

ORIGINAL RESEARCH

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Disseminated hydatid disease treated with albendazole: 15-year experience**Sinem Gungor¹, Murat Yalcinsoy², Olga Akkan¹, Bulent Altinsoy³, Zeynep Ferhan Ozseker⁴,
Aysun Misirlioglu⁵, Semra Bati Kutlu⁶, Sibel Arinc¹, Hatice Turker¹, Esen Akkaya¹**¹*Sureyyapasa Chest Diseases and Thoracic Surgery Education and Research Hospital, Department of Pulmonary Medicine, Istanbul, Turkey*²*Inonu University Faculty of Medicine Department of Pulmonary, Malatya, Turkey*³*Bulent Ecevit University, Faculty of Medicine Department of Pulmonary, Zonguldak, Turkey*⁴*Istanbul University, Cerrahpasa Faculty of Medical Department of Pulmonary, Istanbul, Turkey*⁵*Sureyyapasa Chest Diseases and Thoracic Surgery Education and Research Hospital, Department of Thoracic Surgery, Istanbul, Turkey*

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Abstract

Medical therapy is recommended in various situations such as multiple cysts, high risk surgery, presence of small cyst and perioperative phase in the treatment of hydatid cyst. Present study was designed to determine the features of disseminated hydatid cyst cases, outcome of albendazole treatment, diagnosis and management of complications and patients' outcome. Methods: 21 patients who had the diagnosis of hydatid cyst based on clinical, radiological, and pathological findings with multiple hydatid cyst in a single organ and/or more than one organ were retrospectively analyzed. The mean age was 34±17.9 (range, 7-71) and F/M was 17/4. Hydatid disease was detected as multiple cysts in the lung in four patients, as multiple cysts in the lung and pleura in one case, and as multiple organ involvement in 16 cases. The most common presentation was the involvement of both lung and liver. The most common symptom was cough. Four asymptomatic patients were detected during family screening. In six patients, Albendazole was started before the operation and the remainders were started after the operation. Cure was achieved in eight patients at the end of medical and/or surgical treatment. Convenient medical treatment with albendazole treatment in appropriately selected patients is an effective treatment option with minimal side effects in hydatid cyst disease.

Keywords: Hydatid cyst, albendazole, multiple organ involvement**Introduction**

A hydatid cyst is the larval stage of *Echinococcus granulosus* at the metacystic phase. It is one of the major zoonoses [1]. Prevalence has been reported 5 to 10/100,000 [2,3]. It is estimated that 1,300 cases are newly diagnosed each year in Turkey [4,5]. The disease is most commonly observed in liver, followed by the lungs and it can involve any organ at a rate of 10% [2,3]. About 60% of the cases are solitary cysts, and multiple cysts are observed in 20 to 50% [6].

Although the process of the disease could be asymptomatic, it can lead symptoms which are specific to the involved organ depending on the localization and size of the cyst [7]. Surgery is accepted as the first treatment option. Medical therapy is recommended in multiple cysts, high risk surgery, the presence of small cyst, and perioperative phase [8].

The mortality rate has been reported as In the present study, we aimed to determine the clinical and radiological characteristics of the patients with multiple/disseminated hydatid cyst. Furthermore current study was designed to examine the effectiveness of albendazole treatment and possible complications, presence of relapse, etiological factors and treatment results based on our experience in the management and treatment of rarely seen complications.

Materials and Methods

Study design, setting, and population: The study was designed as a retrospective case-series study in a tertiary teaching hospital for chest diseases and thoracic surgery center between 2000-2015. The study protocol was approved by the institutional Ethics Committee and it was conducted in accordance with the principles of the Declaration of Helsinki. As the study was a retrospective study, no informed consent was obtained and the Scientific Committee of the hospital granted permission for the use of patient data in accordance with the patient privacy. During hospital procedure, all treatments and medications were done after obtaining informed consent of the patients.

***Corresponding Author:** Murat Yalcinsoy, Department of Pulmonary Medicine, Sureyyapasa Chest Diseases and Thoracic Surgery Education and Research Hospital, Istanbul, Turkey, **E-mail:** mrtyalcinsoy@yahoo.com

Patient Selection: The patients who were diagnosed with a hydatid cyst according to clinical, radiological, and pathological findings were included. The diagnosis was confirmed by the detection of positive indirect hemagglutination (IHA) test and pathological examination. The titration of 1/320 and above in IHA was considered positive. Exclusion criteria were as follows: the presence of a solitary cyst, lack of albendazole treatment, and refusing treatment.

Data source: The data were gathered retrospectively from a password-protected database.

Additional covariates: Demographic characteristics and symptoms, diagnostic methods, organ involvement, type of operation, results of treatment and follow-up were recorded. Living areas (country side/urban), occupation, dog contact, and family history were noted. Posteroanterior chest X-ray and radiological images, complete blood count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), and alkaline phosphatase (ALP) levels were recorded at the beginning of the treatment and during follow-up. Drug-related side effects such as alopecia, vertigo, nausea, and allergic reactions were recorded. Furthermore, type of surgery, treatment-related complications, relapse, and mortality were noted.

Definitions: Risk factors were determined as living area, livestock breeding, and household transmission [10,11]. The results of treatment were checked radiologically using X-ray, computed tomography (CT), and ultrasound (US). According to the US findings, cysts were classified as active, transitional, and inactive [12].

Medical treatment: At the beginning of treatment, cranial CT is performed and medical treatment of complicated, multiple/disseminated hydatid cyst cases without cranial involvement is performed with albendazole 10-15 mg/kg/day for three consecutive weeks and with a drug-free interval of a week [13]. The patients who had intracranial hydatid cyst are primarily operated. Following the operation, these patients are re-evaluated for medical treatment. Indications for surgery are complicated cysts, large cysts, and cysts involving the vital organs such as central nervous system, spinal cord, and the heart [8].

Statistical analysis

Statistical analysis was performed using the Microsoft Office Excel program 2010 (Richmond, WA). Descriptive data were expressed in median with interquartile ranges for the non-parametric continuous variables and in mean±standard deviation for the parametric continuous variables. Counts and percentages were also used, where applicable.

Results

Demographic characteristics of patients: Mean age was 34±17.9 (range, 7 to 71) year and majority of the patients were females (81%). Considering the risk factors, there were no farmers. In terms of transmission of household contacts, there were six patients from two families and there were two patients who were neighbours of one of these families. All these patients were living in the rural area. Four patients had comorbidities. Two of them

had hypertension, while the remaining two patients had diabetes mellitus (DM). Also, three patients had a previous history of tuberculosis.

Clinical characteristics and diagnosis: Hydatid disease was detected as multiple cysts in the lung in four patients, multiple cysts in the lung and pleura in one patient, and multiple organ involvement in 16 patients. The most common presentation was involvement of both lung and liver (Figure 1). As rarely seen, three patients had muscle, vertebra, heart, and kidney involvement. The most common symptoms were cough, hemoptysis, pain, fever, and headache. Four asymptomatic patients were detected during family screening. Three patients were admitted to neurosurgery clinic with the symptoms of compression of the cranial lesion, and they were referred to our center with the diagnosis of a hydatid cyst following surgery. The diagnosis of a hydatid cyst was done by pathological examination in 14 patients, and radiologically in seven patients. IHA was found positive in 16 patients and negative in four patients.

Treatment: The mean duration of albendazole treatment was 27±22 months. Twelve patients underwent several operations before the diagnosis. Albendazole was started before surgery in six patients and after surgery in other patients. Operation for several reasons was required in seven patients during follow-up. Splenectomy was performed in two patients among three patients with splenic involvement, while one patient received medical treatment due to the deep localization and cure was achieved following treatment (Figure 2).

Cure was achieved in eight patients, whereas 11 patients recovered with sequelae. Two patients died due to other reasons independent from a hydatid cyst.

Relapses: Relapse was observed in five patients. Relapses were determined as pulmonary and pleural involvement in four patients and cardiac involvement in one patient. All relapsed patients had multiple cysts with multiple organ involvement.

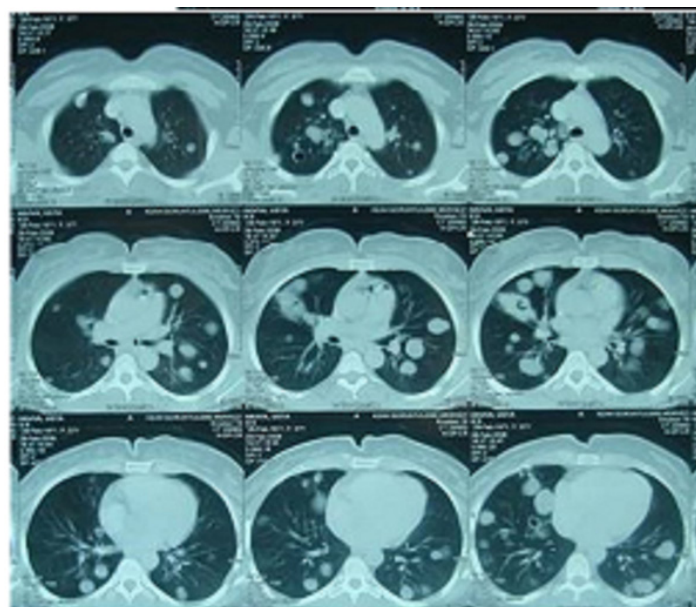


Figure 1. Computed tomography scan showed bilateral and multiple cyst.

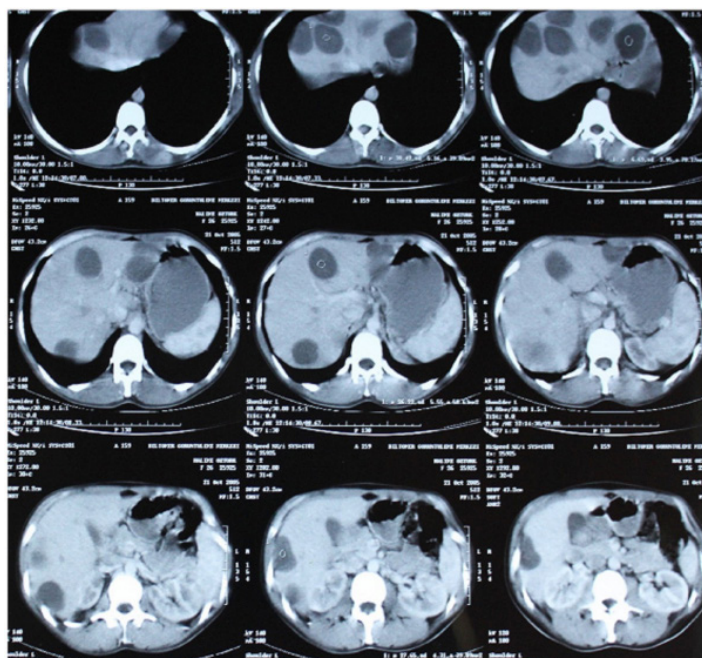


Figure 2. Case has multiple intraabdominal cysts

Table 1. Characteristics of 21 hydatid disease cases treated with albendazole

Case No	Sex	Age	Rural Area	Family history	Organ involvement	Surgery before albendazole treatment	Surgery during albendazole treatment	Treatment duration (month)	Relapse	Time to relapse (year)	Result
1	M	27	-	-	Lung, liver, brain, heart, kidney	Cerebral cystectomy, Nephrectomy, Cardiac cystectomy		15	+	17	Cure
2	F	20	-	-	Lung, pleura	Decortication, pulmonary cystectomy	Lung cystectomy	24	-		Cure
3	F	7	-	-	Lung, vertebra	Vertebra cystectomy		3	-		Cure
4	F	38	-	-	Lung, liver, spleen, brain	Cerebral cystectomy	Pleural decortication, cystectomy				
5	F	36	-	-	Lung, liver	Hepatic cystectomy	Hepatic cystectomy, pulmonary cystectomy	67	+	3	Cure in lung, liver inactive
6	F	33	-	-	Lung, liver			16	-		Cure in lung, liver inactive
7	F	36	-	-	Lung, liver			6	-		Cure
8	F	45	-	-	Lung, liver Peritoneal cavity			50	+	5	Sequela in lung, liver inactive
9	F	21	-	-	Lung,	Lung cystectomy		3	-		Exitus
10	M	69	-	-	Lung			3	-		Exitus
11	F	68	+	+	Lung			22	-		Sequela in lung
12	M	12	+	+	Lung, liver			20	-		Cure in lung, liver inactive
13	F	41	+	+	Lung, liver, spleen, brain	Cerebral cystectomy	Splenectomy	42	-		Sequela in lung, liver inactive
14	F	26	+	+	Lung, liver	Hepatic cystectomy		20	-		Cure
15	F	23	+	+	Lung, liver			24	-		Cure in lung, liver inactive
16	F	34	+	+	Lung, liver, brain	Cerebral cystectomy	Pulmonary cystectomy	26	-		Cure in lung, liver inactive
17	F	35	-	-	Lung, liver, muscle		Pulmonary cystectomy	36	-		Sequela in lung, liver inactive
18	F	71	-	-	Lung, liver	Pulmonary cystectomy	Pulmonary cystectomy	6	-		Cure
19	F	29	-	-	Lung, liver,	Pulmonary cystectomy	Pulmonary cystectomy	36	+	5	Cure
20	F	27	-	-	Lung, liver, spleen, peritoneal cavity, subcutaneous tissue	Splenectomy		84	+	5	Cure in lung, liver inactive, peri-toneum inactive
21	M	30	-	-	Lung	Pulmonary wedge resection, cystotomy, capitonnage		12	-		Cure

Complications during albendazole treatment

Ruptured cyst-related complications: Eleven complications due to a ruptured cyst was observed in eight patients (38%). Hemoptysis due to ruptured cyst was seen in six patients. During treatment, hydropneumothorax was detected and thoracotomy was planned in two patients (Figure 3).

Medical treatment-related complications: Liver enzymes were elevated in five patients (24%). Therefore, treatment was discontinued for one cycle. Treatment was re-initiated, when the enzyme levels returned to normal limits. None of the patients had alopecia, vertigo, nausea, urticaria, allergic shock, leukopenia, and thrombocytopenia.

Table 1 shows the characteristics of 21 patients treated with albendazole.

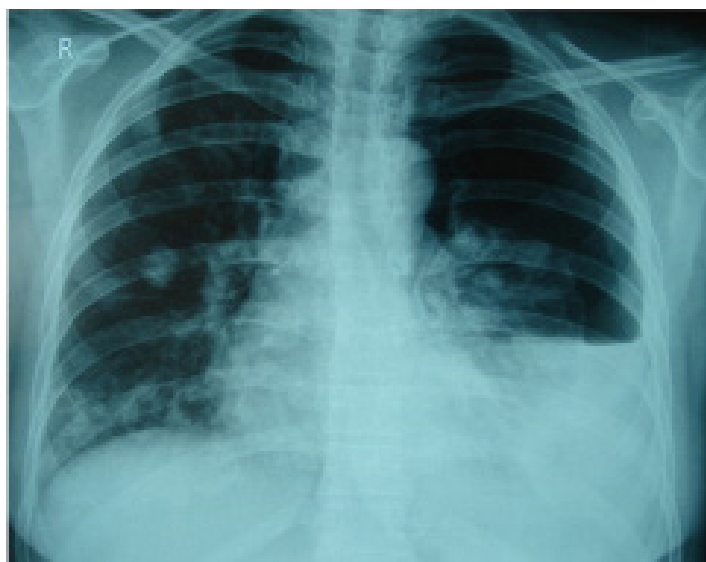


Figure 3. Left hydropneumothorax developed during treatment

Discussion

In the present study including patients with a disseminated hydatid cyst treated with albendazole, we found that albendazole treatment is effective and safe with minimal side effects in selected patients.

Hydatid cyst disease is frequently seen in females [3,14]. In the present study, the majority of patients were females. This can be associated with the fact that females meet the environmental factors more frequently. Although hydatid cyst disease is seen at all ages, in a meta-analysis including 1,211 patients, its prevalence increased at the age of 40 and above [15]. Cappello et al. also reported that the ratio of multiple hydatid cysts were significantly higher at the age of 50 and below [3]. Similarly, the mean age of our study population was consistent with the literature

Although the incidence of intrafamilial hydatid cyst disease is not exactly known, there are some case reports about intrafamilial spread [16,17]. Incidence of the disease in four large families living in an endemic region was found 14.9% [10]. In our study, six patients from two families and two patients who were neighbours of one of these families were examined for environmental exposure. Their common features were living in the rural area.

Pulmonary hydatid cyst disease was found to be 7 to 9 times more symptomatic than hepatic disease, which was attributed to the slow-growing nature of the cyst in the liver with less morbidity [18]. Except four patients who were detected during family screening, the majority of our patients were symptomatic. This can be related to the fact that the patients had multiple cysts or multiple organ involvement. Cough was frequently seen in our patients, which can be related to the presence of pulmonary involvement.

Multiple hydatid cysts were reported at a rate of 60%, and the ratio of early diagnosed multiple hydatid cysts was significantly higher [3]. Rare organ involvement like muscle, bone, isolated spleen, cardiac hydatid cyst varies between 7-13% [19,20]. In the present study, 7 patients had rare organ involvement.

The diagnosis of a hydatid cyst was done by pathological examination in most of the patients. Abdominal US, which is the main non-invasive diagnostic method, is particularly essential

in the staging of a liver hydatid cyst and in the evaluation of treatment response [12,21]. In patients with a hepatic hydatid cyst, inactive cyst presentation which was confirmed by abdominal US is the treatment discontinuation criteria. Furthermore, CT scan can provide detailed information such as localization, size, invasiveness, and structure of the cyst. Follow-up of the treatment had an important effect on the determination of recurrences and follow-up of the calcified cysts [22]. Beyond being beneficial for the initial diagnosis, immunological tests are also used for the evaluation of surgery and treatment response [23]. In our study, serological tests were rarely useful to establish a definite diagnosis.

According to the World Health Organization (WHO), the usual dose of albendazole is 10 to 15 mg/kg/day in several one-month intervals separated by 14-day intervals. Treatment protocol as “three courses are routinely suggested, and more than six are usually not necessary” is recommended [8]. The reason for long duration of treatment in our patients is that all patients were complicated, and had more than one organ involvement. Furthermore the patients with hepatic involvement had late response to the treatment. In our patient group, high rate of cure was achieved with albendazole treatment. In Cappello et al. study, the mean duration of treatment was six months, except 120 months in one patient and reported that this patient had multiorgan involvement, same as in our study population [3]. Furthermore, it was concluded that it might be associated with prolonged treatment, advanced patient age, drug-cyst interaction, and disease severity [3,24]. However, an important issue in this setting is the patients’ compliance to the long treatment duration. In our study, the patients who were initially admitted to internal medicine attended to their scheduled visits more regularly. One patient with splenic involvement completely recovered with only albendazole treatment, while he was in the waiting list for surgery. Among the patients with muscle, vertebra, heart, spleen, brain, and kidney involvement, those with muscle involvement recovered with only albendazole treatment. No complications were observed. In other types of involvement, surgery was preferred due to the presence of life-threatening risks.

According to the WHO data, in more than 1,000 cases treated with benzimidazole and followed for 12 months, cure (complete disappearance of a cyst) was seen at a rate of 30%, whereas 30 to 50% showed cyst degeneration or significant reduction in the cyst size (improvement), and 20 to 40% showed no morphological changes (failure) [8]. Reporting the results of albendazole treatment, the cure rate was found to be 50 to 70% during a 12-month follow-up [25]. The high cure rate in the current study can be related to the use of albendazole, which is more effective compared to mebendazole, surgical intervention for complications, and prolonged medical therapy.

In the current study, relapse was seen in 23% patients following the treatment, and all patients with relapse had multiple cysts with multiorgan involvement. The mean time to relapse was 7 years, and relapse was seen 17 years after the initial treatment in one patient, which can be associated with re-infection. In other cases, relapse was thought to be related to re-activation. In the previous studies, the relapse rate was reported as 0 to 30% with mean time to relapse 3 to 4 years [8,26].

In addition, the most common complication in endemic regions is biliary tract rupture and superinfection 5 to 17% and of 5.1% respectively. The most common side effect related to albendazole treatment is elevated liver enzymes. In about 10 to 20% of

patients, elevated liver enzymes can be seen at any time during treatment. The levels usually return to normal by discontinuation of the treatment [8]. In our study, none of treatment-related side effects such as alopecia, vertigo, nausea, and allergic reactions were observed. Although elevated liver enzymes are rare, monthly control was performed. In patients with elevated liver enzymes, enzyme levels returned to normal in all patients when one cycle was cancelled. Furthermore, cyst-related complications such as massive hemoptysis were not observed, while short-term hemoptysis was seen during or after cyst rupture in patients with post-obstructive pneumonia. However, this complication was resolved with medical treatment and no recurrence was observed.

In conclusion, taking preventive measures are very crucial for the hydatid cyst disease, which is an important health issue in Turkey. Our study results suggest that albendazole treatment is an effective treatment option with minimal side effects in conjunction with appropriate patient selection and close collaboration with surgery.

Author Contributions

Sinem Gungor conceived paper, participated in study design, wrote manuscript, data analysis and interpretation, critically revised manuscript and approved final version. Murat Yalcinsoy conceived paper, oversaw data collection, conducted data analysis, wrote manuscript and approved final version. Olga akkan participated in study design, data analysis, and interpretation of data and revision of manuscript and approved final version. Bulent Altinsoy participated in study design, interpretation of data and revision of manuscript and approved final version. Zeynep Ferhan Ozseker participated in study design and interpretation of data; critically revised manuscript and approved final version. Aysun Misirlioglu participated in study design and interpretation of data, and performed surgical procedures and critically revised manuscript and approved final version. Semra Bati Kutlu participated in data interpretation and revision of manuscript, and performed laboratory procedures and approved final version. Sibel Arinc participated in study design and interpretation of data; critically revised manuscript and approved final version. Haitce Turker participated in study design and interpretation of data; critically revised manuscript and approved final version. Esen Akkaya participated in study design and interpretation of data; critically revised manuscript and approved final version. The authors declare that they have no conflicts of interest.

Competing interests

The authors declare that they have no competing interest

Financial Disclosure

The financial support for this study was provided by the investigators themselves.

Ethical approval

The study protocol was approved by the institutional Ethics Committee and it was conducted in accordance with the principles of the Declaration of Helsinki.

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