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Evaluation of the prevalence and clinical impact of toxocariasis in patients with eosinophilia of unknown origin

Hong-Beum Kim[1,*,†], Jun-Won Seo[2,*], Jun-Hyung Lee[2], Byung-Seok Choi[3], and Sang-Gon Park[2]

[1]Department of Natural Medical Sciences, Chosun University College of Health Science, Gwangju; [2]Department of Internal Medicine, Chosun University Hospital, Gwangju; [3]Department of Medicine, Chosun University Graduate School of Medicine, Gwangju, Korea

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Correspondence to
Sang-Gon Park, M.D.
Division of Hematology-Oncology, Department of Internal Medicine, Chosun University Hospital, 365 Pilmun-daero, Dong-gu, Gwangju 61453, Korea
Tel: +82-62-220-3984
Fax: +82-62-234-9653
E-mail: sgpark@chosun.ac.kr

*These authors contributed equally to this work.

†Current affiliation: Department of Premedical Course, Chosun University College of Medicine, Gwangju, Korea

Background/Aims: Eosinophilia has numerous diverse causes, and in many patients, it is not possible to establish the cause of eosinophilia. Recently, toxocariasis was introduced as one cause of eosinophilia. The aims of this study were to evaluate the prevalence of toxocariasis and the clinical impact of albendazole treatment for toxocariasis in patients suspected of eosinophilia of unknown origin.

Methods: We performed a retrospective chart review. After evaluation of cause of eosinophilia, the patients suspected of eosinophilia of unknown origin performed immunoglobulin G antibody specific assay for the *Toxocara canis* larval antigen by enzyme-linked immunosorbent assay.

Results: This study evaluated 113 patients, 69 patients (61%) were suspected of eosinophilia of unknown origin. Among these 69 patients, the frequency of *T. canis* infection was very high (45 patients, 65.2%), and albendazole treatment for 45 eosinophilia with toxocariasis was highly effective for a cure of eosinophilia than no albendazole group regardless of steroid (82.3%, p = 0.007). Furthermore, among the nonsteroid treated small group (19 patients), albendazole treatment for eosinophilia were more effective than no albendazole group, too (83.3% vs. 28.6 %, p = 0.045).

Conclusions: The prevalence of toxocariasis was high among patients suspected of eosinophilia of unknown origin; therefore, evaluation for *T. canis* infection is recommended for patients with eosinophilia of unknown origin. Furthermore, for patients suspected of eosinophilia of unknown origin who have positive results for *T. canis*, albendazole treatment may be considered a valuable treatment option.

Keywords: Eosinophilia; Toxocariosis; Hypereosinophilic syndrome; Abendazol

INTRODUCTION

Toxocariasis is an illness caused by a zoonotic infection due to the ingestion of *Toxocara canis* or *cati* larvae from the feces of infected dogs or cats. The larvae from the ingested egg travel through the small intestines, spread to the bloodstream, and finally, infiltrate the organs, such as the liver and lungs. This parasite infection induces variable manifestations, including muscle pain, fever, hepatosplenomegaly, respiratory symptoms, and abdominal pain. However, most patients do not manifest definitive symptoms [1-3]. When *T. canis* infects hu-

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mans, the eosinophil count may increase owing to the host's protective response to the infection, and eosinophilia was found in 38.98% of children with *Toxocara* positive immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) results. However, studies of the features and incidence of *T. canis* infection in adults are rare [3-5]. Among patients with asymptomatic eosinophilia of an unknown origin, 65% to 70% had positive in *T. canis* serology, but the number of study patients was not substantial. Moreover, the effect of albendazole on the level of eosinophilia in patients with *T. canis* infection remains unknown [6,7].

Therefore, we evaluated the prevalence of *T. canis* infection and the clinical impact of albendazole treatment for toxocariasis in patients suspected of eosinophilia of unknown origin.

METHODS

Research target

Patients who presented with peripheral blood eosinophilia (> 500 cells/μL or ≥ 10% of white blood cell count) were enrolled in the study between July 2010 and February 2013 [8].

We performed a retrospective chart review of clinical data, including symptoms and medical history, especially allergic illness, connective tissue disorder, and history of receiving medicines in the last 6 months. We also evaluated their history of ingesting raw meat (beef, fish, and beef liver and stomach) [9,10].

Diagnosis

To establish the cause for eosinophilia, enrolled patients with eosinophilia were usually evaluated basic laboratory test (liver function test, renal function test, and electrocardiogram) with numerous additional laboratory examinations, including fecal exam for parasites; ELISA for parasite infections, such as *Clonorchis sinensis*, paragonimiasis, sparganosis, and cysticercosis; the multiple allergen simultaneous test (MAST) for evaluation of allergic causes; and the peripheral blood smear for evaluation of hematologic malignancy. Additionally, based on medical judgment, chest and abdominal computed tomography (CT) was sometimes performed. We diagnosed eosinophilia as due to allergic disease when MAST score was higher than 3+ and allergic symptoms were reported. Eosinophilia due to a drug reaction was diagnosed in patients with a recent history of a new medication or health products and spontaneous resolution of eosinophilia. Finally, eosinophilia due to a parasite infection was diagnosed based on positive results of a fecal examination for parasite eggs or an ELISA for *C. sinensis*, paragonimiasis, sparganosis, or cysticercosis. After establishing the aforementioned causes of eosinophilia, the remaining patients who were suspected of eosinophilia of unknown origin were evaluated for serum levels of the IgG antibody specific for the *T. canis* larval antigen by ELISA.

In addition, CT scan were performed on most patients to evaluate end organ infiltration; patients showing multi-shade infiltration or nodule on abdominal and thorax CT were defined as liver and lung invasions, respectively.

T. canis-specific ELISA

For serological examination for *T. canis* infection, a *Toxocara*-specific ELISA kit (Bordier Affinity Products, Crissier, Switzerland) was used. Using the standard ELISA method, the levels of unique IgG antibodies against the *Toxocara* excretory/secretory antigens of *T. canis* larvae were measured. By setting a negative control group as the standard, the patients that appeared to be partially positive were judged as positive. The sensitivity and specificity of the method are 78% to 100% and 90% to 92%, respectively [11]. Patients without eosinophilia due to drug reaction, parasite infection, or allergic disease, who were positive for *T. canis* in the ELISA, were diagnosed as having eosinophilia due to *T. canis* infection.

Treatment

Albendazole, 800 mg/day, was administered for 5 to 7 days to most of the *T. canis* ELISA positive patients; however, some patients suspected of eosinophilia of unknown origin were given albendazole despite having a negative *T. canis* ELISA, according to the physician's judgment.

Most patients with an eosinophil count more than 1,500 cells/μL in the peripheral blood or with end organ invasion of the lung or liver (with findings such as abnormal liver function test, chest tightness, or general fatigue) were administrated oral steroids regardless of

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other causes (allergic disease or any parasite infection) according to the physician's decision. After the eosinophil count became normal, the steroid dose was tapered for steroid-treated patients, and then we observed for 3 to 6 months. The non-steroid-treated group were also observed for 3 to 6 months.

We defined a cure of eosinophilia as a decline in the number of eosinophils to fewer than 500 cells/μL and below 8% of complete white blood cells, disappearance of organ invasion, and continuation of this recovery state over 3 months after albendazole treatment ended or tapering of the steroids. Above mentioned treatment definition, a cure patients of eosinophilia were observed every 3 months or transferred to local clinic according to the patients' decision.

RESULTS

Clinical characteristics of the study subjects

Among the 113 patients who were adequately evaluated for eosinophilia, 75 (66%) were men and 38 (34%) were women. The median age of patients was 56 years (range, 18 to 87), and the median eosinophil count was 2,251 cells/μL (range, 510 to 22,958). In addition, among these 113 patients, 19 had eosinophilia due to allergic disease, diagnosed based on a MAST score higher than 3+ and the presence of asthma, allergic rhinitis, etc. Eosinophilia due to a drug reaction was diagnosed in two patients. Of the patients, 23 were verified to have a well-known parasite infection. Despite numerous examinations, 69 patients (61%) were suspected of eosinophilia of unknown origin (Table 1).

Table 1. Clinical characteristics of the eosinophilic patients

Characteristic	All patients (n = 113)
Age, yr	56 (18–87)
Eosinophili count, cells/uL	2,251 (510–22,958)
Sex	
Male	75 (66.4)
Female	38 (33.6)
Cause of eosinophilia	
Allergic disease	19 (16.8)
Drug	2 (1.7)
Other parasitic infection	23 (20.4)
Unknown	69 (61.1)
Organ involvement (n = 51)	
Lung	18 (35.2)
Liver	23 (45.1)
Lung and liver	12 (23.5)

Values are presented as median (range) or number (%).

Clinical characteristics with eosinophilia of unknown origin

Among the 69 patients suspected of eosinophilia of unknown origin, *Toxocara* positive patients were 45 (65.2%) and *Toxocara* negative patients were 24 (34.8%), respectively. The median age of the 45 toxocariasis patients was 56.2 years (range, 49 to 80) and the median age of the 24 patients with a negative *T. canis* ELISA was 46.7 years (range, 22 to 83) (Table 2). Among the former, 32 (71%) were men, 13 (29%) were women and the median eosinophil count was 2,590 cells/μL (range, 510 to 14,820). In contrast, the median eosinophil count (1,563 cells/μL [range, 524 to 22,958]) was lower in *T. canis* ELISA negative patients. Twenty-eight of the toxocariasis patients (62%) lived in urban areas, whereas 17 (28%) lived in rural areas (Table 2).

Organ invasion and symptom frequency

Among the 113 patients with eosinophilia, 51 patients underwent chest and abdominal CTs, and liver and lung invasions were found in 29 patients (56.8%). Of these 51 patients, 23 (45%) had liver invasion, and 18 patients (35.2%) had lung invasion. Invasion of both the liver and lung occurred in 12 patients (23.5%) (Table 1). Among the 69 patients suspected of eosinophilia of unknown origin, 41 underwent CT. Among the 45 patients suspected of eosinophilia of unknown origin with toxocariasis, 30 underwent CT, and the result was followed: 16 (53.3%) had liver invasion; 13 (43.3%) had lung invasion; and nine (30%) had both liver and lung invasions. Among the *T. canis* ELISA negative patients, 11 also underwent CT, and the result showed lower frequently followed: three (27.2%) had liver invasion; four (36.3%) had lung invasion; and two (18.2%) had both liver and lung invasions (Table 2).

Clinical course and treatment

Among the 45 patients suspected of eosinophilia of un-

Table 2. Clinical characteristics of patients suspected as eosinophilia of unknown origin

Characteristic	Eosinophilia of unknown cause	
	Toxo-ELISA positive (n = 45)	Toxo-ELISA negative (n = 24)
Age, yr	56.2 (49–80)	46.7 (22–83)
Sex, male/female	32 (71)/13 (29)	11(45.8)/13(54.2)
Eosinophili count, cells/uL	2,590 (510–14,820)	1,563 (524–22,958)
Residence, urban/rular	28 (62.2)/17 (37.8)	14 (58.3)/10 (41.7)
Raw meat ingestion	28 (62.2)	12 (50)
Organ involvement (n = 41)	Evaluation (n = 30)	Evaluation (n = 11)
Lung	13 (43.3)	3 (27.2)
Liver	16 (53.3)	4 (36.3)
Lung and liver	9 (30)	2 (18.2)
Cure of eosinophilia	32/45 (71.1)	5/24 (20.8)
Albendazole alone	10/12 (83.3)	1/2 (50)
Albendazole + steroid	18/22 (81.8)	1/1 (100)
Steroid alone	2/4 (50)	2/6 (33)
No albendazol, no steroid	2/7 (28.6)	1/15 (6.7)
Medication for the chronic disease[a]	11 (22.2)	7 (29.2)

Values are presented as median (range) or number (%).
ELISA, enzyme-linked immunosorbent assay.
[a]Diabetes, hypertension, ect.

known origin with toxocariasis, 34 (75%) received albendazole and 26 (57%) received steroids. Twelve (26%) were treated solely with albendazole, and four (9%) were treated solely with steroids. Twenty-two patients (49%) were treated with a combination of steroids and albendazole, and the other seven (15.5%) were treated neither steroid nor albendazole (Table 2). Thirty-seven patients (53.6%) achieved a cure of eosinophilia among the patients suspected of eosinophilia of unknown origin (n = 69), and time to respond to treatment varied from 1 week to 4 months.

Especially, among the 45 patients with toxocariasis, eosinophilia treated more frequently (82.3% vs. 36.4%) in the group treated with albendazole than in those not treated with albendazole regardless of the treatment of steroid (p = 0.007). However, many eosinophilia patients received steroids; therefore, we categorized non-steroid-treated patients to evaluate the efficacy for eosinophilia of albendazole alone. In the non-steroid-treated group, the patients who received albendazole experienced improvement of eosinophilia more frequently (83.3% vs. 28.6%) than the patients who did not receive albendazole (p = 0.045) (Table 3).

DISCUSSION

Eosinophilia is defined as an eosinophil count of more than 500 cells/μL in the peripheral blood and is related to parasite infection, hypersensitivity reaction to drugs, allergic illness, connective tissue diseases, malignancies, and idiopathic hypereosinophilic syndromes (HESs) [8-10,12,13]. Various tests can be performed to diagnose this illness; however, if the eosinophil count in peripheral blood is more than 1,500 cells/μL with an unknown origin, persists for longer than 6 months, and the main organs, such as the liver, spleen, heart, lung, or nerves are invaded, these conditions can be described as idiopathic HES. If idiopathic HES is not treated appropriately, some patients with idiopathic HES develop severe, often fatal, complications due to end organ failure, such as myocardial infiltration. Therefore, early diagnosis and treatment are required in these patients [9,10].

However, eosinophilia has so many causes that often it is not possible to know the cause accurately. In particular, when the cause of the eosinophilia is not clear, appropriate guidelines for evaluation and treatment are needed. In South Korea, people enjoy eating fresh

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Table 3. Treatment with albendazole for patients suspected as eosinophilia of unknown origin with toxocariasis antibody-positive regardless of the treatment of steroid and except steroid

Variable	Number	Cure of eosinophilia	*p* value
Toxo-positive patients	45		0.007[a]
Albendazole (+)	34	28/34 (82.3)	
Albendazole (–)	11	4/11 (50)	
Non-steroid dosed group	19		0.045[a]
Albendazole (+)	12	10/12 (83.3)	
Albendazole (–)	7	2/7 (28.6)	

Values are presented as number (%).
[a]$p < 0.05$.

liver or raw beef, which might result in eosinophilia of unknown origin; parasite infection should be considered in such patients [9,12]. Notably, *T. canis* infection in patients with a history of eating fresh liver and lamina superficialis accounts for a 7.8 times higher rate of *T. canis* infection in the general population. Thus, an eosinophilic patient should be examined for possible *T. canis* infection upon presentation at the hospital. Moreover, eosinophilia due to *T. canis* must be considered in patients with a history of eating fresh liver and lamina superficialis [6].

In studies of asymptomatic patients, the reported seropositive rates were diverse, ranging from 2% to 80% [14]. For example, in recent studies reported from Europe, seropositive rates of 2% to 5% and 14% to 37% were found in urban and rural areas, respectively; however, in India and Denmark, the seropositive rates were 6.4% and 2.4%, respectively. Among patients with eye symptoms in Slovenia, 28% were *Toxocara* seropositive, and 31.6% of rural residents in Argentina were *Toxocara* seropositive [15-19]. In addition, a domestic report from a region in South Korea indicated that healthy residents who were asymptomatic had an approximately 5% seropositive rate, and 68% of the eosinophilic patients who visited the hospital were seropositive [6,15,20].

In the present study, 65% of the patients with eosinophilia of an unknown origin had *T. canis* positive serology results. This is similar to the 68% seropositive rate reported by other studies of eosinophilia in South Korea. Considering that the *T. canis* seroprevalence of healthy Koreans is 5%, this higher seroprevalence indicates that *T. canis* is a major cause of eosinophilia [6].

Usually, asymptomatic *T. canis* infection does not require treatment; however, when symptoms such as eosinophilia or organ infiltration are present, as in this study, treatment is recommended, usually with albendazole at a daily dose of 800 mg for 5 days [14]. Notably, patients with *T. canis* positive eosinophilia who received albendazole showed significant increased rate of a cure of eosinophil compared with the patients who not received albendazol. Furthermore, a similar albendazole effect was observed in the group of patients who did not receive steroids, too.

This study has a few limitations. First, this study might have several biases because the review was performed retrospectively. Second, this study was not able to determine whether improvement of eosinophilia was caused by albendazole administration or by spontaneous recovery. Third, it was not possible to determine how many patients recurred because follow-up was not uniformly performed. Fourth, bone marrow examination and platelet derived growth factor receptor identification were not executed for all study patients. Finally, frequently the ELISAs for *C. sinensis* and paragonimiasis were repeated to confirm negative results. However, in this study, among patients with eosinophilia due to toxocariasis who were treated with albendazole, only seven patients underwent post-treatment *Toxocara*-specific ELISA. The post-treatment interval varied, as follows: 1 week, 4 months, 6 months, 7 months, 8 months, 11 months, and 12 months. Among these seven patients, the *Toxocara*-specific ELISA was negative in only the two patients reexamined after 11 and 12 months. However, no published studies indicate when post-treatment reexamination of *Toxocara* ELISA should be performed. Therefore, it remains unclear when this serology should

be repeated to evaluate treatment failure. Furthermore, the correlation between the *T. canis* negative results and the improvement in the eosinophil counts was unclear.

Up to now, most studies of toxocariasis only reported the incidence of toxocariasis. In patients suspected of eosinophilia of unknown origin, the frequency of *T. canis* infection was very high (65%). Thus, an evaluation for possible *T. canis* infection is recommended for patients with eosinophilia of an unknown origin. In addition, the results indicate that this evaluation might prevent misdiagnosis of other illnesses, such as idiopathic eosinophilia. For patients suspected of eosinophilia of unknown origin, who have positive findings for *T. canis*, administration of albendazole at the recommended dose is warranted.

Nevertheless, additional well designed prospective studies are needed. These studies need to include clearly defined treatment criteria, have an adequate observation period and repeat the *Toxocara*-specific ELISA.

KEY MESSAGE

1. Many cases of eosinophilia of an unknown origin may be due to *Toxocara canis* infection; therefore, *T. canis* enzyme-linked immunosorbent assay (ELISA) may be an essential diagnostic tool to evaluate patients with eosinophilia.
2. This study is clinically relevant because it supports the efficacy of albendazole treatment for patients suspected of eosinophilia of unknown origin with toxocariasis.
3. Conversion to a negative *T. canis* ELISA can occur after 10 or more months post-treatment, although only a few patients underwent a post-treatment ELISA.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Akao N, Ohta N. Toxocariasis in Japan. Parasitol Int 2007;56:87-93.
2. Morris PD, Katerndahl DA. Human toxocariasis: review with report of a probable case. Postgrad Med 1987;81:263-267.
3. Despommier D. Toxocariasis: clinical aspects, epidemiology, medical ecology, and molecular aspects. Clin Microbiol Rev 2003;16:265-272.
4. Johkoh T, Muller NL, Akira M, et al. Eosinophilic lung diseases: diagnostic accuracy of thin-section CT in 111 patients. Radiology 2000;216:773-780.
5. Obwaller A, Jensen-Jarolim E, Auer H, Huber A, Kraft D, Aspock H. Toxocara infestations in humans: symptomatic course of toxocarosis correlates significantly with levels of IgE/anti-IgE immune complexes. Parasite Immunol 1998;20:311-317.
6. Kwon NH, Oh MJ, Lee SP, Lee BJ, Choi DC. The prevalence and diagnostic value of toxocariasis in unknown eosinophilia. Ann Hematol 2006;85:233-238.
7. Arias Irigoyen J, Senent Sanchez CJ. Toxocariasis: a cause of hyper IgE and eosinophilia. J Investig Allergol Clin Immunol 1995;5:232-234.
8. van Assendelft OW. Reference values for the total and differential leukocyte count. Blood Cells 1985;11:77-96.
9. Roufosse F, Weller PF. Practical approach to the patient with hypereosinophilia. J Allergy Clin Immunol 2010;126:39-44.
10. Brito-Babapulle F. The eosinophilias, including the idiopathic hypereosinophilic syndrome. Br J Haematol 2003;121:203-223.
11. Roldan W, Cornejo W, Espinoza Y. Evaluation of the dot enzyme-linked immunosorbent assay in comparison with standard ELISA for the immunodiagnosis of human toxocariasis. Mem Inst Oswaldo Cruz 2006;101:71-74.
12. Kim DW, Shin MG, Yun HK, et al. Incidence and causes of hypereosinophilia (corrected) in the patients of a university hospital. Korean J Lab Med 2009;29:185-193.
13. Lim JH, Lee KS. Eosinophilic infiltration in Korea: idiopathic? Korean J Radiol 2006;7:4-6.
14. Pawlowski Z. Toxocariasis in humans: clinical expression and treatment dilemma. J Helminthol 2001;75:299-305.
15. Kim YH, Huh S, Chung YB. Seroprevalence of toxocariasis among healthy people with eosinophilia. Korean J Parasitol 2008;46:29-32.
16. Magnaval JF, Michault A, Calon N, Charlet JP. Epidemiology of human toxocariasis in La Reunion. Trans R Soc Trop Med Hyg 1994;88:531-533.
17. Malla N, Aggarwal AK, Mahajan RC. A serological study

https://doi.org/10.3904/kjim.2014.270

of human toxocariasis in north India. Natl Med J India 2002;15:145-147.
18. Logar J, Soba B, Kraut A, Stirn-Kranjc B. Seroprevalence of Toxocara antibodies among patients suspected of ocular toxocariasis in Slovenia. Korean J Parasitol 2004;42:137-140.
19. Stensvold CR, Skov J, Moller LN, et al. Seroprevalence of human toxocariasis in Denmark. Clin Vaccine Immunol 2009;16:1372-1373.
20. Yoon YS, Lee CH, Kang YA, et al. Impact of toxocariasis in patients with unexplained patchy pulmonary infiltrate in Korea. J Korean Med Sci 2009;24:40-45.