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Case report

Isolated splenic cystic echinococcosis and albendazole hepatotoxicity

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ABSTRACT

Isolated splenic cystic echinococcosis is a rare condition. In Greece the number of cases has declined substantially in the last 20 years. The spleen is the second most common extrahepatic site of cystic echinococcosis. Albendazole is safe, but mebendazole can be used as a substitute, in case of adverse reaction. Our patient was diagnosed with isolated splenic echinococcal cyst, during the investigation for newly diagnosed type 2 diabetes mellitus. We opted for elective splenectomy, based on a risk assessment due to the patient's working conditions, and treatment with albendazole represented a safety measure until surgery was possible. The patient developed acute hepatocellular injury to albendazole after eight weeks of treatment. This was confirmed through rechallenge with albendazole after discontinuation of the drug. Postsplenectomy the treatment with mebendazole proved to be safe with no adverse reactions. Even though, albendazole is known to be safe, monitoring of hepatic enzymes and full blood count should be offered. In case of toxicities, mebendazole with or without praziquantel can be used. Toxicity to mebendazole can be similar to albendazole but a trial is worthwhile. In our patient, treatment with mebendazole was uneventful

Introduction

Isolated splenic cystic echinococcosis is a rare condition. Greece, like other Mediterranean countries, is endemic for *Echinococcus granulosus*; however, cystic echinococcosis is sporadic, and the number of cases has declined substantially in the last 20 years. Splenic involvement is also very rare at the global level, having been described in only 0.9–8% of cases [1]. Despite its rarity, few cases have been reported in hospitals from Greece. Lianos et al. [2] reported that the spleen is the second most common extrahepatic site of cystic echinococcosis. Treatment with albendazole is safe, or in cases where toxicity occurs, mebendazole can be used as a substitute.

Case report

A 53-year-old man presented to hospital with elevated blood glucose levels and was admitted for newly diagnosed diabetes mellitus type 2. He worked in maritime transportation, traveled internationally, and was married without children. The patient did not smoke or use of illicit drugs and he reported only social drinking. His travel history included South and North America, Africa, and Asia. While traveling, he mostly resided on the ship, but went ashore to dine in restaurants and local cuisines. He had no contact with livestock animals. At home he lived in an apartment with his wife and had a clean water supply connected to the national water system.

The patient denied eating unwashed vegetables or raw meat, but he admitted to consuming local food served in restaurants during his travels, some of which may have been undercooked.

The patient's symptoms included abdominal discomfort, increased thirst, and polyuria; all symptoms had been progressive for the past two weeks before admission. His Physical examination revealed mild discomfort during palpation of epigastrium and left hypochondrium. The liver edge was palpated two centimeters below

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the right hypochondrium with a round edge but was not tender. The spleen was palpated with a round edge, three centimeters below the left hypochondrium, extending four centimeters or more in deep breath, and was not tender. The patient's vital signs were normal.

The initial workup was notable for glycemia (690 mg/dL), a small elevation of blood urea level (54 mg/dL), increased C-reactive protein level (1.4 mg/dL, normal values (n.v.) < 0.5) and high serum amylase level 295 U/L (n.v. < 125); urine amylase levels were within the normal range values (460 U/L). His biochemical status was compatible with a pancreatic reaction in the context of uncontrolled hyperglycemia with a compensated metabolic profile (normal blood gases, pH, sodium, small elevation of blood urea and no ketones in serum or urine). The patient was given subcutaneous long-acting insulin (glargine insulin) and short-acting insulin (human biosynthetic insulin) before major meals which resulted in an almost immediate improvement in his glycemic profile. His glycated hemoglobin level was 7.2%.

An abdominal computed tomography (CT) scan revealed cystic echinococcosis of the spleen. Abdominal magnetic resonance imaging (MRI) was performed for better visualization of the pancreas and liver; no other pathology was found, and a head CT scan was also negative. Two cystic lesions were found in the spleen, with the largest measuring 8.7 × 9.5 × 11 cm (Figs. 1–5). Located at the lower edge of the first, a second lesion of 4.3 × 2.7 × 4 cm in dimension was identified that reached the splenic capsule (Figs. 6 and 7). Calcifications were observed in both lesions, but the latter was described as more heterogenous. A renal cyst was observed in the left kidney, which was 2 cm in diameter and was in proximity to the lower pole of the enlarged spleen. Anti-echinococcal IgG antibodies were also detected.

The differential diagnoses were limited to parasitic diseases and cystic lesions in the spleen. The CT result hinted at cystic echinococcosis as being the principal diagnosis, and the description of the lesions was compatible with only a limited number of other pathological processes. The patient denied diarrheal illness, fever or other gastrointestinal symptoms aside from discomfort. Anti-amoebic antibodies were negative, and the isolation of lesions solely in the spleen made the diagnosis of amoebic abscess less probable. The patient had no history of trauma to the lower chest or abdomen, lessening the possibility of post-traumatic hematoma with subsequent cystic formation. The lack of history of infective endocarditis or thromboembolic phenomena decreased the possibility of splenic

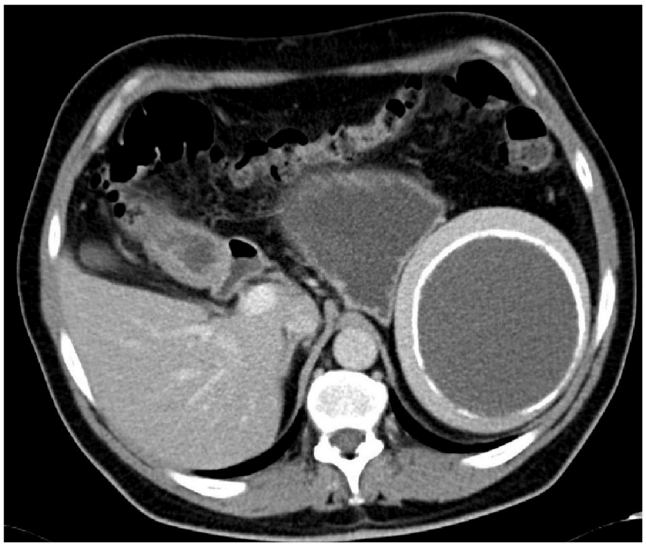

Fig. 1. CT slice of the splenic cystic lesion with dimensions of 8.7 × 9.5 × 11 cm, with a thick calcified wall.

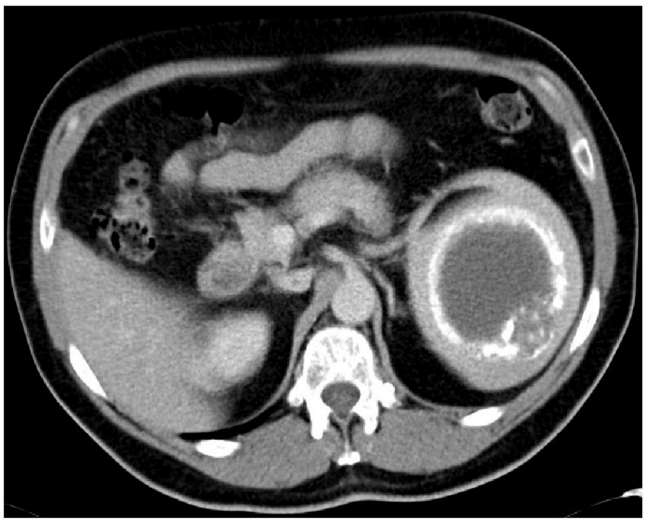

Fig. 2. CT slice of the lower edge of the cystic lesion; a smaller, more heterogenous lesion is noted with dimensions of 4.3 × 2.7 × 4 cm.

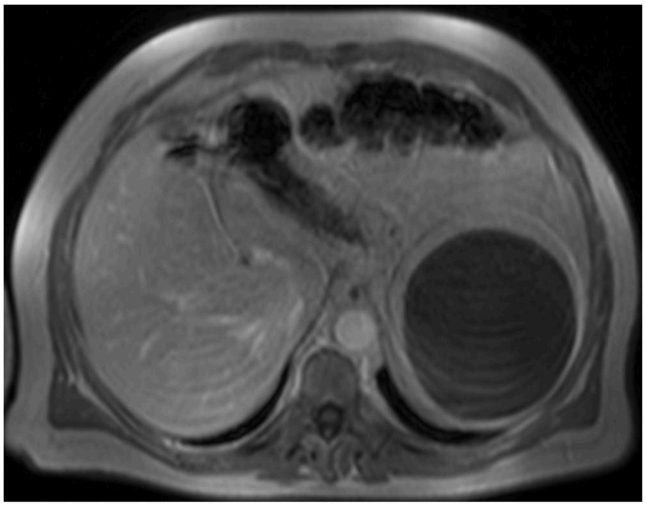

Fig. 3. Axial MRI slice of the larger cystic lesion.

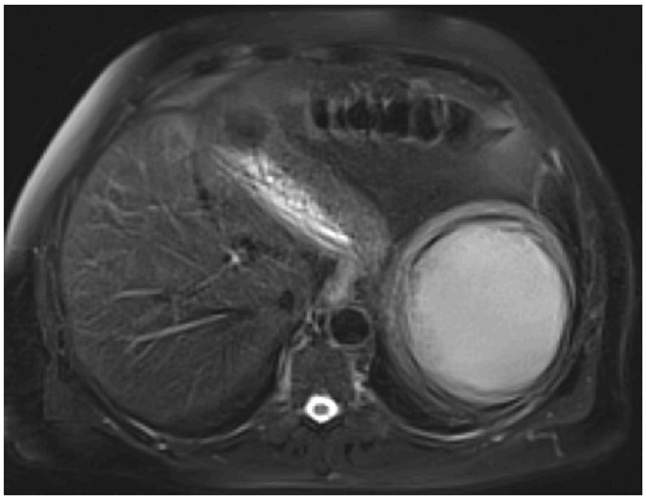

Fig. 4. Axial MRI slice of the large cystic lesion with high signal in T2 and low in T1.

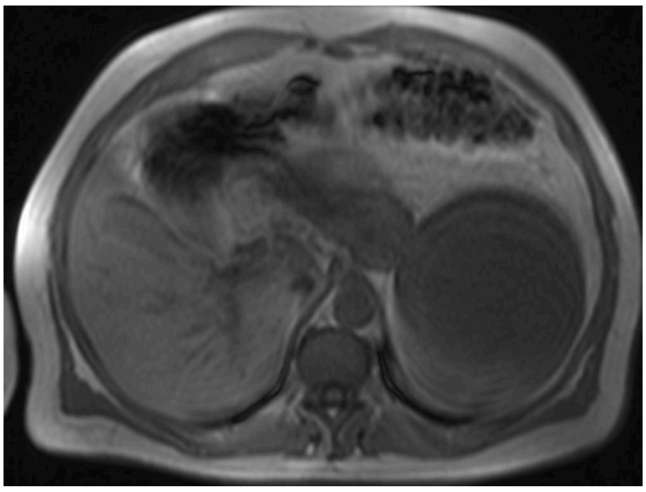

Fig. 5. Axial MRI slice of the larger cystic lesion, described with high signal in T2 and low in T1.

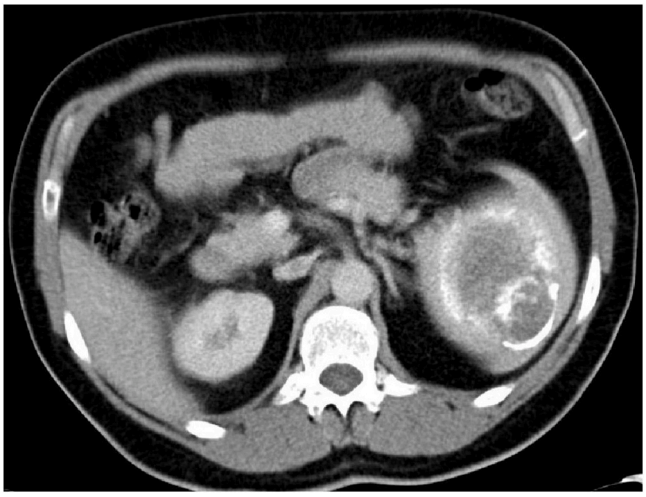

Fig. 6. CT slice of the second smaller lesion that was more heterogenous.

infarcts. Normal transthoracic cardiac ultrasound, lack of ova and parasites on stool, and CT imaging combined with the presence of reactive echinococcal antibodies made cystic echinococcosis the most probable diagnosis.

The patient was informed of the diagnosis of echinococcosis, and an elective splenectomy was proposed. This decision was made on the bases of the nature of the patient's job, as he spent much of his time on ships in the open sea where spontaneous or traumatic splenic rupture could be fatal. The patient refused surgery for the next five months, owing to his work schedule; a new treatment plan consisting of long-term treatment was therefore agreed upon until his return to Athens. Albendazole 400 mg bid was prescribed, and frequent laboratory work-ups were planned (initially in 5 days, and every 10 days thereafter). The patient agreed to undergo a 5-month treatment course until he was able to undergo surgery, and was given clear instructions to stop treatment and seek medical advice in case of laboratory abnormalities.

Due to the coronavirus disease 2019 pandemic, the patient's travel for work was canceled; at that point, he had undergone one month of albendazole treatment. The patient was scheduled for vaccinations against *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*. It was decided he would be kept on albendazole treatment due to lack of any adverse reactions and as his blood test results were normal. Six weeks after treatment with

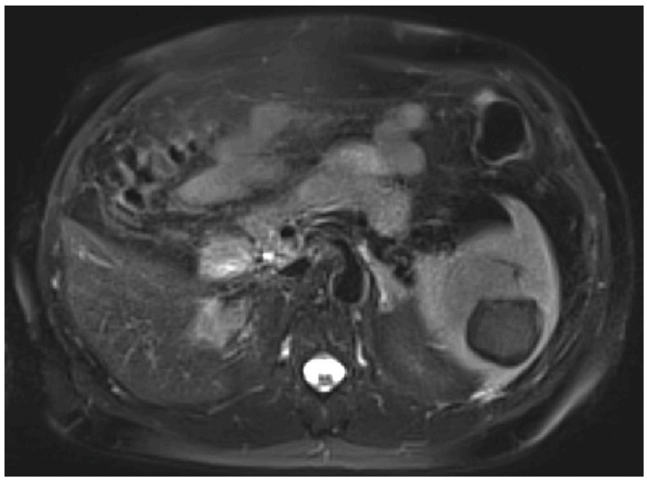

Fig. 7. MRI slice of the smaller cystic lesion with low intensity signal in both T1 and T2 sequences.

albendazole and three weeks during vaccination period, he presented with slightly raised aminotrasferases [aspartate aminotransferase (AST) 147 U/L, normal values (n.v) < 34 and alanine aminotransferase (ALT) 230 U/L, n.v < 49]. Continuation of treatment with weekly blood work was recommended; however, in the eighth week of treatment, he presented a > 10 increase in aminotransferases, following which hospitalization was recommended and albendazole was discontinued because of possible drug-induced liver injury. During the second day, the level of AST was 359 U/L, ALT was 732 U/L, γ-glutamyl transferase (γGT) was 158 U/L (n.v < 36 U/L), alkaline phosphatase (ALP) was 51 U/L, total bilirubin was 1.33 mg/dL (n.v < 1.20), direct bilirubin was 0.79 mg/dL (n.v < 0.3); the patient had normal indirect bilirubin with normal renal function and full blood count. The investigation of infectious, metabolic, and autoimmune causes of hepatic liver injury (HLI) was unremarkable.

Follow-up serology after 10 days was also negative for cytomegalovirus, Epstein-Barr virus and *Toxoplasma gondii*. A new CT scan of the abdomen did not reveal new pathology, and the dimensions of splenic cyst were unchanged. Serum albumin levels and coagulation studies (prothrombin time/international normalized ratio; PT/INR, and activated partial thromboplastin time; aPTT) were normal. He was hospitalized for five days, with gradual improvement in liver enzymes, and was then discharged, with recommendations for blood work every 5 days. He further improved 10 days after discharge, and 15 days later, a rechallenge with 400 mg of albendazole daily was administered, with close follow-up. A new increase in aminotranferases was noted and the patient was advised to stop the drug intake completely.

The patient was scheduled to undergo elective splenectomy in mid-January of 2021. He received a single dose of praziquantel (40 mg/Kg). The patient underwent surgery uneventfully, and the spleen was removed en-bloc with no visible spillage (Figs. 8–12). His postsurgical recovery was notable for leukocytosis and elevated C-reactive protein levels; therefore, broad-spectrum antibiotics were used (linezolid and piperacillin/tazobactam). After the fourth day, he was able to eat and drink; because of this, treatment with mebendazole was initiated at a dose of 20 mg/Kg/day, divided in three daily doses.

His laboratory workup was normal during treatment with mebendazole, including albumin and aPTT. Eighteen days under treatment with mebendazole showed no signs of toxic hepatic effects, and when pathology report became available (showing an extensively calcified inactive echinococcal cyst) treatment was discontinued.

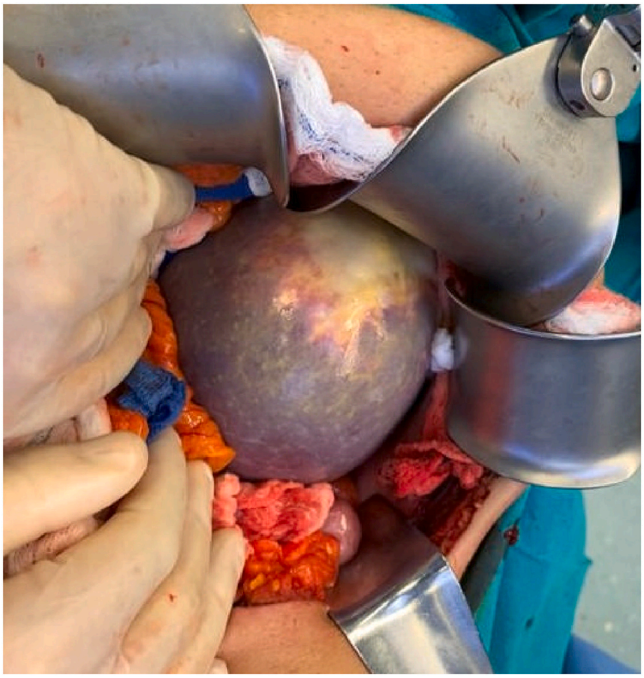

Fig. 8. The spleen during first stages of operation.

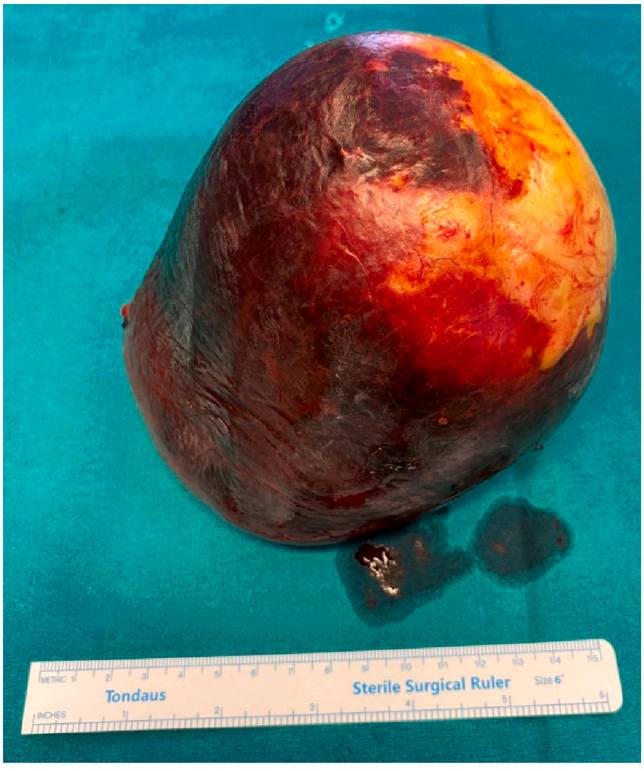

Fig. 9. Diaphragmatic surface of the spleen after splenectomy.

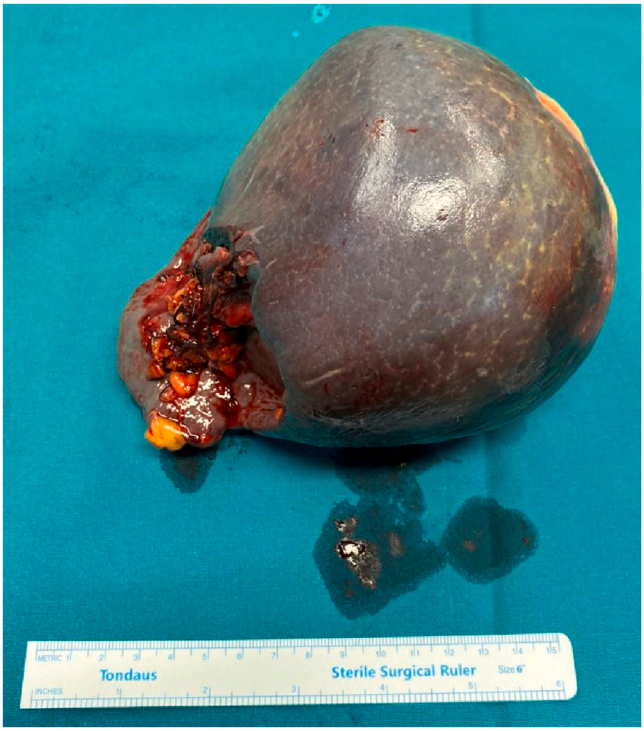

Fig. 10. Visceral surface of the spleen after splenectomy.

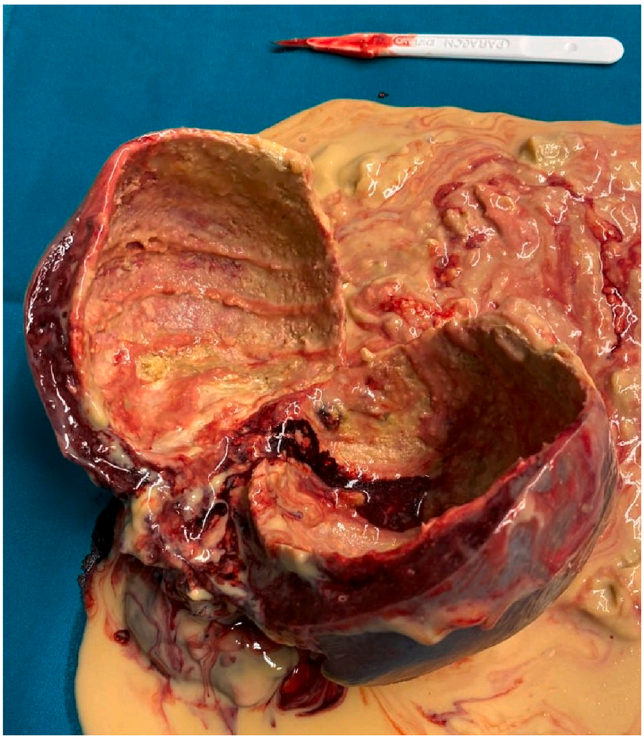

Fig. 11. Details of surgical specimen dissected.

Discussion

Cystic echinococcosis is a zoonotic infection for which humans are incidental intermediate hosts. The causative agent is *Echinococcus granulosus senso lato*, a cestode (tapeworm) with different genotypes. The definitive hosts are domestic and wild canids, whereas the intermediate hosts are sheep, goats, cattle, and other ungulates. Humans become infected by ingesting eggs that release six-hooked oncospheres in the intestinal lumen. These oncospheres then penetrate the lumen and develop into thick-walled hydatic cysts in different organs, most often in the liver and the lungs. Other species of *Echinococcus* are *E. multilocularis* (causative agent of alveolar hydatid cyst) and the rarer *E. vogeli* and *E. oligarthrus* (causing neotropical echinococcosis in the New world).

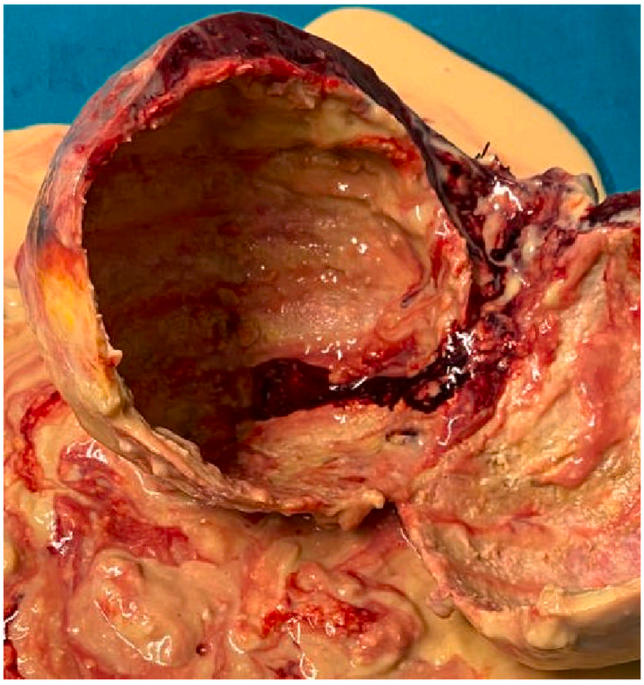

Fig. 12. Details of dissected spleen, layers of calcifications are visible. Extended haemorrhagic infarct can also be seen.

Diagnosis is primarily based on imaging techniques, as clinical signs can be non-specific. Epidemiological history and serology can complete the diagnosis, but pathological examination of the resected cyst or fluid aspirate can confirm the viability of protoscoleces [3]. Standardized classification through ultrasound can be used, based on the World Health Organization and Informal Working Groups on Echinococcosis (WHO - IWGE) consensus, to divide the cysts into three groups: active (CE1 and CE2), transitional (CE3) or inactive (CE4 and CE5). CT and MRI can be used to define complications, track dissemination, or to aid the decision of interventions (surgical excision or puncture, aspiration, injection, and re-aspiration (PAIR)). Although ultrasonography was not performed in this case, observations were compatible with the CE4 or CE5 cyst type [4]. In this type of lesion, the WHO-IWGE suggests a watch and wait stance be adopted. In the context of optimal resources, patient could be observed with repeated ultrasound scans for a long period. Here, the decision for elective splenectomy was based on a risk assessment due to the patient's working conditions, and treatment with albendazole represented a safety measure until surgery was possible. Nevertheless, splenic echinococcal cysts compatible with CE4 or CE5 can prove active in pathology examination [5].

Albendazole is an effective and safe anthelminthic drug; however, hepatic toxicity occurs in rare cases [6]. In a meta-analysis from 2003, elevation of liver enzymes was reported to be 0.7% (in 13 of 1681 patients), with 0.7% of patients (7 of 952 patients) reported to have developed liver fibrosis or failure [7]. Acute severe hepatitis and liver failure are extremely rare [8,9].

Total splenectomy is favored in cases of larger cysts, since there is a reduction in the splenic parenchyma due to atrophy and pressure. In these cases, there is an increased probability of complications such as intraoperative rupture and hemorrhage [10]. In this case, atrophy, hemorrhage, and infarction of the remaining splenic tissue was observed macroscopically (Fig. 11 & 12).

Conclusion

Hepatotoxicity is a possible side effect of albendazole, and the patient in this case study experienced hepatocellular injury after six weeks of treatment. The rapid decline of liver enzymes after discontinuation of the offending drug and recrudescence after rechallenge clearly defined albendazole as the cause of hepatotoxicity. A high Roussel Uclaf Causality Assessment Method score also supports this observation. Treatment with mebendazole had no adverse effects on hepatic biology since patient received the agent until the result of pathology was available (18 days total).

Ethics approval and consent to participate

This is not applicable as no studies conducted on the patient.

Consent

Informed consent was obtained for this publication.

Author contribution

Moussas Nikolaos, Adamidis Sotirios, Adamidis Nikolaos, Stratopoulos Charalampos and Gargalianos – Kakolyris Panagiotis contributed to either patient management and manuscript preparation or correction of and commenting upon the manuscript.

CRediT authorship contribution statement

Nikolaos Moussas: Conception and design of study, Acquisition of data, Analysis and/or interpretation of data, Drafting the manuscript, Revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published. **Sotirios Adamidis:** Analysis and/or interpretation of data, Revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published. **Nikolaos Adamidis:** Acquisition of data, Drafting the manuscript, Approval of the version of the manuscript to be published. **Charalabos Stratopoulos:** Acquisition of data, Approval of the version of the manuscript to be published. **Panagiotis Gargalianos-Kakolyris:** Analysis and/or interpretation of data, Drafting the manuscript, Revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published.

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Disclosure

No conflict of interest to disclosure for all authors.

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