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Forty-five patients with hydatid liver cysts: Preoperative eosinophil and postoperative liver enzyme elevations after cystectomy and resection

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Abstract

Aim: Although the individualized and multidisciplinary treatment approach is important in the management of liver hydatid cyst, treatment modalities include medical, interventional or minimally invasive, and surgical. Our aim of the study was to investigate the efficacy of eosinophil number and percentage as an inexpensive and practical method that may be useful in the prediction of preoperative recurrence in patients who have undergone surgery for hydatid cysts.

Materials and Methods: Patients who underwent surgery for hydatid cyst of the liver at Ege University Hospital in the last 8 years were retrospectively reviewed. Age, sex, history of animal contact, cyst size, ELISA tests, preoperative neutrophils, preoperative eosinophils, preoperative albendazole use, postoperative albendazole use, postoperative AST, postoperative ALT, postoperative INR, complications, and recurrences were analyzed.

Results: A total of 45 patients with complete data sets were included. The mean preoperative neutrophil and eosinophil percentages were 60.20% (30%-96%) and 4.57% (1%-41%), respectively. Postoperative complications were seen in 2 patients (4.4%); these complications were collections in the operating lung and cystobiliary fistula. The mean postoperative AST, ALT, INR were 139.13 (12-636), 155.31 (7-569), 1.06 (0.9-2.6), respectively. The mean hospital stay was 13.4 days (2-90). The mean duration of albendazole use in the postoperative period was 3.66 months (1-24 months). Recurrence was observed in 9 cases (20%) during the follow-up period.

Conclusion: Although hydatid cysts and eosinophilia are reported in literature, association of eosinophilia with recurrence, size and prognosis is not reported. Our study showed that testing preoperative eosinophils and eosinophil/neutrophil ratio are inexpensive, easily accessible and effective in predicting recurrence. We believe that the validity of the tests will increase as eosinophil percentage and eosinophil/neutrophil percentage (ENPR), for which cut-off values have been established, become more widely used and tested in prospective controlled studies with larger groups.

Introduction

Hydatid cyst is a multisystemic disease caused by *Echinococcus granulosus* larvae. It is most commonly seen in the liver (50-70%) after human infection with hydatid larvae. Although less common, it may also be seen in the brain, lungs, and spleen. Some studies have reported that it can occur in the heart, oromaxillofacial region, wrist, pancreatic cyst, ischioanal fossa hydatid cyst, recipient kidney after renal transplantation, orbita, spinal canal, bladder and retroperitoneum [1-3].

The definitive host of echinococcus parasite is the canid dog. Intermediate hosts include cattle, sheep and humans. When vegetables in contact with eggs reach the intermediate host, echinococcus eggs are opened by pepsin and acid secretion in the stomach and the larvae enter the systemic circulation and can settle in the liver and other organs and cause disease. The response of mononuclear cells and eosinophils in the bod y to larvae reaching peripheral tissues in intermediate hosts causes inflammation [4-5].

Although the individualized and multidisciplinary treatment approach is important in the management of liver hydatid cyst, treatment modalities include medical, interventional or minimally invasive, and surgical. There is

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no clear-cut algorithm that can be said to be specific and correct for each and every patient.

Hepatic hydatid cysts are often asymptomatic until diagnosis. Especially in countries such as ours where agriculture is prevalent, patients may postpone going to a hospital. As a result of cyst enlargement, the patient may experience abdominal discomfort, abdominal pain and compression symptoms. It is important to be vigilant in diagnosing patients, as each patient may present with different symptoms. A hydatid cyst opening into the retroperitoneum may cause anaphylaxis, while a cyst growing in the liver may fistulize into the biliary tree. Increases in liver function tests and cholestatic enzymes may be seen after fistulization into the liver or compression of the biliary tree [6-7].

Indirect hemagglutination and ELISA tests have a sensitivity of 90%. Serologic tests may be false positive due to cross-reaction in cestode infections such as *E. multilocularis* and tapeworm Taenia solium, some helminthic diseases, malignancies, liver cirrhosis, and in patients with positive Ant-P1 antibodies. Detection of antigen 5 by immunodiffusion and immunoelectrophoresis aids in the diagnosis. Negative results of serological tests in the blood do not exclude the presence of the disease [8-9].

USG, CT and MRCP are important diagnostic tools. In general, the diagnosis is made by USG, but in some lesions the accuracy rate is increased by CT and MR. MRCP plays an important role in lesions involving the bile ducts. Albendazole treatment is an effective method in the treatment and follow-up of the disease [4,10].

Surgical procedures are recommended for cysts that are large, located superficially in the liver (in cases where the risk of spontaneous rupture is high and percutaneous surgery is inappropriate), in the WHO (IWGE) CE2-CE3b stage, septated with daughter vesicles, secondary infected, open to the bile duct or compress surrounding organs [11]. Surgery can be classified as conservative or radical. In radical procedures, the cyst is completely removed (such as regular hepatectomy, total pericystectomy), while in conservative procedures, the residual cyst cavity is left.

Materials and Methods

Patients who underwent surgery for hydatid cyst of the liver at Ege University Hospital in the last 8 years were retrospectively reviewed through the electronic patient record system. Age, sex, history of animal contact, cyst size, ELISA tests, preoperative neutrophils, preoperative eosinophils, preoperative albendazole use, postoperative albendazole use, postoperative AST, ALT, and INR values, complications, and recurrences were analyzed.

The study was conducted in accordance with the tenets of the Declaration of Helsinki, and ethical approval was granted by the Ethics Committee of Ege University Hospital with decision number 23-9.1T/42.

Statistical analysis

The data were analyzed using SPSS v26.0. After descriptive statistics, normality was assessed by Kolmogorov-Smirnov test. Student's t test was used to compare normally distributed data between groups, and Mann-Whitney U test was used to compare non-normally distributed data between groups. ROC analysis was used to determine the significance of the cut-off value, and the cut-off value was determined using the Youden index. Factors influencing recurrence were evaluated by logistic regression analysis.

Results

A total of 45 patients with complete data sets were included in the study. 13 patients were male (28.9%) and 32 were female (71.1%) with a mean age of 48.22 years (23-73). Animal contact was present in 30 patients (66.7%). The mean cyst size was 8.44 cm (1-24 cm) and the locations of the cysts are summarized in Figure 1 with their percentages.

The characteristics of the cysts according to Gharbi clas-

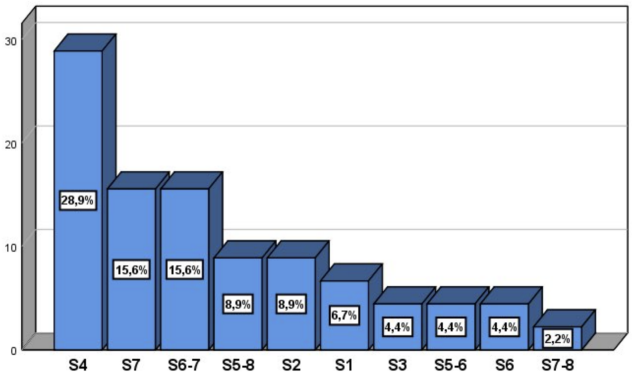

Figure 1. Location of the cysts and percentages.

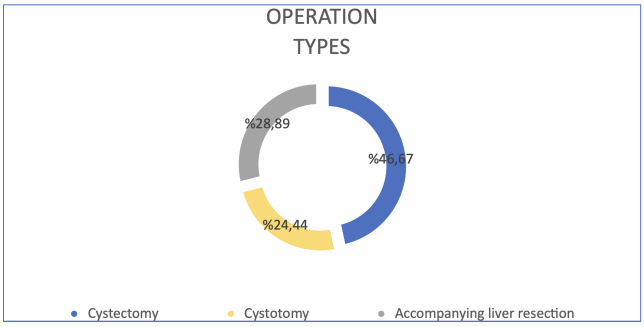

Figure 2. Types of operation and percentages

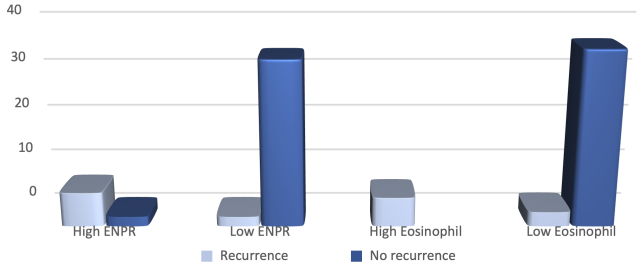

Figure 3. Difference between ENPR and eosinophil groups and recurrence.

Table 1. Continuous data set including demographic, laboratory values and treatment.

Parameters	Number	Min.	Max	Mean
Age	45	23	73	48.22
Size of the cyst	45	1.0	24.0	8.447
Neutrophil percentage	45	30	96	60.20
Eosinophil percentage	45	0	41	4.57
Preop. Albendazol use	17	1	12	3.53
Postoperative AST	45	12	636	139.13
Postoperative ALT	45	7	569	155.31
Postoperative INR	45	.9	2.6	1.067
Length of hospital stay	45	2	90	13.40
Postop, Albendazol use	40	1	24	2.78

Table 2. Comparisons between recurrence and non-recurrence groups.

	No recurrence	Recurrence	p value
Gender			
Female	26 (%81.3)	6 (%18.8)	0.742
Male	10 (%76.9)	3 (%23.1)	
Age (years)	50.44 (23-73)	39.33 (23-63)	0.062
Animal contact	24 (%80.0)	6 (%20.0)	1.000
Cyst size (cm)	8.46 (1-24)	8.38 (4-15)	0.944
ELISA positivity	28(%76.5)	8 (%23.5)	0.298
PAIR application	3 (%75.0)	1 (%25.0)	0.793
Neutrophil percentage	62.13 (37-96)	52.47 (30-66)	0.054
Eosinophil percentage	2.59 (1-8)	12.50 (2-41)	<0.001
Preop. Albendazol (months)	3.50 (1-12)	3.60 (2-6)	0.442
Type of operation			
Cystectomy	16 (%76.2)	5 (%23.8)	
Cystotomy	9 (%81.8)	2 (%18.2)	0.824
Liver res.	11 (%84.6)	2 (%15.4)	
Postop. AST	136.33 (12-636)	150.33 (49-259)	0.320
Postop. ALT	140.94 (7-569)	212.78 (37-493)	0.172
Postop. INR	1.033 (0.9-1.3)	1.20 (0.9-2.6)	0.548
Pathology – Active	26 (%81.3)	6 (%18.8)	0.742
Echinococcus			
Postop Albendazol (months)	3 (1-24)	1.50 (1-3)	0.109
Length of hospital (days)	12.83 (2-90)	15.67 (7-30)	0.110

sification were Gharbi 1 in 3 patients (6.7%), Gharbi 2 in 7 patients (15.6%), Gharbi 3 in 6 patients (13.3%) and Gharbi 4 in 2 patients (4.4%). In the remaining 27 patients, the Gharbi classification could not be determined on preoperative USG imaging. 34 patients (75.6%) had a positive Elisa test in the preoperative period and 11 patients (24.4%) were negative. 4 patients (8.9%) underwent PAIR before surgery. The patients who underwent surgery are summarized in Figure 2 according to the type of surgery.

The mean preoperative neutrophil and eosinophil percentages were 60.20% (30%-96%) and 4.57% (1%-41%), respectively. The mean duration of preoperative albendazole use was 3.53 months (1-12), and patients were discontinued at 3-week intervals and control liver function tests were evaluated.

Pathology reports showed that 13 patients (28.9%) had no active *Echinococcus granulosus* and 32 patients (71.1%) had active *Echinococcus granulosus*. Postoperative complications were seen in 2 patients (4.4%); these complications were collections in the operating lung and cystobiliary fistula. The mean postoperative AST, ALT, INR were 139.13 (12-636), 155.31 (7-569), 1.06 (0.9-2.6), respectively. The mean hospital stay was 13.4 days (2-90). The mean duration of albendazole use in the postoperative period was 3.66 months (1-24 months). Recurrence was observed in 9 cases (20%) during the follow-up period. The median disease-free survival was 56.23 months [50.37-62.11]. These parameters are summarized in Table 1.

History of animal contact, cyst location, Eliza results, preoperative PAIR use, type of surgery, pathologic results, age, cyst size, neutrophil percentage, eosinophil percentage, preoperative albendazole use duration, postoperative albendazole use duration were compared between recurrent and non-recurrent groups. The corresponding comparison results and p-values are summarized in Table 2. Only the eosinophil percentage showed a statistically significant difference between the two groups (<0.001).

When eosinophil percentages were found to be significantly different between the recurrence groups, Cox regression analysis was used to evaluate other parameters that could be used to predict relapse; in the model developed, neutrophil percentages, eosinophil percentages, and eosinophil percentage/neutrophil percentage ratio (ENPR) were compared; p values were $p=0.158$, $p=0.006$, $p=0.023$, respectively. Cut-off values for eosinophil percentage and ENPR that were found to be effective in predicting recurrence were evaluated by ROC analysis.

In the ROC analysis for ENPR, the area under the curve was 86.7% and the p-value was 0.001. Youden analysis was used for the cut-off value, which was found to be 0.1137. According to this cut-off value, patients were divided into 2 groups with high and low ENPR rates. In the recurrence group, 2 patients (22.2%) had a low ENPR rate while 7 patients (77.8%) had a high ENPR rate, p value <0.001. Similarly, ROC analysis was used for eosinophil percentage, the area under the curve was 86.7% and the p-value was 0.001. Youden analysis was used for the cut-off value, which was found to be 8%. According to this cut-off value, patients were divided into two groups as high eosinophil percentage and low eosinophil percentage. In the high eosinophil group, recurrence was found in 6 of 6 patients (100%), while in the low eosinophil group, recurrence was found in 3 of 39 patients (7.7%), and the difference was statistically significant ($p<0.001$). The comparison is shown in Figure 3.

Discussion

In our study, 45 patients were enrolled, and the aim of the study was to search for an inexpensive and practical method that may be useful in the prediction of preoperative recurrence in patients who have undergone surgery for hydatid cysts. Known recurrence factors include loss of cyst wall integrity during surgery and cyst wall integrity disruption during interventional procedures [12].

In this context, gender, age, history of animal exposure, cyst size, ELISA positivity, preoperative PAIR use, preoperative neutrophil percentage, preoperative eosinophil percentage, preoperative albendazole use, type of surgery, postoperative AST, ALT, INR levels, pathology reports, postoperative albendazole use, and length of hospital stay were compared in patients who developed recurrence during the follow-up period. In these comparisons, only eosinophil percentage was found to be significant in the recurrence group.

Yosra et al. showed the effect of postoperative albendazole use on recurrence in a pediatric study and emphasized the importance of this issue [13]. In our study, no association was found between postoperative albendazole use and recurrence, and it is believed that this may be due to patients' low compliance with treatment in the postoperative period. It was observed that patients' compliance with albendazole treatment was low, both because of its side effects and because of continued general discomfort after surgery.

PAIR and the newly developed modified catheteterization technique (MoCaT) technique are safely used in hydatid cyst disease, especially in Gharbi type 1 and 2 patients. Akhan et al. mentioned that PAIR and MoCaT technique can be used effectively and safely for Gharbi type 1 and 2 and is advantageous compared to surgery in terms of hospitalization and complication rates. It is effective and safe under appropriate conditions and must be supported by medical treatment [14]. In our study, PAIR was performed in only 4 patients and no significant statistical difference was found between PAIR and recurrence. Although it is believed that there was no significant difference due to the small number of patients, prospective studies with a large number of patients are needed in this regard.

The importance of medical treatment in patients with hydatid cysts treated with surgical or percutaneous interventional methods is well known and used in current treatment algorithms. Botezatu et al. mentioned the importance of medical treatment in their treatment algorithm and emphasized that combined treatment and multidisciplinary approach is the best treatment option [15].

On the other hand, Chiodini et al. emphasized that there have been no new drugs developed for hydatid cysts for a long time, albendazole has been used in this field for about 40 years and new targeted agents should be used. In this context, there is a need for new treatment agents that can reduce recurrence and help us to control the course of the disease [16].

In the study conducted by Fan et al. evaluating inflammatory parameters as predictive values in patients with hepatic hydatid cyst, platelet change interval, eosinophil percentage, neutrophil-lymphocyte ratio, ggt platelet ratio and ALP platelet ratio were evaluated in 114 patients. The ALP platelet ratio was found to be significant, and it was found that the platelet change interval and ALP platelet ratio decreased after successful surgery [17].

Similarly, Peters et al. evaluated serum IgE, parasite-specific serology, serum amyloid A, C-reactive protein, interleukin-2 receptor, cytokeratin fragments, eosinophil cell count and eosinophil cationic protein levels and found a statistically significant correlation only between PET/CT and serum Ig E levels in their study of 179 patients. They emphasized that it can be used both in the course of the disease and in early diagnosis [18].

Similarly, Cao et al. analyzed TGF-β1, p38MAPK and BMP-7 proteins in liver samples from 20 patients. They pointed out that the proteins known to be associated with fibrosis were significantly higher in the samples and emphasized their utility [19].

The problem of postoperative recurrence of hydatid cysts is an ongoing issue today. In order to prevent recurrence, parameters that affect recurrence and that can predict the development of recurrence are the subject of continuous study. To evaluate a test as a predictor, it should be inexpensive, effective, and have high sensitivity/specificity. In our study, we wanted to develop a new perspective on this issue and evaluated eosinophil percentage and eosinophil/neutrophil percentage ratio (ENPR). A cut-off value above a certain level could be determined and these tests were shown to be significant preoperatively in patients with recurrence.

Conclusion

Although there are many successful techniques used in the treatment of hydatid disease of the liver, the recurrence rate can be kept at a low level without major resection with minimal intervention. Although hydatid cysts and eosinophilia are reported in literature, association of eosinophilia with recurrence, size and prognosis is not reported. Our study showed that preoperative eosinophils and eosinophil/neutrophil ratio are inexpensive, easily accessible and effective in predicting recurrence.

We believe that the validity of the tests will increase as eosinophil percentage and eosinophil/neutrophil percentage (ENPR), for which cut-off values have been established, become more widely used and tested in prospective controlled studies with larger numbers of patients.

Ethical approval

Ethical approval for this study was received from Ege University Hospital Ethics Committee (decision number: 23-9.1T/42).

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