Alveolar echinococcosis of the liver: a single center experience

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INTRODUCTION

In humans, alveolar echinococcosis (AE) of the liver is caused by canine tapeworm called *Echinococcus multilocularis*. The disease is most prevalent in the northern hemisphere and in the eastern part of Turkey.

OBJECTIVES

The aim of the study was to review the natural history of AE and its clinical and radiological features.

PATIENTS AND METHODS

The retrospective study involved 23 patients (10 men, 13 women), aged 34–75 years with AE who had been referred to our liver disease clinic in the past 4 years. Only patients with pathologically proven AE were included in the study. The sociodemographic, clinical, and radiological features of AE were also evaluated.

RESULTS

The main laboratory characteristics of AE included mild eosinophilic leukocytosis with hyper-gammaglobulinemia, elevated C-reactive protein levels, near-normal liver transaminases, and increased levels of cholestatic enzymes and immunoglobulin E. Eight patients (35%) had hepatitis B e antigen-negative hepatitis B infection. Budd-Chiari syndrome was identified in 3 of 23 patients (13%). Eighty-three percent of the patients had a seropositive test result for AE, and approximately one-third of the patients had distant metastasis. Surgical treatment was administered in 4 patients. Four patients died due to complications during follow-up.

CONCLUSIONS

Patients with AE have numerous complications and advanced disease at the time of diagnosis. The clinical picture of AE comprises a number of hepatic and extrahepatic disturbances related both to destructive and mass effects of the tapeworm.
estimated and the parasite is still a major health concern for eastern and central Europe. Most of the cases were reported in France, Germany, and Switzerland. From 1998 to 2000, 559 cases were reported to the European Echinococcosis Registry. Notably, the mortality rate of the disease exceeds 95% if left untreated. A recent epidemiological study from central Europe has suggested that the incidence of human AE is increasing because of the expansion of the fox population.

Clinical features of AE may include those observed in a malignant liver tumor, such as abdominal pain, icterus, weight loss, and a mass in the right upper quadrant. Despite the availability of serologic tests, most patients have advanced disease. The alveolar cysts typically grow slowly and are difficult to detect. Blood tests show increased levels of eosinophils. Elevated levels of liver-related transaminases and cholestatic enzymes may be observed in patients with AE. A serologic assay with an enzyme-linked immunosorbent assay (ELISA) can also be used to identify tapeworm. This test can confirm the presence of AE with a sensitivity rate of 84% to 90%.

Liver ultrasonography is the major part of the diagnosis. Advanced radiological techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have been used to identify the extent of the disease, metastasis, and vascular complications. Human AE is staged according to the World Health Organization (WHO) parasite neighboring organ metastasis (PNM) classification system. Classification is based on the radiological features of the disease.

Although AE is a parasitic disease, the outcome depends on the degree of liver involvement, which evolves over time. Sustained tapeworm control by medical treatment with albendazole is critical in patients with advanced liver disease. It is also important to identify those who may benefit from liver transplantation or hepatic resection, which are established as gold standard therapies.

There are few published reports on the progression and complications of AE. We therefore aimed to investigate the characteristics of the disease.

**Patients and methods** Twenty-three patients (10 men/13 women; mean age, 44.2 ±21.4 years) with AE were included in a retrospective study. AE was diagnosed by ultrasonography-guided liver biopsy in each patient. Socioepidemiologic features, hematological and biochemical parameters, and radiological aspects were assessed at the time of the diagnosis.

A cyst bydatid ELISA test (Novagnost-Dade Behring, Illinois, United States) was used to detect the tapeworm. This test may not be able to differentiate AE from cystic echinococcus accurately. False-negative reactions may occur in 30% of the cases with low antibody levels.

The serum samples collected at baseline and during follow-up examinations were tested for hepatitis B surface antigen. Patients were classified according to the WHO guidelines for AE.

The presence of Budd-Chiari syndrome (BCS) and distant metastasis was also assessed by CT of the abdomen, thorax, and brain. We therefore administered albendazole orally twice per day at 15 mg/kg in all patients. All patients were also closely followed by hematological evaluation and liver ultrasonography.

The study protocol was conducted in accordance with the Helsinki Declaration as revised in 2002. All patients were duly informed and provided their written consent to participate in the study.

**Statistical analysis** Numeric values were determined as a percentage or the mean ± standard deviation. The nonparametric Kruskal-Wallis test was used for qualitative results, and the χ² test was used to compared qualitative results.

**RESULTS** A total of 23 individuals with AE were enrolled in the study. The median age at the time of admission was 44 years (12–81 years). All patients were farmers who lived in the rural areas of Van Province. Biopsy revealed that all patients had pathologic evidence of AE. All patients were followed up for at least 3 years and were evaluated by routine examination every 3 months.

At the time of presentation, the white blood cell count was 11,140 (5300–35 200)/mm³, and the eosinophil count was 592 (10–3600)/mm³. The mean sedimentation rate was 54 (20–100) mm/h. The mean levels of liver-related transaminases were close to normal limits. However, despite the normal values, the levels of cholestatic enzymes (alkaline phosphatase and gamma-glutamyl transferase) were elevated. The median globulin level was 5.2 (3.4–7.1) g/dl. We also found higher levels of C-reactive protein (CRP), immunoglobulin E (IgE), and lactate dehydrogenase (LDH) levels in patients with AE. The details are provided in **Table 1**.

All patients underwent serologic testing to determine the presence of AE. The ELISA test results were positive for *E. multilocularis* in 19 of 23 patients.

In our study, 8 patients (35%) had hepatitis B e antigen-negative hepatitis B infection. Only 2 of 8 patients were treated by lamivudine as an antiviral therapy. No chronic hepatitis B cases were identified prior to the infestation. All hepatitis B cases were detected during the diagnosis of liver echinococcosis. None of the patients had hepatitis C infection.

Abdominal CT was performed for all patients during the initial examination. In 18 patients, the lesion was located in the right hepatic lobe; in 5 patients, it was located in the left hepatic lobe. Hepatomegaly was observed in 10 patients. According to the PNM classification, 14 patients (61%) had P3 or P4 disease. Seven patients (30%) had N1 disease, and 7 patients (30%) had distant metastasis or M1 disease. Five patients (22%) exhibited invasion of the inferior vena cava. Portal vein involvement was detected in 1 patient and
One of the high-incidence areas for AE is the eastern part of Turkey, which has a cold climate and mountain ranges and thus is optimal for fox habitat. The disease is found mostly in the rural areas of Turkey, particularly along the Iranian border of the country and in Van city.

The major risk factors for AE are female sex, age older than 20 years, residence in rural areas or in high-altitude locations, and close contact with carnivores. The Van province is located at an altitude above 1500 m. As expected, almost all patients derived from villages in the Van province, which is an epidemic area of AE in Turkey. It has been suggested that the higher incidence in rural areas may be related, in a way, to environmental factors, particularly close contact with foxes. The predominance of female sex was in line with the previous studies. This phenomenon may result from the predominance of women among the working population in the rural areas of eastern Turkey.

The clinical manifestations of AE depend on the location and the extent of the disease. In patients who have early-stage disease, there are no specific symptoms. In advanced disease, a large mass may be felt on the right upper abdomen. Examination of the abdomen reveals tender hepatomegaly. Furthermore, AE may spread to the vascular bed of the liver, resulting in BCS and ascites.

In our study, all patients reported abdominal dullness in the right upper abdomen, and 3 patients had BCS-related ascites. Laboratory findings in patients with AE are nonspecific and may include eosinophilic leukocytosis, decreased serum albumin, hyperglobulinemia, and abnormal liver function. The persistent hepatic vein involvement in 2 patients. BCS was identified in 3 of 23 patients (13%). As expected, 18 of 23 patients (78%) had stage III or stage IV disease; 7 of 23 patients (30%) had distant metastases. There were 3 pulmonary, 3 renal, and 1 skeletal metastasis. One of the patients with pulmonary metastasis presented with hemoptysis. One patient with bone metastasis presented with a femur fracture. The rest of the patients with extrahepatic involvement had no clinically overt symptoms. The detailed results are presented in Table 2.

Parasitostatic therapy with albendazole was administered in 19 of 23 patients (twice per day at 15 mg/kg orally). No case of clinically relevant drug-related leukopenia was observed. Orthotopic liver transplantation was performed in 2 of 23 patients. Hepatic resection was also performed in 2 patients. The most relevant factors for mortality were BCS and hypoalbuminemia. Three patients with BCS died due to liver failure within a few months.

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of calcified necrotic tissue. MRI of the abdomen can provide further diagnostic information in the assessment of patients with AE.

Unlike most other zoonotic diseases, which are not staged using a staging system, human AE is classified as a malignant liver tumor. The WHO PNM classification system, which is based on imaging findings, has been established to facilitate appropriate therapeutic recommendations. The P category denotes hepatic localization of the parasite. The N category represents extrahepatic involvement of the neighboring organs. M status is used to describe distant metastasis of the larva.

In the current study, peripheral lesions without proximal vascular and/or biliary involvement (P1 disease) were observed only in 17% of the patients. The presence of higher rates of advanced disease (N1 and M1 groups) was a striking finding. In our study, 30% of the patients had pulmonary, renal, and bone metastases. These results indicate that advanced-stage disease is prevalent among Turkish patients.

Hepatectomy is still the gold standard therapy for AE, if complete resection is feasible and if the parasitic mass can be removed completely. In most patients, the disease is already in an advanced stage when the diagnosis is established. Therefore, curative resection rates have been reported to be as low as 20%.

Elevation of cholestasis enzymes certainly necessitates the intensive exclusion of biliary involvement. A cyst hydatid ELISA test should be performed in all patients with suspected AE. Furthermore, newer tests that use Em2, a species-specific native antigen obtained from larval-stage E. multilocularis, can also be used for the diagnosis of AE.

In our current study, despite the near-normal levels of liver transaminases, elevated cholestatic enzymes, hyperglobulinemia, eosinophilia, higher CRP, LDH, and sedimentation levels were observed. As expected, IgE levels were elevated. This result was considered to be a universal finding related to invasive parasitic disease as well as AE.

In the present study, the sensitivity of detecting echinococcosis multilocularis was 82%, because examinations performed prior to abdominal imaging were positive for echinococcosis in 19 of 23 patients.

Ultrasonography and liver biopsy in connection with serologic tests are sufficient to establish the diagnosis of AE. Ultrasonographic examination of the abdomen revealed nonhomogenous echogenic infiltration of the liver parenchyma. Abdominal CT more accurately reveals the extent of the disease and frequently shows biliary and vascular invasion as well as distant metastasis. Moreover, abdominal CT usually shows scattered areas of calcified necrotic tissue. MRI of the abdomen can provide further diagnostic information in the assessment of patients with AE.

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TABLE 2 Radiological features of the cases

<table>
<thead>
<tr>
<th>Case</th>
<th>PNM</th>
<th>Stage</th>
<th>Invasion of HV</th>
<th>Invasion of PV</th>
<th>Invasion of VCI</th>
<th>Lung metastasis</th>
<th>Bone metastasis</th>
<th>Renal metastasis</th>
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Abbreviations: BCS – Budd-Chiari syndrome, HV – hepatic vein, PNM – parasite neighboring organs metastasis, PV – portal vein, VCI – vena cava inferior
In a recent study from Japan, reduction surgery followed by parasitostatic therapy with albendazole was as effective as curative resection and was established as a promising approach in the treatment of AE. Additionally, overall survival and progression-free survival have been related to portal vein invasion in Japanese patients.\(^7\) For those with advanced or metastatic disease, medical treatment with albendazole may represent a palliative alternative treatment option. Treatment with albendazole (twice per day at 15 mg/kg) has a limited effect in complicated cases.\(^8^n\)

In our study, 4 patients died during a 4-year follow-up. Hepatic resection and liver transplantation were performed in 4 patients. Lower rates of orthotopic liver transplantation for AE are mainly due to advanced disease.

As a rule, detecting earlier-stage AE in asymptomatic patients is needed to prevent advanced-stage disease. Therefore, the early diagnosis of AE is crucial for improving survival rates and prognosis. Further research will be needed.

There are several limitations to our study. First, it has a retrospective design. Second, the number of patients was small. Larger studies are needed to evaluate the characteristic features of the disease in Turkey and in Eastern Europe.

Patients with AE have a high prevalence of complications and typically have advanced disease at the time of diagnosis. AE also involves a number of hepatic and extrahepatic disturbances related to both destructive and mass effects. During the study, we made several striking observations. First, the coexistence of hepatitis B virus infection with AE was very common. Second, the development of BCS was the most important factor for survival. Third, higher serum IgE levels were observed among study patients. Finally, most patients had advanced-stage disease at the time of diagnosis.

REFERENCES

Bąblowica wielojamowa wątroby – doświadczenia kliniczne pojedynczego ośrodka

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STRESZCZENIE

WPROWADZENIE Infekcja psim tasiemcem Echinococcus multilocularis prowadzi u człowieka do rozwoju bąblowicy wielojamowej wątroby (alveolar echinococcosis – AE). Chorobę tę spotyka się najczęściej na półkuli północnej oraz we wschodniej części Turcji.

CELE Celem badania był przegląd historii naturalnej AE oraz jej cech klinicznych i radiologicznych.

PACJENTI I METODY W badaniu retrospektywnym udział wzięło 23 pacjentów (10 mężczyzn, 13 kobiet) w wieku 34–75 lat, przyjmowanych do naszej kliniki w ciągu 4 ostatnich lat. Do badania zostali zakwalifikowani jedynie pacjenci z AE udowodnioną w badaniu patomorfologicznym. Ocenie poddano również cechy socjodemograficzne, kliniczne i radiologiczne AE.

WYNIKI Główne charakterystyczne cechy AE wykrywane w badaniach laboratoryjnych to umiarkowana leukocytoza eozynofilowa z hipergammaglobulinemią, zwiększone stężenie białka C-reaktywnego, bliski normy poziom transaminaz oraz zwiększone stężenia enzymów cholestatycznych i immunoglobuliny E. U 8 chorych (35%) zdiagnozowano zapalenie wątroby typu B z negatywnym antygenem HBe. Zespół Budda i Chiariego wykryto u 3 chorych (13%). U 83% badanych AE została potwierdzona serologicznie, a u ~1/3 wystąpiły przerzuty odległe. Leczenie chirurgiczne podjęto u 4 pacjentów. Cztery osoby zmarły z powodu komplikacji, które wystąpiły w trakcie obserwacji.

WNIOSKI U chorych z AE występują liczne komplikacje i wysoki stopień zaawansowania choroby w momencie diagnozy. Na obraz kliniczny AE składa się wiele zaburzeń wątrobowych i pozawątrobowych spowodowanych zarówno działaniem destrukcyjnym pasożyta, jak i jego wzrastającą masą.