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ORIGINAL ARTICLE

Hematological and Pro-inflammatory Immune Profiles in Patients with Cystic Echinococcosis: A Comparative Study of Total and Differential White Blood Cell Counts

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ABSTRACT

Cystic echinococcosis (CE), caused by *Echinococcus granulosus*, represents a chronic zoonotic infectious disease characterized by complex immune responses in the host. This study evaluated total and differential counts of white blood cells (WBCs) as well as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) in serum from patients with hydatid disease compared to matched healthy controls. Fifty-one patients diagnosed with cystic echinococcosis and twenty-nine matched healthy controls in terms of age and sex were enrolled in this study. Automated complete blood count (CBC) analysis was performed for evaluation of the hematological parameters and ELISA was used for evaluation of the cytokines. Results revealed significantly elevated total WBC counts among patients >15 years of age, but not in the <15 group ($p < 0.05$). The differential analysis revealed eosinophilia in all groups of infected persons compared to healthy controls for each group; elevated proportions of neutrophils and decreased proportions of lymphocytes compared with healthy controls were also present in all groups of infected persons compared to healthy controls. The absolute eosinophil counts from the patients (277-371/mm³) were significantly greater than those of the controls (91-127/mm³). The mean concentration parameters for cytokines from patients had indicated an average of 14 times as much IFN-γ (119.05 vs. 81.22 pg/ml, p=<.05) and 3 times more TNF-α (161.50 vs. 58.06 pg/ml), relative to control subjects. These results suggest that CE demonstrates a clear predominance of a Th1-like immune response coupled with significant alterations of peripheral leukocytes. Based on the findings related to the hematology and cytokine parameters, additional potential biomarkers for the diagnosis and follow up of CE exist.

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1- INTRODUCTION

Hydatid disease (cystic echinococcosis), a major public health issue around the world (especially in endemic regions) [1], is caused by the larval stage of tapeworms belonging to the genus *Echinococcus*. *E. granulosus* is the primary cause of cystic echinococcosis; *E. multilocularis* is the only other genus to cause alveolar hydatid disease but does so at much lower rates [2]. Humans become accidentally infected and serve as an intermediate host when they come into contact with an infected dog (especially children) or consume foods that have not been washed correctly (especially those that contain parasite eggs) and are contaminated with dog feces [3]. After entering a human (definitive) host, the parasite has numerous methods to bypass host immune responses to ensure persistence and give rise to a long-term infection. A state of chronicity is indicated by the presence of both humoral and cellular immune responses against the parasite being readily detectable [2].

Hydatid cysts can stay asymptomatic until they have a sufficient amount of growth. How they present clinically may vary further according to the organ involved and size of the cyst(s). An example would be, if the cyst is small and its wall is calcified, no symptoms would be produced. There is a complex and dynamic process of the interaction of hydatid cysts with the human immune system, which greatly impacts both the development of the hydatid infection and how the infection will typically manifest in the individual and the outcome of that infection [4]. Once the cyst becomes established in its host, it becomes enclosed in fibrous tissue that includes epithelial cells, eosinophils, and giant cells, therefore reflecting the hosting body's immune attempt to wall off the infection [4].

In addition to having a local presence, hydatid cysts impact the whole body by affecting blood cells at multiple locations throughout the body and causing select types of anemia [6] as well as altering the profile of all white blood cells. A recent 2024 study on inflammatory markers in patients with pulmonary hydatid cysts demonstrated that specific subsets of white cells (leukocytes) may serve as predictors for significant clinical complications. Following surgery, eosinophil counts greater than 230 cells/μL were found to be associated with a seven-and-a-half times greater likelihood of perforation of the cyst; neutrophil counts above 8,815 cells/μL were associated with a thirteen-and-six-tenths increase in the likelihood of perforating a cyst [7]. This suggests that leukocyte profile could potentially serve not only as an indicator of the host's immune status, but also as a potential predictor of the likelihood of cyst rupture and subsequent dissemination/secondary cyst development.

Despite these advances, significant knowledge gaps persist regarding the precise mechanisms by which *Echinococcus granulosus* modulates leukocyte function. Furthermore, the factors determining individual variation in hematological responses and the prognostic value of specific leukocyte subsets across different clinical scenarios remain to be fully elucidated [8]. In Iraq, the effects of hydatid cyst infection on biochemical and hematological parameters have been investigated by several researchers, including [9] and [10] highlighting the local relevance of this disease. This research was conducted to assess changes in total and differential white blood cell counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and serum IFN γ and TNF α as indicators of pro inflammation involving patients suffering from cystic echinococcosis due to *Echinococcus granulosus*. Additionally, the study compared the hematological and immunological parameters between infected and healthy individuals of different sexes and age groups.

2- MATERIALS AND METHODS

2.1 Study Population and Design

This study included a total of 51 patients who have been diagnosed with cystic echinococcosis (hydatid disease) at the time of enrollment, and the patient's group was subdivided based on age and sex into three groups: 1) children aged 5 through 14, 12 subjects, comprising approximately 23.5% of the entire patient population; 2) adult women aged 18 to 70, 24 subjects, comprising approximately 47% of the population; and 3) adult men aged 18 to 50, 15 subjects, comprising approximately 29.4% of the population. The control group consisted of 29 research participants, all of whom were healthy and did not suffer from any clinical or laboratory evidence of hydatid disease. Similar to the patient group, the control group was subdivided based on age and sex into three groups of healthy subjects: 7–15 - 8 children representing approximately 27.5% of the entire control population; 18–50, 11 females representing approximately 38% of the entire control population; and 16–48, 10 males representing approximately 34.5% of the entire control population. All research participants as well as the legal guardians of research participants who were minors provided written informed consent before being enrolled in the study.

2.2 Sample Collection

The blood samples collected from the patient and control groups were done according to the protocol set out by the Iraqi Ministry of Health. Blood collection was performed in private diagnostic labs and two major hospitals: Rafic Hariri Hospital and Baghdad Teaching Hospital. Blood was collected using standard aseptic methods through venipuncture using standard tubes for collecting the appropriate samples (i.e., EDTA tubes for the collection of hemostatic samples). All blood samples were processed within a few hours of collection. Every aspect of the blood collection, blood handling, and blood storage processes was conducted following standard clinical laboratory guidelines to guarantee that the sample was maintained in its original state, therefore producing reliable results.

2.3 Hematological Analysis

An automated complete blood count (CBC) machine was used to determine total and differential WBC levels from all blood samples. This analysis strictly followed the manufacturer's instructions, including daily quality control checks and calibration procedures. The automated system provided quantitative measurements of total WBC counts (as cells per microliter) and relative and absolute counts for differential populations of neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Results were documented and compared between hydatid disease patients and their healthy controls.

2.4 Assays for cytokines

Quantifiable cytokines IFN-gamma and TNF-alpha were measured in serum samples by using prepared ELISA kits (purchased from USBiological, USA) according to the protocols specified by their manufacturers.

2.5 Statistical analysis

The results were statistically analyzed by student t-test and single factor ANOVA using Microsoft office Excel 2007. P value ≤ 0.05 was considered statistically significant.

3- RESULTS AND DISCUSSION

3.1 Effect on Total White Blood Cell Count

The total white blood cell count was significantly greater ($P < 0.05$) for individuals above 15 years of age (both genders) who were infected with *Echinococcus granulosus* than it was for matched healthy controls (see Table 1); however, no difference was seen in individuals under 15 years compared to their respective healthy control group.

3.2 Effect on Differential White Blood Cell Count

The table (1) shows a statistically significant difference ($P < 0.05$) between the percentages of neutrophils in both sexes and in the entire age range of individuals with blood samples compared to healthy controls. In addition, a statistically significant increase ($P < 0.05$) was detected for the percentage of eosinophils in all infected individuals across all age groups. There was no statistically significant difference between the percentages of monocytes for either sex or across the entire age range when comparing infected blood samples to repective healthy controls. In contrast, there was a statistically significant decrease in the percentage of lymphocytes in blood samples of both sexes and across all age groups, when compared to the corresponding healthy groups.

3.3 Effect on Eosinophil Count

Eosinophil counts of blood specimens from both male and female subjects, or of differing ages from Dunger's solution, were all significantly elevated ($P < 0.05$) when compared with those of the healthy controls.

Table (1): Percentage of White Blood Cells in Differential Count according to age and gender

Group	Neutrophils (%)	Eosinophils (%)	Monocytes (%)	Lymphocytes (%)	Eosinophils / mm³	Total WBC / mm³
Healthy Females >15 yrs	63.545 ± 9.180	1.545 ± 0.207	3.727 ± 0.619	31 ± 2.236	94.295 ± 13.339	6354.5 ± 2767
Female Patients >15 yrs	70.333 ± 8.775	4.125 ± 0.290	2.33 ± 0.419	22.5 ± 1.859	371.729 ± 34.420	10227 ± 958
Healthy Males >15 yrs	55.333 ± 2.360	1.7 ± 0.260	2.7 ± 0.495	37.1 ± 1.940	127.573 ± 29.549	5940 ± 658.82
Male Patients >15 yrs	69.333 ± 2.953	3.8 ± 0.499	3.866 ± 0.827	22.466 ± 2.523	347.383 ± 55.852	9410 ± 1174.83
Healthy <15 yrs	61.125 ± 1.245	1.5 ± 0.188	2.625 ± 0.3753	34.5 ± 1.052	91.125 ± 18.639	6025 ± 443.7
Patients <15 yrs	98.833 ± 2.846	3.8 ± 0.708	3.83 ± 0.964	24.666 ± 2.646	277.583 ± 69.440	8132.5 ± 1024.79

*** Significant difference at (P < 0.05)**

Vqalues are expressed as Mean ± Standard Error (SE). (Eosinophils / mm³ Using Dunger's Solution and Total WBC Count / mm³).

3.4 Effect on cytokines

Based on the information provided in the table, we can determine that individuals suffering from Cystic Echinococcosis (CE) exhibit a strong and very statistically significant pro-inflammatory immune response compared with non-infected individuals (healthy controls). For example, the level of IFN-gamma (a pro-inflammatory cytokine) in CE patients (1119.05 pg/ml) is approximately 14 times greater than the level of IFN-gamma measured in the healthy control group (81.22 pg/ml); hence this difference was statistically significant ($p<0.05$). Additionally, the level of TNF-alpha (another pro-inflammatory cytokine) in CE patients (161.50 pg/ml) was approximately three times greater than that measured in the healthy control group (58.06 pg/ml), which again represents a statistically significant difference ($p<0.001$).

Table (2): IFN-γ and TNF-α Levels in Patients with cystic echinococcosis (hydatid disease) vs. Controls

Cytokine	Group	Mean (pg/ml)	Standard Deviation (SD)	p-value	Statistical Significance
IFN-γ	Patients (n=30)	119.05	28.5	<0.05	Significant
	Controls (n=10)	81.22	19.2		
TNF-α	Patients (n=30)	161.50	35.7	<0.001	Highly significant
	Controls (n=10)	58.06	18.4		

A rise in total white blood cell (WBC) count was observed among patient populations affected by Hydatid disease in this study, particularly in older patients (i.e., older than 15 years of age). This rise may represent a chronic inflammation developing as a result of the foreign object (hydatid cyst) being present in tissues of the host and producing a continuing immunological response that produces an increase in the leukocyte (WBC) count to repair damage (due to the cyst) to the surrounding tissues and provide increased exposure to the antigens from the cyst. Even though the WBC increase was significant, it did not rise to an acute level (acute leukocytosis), which

corresponds to findings that cystic echinococcosis primarily causes a moderate systemic inflammatory response rather than an overwhelming acute systemic inflammatory response [11, 12]. Patients who were younger than 15 years did not demonstrate any significant increase in their total WBC count. An early or immature stage of the serous cyst on the host's immune response often resulting in limited amounts of antigen being released from the cyst, and corresponding reduction in generalized immune stimulation. There is a variable host response to hydatid cysts depending on size, location, time since infection.

In patients infected with the parasite, differential leukocyte counts showed a significant increase in both relative and absolute eosinophil counts. Eosinophils are often elevated in individuals with helminthic infections because of the Th2 cytokine signaling, specifically IL-5, which stimulates both the differentiation of eosinophils in the bone marrow and their activation after entering the circulation [13]. Additionally, the presence of antigens from the parasite may also have caused the increased relative number of eosinophils in this study's patients due to eosinophil recruitment, as was previously observed in immunologic studies [14]. Neutrophil counts were also statistically greater than the control group but, when assessed clinically, the patients did not demonstrate neutrophilia (neutrophil count above 7,000/μL). This may have occurred because neutrophils that are recruited to the area immediately surround the cyst are less likely to be detected systemically. Studies using histopathology have classified both neutrophils and mononuclear cells, including giant cells, as being present in the inflammatory tissue surrounding hydatid cysts [13]. Furthermore, the fibroelastic capsule that surrounds the cyst and the chronic nature of the cystic infection appear to limit the release of antigens, thereby preventing systemic activation of neutrophils [15].

The mean number of monocytes did not show a statistically significant difference from controls, but there were noticeable variations. Monocytes likely travel out of peripheral circulation, entering areas of infection and differentiating into macrophages, which may aid the formation of granulomas and contribute to antigen presentation [13]. This recruitment of monocytes may serve to establish a balance in the levels of cells found in peripheral circulation, resulting in no detected changes in circulating monocyte populations being reported. The percentage of lymphocytes in infected patients was significantly lower than that of non-infected patients. Relative lymphopenia is thought to result from the redistribution of lymphocytes from peripheral blood to infected tissues and represents the role that lymphocytes play in the humoral and cellular responses to parasitic antigens [11]. Hydatid fluid has also been found to have immunomodulatory activity on lymphocytes, thereby influencing their function and contributing to immune regulation [16].

This current study demonstrated that alterations in the host’s blood cells (hematology) reflect chronic worm infection and include eosinophilia (high eosinophil count) without major alterations to the number of leukocytes (white blood cells - monocytes, neutrophils, basophils, and lymphocytes), and show that the use of differences between types of leukocytes as a measure of diagnostic utility for hydatid disease is possible. This research results also suggest a complex relationship between the host’s immune system and the physical and chemical characteristics of the antigens produced by the parasites.

In this study, the significant elevation of IFN-γ and TNF-α in hydatid disease patients indicates a strong Th1-type immune response. IFN-gamma is typically thought of as a typical Th1 cytokine and is mainly produced by T-lymphocytes and NK cells, and plays a critical role in macrophage activation [17, 18]. The results of previous studies have supported this interpretation by showing that Echinococcus infected hosts have significantly increased whole-tissue expression ($P < 0.0001$), relative to uninfected hosts, of the IFN-gamma gene (and maybe its receptor gene) (19). TNF-alpha is an important pro-inflammatory cytokine that plays a role in the development of granulomas, which "wall off" hydatid cysts to prevent further spreading [17]. The evaluation of TNF-alpha levels shows a significant increase ($p < 0.001$). This elevation of TNF-alpha correlates with studies demonstrating increased expresion of TNF-α and it’s related signaling pathways (such as NF-κB) at the time of an infection. This shows that, although the parasite is still alive, the immune system of the host body is actively responding to tried to contain the parasite and to set up inflammation to destroy the cyst wall [19, 20].

There is strong consistency between your findings and those reported by the authors of the previous study conducted on hydatidosis from persons in Erbil Iraq in 2011. The 2011 study also reported a significant elevation of IFN-γ ($P<0.01$) in patients compared to control subjects. In contrast, the previous study reported no significant differences in TNF-α, whereas you found a highly significant difference ($P<0.001$) in TNF-α, which suggests that there may be a greater inflammatory response in your cohort of patients relative to the 2011 study. Alternatively, cyst fertility and/or cyst location may differ between the two studies (21). The current study findings support previous studies completed in animal models. A recent 2020 study showed that livestock infected with E12 had a primarily Th1 (TNF-α high) profile. The results from an earlier 2025 study showed that an equine was euthanized from cystic

echinococcosis with a thorough inflammatory response (IFN-γ and TNF-α) further confirming both are important biomarkers of infection across the mammalian host [18, 19].

4- CONCLUSION

It can be concluded from the study results that infected individual, with cystic echinococcosis, mounted a significant Th1-type pro-inflammatory immune response, as evidenced by high levels of IFN-γ and TNF-α in the serum of infected subjects. Patients over the age of 15 had significantly higher total white blood cell counts, and consistent eosinophilia, neutrophilia, and relative lymphopenia were noted in all age groups and genders when performing differential analysis. The significant increases in the above-mentioned cellular components reflect the active inflammatory response being utilized by the host to contain the hydatid cyst. These immunological and hematologic parameters could prove to be useful adjunctive biomarkers in both diagnosing cystic echinococcosis and tracking disease progression. Therefore, routine complete blood counts with differential analysis and cytokine measurements are recommended as part of the clinical evaluation of patients with hydatid disease.

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