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Case report

Severe adverse reaction induced by albendazole and praziquantel for cystic echinococcosis

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ABSTRACT

Albendazole and praziquantel have been used to treat various parasitic infections for many years. Studies have confirmed the efficacy in the treatment of cystic echinococcosis (CE). We reported the case of a 45-year-old Chinese patient with pulmonary CE. He experienced diarrhea, stomachache, increase bilirubin, hair loss and acute fatal pancytopenia 10 days after albendazole and praziquantel treatment. We performed a literature review of severe adverse reaction caused by albendazole and praziquantel. It showed that severe adverse reactions such as bone marrow suppression caused by albendazole or praziquantel are rare, but patients with a course of treatment exceeding 10 days or with liver diseases are more likely to experience. Clinicians should pay attention to monitoring the patient's gastrointestinal tract reaction and peripheral blood cells (PBCs). If the patient showed a progressive disease, the medication should be immediately stopped. Supportive treatments should be considered, such as the administration of granulocyte colony-stimulating factor (G-CSF) against neutropenia or antibiotics to prevent infection.

Introduction

Albendazole and praziquantel are broad-spectrum drugs which are used for the treatment of many parasitic infections, including cysticercosis,tapeworm disease and clonorchiasis. We treated a 45-year-old Chinese man with albendazole and praziquantel for CE. The patient experienced many adverse reactions including diarrhea, stomachache, increase bilirubin and fatal pancytopenia during the treatment. We analyzed the possible causes for this outcome and performed a literature review.

Case description

A 45-year-old man was admitted to the Department of Pulmonary and Critical Care Medicine on May 16, 2022. He had been diagnosed with hepatic echinococcosis with right abdominal distension pain 8 years ago and pulmonary echinococcosis 5 years ago. The patient had been treated with surgery 6 years ago. He was admitted to the hospital to treat pulmonary hypertension and evaluate the surgery time needed to completely clear the CE. Computerized tomography pulmonary angiography (CTPA) showed that the filling defects of the pulmonary artery were not resolved (Fig. 1.). During admission, the patient's peripheral blood cells (PBC) and bilirubin (TBIL) was normal. The patient was prescribed enoxaparin 4000 IU twice a day for pulmonary embolism, torsemide 10 mg once a day with spironolactone 20 mg once a day to reduce edema. From May 18 th to June 8 th, 2022, the patient was prescribed albendazole (Tianjin Smith Kline &French Laboratorles Ltd) 400 mg twice a day, and praziquantel 600 mg (Hongqi Pharmaceutical Co., Ltd) once a day was added from May 26 th to June 8 th, 2022 to enhance the therapeutic effect. On May 23th,2022, the patients total bilirubin increased two times (from 30.32 umol/L to 65.94 umol/L). The blood counts showed severe myelosuppression on June 7, 2022, including WBC 1.35 $\times$ 10^9/L, NEUT 0.73 $\times$ 10^9/L, and Hgb 97 g/L. At the same time, the patient experienced febrile, diarrhea, stomachache, and severe hair loss. The patient's blood count further decreased with WBC 0.46 $\times$ 10^9/L, NEUT 0.13 $\times$ 10^9/L, and Hgb 88 g/L on June 9th, 2022. Doctors stopped albendazole and praziquantel immediately and treated with parenteral nutrition, omeprazole, glutathione, meropenem and granulocyte colony-stimulating factor. The gastrointestinal tract reaction recovered gradually. But the PBC was still very low, including WBC 0.86 $\times$ 10^9/L, NEUT 0.25 $\times$ 10^9/L, PLT 78 $\times$ 10^9/L, and Hgb 92 g/L. The patient got very high risk for severe infection.Fortunately, after 8

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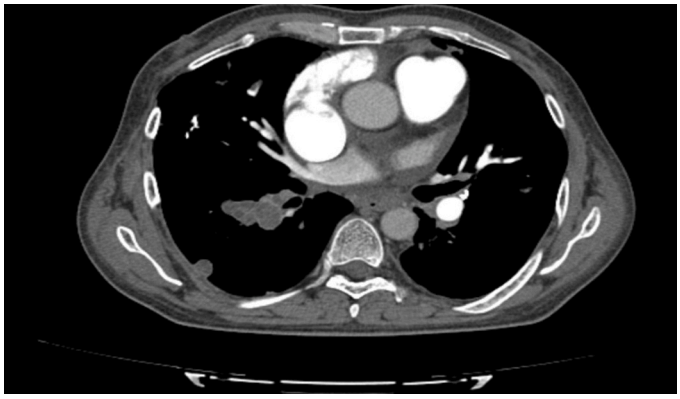

Fig. 1. Computed Tomography Pulmonary Angiography(CTPA). The trunk of the pulmonary artery widened and pulmonary artery branches as subsegmental or segmental filled defects.

days of stopping albendazole and praziquantel,the patient PBC began to increase slowly. The changes in the blood count and the doses of the drugs used for treating CE are shown in Figs. 2 and 3, respectively.

Discussion

Echinococcus granulosus infection is initially asymptomatic and may remain so for many years. Its subsequent clinical features and complications depend on the size of the cyst(s) and their location. The liver and lungs are affected in approximately 67 % and 25 % of cases, respectively. Most patients experience single-organ involvement, and a single cyst is present in more than 70 % of cases. Enlarged cysts can cause hepatomegaly, with or without right upper quadrant pain, nausea, and vomiting. The most common symptoms of pulmonary CE are cough, chest pain, dyspnea, and hemoptysis. Approximately 60 % of pulmonary hydatid disease affects the right lung, and 50–60 % of cases involve the lower lobes [9]. Multiple cysts are common. Approximately 20 % of patients with lung cysts also have liver cysts [10].

Albendazole is the primary antiparasitic agent for the treatment of *E. granulosus* [24]. Albendazole inhibits microtubule assembly, leading to impaired glucose absorption and causing glycogen depletion, followed by degeneration of the endoplasmic reticulum and mitochondria of the germinal layer, resulting in cell death [9]. Albendazole is poorly absorbed and should be ingested with food, ideally a fatty meal, to increase bioavailability (15 mg/kg/day, divided into two doses to a maximum of 800 mg). Oral absorption in humans is approximately 1–5 % at the therapeutic dose, and the half-life is 8–12 h. Albendazole undergoes rapid first-pass metabolism, primarily via CYP1A1 and CYP3A4 as well as flavin enzymes, generating two metabolites (sulfoxide and sulfone). Albendazole sulfoxide is the active metabolite responsible for the therapeutic effects [11,12]. Peak concentrations of albendazole sulfoxide are detected in serum 2–5 h after a therapeutic dose, with a reported half-life of 12–18 h [13].

Albendazole is generally well-tolerated, with a low incidence of gastrointestinal discomfort. It is rarely associated with more severe adverse effects such as leukopenia (0.044 %), anemia (0.004 %), and raised liver enzymes (0.035 %) [14]. Pancytopenia is a rare effect that occurs more commonly in patients with preexisting liver disease [15]. Death is occasionally reported after therapeutic albendazole use due to pancytopenia and subsequent septic shock [5].

Praziquantel exhibits protoscolicidal activity. However, its efficacy in clinical studies is variable, and, thus far, it does not have a definitive role in primary drug therapy [16–19]. Limited case studies suggest that the combination of albendazole and praziquantel may be superior to albendazole alone, but further research is needed [20].

The most commonly reported adverse effects of praziquantel involved the neuromuscular system, digestive system, cardiovascular system, and anaphylaxis, with incidence rates of 3.80 %, 2.44 %, 0.542 %, and 0.542 %, respectively [21–23]. According to Olds et al. [21], the adverse effects of praziquantel were mainly nausea, vomiting, abdominal pain, headache, and bloody diarrhea. In 2020, one case of neurocysticercosis caused by acute pancytopenia that resulted from a high

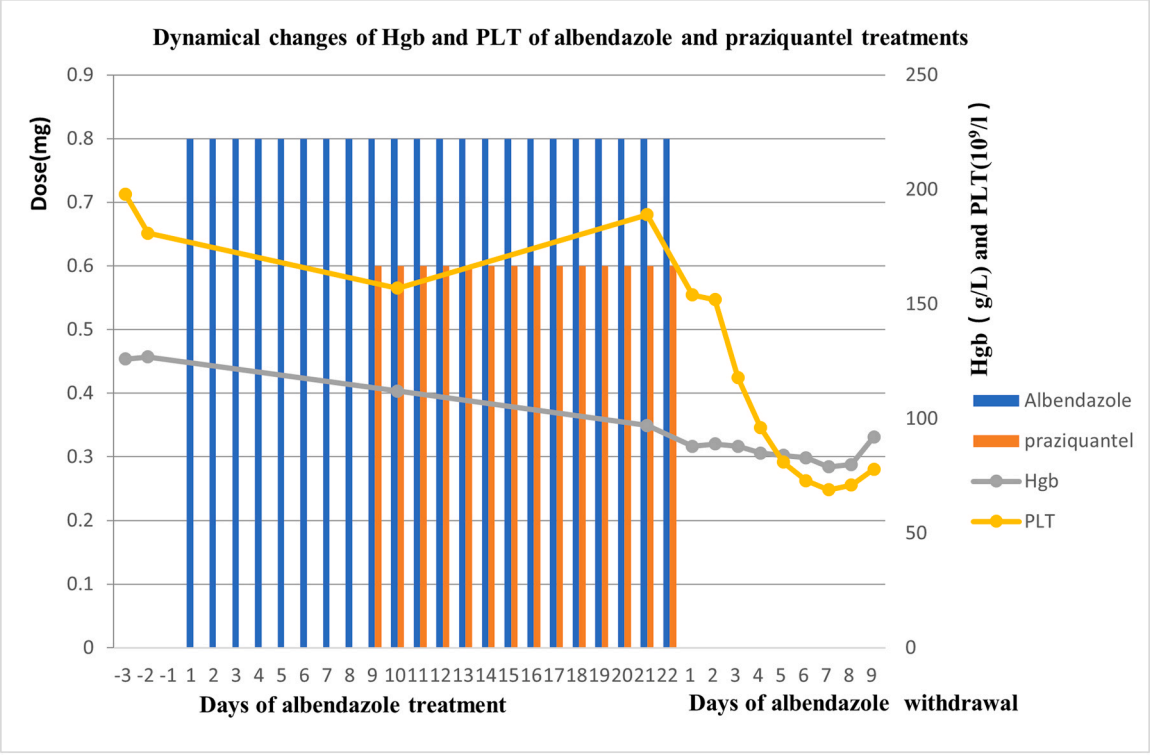

Fig. 2. Dynamical changes of Hgb and PLT of albendazole and praziquantel treatments. Hgb: hemoglobin, PLT: platelets.

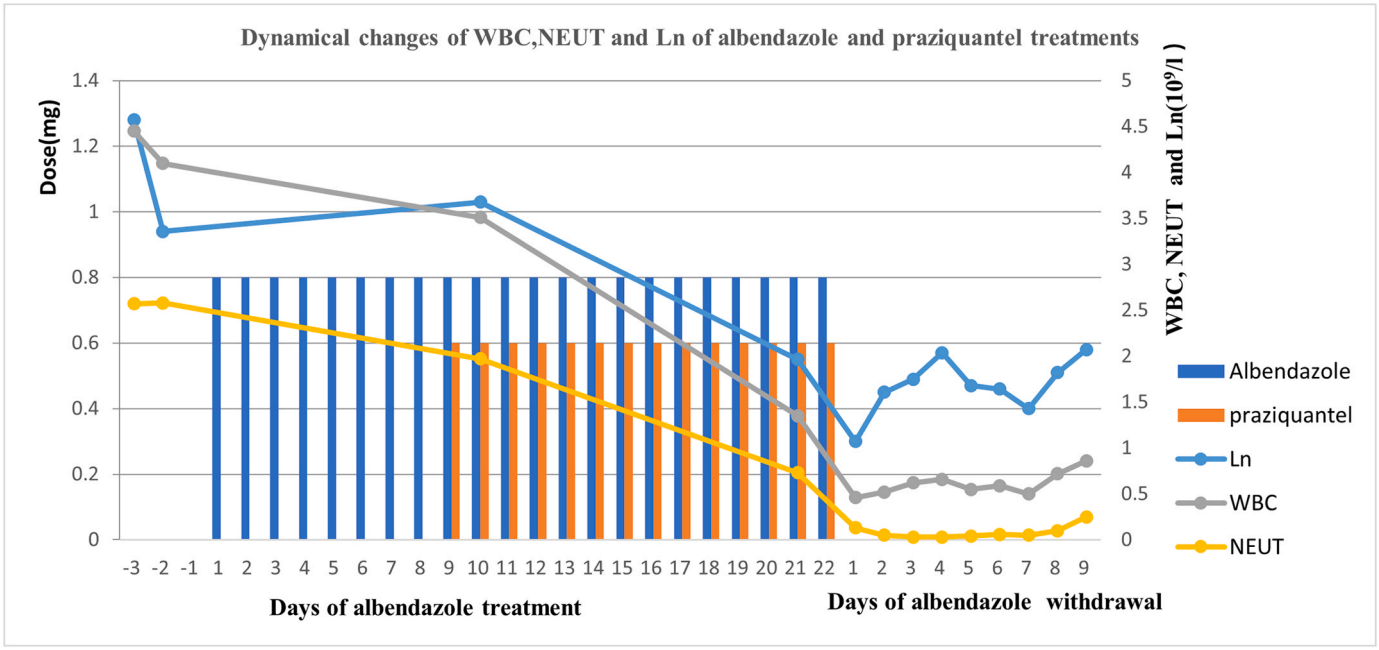

Fig. 3. Dynamical changes of WBC, Ln and NEUT of albendazole and praziquantel treatments. Ln: lymphocytes, WBC: leukocyte, NEUT: neutrophils.

dose of praziquantel was reported in China [6]. In that case, no adverse effects were observed with a 10-day course of albendazole (20 mg/kg qd) or praziquantel (20 mg/kg qd) in 2011. However, the patient was prescribed an increased dose of praziquantel (40 mg/kg qd for 5 days) twice in June and December 2018. As a result, acute pancytopenia occurred repeatedly. Each time, the cell count gradually recovered 2 weeks after praziquantel withdrawal. Thus, the praziquantel-related adverse effects were caused by the high dose of the drug. In the present study, the patient weighed 68 kg and was prescribed praziquantel 600 mg once a day (8–9 mg/kg), which was much lower than the high dose of praziquantel reported above (40 mg/kg).

Our patient was prescribed albendazole 400 mg twice a day on the fourth day of admission and praziquantel 600 mg once a day on the 12th day of admission. Although the patient took enoxaparin and torsemide at the same time, these two drugs were taken by the patient before and no adverse reaction occured.The patient suffered diarrhea, stomachache, increased bilirubin, hair loss and acute fatal pancytopenia after 10 days of albendazole and praziquantel administration. After 21 days of treatment, the patient exhibited neutropenia and stopped taking albendazole and praziquantel. The patient's white blood cells, neutrophils, and platelets further decreased in the first few days after albendazole and praziquantel withdrawal, suggesting that the drug was not cleared completely from his body or the hematopoietic function of bone marrow did not return to normal. Eight days after discontinuation, the patient's blood cells began to return to normal levels.

Opatrny [5] reported the case of a patient who died with severe prolonged pancytopenia that began during the third week of therapy for a pulmonary echinococcal cyst. In 2014, two cases of bilineage cytopenia were reported separately [2,3], both following a month of albendazole treatment for hydatid cyst disease. The case reported by Fredj [2] developed leukopenia and thrombocytopenia, and another reported by Aç ıkgöz [3] developed thrombocytopenia and anemia. Our patient developed pancytopenia after 10 days of albendazole and praziquantel treatment. This effect may be exacerbated in patients with pre-existing liver failure. Our patient was admitted with increased bilirubin and prescribed albendazole for more than 10 days, which may prolong the clearance time of albendazole and praziquantel in the body. Thus, we speculated that the severe adverse reaction was caused by the accumulation of albendazole and praziquantel because of the liver dysfunction of the patient. Table 1 shows the summary of the clinical features of the patients with pancytopenia induced by albendazole or praziquantel.

Pancytopenia, neutropenia, and agranulocytosis are not mentioned on the label of albendazole and praziquantel in China. Clinicians lack experience in the diagnosis and treatment of echinococcosis. We analyzed the time and occurrence of adverse reactions to albendazole and praziquantel. Clinicians should pay attention to monitoring the reaction during treatment period.

Conclusion

We suggest that patients who take albendazole and praziquantel, especially those who have been treated for more than 10 days and have liver dysfunction should closely monitor the treatment reaction such as gastrointestinal tract reaction, hair loss or complete blood count. Once severe adverse reaction occurs, the drug should be immediately stopped. Supportive treatments such as the administration of granulocyte colony-stimulating factor (G-CSF) against neutropenia or antibiotics to prevent infection should be considered.

Ethical approval

The data in this paper are from clinical cases, no ethics involved.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Table 1
Summary of the clinical features of the patients with pancytopenia induced by albendazole and praziquantel.

Case No.	Age	Sex	Infected disease	Suspected drug	The process of suspected drug	Occurrence time and manifestation of bone marrow suppression / alopecia	Hematological Parameters	Management of adverse reaction	Outcome
1[1]	77	M	Strongyloides stercoralis infection	Albendazole	Albendazole 400 mg × 15 days	After 15 days, albendazole-induced pancytopenia occured	-	-	Death due to polymicrobial Infections complicating pneumonia albendazole-induced pancytopenia
2[2]	26	M	Hepatic cysts	Albendazole	Albendazole 500 mg/d for 3months , Two years later, he suffered a relapse with multiple new hydatic cysts in the liver and was treated with albendazole 800 mg daily.	One month later, the patient suffered upper right abdominal pain associated with jaundice	A Hgb level of 8.9 mg/dL (mean corpuscular volume (MCV) 89 fL, mean corpuscular hemoglobin (MCH) 29 pg, reticulocyte count 53,000/mm^3), a white blood cell count of 5400/L, and a platelet count of 119 × 10^3 /L. Serum levels of hepatic enzymes were as follows: alanine aminotransferase (ALT) 2454 IU/L (normal value 10– 49 IU/L), aspartate aminotransferase (AST) 1451 IU/L (normal value 10– 46 IU/L), and alkaline phosphatase 198 IU/L(normal value 100 – 290 IU/L); total bilirubin was 341 mg/dL (normal value 1–17 mg/dL).	Albendazole withdrawal	Clinical symptoms resolved within 1 week and laboratory tests showed progressive improvement, with complete resolution of the hematologic and hepatic disorders at 4 and 15 days after drug withdrawal, respectively.
3[3]	25	F	Hepatic cysts	Albendazole	10 mg/kg/d	prolonged menstrual bleeding, fatigue, and the complaint of gum bleeding.	Prior to the operation, blood tests were normal: PLT 283 × 10^9/L， Hb 109 g/L ； one month after the operation, while she was being treated with albendazole, PLT 8 × 10^9/L, Hgb 35 g/L	Albendazole withdrawal	Clinical resolution
4[4]	53	M	-	Albendazole	Average albendazole dose was 5.4 g/d	Pancytopenia, hair loss, rash and fever	WBC 0.4 × 10^3/mm^3, NEUT 0 × 10^3/mm^3, AST 268 IU/L , ALT 89 IU/L	Treated with antibiotics and colony-stimulating factors for presumed neutropenic bacteremia	Clinical resolution
5[5]	68	M	Pulmonary echinococcal cyst	Albendazole	400 mg bid	Two weeks later, the patient presented severe prolonged pancytopenia, septic shock	Before taking albendazole: PLT 118 × 10^9/L, Hgb 132 g/L, WBC 5.96 × 10^9/L , 2 weeks later, Hgb 68 g/l, WBC 0.05 × 10^9/L, NEUT 0, PLT 11 × 10^9/L。	Treatment with albendazole was stopped on admission to the hospital and replaced with praziquantel, 900 mg intravenously, twice a day. The patient was given granulocyte colonystimulating factor and intravenous immunoglobulin for bone marrow stimulation, and amphotericin B was given for candidemia. Seven days following admission to the ICU, there was still no	The patient died following unsuccessful resuscitation

(*continued on next page*)

Table 1 (*continued*)

Case No.	Age	Sex	Infected disease	Suspected drug	The process of suspected drug	Occurrence time and manifestation of bone marrow suppression / alopecia	Hematological Parameters	Management of adverse reaction	Outcome
								peripheral evidence of marrow recovery	
6[6]	56	M	Cerebral cysticercosis	praziquantel	40 mg/kg/d for 5 days	10 days later, pancytopenia	Two times following praziquantel treatment (40 mg/kg per day for 5 days) and gradually recovered after praziquantel withdrawal	Treated with granulocyte colony stimulating factor (300 mg, subcutaneous injection once daily) from the 10th to 15th day	Clinical resolution
7[7]	17	M	Hepatic cysts	Albendazole	900 mg/d,14 days later, dose was increased to 900 mg, bid.	1 week later , the patient suffered hair loss, pancytopenia, and fever	WBC 1.7 $\times$ 10^9/L , NEUT 0.30 $\times$ 10^9/L , Hgb 39 g/L , PLT 125 $\times$ 10^9/L	Treated with antibiotics, immune globulin and albumin	Clinical resolution
8[8]	19	F	Hepatic cysts	Albendazole	400 mg bid	2 weeks later , the patient suffered hair loss and pancytopenia	Before taking albendazole, WBC 4.46 $\times$ 10^9/L, NEUT% 58.5 %, 14 days later, WBC 0.99 $\times$ 10^9/L , NEUT% 15 %.	Treated with granulocyte colony stimulating factor 150 ug QD	Clinical resolution

CRediT authorship contribution statement

Li Zhao designed the study and wrote the manuscript. Professor Wanmu Xie determined the clinical diagnosis and the treatment. Professor Pengmei Li provided guidance on drafting the manuscript and revised the manuscript.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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