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-
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).

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 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 (%).
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 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)         |
| Eosinophil count, cells/μL             | 2,590 (510–14,820)         | 1,563 (524–22,958)          |
| Residence, urban/rural                 | 28 (62.2)/17 (37.8)        | 14 (58.3)/10 (41.7)         |
| Raw meat ingestion                     | 28 (62.2)                   | 12 (50)                     |
| Organ involvement (n = 41)             |                              |                             |
| 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 albendol, no steroid                | 2/7 (28.6)                  | 1/5 (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.
aDiabetes, hypertension, etc.
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 albendazole. 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 toxocarasis 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 re-examination of _Toxocara_ ELISA should be performed. Therefore, it remains unclear when this serology should

### 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<sup>a</sup> |
| Albendazole (+)           | 34     | 28/34 (82.3)         |         |
| Albendazole (-)           | 11     | 4/11 (50)            |         |
| Non-steroid dosed group   | 19     |                      | 0.045<sup>a</sup> |
| Albendazole (+)           | 12     | 10/12 (83.3)         |         |
| Albendazole (-)           | 7      | 2/7 (28.6)           |         |

Values are presented as number (%).

<sup>a</sup>p < 0.05.
be repeated to evaluate treatment failure. Furthermore, the correlation between the \textit{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 \textit{T. canis} infection was very high (65%). Thus, an evaluation for possible \textit{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 \textit{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 \textit{Toxocara}-specific ELISA.

### KEY MESSAGE

1. Many cases of eosinophilia of an unknown origin may be due to \textit{Toxocara canis} infection; therefore, \textit{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 \textit{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.

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