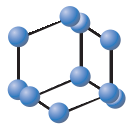


## REVIEW ARTICLE


**BENTHAM  
SCIENCE**

## Helminth Infections and Cardiovascular Diseases: *Toxocara* Species is Contributing to the Disease



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**Abstract:** Toxocariasis is the clinical term used to describe human infection with either the dog ascarid *Toxocara canis* or the feline ascarid *Toxocara cati*. As with other helminths zoonoses, the infective larvae of these *Toxocara* species cannot mature into adults in the human host. Instead, the worms wander through organs and tissues, mainly the liver, lungs, myocardium, kidney and central nervous system, in a vain attempt to find that, which they need to mature into adults. The migration of these immature nematode larvae causes local and systemic inflammation, resulting in the “larva migrans” syndrome. The clinical manifestations of toxocariasis are divided into visceral larva migrans, ocular larva migrans and neurotoxocariasis. Subclinical infection is often referred to as covert toxocariasis. One of the primary causes of death all around the world is cardiovascular disease that accounted for up to 30 percent of all-cause mortality. Cardiovascular disease and more precisely atherosclerotic cardiovascular disease, is predicted to remain the single leading cause of death (23.3 million deaths by 2030). A-quarter of people presenting the disease does not show any of the known cardiovascular risk factors. Therefore, there is considerable interest in looking for novel components affecting cardiovascular health, especially for those that could improve global cardiovascular risk prediction. This review endeavours to summarize the clinical aspects, new diagnostic and therapeutic perspectives of toxocaral disease with cardiovascular manifestations.

**Keywords:** Toxocariasis, cardiovascular, visceral larva migrans, epidemiology.

**INTRODUCTION**

*Toxocara canis* (*T. canis*) and *Toxocara cati* (*T. cati*), roundworms of dogs and cats, are probably the most common gastrointestinal zoonotic helminths of domestic canids and felids world-wide [1]. Natural hosts as well as paratenic hosts, including the human become infected by ingesting either embryonated eggs containing third-stage larvae, from soil (geophagia, pica), dirty hands or raw vegetables, or larvae from undercooked giblets, meat or offals [2]. *Toxocara* larvae hatch in the stomach and migrate into the mucosa of upper small intestine and penetrate via blood and lymphatic vessels throughout the body, resulting in somatic in many types of tissues. The liver is an important site for controlling the migration of *Toxocara* larvae. Dissemination occurs via the blood-borne route, through tissues and body cavities [3]. The classical clinical syndromes of *Toxocara* infection are divided into visceral larva migrans (VLM) and ocular larva migrans (OLM). VLM syndrome most commonly affects the

liver, skin, and lungs, but involvement of the central nervous system and myocardium are rare. In OLM, migrating larvae can induce granulomatous retinal lesion, which are characterized by complaints of loss of visual acuity, squint and seeing lights. A third clinical syndrome, called covert toxocariasis (CT), was found in patients with clinical symptoms that are non-specific by itself and do not fall within the categories VLM or OLM, but form together a vague complex of symptoms [4]. The prevalence of patent *Toxocara* infections is highest in dogs and cats and is much less common in adult animals in many countries all over the world [5]. Several epidemiological and clinical studies have reported that regular contact to dog and cats, rural residence, geophagia or dementia has been identified as risk factors for the acquisition of human *Toxocara* infection [6-10].

One of the primary causes of death all around the world is cardiovascular disease that accounted for up to 30 percent of all-cause mortality [11]. Cardiovascular disease and more precisely atherosclerotic cardiovascular disease, is predicted to remain the single leading cause of death (23.3 million deaths by 2030) [12]. Despite the fact that major risk factors for cardiovascular disease have been firmly established, twenty-five percent of people presenting the disease do not

\*Address correspondence to this author at the Department of Parasitology and Mycology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran, P.O. Box: 3149779453; Tel/Fax: + 98 26 32563325; E-mail: [zibaeim@sums.ac.ir](mailto:zibaeim@sums.ac.ir)

show any of the known cardiovascular risk factors [13]. Therefore, there is considerable interest in looking for novel components affecting cardiovascular health, especially for those that could improve global cardiovascular risk prediction.

Based upon the immuno-inflammatory response elicited by infectious disease, the parasitological contribution to atherosclerosis, the pathological basis of the vast majority of cardiovascular disease, represents a long-standing controversy [14, 15].

Previous studies have suggests that some parasitic agents such as *Trypanosoma cruzi*, cause Chagas disease, might contribute to atherosclerotic vascular diseases [16]. In human toxocariasis (VLM syndrome) the larvae can enter the liver, the lung, the kidney, brain or the heart. The association between *Toxocara* spp infection and vasculitis manifestations is unusual but has been previously reported [17, 18].

To improve knowledge regarding the role of *Toxocara* in contributing to the disease, the present review conducted to the clinical manifestation cardiovascular consequences, diagnostic and treatment perspectives in human toxocariasis.

## AGENTS

*Toxocara* species are nematodes, taxonomically included within the order and family Ascaridida.

Our concept is *T. canis* is more important than *T. cati* in causing human infection and disease because cats, not dogs, bury *Toxocara* ova contamination faeces, making infectious ova less accessible to susceptible individuals. Further reasons include the fact that morphometry of larvae in histological sections and early serology, using cross-reactive antigens, failed to implicate *T. cati* over *T. canis* in human cases and also the lesser tendency for brain involvement in the murine model of *T. cati* toxocariasis [19]. Based on generalized exclusion, *T. canis* was deemed to be the more important aetiological agent of human toxocariasis.

There are reports on the location of *T. cati* larvae in paratenic hosts as a causative agent of *Toxocara* infection in human [20]. Both visceral toxocariasis and ocular larva migrans, caused by migrating larvae, as well as adult *T. cati* infections of humans have been described [20]. *T. cati* has been reported in case of decreased visual acuity caused by a macular lesion of the eye, where the patient's serum was positive reactive to *T. cati* antigens [21]. The studies by Zibaei *et al.* showed the role of *T. cati* in *Toxocara* infections of animal model [22, 23].

## LIFE CYCLE

A wide variety of animals, including humans can become infected with *Toxocara* species by ingesting eggs contain larvae from contaminated soil and the consumption of contaminated raw meat or liver. In the paratenic or transport hosts, the larvae do not develop to maturity, but migrate for months throughout host tissues before lodging within host tissues in state of arrested development. The larvae do not encyst but remain exposed to the host environment, absorbing nutrients across the nematode cuticle. The larvae can

survive in tissue for several years despite vigorous host immunologic responses to parasite antigens (Fig. 1).

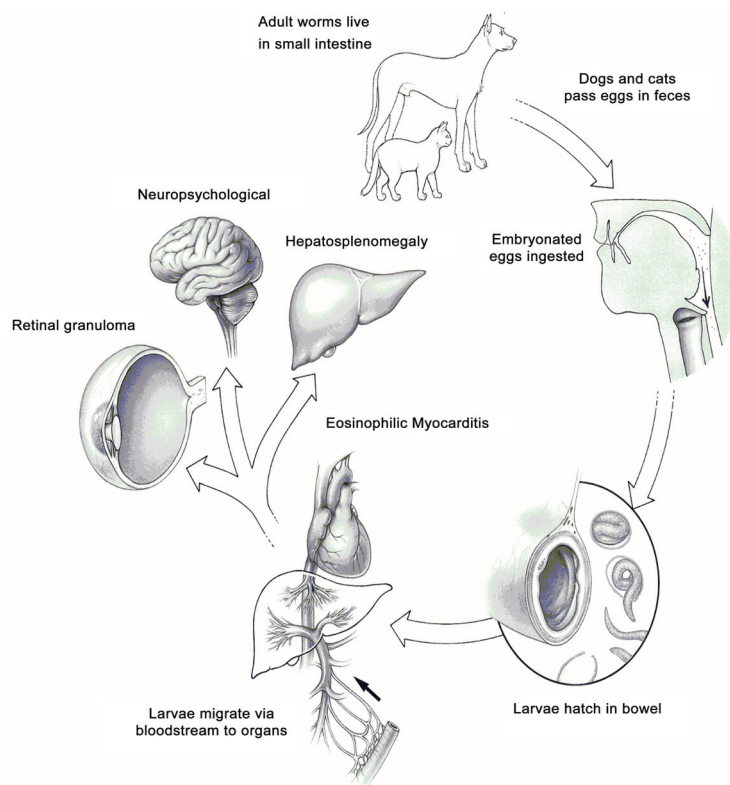
## EPIDEMIOLOGY

*T. canis* and *T. cati* are nematode, which infects canines and felines worldwide, respectively, and as widespread environmental results dissemination of them ova in hosts faeces, other unnatural or paratenic hosts contains earthworms, ants, poultry, cockroach, and mammals are contacted to the parasite. These helminths appear to have caused disease for millennia [24]. Toxocariasis in man is presumed to be contracted through the ingestion of eggs from contaminated soil (sapro-zoonosis); children with pica and contact to puppies appear to be particularly vulnerable [25]. Recent data suggests that dogs affected with *T. canis* may cause people infected through direct contact [26]. Additional risk factors include mental retardation requiring institutionalization and ingestion meat from paratenic hosts such as chicken and lamb [27-30]. Cats and other felines act as definitive hosts for the cat roundworm, *T. cati*, which is responsible for toxocariasis. The majority of reported human cases of toxocariasis in the past have been associated with *T. canis* not with *T. cati*. The habit of cats covering their faeces in soil tends to prevent the spread of eggs, give further support to this preference for *T. canis* infection [31]. For religious reasons, dogs are avoided in the more of Islamic regions, whereas cats are favorite pet. Worldwide studies of *T. canis* and *T. cati* have demonstrated a distribution between 1-45% and 0.8-59.3% in dogs and cats, respectively [32, 33].

Because toxocariasis does not become patent in humans, estimates of prevalence of humans depend on immunosurveys. These sero-epidemiologic surveys revealed wide difference depending on the man tested. The seroprevalence of most adults were 3.1% in Spain and 7.5% in Australia (developed countries), but the higher seroprevalence of *Toxocara* infection was found in 30.4% in Nigeria and 20.5% in Brazil (developing countries and tropical regions) [34-37]. Serological studies demonstrated primarily among children in developed countries have indicated sero-prevalence levels of *T. canis* in New Zealand (0.7%), Japan (1.6%), Denmark (2.4%), Australia (7.5%), the United States (14%), and 15% in Poland [32, 38, 39]. By contrast, the higher values of seroprevalence have been revealed in tropical and tropical regions or developing countries including Nigeria (30%), Swaziland (45%), La Reunion (93%), Nepal (81%), Indonesia (63.2%), Malaysia (58%), Brazil (36%) and 37% in Peru [40-42].

## PATHOGENESIS

The compounds surface coat of *Toxocara* larvae is a dynamic structure that turns over quite rapidly and generates large quantities of glycosylated excretory-secretory proteins [43]. Majority of these proteins are formed a family of highly antigenic mucins that induce the cellular immunity, which determined by the secretion of cytokines that increasing of eosinophilia and the production of IgE antibodies [44]. The recruited eosinophils adhere to a membranous layer that is frequently detached from larval epicuticle, allowing the antigens [45]. *Toxocara* larva elicits humoral and cellular immune responses in humans. Due to host inflam-



**Fig. (1).** Life cycle of *Toxocara* spp. Although VLM is characteristic for *Toxocara canis*, it may occur with *Toxocara cati* from cats.

matory responses tissues damage is more than the infection itself. In *Toxocara* infection, larval antigens induce granulomatous inflammation with eosinophils, histocystes and fibrous tissue. The granulomatous are found most often in liver and less in the lungs, eyes, brain, and the other organs. These eosinophil-mediated granulomatous responses are almost exclusively responsible for the clinical manifestation of *Toxocara* infection including overt toxocariasis (VLM and OLM), and covert toxocariasis (Table 1).

### CHRONIC HELMINTHIC INFECTION AND ATHEROSCLEROSIS

The causative agents and processes, which may be involved in the pathogenesis of atherosclerosis, are being interested. The occurrence rate of atherosclerosis and cardiovascular diseases are much lower in developing countries. Due to the present knowledge of immune and infectious mechanisms related to atherosclerosis, it is proposed that chronic helminthic infections can have a significant bearing on the epidemiology of cardiovascular diseases.

Helminth infection can be increased the risk of atherosclerosis: (1) helminths evade or suppress host immune responses, by producing anti-inflammatory and other immunomodulatory molecules; (2) helminths induce chronic Th2 activation, which can modify cytokine profiles and immunological responses to heat shock proteins (HSP); (3) The chronic Th2 profile may modulate monocyte and macrophage activation and chemotaxis to inflammatory sites (atherosclerotic plaques); (4) Chronic Th2 activation may lead to a cytokine profile that could be beneficial for

attenuation of atherosclerosis development (involved in producing IL-4, IL-10 and IL-13 and **inhibition** of proinflammatory cytokines); and (5) helminthic infections may reduce plasma LDL level not only by affecting the host nutrition, but also via modulation of naturally occurring antibodies to cholesterol [46].

Since the *Toxocara* species can be cause chronic parasitic infection and considering that a link between atherosclerosis and helminth infections has not been investigated, studies are needed to clarify these suggestions.

### TOXOCARA INFECTION AND CARDIOVASCULAR DISEASE

Human toxocariasis is widespread as evidenced by seropositivity. Ocular toxocariasis is almost certainly an organ specific subdivision of visceral toxocariasis. Visceral toxocariasis may be overt or covert. Covert toxocariasis is much more common than overt toxocariasis. Initial reports of overt toxocariasis were of severe cases in children under the age of four years [47]. Extreme eosinophilia (50% or more of the total white blood cell count) was regarded as an essential criterion for diagnosis with varying accompanying features of increasing the body temperature (fever), pulmonary infiltration, hepatosplenomegaly, muscle and joint pains, abdominal pain, and cardiac involvement rarely occurs but can be serious [48, 49].

#### Eosinophilic Myocarditis

Myocardial damage and endomyocardial fibrosis has been associated clinically with chronic eosinophilia [50].

**Table 1. Clinical forms of *Toxocara* infection and logical reasons for clinical treatment and prevention.**

Clinical forms	Clinical characteristics of patients			Treatment reasons	
	Signs and Symptoms	Eosinophilia	Serology	Clinical	Prevention/Control
Visceral Larva Migrans	High/Mild	High	High/Mild	Yes*	Yes**
Ocular Larva Migrans	High	Doubtful	Mild	Yes	Yes
Neurotoxocariasis	Mild	Doubtful	Mild	Yes	Yes
Covert toxocariasis	Doubtful	Doubtful	Mild	Yes	Doubtful
Asymptomatic toxocariasis	None	Doubtful	Mild	No	Doubtful

\* In cases of clinical toxocariasis, thiabendazole (15 mg/kg/body weight/day) for 5 days.

\*\* Positive results for eosinophilia and serological testes.

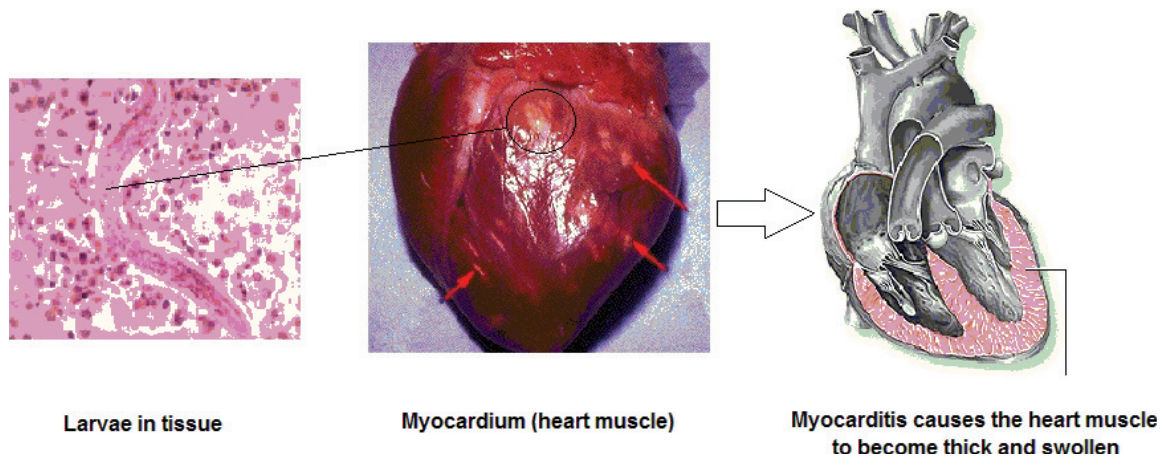
Chronic eosinophilia can be due to helminthic infection such as toxocariasis, drug reactions, allergic disorders, or other causes. Dramatic eosinophil counts (up to 90 percent), may occur in patients as VLM, who often present with leukocytosis. Visceral larva migrans syndrome results from the ingestion of embryonated eggs of *Toxocara* spp. After ingestion, hatching occurs in duodenum (upper small intestine). The larvae penetrate into the mucosa and via the portal circulation migrate to the liver, heart, lungs and enter systemic circulation. Because the larvae size is larger than diameter blood vessels, it may bore through the vessel wall of the host, migrate within the tissues, and elicit an immune response. Eventually, a larva becomes enmeshed in a fibrotic encapsulated granuloma [51-53]. Severe myocarditis ensues when the third-stage larvae (L3) invade cardiac tissue (Fig. 2). Several cases of myocarditis associated with VLM syndrome have been reported [54]. Myocarditis may occur in up to 15 percent in patients with visceral larva migrans and the myocarditis is accompanied by significantly increased levels of circulating eosinophils in all of patients. Brockington and Olsen [55] described that eosinophilic endomyocardial disease occurs in three stages: I) the acute necrotic stage, the thrombotic stage, and the late fibrotic or end stage. The acute necrotic stage is seen in patients ill for only a few weeks, and is characterized by areas of acute necrosis and inflammatory cell infiltrates into the endomyocardium, with focal areas of damage to the subendocardium, II) the second stage, after several months, begins when a layer of granulation tissue develops between the endocardium and subendocardium, accompanied by intraventricular thrombi and thrombi in small and medium sized blood vessels, and III) the end stage occurs when dense endomyocardial fibrosis is seen that produces a restrictive cardiomyopathy. Friedman and Hervada in 1960 described a child with strong evidence of toxocaral infection who suffered from severe myocarditis that resolved on treatment [56]. Spry *et al.* described myocardial lesions in patients with eosinophilic endomyocarditis and tropical endocardia fibrosis [57]. In a case of *Toxocara* infection associated with myocarditis has previously been showed in which elevated C-reactive protein (1.4 mg/dl), creatinine phosphokinase (679 IU/l), aspartate aminotransferase (124 IU/l), alanine aminotransferase (182 IU/l) and lactic dehydrogenase (733 IU/l) [58].

### Pericarditis and Pleural Effusion

The clinical spectrum of *Toxocara* infection is broad, producing pulmonary effusion, cardiac tamponade, and ascites [59-61]. Less commonly, toxocariasis can be self-limiting with few clinical manifestations. A case report revealed systematic effusion in a woman cardiomyositis with congestive heart failure, serositis with collagen vascular disorders. Elevation in with blood cell count (13,900/ $\mu$ l) with 5% eosinophils, serum brain natriuretic peptide to 340 pg/ml (normal < 18.4 pg/ml), and chest roentgenogram with chest computed tomography has been observed in patient diagnosed with toxocariasis-associated pericarditis [62]. Bachmeyer *et al.* in a case found fever, night sweats, weight loss, hilar and mediastinal lymphadenopathy, bilateral pleural effusion, and eosinophilia-mimicking lymphoma related to *T. canis* infection [59]. The patient appeared pneumonia with eosinophilia that responsible for acute respiratory disorders. The patient was healthy (physical examination) and her medical history was unremarkable. Laboratory examinations of the peripheral blood showed the white blood cells count  $10.8 \times 10^3/\mu$ l with eosinophilia (26%). Results of serum electrophoresis revealed an albumin level of 32.8 g/l (normal range more than 39 g/l);  $\alpha$ 2-globulin, 9.8 g/l (normal range more than 7 g/l); and polyclonal  $\gamma$ -globulinemia, 16.9 g/l (normal range more than 10 g/l). After diagnosis the disease, the patient treated with oral albendazole (400 mg daily for 10 days). Unusually, in a case of life-threatening *Toxocara* infection, Henry *et al.* demonstrated that the chest roentgenograms was revealed bilateral pleural effusion with normal parenchyma but an enlarged cardiac image [63]. Laboratory tests showed a leukocyte count of  $15.4 \times 10^3/\text{mm}^3$  with  $2.2 \times 10^3$  eosinophils/ $\text{mm}^3$ . On pericardiectomy of the patient, more than 800 ml of pericardial fluid with a cellular component of 20% eosinophils evacuated. Serology was positive for *T. canis* antibodies. On basis of the clinical pictures and the conducted tests a diagnosis of acute toxocariasis was established; ivermectin 200  $\mu$ g/kg/day at day 10 and day 25 was applied in treatment.

### LABORATORY DIAGNOSIS

The diagnosis of toxocariasis, like most parasitic infection, is made initially on clinical signs such as hepatomegaly, fever or wheezing, with confirmatory testing playing a sec-



**Fig. (2).** Helminths infection and cardiovascular diseases.

ondary role. Blood cells count always showed the presence of blood eosinophilia, which was usually marked and was sometimes massive: approximately  $1 \times 10^3$  cells/mm<sup>3</sup> [64-66]. In the absence of hepatomegaly, the symptoms and signs of toxocariasis mimic tropical pulmonary eosinophilia.

Diagnosis of human toxocariasis is confirmed by visual methods (as called the gold standard). Microscopic observation of biopsies or organ fragments can find larval sections or debris [67, 68]. Other laboratory results include increase in immunoglobulin and elevated isomemagglutinin titers to A and B antigens (blood group antigens) [69]. Radiographic imaging of involved organs using ultrasound, computed tomography (CT) scan, and magnetic resonance imaging (MRI) can describe focal lesions [70]. Advance in serological techniques was obtained due to the difficulties and uncertainties of direct visual detection. The diagnosis is most established by confirmatory serological testing using an ELISA (enzyme linked-immunosorbent assay) that detecting IgG antibodies against TES (*Toxocara* excretory-secretory) antigens (TES-ELISA). ES proteins from second stage *T. canis* or *T. cati* larvae maintained *in vitro* form the substrate for ELISA [71, 72]. The sensitivity and specificity have been estimated to be approximately 78.0% and 92.0% for *T. canis* and 97.0% and 96.7% for *T. cati*, respectively [73-75]. Limited data indicate no significant cross-reactivity in individuals infected with common helminthic infections [76, 77]. A Western blotting assay using TES antigens is more specific [75, 78]. In the past decade, immunoblot assays have been developed using recombinant ES proteins [79, 80]. Antigens capture testes using monoclonal antibody to toxocaral ES proteins offers the ability to distinguish current infection [81].

Molecular diagnostic methods have proven to be useful to investigate of parasite in tissue fragments from surgical operations or dissections and in cerebrospinal fluid, but this approach are currently not used practically [23, 82-84].

### TREATMENT AND PROGNOSIS

The majority of patients with *Toxocara* infection do not require treatment, since toxocaral infections are usually sub-clinical and self-limited, nevertheless, the disease can be fatal with severe clinical manifestation. Treatment is gener-

ally reserved for cases with severe toxocariasis, although this remains a controversial point. Usually, acute toxocariasis is treated either symptomatic or with specific anti-parasitic treatment, depending on the severity of clinical disease. Patients with either peripheral eosinophilia or mild toxocariasis are often treated cautiously. Asymptomatic cases with increased eosinophils and those with mild *Toxocara* infection in the absence of increased eosinophils normally do not need any special treatment. Mebendazole, albendazole, thiabendazole, ivermectin and diethylcarbamazine have been reported as treatment for human toxocariasis. In cases of clinical toxocariasis, thiabendazole (15 mg/kg/day) appeared to be effective; however, a similar course of albendazole resulted in more frequented clinical cure and a measurable decrease in eosinophils count. A dose of 400 mg of albendazole twice a day for 5 days is the currently recommended therapy [84]. A twenty-one days course of mebendazole with dose of 20-25 mg/kg/day has been shown to be effective, alternatively [85]. Severe symptomatic treatments, including either albendazole or mebendazole, and corticosteroids (prednisone) with dose of 0.5-1.0 mg/kg daily are often administered concomitantly.

Abe *et al.* in a case report demonstrated that a 4-weeks course of oral albendazole and prednisolone results in resolution of clinical symptoms in myocarditis-associated with *Toxocara* infection [58]. Enko and colleagues reported a case of fulminant eosinophilic myocarditis associated with toxocariasis that treated with both oral albendazole for four weeks and intravenous methylprednisolone (~500 mg/d) for 3 days, followed by oral medications of prednisolone (50 mg/d) for 2 weeks. Following treatment with those drugs, significantly improved ventricular function and quickly reduced the number of eosinophils and normalized [86].

### CONCLUDING REMARKS

*Toxocara canis* and *Toxocara cati*, roundworms of dogs and cats respectively, are zoonotic parasites that cause widespread and common human toxocariasis. The infective larvae both *Toxocara* species cannot mature into adults in the human host. The worms wander through tissues and organs in a vain attempt to find that which they need to mature into adults. A variety of disease states are described but symp-

toms are not well understood and require further elucidation. The migration of immature larvae causes local and systematic inflammation, resulting in the “larval migrans syndrome”. Visceral larva migrans is defined not only by chronic increased eosinophils and increased  $\gamma$ -globulin in the blood, but also by involvement of the liver, lungs, eyes, the cerebral nervous system, skin and the heart as a result of migration the local larval. In toxocariasis inflammation of the heart muscle (myocarditis) may be caused by direct larval invasion to the myocardium and hypersensitivity reactions to the parasite. Several cases of pleural effusion and pericardial associated with *Toxocara* infection have been reported. With the exception of overwhelming infections, widespread of small numbers of tissue-dwelling larvae dictates that serology tool of choice for diagnosing human infection. Strategies for the treatment of this disease in human, is use of mebendazole, albendazole, thiabendazole, ivermectin, diethylcarbamazine with corticosteroids.

### CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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