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Pulmonary presentation of *Toxocara sp.* infection in children

The authors declare no financial disclosure

Abstract

Introduction: The aim of this study was to investigate the associations between radiological findings, blood eosinophilia, hyperimmunoglobulinemia E and G and *Toxocara* seropositivity in Polish children with newly diagnosed pulmonary infiltration.

Material and methods: We retrospectively analyzed the documentation of 119 patients, aged 1 to 18 years (mean age: 7.21 ± 4.82), who were seropositive in regards to *Toxocara sp.* antibodies. In all cases, peripheral blood eosinophils and leukocyte counts, serum total IgE, IgG levels and specific IgG antibodies against excretory and secretory *Toxocara sp.* antigens were measured at the first presentation. After the confirmation of seropositivity, all children had a routine radiological examination.

Results: In the documentation of 23 children (mean age 3.58 ± 2.63 years) we found abnormalities in the radiological examination of their lungs. Fifteen children who had abnormalities in radiological findings presented clinical respiratory complaints such as chronic cough, wheezing, asthma and haemoptysis. Eight children were asymptomatic. The analysis of peripheral eosinophils and leukocyte number, the level of IgE and specific anti-*Toxocara* IgG presented significantly higher values in children with radiological lesions than in children who had correct radiology. The levels of total IgG and gamma globulins were not significantly different. In 10 patients CT showed irregular round nodules with and without halo ranging from 1 to 13 mm. The number of nodules varied from a single lesion to multiple, disseminated ones. All nodules were located in peripheral areas of the lungs. None of them were found in the central areas. In 13 patients, CT images showed ground-glass opacities with ill-defined margins. None of the CT images presented lymphadenopathy and pleural effusion.

Conclusion: The pulmonary lesions in small children with high eosinophilia and hyperimmunoglobulinemia E could be related to toxocariasis and for this reason they are eligible to undergo therapy with prolonged observation for several months, rather than start invasive malignancy investigations.

Key words: toxocariasis, computer tomography, children

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Introduction

Human toxocariasis is a helminthozoonosis resulting from infestation of humans by roundworms *Toxocara canis* (*T. canis*) and *cati* (*T. cati*) [1]. The disease was first described in the 1950s and for many years was regarded as uncommon in children. The current data indicates that toxocariasis is the most common worm infection in many countries, which suggests that its global importance may

be greatly underestimated. Seroprevalence surveys in Western countries vary from 2 to 5 per cent of healthy adults in urban areas to 14 or 20 to 37 per cent in rural areas. In tropical countries the seroprevalence of *Toxocara species* (*sp.*) is higher (e.g. 86% in India) [2]. Children are the major infected group. Some of their common behaviors, especially geophagia, poor personal hygiene, close contact with animals and the lack of parental supervision, increase the risk of infection [3].

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Human infection occurs through accidental ingestion of embryonated eggs of the parasite found in contaminated soil. The eggs hatch in the stomach and infective larvae migrate to a wide variety of tissues, causing a local inflammatory and allergic reaction in different organs (eyes, lungs, liver and brain) [4]. Although it is rare, people can also become infected from eating undercooked meat containing *Toxocara* larvae [5].

Toxocariasis develops into five clinical forms: systemic (visceral larvae migrans syndrome — VLM), ocular (ocular larvae migrans syndrome — OLM), neurological (NLM — neurological larvae migrans syndrome), covert and asymptomatic. VLM is connected with enlargement of the liver, spleen and peripheral lymph nodes, and lung involvement [3]. OLM is a localized eye infection that may cause severe inflammation and progressive ocular damage [6]. NLM symptoms range from minor neurological deficiencies to eosinophilic meningoencephalitis [7]. The covert form is connected with non-specific symptoms produced by the stimulation of a parasite antigen in the host's immune system. The asymptomatic form occurs when eosinophilia and *Toxocara sp.* antibodies are accidentally detected in the patient without typical symptoms [3].

The clinical findings of lung involvement associated with *Toxocara sp.* infection is usually non-specific. There are only few case reports regarding radiographic imaging of lung involvement in pulmonary VLM. Lung involvement causes pulmonary infiltration, and the mechanism of the infiltration is described as the allergic reaction to the larvae [8].

The form of the infection depends on the intensity of the infestation, the larvae localization, reinfestation, and the efficiency of the host's immune system and the age of the child [9].

The aim of this study was to investigate the associations between radiological findings, blood eosinophilia, hyperimmunoglobulinemia E and G and *Toxocara* seropositivity in Polish children with newly diagnosed pulmonary infiltration.

Material and methods

We retrospectively analyzed the documentation of 119 patients hospitalized in the Department of Infectious Diseases and Child Neurology in Poznan. Data were selected from patients hospitalized with *Toxocara sp.* infection from August 2009 to December 2013. The children were 1 to 18 years old (with a mean of 7.21 ± 4.82).

The subjects comprised 67 boys and 52 girls (Table 1).

Table 1. Characteristics parameters of children with pulmonary lesions and asymptomatic ones in the course of *Toxocara sp.* infection

Groups	T+/P-	T+/P+	p
n	96	23	
Boys	51	16	
Girls	45	7	
Age	8.08 ± 4.83	3.58 ± 2.63	< 0.0001
Toxocara positive children with pulmonary lesions (n=23)			
Chronic cough		10	
Wheezing		7	
Dyspnoe		2	
Haemoptysis		1	
Asymptomatic		8	

T+/P- — *Toxocara* seropositive, without radiological findings

T+/P+ — *Toxocara* seropositive, with radiological findings

The retrospective analytical study was created using history, physical examination data and interpretation of laboratory results.

In all cases, peripheral blood eosinophils and leukocyte counts, serum total IgE, IgG levels and specific IgG antibodies against excretory and secretory *Toxocara sp.* antigens were measured at the first presentation. After the confirmation of seropositivity, all children had a routine radiological examination. Those children whose radiological imaging presented any lesions in the lungs underwent a CT scan of the chest as an additional examination.

Medical history

Detailed questionnaires were completed by the doctor based on the medical history of the children from the perinatal period, exposure to infections, risk factors for *Toxocara* infection, the severity and nature of the symptoms, medications used, environmental factors and family history.

Laboratory measurements

For hematological and immunological tests, blood was collected in BD Vacutainer Collection Set with and without EDTA. The analysis was done using the Sysmex XT2000i automated haematology system, utilizing the power of fluorescent flow cytometry and hydrodynamic focusing technologies.

The haemogram included leucocyte count and leukocyte differential formula. Eosinophilia was defined as an absolute eosinophil count of more than 600 cells/ μ l.

Total immunoglobulin E class concentration was estimated using an immunoenzymatic method (Fluoroenzyme Analyzer Unikap 100 — Phadia). Normal levels for different age groups were provided by the producer. There were: 40 $\mu\text{g}/\text{mL}$ for 0–3 year-old patients; 60 $\mu\text{g}/\text{mL}$ for children aged 4–6 years; 70 $\mu\text{g}/\text{mL}$ for 7–15 years; and 63.6 $\mu\text{g}/\text{mL}$ for 16–18-year-olds.

The level of G class immunoglobulin was measured using the immunonephelometric technique. Based on information provided by the producer, the upper limits for each age group were: 1360 mg/dL for children aged 0 to 3 years; 1410 mg/dL for children aged 4–6; 1510 mg/dL for 7–15; and 1610 mg/dL for 16–18.

Anti-*Toxocara* IgG antibodies were detected by a commercial enzyme-linked immunosorbent assay (NovaLISA *Toxocara canis* IgG/NovaTec Immunodiagnostica) using an excretory/secretory (E/S) antigen derived from second-stage larvae. The minimum value regarded as a positive was 11 IU/mL. All patients had been differentially diagnosed for parasites that are typical in the Polish climate: *Ascaris lumbricoides*, *Toxoplasma gondi* and *Trichinella spiralis*. Tests for *Dirophilaria* and *Strongyloides* had not been performed, because such nematodes are not seen in our country [8].

Radiology

All children positive for *Toxocara* antibodies children (symptomatic and asymptomatic) had been examined using classical chest radiography. All children who had presented abnormalities in their chest radiography had performed the conventional computer tomography (CT). CT was performed using a 128-layer Somatom Definition AS apparatus (Siemens). These CT images were obtained from lung apices to lung bases. The intravenous contrast in the dosage of 1 ml/kg of body weight was given with a flow rate of 1 ml/sec. The investigations in the pulmonary and mediastinal windows were reviewed by two independent radiologists. Both of were informed about patients' clinical status, not about the diagnosis.

CT investigation was focused on the location, size and type of pulmonary lesions, pleural effusion and mediastinal lymphadenopathy. The internal features were classified into ground-glass opacities (GGO), nodules with halos and consolidations with calcifications. Ground-glass opacities were defined as hazy areas of increased attenuation of the lung with the underlying lung vessels not obscured. A nodule was defined as rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in diameter. Nodular

attenuation surrounded by a halo of GGO was called a nodule with a GGO halo. Pleural effusion was classified as present or absent. A mediastinal or hilar lymph node > 10 mm in the short-axis diameter was regarded as a significantly enlarged node. A consolidation was defined as an area of increased attenuation with the underlying lung vessels obscured.

This study was a retrospective analysis and all procedures were elements of routine diagnostic procedure in children with toxocariasis. This study was approved by Local Human Investigation Review Board and Ethics Committee of the Department of Infectious Diseases and Child Neurology in Poznan. All the procedures were documented in our patient record files.

Statistical analysis

GraphPad Prism version 5.01 for Windows, GraphPad Software Inc., was used for statistical evaluation.

Data are expressed as means \pm standard error of the mean. Blood cell counts, total IgE, IgG, serum levels of specific IgG antibodies and the gamma globulin level were calculated using the Mann-Whitney test between groups at the beginning of the study. A P-value < 0.05 was considered statistically significant.

Results

The medical documentation of 119 children was analyzed. All children were positive for *Toxocara sp.* antibodies.

In the documentation of 23 patients (T+/P+) we found abnormalities in the radiological examination of their lungs. There were 16 boys and 7 girls. The mean age was 3.58 ± 2.63 years. Their history and laboratory results were compared with the results of the rest of the seropositive patients (T+/P-) (Table 1). Only 15 children, who had abnormalities in radiological findings, presented clinical respiratory complaints such as a chronic cough, wheezing, asthma or haemoptysis. A cough (67%, 10/15) was the most common symptom among the patients. Other symptoms included chronic wheezing (47%, 7/15), dyspnoea (13%, 2/15), haemoptysis (7%, 1/15) and general weakness (7%, 1/15) (Table 1). Eight children were asymptomatic and their radiological abnormalities were the effect of routine control. The analysis of peripheral eosinophils and leukocyte number, and the level of IgE and specific anti-*Toxocara* IgG presented significantly higher values in (T+/P+) children than in (T+/P-)

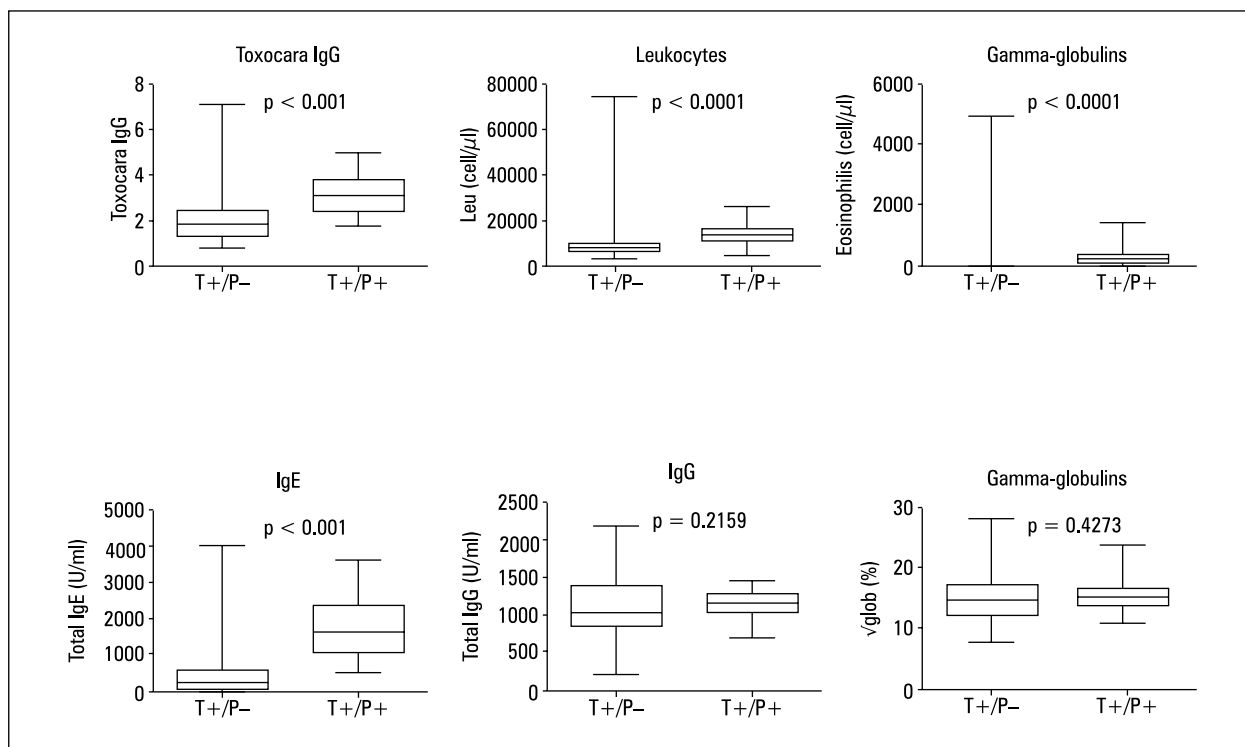


Figure 1. Laboratory parameters of children with pulmonary lesions and asymptomatic ones in the course of *Toxocara sp.* Infection
T+/P- — *Toxocara* seropositive, without radiological findings; T+/P+ — *Toxocara* seropositive, with radiological findings

group. The concentrations of total IgG and gamma globulins were not significantly different (Fig. 1).

The chest radiography showed defined lesions, which were confirmed in the CT scan. In 10 patients, CT showed irregular round nodules with and without halo ranging from 1 to 13 mm. The number of nodules varied from a single lesion to multiple, disseminated ones. All nodules were located in peripheral (subpleural) areas of the lungs. None of them were found in the central areas (Fig. 2). CT (mediastinal window) did not present lymphadenopathy and pleural effusion. In 13 children, CT imaging showed ground-glass opacities (GGO) with ill-defined margins. There were located bilaterally in the lower lobes of the lungs (Fig. 3). Central lymphadenopathy and pleural effusion were not found.

All (T+/P+) patients were treated with albendazole at a daily dose of 10 mg/kg of body weight in a 5-day administration. Six months after therapy the children had the radiological examination repeated. The patients presented two models of recovery. The children with well defined lesions in their first examination, developed pulmonary calcifications located in peripheral (subpleural) areas of the lungs. The pulmonary nodules calcification suggested the granulomas formation, in the response to healed infection (Fig. 4). The children, who had GGO in

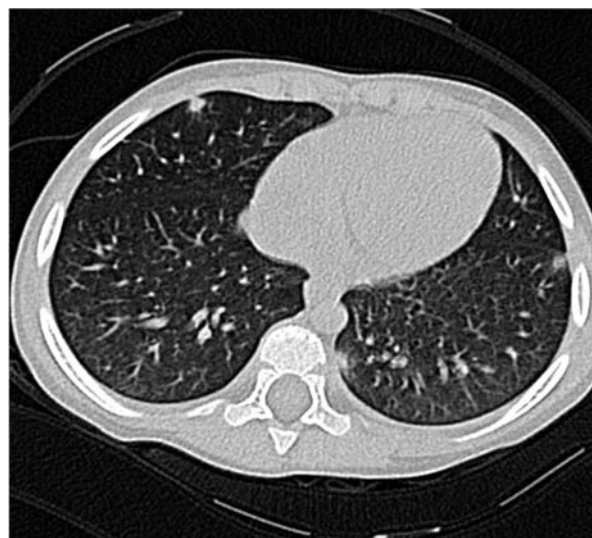


Figure 2. Irregular, well-defined nodules and round, interstitial consolidation mainly located in subpleural parts of both lungs. Chest CT with contrast — pulmonary window

their first CT, did not present any abnormalities in the second imagination.

Discussion

In 1952, Beaver identified the *T. canis* larva in the liver and produced the term “visceral larva migrans syndrome” to describe the clinical



Figure 3. Non-marginated areas of ground-glass opacities (black marker) in basal lobes of both lungs. Chest CT without contrast — pulmonary window

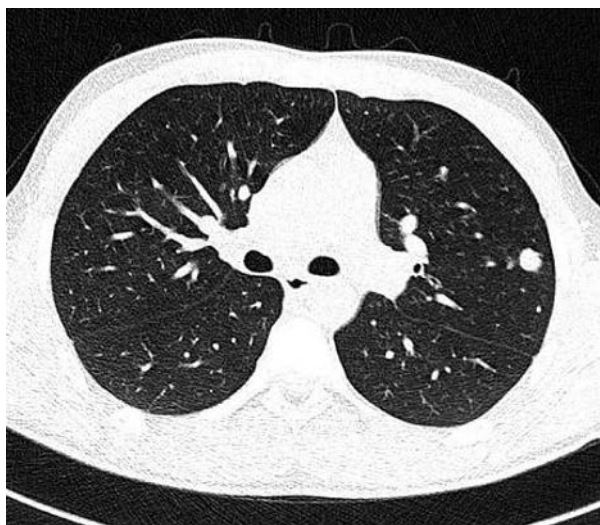


Figure 4. Calcified pulmonary nodules as the effect of treatment with albendazole. Chest CT without contrast — pulmonary window

manifestations of larval migration in the human body. The syndrome was characterized by leucocytosis, eosinophilia, hepatomegaly, respiratory symptoms and pulmonary infiltration in young patients with geophagia [9].

Currently toxocariasis is considered a zoonosis of a wide geographic distribution occurring in developed and undeveloped countries. In Poland, the number of newly diagnosed infections is also increasing successively.

The pulmonary manifestation of toxocariasis is called “covert”. It is characterized by non-specific symptoms that are not associated with the categories of classical VLM, incomplete

larva migrans, OLM or NLM. The clinical presentation of covert toxocariasis varies widely, with pulmonary involvement, such as asthma, acute bronchitis and pneumonia, with or without Löffler’s syndrome. The presence of asthma or a wheezing breath in patients with toxocariasis was confirmed by many authors [10, 11]. The frequency of both symptoms varies from 9% to more than 30% of adult patients [12]. Haemoptysis as the symptom of pulmonary toxocariasis was not described in children; however, a few descriptions were found for adults [13].

The ELISA test is the most often used for diagnosing toxocariasis and for epidemiologic studies, as the disease is difficult to detect by applying direct diagnostic methods. The method is reported to have a high sensitivity and specificity with very low levels of cross-reactivity when the excretory and secretory antigens of the second-stage *T. canis* larvae are used [14]. Regarding the variability of symptoms in the “covert” form, it is very important to perform radiological imaging to confirm the presence of *T. canis* larvae. According to our study, the routine radiological examination performed in children with seropositive *Toxocara* demonstrated that pulmonary abnormalities are more common than in the clinical presentation. In our study, all seropositive children underwent X-ray screening. Lesions were presented by 32% of patients in radiological imaging. The comparison between groups confirmed that pulmonary lesions are more typical for young children (Table 1). We didn’t find any information about the frequency of pathological lesions in children in available literature. Located subpleurally, characteristic pulmonary lesions measure approximately 1 cm in diameter. They are rather round, comprising a central, tiny, dot-like lesion and a surrounding halo of ground-glass opacity. They should be differentiated with metastases [15]. With the development of infestation, bilateral, patchy airspace/alveolar areas of increased opacity and segmental or even lobar areas of opacification may develop. Serial radiographs may show migration of areas of increased opacity. Such findings are associated with several pulmonary processes. Regarding inflammatory diseases, a pulmonary nodule with a halo is occasionally seen in patients with eosinophilic lung diseases such as simple pulmonary eosinophilia, idiopathic hypereosinophilic syndrome and parasitic infections [16]. Kim et al. reported that a halo of ground-glass attenuation resulted histopathologically from pulmonary infiltrations by eosinophils and other inflammatory cells; however, they did not mention the loca-

tions of eosinophilic infiltrations in detail [17]. Moreover, a halo of ground-glass attenuation corresponded to infiltration by inflammatory cells, including eosinophils, into the alveolar septa [18]. In our study, the comparative data was taken from the adult group of patients. The analysis conducted presented a close correlation between the age of patients and the frequency of appearance of changes in the lungs. The younger patients were more likely to develop the pulmonary lesion. When pulmonary infiltrates are found on the chest images of a child, it is fundamental and mandatory to distinguish malignant from benign lesions. Pulmonary infiltrates such as GGO, nodules, consolidation or mixed lesions can be found in bacterial or parasitic infectious diseases as well as malignancy. In some cases, malignant lesions mimic infectious processes in imaging studies [19]. Clinicians should decide when to start an invasive investigation of infiltrates seen on chest images. This should be based on a patient's symptoms, laboratory findings, characteristics and changes in pulmonary lesions over time. Based on our observation, pulmonary lesions in young children with eosinophilia and hyperimmunoglobulinemia E could be related to toxocariasis, and for this reason they rather require follow-up, than immediate invasive diagnostic work-out.

Conflict of interest

The authors declare no conflict of interest.

References:

- Espinoza YA, Huapaya PH, Roldani WH, Jimenez S, Arce Z, Lopez E. Clinical and serological evidence of *Toxocara* infection in school children from Morrope district, Lambayeque, Peru. *Rev Inst Med Trop S Paulo* 2008; 50: 101–105.
- Hotez PJ, Wilkins PP. Toxocariasis: America's most common neglected infection of poverty and helminthiasis of global importance? *Plos Negl Trop Dis* 2009; 3:e 400 www.plosntds.org. doi: 10.1371/journal.pntd.0000400.
- Magnaval JF, Glickman LT, Dorchie P, Morassin B. Highlights of human toxocariasis. *Korean J Parasitol* 2001; 39: 1–11. doi: 10.3347/kjp.2001.39.1.1v.
- Dispomier D. Toxocariasis: Clinical Aspects, Epidemiology, Medical Ecology, and Molecular Aspects. *Clin Microbiol Rev* 2003; 16: 265–272.
- Lee KT, Min HK, Chung P, Chang JK. Studies on the including possibility of human visceral larva migrans associated with eating habit of raw liver of domestic animals. *Korean J Parasitol* 1976; 14: 51–60.
- Paul M, Stefaniak J, Twardosz-Pawlik H, Pecold K. The co-occurrence of *Toxocara* ocular and visceral larva migrans syndrome: a case series. *Cases J* 2009; 2: 6881–6888. doi: 10.1186/1757-1626-2-6881.
- Kazek B, Jamroz E, Mandera M, Bierzyńska-Macyszyn G, Kluczevska E, Marszał E. The cerebral form of toxocarosis in a seven-year-old patient. *Fol Neuropathol* 2006; 44: 72–76.
- Yoshikawa M, Koyama N, Hontsu S, Yamamoto Y, Mikasa K, Kimura H. Lessons from eight cases of adult pulmonary toxocariasis: Abridged republication *Respirology* 2011; 16: 1014–1015. doi: 10.1111/j.1440-1843.2011.02000.x.
- Pawłowski Z. Toxocariasis in humans. Clinical expression and treatment dilemma. *J Helminthol* 2001; 75: 299–305.
- Perlingiero JG, Gyorgy P. Chronic eosinophilia. Report of a case with necrosis of the liver, pulmonary infiltrations, anemia and ascariis infestation. *Am J Dis Child* 1947; 73: 34–36.
- Buijs J, Egbers MW, Lokhorst WH, Savelkoul HF, Nijkamp FP. *Toxocara*-induced eosinophilic inflammation. Airway function and effect of anti-IL-5. *Am Respir Crit Care Med* 1995; 151: 873–878.
- Carvalho E, Rocha R. Toxocariasis: visceral larva migrans in children. *J Pediatr (Rio J)* 2011; 87: 100–110. doi:10.2223/JPED.2074.
- Cojocariu IE, Bahnea R, Luca C, Leca D, Luca M. Clinical and biological of adult toxocariasis. *Rev Med Chir Soc Med Nat* 2012; 116: 1162–1165.
- Kustimur S, Dogruman F, Oguzulgen K et al. *Toxocara* seroprevalence in adults with bronchial asthma. *Trans R Soc Trop Med Hyg* 2007; 101: 270–274.
- Izumikawa K, Kohno Y, Izumikawa K. Eosinophilic pneumonia due to visceral larva migrans possibly caused by *Ascaris suum*: a case report and review of recent literatures *J Infect Dis* 2011; 64: 428–432.
- Kang YR, Kim SA, Jeon K et al. Toxocariasis as a cause of new pulmonary infiltrates. *Int J Tuberc Lung Dis* 2013; 17: 412–417. doi: 10.5588/ijtld.12.0273.
- Lim Y, Kim JH, Oh SH, Jeon SC, Koh HC, Lee YH. Pulmonary toxocariasis masquerading as metastatic tumor nodules in a child with osteosarcoma. *Pediatric Blood & Cancer* 2009; 53: 1343–1345. doi: 10.1002/pbc.22213.
- Kim Y, Lee KS, Choi DC et al. The spectrum of eosinophilic lung disease: radiologic findings. *J Comput Assist Tomogr* 1997; 21: 920–930.
- Kim HY, Shim YM, Lee KS, Han J, Yi CA, Kim YK. Persistent pulmonary nodular ground-glass opacity at thin-section CT: histopathologic comparisons. *Radiology* 2007; 245: 267–275.