

Observed or Predicted Albendazole Hepatotoxicity as an Indication for a Resection Procedure in Hepatic Hydatid Disease – A Short Series of Cases

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Rezumat

Hepatotoxicitate cauzată de Albendazol ca indicație pentru procedura de rezecție în hidatioză - Serie de cazuri

Obiectiv: Evidențierea rolului hepatotoxicității cauzată de Albendazol în alegerea între drenaj sau rezecție în cazul hidatiozei.
Metode: Fișele medicale a patru pacienți au fost analizate retrospectiv. În cazul a trei pacienți, albendazol a cauzat o creștere de 10 ori a transaminazelor și a fost întrerupt. Unul din pacienți a prezentat concomitent o hepatită autoimună.

Rezultate: În primul caz, au fost identificate două chisturi hidatice mari care cuprind vena hepatică stângă și dreaptă. Mai întâi, au fost efectuate o secționectomie laterală stângă și o ligatură a venei porte posterioare drepte. Hipertrofia ficatului rămas a permis o secționectomie dreaptă posterioară sigură două luni mai târziu. În cazul celui de-al doilea pacient, un chist de 9 cm în segmentele 6 și 7 a fost tratat prin perichistectomie. Cel de-al treilea pacient a prezentat un chist de 6 cm localizat central. Au fost efectuate o perichistectomie, îndepărarea unor vezicule mici din secțiunea anterioară a coledocului și explorarea coledocului prin plasarea unui tub în formă de T. În cazul pacientului cu hepatită autoimună, s-a optat pentru perichistectomie cu scopul: 1) de a elimina cavitatea predispusă la recidivă în cazul pacientului cu tratament imunosupresiv, 2) de a evita administrarea de albendazol, care poate complica interpretarea testelor de funcționare a ficatului. Perioada postoperatorie și începutul perioadei de urmărire s-a desfășurat fără evenimente deosebite. Cel de-al doilea și cel de-al patrulea pacient au fost urmăriți timp de 56, respectiv 17 luni, fără detectarea nici unei recidive.

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Concluzii: Procedura de rezecție elimină cavitatea și nevoia de tratament adjuvant cu albendazol. Acesta este un avantaj vital pentru cazurile restrânse de pacienți cu hepatotoxicitate severă cauzată de albendazol.

Cuvinte cheie: boală hidatică, rezecția *Echinococcus granulosus*, perichistectomie, drenaj, hepatotoxicitate albendazol

Abstract

Objective: To highlight the role of albendazole hepatotoxicity in the choice between drainage versus a resection procedure in hepatic hydatidosis.

Methods: The charts of four patients were reviewed retrospectively. In three patients, albendazole caused more than 10-fold increases in transaminase levels and was stopped. One patient had concomitant autoimmune hepatitis.

Results: In the first case, two large hydatid cysts involving the right and the left hepatic veins were detected. First, left lateral sectionectomy and ligation of the right posterior portal vein branches were performed. Hypertrophy of the remnant liver allowed a safe right posterior sectionectomy two months later. In the second patient, a 9-cm cyst in segments 6 and 7 was treated with pericystectomy. The third patient had a 6-cm centrally located cyst. Pericystectomy, removal of small vesicles from the anterior section bile duct, common bile duct exploration with a T-tube placement were performed. In the patient with auto-immune hepatitis, pericystectomy was chosen for two objectives: 1) to eliminate a cavity prone to recurrence in an immunosuppressed patient 2) to avoid albendazole that may complicate the interpretation of liver function tests. The postoperative period and early follow up of all patients was uneventful. The second and the fourth patients have been followed for 56 and 17 months respectively and no recurrence has been detected.

Conclusions: A resection procedure eliminates the cavity and the need for adjuvant albendazole treatment. This is a vital advantage for the small subset of patients with severe albendazole hepatotoxicity.

Key words: hydatid disease, *Echinococcus granulosus* resection, pericystectomy, drainage, albendazole hepatotoxicity

Introduction

The treatment options in hepatic hydatid disease are surgical (open or laparoscopic surgery), radiologic and medical approaches. Most hepatic hydatid cysts require some form of invasive intervention because medical treatment takes 1-2 years and is curative in approximately 30-60% of the patients (1-2). Even small (< 5-6 cm) unilocular cysts, which show the best response, may reactivate in approximately 25 % of the cases (3). Percutaneous treatment combined with albendazole is successful in up to

97-100 % of the cases in Gharbi I-II (WHO Informal Working Group Classification - CE1, CE3a, CE3b) cysts (1,3-5). Surgery is usually preferred in Gharbi III-IV (CE2, CE4) cysts as well as patients with complications such as intrabiliary rupture (6). Because this is a benign disease treated by general surgeons (not solely by hepatobiliary surgeons), drainage operations are often preferred over resection procedures. Neoadjuvant and adjuvant albendazole treatment is considered to be crucial for decreasing the risk of recurrence after a drainage procedure (1,2,6). An intriguing issue

is the optimal choice of treatment if chemotherapy is contraindicated. We present our experience on 4 patients who had observed or predicted hepatotoxicity and thus, were treated with a respective procedure to eliminate the cavity altogether.

Patients and Methods

Case 1

A 29-year-old woman with abdominal discomfort underwent ultrasonography (USG) that showed two hepatic hydatid cysts in the right lobe (8 cm, CE3b) and the left lobe (9 cm, CE2). Subsequent magnetic resonance imaging (MRI) confirmed the diagnosis and showed that the cysts extended to the close proximity of the right and left hepatic veins respectively *Fig. 1A,B*.

Albendazole (10 mg/kg/day) was initiated but follow up biochemical examination showed marked increases in the transaminase levels (ALT: 677 U/L, AST: 562 U/L) with no significant changes in GGT, ALP and bilirubin levels; albendazole was stopped

immediately. Serologic tests for hepatitis B and C infection were negative. Consistent but very slow recovery of the transaminase levels took 4.5 months. A challenge treatment to confirm the diagnosis was considered to be contraindicated.

Resective procedures that eliminate the residual cavity were considered. Proximity of the cysts to the roots of the hepatic veins and three dimensional relationships with the segment 2 and right posterior sectional pedicles precluded pericystectomy with preservation of the adjacent parenchyma. Consequently, a left lateral sectionectomy and right posterior sectionectomy were considered. Such a resection, if performed in a single stage would leave a remnant liver of approximately 422 cm³ in a 62 kg woman. Because, the remaining segments would be, for practical purposes, drained by a single hepatic vein, and the venous drainage of the anterior section would be partially compromised, a two-stage procedure was chosen. In the first operation, a left lateral sectionectomy and ligation of the right posterior sectional portal vein branches were performed (*Fig. 1C*). The

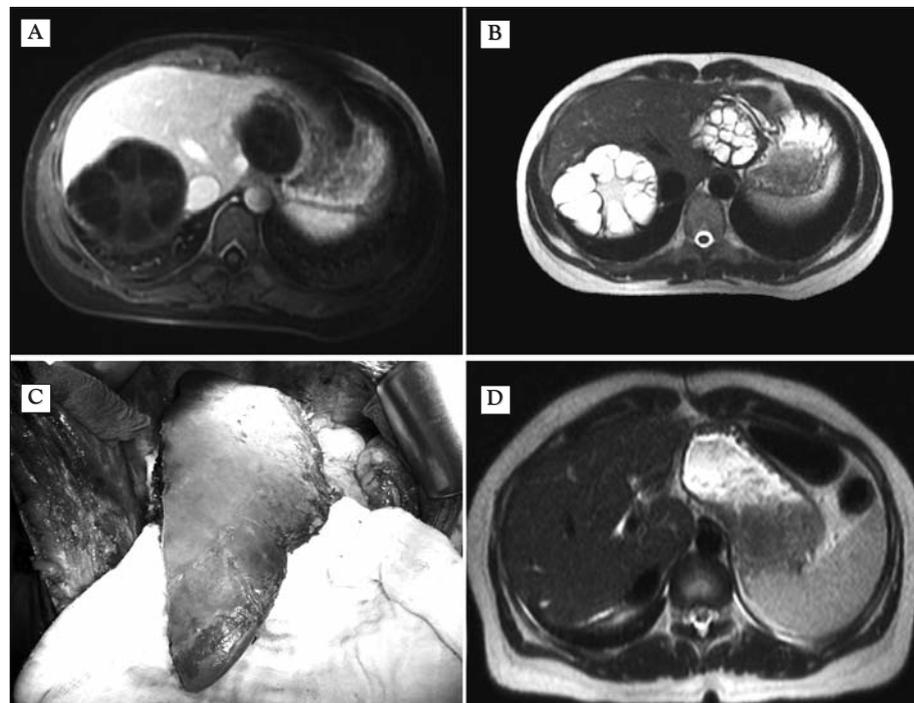


Figure 1. The first patient:
A,B : Preoperative MRI images;
C: The final liver remnant
D: Follow up MRI examination
6 months later

subsequent hypertrophy allowed for a safe right posterior sectionectomy two months later with remnant liver of approximately 692 cm³. The recovery of the patient was uneventful. No recurrence has been detected on the first control examination 6 months later (*Fig. 1D*).

Case 2

A 50-year-old patient with pain in right upper abdominal quadrant underwent a computer tomography (CT) and MRI. A Gharbi III/CE2 hydatid cyst 9 cm was detected in the right posterior section of the liver. The mass was situated in liver segments 6 and 7. After the initiation of albendazole, elevation of the liver enzymes developed (AST 720 U/L, ALT 642 U/L; T.Bil: 0.93 mg/dL, D.Bil: 0.19 mg/dL and INR: 1.14). Because of this hepatotoxicity the treatment was discontinued. Consistent recovery of the transaminase levels took 13 days. A pericystectomy was performed. The patient was discharged on the 6th postoperative day without complications. No recurrences have been detected during 56 months of follow-up.

Case 3

A 47-year-old male patient was diagnosed with hydatid cyst in liver segments 4, 5, and 8 and was referred to our institution. After initiation of albendazole treatment the AST and ALT levels rapidly increased to 199 and 482 U/L, respectively. The treatment was discontinued and the enzyme levels normalized in several days. We performed an MRI which demonstrated a centrally located hydatid lesion (6 cm, CE2) with an edematous periphery region due to compression of the surrounding tissues. A connection to the biliary tree was not detected on MRCP. A closed pericystectomy was attempted and almost realized. However, at the end stage of the operation a 1-cm fistula was identified between the cyst and the biliary tree. The connection was dissected with subsequent pericystectomy and removal of small vesicles from the anterior section bile duct was

performed. Common bile duct exploration did not yield any additional cysts and a T-tube was placed. Intraoperative cholangiography did not detect any additional hydatid material in the biliary tree. The opening of the fistula was sutured. The postoperative period was uneventful and the patient was discharged on the 6th day. No medical treatment could be given. The control examination on the first postoperative month did not show any complications and the patient was re-scheduled for next examination after 5 months.

Case 4

A 35-year-old patient who had been receiving both prednisolone and azathiopurine for autoimmune hepatitis was referred for a hydatid cyst in left lobe of the liver, (9 cm, CE2). She had no biochemical or radiologic evidence of cirrhosis. In order to avoid albendazole that may complicate the interpretation of liver function tests or trigger a hepatotoxic reaction and additionally aggravate the leucopenia radical surgery was chosen. A pericystectomy was performed to eliminate the cavity prone to recurrence in an immunosuppressed patient. The postoperative period was uneventful. No recurrence has been detected during 17 months of follow-up.

Discussion

Benzimidazoles, have long been the only agents available for primary and adjuvant treatment for EG (1-3). Albendazole is usually the preferred agent because it is more active than mebendazole in vitro (7), easier to use and clinically more effective (8-9).

Although the list of possible side effects is long - headache, nausea, gastrointestinal disturbances, neurological symptoms (vertigo/dizziness), neutropenia, hair loss, thrombocytopenia, allergic shock (due to cyst collapse and release of *E. granulosus* cyst fluid), hepatotoxicity and myelotoxicity treatment is generally well tolerated. The need of permanent discontinuation of the treatment had been reported in 0% to 3.8% of the cases (1-4,8-

10). A common complication after prolonged albendazole admission is mild elevation of hepatic enzymes reported in approximately 16% of patients (1,4,8-10). Although they generally return to normal after discontinuation of treatment, re-administration of albendazole causes recurrent increases in the liver enzymes (11). There have been case reports of severe hepatitis and even acute liver failure (12-17).

There are no absolute criteria for the diagnosis of albendazole induced hepatotoxicity. The most commonly used is the Roussel-Uclaf Causality Assessment Method of the Council for International Organizations of Medical Sciences (RUCAM/CIOMS) scale (18-19). A rechallenge test with albendazole was not performed because of the potential risk of severe liver injury and delay of the surgical treatment leading to unnecessary progression in the disease. Nevertheless, the hepatotoxic reaction which appeared soon after albendazole administration without other possible causes is suggestive of the causative role for this drug. In our first three cases, the RUCAM/CIOMS score was >8, and therefore, they were defined as toxic hepatitis with "high probability". In the fourth case, the albendazole treatment was avoided, because it could complicate the interpretation of liver function tests, trigger a hepatotoxic reaction and aggravate the leukopenia.

Severe albendazole hepatotoxicity puts the clinician into a difficult situation because there is no real alternative except for the inadequately documented praziquantel therapy (1-3). Published reports on patients with severe albendazole hepatotoxicity offered no suggestions and did not report long-term follow up results in relation to disease recurrence.

Most patients with hepatic *E. granulosus* cysts are treated by general surgeons (not hepato-pancreato-biliary surgery specialists) leading to wider preference of drainage over resective procedures and the perioperative use of albendazole (2,3). Two small prospective randomized trials conducted by the same

group support the widespread use of perioperative albendazole treatment to prevent recurrences (20,21). On the other hand, recent experience has shown that in experienced hands, radical procedures are generally associated with lower complication rates (23-25). The generally accepted rule of thumb is that the conservative drainage procedures combined with albendazole therapy should be preferred in cases with cysts close to major vessels (vascular or biliary) in order to preserve healthy liver parenchyma and prevent catastrophic injuries (2-3,25). In the special situation when chemotherapy is contraindicated, the need for albendazole could be circumvented by resection of the cavity without opening the cyst (hepatectomy or closed pericystectomy). The rule of thumb stated above may have to be relaxed to realize this objective. The rare recurrences occur at another part of the liver or the body; they are probably due growth of an initially missed lesion, intrahepatic migration residual vesicles via bile (a risk factor in Case 3) and to reinfection (2-3,25). We do not advocate a pivotal change in the surgical strategy in general but state that in difficult situation of severe albendazole toxicity, hepatobiliary surgeons could offer a potentially curative solution with a resection procedure.

Conclusion

A resection procedure not only eliminates the cavity but also the need for adjuvant albendazole treatment in hepatic hydatid disease. This is a vital advantage for the small subset of patients with severe observed or predicted albendazole hepatotoxicity.

Author's Contributions

Yavor Asenov and Ilgin Özden: wrote the paper. Melih Akin and Cem Ibis: collected the data. Yaman Tekant: revised the manuscript for important intellectual content and technical details.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Statement and Consent

For this type of study formal consent is not required.

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