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Demographic and Clinical Characteristics of Patients with Anaphylactic Shock after Surgery for Cystic Echinococcosis

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Abstract. We reviewed the records of 446 patients who were treated surgically for cystic echinococcosis (CE) to identify risk factors for anaphylactic shock. Of 446 patients, 10 had final diagnoses of anaphylactic shock induced by CE; none died. The incidence of anaphylactic shock was significantly higher in younger age groups ($P < 0.001$) and in patients with pulmonary cysts. Anaphylactic shock induced by CE appears to differ from type I immediate hypersensitivity shock, which suggests that in CE, shock may be caused by a combination of immediate hypersensitivity and endotoxic shock. This possibility suggests that additional precautions should be taken during surgery. These precautions include reducing intracystic pressure, which would prevent possible leaked liquid from reaching other organs by surrounding the cyst with sterile gauze and decrease the chance of spreading the echinococcus; preventing antigen from contacting other tissues where it might trigger anaphylaxis; and resecting the cyst completely when feasible.

INTRODUCTION

Cystic echinococcosis (CE) is an anthropozoonosis with a worldwide distribution and is caused by the cestode *Echinococcus granulosus*. Cysts represent the larval stage of the helminth and are found in intermediate hosts such as sheep, goats, camel, and cattle. Humans are accidental intermediate hosts; dogs and other canids are definitive hosts.[1] Humans become infected by ingesting eggs of the parasite. Infection can occur when humans eat foods contaminated with canine feces or pet dogs that harbor eggs on their fur and then touch their fingers to their lips.[2]

Anaphylaxis, including urticaria, edema, and respiratory symptoms, may occur in persons infected with *E. granulosus.* Shock may result if fluid from the cyst is released into a host who has developed IgE from previous leakage of fluid.[2] A severe anaphylactic shock response can result from release of fluid from the cyst, either spontaneously or after trauma or surgery.[2]

This study was undertaken to attempt to determine the risk factors for anaphylactic shock to minimize the risk for perioperative anaphylaxis.

MATERIALS AND METHODS

A single investigator reviewed the records of 446 consecutive patients with CE who were treated surgically at First Affiliated Hospital of Xinjiang Medical University (Urumqi, People's Republic of China) during January 2008–August 2009. The reviewer recorded the demographic and clinical features of the patients. A diagnosis of anaphylactic shock caused by CE was confirmed in 10 of the patients (6 female patients and 4 male patients). We ruled out perioperative complications, such as infections and allergic shock caused by medication, other parasitic infections, or atopic diseases by means of clinical, laboratory, and imaging methods appropriate for each patient. To analyze the results, we designated the 10 patients with anaphylactic shock as group I and the 436 patients without anaphylactic shock as group II.

General anesthesia was used for all patients. Before the cysts in both groups of patients were surgically treated, the patients' American Society of Anesthesiologists grade was II, which was defined as "patient has mild to moderate systemic disturbance that may or may not be related to the disorder requiring surgery (e.g., essential hypertension, diabetes mellitus)."[3] All patients underwent pericystectomy; cysts in bone were removed by radical resection of the affected bone.

Our research focused on cases of perioperative anaphylactic shock in patients who were under continuous surveillance by anesthesiologists. Diagnostic criteria followed the standards of the National Institute of Allergy and Infectious Diseases.[4] Of the symptoms and signs listed in the standards, the most pertinent in our surgical setting included hypotension; dysrhythmia; bronchospasm; flushing; urticaria; angioedema; morbilliform rash; piloerection; edema of lips, tongue, and uvula; periorbital erythema; conjunctival erythema; excessive tear formation; cough; stridor; and rhinorrhea.

To investigate a possible correlation with levels of antibodies, we used the dot immunogold filtration assay (DIGFA).[5] This technique is a method of immunologic detection with a microporous membrane as solid support and immunogold for labeling. The procedure is used to detect antibody against *E. granulosus* in serum. Its advantages are simplicity and rapidity, and it does not need special equipment. We performed four tests with the DIGFA to determine the correlation between reaction intensity and incidence of anaphylactic shock.

The Internal Review Board of the First Affiliated Hospital of Xinjiang Medical University granted permission for this retrospective review of hospital records.

Statistical analysis. Continuous variables are presented as median and interquartile range. The Mann-Whitney U test was used to compare continuous data between groups. Categorical variables are presented as counts and percentages, and Fisher's exact test was used to assess associations between discrete and group variables. Analyses required a P value ≤ 0.05 to be considered statistically significant and were performed by using SPSS 15.0 statistics software (SPSS Inc., Chicago, IL).

RESULTS

Patients. Patient age distributions are summarized in Table 1. The 10 patients in group I were significantly younger than

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TABLE 1

Age distribution of patients who underwent surgery for cystic echinococcosis with and without anaphylactic shock during the perioperative period, People's Republic of China*

Age intervals (years)	Group I: anaphylactic shock, no. (%)	Group II: no anaphylactic shock, no. (%)
0–10	2 (20)	14 (3.2)
11–20	3 (30)	21 (4.8)
21–30	0 (0)	99 (22.7)
31–40	4 (40)	115 (26.4)
41–50	0 (0)	100 (22.9)
51–60	0 (0)	46 (10.6)
61–70	0 (0)	26 (6.0)
71–80	1 (10)	14 (3.2)
81–90	0 (0)	1 (0.2)

*Difference between the two groups was statistically significant ($P < 0.001$, by Fischer's exact test).

those in group II ($P < 0.001$). As indicated in Table 2, there was no significant difference between groups I and II for other variables such as sex, ethnicity, residence in a livestock farming area, history of drug allergy, time of residence in a farm area, or having had contact with dogs or cattle.

Cystic echinococcosis. Variables related to CE are summarized in Table 3. There was no significant difference between the two groups for number of patients with a unilocular or multivesiculated cyst, cyst infection, recurrence of echinococcosis, and results of DIGFA. Cysts that occurred in the lungs and cysts that ruptured were significantly associated with anaphylactic shock. Fifty percent of the patients in group I, but only 9.4% in group II, had cysts in the lung ($P = 0.002$). Forty percent of patients in group I, but only 11.2% in group II, had a ruptured cyst ($P = 0.022$). Hepatic cysts were classified as shown in Table 3. Most hepatic cysts were CE2[6] (85.7% in group I and 66.6% in group II), and there was no significant association between the classification and anaphylactic shock.

TABLE 2

Characteristics of patient with cystic echinococcosis, People's Republic of China*

Characteristic	Group I: anaphylactic shock, n = 10	Group II: no anaphylactic shock, n = 436	*P*
Sex, no. (%)			
F	6 (60.0)	227 (52.1)	0.754
M	4 (40.0)	209 (47.9)	
Ethnic origin, no. (%)			
Hui	0 (0)	24 (5.5)	1.000
Kazakh	1 (10.0)	42 (9.6)	
Mongolian	0 (0)	22 (5.0)	
Han	7 (70.0)	261 (59.9)	
Uigur	2 (20.0)	78 (17.9)	
Other	0 (0)	9 (2.1)	
Patients from livestock-farming areas, no. (%)			
Yes	8 (80.0)	225 (51.6)	0.109
No	2 (20.0)	211 (48.4)	
Mean years in farm area (IQR)	4.5 (0.0–13.0)	18.0 (0.0–30.0)	0.133
Mean years of contact with dogs (IQR)	9.5 (5.0–13.0)	6.5 (0.0–20.0)	0.654
Mean years of contact with cattle (IQR)	5.0 (1.0–8.0)	0.0 (0.0–20.0)	0.786
History of drug allergy, no. (%)			
Cefalotin	0 (0)	3 (0.7)	1.000
Penicillin	1 (10.0)	32 (7.3)	0.540
Sulfa	0 (0)	9 (2.1)	1.000
Thromycin	0 (0)	3 (0.7)	1.000

*$P > 0.05$; IQR = interquartile range.

TABLE 3

Characteristics of cysts and serologic values for patients with cystic echinococcosis, People's Republic of China*

Characteristic	Group I: anaphylactic shock, n = 10	Group II: anaphylactic shock, n = 436	*P*
No. cysts			
≤ 3	5 (50)	319 (73.2)	0.146
> 3	5 (50.0)	117 (26.8)	
No. daughter cysts			
≤ 3	2 (20.0)	109 (25.0)	1.000
> 3	8 (80.0)	327 (75.0)	
Ruptured cysts	4 (40.0)	49 (11.2)	0.022†
Infected cysts	3 (30.0)	41 (9.4)	0.066
Recurrence	2 (20.0)	136 (31.2)	0.731
Location of cysts			
Liver‡	7 (70.0)	368 (84.4)	0.202
CE1	1 (14.3)	42 (11.7)	1.000
CE2	6 (85.7)	239 (66.6)	
CE3	0 (0.0)	29 (8.1)	
CE4	0 (0.0)	30 (8.4)	
CE5	0 (0.0)	19 (5.3)	
Lung	5 (50.0)	41 (9.4)	0.002†
Bone	0 (0)	33(7.5)	1.000
Abdomen	0 (0)	16 (3.7)	1.000
Spleen	0 (0)	6 (1.4)	1.000
Thorax	1 (10.0)	4 (0.9)	0.108
Cardiac muscle	0 (0)	1 (0.2)	1.000
DIGFA§			
EgCF			
–	2 (20.0)	124 (28.4)	0.308
±	3 (30.0)	79 (18.1)	
+	2 (20.0)	143 (32.8)	
++	3 (30.0)	45 (10.3)	
+++	0 (0)	5 (1.1)	
EgP			
–	2 (20.0)	153 (35.1)	0.250
±	3 (30.0)	82 (18.8)	
+	3 (30.0)	110 (25.2)	
++	1 (10.0)	45 (10.3)	
+++	1 (10.0)	6 (1.4)	
EgB			
–	3 (30.0)	176 (40.4)	0.268
±	1 (10.0)	56 (12.8)	
+	2 (20.0)	103 (23.6)	
++	3 (30.0)	46 (10.6)	
+++	1 (10.0)	15 (3.4)	
Em2			
–	6 (60.0)	259 (59.4)	0.837
±	3 (30.0)	81 (18.6)	
+	1 (10.0)	45 (10.3)	
++	0 (0)	11 (2.5)	

*Values are no. (%). DIGFA = dot immunogold filtration assay; EgCF = crude hydatid fluid cyst; EgP = *Echinococcus granulosus* protoscolex antigen; EgB = *E. granulosus* antigen B; Em2 = *E. multilocularis* metacestode antigen.

†$P < 0.05$ indicates a significant difference between those with and without anaphylactic shock.

‡Liver cysts were classified as CE1 = unilocular spherical cysts with a clear visible wall; CE2 = multiple daughter cysts entirely filling the maternal cyst; CE3 = cyst with multiple cysts arranged peripherally along the cyst wall and the membrane may be collapsed or detached showing the water-lily sign; CE4/CE5 = inactive cysts that have lost their fertility and appear as a ball of wool and may have calcifications in the wall (CE5).

§There were 40 (9.2%) missing values for those without anaphylactic shock.

Laboratory examination. Laboratory examination results for patients in group I before and within 24 hours after surgery are summarized in Table 4. The neutrophil count increased significantly after the surgery, and the lymphocyte and eosinophil counts decreased significantly.

Clinical aspects. The right lung of one patient in group I contained a single echinococcal cyst that ruptured and became infected. Other patients had multiple stage CE2 cysts that did not rupture or become infected. Two patients had a cyst more than 10 cm in diameter.

Uninfected cysts and cysts with high pressure were punctured before detachment to avoid rupture during detachment.

TABLE 4
Laboratory results before and within 24 hours after surgery for 10 patients with cystic echinococcosis who had anaphylactic shock, People's Republic of China*

Cells	Before surgery, no. (IQR)	After surgery, no. (IQR)	*P*
Total leukocytes (10^9/L)	7.79 (6.10–8.50)	9.71 (8.34–12.74)	0.064
Neutrophils (10^9/L)	3.63 (2.60–5.21)	9.08 (7.27–10.57)	0.004†
Lymphocytes (10^9/L)	2.20 (1.90–3.31)	1.21 (0.78–1.52)	0.004†
Monocytes (10^9/L)	0.54 (0.40–0.70)	0.48 (0.36–1.16)	0.309
Eosinophils (10^9/L)	0.49 (0.37–0.70)	0.19 (0.11–0.49)	0.020†
Basophils (10^9/L)	0.01 (0.00–0.06)	0.02 (0.00–0.03)	0.297

* IQR = interquartile range.
† $P < 0.05$.

Cysts ruptured with minimal leakage during cyst dissection in five patients in group I and with moderate leakage in the other five patients in group I.

Anaphylactic shock occurred 5–25 minutes after cyst puncture. Five patients had rashes. Within 5–25 minutes from cyst puncture or rupture, eight patients had increasingly coarse breath sounds with wheezing, airway resistance exceeding the baseline resistance of 10 cm of H_2O/liter/second, hypoxemia, and hypotension at the same time or later with a decrease of more than 30% from the baseline value. Six patients had sinus tachycardia with more than 120 beats per minute.

All 446 cases received corticoid[7] before surgery to prevent anaphylactic shock. Patients with anaphylactic shock were given pure oxygen and fluid therapy while under general anesthesia. The fluid therapy, which aimed to supplement the third-space fluid, included lower substituted (i.e., a low ratio of hydroxyethyl groups to glucose residues) hydroxyethyl starch solutions (hydroxyethyl starch 130/0.4 and NaCl injection; Voluven®; Fresenius Kabi, Bad Homburg, Germany), Ringer's, gelofusine, serum suspension, erythrocyte suspension, and others, at an average rate of 14.6–60.5 mL/kg.

We used epinephrine immediately for patients whose systolic pressure was less than 60 mm of Hg. Patients with shock with systolic pressure more than 60 mm of Hg received dopamine for 2–3 minutes and observed. If the blood pressure continued decreasing, epinephrine was given. If the blood pressure increased, dopamine was continued. Five patients received epinephrine (total amount = 50 µg–1 mg at 5–25 µg/minute. Epinephrine was given as a single dose in the beginning and a second dose five minutes later. The epinephrine pump was used if the blood pressure could not be sustained after three single doses. Four patients had persistent hypotension, and a dopamine pump with 2 mg/kg/minute continuous infusion for 35–125 minutes was used for them.

DISCUSSION

Although the occurrence of anaphylactic shock remains unpredictable, the important findings in this study are that most patients with hydatid cysts and anaphylactic shock were young and most of the lesions were in the lungs.

Age-related occurrence of anaphylactic shock was reported by Alves and Sheikh in their study of emergency department admissions in the United Kingdom. Anaphylactic shock caused by foods was significantly more common in young people, response to drugs was higher in older persons, and there was no age relationship for shock from venoms.[8] The incidence of anaphylactic shock caused by all factors increased with age up to approximately 55 years, then decreased, and was most common in persons 15–54 years of age.[9] The possible reasons for the higher incidence of anaphylactic shock we observed in younger persons and the reported higher incidence of food reactions might reflect relative differences in immune reactions to different allergens,[4] with possible different amounts of IgG and IgE produced, resulting in different likelihoods of shock. An alternative hypothesis is that in crossing the intestinal wall after ingestion, the larvae set up an immune reaction resembling that of food allergy, which could account for the similar incidences with age. Another possibility is that children have lower immunity, and the complex of antigen and antibody caused by cyst leakage is relatively in excess in children, resulting in a stronger hypersensitivity reaction leading to shock.

Minor signs of anaphylactic reaction caused by echinococcal fluid include rash, macules, urticaria, pruritus, conjunctival edema, and coughing. More severe symptoms range from dyspnea, hypotension, bronchospasm, throat spasm, and convulsions to overt anaphylactic shock and death. The reactions usually occur in the first 1–15 minutes after contact with hydatid fluid, but mostly within 3–5 minutes.[10] In the patients we reported in this study, the reactions appeared 5–15 minutes after fluid leakage that was visible to the surgeon or anesthesiologist. This slower onset of symptoms may be caused by improved surgical techniques and restriction of practice to liver and thoracic surgeons who were highly experienced in surgery on cysts in the part of the body containing the cyst and to adequate measures to protect against cyst puncture, all of which lead to less leakage. We believe that minimizing exposure of tissues and blood to cystic fluids may be crucial in avoiding anaphylactic shock and sudden death.

Felix and others[11] found that cardiac failure occurred earlier than respiratory failure in type I hypersensitivity under therapy of pure oxygen. They reported that cardiac muscle injury and left ventricular pump failure occurred earlier than hypoxemia. However, in our study, the abnormal augmentation of airway resistance was accompanied with wheezing by auscultation, and hypotension occurred with or after the decrease of blood oxygen concentration. These findings suggest that the mechanism of anaphylactic shock caused by CE might be different from that of type I hypersensitivity.

Some authors have considered that anaphylactic shock caused by CE might be IgE-mediated type I hypersensitivity. However, levels of IgG also increase in patients with CE,[12] and IgG, like IgE, can induce anaphylactic shock.[13]

Eosinophils concentrate in the airway and are activated during hypersensitivity; the release of multiple basic proteins is an important reason for high reactivity in the airway.[14] Eosinophils participate in inflammation and are associated with cell activation, such as synthesis and release of leukotriene C4,LT-C4. However, in our study, eosinophil counts decreased significantly compared with those before surgery, differing from the pattern of eosinophil change in type I hypersensitivity. This finding also supports the hypothesis that the mechanism of anaphylactic shock caused by cystic fluid might be different from that of type I hypersensitivity.

Once the diagnosis of anaphylactic shock caused by cystic fluid is confirmed, it is essential to support the circulatory and respiratory systems with immediate injection of epinephrine, adrenocortical hormones, fluid treatment, and vasoactive agents, in addition to anti-shock treatment, such as pure oxygen, thermal insulation, and cardiac drugs. Leakage

from an echinococcal cyst, similar to what happens with type I hypersensitivity shock, releases large amounts of vasoactive materials that block vasoconstriction and cause failure of peripheral circulation. Therefore, besides the general measures of anti-shock treatment indicated above, epinephrine should be used immediately in small doses: up to 50 μg each time for adults, and pediatric dosing for children, with a dosing interval of 5 minutes (Li Y and others, unpublished data).

Persistent and severe hypotension unresponsive to three consecutive doses should be considered to have cytotoxic and synergic effects that require use of vasoactive agents until the condition stabilizes. Four patients in our group I had persistent hypotension after the use of epinephrine; their circulatory system was gradually stabilized with a dopamine pump infusion. Adrenocortical hormones can inhibit the differentiation and proliferation of immune cells, consequently reducing the production of antibodies, decreasing vessel permeability, reducing inflammation, stabilizing lysosomal membranes, and preventing release of a variety of enzymes. Therefore, the use of intravenous dexamethasone can be advantageous.

Anaphylactic shock caused by CE might also share some characteristics with endotoxic shock, in which fluid shifts into the third space and presents as circulatory failure. A single dose of vasoconstrictive drugs may not be enough to maintain effective circulation. Fluid loss in the third space requires immediate fluid replacement with options ranging from Ringer's, hydroxyethyl starch solutions, gelofusine, and other artificial colloid fluids to the infusion of plasma and packed erythrocytes. We believe that once rupture of an echinococcal cyst is diagnosed and there is hypersensitivity or shock, which requires immediate management, immediate surgical intervention is also important. Surgery should be as radical as possible.

Early detection of reactivity in patients with CE would be a step toward reduction of deaths from anaphylactic shock, but this is impossible with the current state of our knowledge. We found that DIGFA results have no predictive value for susceptibility to anaphylactic shock. However, our study shows that younger age and presence of a pulmonary cyst are risk factors for anaphylactic shock. Anaphylactic shock caused by CE appears to have different characteristics from type I rapid-onset hypersensitivity and might have some of the characteristics of endotoxic shock. The cause of anaphylactic shock is still unclear, but antigens in the cyst and cyst fluid may have a role in inducing shock.

The main findings of our study are that most patients with anaphylactic shock were young and most of the lesions were in the lung. Other than these findings, anaphylactic shock as a result of surgery on an echinococcal cyst remains unpredictable and its pathogenesis remains elusive. More research is needed to explore this field.

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