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Gh. Plăcintă[1, 2], associate professor

LYMPHADENOPATHY WITH PROLONGED HYPEREOSINOPHILIA (FOR 8 YEARS) DURING TOXOCARIASIS — CASE REPORT

[1] Department of Infectious Diseases, SMPhU "Nicolae Testemitanu", Chisinau, Republic of Moldova,

[2] Clinical Hospital of Infectious Diseases "T. Ciorba", Chisinau, Republic of Moldova

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Г. Плечинте[1, 2]

ЛІМФАДЕНОПАТІЯ З ТРИВАЛОЮ ГІПЕРЕОЗИНОФІЛІЄЮ (8 РОКІВ) ПІД ЧАС ТОКСОКАРОЗУ — КЛІНІЧНИЙ ВИПАДОК

[1] Державний медичний і фармацевтичний університет ім. Ніколає Тестеміцану, Кишинів, Республіка Молдова,

[2] Клінічний госпіталь інфекційних хвороб ім. Т. Чорбе, Кишинів, Республіка Молдова

Токсокароз є досить частим захворюванням, особливо у дітей дошкільного віку. Симптоми захворювання вельми різноманітні, тому зіткнутися з ним можуть фахівці різних галузей: педіатри, гематологи, терапевти, окулісти, невропатологи, гастроентерологи, дерматологи і багато інших. У деяких випадках захворювання може перебігати малосимптомно, що ще більше ускладнює діагностику. При цьому воно є серйозним і без лікування може призвести до ураження багатьох органів. Вісцеральний токсокароз реєструється переважно у дітей віком 1,5–5 років. Захворювання характеризується тривалим перебігом і тяжким ураженням багатьох органів і систем. Одним із постійних проявів вісцерального токсокарозу є стійка і тривала еозинофілія крові, аж до розвитку еозинофільно-лейкимоїдної реакції. У представленому нами випадку, захворювання перебігає без скарг і порушення самопочуття дитини, але з виразними змінами в клінічному аналізі крові (гіпереозинофілія і лейкоцитоз) і високими титрами антитіл до токсокарів.

Ключові слова: вісцеральний токсокароз, гіпереозинофілія.

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Toxocariasis is a pretty common disease, especially in children of preschool age. Symptoms of this disease are very diverse, so a variety of specialists can meet them: pediatricians, hematologists, internists, ophthalmologists, neurologists, gastroenterologists, dermatologists, and many others. In some cases, the disease can occur with a few symptoms that are more difficult to be diagnosed. However, the disease is a serious one, and without treatment can cause multiorgan damage.

Visceral toxocariasis is registered mainly in children aged 1.5 to 5 years. The disease is characterized by a prolonged course and the heavy defeat of many organs and systems. One of the most constant manifestations of visceral toxocariasis is a persistent and prolonged blood eosinophilia, until the development of hyper eosinophilia with hyper leukocytosis reaction.

In the presented case, the disease developed without any complaints and breach the child's state of health, but with pronounced changes in the clinical analysis of blood (hypereosinophilia, and leukocytosis) and high titers of antibodies to toxocara.

Key words: larval toxocariasis, hypereosinophilia.

Introduction

In the last years parasitic diseases returned to medical practice raising concerns and issues of diagnosis, treatment and evolution. Geographic studies of parasitosis, as well as the large number of human and animal diseases increase the importance of a few relevant ways designed to prevent and exercise effective control of these infections [1–3; 6].

Parasitic cycles seem simple at first sight, however, the mechanisms that allow the installation of the parasitic agent in the hosts, are often difficult to assess. Parasitosis which include a systemic element in the evolutionary cycle with hematogen dissemination and multiple organ localization is the visceral larva migrans form of Toxocara canis that is a common event in senior medical practice [1]. Toxocariasis is a zoohelmintosis, human migration being caused by different species of Toxocara larvae through the body, with further systemic lesions [2; 3].

There are four known species of Toxocara: *Toxocara canis, Toxocara mistax (cati), Toxocara vitulorum* and *Toxocara leonina*. In medical practice the best known and studied are species: *Toxocara canis* and *Toxocara mistax*.

Children's play habits and their attraction to pet exposes them to a greater risk of infection than adults. The most exposed are children who insert objects in the mouth or those whose families have pets [2].

It is well known and widely accepted that the disease can also occur in people who are not in contact with dogs, the phenomenon leading to the concept of the possibility of the environment contamination (parks, playgrounds, streets etc.) with infected eggs and larvae [2; 10].

Toxocariasis seroprevalence varies from country to country. Thus in the Netherlands — 19% of the studied soils is infested, in Germany — 2.5%, Czech Republic — 36%, Brazil — 39%, Spain — 37%, Jordan — 9.8%. It is estimated that 20% of dogs in the US excreted *T. canis*. Often these dogs infects the children playgrounds. A study of 800 soil samples taken from the parks in the UK demonstrated that 24% of these samples contained eggs of *T. canis* [4; 5].

The helminthology sanitary examinations of soil samples from different districts from R. Moldova carried out in parasitological laboratory of the National Center for Public Health have found eggs of Toxocara spp. In 23.7% of soil samples in 2008, 20.7% — in 2009, 33.8% — 2010 and 37.5% in 2012. The seroprevalence increases with age, the risk of infestation being highest in children aged 1–10 years [9].

Adult worms of *T. canis* are found in the digestive tract of the dogs. Here, the females lay between 20 000 and 200 000 eggs per day, which further are eliminated with dog feces. The eggs reaching the ground (under favorable conditions of temperature and humidity) embryonate in 2–5 weeks and become infested, producing larvae of type II (L2); These larvae are ingested by the dogs and get into the digestive tract, cross the intestinal wall suffering two types of migration, depending on the age of the dog: to puppies (under 5 weeks) cycle is performed entero-pneumo-tracheal and then again enteral and at adult dogs is made entero-pneumo-somatic [7; 8].

Basically, puppies are infested either by transplacental way or during feeding, or through using the residues containing larvae L2.

In humans, the ingestion of L2 eggs is followed by their hatching in small intestine, the perforation of the intestinal wall and reaching the liver, lung, brain, eye, heart of the larva. The migration of the larva anywhere in the body is a condition known as Visceral Larva Migrans. Since human being is an abnormal host, the larvae is no longer developing after this stage and not becomes an adult worm [4; 5; 7].

During the visceral migration phase, eosinophilia and tissue necrosis occurs; the reaction is less intense in the eye, where you can find rare mononuclear cells and eosinophils [4; 5].

Major host response of *T. canis* surface antigens include a marked eosinophilia (granulomatous response) and hypergammaglobulinemia with hyper-IgE (as a manifestation of Th2 subset of T helper lymphocytes).

Chronic parasite antigen production and continuous stimulation of the immune system can lead to a permanent "alert immune," which may underlie the recurrences of the respiratory and/or cutaneous manifestations [1; 2].

Although it is common, especially in children, human Toxocariasis remains a less known topic in medical practic. Toxocariasis has varied symptoms, affect a broad spectrum of clinicians — family doctors, pediatricians, internists, infectious disease physicians, ophthalmologists, neurologists, allergists, hematologists etc.

Depending on the symptoms, which is highly polymorphic, there are four clinical form of infection with Toxocariasis:

1. Larva migrans visceralis — mainly affects children under 5 years. Symptoms of infection depends on the intensity, location and sensitivity of the infected person. In 50% of the infected children are present:

— General symptoms: fever (80%), asthenia, anorexia, weight loss;

— Respiratory symptoms: cough (60–80%), asthmatic dyspnea;

— Skin signs: rash (20%), erythema nodosum, edema quincke;

— Hepatosplenomegaly (65–87%) [1; 2; 9; 10].

Myocardial and neurological localization is rare. Neurological simptoms appear because of CNS larval location and are represented by: epileptic episodes, seizures (20–30%), hemiparesis, eosinophilic self-limiting meningitis and rarely encephalitis [2; 6; 8; 10].

2. Larva migrans ocularis — most commonly affects children aged 5–16 years and adults and is characterized by unilateral eye disease. Ocular complications are the result of the forming of the granulomas in vitreous: chorioretinitis, chronic endophthalmitis. The most severe complication is retinal detachment and blindness. Eye symptoms include strabismus (10%), decreased visual acuity (84%), endophthalmitis (6%), periorbital edema (2%) [2; 3; 6; 7; 10].

3. Atypical Toxocariasis (occult) — More frecvent in adults and teens. This form has been described in patients presenting symptoms less specific than the

larva migrans: asthenia, abdominal pain, skin lesions, respiratory distress, cough, wheezing, anorexia, hepatomegaly, headache, fever, myalgia, nausea, growth disorders . This form is accompanied by increased titres of Toxocara antibodies, eosinophilia was detected in only a small proportion of cases. It is considered that patients with atypical Toxocariasis are less able to develop a protective immune response allowing unlimited larval migration with serious injuries [1–3; 6; 7; 10].

4. Asymptomatic Toxocariasis — is diagnosed only in the context of serological assessments. We should mention that eosinophilia is rare, and the titer of anti Toxocara are moderately increased. This form is common in the population of many countries [2; 3; 10].

Diagnosis is established based on clinical and laboratory data. Clinical manifestations in visceral larva migrans are extremely varied, from symptomatic to associated forms with "asthmatic" events. Determining the etiology of visceral larva migrans syndrome is difficult because the larvae can be detected only in sputum or tissue biopsy, which is rarely indicated. Therefore immunoassay test is a specific diagnostic method. Serological test allows the determination of IgE antibodies and IgG antibodies by ELISA or Western — blot being positive in 78% of cases in visceral larva migrans and 45% of the larvae migrans ocularis [7; 8].

The diagnosis is suggested by biological changes indi: hyperleukocytosis (20000–100000/mm^2) with major hypereosinophilia (40%) that is persistent for months or even years. Hypereosinophilia appear abruptly in onset and persist at very high values. It also noted an ESR and gammaglobuline increase. [2; 3; 8; 9]

People with larva migrans ocularis have no systemic clinical manifestations characteristic for Lavra migrans visceralis. Clinical signs are unobtrusive and should be differentiated from other eye diseases, including retinoblastoma with which it is sometimes confused [1; 2; 9; 10].

Unlike the LMV, eosinophilic value does not exceed 10%. The presence of eosinophils in the aqueous humor suggests a parasitic ophthalmia, but it is not specific for Toxocariasis. Instead, the presence of antibodies in eye fluids indicates the presence of Toxocara parasite especially when the titer of this antibodies is higher than that of serum antibodies.

The new imagistic techniques as ultrasound exam, CT, MRI can be used to detect and locate granulomatous lesions caused by Toxocara [2; 6; 9].

Treatment is complex and aims to: decrease the inflammatory response that occured as a result of larvae metabolic products with antihistamines and corticosteroids, indicated especially in patients with myocardial and CNS touch and larvae destruction by anthelmintic medication. [4; 5; 7]

According to the literature the most frequently recommended medication in visceral forms is Diethylcarbamazine (piperazine derivatives) at a dose of 6 mg/kg/day divided into 3 doses for 21 days. The doses are gradually increased to avoid the danger of the Herxheimer reaction (endotoxin shock). Another therapeutic option are albendazole group (benzimidazole derivative) that is as effective as other drugs and is available in Moldova. It is indicated in dose 10–15 mg/kg into 2 doses for 5–21 days taken during meals and in combination with silymarin. It is contraindicated in children younger then 1.5–2 years and pregnant women. Mebendazole is indicated at a dose of 10–15 mg/kg 3 days/week for 6 weeks and in severe forms at a dose of 20 to 25 mg/kg/body weight/day, for 21 days. It is contraindicated in children younger than 2 years old, pregnant women. Thiabendazole is indicated at a dose of 25–50 mg/kg/day, for 5 to 21 days, but has very rare indications due to adverse reactions. Ivermectin is indicated at a dose of 200 mg/kg/day, with 2 doses in 14 days [2; 3; 6; 8; 11]. As diethylcarbamazine, Ivermectin is not available in R. of Moldova.

The effectiveness of treatment can be evaluated by progressively decreasing eosinophilia, regression of the clinical manifestations and reduction of the specific antibody titer.

The actuality of this issue had increased in the past decade, growing on the background of the canine loitering, which caused massive pollution of the environment with eggs of this parasite, the fact that transformed this disease in a serious medical and social problem.

Case presentation, results, discussion

We present the case of child C.D. age 10 years from urban areas.

From personal history: born from V pregnancy at 39 weeks, cranial presentation, birth weight 3700 g. Vaccinated according to schedule, developed according to age.

From pathological history: up to 4 years of age often acute respiratory infections developed (3–4 times/year), acute laryngo-tracheitis, acute tonsillitis; in May 2014 — tracheobronchitis; in June 2014 — acute tonsillitis, in June 2014 — right bronchopneumonia.

Mental and motor development corresponding the age of the child.

Living conditions are correlated with measures of hygiene compliance, source water supply, had not have pets.

Disease history: at the age of 2 the child present for the first time unexplained right submandibular lymphadenopathy. It was directed at otolaryngologist, where it is established the diagnosis of acute submandibular lymphadenopathy. Clinical examinations were performed: WBC — 10.9×10^9/l, unsegmented — 3%, segmented — 58% eosinophils — 4%, lymphocytes — 32% monocytes — 3%, ESR — 4 mm/h. Antibiotic treatment started with (Amoxicillin), antihistamines, antiinflammatory drugs. Lymphadenopathy regressed very fast. Later at the age of 4 (in November 2008), the child addressed to the family doctor for routine investigations. During investigations is was determined the presence of leukocytosis (26.7×10^9/l) and hypereosinophilia (15%) with unknown cause. Chest Rx — normal. Pediatrician indicates treatment with Cefazolin, antihistamines, immunomodulatory drugs for 10 days. After finishing the treatment: WBC — 6.0, eosinophils — 3%, with maintainance of the normal values for the next 7 months. In August 2009, appears low grade fever (37.2–37.4 °C), the child become passive, complains on discomfort in the abdomen, right submandibular lymphadenopathy. CBC: WBC — 29.3×10^9/l, nes. — 7% segm. — 44% eos. — 24%, limf. — 20% mono — 5%, ESR — 8 mm/h.

Based on inconsistencies between peripheral blood and clinical data, the child is directed to hematology department of the Oncology Institute for diagnosis and treatment. The child was repeatedly investigated revealing the increase of eosinophilia up to 80%, leukocytosis — $36.7\cdot10^9$/l. During the next two years the child was hospitalized 3 times in the hematology department. All performed tests resulted in various hypotheses finally was leukocytic reaction of eosinophilic type.

Because that fact that eosinophilia was central type, it was indicated the serological test for Toxocara canis, Ascaridae, Giardiasis and total IgE. Due to the positive IgG result for Ascaridae (0.90/0.27) is was set a short 3 day-course of treatment with Albendazole 2 times per day. The child's condition improves, leukocytosis and hypereosinophilia regressed.

In July 2014 the mother noticed again a submandibular lymphadenopathy without additional clinical manifestations. The child had no complaints. The family addresses to GP were the child is examined clinically and serologically.

The positive results of serological tests for Toxocara IgG (2.26/0.24), Ascaridae IgG (1.14/0.27) and a marked hypereosinophilia allowed targeting the child to CHID "Toma Ciorba" for diagnosis and treatment.

The diagnosis of Toxocariasis. Larva migrans visceralis, severe form was established based on clinical and laboratory investigations.

Although it was not established the acute or chronic caracter of infection with Toxocara canis, the anti-parasite treatment was indicated (Albendazole 400 mg/day p. o., 10 consecutive days). Before that, the child attended short courses of albendazole (3 days) in 2012. We must mention that before initiation of anti-parasite treatment, the absolute number of leukocytes and eosinophils was increasing. Biochemical test results were within normal limits.

Equally relevant are the results of laboratory investigations carried out during 2009–2012. (Table 1).

It must be noted that each rise of leukocytes and eosinophils in peripheral blood was preceded by a

Table 1

The CBC Data During 2009–2012

Indicators	Date						
	18.08.09	28.12.09	05.02.10	13.01.10	01.11.11	10.05.11	23.03.12
Hemoglobin, g/l	120	118	103	117	119	114	131
Erythrocytes, 10^{12}/l	4.1	3.5	3.5	3.8	3.8	3.8	4.4
Color index	0.89	0.89	0.8	0.9	0.9	0.9	1.0
Thrombocytes, 10^9/l	328	198	–	217	–	–	+
Leukocytes, 10^9/l	36.7	15.2	8.3	6.8	5.2	24.9	7.4
Myelocytes, %	–	–	–	–	+	–	–
Metamyelocytes, %	–	–	–	–	+	–	–
Nonsegmented, %	2	10	9	4	6	4	8
Segmented, %	12	12	45	42	35	25	42
Eosinophils, %	**80**	**51**	**8**	**14**	**5**	**40**	**4**
Lymphocytes, %	5	24	35	38	49	26	45
Monocytes, %	1	3	3	2	5	5	1
ESR, mm/h	20	28	5	8		8	7

Table 2

The CBC Data During 2014–2015

Indicators	Date					
	22.07.14	29.08.14	28.10.14	04.11.14	13.11.14	12.01.15
Hemoglobin, g/l	101	115	110	115	113	112
Erythrocytes, 10^{12}/l	3,4	3,7	3,7	3,9	3,9	3,8
Color index	0,9	0,9	09	0,8	0,8	0,9
Thrombocytes, 10^9/l	—	268	—	—	296	245
Leukocytes, 10^9/l	14,3	5,8	13,9	38,0	5,4	30
Myelocytes, %	—	—	—	—	—	—
Metamyelocytes, %	—	—	—	—	—	—
Nonsegmented, %	3	3	12	1	1	10
Segmented, %	18	40	32	17	38	9
Eosinophils, %	**48**	**17**	**38**	**71**	**7**	**59**
Lymphocytes, %	27	37	14	9	46	20
Monocytes, %	4	3	4	2	8	2
ESR, mm/h	6	10	8	26	20	6
Anizocitoza	+	—	—	—	—	—

submandibular or latero-cervical lymphadenopathy. With the initiation of the treatment, the number of eosinophils, leukocytes, and the lymphadenopathy are in regression. After the end of the treatment during the next two months the child's condition was satisfactory. During 2014, the child had 4 courses of 10 days of anti-parasite treatment followed by clinical and laboratory improvement (Table 2).

The severe form of the disease was caused by a massive infestation and the lenght of the evolution was due to the fact that specific treatment was not applied properly. Due to the duration of the desease and lack of appropriate treatment by using repeated short courses of anti-parasite drugs, it was installed a state of immune deficiency. Relevant is that serology for Toxocara canis IgG positive had a cyclical rise with highlighting leukocytosis and eosinophilia in peripheral blood. The high values of antibodies against Toxocara (1.441 to 2.463) associated with changes in the peripheral blood, demonstrates the direct action of the parasite on host immune profile.

Discussion and conclusions

1. The presented case correlates with the categories of those without any specific clinical entity. Silent onset and clinical expression guides us in the beginning toward a haematological etiology.

2. Leukocytosis is the result of Toxocariasis a proof being the improvement of leukocytosis after anti-parasite treatment initiation.

3. The anti-parasite treatment was well tolerated in the presented case, but the larvae remain in the tissue even after treatment, being a continuous source of stimulation for the immune system.

4. The presence of a chronic parasite antigen in the tissues causes permanent stimulation of the host immune system, what reperesent the reason for leukocytosis and marked hypereosinophilia.

5. It is necessary to carry out epidemiological studies to assess the degree of infestation of the children playgrounds with Toxocara.

Ключові слова: вісцеральний токсокароз, гіпереозинофілія.

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