CASE REPORT

Dramatic response to albendazole in transplantation candidates with unresectable hepatic alveolar hydatid disease

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Abstract
Long-term albendazole treatment should be given to all patients with unresectable hepatic alveolar echinococcosis as dramatic regression is possible in 15%–20%. It may be prudent to prepare a living donor for possible salvage transplant in case of a severe complication. Preemptive transplantation in mildly symptomatic patients should be discouraged.

KEYWORDS
Albendazole, alveolar hydatid, dramatic regression, *Echinococcus multilocularis*, liver transplantation

1 | INTRODUCTION

Hepatic alveolar echinococcosis (AE) lesions caused by Echinococcus multilocularis, behave like malignant tumors: they invade the surrounding liver parenchyma, metastasize to the regional lymph nodes and also disseminate to the lungs, and the brain via the hematogenous route.[1] The prognosis of untreated AE is very poor: 15-year survival is practically 0%.[2] Radical surgery followed by two years of chemotherapy with benzimidazole derivatives is the only curative option but approximately 25%–70% of the patients are suitable for this treatment.[1,3-10] Mass screening in endemic regions increases the probability of resection.[11]

The remaining patients receive life-long benzimidazole treatment because interruption may result in exacerbation, except in highly selected cases.[3,12-15] Albendazole is used more often than mebendazole as it is effective at lower doses and has better intestinal absorption.[3] Benzimidazole treatment is believed to be parasitostatic rather than parasiticidal in the high majority of the cases.[3,16] In a review of 19 studies including 5 or more patients, success rate varied between 55% and 100%; "treatment was classed as successful if the disease had not progressed for >1 year and if there were no side-effects necessitating a change of treatment."[17] Death due to progressive disease occurs in approximately 20–25% of the cases in 10 years.[3,18] In other words, a patient who receives albendazole as a primary treatment is, in principle, considered to be a candidate for life-long palliation or transplantation (in highly selected cases with liver-only disease).[10,19-23]

In this case series, we present 4 patients who were possible candidates for liver transplant due to giant (>15 cm) unresectable AE lesions and in whom dramatic regression under albendazole treatment was observed.

2 | CASE SERIES

Forty-two patients with AE were treated between 2002 and 2016. Partial hepatectomy was performed in 12 patients; long-term albendazole was started in the remaining 30. Eventually, liver transplantation was required in two patients (for recurrent cholangitis and albendazole hepatotoxicity precluding treatment in one patient each).

Of the remaining 28 patients, two died early due to septic complications and six were lost to follow-up. Two patients had slow progression. Thirteen patients have had stable disease. One patient had mild regression. The data of the four patients with dramatic regression were presented in this report. Lesion volume was estimated by multiplying the three largest perpendicular dimensions of the lesion and $\pi/6$ and % decrease of the lesion was calculated for all cases.

2.1 | Case 1

A previously healthy 45-year-old woman attended the outpatient clinic for abdominal pain and discomfort. The results of the liver biochemistry tests were as follows: AST: 23 U/L ALT: 19 U/L, GGT: 85 U/L (<85), ALP: 171 U/L (35–105), total bilirubin: 0.4 mg/dL, INR: 0.93. Abdominal magnetic resonance imaging (MRI) revealed a heterogeneous, 19-cm liver mass filling the left lobe and extending to the right lobe (Figure 1A). The left hepatic and the middle hepatic veins and the left branch of the portal vein were thrombosed. Also, the right anterior portal vein branch was compressed by the mass. Ultrasonography-guided core-needle biopsy confirmed the radiologic diagnosis of AE. The MELD score of the patient was 6, that is, she was not eligible for the cadaveric waiting list. Because there was a high risk of portal vein thrombosis, a living donor was prepared. Simultaneously, albendazole at 10 mg /kg/day (3 weeks of treatment with 1-week intervals) was started. At 4 months, the lesion size and appearance were unchanged. At 8 months, liquefaction of some of the previously solid areas was detected (Figure 1B); albendazole dose was increased to 15mg/kg/day. Subsequent films showed progressive liquefaction of the lesion; for example, the MRI image at 21 months (Figure 1C). Lesion size had decreased to 5.3 cm at 38 months (Figure 1D). Although the results of the biochemical tests were within normal limits (AST: 16 U/L, ALT: 11 U/L, ALP: 46 U/L, GGT: 16 U/L, total bilirubin: 0.4 mg/dL), the magnetic resonance cholangiopancreatography (MRCP) showed a persistent complex hilar stricture not suitable for surgical reconstruction. She is receiving albendazole treatment and will be re-evaluated for liver transplantation if the mass regrows or she experiences cholangitis attacks.
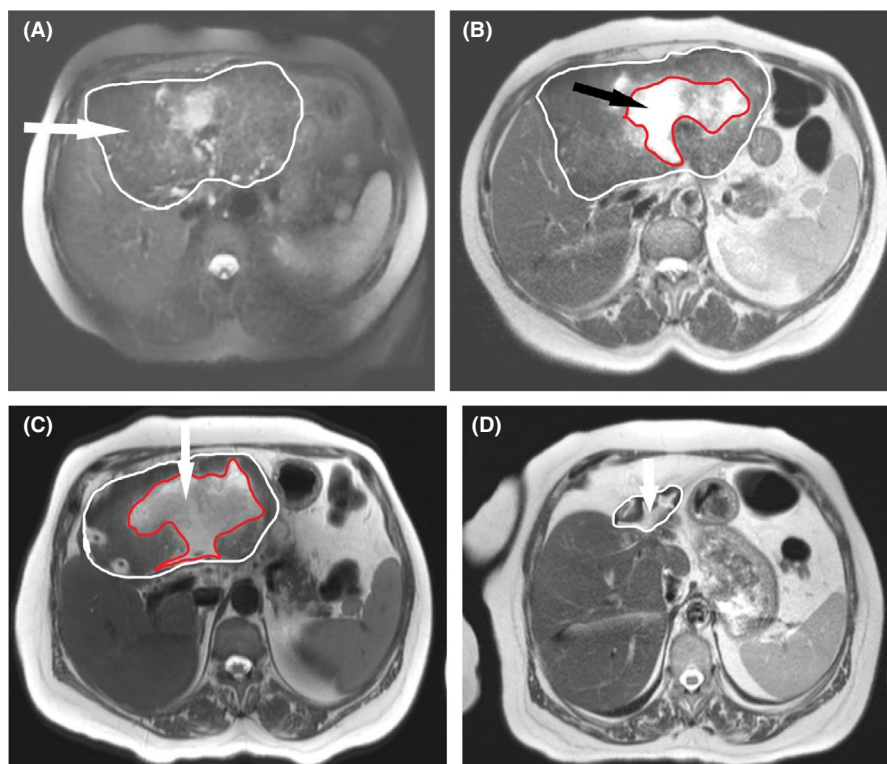

FIGURE 1 A: The 19-cm AE mass filling the left lobe and extending to the right lobe. Estimated lesion volume was 1704 cm^3. B, Eight months after proper albendazole treatment, liquefaction of some of the previously solid areas were detected. C, Progressive liquefaction of the lesion was shown on the MRI image at 21 months. D, The lesion size was dramatically decreased at the 38 months. The final lesion volume was 8 cm^3 (99% decrease)

2.2 | Case 2

A 52-year-old woman was examined for a 17-cm liver mass in segments 4–5–6 (Figure 2A). Ultrasonography-guided core-needle biopsy confirmed the radiologic diagnosis of AE. Right portal vein branch embolization was performed as a preparation for extended right hepatectomy. However, adequate hypertrophy of the future remnant liver could not be achieved. The patient was considered for liver transplantation but was excluded because of her severe bipolar disorder. After a few months of albendazole treatment, the patient was lost to follow-up. She returned 4 years later. She had continued albendazole regularly except for the last 5 months. The computed tomography (CT) scan showed dramatic regression of the mass to 8 cm as well as liquefaction of its content (Figure 2B). In the fifth year of treatment, she developed febrile neutropenia (neutrophil count: 66 /mm^3). An expert hematologist identified albendazole as the sole likely cause. Albendazole was stopped and neutropenia responded to the granulocyte colony-stimulating factor. The mass has been stable for 6 years without treatment (Figure 2C).

2.3 | Case 3

A 55-year-old woman was referred for possible liver transplantation for unresectable AE refractory to albendazole. The lesion (longest dimension: 28 cm) had remained stable for 6 years of treatment. A very encouraging aspect was that the content had been extensively liquefied (Figure 3A). Her relevant laboratory test results were as follows: AST: 36 U/L, ALT: 37 U/L, ALP: 302 U/L (35–105), GGT: 110 U/L (< 85), total bilirubin: 0.8 mg/dL, INR: 1.2. The results of the whole blood count were within normal limits. A percutaneous catheter was placed from the left side. Initially, 2500 mL of bile-colored fluid was drained; the volume decreased to 30 mL on day 6. The patient was discharged on the 7th day with albendazole treatment. Follow-up CT after 15 months later showed dramatic regression of the lesion (Figure 3B). All intrahepatic branches of portal vein except that of the right anterior were thrombosed; grade 1–2 esophageal varices were observed on esophagogastroduodenoscopy. Her MELD score was 8. Although the presence of the catheter had a negative effect on her quality of life, the result of our risk-benefit analysis did not favor living-donor liver transplantation. The catheter was eventually removed but had to be reinserted only to be removed again. She has been under albendazole treatment for a total of 14 years and catheter free for the last 6 months. The final lesion size is 5 cm (Figure 3C).

2.4 | Case 4

A 31-year-old man with hepatic AE diagnosed two years ago had been referred to our department for liver transplant.

He admitted that he did not use albendazole regularly. CT demonstrated a 16-cm mass filling the entire right lobe of the liver and containing a central necrotic area in the center. The trajectories of the right and middle hepatic veins were completely occupied by the mass which abutted the left hepatic vein in the parenchyma. Additionally, there was another mass measuring 6 cm at the tip of the left lobe; the hypertrophy of left lobe was not evident. (Figure 4A). Therefore, the case was considered inoperable. No metastases were detected in the brain or the lungs. The patient was considered for liver transplantation because of the risk of Budd-Chiari syndrome that could be developed after thrombosis of the only remaining hepatic vein. On one hand, his wife was prepared for possible liver donation. On the other hand, proper albendazole treatment was instituted. After 3 months, the patient was hospitalized for abscess in the right AE cavity. A percutaneous catheter was placed and about 1500 ml of pus was drained. After resolution of acute infection, the patient was discharged with the catheter; albendazole at 10mg/kg/day was continued. Follow-up CT taken one month later (Figure 4B) demonstrated that almost all the liquid component of the cyst had disappeared and the lesion was dramatically smaller. The catheter could be removed three months later. He took albendazole regularly for 5 months after drainage but then discontinued the therapy. Abdominal CT obtained 10 months after drainage revealed that the mass had regressed to 6 cm. Albendazole was started again but he did not take the drug and attend the outpatient clinic regularly. The remnant mass remained practically stable for 6 years (Figure 4C); the patient was urged to take his condition seriously. Partial compliance could be achieved.

3 | DISCUSSION

Liver transplantation—the most extensive liver resection—has been proposed as an alternative approach for unresectable hepatic alveolar hydatid disease.[24] To date, approximately 100 liver transplantations have been reported by various authors.[10,19-23] The published indications for these mostly cadaveric liver transplantations were end-stage liver failure, bilobar disease with hilar involvement, recurrent cholangitis, and chronic Budd-Chiari syndrome.[19] The perioperative mortality was higher than experienced in patients with other causes of end-stage liver disease; however, 5-year survival rates (70–85%) were encouraging.[19,23] Bresson-Hadni et al suggested that "*The early deaths could certainly be avoided in the future by selecting patients before the terminal stage of the disease.*"[19] This proposal is logical but difficult to implement in the Na-MELD era because most patients with AE are not cirrhotic; in other words, they would not be eligible for a cadaveric liver in the absence of severe complications.
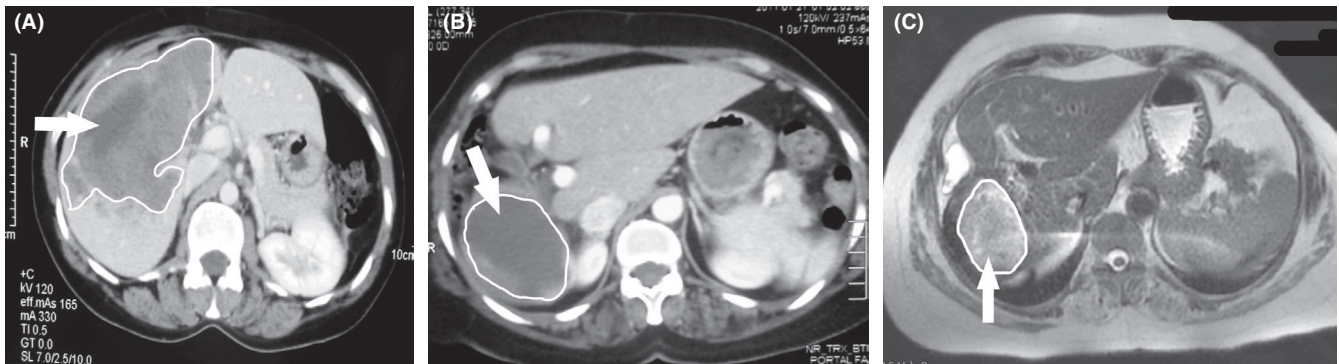
FIGURE 2 A, A 17-cm AE mass extending from the right lobe and segment 4 of liver. Estimated lesion volume was 1127 cm^3. B, Liquefaction and dramatic regression were detected after 4 years of albendazole treatment. The final lesion volume was 240 cm^3 (79% decrease). C, The mass has been stable for six years after cessation of albendazole treatment
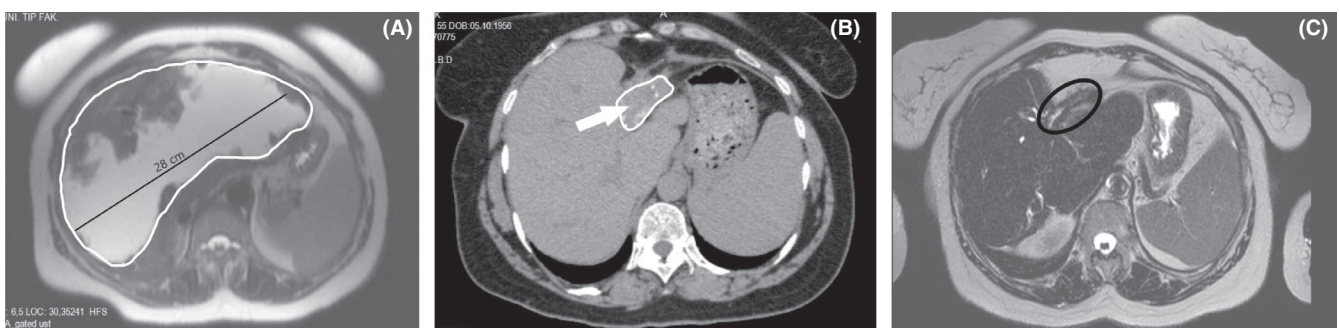

FIGURE 3 A, Initial MRI image of the lesion measuring 28 cm. Estimated lesion volume was 2749 cm^3. B, After percutaneous drainage, the lesion volume was reduced dramatically. C, The patient was has been catheter free for six months and final lesion size was 5 cm. The final lesion volume was 18 cm^3 (99% decrease)
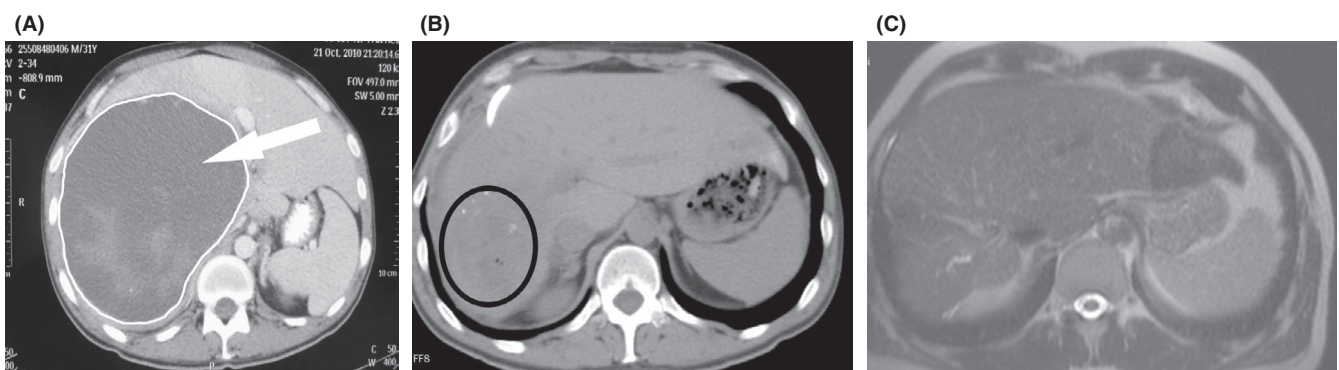

FIGURE 4 A, A 31-year-old man with bilobar (right lobe 16 cm, left lobe 6 cm) hepatic AE. Estimated lesion volume was 1845 cm^3. B, A percutaneous catheter was replaced into the liquefied-infected right lobe lesion. C, The shrunken mass has been practically stable for 6 years despite partial patient compliance. The final lesion volume was 42 cm^3 (98% decrease)

On the other hand, living-donor liver transplantation may provide flexibility because the decision to transplant can be made at an earlier stage. The points to consider are as follows:

1. There is a risk of recurrence and distant organ metastasis due to immunosuppressive treatment especially in cases which the AE mass cannot be removed with wide negative margins.[25] This risk is a much more disturbing concern in "early" transplantations than in operations for end-stage liver disease.

2. There are morbidity and mortality risks for the living donor.[26]

3. There is a risk of premature or unnecessary transplantations. It has been stated that

"*In the other situations*, *represented by chronic parasitic Budd-Chiari syndrome and/or huge pseudo-tumoral AE, the decision to perform LT is far more difficult to make. In fact, such patients, even with very impressive radiological imagings, may be asymptomatic or pauci-symptomatic, due to the very slow progression of the parasitic larvae. .... The natural history of these "tumoral" and/or "vascular" AE was unknown. That explains the initial tendency for early indication for LT in such cases, due to the fear of acute Budd-Chiari syn- drome occurrence or extra-hepatic progression via the inferior vena cava....However, to our knowledge, acute parasitic Budd-Chiari syndrome has never been reported in AE.".*[19]

At the crux of the issue is the definition of treatment failure under proper albendazole administration. Although the desired goal of the treatment is the regression of the tumor, lack of disease progression is considered as a success because the enlarging mass may cause severe problems such as biliary obstruction, cholangitis, abscess, cirrhosis, and portal hypertension.[1,2] To complicate the issue further, it has been reported that "Despite successful long-term chemotherapy, late complications such as esophageal variceal bleeding or cholestatic complications-probably due to postchemotherapy fibrosis with involvement of hilar structures- may occur."[27] Although long-term benzimidazole treatment stabilizes the disease in 55–100% of the patients, disappearance of the lesions was reported in two patients only (a total of 3 small lesions measuring 2, 3, and 4 cm).[17,18,28,29] Marked regression has been noted in 3 patient series.[18,27,28] Amman et al reported regression in 48.6% of their patients (n: 18); of these 18 patients had lesions measuring 12 cm or larger; the degree of regression in this subgroup was 40–70%.[27] Ishizu et al reported volume reductions between 70 and 100% in 5 out 9 patients with measurable lesions.[28] Unfortunately, the largest dimensions and the actual volumes were not reported except for a single case.[28] Liu et al reported regression in 7 out of 20 patients; the stated dimensions are incompatible with regression in one patient; in the remaining 6 patients, the largest dimensions of the lesions measuring initially median (range) 10.5 cm (5–14) decreased by 10–40%.[18] A very important original finding in the present report is that marked regression of giant lesions (> 15 cm) is possible in 15–20% of the patients with unresectable AE (4/28 of all patients, 4/22, excluding 6 patients lost to follow-up).

The data summarized above show that proper albendazole treatment is indicated before a decision to transplant is made, except in patients with end-stage liver disease. However, only 60–70% of the patients in two reviews received pretransplant benzimidazole treatment.[19,23] In a single-center report by Özdemir et al, six of ten patients received albendazole, albeit irregularly, and adjuvant treatment was given only if a residual mass was left.[21] Similarly, Aydinli et al stated that all of their 27 patients were given albendazole since the time of

diagnosis but response of the mass (regression, stable, or progression) was not reported.[20] In the report on 20 patients by Patkowski et al, albendazole was given for only 6 weeks before transplantation.[22] All 4 patients presented in this report had giant AE masses. Three of them had been referred to our institution for liver transplantation. The patient with bipolar disorder was considered for transplant after failure of portal vein embolization to render extended right hepatectomy safe but finally excluded. The common finding of all 4 patients was that the lesions were liquefied. Azizi et al reported that Kodama type 5 lesions (large cyst without a solid component) showed negligible FDG uptake on PET/CT whereas most of the calcified lesions were metabolically active.[30,31] The radiological evolution in our cases is in accordance with these findings. AE may present as a large hepatic abscess,[32] presumably as a result of bacterial infection of the liquefied mass as was observed in Case 4. Percutaneous drainage is the recommended treatment.[33] A case reported by Köroğlu et al showed a very striking course: a 9-cm lesion AE lesion that was solid on ultrasonography(US) became partially liquefied on US and CT after two years of albendazole treatment; 4 months later, he presented with a hepatic abscess: the liquefied component had enlarged and became infected. Percutaneous drainage resulted in complete resolution of the lesion.[34] The right lobe lesion Case 4 in the present report showed a similar course; had the patient been more compliant with albendazole treatment, complete resolution might have been achieved.

An intriguing question is—which factors account for the discordant courses (regression-stable disease-progression) of the patients receiving the same treatment? The two likely candidates are plasma drug levels and sensitivity of the parasite to albendazole. Plasma drug levels exhibit a very wide variation and do not seem to explain the differences between patients.[27] More data are required to translate the favorable experience in a small subset of patients (marked regression) to all inoperable patients.

Hepatotoxicity and myelotoxicity are the most serious adverse effects of albendazole; discontinuation of treatment may be required in up to 4% of the cases.[3] Among the 30 patients who were candidates for long-term albendazole treatment in the present series, severe hepatotoxicity (one of the two patients who underwent liver transplantation), and aplastic anemia (Case 2) developed in one patient each.

In conclusion, long-term albendazole treatment should be given to all patients with unresectable hepatic AE. It may be prudent to prepare a living donor for possible salvage transplantation in case of a severe complication such as recurrent cholangitis, acute portal vein thrombosis, or albendazole hepatotoxicity. Liquefaction may be a sign of response to albendazole. Percutaneous drainage of the liquefied mass may be beneficial for reducing the risk of bacterial infection and relieving symptoms due to large masses. Dramatic regression

with proper albendazole treatment is possible in 15–20% of the patients with unresectable hepatic AE masses. Preemptive liver transplantation in asymptomatic/mildly symptomatic patients should be discouraged.

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