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Original Article IMMUNOLOGY & ALLERGY

Allergic symptoms in hydatid cyst; common or rare?

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ABSTRACT

OBJECTIVE: Hydatid cyst infections may follow a different course, ranging from asymptomatic to life-threatening conditions. The rupture of a hydatid cyst can lead to a variety of allergic reactionsfromurticaria to anaphylactic shock. This study aimed to investigate the frequency and diversity of allergic symptoms in patients with hydatid cysts and to explore their relationship between clinical and laboratory findings.

METHODS: This study included 106 patients diagnosed with hydatid cysts of the liverbetween January 2017 and February 2024.The demographic characteristics such as age, gender, clinical symptoms and laboratory results were recorded. The characteristics of patients with allergic symptoms were analyzedin addition to cyst rupture.

RESULTS: The median age of patients was 33 and 77% were male. Allergic symptoms were present in one out of every ten patients. Allergic symptoms were pruritus in 5 patients, acute urticaria in 2 patients, and anaphylaxis in 3 patients. Only 22% (n=23) of the patients had eosinophilia. The characteristics of ruptured and non-ruptured patients were compared and it was observed that hemoglobin level was lower and □-glutamyl transferase (GGT) level was higher in ruptured patients (p=0.032, p=0.015 respectively).

CONCLUSION: Although allergic symptoms are not very common in hydatid cysts, life-threatening events such as anaphylaxis may still occur. This risk should always be considered, especially in cysts at risk of rupture.

Keywords: Allergy; anaphylaxis; echinococcus; eosinophil; hydatid cyst; urticaria.

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Hydatid cyst (HC) disease, caused by Echinococcus granulosus, is a widespread parasitic infection that frequently occurs in endemic regions such as the Middle East, Mediterranean, and South America [1] Small cysts, which do not cause significant illness, may remain asymptomatic for many years or even permanently [2] Symptoms may develop if the cysts rupture or exert a mass effect. The most common presenting symptoms include fatigue, weight loss and right upper quadrant pain [3].

Allergic reactions and anaphylaxis are remarkable characteristics of HC [4]. These parasites are strongly associated with allergies due to their immunological properties, which help sustain the larvae within the human host, as well as their capacity to provoke clinical anaphylactic reactions in certain individuals [5]. Anaphylactic shock can occur spontaneously or as a result of cyst rupture, as described in various studies [6–8]. Several intraoperative factors may lead to hydatid fluid contamination, which can trigger anaphylacticand anaphylactoid reactions. These reactions range from mild urticaria to severe anaphylactic shock [9, 10].

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The incidence of intraoperative anaphylaxis varies, and the underlying mechanisms are complex. The incidence of immune-mediated anaphylaxis during anesthesia ranges from 1 in 10,000 to 1 in 20,000 [11]. In some cases, these reactions follow a type I hypersensitivity response, mediated by immunoglobulin E, in reaction to high plasma concentrations of echinococcus antigens [12]. Anaphylactic or anaphylactoid responses may also result from complement activation, leading to the release of anaphylatoxins such as complement 3a and 5a [13].

Research on the frequency and severity of allergic symptoms in hydatid cyst infection are limited [14–16]. In addition, the clinical characteristics of patients who have experienced allergic reactions and their relationship with cyst status have not been well studied [9, 17]. We aimed to comprehensively analyze patients diagnosed with hydatid cysts in terms of allergic reactions.

Highlight key points

- Hydatid cyst infections may cause allergic reactions ranging from mild pruritus to life-threatening anaphylaxis.
- Eosinophil count alone is insufficient to predict allergic manifestations in hydatid cyst disease.
- Even though allergic symptoms are uncommon, the potential for severe reactions necessitates heightened clinical vigilance in cysts at risk of rupture.
- Rupture of hepatic hydatid cysts during ERCP may precipitate acute allergic reactions, including anaphylaxis.
- Awareness of anaphylaxis risk is essential during ERCP and surgical management of hepatic hydatid cysts.

MATERIALS AND METHODS

This study was conducted in accordance with the World Medical Association's Declaration of Helsinki (2000). This study was approved by Health Sciences University Van Training and Research Hospital Non-Interventional Ethics Committee (date of the approval: 20.12.2024 decision number: GOKAEK-2024-02-18), and written informed consent was obtained from all patients.

We retrospectively screened electronic or record-based medical data of 104 patients diagnosed with a hydatid cyst of the liver. They were referred to our gastroenterology department with the suspicion of choledocolithiasis between January 2017 and February 2024. The hydatid cyst was detected using computed tomography (CT) and/or ultrasonography (USG), after which all patients underwent endoscopic retrograde cholangiopancreatography (ERCP). Hydatid cyst cases in the liver were radiologically categorized according to the World Health Organization Informal Working Group on Echinococcosis (WHO/IWGE) and the Gharbi classification [18]. Demographic characteristics such as age, gender, and clinical symptoms wereevaluated. The allergic symptoms in patients such as anaphylaxis, urticaria and pruritus were questioned in detail.Routine blood tests, including complete blood cell count, C-reactive protein (CRP), and liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, and direct bilirubin], were assessed in the patients.Patients were classified based on their eosinophil count as normal (<500/mm³) or eosinophilic (≥500/mm³). Additionally, eosinophilia is divided into 3 categories as mild (500–1500/mm³), moderate (1500–5000/mm³) and severe (>5000/mm³) according to the count of eosinophils in peripheral blood [19]. Serological diagnosis testscould not be performed because the required kits were not available in our hospital.The diagnosis was madebased on imaging methods and improvement after anti-parasitic treatment. ERCP demonstrated a radiolucent, roughly crescent-shaped shadow in the common bile duct in all patients. Cyst rupture was defined primarily according to radiological findings, and when applicable, confirmed intraoperatively. Clinical presentation alone was not considered sufficient for diagnosing rupture. After standard sphincterotomy, the hydatid cyst was removed from the extrahepatic bile ducts using a balloon catheter.In accordance with the WHO recommendation, albendazole was started 4 hours before the procedure and given to patients at a dose of 10 mg/kg for one month after the procedure [20].

Statistical Analysis

The statistical evaluation was performedusing SPSS software (version 21.0 for Windows; SPSS Inc., Chicago, IL, USA). The variables were assessed by using analytical methods (Kolmogorov-Smirnov and/or Shapiro-Wilks test) to determine whether they were normally distributed. Categorical variables were presented as frequencies and percentages, whereas continuous variables were expressed as means and standard deviations for normally distributed data and as medians with interquartile ranges for non-normally distributed data. In the comparison of numerical variables, the Mann-Whitney U test was used. The p-values less than 0.05 were considered statistically significant.

Table 1. The demographic, laboratory and radiological characteristics of the patients (n=104)

Age, years, median (IQR)	33 (25–56)
Gender, male/female n	60/44
CRP, mg/dL	10.00 (3.54–40.00)
Leukocyte /mm³	8640 (7980–12182)
Neutrophil mcL	5700 (4137–8947)
Lymphocyte mcL	1850 (1405–2352)
Hemoglobin g/dL	13.9 (12.4–15.3)
Eosinophil count (%)	
Normal 500> /mm³	77.9
Eosinohilia ≥500 /mm³	22.1
Mild	15.4
Moderate	3.8
Severe	2.9
AST, U/ L	33 (19–96)
ALT, U/L	41 (18–130)
GGT, U/L	68 (33–152)
ALP, IU/L	125 (82–236)
Total bilirubin, mg/dL	0.69 (0.45–1.75)
Direct bilirubin, mg/dL	0.30 (0.17–1.08)
USG cyst grade (%)	
Grade 1	16.3
Grade 2	28.8
Grade 3	40.4
Grade 4	12.5
Grade 5	1.9

The variables are shown as median (interquartile range) CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: □-glutamyl transferase; ALP: Alkaline phosphatase; USG: Ultrasonography.

RESULTS

A total of 104 patients with a median age of 33 [25–56] years and 57% malewereincludedin the study. The demographic, clinical, and laboratory characteristics of patients are summarized in Table 1. When patients were grouped according to eosinophil level; 81 (77.9%) patients had normal eosinophil level, 16 (15.4%) patients had mild eosinophilia, 4 (3.8%) patients had moderate eosinophilia, 3 (2.9%) patients had severe eosinophilia. Hydatid cyst cases located in the liver were radiologically categorized according to the WHO/IWGE and Gharbi classification; grade 3 cyst (n=42, 40%) was seen the most, grade 5 cyst (n=2, 2%) was seen at least ratio.

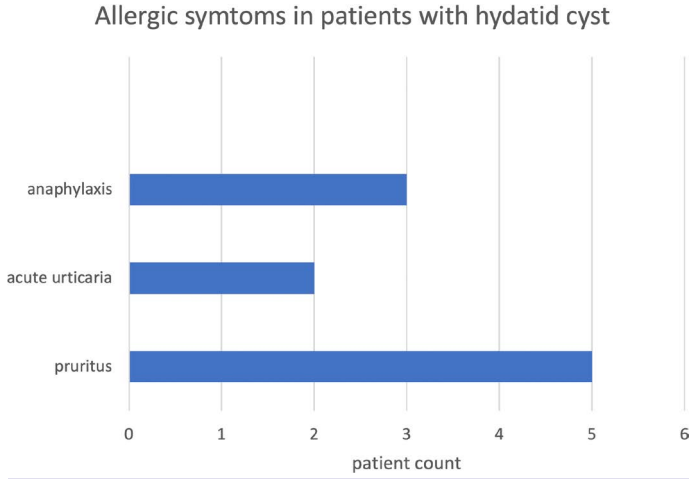


Figure 1. Distribution of allergic symptoms among patients with hydatid cyst.

Among the 104 patients analyzed for allergic symptoms, 10 reported complaints of pruritus, acute urticaria, hypotension, or shortness of breath (Fig. 1). Three patients experienced anaphylaxis (hypotension, shortness of breath) due to the antigenic properties of cyst fluid, which resulted from the rupture of the cyst into the biliary tract during ERCP. Acute urticaria was observed in 2 patients, while 5 patients only complained of itching. Detailed clinical and laboratory characteristics of the 10 patients with allergic symptoms are summarized in Table 2. It was observed thatGGT levelswere higher in ruptured hydatid cysts compared to non-ruptured cysts (117 U/L vs 55 U/L; p=0.01) and hemoglobin count lower in ruptured cyst (13.6 g/dL vs. 14.4 g/dL; p=0.03). Grade 3 cysts were the most common in both the ruptured and non-ruptured groups. In the ruptured group, the proportion of grade 4 cysts was significantly lower compared with both grade 2 and 3. Other clinical and laboratory comparisons are shown in Table 3. No statistically significant differences were observed between patients with elevated eosinophil counts and those with normal eosinophil counts (p>0.05).

DISCUSSION

Allergic symptoms were infrequent in this selected cohort of patients with hydatid cysts, highlighting the need for careful monitoring, especially in cases with cyst rupture risk, and observed that eosinophil counts were normal in the majority of patients despite the parasitic disease. In addition, a decrease in hemoglobin levels and increase in GGT were notable in cyst rupture.

TABLE 2. Demographic and clinical features of hydatid cyst patients with allergic symptoms

	Age years	G	Allergic symptom	USG cyst grade	Eos/ mm^3	CRP, mg/dL	WBC/ mm^3	NEU/ mcL	AST, U/ L	ALT, U/L	GGT, U/L	ALP, IU/L	Total bilirubin mg/dL	Direct bilirubin mg/dL
P 1	58	F	Pruritus	Type-3	250	4.5	7280	6320	153	207	21	86	2.98	2.09
P 2	56	M	Pruritus	Type-3	10	253	18400	16570	118	188	592	89	4.97	4.5
P 3	50	M	Pruritus	Type-3	280	136	11950	9950	72	68	95	236	15.90	9.95
P 4	66	F	Pruritus	Type-1	740	5.66	6170	2880	13	12	75	121	1.77	1.35
P 5	32	M	Pruritus	Type-3	10	136	19000	16480	233	329	689	740	6,28	5.57
P 6	24	M	Acute urticaria	Type-2	1380	160	8930	5680	13	17	41	60	0,48	0.24
P 7	28	F	Acute urticaria	Type-3	9020	3.5	21810	9950	73	313	298	387	2.69	1.79
P 8	57	M	Anaphylaxis	Type-1 (rupture of the biliary tract)	440	3.67	5770	4230	235	338	308	409	2.46	2.06
P 9	68	M	Anaphylaxis	Type -2 (rupture of the biliary tract)	190	15.4	6050	3660	37	140	377	350	0.64	0.32
P 10	26	M	Anaphylaxis	Type-3 (rupture of the biliary tract)	460	2.5	8040	7530	841	1365	39	80	3.90	3.01

P: Patient; G: Gender; F: Female; M: Male; USG: Ultrasonography; Eos: Eosinophil; CRP: C-reactive protein; WBC: White blood cell; NEU: Neutrophil; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: □-glutamyl transferase; ALP: Alkaline phosphatase.

Table 3. Comparison of characteristics of Hydatid cyst groups

	Ruptured hydatid cyst n=52	Non-ruptured hydatid cyst n=52	p
Age, years	32 (24–57)	34 (26–54)	0.961
Gender, male/female (%)	50/50	65.4/34.6	0.112
CRP, mg/dL	16.5 (3.6–60.7)	8.9 (2.7–28.2)	0.142
Leukocyte /mm³	9200 (7700–13300)	7980 (7027–11145)	0.130
Neutrophil mcL	6165 (4342–9950)	5085 (4002–8000)	0.148
Lymphocyte mcL	1810 (1470–2320)	1995 (1380–2367)	0.694
Hemoglobin g/dL	13.6 (12.0–14.6)	14.4 (12.9–15.6)	**0.032**
Eosinophil /mm³	245 (82–617)	175 (102–400)	0.443
AST, U/ L	42 (19–105)	24 (17–75)	0.133
ALT, U/L	54 (20–150)	31 (18–83)	0.180
GGT, U/L	117 (55–166)	55 (24–101)	**0.015**
ALP, IU/L	151 (89–259)	101 (65–221)	0.225
Total bilirubin, mg/dL	0.80 (0.48-2–08)	0.57 (0.26–1.00)	0.154
Direct bilirubin, mg/dL	0.34 (0.20–1.69)	0.25 (0.15–0.50)	0.087
USG cyst grade (%)			**0.001**
Grade 1	9.6	23.1	
Grade 2	38.5	19.2	
Grade 3	50	30.8	
Grade 4	1.9	23.1	
Grade 5	0	3.8	

The variables are shown as median (interquartile range). CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: □-glutamyl transferase; ALP: Alkaline phosphatase; USG: Ultrasonography.

In approximately 40–60% of patients with hydatid cysts, no clinical signs may be detected [21, 22]. Findings related to the disease may occur depending on the organ involved, the localization of the cyst, the pressure exerted by the cyst on the tissue where it is located, complications and immune reactions [21]. In some cases, allergic symptoms such as redness, itching, and blistering may be the only signs of hydatid cyst rupture [15]. Anaphylactic shock is a severe complication of echinococcosis treatment, but it is challenging to predict whether patients infected with Echinococcus will experience this complication during surgery. Although studies have shown that HC can be diagnosed at any age, it is generally reported that the disease becomes symptomatic years after initial contact, typically in childhood [23, 24]. In the HERACLES study, it was found that the prevalence of HC increased gradually with age in Turkiye [25]. In the study conducted in Erzurum by Yılmaz et al. [24], the highest HC positivity was found in the 31–45 age group (28.3%). Similarly, the median age was 33 years in our study. This may be due to the fact that the disease remains asymptomatic for many years after contact.

In general, there are no biochemical and hematological diagnostic tests specific for HC or changes in these tests indicating the disease. Elevated bilirubin and transaminase levels may be observed in patients with liver involvement and biliary obstruction. In cases of cyst leakage or rupture, eosinophilia may be observed in hemogram or peripheral smear, generally different from cases with intact cyst membrane [26]. In the study conducted by Sahin et al. [27] total bilirubin value was found to be high in 16.7% of the patients and AST and ALT levels were found to be high in 19.1%. In a study conducted by Isik et al. [28] with 170 patients, the most common laboratory finding was anemia (25.3%), while 19% of the patients had eosinophilia, 15% had AST, 19% had ALT, and 11% had elevated total bilirubin. In our study, 45.1% of patients AST and ALTlevels were found to be high

and 29.8% of patients total bilirubin level was found to be high. The absence of anemia in our patients may be due to the high altitude of Van. However, haemoglobin level was lower and GGT level was higher in the ruptured hydatid cyst group. This was thought to be due to leakage of antigenic cyst fluid into the bile duct due to rupture.

Eosinophilia in tissue and peripheral blood is observed during infections caused by helminths, along with increased mast cell activity. Eosinophils cause parasite death by releasing enzymes from their granules in the presence of complement and/or antibodies [29]. Eosinophil-mediated parasite expulsion is associated with increased Th2 responses following the production of cytokines such as IL-4, IL-5, and IL-13 [26, 30, 31]. In cases of cyst leakage or rupture in patients with hydatid cysts, eosinophilia may be seen on haemogram or peripheral smear, unlike in patients with intact cyst membrane [26]. Various studies have shown that the eosinophil ratio in hydatid cyst cases ranges from 18% to 34% [32–35]. In our study, the rate of eosinophilia was calculated as 22%. The variability in the reported percentages may be due to the concomitant presence of other parasitic diseases that can cause eosinophilia, or the location of the cysts and the disruption of the integrity of the cyst.

Major factors such as the organ involved with the cyst (such as lung, liver, pancreas), its location within the organ, its relationship with surrounding structures, the size of the cyst and whether the wall integrity is preserved may affect the clinic [26]. If the cysts rupture, they may remain asymptomatic or may cause pruritus, urticaria, angioneurotic edema, systemic anaphylaxis, and even anaphylactic shock which may lead to death after the allergic proteins in the cyst content enter the systemic circulation [5]. A total of 5 patients had pruritus and sensitivity in the right upper quadrant, 2 patients had urticarial plaques all over their bodies.Laboratory tests revealed eosinophilia. Hydatid cysts should be considered in the differential diagnosis if urticarial lesions are accompanied by elevated eosinophil levels, as seen in these cases, which may be observed in patients with hydatid cysts. Intermittent leakage of echinococcal cyst fluid can cause eosinophilia and lead to urticaria [36]. This suggests that urticaria occurs secondary to hyperinflammation in the body. In addition, eosinophils may play a role in the immune response to secondary infections, suggesting a more immunomodulatory role [37].

In the literature, the incidence of anaphylactic shock following cyst rupture has been reported as 2% [38, 39]. Jianrong Ye et al. [17] observed that intraoperative anaphylactic shock occurred in 18 out of 1426 patients who underwent surgery for echinococcosis over a five-year period. In our study, anaphylaxis was observed in 3 of 104 patients, similar to the other studies [17, 38, 39].

Limitations

This study has several limitations. Firstly, its retrospective design inherently limits the ability to establish causal relationships. Secondly, it was conducted at a single center, which may affect the generalizability of the findings to broader populations. Lastly, the relatively small number of patients presenting with allergic symptoms reduces the statistical power and reliability of subgroup analyses. These factors should be considered when interpreting the results.

In this study, patients with pulmonary hydatid cysts were excluded, as only patients who were diagnosed by ERCP in the gastroenterology clinic were included. The other limitation of our study is that a serological test could not be performed due to the lack of necessary reagents and equipment during testing. It was identified as a hydatid cyst through ERCP and imaging methods. In addition to the host's immunity, the integrity of the cyst wall, the stage of the cyst and the organ involved also affect the immune marker test result. Therefore, a negative serological test result never excludes the presence of a hydatid cyst [40]. Since serological tests were not available during the study period, the diagnosis was based mainly on imaging and clinical response, which may have introduced a risk of misclassification.

Due to the limited number of patients with allergic symptoms and cyst rupture, a multivariate logistic regression analysis could not be reliably performed; therefore, the observed associations should be considered descriptive rather than independent predictors.

The small number of patients with allergic manifestations limits the statistical power and reliability of subgroup analyses; therefore, these findings should be interpreted as descriptive rather than conclusive.

Conclusion

Hydatid cyst disease remains a significant public health concern in our country. It is particularly important to carefully evaluate patients presenting with vague abdominal complaints or allergic symptoms, as well as those with anamnesis raising suspicion for hydatid cysts, especially in regions endemic for the disease. Given the risk of anaphylaxis associated with cyst rupture, appropriate preventive measures should be implemented during surgical procedures.

Ethics Committee Approval: The Health Sciences University Van Training and Research Hospital Non-Interventional Ethics Committee granted approval for this study (date: 20.12.2024, number: GO-KAEK-2024-02-18).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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