Hepatic alveolar echinococcosis: clinical report from an endemic region

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Objective: To review the clinical management of alveolar echinococcosis. **Design:** A retrospective analysis. **Setting:** A university-affiliated hospital in Turkey. **Patients:** Forty patients treated for alveolar echinococcosis between 1987 and 2000. **Interventions:** Curative resection followed by chemotherapy, or medical palliation with chemotherapy only. Palliative procedures such as bilioenteric or external drainage were done for cholestatic jaundice and liver abscess. **Outcome measures:** Results of medical and surgical treatment. **Results:** Seventeen patients had a resectable tumour and all underwent curative resection. Of the other 23 patients with nonresectable tumour, 11 underwent palliative surgical procedures such as bilioenteric or external drainage for cholestatic jaundice or liver abscess. All patients received long-term albendazole therapy. Four patients with nonresectable tumour died because of chronic liver failure. In a 6.5-year follow-up, there was no recurrence in patients who underwent curative resection. The efficacy of chemotherapy is limited in nonresectable disease. **Conclusions:** To increase the rate of early detection and curative resection, screening programs are essential. Research on new chemotherapeutic approaches should be made to improve survival in patients with nonresectable disease.

Objectif : Examiner le traitement clinique de l'échinococcose alvéolaire. **Conception :** Analyse rétrospective. **Contexte :** Hôpital affilié à une université en Turquie. **Patients :** Quarante patients qui ont reçu un traitement contre l'échinococcose alvéolaire entre 1987 et 2000. **Interventions :** Résection curative suivie d'une chimiothérapie ou traitement médical palliatif associé seulement à une chimiothérapie. Les interventions palliatives, comme le drainage bilioentérique ou externe, ont été pratiquées chez les patients atteints d'ictère hépatocanaliculaire ou d'hépatite suppurée. **Mesures de résultats :** Résultats des traitements médical et chirurgical. **Résultats :** Dix-sept patients présentaient une tumeur résécable. Ils ont tous subi une résection curative. Au nombre des 23 autres patients dont la tumeur n'était pas résécable, 11 ont subi des interventions chirurgicales palliatives, comme un drainage bilioentérique ou externe contre l'ictère hépatocanaliculaire ou l'hépatite suppurée. Tous les patients ont reçu un traitement de longue durée faisant appel à l'albendazole. Quatre patients atteints d'une tumeur non résécable sont décédés des suites d'une insuffisance hépatique chronique. Au cours du suivi de 6,5 ans, il n'y a pas eu de récidive parmi les patients qui avaient subi la résection curative. L'efficacité de la chimiothérapie est limitée dans les cas où la tumeur n'est pas résécable. **Conclusions :** Les programmes de dépistage sont essentiels pour l'amélioration des taux de dépistage rapide et de résection curative. Il faudrait effectuer des recherches sur les nouvelles méthodes chimiothérapeutiques afin d'améliorer la survie chez les patients dont la tumeur n'est pas résécable.

Alveolar echinococcosis (AE) is a serious disease caused by the larvae of *Echinococcus multilocularis* (EM) and is characterized by tumour-like infiltrative growth.[1–3] Before 1895, when Virchow recognized the tumour-like lesions, the disease was called "colloid carcinoma of the liver."[1] In the human host the parasite primarily invades the liver. Biologically AE has the characteristics of malignant disease: destructive tissue growth, invasion of adjacent organs and metastasis to distant organs.[1,2,4,5]

The geographic distribution of AE differs from that of cystic echinococcosis, being mostly restricted to the northern hemisphere.[1,2] The disease is endemic in Central, Western and Eastern Europe, Asia and the northern regions of North America.[1,2,6] In some restricted areas, such as Hokkaido, Japan, St. Lawrence Island, Alaska, and the Franche-Comté region, France, higher rates have been reported.[6–8] In Turkey, the east of

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Anatolia is an endemic region for both cystic echinococcosis and AE.[9,10]

The diagnosis of AE is based on clinical findings, lesion morphology as determined by imaging techniques, and immunodiagnostic and other laboratory tests. The most frequent clinical symptoms are epigastric pain and cholestatic jaundice. Incidental detection of the disease during medical examination for symptoms such as fatigue, hepatomegaly or an abnormal finding on routine liver testing is common. Imaging reveals a heterogeneous hypodense mass, often associated with necrotic cavities and irregular contours. Routine laboratory tests are not specific, but immunodiagnostic tests have high sensitivity and specificity.

The therapeutic strategy of AE for resectable disease is radical resection of involved liver segments and other affected organs, and complementary chemotherapy with benzimidazole derivatives (albendazole, mebendazole).[1,2,5,8] In nonresectable disease, long-term chemotherapy is recommended (at least 10 yr). Liver transplantation is advised only for patients with chronic liver failure.[8]

We report our experience with AE and the results in patients who underwent curative surgical resection and who had received long-term chemotherapy.

Patients and methods

The charts of 40 patients (mean age 47.3 yr [range from 17–66 yr]) who were treated for AE between February 1987 and December 2000 were analyzed with respect to results of medical and surgical treatments. The male-to-female ratio was 1.2:1. Curative surgical resection was performed in 17 patients (42%). In the other 23 patients the disease was nonresectable. The Nakajima system was used for staging.[11] Fine-needle aspiration or true-cut biopsy was used for histopathological diagnosis. Hematologic examination, liver function tests, serologic tests (enzyme-linked immunosorbent assay [ELISA], *E. multilocularis*2 [Em2] antigen), ultrasonography, computed tomography and magnetic resonance imaging were used in the diagnosis and follow-up. Albendazole was used as the chemotherapeutic agent. The chemotherapy protocol comprised albendazole adminstered orally in a daily dose of 10 mg / kg in a treatment cycle of 30 days with 10-day drug-free intervals. After curative resection, the period of chemotherapy averaged 2 years. For nonresectable disease, this period averaged 6.5 years (range from 8 mo–14 yr). There were no major adverse reactions to discontinuing the chemotherapy. To evaluate the response to chemotherapy, we used modified WHO criteria[11,12] as follows:

- Success: significant decrease in volume of the lesion (i.e., > 50% reduction, disappearance, distinct changes in morphology such as > 25% increase in calcification of the lesion).
- Some improvement: insignificant changes in morphology of the lesion (stationary) or some amelioration in clinical symptoms and signs.
- No success: progression of the disease.

For measuring and evaluating the volume of the lesion, the method proposed by Ishizu and associates[13] was used. Estimated actual volume was calculated by the equation $4\pi ab^2 / 3$ (where a = largest diameter, and b = shortest diameter of the lesion on CT).

Results

Initial clinical symptoms in our patients were mainly cholestatic jaundice in 18 (45%), epigastric pain in 14 (35%) and dyspepsia in 16 (40%) patients. The disease in 15 (38%) patients was found incidentally during a "check-up."

The diagnostic procedures are shown in Table 1. Pathologic changes in the lesion related to the vascular system were best visualized by MRI. With respect to staging (Table 2), the majority of patients were type IV, followed by type IIIa; 7 patients had distant metastases, 3 had affected regional lymph nodes, and metastasis was found in 4 patients (pulmonary in 2, left adrenal gland in 1 and brain in 1).

The operative procedures in patients who underwent curative resection are listed in Table 3. We performed 2 right extended hepatectomies because of invasion into the middle hepatic vein (Fig. 1). Major complications, such as liver failure, biliary leakage and major bleeding did not develop. There were no operative deaths. The average follow-up period after curative resection was 3.5 years. At the time of writing there had been no recurrences. We

Table 1

Diagnostic Procedures for Alveolar Echinococcosis

Test	Patients, no	Diagnostic	Sensitivity, %
ELISA	34	30	88
Ultrasonography	40	37	92
Computed tomography	35	34	97
Magnetic resonance imaging	20	18	90
Biopsy	31	31	100

ELISA = enzyme-linked immunosorbent assay.

Table 2

Distribution of the 40 Patients According to the Nakajima Staging System[11]

Type	Patients, no. (and %)
I	3 (8)
II	4 (10)
IIIa	8 (20)
IIIb	2 (5)
IV	23 (58)

did not perform palliative resection in nonresectable cases. However, because of cholestatic jaundice and liver abscess (Fig. 2) we performed palliative procedures in 11 patients who had nonresectable AE (biliary diversion in 6 [segment III cholangiojejunostomy 3, modified Longmire procedure 3] and external drainage in 5). The other 12 patients with nonresectable disease were treated with chemotherapy only. All patients with nonresectable disease received long-term chemotherapy with variable success (Table 4).

Table 3

Operative Procedures in 17 Patients With Resectable Alveolar Echinococcosis

Operation	Patients, no. (and %)
Right hepatectomy	4 (24)
Left hepatectomy	4 (24)
Left lateral segmentectomy	3 (18)
Nonanatomical resection	4 (24)
Right extended hepatectomy	2 (12)

Four patients who had nonresectable lesions died in the follow-up period. In all, the causes of death were liver failure and its complications. The other patients are alive. Three patients were listed for liver transplantation because of advanced AE with chronic liver failure (Fig. 3).

Discussion

AE is a serious disease that carries a high mortality if it is untreated.[1,2,4,5] The metacestodes of EM have a slow growth rate in the liver, giving rise to a chronic progressive clinical course. Ninety percent of untreated patients die within 10 years of diagnosis.[1,3] Initially, metacestodes of EM develop exclusively in the liver,[2] and to date no primary extrahepatic localization has been reported. In an in-vitro study of AE, it has been demonstrated that soluble growth factors secreted by primary hepatocytes of the intermediate host direct the development of parasitic tissue,[14] which could explain why primary localization is exclusively in the liver.

In contrast to malignant neoplasms of the liver, patients with AE have no important clinical symptoms until major complications develop.

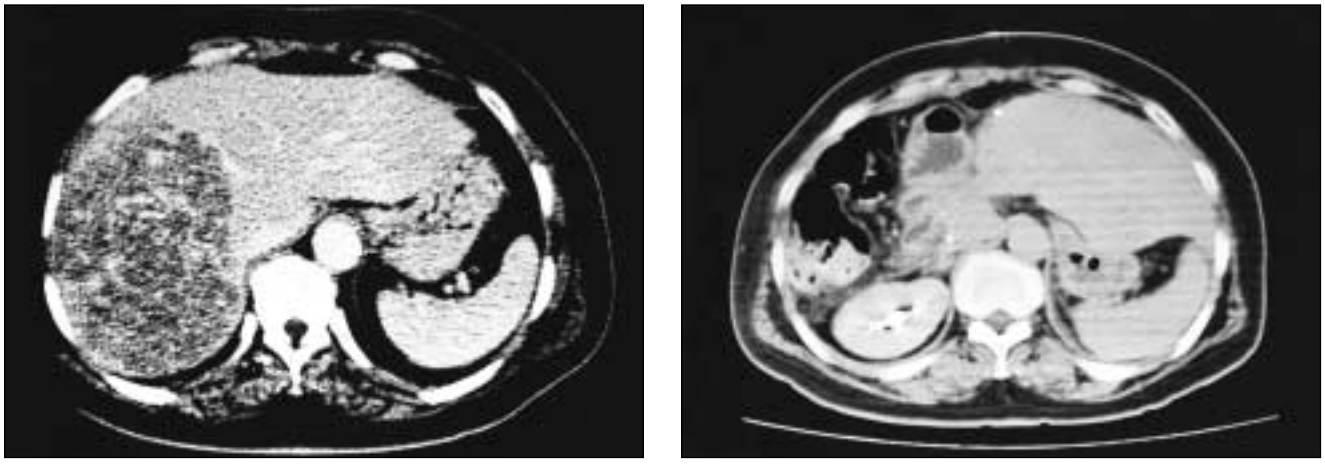

FIG. 1. Left: computed tomography scan in a patient with alveolar echinococcosis showing invasion of the middle hepatic vein. Right: CT scan of the same patient 1 month after right extended hepatectomy.

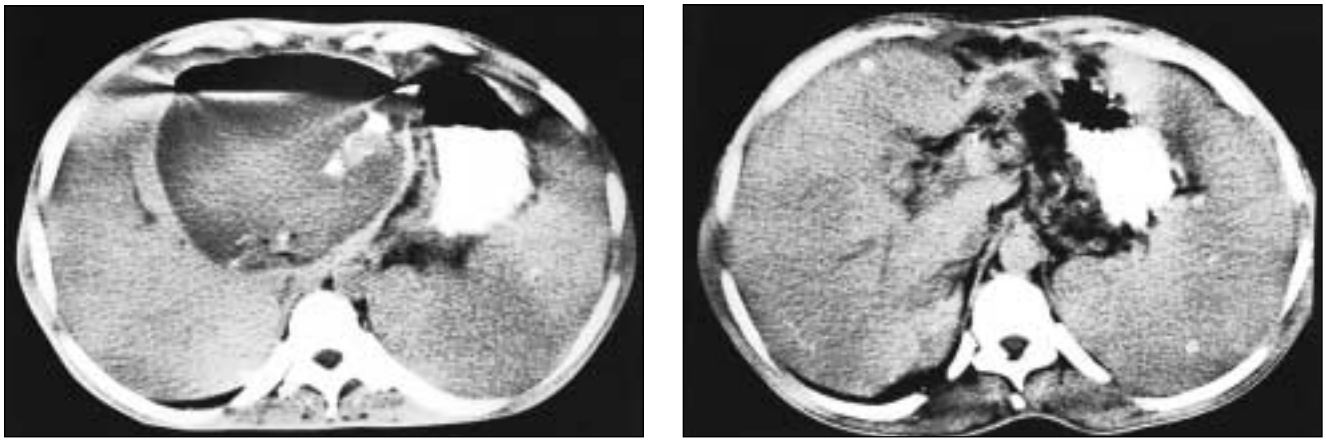

FIG. 2. Left: computed tomography scan of showing a large necrotic cavity in the liver due to alveolar echinococcosis. Right: appearance of the liver 6 months after drainage of the abscess.

In about one-third of patients, the disease is found incidentally during routine examination.[1,15,16] Therefore, the curative resectability rate is low (20%–40%) when the diagnosis is made. In some Japanese series, higher resectability rates (60%–100%) could be related to early detection of the disease in a screening program.[17] In our series the main clinical symptoms were cholestatic jaundice (45%) and dyspepsia (40%), epigastric pain (35%); in 15 patients (38%) there were no symptoms, and the diagnosis was made incidentally. The resectability rate was 42%.

The clinical diagnosis is based on the patient's history, epidemiologic data and clinical findings, immunodiagnostic tests, and the morphology of the lesion on imaging techniques such as ultrasonography, CT and MRI.[1,2,5,18] In contrast to advanced malignancy of the liver, the general condition of the patients with AE is good.[1,2,8] The immunodiagnostic tests have high specificity and sensitivity for AE.[7] Em2 plus ELISA is useful for both the initial diagnosis and determining complete versus incomplete surgical resection.[3,19] In some cases (5%), infected patients are not seropositive.[1] Recently, new diagnostic methods have been developed, such as detection of messenger RNA.[4] With the use of the imaging techniques, typical pictures are characterized by a heterogeneous and hypointense mass with indistinct, irregular margins, often associated with cavities. Calcifications within the liver lesions are a characteristic feature of AE.[1,2,19,20] The diagnosis must be confirmed by fine-needle aspiration or true-cut biopsy. It is believed that there is no associated risk of dissemination.[5,21] In our series we performed percutaneous biopsy in 31 patients and in follow-up there was no apparent dissemination to the abdominal wall.

Table 4

Results of Long-Term Chemotherapy (Mean 6.5 Years) in 23 Patients With Nonresectable Alveolar Echinococcosis*

Results	Patients, no. (and %)
Success	0 (0)
Some improvement	8 (35)
No success	9 (39)
Unknown†	6 (26)

*According to modified WHO criteria
†Could not be evaluated.

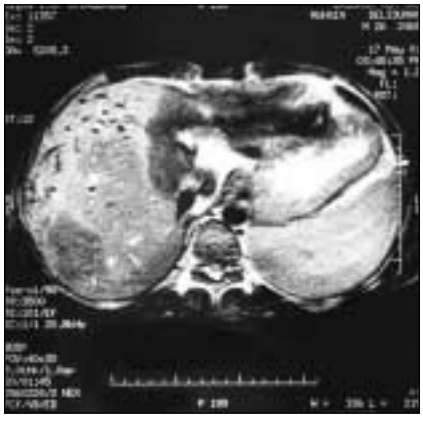

FIG. 3. Magnetic resonance image of a patient with diffuse alveolar echinococcosis of the liver who was listed for transplantation because of chronic liver failure.

There is no doubt that the first choice for treatment of AE is surgical resection.[1,2,8] The resectability rate of AE depends on the age and general condition of the patient and localization and extension of the disease. The competence of the surgical team is also an important factor. However, even after curative resection, recurrence can occur.[8] It seems to be related to invisible remnant parasitic tissue in the liver. Therefore chemotherapy is recommended for 2 years after curative resection.[2,4,8] In our series there were no major complications and operative morbidity in patients who underwent curative resection and there was no recurrence in a mean 3.5-year follow-up. Liver transplantation should be considered in patients who have severe hilar extension, leading to uncontrolled biliary infection, symptomatic secondary biliary cirrhosis with ascites or severe variceal bleeding owing to portal hypertension.[1,2,8] However, after liver transplantation it has been shown that parasitic disease can persist. Bresson-Hadni and associates[8] reported that the disease recurred in 4 of 7 patients who underwent liver transplantation. Such recurrence may be related to contagious progression from residual diaphragmatic AE foci or may be associated with peripheral and splenic metastases.[8] We did not perform liver transplantation for AE, but 3 patients were scheduled for liver transplantation.

Long-term chemotherapy is used in nonresectable cases. There is a consensus that long-term chemotherapy is useful. In an animal model, Eckert and colleagues[22] reported that long-term chemotherapy with benzimidazole derivatives inhibits metacestode proliferation and prolongs the survival rate of hosts. However, in humans, assessment of the efficacy of chemotherapy is extremely difficult for ethical reasons against controlled clinical studies, and the undefined natural course of AE. No controlled clinical studies have definitely shown the effectiveness of albendazole or mebendazole in humans. In some studies, it has been shown through imaging that these drugs can slow down the parasitic growth and reduce the size of liver lesions.[1–4,15] According to modified WHO criteria, in our series there were no successful (complete response) results with chemotherapy. Seven patients had some improvement (clinical amelioration, stationary lesions), and 9 had progression of the lesions. In contrast to our results of long-term chemotherapy, Liu and associates[23] reported that the lesions were completely calcified and cured in 7 patients (64%). They used high-dose, continuous therapy with albendazole. We believe that long-term chemotherapy should be used in nonresectable cases. Also, we believe that long-term chemotherapy is parasitostatic rather than parasitocidal. In their case report, Ammann and colleagues[3] suggested that long-term chemotherapy with mebendazole may be parasitocidal. It is known that in an undefined proportion of

cases the disease is abortive, because of the spontaneous death of metacestodes. These different responses could result from differences in host defence mechanisms or strains of EM among geographic regions, or both.

In endemic regions, screening programs are important for early detection. Such programs may increase the rate of curative surgical resection. More research is needed on new chemotherapeutic agents in an effort to obtain better results in nonresectable cases.

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