TREATMENT OF ECHINOCOCCUS MULTILOCULARIS INFECTION WITH BENZIMIDAZOL CARBAMATES

(Received 3 March, 1993)

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SUMMARY

We report here five cases of Echinococcus Multilocularis infection. Of these five cases four were diagnosed by explorative laparotomy and one with ultrasonography - guided needle biopsy. Patients whose dieseases showed no improvement with mebendazole were given albendazole. Two of these patients died despite treatment while the other three are still alive and on albendazole treatment, under periodical controls. Because echinococcus multilocularis infection is an extremely rare disease and the diagnosis can generally be made at late stages of the disease, it should be kept in mind for the differential diagnosis of the hepatic masses. We believe that albendazole is an effective agent for the treatment of this disease.

Key Words : Albendazole, mebendazole, alveolar cyst disease.

INTRODUCTION

Alveolar cyst disease is a tissue infection of humans caused by the larval stage of echinococcus multilocularis, which causes multilocular (alveolar) lesions that are locally invasive. The disease usually presents as a slowly growing hepatic tumor, with a minority of patients having metastatic disease to lung, brain or other tissues. The natural course is one of malignant growth with massive destruction of the liver and extension into vital structures. The lesion is usually found to be nonresectable at the time of diagnosis, because of the slow progression of the disease. Benzimidazol carbamates have been known to be effective against the larval stages of echinococci for 15 years and they are now available for clinical usage (1).

In many clinical trials, continuous application of mebendazole or albendazole was found to improve the clinical course, to regress both primary and metastatic lesions and to increase the survival rates (2-5). In the majority of the trials both drugs were found to be parasitostatic rather than parasitocidal and that they hinder the larval growth effectively (6). Unfortunately, there were no control groups in almost all the trials, so the optimal dosages and the treatment regimens of these drugs were far from being decisive. For mebendazole, the dosage and time schedule proposed by WHO for the treatment of

hydatid cyst disease is 50 mg/kg/day for 4-8 months (2, 7).

These drugs cause degenerative alterations in the mitochondria and endoplasmic reticulum of germinal plaque by tubulin inhibition, blocking the absorption of glucose and degradation of glycogen. Although mebendazole is poorly absorbed when administered orally and the plasma levels of the drug are far from the desired amounts, 10% of the plasma level can be detected inside the cyst. Albendazole is absorbed better than mebendazole. It is rapidly metabolized to its active metabolite, albendazole sulphoxide. When both drugs were given in equivalent doses by oral route albendazole sulphoxide was found to be tenfold more than mebendazole in the plasma of patients (8 - 10).

Treatment with benzimidazole carbamates has increased the cure chance of inoperable alveolar cyst patients. We report here the clinical and histopathological results of 5 cases treated with benzimidazole carbamates.

CASE REPORTS

CASE 1: A 21-year-old man was first seen in the outpatient clinic in October 1989 with the complaints of right upper abdominal discomfort and fullness. Alveolar cyst disease was considered by ultrasonography and tomography. Explorative laparotomy revealed an irregular and cystic mass lesion of 19x14x14 cm. in size, which completely occupied right lobe of the liver and open biopsy was performed without resection. Serological tests and histopathological examination confirmed the diagnosis (Fig. 1). He was put on mebendazole 50 mg/kg/day in December 1989. He had been on mebendazole for 6 months, after when no improvement was observed both clinically and by laboratory and tomographic examinations. In June 1990, mebendazole was withdrawn and albendazole 400 mg/day was initiated. He was followed up weekly, and ascites and jaundice appeared in August 1990 and he died of hepatic encephalopathy in September 1990.

CASE 2 : A 21-year-old man who had been suffering from abdominal pain and dullness for more than a year, was admitted to the hospital in November 1990, with a history of dyspnea of 2-week-duration. He was orthopneic when he was seen in the outpatient clinic and he was found to have massive ascites with bilateral pleural effusion. CT examination revealed a cystic heterogeneous mass of 13.5x9x15 cm. in size. An attempt to surgically drain the lesion failed because it was found to be inoperable. Histopathological examination of the biopsy specimen

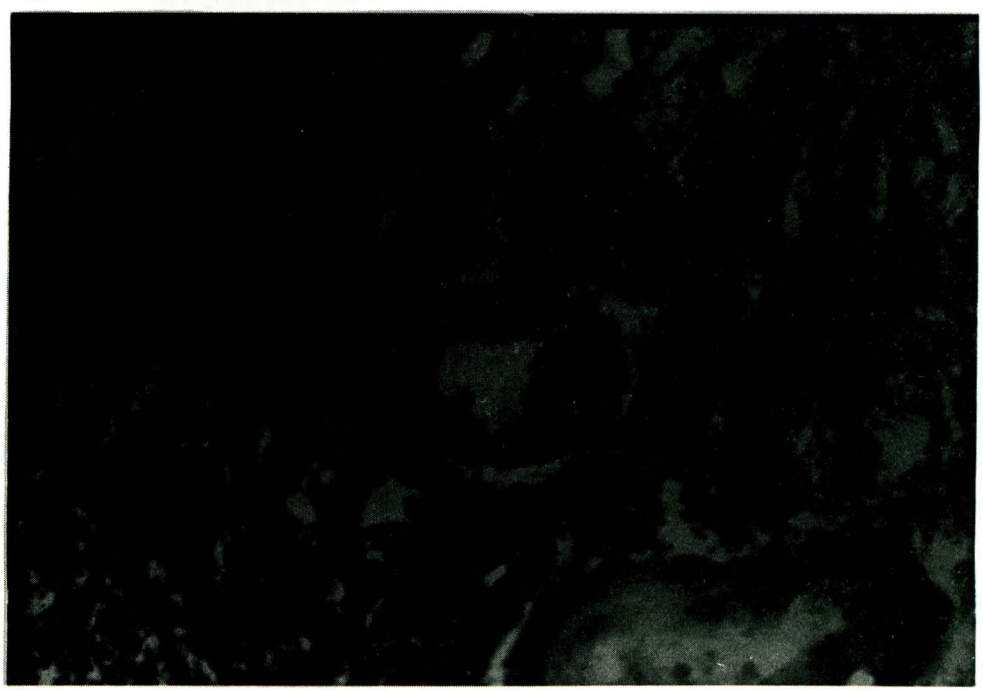

Fig. 1. Cysts with distinct germinal membranes in liver tissue (H&E x 200).

Fig. 2. Germinal membranes of the cyst and scolices (H&E x 400).

revealed alveolar cyst disease (Fig.2) and serologic examination also confirmed the diagnosis. Examination of the serofibrinous pleural fluid revealed a lymphocyte ratio of 100 %. Pleural biopsy revealed tuberculosis and appropriate treatment was initiated. He was also put on mebendazole 50 mg /kg/day and 6 months later mebendazole was withdrawn and albendazole 400 mg/day initiated in June 1991. He was discharged in the same month. He had never come to follow up visits since then and we had never been able to get in touch with him and his family.

CASE 3 : A 21-year-old man was admitted to the hospital with fatigue, jaundice and abdominal pain in August 1990. A painless and firm hepatomegaly was detected on physical examination and CT revealed a heterogeneous cystic lesion localized to the left lobe of the liver. He underwent explorative laparotomy and cholecystectomy with T-tube drainage procedures. Mebendazole was started 50 mg/kg/day. 6 moths later, in May 1991 mebendazole was replaced by albendazole 400 mg daily. On the follow up of this patient, his life quality improved and his enlarged liver regressed considerably. He is currently on albendazole treatment with minimal hepatomegaly.

CASE 4 : A 55-year-old woman who had been suffering from fatigue, abdominal pain and fever for five years was admitted to the hospital because of accompanying complaint of abdominal right upper quandrant pain in August 1990. She had a firm and painless hepatomegaly and US and CT examinations revealed a solid lesion in the right lobe of the liver. The lesion had cyctic and pathcy necrotic areas and was 15x11x10 cm. in size (Fig. 3). Ultrasonography-guided fine needle biopsy was performed and histopathological examination revealed alveolar cyst disease. Carcinoembryonic antigen and alpha feto protein levels were in normal range. Serologic examination confirmed the diagnosis. Albendazole (400 mg/day) treatment was initiated in September 1990. On periodical controls the patient was found to improve clinically and US examinations performed every six months beginning from May 1991, revealed that the lesion had regressed. The lesion was found to be 10x8x8 cm in size on the last examination. She has been on albendazole since then without deterioration of her clinical status.

CASE 5: A 39-year-old woman was admitted to the hospital with the history of jaundice, diarrhea. pruritus and fatigue of more than one-year-duration, in January 1989. US and CT examinations revealed a right hepatic mass which arised the suspicion of a malignant process (Fig. 4). She underwent

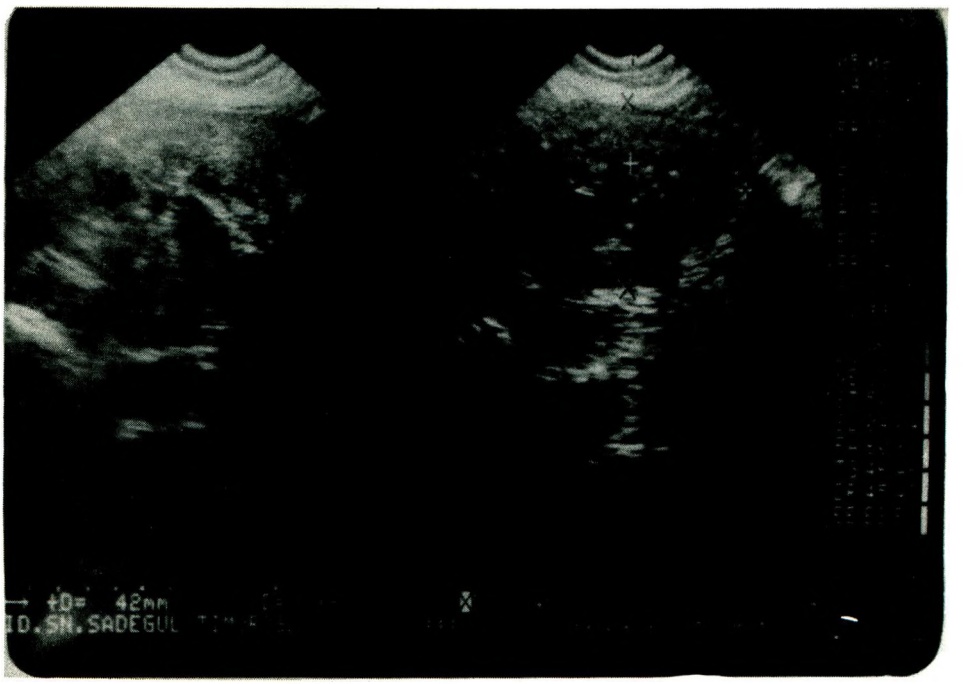

Fig. 3. Ultrasonography showing the cystic and patchy necrotic areas in the liver.

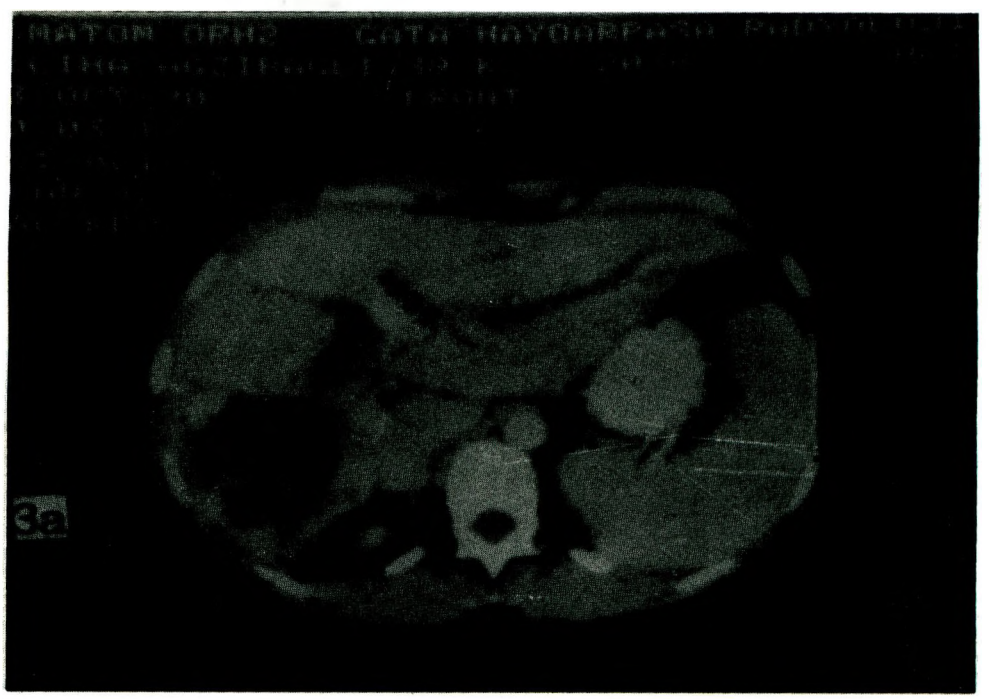

Fig. 4. Computerized tomography revealing the right hepatic mass of our case number 5.

explorative laparotomy, during which open biopsy, gastrojejunostomy, external drainage of intrahepatic biliary ducts and portal catheterization procedures were performed. Histopathological examination of the biopsy specimen revealed alveolar cyst disease. She was put on albendazole 400 mg/day in January 1989. At the end of the first year of treatment, because of the repeated episodes of cholangitis she was hospitalized again to perform an endoscopic retrograde cholangio-pancreatography and a self-

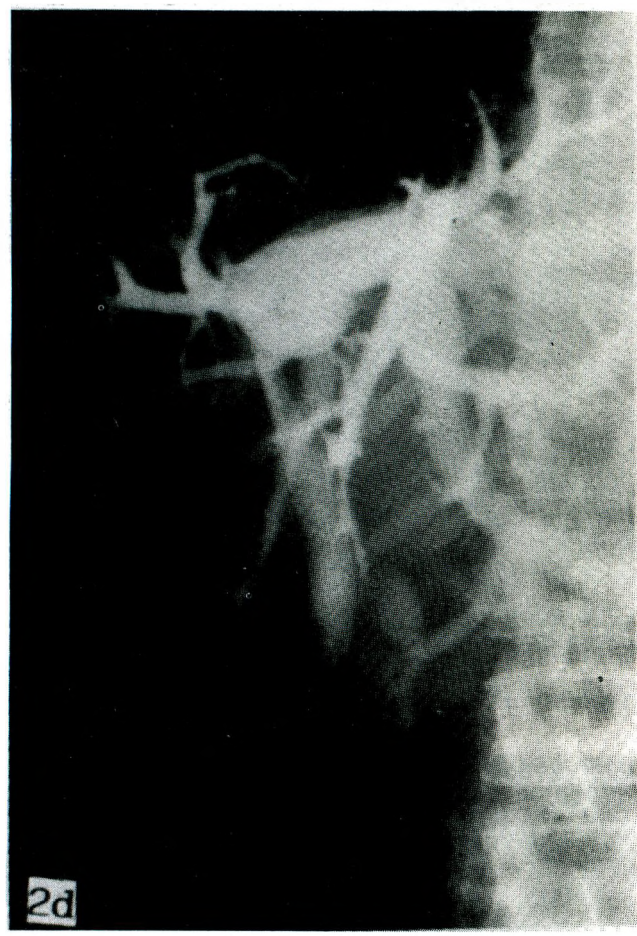

Fig. 5 - Self-expanding wall stent (arrow) which was placed transendoscopically through the strictured segment of the main biliary duct.

expanding wall stent was placed transendoscopically through the strictured segment of the main biliary duct (Fig. 5). She is still under control and on albendazole treatment without any serious problems.

DISCUSSION

We studied the efficiency of benzimidazole carbamates in the treatment of hepatic alveolar cyst disease in five cases. Although albendazole is poorly absorbed, its main metabolite albendazole sulphoxide has been found in high concentrations in plasma, body tissues and cyst fluids (2). The absorption of albendazole depends on intact enterohepatic circulation (10). The absorption half life is significantly prolonged in patients with extrahepatic cholestasis and a fatty meal improves it. These observations suggest that bile is required for the rapid absorption of albendazole (11, 12).

Long term treatment of experimentally infected animals with mebendazole-medicated feed reduced metacestode weights by an average of 89%- 95%, and prolonged survival of the hosts (13). When administered in food or by gavage to animals experimentally infected with E. Multilocularis, albendazole has consistently caused statistically significant reductions in metacestode weights in comparison with those in control groups (13-15, 17). The effect of albendazole was superior to that of mebendazole in two studies (14, 15) and inferior in three others (13, 16, 17).

Albendazole at doses generally considered acceptable for humans and lower mammals is highly effective for limiting larval echinococcus multilocularis growth and development but is not rapidly parasitosidal (6).

The recurrence problem after albendazole and mebendazole therapy indicates that benzimidazoles are parasitostatic rather than parasitosidal in some cases (9). It was reported than mebendazole treatment seemed to be more effective against pulmonary and abdominal cysts than against hepatic cysts, with albendazole no difference of effectiveness between pulmonary, hepatic and abdominal cysts was observed (9).

Each cyst has its intrinsic sensitivity to albendazole and therefore each cyst has its own responsiveness to the treatment (9). Results, however differed widely from one patient to another. In our patients we observed different responses to albendazole.

Of the 5 patients in our study, two women were given albendazole 400 mg/day and three men were given mebendazole 50 mg/kg/day. Case 1 and 2 showed no responses to mebendazole. Case 1 died of hepatic encephalopathy in September 1990, Case 2 was also on antituberculous therapy because of pulmonary tuberculosis, and probably died since he never came to any periodical controls. Case 3 has benefited from both drugs and he has been under periodical controls with a relatively high quality of life. Case 4 has also benefited from albendazole and is still on this drug with regression of the lesion. Case 5 has been on albendazole since the confirmation of the diagnosis: she underwent ERCP and a stent was placed through the main bile duct (18).

In conclusion the surgical resection of the whole cyst. when possible should remain as the first choice for the treatment of alveolar cyst disease. When radical resection is not possible, long term chemotherapy with albendazole offers the next best option. Because the infection cannot usually be diagnosed until an advanced stage, the lesion is often nonresectable.

The course of the disease has often been compared with that of a malignant tumor. At least 18 to 24 months of continuous mebendazole treatment 40 mg/kg/day apparently is needed in order to attain a high probability of death of larval E. Multilocularis (8). Albendazole is well tolerated in 30-day courses separated by 2-week-intervals and when given 10-14 mg/kg/day (19).

The results of this study in combination with other data,indicate that benzimidazole treatment alters the clinical course of alveolar cyst disease. In nonresectable cysts longterm therapy with albendazole offers the next best treatment choice, but liver transplantation should also be kept in mind as an alternative treatment.

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