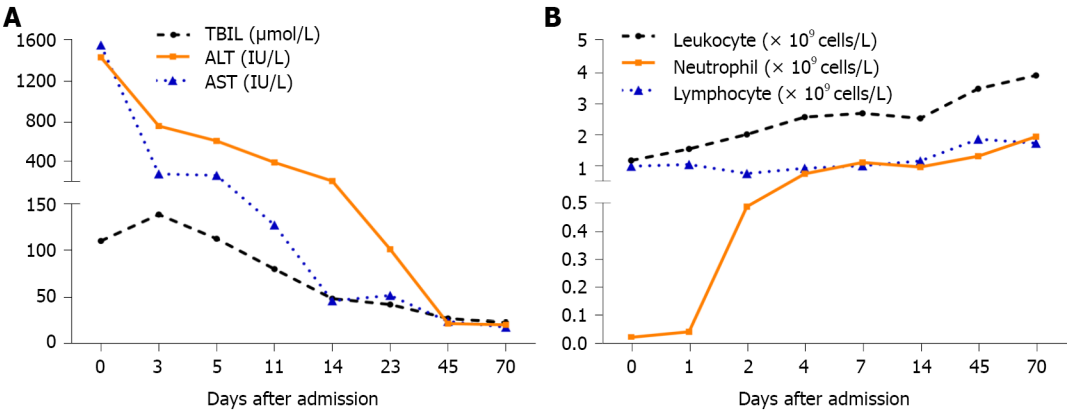

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Figure 2 Clinical course of the patient. A: Changes in levels of alanine aminotransferase, aspartate aminotransferase, and total bilirubin; B: Changes in the count of leukocytes, neutrophils, and lymphocytes. TBIL: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

eroids may be beneficial[9,16]. Compound glycyrrhizin is a safe and effective treatment for patients with DILI[17].

In addition to hepatotoxicity, agranulocytosis is another common adverse drug reaction[18]. In blood, absolute neutrophil count < 1.5 × 10^9 cells/L was defined as neutropenia and < 0.5 × 10^9 cells/L as agranulocytosis. Individuals with absolute neutrophil count < 0.1 × 10^9 cells/L had a significantly increased risk of morbidity and death owing to infection[18]. The clinical manifestations of idiosyncratic drug-induced agranulocytosis range from asymptomatic to various infections, and serious infections are often life-threatening[5]. There is approximately 5% of mortalities associated with idiosyncratic drug-induced neutropenia[19]. Poor prognosis is associated with individuals aged ≥ 65 years, absolute neutrophil count < 0.1 × 10^9 cells/L, severe infection, and comorbidities[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[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[21,22], clozapine[23],

methotrexate[24], and fusidic acid[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 granulocyte-colony stimulating factor (G-CSF)[26]. G-CSF at 300 μg/d helped reduce the time to recovery of blood counts without causing any major toxicity or adverse effects[27]. Our patient was a 65-year-old woman with a minimum neutrophil count of 0.02 × 10^9 cells/L. Fortunately, after receiving a dose of 300 μg 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.

FOOTNOTES

Author contributions: Shao YL analyzed and interpreted the clinical data, and wrote the draft of this manuscript; Zhang SC reviewed the manuscript; Ma CM, Wu JM, and Guo FC collected the patient's clinical information; all authors read and approved the final manuscript.

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