

Intact germinal layer of liver hydatid cysts removed after administration of albendazole

A. Manouras*, M. Genetzakis, E.E. Lagoudianakis, A. Papadima, C. Triantafillou, P.V. Kekis, K. Filis, V. Katergiannakis

Department of General Surgery, First Department of Propaedeutic Surgery, Hippocrateion Hospital, Athens Medical School, Q. Sophia 114, 11527, Athens, Greece, *corresponding author: tel.: +30 6977304422, fax.: +30 2107707574, e-mail: amanouras@hippocratio.gr

ABSTRACT

Background: Hydatid disease is a common health problem especially in Mediterranean and sheep-farming countries, caused by infection with the metacestode stage of the tapeworm *Echinococcus*. The liver is the most frequent primary site of *Echinococcus granulosus* infection in humans. Surgery remains the main treatment modality for cystic hepatic hydatid disease, with complete resection of the germinal layer being of major importance for recurrence. Perioperative administration of albendazole has been reported to improve surgical outcome but the results are controversial. We report here our observations on the usefulness of preoperative chemotherapy in surgical outcome in terms of morbidity and recurrence.

Methods: Five patients with complex liver hydatid cysts received 28 days of albendazole prior to partial cystectomy. Radiological examinations with computed tomography and ultrasound and surgical outcome were used to assess the efficacy of the regimen.

Results: Three patients underwent a complete removal of the germinal layer of the cyst and there were no cases of biliary fistula in these patients. There were no relapses in any of the patients at 12 months' follow-up.

Conclusions: Preoperative use of medical therapy consisting of albendazole facilitates complete resection of the germinal layer by detaching it from the laminar layer, thus reducing not only the recurrence rates but also the postoperative complications, especially biliary fistulas.

KEYWORDS

Liver hydatidosis, albendazole, biliary fistula

INTRODUCTION

Echinococcal cystic disease is caused by infection with the tapeworm *Echinococcus granulosus*. In the liver, the most frequent primary site, an active cyst wall consisting of an innermost single cell germinal layer (endocyst) and a thicker gelatinous laminar acellular layer (ectocyst) is formed. An outermost reactive fibrous layer of liver parenchyma, called the pericyst, surrounds the active cyst. The germinal layer produces the hydatid fluid and small secondary cysts known as brood capsules. Protoscolices are produced within the brood capsules over time. The detached brood capsules and protoscolices form the hydatid sand, with potential infectious features. Fragmentation of the germinal layer and brood capsules results to the daughter cysts.^{1,2}

Surgery is the mainstay of treatment for cystic hepatic disease. Surgical options include the radical operations of hepatectomy and pericystectomy and the more conservative ones such as partial cystectomy.

The ideal surgical procedure should effectively deal with the parasite and the residual cavity with the minimal morbidity and mortality.³ There is a continuing debate over the appropriate surgical procedure for the treatment of hepatic echinococcal disease, and the role of antiparasitic chemotherapy as an adjunct to surgery has not been clarified either.

We report on the surgical outcome of five patients with complex echinococcal cysts of the liver who received albendazole preoperatively, followed by computed tomography evaluation of the cyst status prior to surgery. Furthermore, based on our findings, we advocate that preoperative administration of antiparasitic chemotherapy facilitates the surgical treatment and possibly reduces postoperative complications, particularly biliary fistulas.

MATERIAL AND METHODS

From 2003 to 2005 five patients, three men and two women, presented with liver hydatid disease. All five cases had either complex or relapsing hydatid cysts. The diagnosis was based on radiological imaging and clinical history, while serological tests were also performed.

Informed consent was acquired from all patients. Afterwards, albendazole was administered for a specific period of 28 days, at a dose of 10 mg/kg/day, orally, in two doses a day. Evaluation of the medical treatment was performed by radiological investigation with abdominal CT scan prior to surgical intervention. Complete blood count analysis and liver function tests were assessed weekly.

The surgical procedure performed in all these patients was partial cystectomy. After isolation of the cyst with gauzes irrigated with 25% NaCl solution, the cyst was punctured with a trocar suction device. The cyst was then filled with 25% NaCl solution and reaspirated. The contents of the cyst were removed with forceps, suction or a spoon and afterwards the germinal layer was removed with forceps. The cyst cavity was again filled with the scolicedal solution. Finally the cyst cavity was inspected for bile leaks that are oversewn. We did not perform any obliteration of the cyst cavity and two drains were inserted before abdominal closure. A latex drain was positioned inside the cyst cavity and a Jackson-Pratt drain was placed in the proximity of the lesion.

The cyst contents were sent for pathological evaluation, which verified the diagnosis. However, no assessment of the germinal layer or scolices viability was performed.

Radiological examinations evaluated the status of the germinal membrane, with the detachment of the membrane as the sign of good response to medical therapy. Other objective evidence of cyst response to chemotherapy, such as solidification or calcification, disappearance of the cyst, egg shell-like calcification of cyst wall, improved volumetric reduction, splitting or floating signs were also recorded.

Finally, complications in the 30 days after surgery were recorded and follow-up examination was performed at 12 months postoperatively.

RESULTS

The mean age of our patients was 68 years, with a range from 47 to 78 years (*table 1*). Clinical findings included upper abdominal pain or palpable mass and hepatomegaly. Fever and loss of appetite were accompanying symptoms. The cysts averaged 8.3 cm in diameter, ranging from 7 to 12 cm (*table 1*). No patients discontinued treatment due to drug side effects such as abdominal pain, nausea, vomiting, and increased hepatic transaminases.

The cysts were located in the right lobe in two patients and in the left lobe in one patient. Both liver lobes were affected in two of the patients. Three cases had a single cyst while multiple cysts were documented in the others (*table 1*).

After completion of the medical treatment, computed tomography showed partial detachment of the germinal layer in three of our patients (*figure 1*). Other radiological evidence implying cyst response to chemotherapy was not observed. These findings are to be expected since calcifications are usually seen after three months of successful treatment and changes in size are evident with even more prolonged regimens.⁴

There was no radiological evidence of response to medical treatment in the other two patients.

During surgery complete removal of an intact germinal layer was performed in three patients (*figure 2*) while in the remaining two patients the germinal layer was partially removed by repeated traction with forceps and forceful evacuation with a spoon.

There were no biliary fistula recorded in the patients with the intact removal of the germinal layer, while in one patient with partial removal of the germinal layer a low output biliary fistula (>50 ml bile per day) was evident on the fourth postoperative day. Resolution of the bile leak was

Table 1. Summary of observations

No.	Age	Cyst size	Location segments	Number of cysts	Preoperative, postchemotherapy CT findings	Intraoperative observations	Complications	Recurrence 12 months
1.	47	7x5 4x3	IV, V, VIII	2	Partial detachment of the germinal layer	Complete removal of the germinal layer	Infection	No
2.	76	12x8	IV, V, VIII	1	Partial detachment of the germinal layer	Complete removal of the germinal layer	Atelectasis	No
3.	65	8.3x6 3.5x3 4.5x3	VII, VIII	3	No	Partial removal of the germinal layer	No	No
4.	78	7.8x5	III	1	Partial detachment of the germinal layer	Complete removal of the germinal layer	No	No
5.	68	8.6x4,2	V,VIII	1	No	Partial removal of the germinal layer	Biliary fistula	No

Figure 1. Abdominal computed tomography demonstrates partial detachment of the germinal layer of a liver hydatid cyst in a patient after 28 days of preoperative administration of albendazole

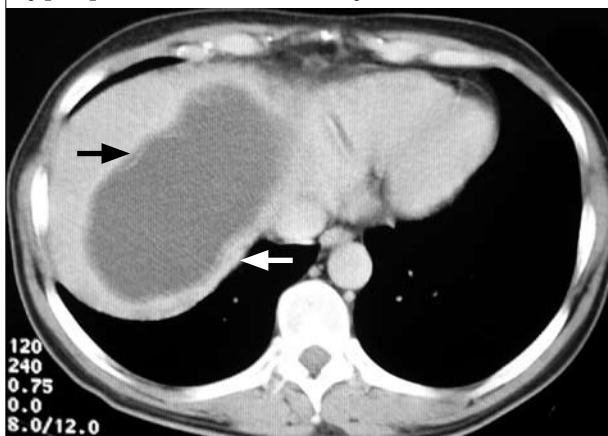


Figure 2. Intact removal of the germinal layer of the liver cyst in the same patient



accomplished after the insertion of a nasobiliary catheter on the 13th postoperative day.

Infection of the residual cyst complicated the progress of a patient with intact removal of the germinal layer which was successfully treated by removal of the drain and antibiotics. We attributed this complication to the presence of a long-standing foreign body (drain) inside the cyst cavity, since repeated ultrasound examinations failed to show any fluid collections and the infection resolved with removal of the drain.

There were no relapses at 12 months of follow-up.

DISCUSSION

Chemotherapy consists of the benzimidazoles, mebendazole and albendazole. Benzimidazoles inhibit the assembly of tubulin into microtubules, thus impairing

glucose absorption through the wall of the hydatid parasite. This causes glycogen depletion and degeneration of the endoplasmic reticulum and mitochondria of the germinal layer of the metacestode, and results in an increase in lysosomes and subsequent cellular death.^{5,6} However, recurrence rates after medical treatment alone can be as high as 80%, rendering this option nonviable as sole therapy.^{7,8} Thus, it should be used only as a supplementary therapy, in combination with a drainage procedure, either surgery or the PAIR procedure.

With regards to cystic liver disease, chemotherapy is indicated for patients unfit for surgery, when there is difficulty in reaching the lesion, if patients refuse to undergo surgery, advanced age, pregnancy, severe comorbidity, multiple cysts difficult to access, dead cysts either partially or totally calcified, very small cysts, and in some highly endemic regions where waiting lists are long and there is a lack of adequate medical facilities or experienced staff.^{9,10}

Medical therapy is also combined with surgery to preoperatively decrease the size of the cysts and reduce postoperative recurrences.^{11,12}

Albendazole is more effective than mebendazole, because its pharmacokinetic profile leads to higher serum and cyst fluid concentrations.¹³ It has been also used pre- and postoperatively to avoid relapses in case of both multiple and large cysts.^{4,14} The success of the treatment is based upon the capacity of the drug to operate on the germinal layer and the protoscolices of the hydatid cyst interior at adequate concentrations for sufficient periods. Albendazole sulphoxide penetrates the cyst membrane and reaches the hydatid fluid, being calculated at 13 to 22% of the serum concentration.¹³ Thus, parasite structures, protoscolices, and germinal layer are reached by albendazole's active form.^{15,16} However, efficacy seems to be correlated more with the duration of therapy than with the serum or cyst levels achieved.⁶

Although the majority of the reports state that preoperative administration of albendazole reduces the recurrence of the cystic echinococcal disease,^{11,12,17-19} in the report by Mentis *et al.* albendazole pretreatment failed to show any advantage.²⁰ Furthermore, reports addressing cyst and protoscolice viability provided conflicting data. Firstly, Moris *et al.* reported that 10 mg/kg/day for a month resulted in sterilisation of 93.75% of the cysts studied.²¹ Additional reports support these findings.^{11,12,22} When viability is assessed by radiological appearance, albendazole therapy leads to an improvement in the appearance of the cyst in approximately 75 to 85% of patients.²³⁻²⁷ On the other hand, Manterola *et al.* reported only a 40% success rate for the preoperative regimen in sterilising the cyst.^{28,29} He has also reported that there was no association between the concentration of albendazole in the hydatid fluid and the viability of the scolices.²⁹

The optimal duration of the drug is also controversial. Preoperative treatment with albendazole, ranging from one to three months in duration, has been clearly shown to reduce recurrence when cyst spillage, partial cyst removal or biliary rupture has occurred.^{11,17} Although in the majority of reports albendazole is administered for a month or longer,^{11,18,30} successful results have been documented with shorter periods in association with the PAIR procedure.^{31,32}

So, to achieve improved results, the combined preoperative chemotherapy of albendazole and praziquantel seems promising.³³ Cobo *et al.* used the combination regimen in 26 patients and compared the results with albendazole monotherapy.³⁴ They found that the combined treatment resulted in significantly higher sterilisation rates and higher albendazole sulphoxide levels in the serum and the cyst fluid than monotherapy. Moreover, the combination regiment did not show higher morbidity than monotherapy.

Albendazole has low toxicity and no apparent cumulative effect, thus is considered safe and effective. In systemic administration, the side effects are minimal, dose-dependent and reversible.^{4,18} Haematological toxicities and hepatic dysfunction are the most frequent and serious side effects. Gastrointestinal symptoms (nausea, abdominal pain), alopecia and rash may develop. None of the patients in our series discontinued treatment due to drug side effects, but in more prolonged regimens close monitoring of haematological parameters and hepatic function is essential.²⁹

Surgery is the mainstay of treatment, with unroofing (partial cystectomy) and external drainage of the cyst the most frequently performed technique. Apart from partial cystectomy, total pericystectomy and hepatic resections are commonly performed surgical procedures. The goals of surgery in hydatid disease are to inactivate the cestode parasites, evacuate the cyst cavity, remove the germinal layer, and obliterate the residual cavity.³⁵ An overall recurrence rate of 4.5% at a median of 4.5 years, regardless the surgical technique followed, has been reported.³⁶ Disadvantages of cyst drainage include spillage into the peritoneal cavity, causing a high rate of recurrence, bleeding and damage to bile ducts in close proximity to the cyst wall, as the cyst's contents are manually removed. These complications constitute potential risks, especially in case of complex hydatid liver cysts, such as those >10 cm in diameter, especially if associated with multiple daughter cysts, superficially located single cysts at high risk of rupture and complicated cysts such as those accompanied by infection, compression or obstruction. Completing resection of the whole germinal layer without any spillage is obviously of major importance to reduce the recurrence rate.

We advocate that preoperative use of albendazole facilitates complete resection of the germinal layer by detaching it

from the outer cover of the ectocyst. In three out of five patients, ultrasound and abdominal CT scan conducted after completion of the medical therapy, just before surgical intervention, clearly showed detachment of the germinal from the laminar layer. Moreover, we advocate that albendazole also acts by lessening tension and detaching the germinal layer for easier cyst removal.^{12,16} Thus, during unroofing and drainage of the cysts, complete resection of the germinal layer as a whole was achieved without any spillage or partial excision. Furthermore, complete and easy removal of the germinal layer helps to prevent rupture of the small biliary ducts in close proximity to the pericyst and thus postoperative biliary leakage. No external biliary fistulas were observed in these three cases where complete excision of the germinal layer was accomplished. Thus, we suggest that further studies should be conducted to ascertain whether preoperative administration of albendazole or combined with praziquantel, reduces morbidity, especially the postoperative rate of persistent postoperative biliary fistula and recurrences.

If established, this fact could be explained by the detachment of the germinal from the laminar layer of the cyst due to albendazole action that facilitates its excision without rupture of minor biliary ducts adjoining the pericyst.

REFERENCES

- Rogan MT, Hai WY, Richardson R, Zeyhle E, Craig PS. Hydatid cysts: does every picture tell a story? *Trends Parasitol* 2006;22:431-8.
- Filippou D, Tselepis D, Filippou G, Papadopoulos V. Advances in Liver Echinococcosis: Diagnosis and Treatment. *Clin Gastroenterol Hepatol* 2006 Dec 5; [Epub ahead of print].
- Smego RA Jr, Sebanego P. Treatment options for hepatic cystic echinococcosis. *Int J Infect Dis* 2005;9:69-76.
- Senyüz FO, Yesildagi E, Celayir S. Albendazole Therapy in the Treatment of Hydatid Liver Disease. *Surg Today* 2001;31:487-91.
- Schantz PM, Van den Bossche H, Eckert J. Chemotherapy for larval echinococcosis in animals and humans: report of a workshop. *Z Parasitenkd* 1982;67:5-26.
- Franchi C, Di Vico B, Teggi A. Long-term evaluation of patients with hydatidosis treated with benzimidazole carbamates. *Clin Infect Dis* 1999;29:304-9.
- Safioleas M, Misiakos E, Manti C, Katsikas D, Skalkeas G. Diagnostic evaluation and surgical management of hydatid disease of the liver. *World J Surg* 1994;18:859.
- Dziri C, Haouet K, Fingerhut A. Treatment of hydatid cyst of the liver: where is the evidence? *World J Surg* 2004;28:731-6.
- Pawlowski ZS, Eckert J, Vuitton D, et al. Echinococcosis in humans: clinical aspects, diagnosis and treatment. In: Eckert J, Gemmell MA, Meslin FX, Pawlowski Z (eds) WHO/OIE Manual on echinococcosis in humans and animals: a public health problem of global concern. World Organisation for Animal Health and World Health Organisation, 2001, Paris, France, pp 20-71.
- Saimot AG. Medical treatment of liver hydatidosis. *World J Surg* 2001;25:15-20.
- Turkcapar AG, Ersoz S, Gungor C, Aydinuraz K, Yerdel MA, Aras N. Surgical treatment of hepatic hydatidosis combined with perioperative treatment with albendazole. *Eur J Surg* 1997;163:923-8.

12. Aktan AO, Yalin R. Preoperative albendazole treatment for liver hydatid disease decreases the viability of the cyst. *Eur J Gastroenterol Hepatol* 1996;8:877-9.
13. El-On J. Benzimidazole treatment of cystic echinococcosis. *Acta Trop* 2003; 85:243-52.
14. Morris DL, Chinnery JB, Georgiou G. Penetration of albendazole sulphoxide into hydatid cysts. *Gut* 1987;28:75-80.
15. Garcõa-Llamazares JL, Alvarez de Felipe AI, Redondo Cardena PA, Prieto Fernandez JG. Echinococcus granulosus: membrane permeability of secondary hydatid cysts to albendazole sulfoxide. *Parasitol Res* 1998;84:417-20.
16. Erzurumlu K, Hokelek M, Gonlusen L, Tas K, Amanvermez R. The effect of albendazole on the prevention of secondary hydatidosis. *Hepatogastroenterology* 2000;47:247-50.
17. Tsimoyiannis EC, Siakas P, Moutesidou KJ, Karayianni M, Kontoyiannis DS, Gossios KJ. Perioperative benzimidazole therapy in human hydatid liver disease. *Int Surg* 1995;80:131-3.
18. Polat C, Dervisoglu A, Hokelek M, et al. Dual treatment of albendazole in hepatic hydatidosis: New therapeutic modality in 52 cases. *J Gastroenterol Hepatol* 2005;20:421-5.
19. Pelaez V, Kugler C, Correa D, et al. PAIR as percutaneous treatment of hydatid liver cysts. *Acta Trop* 2000;75:197-202.
20. Mentis A, Yalaz S, Killi R, Altuntas N, Poubagher A, Yazar S. The effect of albendazole in the treatment of liver hydatidosis. *Turk J Surg* 1997;13(Addendum): 9. (in Turkish)
21. Morris DL. Pre-operative albendazole therapy for hydatid cyst. *Br J Surg* 1987;74:805-6.
22. Smego DR, Smego RA Jr. Hydatid cyst: preoperative sterilization with mebendazole. *South Med J* 1986;79:900-1.
23. Todorov T, Vutova K, Mechkov G, Petkov D, Nedelkov G, Tonchev Z. Evaluation of response to chemotherapy of human cystic echinococcosis. *Br J Radiol* 1990;63:523-31.
24. Vutova K, Mechkov G, Vachkov P, Petkov R, Georgiev P, Handjiev S, Ivanov A, Todorov T. Effect of mebendazole on human cystic echinococcosis: the role of dosage and treatment duration. *Ann Trop Med Parasitol* 1999;93:357-65.
25. Todorov T, Vutova K, Petkov D, Mechkov G, Kolev K. Albendazole treatment of human cystic echinococcosis. *Trans R Soc Trop Med Hyg* 1988;82:453-9.
26. Horton RJ. Albendazole in treatment of human cystic echinococcosis: 12 years of experience. *Acta Trop* 1997;64:79-93.
27. Luchi S, Vincenti A, Messina F, Parenti M, Scasso A, Campatelli A. Albendazole treatment of human hydatid tissue. *Scand J Infect Dis* 1997;29:165-7.
28. Manterola C, Oberg C, Soto O, et al. Scolex viability of human liver hydatid cysts. *Rev Chil Cir (Chile)* 2000;52:471-6.
29. Manterola C, Mansilla JA, Fonseca F. Preoperative albendazole and scolices viability in patients with hepatic echinococcosis. *World J Surg* 2005;9:750-3.
30. Morris DL, Chinnery JB, Hardcastle JD. Can albendazole reduce the risk of implantation of spilled protoscoleces? An animal study. *Trans R Soc Trop Med Hyg* 1986;80:481-4.
31. Aygun E, Sahin M, Odev K, et al. The management of liver hydatid cysts by percutaneous drainage. *Can J Surg* 2001;44:203-9.
32. Yorganci K, Sayek I. Surgical treatment of hydatid cysts of the liver in the era of percutaneous treatment. *Am J Surg* 2002;184:63-9.
33. Yasawy MI, al Karawi MA, Mohamed AR. Combination of praziquantel and albendazole in the treatment of hydatid disease. *Trop Med Parasitol* 1993;44:192-4.
34. Cobo F, Yarnoz C, Sesma B, et al. Albendazole plus praziquantel versus albendazole alone as a pre-operative treatment in intra-abdominal hydatisosis caused by Echinococcus granulosus. *Trop Med Int Health* 1998;3:462-6.
35. Buttenschoen K, Carli Buttenschoen D. Echinococcus granulosus infection: the challenge of surgical treatment. *Langenbecks Arch Surg* 2003 ;388:218-30.
36. Gil-Grande LA, Rodriguez-Cabeiro F, Prieto JG, et al. Randomised controlled trial of efficacy of albendazole in intra-abdominal hydatid disease. *Lancet* 1993;342:1269.