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Original paper

Toxocara cati larval migration in rats: experimental histopathological study

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ABSTRACT. *Toxocara* spp. (*T. canis* and *T. cati* in particular) are the major etiological nematodes that have contributed to visceral larval migrans (VLM). So to show the ability of *T. cati* to produce such migration in the rats as experimental model and detection through histopathological observations to detect larval migratory patterns. Adult females *T. cati* were collected from naturally infected feral cats. Eight rats, *Rattus norvegicus* had acted as a model for experimental infection, each receiving an infectious dose of about 1000 infective *T. cati* eggs, while 2 rats served as non-infected control group. Two infected rats were sacrificed and examined at 7, 14, 21, and 28 day post infection (dpi) and tissue samples were taken for digestioning order to recover migrated larvae and for histopathological examination. *In vitro* embryonation of *T. cati* eggs was successfully carried out, although the percentage of embryonation was 10%, prepared inoculums were also infective to rats. Larvae recovered from the lungs at 7 and 14 dpi and were also present at 21, and 28 dpi. The larvae of *T. cati* were present in the intestines at 14, and 21 dpi. There were no larvae or less than one larva per gram found in other studied tissues. Histopathological changes in different organs were observed. Generally speaking, a multi-tissue response can be defined as the histopathological response of *T. cati* larval migration. The migratory larvae of *T. cati* can cause severe histopathological alterations in various tissues and organs of infected animals, within the current study shows that the lungs are a favorable site of migration for these larvae. *T. cati* is a zoonotic parasite that is underestimated.

Keywords: *Toxocara cati*, VLM, rats, histopathology

Introduction

Visceral larval migrans (VLM) is a neglected and underestimated parasitic zoonotic disease or syndrome that occurs as a result of invasion of human tissues by certain nematodes larvae [1,2]. As far as our knowledge; nematodes known to be responsible for this syndrome are *Toxocara canis* (dog roundworm), *T. cati* (cat roundworm), *T. malysensis*, *Baliascaris procyonis* (raccoon roundworm), and *Ascaris suum* (pig roundworm) [2–4]. The first two species (i.e. *T. canis, T. cati*) are known to be the most common etiological agents of VLM worldwide, with the majority of confirmed cases of VLM attributed to the larvae of those two species [2,5]. The attention to toxocarosis is increased day after day due to its global expansion and different clinical symptoms associated with human toxocarosis [6]. Clinical manifestations of such infection includes VLM, ocular larva migrans, covert toxocarosis, and may results in neurological toxocarosis, although the later form is rare [3,4–6]. Several epidemiological studies found a wide-spread prevalence of human toxocarosis with different rates worldwide, including in developed countries where the prevalence of human infection thought to be low [2,7,8].

Life cycle of *Toxocara* spp. contributed in VLM is complicated, briefly infected cat/dog shed large numbers of undeveloped eggs with their faeces into the environment. Outside the final host, eggs developed, gave the most common infective form (i.e. egg containing 2nd larval stage), usually this

developmental phase takes about 3–4 weeks depending on the environmental factors [9]. Infective eggs and a broad range of paratenic hosts (small mammals such as rodents and fowls) are capable to infecting the final host again. In the paratenic hosts; larva are excapsulated in the intestines and can invade different organs and tissues, resulting in the 'VLM' disease; but there is no further development. Ingestion of paratenic hosts harboring *T. cati* larva in their tissues is another route of the final host infection, intrauterine infection of puppies has also been reported and intra-mammary infection of kittens has been recorded [10–13].

It is of great importance to study the migratory patterns, mechanisms and pathogenesis of VLM to understand the dynamics of the disease and know how it is produced [6,14]. Experimental infections with *T. canis* and *T. cati* were performed in various animal models, including mice, Mongolian gerbils, pigs, rats, and chickens [15–19].

The purpose of the present work was therefore, to study the migratory pattern of *T. cati* larva in rats and its pathological consequences.

Materials and Methods

In vitro embryonation of T. cati eggs

Feral cats from Alexandria city, northern Egypt were parasitologically examined for *T. cati* infection. Infected cats were euthanized and humanely sacrificed. Adult *T. cati* were collected and identified to species level [20]. In a Petri dish containing 0.85% normal saline, gravid females posterior end were seized by sterile blade and gentile pressures; eggs were evacuated from the uteri. The eggs collected were concentrated through centrifugation of the normal saline solution and counted using modified McMaster technique. By centrifugation-washing alteration, undeveloped eggs were washed twice to remove any debris and decorticated in sodium hypochlorite solution (7% w/v). Embryonation was done in 2.5% formalin/ringer solution while incubation in an atmosphere of 5% carbon dioxide at 37ºC, humidity about 30–40%, for 3–4 weeks [21]. Eggs were microscopically checked weekly for embryonation, after the development of infective stage "egg contains 2nd larval stage" with a sufficient number which is suitable for the experimental inoculums' preparation, inoculums were prepared to make an inoculum of 1000 egg/1 ml normal saline using the modified McMaster technique.

Experimental design

Rats, *Rattus norvegicus* were purchased from the Faculty of Veterinary Sciences, Alexandria University, Egypt, and then were housed in Animal Health Research Institute, Alexandria branch, in compliance to the accepted standards of laboratory animal management. Upon arrival, rats were divided, housed in clean disinfected cages and raised according to the lab animals practices and handling instructions.

Rats were randomly allocated to 4 groups selected to receive the inoculums and the uninfected control was identified as the remaining group. On 7, 14, 21, and 28 day post-infection (dpi), necropsy occurred in each group consisting of two rats euthanized and sacrificed. Larvae were collected and carefully inspected through organs and tissues including livers, lungs, kidneys, hearts and intestines. Each 50 grams tissue sample was submerged in 10% neutral buffered formalin and then processed for histopathology to detect histopathological changes, another 50 grams of the examined tissues were processed to detect larvae by the acid digestion.

Digestion technique to detect larva in-tissues

Tissues collected were placed into digestive solution (Pepsin 5 grams + HCl 37% 10 ml in 1,000 ml/water) and held to recover the larvae overnight at 37ºC. Sediment liquid was poured into a centrifuge tube and centrifuged for 2 minutes at 1,500 rpm, 2 ml of the sediment was collected thoroughly mixed, and 0.1 ml was viewed for larvae detection and count [22], this step was repeated at least twice for each sample.

Histopathological examinations

Formalin-fixed samples were embedded in paraffin and subsequently tissue sections of 4 μm thickness were obtained and stained with hematoxylin and eosin [23].

Ethical consideration

According to institutional animal care and handling guides, all procedures were approved by the Agricultural Center, Animal Health Research Institute (AHRI), Alexandria branch.

Results

In vitro embryonation of T. cati eggs

Embryonation was completed successfully.

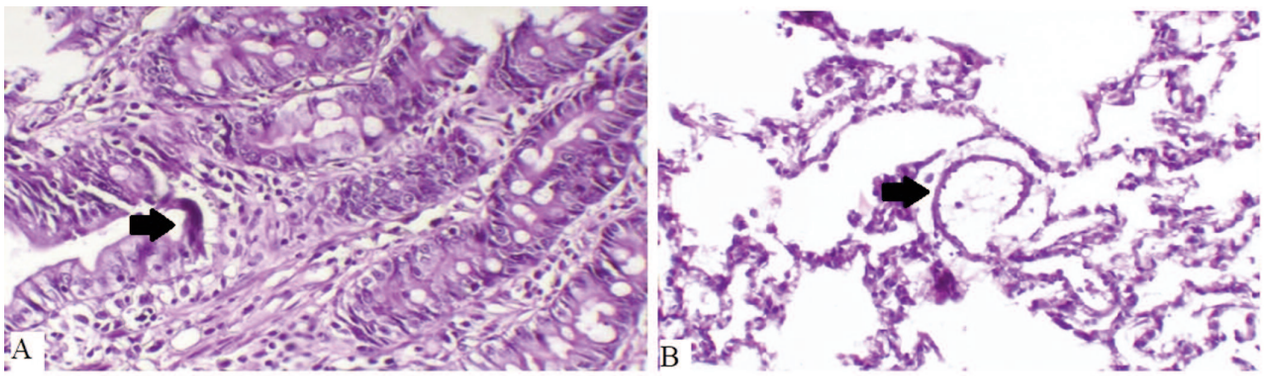

Figure 1. Histopathological features of rats experimentally infected with *T. cati* larva; A – larva "black arrow" in its way of penetration of the intestinal villi at 14 dpi; B – larva "black arrow" in lung alveolar lumen at 14 dpi. All magnification ×200. All stained by hematoxylin and eosin (HE).

About day 28, infective stage "egg containing L2" was obtained. The initial count of eggs was 100.000 eggs, and this number was used for the next step. The percent of embryonation was 10% (i.e. 10.000 developed-larvated eggs were collected from an initial incubated 100.000 eggs).

Experimental infection

All 4 infected groups used in the current study were successfully done. Larval recovery and histopathological sections showing the larvae within tissues illustrate this (Figure 1).

Larval recovery

Briefly, *T. cati* larvae were retrieved at 7 and 14 dpi from the lungs and were also present at 21, and 28 dpi, respectively. Larva were also present in the intestines at 14, and 21 dpi, respectively. No larva or less than one larva per gram was found in other examined tissues (i.e. kidney, heart and brain) was detected (Table 1).

Histopathological examination

During the experiment, the histopathological pictures of examined were as follows;

Intestines: showed that the lesions caused by migratory *T. cati* larva were ranged from degeneration and sloughing of the epithelium of intestinal villi's tips at 7 dpi (Figure 2A). A notable cellular infiltration of esinophils was observed in

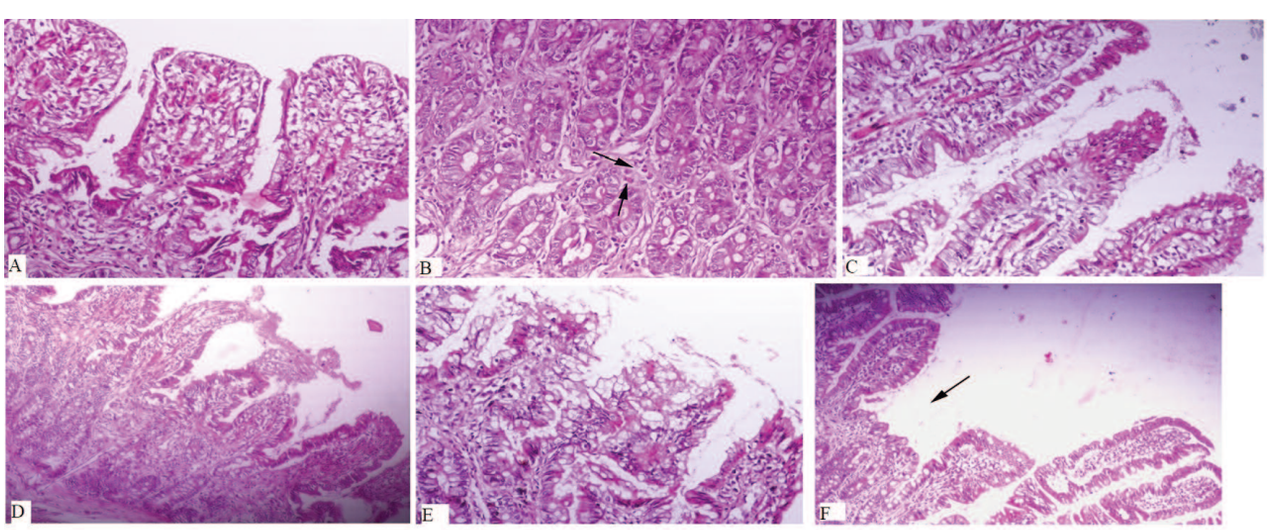

Figure 2. Histopathological features of rats' intestines experimentally infected with *T. cati*
A – degeneration and sloughing of tips of the intestinal villi at 7 dpi; B – marked infiltration of eosinophils "arrows" at 14 dpi; C – necrosis of tips of the intestinal villi at 21 dpi; atrophy "arrow", D – necrosis and sloughing of tips of the intestinal villi at 21 dpi; E – marked necrosis of the intestinal villi at 28 dpi; F – complete necrosis and disappearance of intestinal villi "arrow", along with beginning of necrotic changes on the adjacent villi "star" at 28 dpi. All magnification ×200, except for D and F magnification ×100. All stained by hematoxylin and eosin (HE).

Table 1. *Toxocara cati* larval recovery rate in experimentally infected rats

dpi*	No. of recovered larva						Larval recovery rate as %
	Liver	Lung	Heart	Brain	Kidney	Intestines	
7	2	8	1	0	0	0	1.1
14	0	6	0	0	0	6	1.2
21	0	8	0	0	0	2	1.0
28	0	6	0	0	0	0	0.6

*dpi= days post infection

the submucosa and between the intestinal glands at 14 dpi (Figure 2B). In some parts at 21 dpi, lesions progressed to necrosis of the tips of intestinal villi (Figure 2C) and other parts showed atrophy and thinning of intestinal villi with corrugated epithelium covering (Figure 2D). Marked necrosis of the entire villus was observed at 28 dpi In the severely progressed lesion (Figure 2E) with other sections showing marked shortening of the villi and fully necrosed villi were found in between (Figure 2F).

Liver: hepatic changes showed congestion, mild fatty changes of hepatocytes with pyknotic nucleus and eosinophilic cytoplasm at 7 and 14 dpi (Figure 3A), along with proliferation of sinusoidal cells. The lesions then progressed to multiple small focal areas of hepatic necrosis accompanied by infiltrations of mononuclear cells at 21dpi (Figures 3B,C). Marked hyperplasia of diffuse portal bile ducts surrounded by infiltrations of mononuclear cells and some esinophils at 28 dpi (Figure 3D).

Kidneys: glomerular tufts and inter-tubular blood vessels showed marked congestion of at 7 and14 dpi (Figure 4A). Then advanced to glomerular atrophy

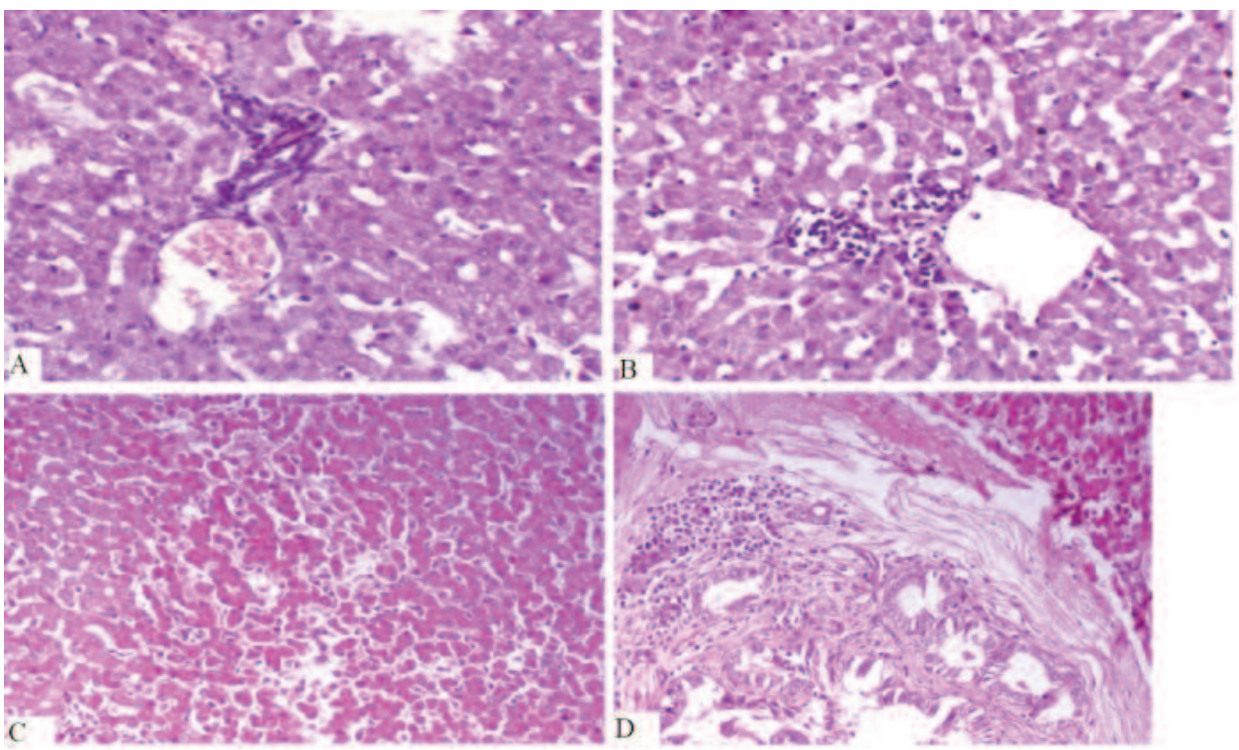

Figure 3. Histopathological features of rats' livers experimentally infected with *T. cati*
A – showed congestion, mild fatty degeneration of hepatocytes at 7 dpi, also this was noticed at 14 dpi;
B – focal areas of hepatic necrosis accompanied with mononuclear cells infiltrations at 21 dpi;
C – another picture of focal areas of hepatic necrosis at 21 dpi; D – marked bile duct hyperplasia with periductal massive cellular infiltrations at 28 dpi. All magnification ×200. All stained by hematoxylin and eosin (HE).

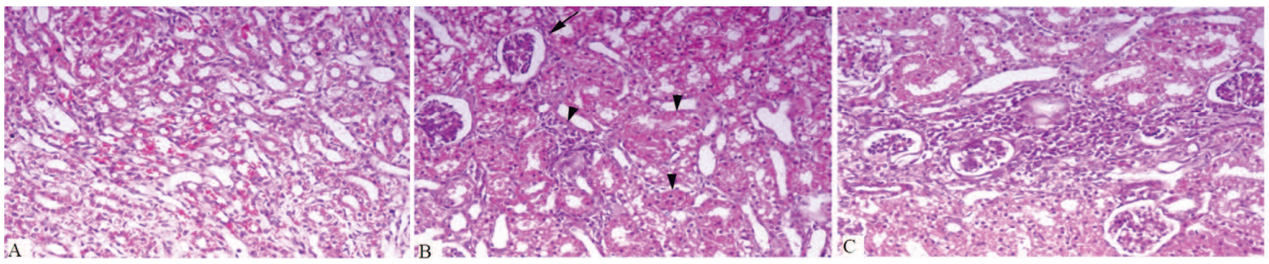

Figure 4. Histopathological features of rats' kidneys experimentally infected with *T. cati*
A – marked congestion of inter-tubular blood vessels at 7 and also noticed at 14 dpi; B – glomerular atrophy "arrow" with widening of Bowman's space, together with marked cytoplasmic rarification and pyknotic nucleus of renal tubules with small focal area of necrosis with mononuclear cells infiltrations "arrow head" at day 21 dpi;
C – focal area of tubular necrosis accompanied with mononuclear cells and eosinophils at 28 dpi. All magnification ×200. All stained by hematoxylin and eosin (HE).

and diffuse tubular degeneration of severely rarified cytoplasm and pyknotic nucleus with focal areas of tubular necrosis accompanied with mononuclear cells infiltrations at 21 dpi (Figure 4B). At 28 dpi, occasional marked tubular necrosis accompanied by massive infiltration of mononuclear cell and esinophils was observed at 28 dpi (Figure 4C).

Lungs: diffuse perivascular mononuclear cells infiltrations was recorded in pulmonary lesions by at 7dpi (Figure 5A). Bronchial epithelium degeneration and desquamation into the lumen accompanied by peribronchial cellular infiltrations were also observed at 7 dpi (Figure 5B). Alternative areas alveolar interstitum thickening with inflammatory cells' infiltration at 14 dpi (Figure 5C), alveolar lumen collapse with atelectasis at 21 dpi (Figure 5D) with other areas showed alveolar expansion causing inter-alveolar septa destruction resulting in alveolar emphysema at 28 dpi (Figures 5E,F).

Heart: diffuse degenerative changes of cardio-myocytes informing of cytoplasmic vaculoation at 21 dpi (Figure 6A), beside focal areas of myocardial necrosis accompanied with mononuclear cells infiltrations at 28 dpi (Figure 6B).

Brain: neuronal injury was ranged from congestion at 21 dpi (Figure 7A). Pericellular and perivascular edema to ischemic neuronal injury of eosinophilic cytoplasm and pyknotic nucleus at 28 dpi were also observed (Figure 7B).

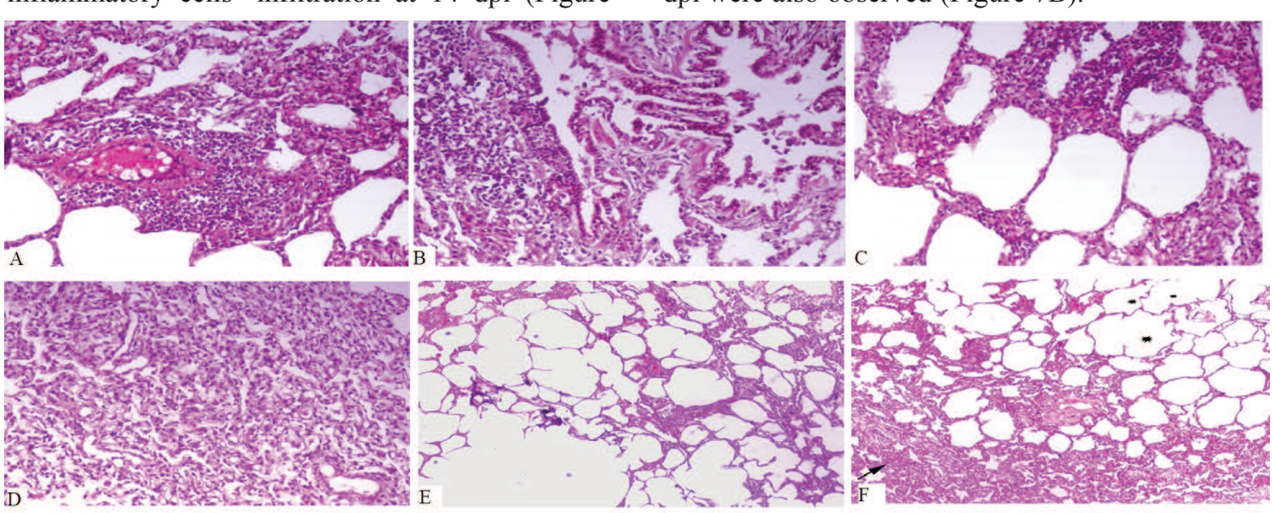

Figure 5. Histopathological features of rats' lungs experimentally infected with *T. cati*
A – perivascular mononuclear cells of lymphocytes and some eosinophils at 7 dpi; B – degeneration and desquamation of bronchial epithelial lining into the lumen with peribronchial mononuclear cells and some eosinophils at 7 dpi; C – thickening of inter-alveolar septa with mononuclear cells infiltration and some eosinophils at 14 dpi;
D – atelectasis which characterized by collapsing of the alveoli at 21 dpi; E – pulmonary emphysema characterized by over distension of alveoli causing destruction of inter-alveolar septa at 28 dpi; F – alternative areas of pulmonary emphysema "stars" and atelectasis "arrow" at 28 dpi. All magnification ×200, except for E and F magnification ×100. All stained by hematoxylin and eosin (HE).

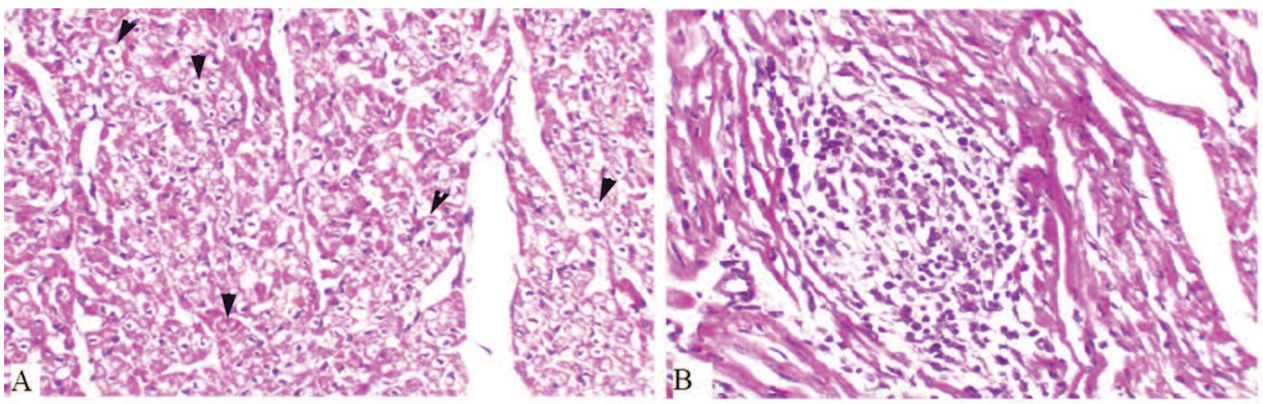

Figure 6. Histopathological features of rats' hearts experimentally infected with *T. cati*
A – marked degeneration of cardiomyocytes with cytoplasmic vacuolation "arrow heads" at 21 dpi; B –. focal area of myocardial necrosis accompanied with mononuclear cells infiltration at 28 dpi. Magnification is ×100 for A. and ×200 for B. All stained by hematoxylin and eosin (HE).

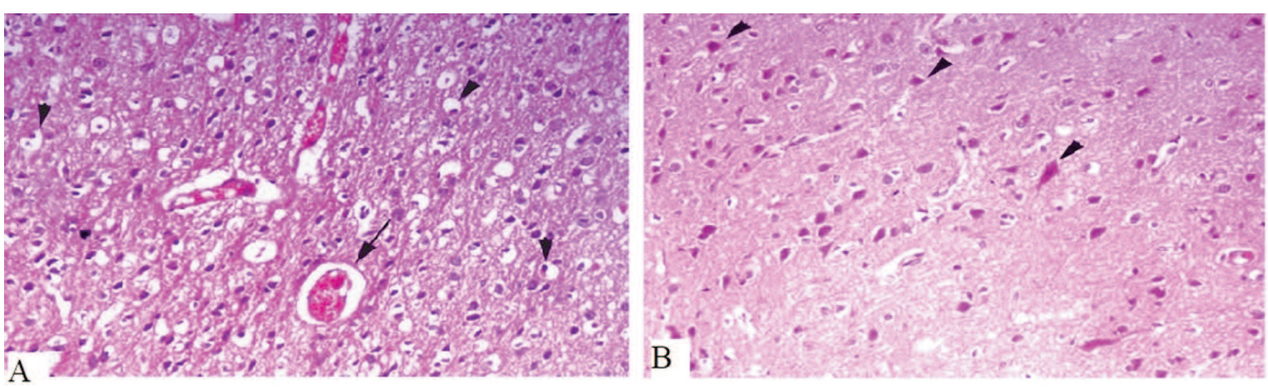

Figure 7. Histopathological features of rats' brains experimentally infected with *T. cati*
A – congestion, peri-vascular "arrow" and peri-cellular edema, "arrow heads" at 21 dpi; B – ischemic neuronal injury which characterized by condensed nucleus and eosinophilic cytoplasm at 28 dpi. All magnification ×200. All stained by hematoxylin and eosin (HE).

Discussion

VLM is a parasitic zoonosis of a great importance. Several studies tried to demonstrate a better understanding of such infection after the study of Beaver et al. [24]. The current study complements the work of other scientists [16–19]. Herein, the embryonation of *T. cati* eggs was completed, embryonation percent was 10%. This shows that not all eggs can be grow into the infective stage, even when incubated in laboratory conditions. Despite this lower percentage of embryonation, the collected fully embryonated eggs were capable of infecting and causing pathological alterations in the infected paratenic host "rat". In our study, the embryonation percentage was much lower than that obtained by Zibaei et al. [21]. In accordance to Zibaei et al. [21], this finding confirms that humidity and moderate temperature are the two most important factors for ebmryonation and development of *T. cati* eggs. This concept should be considered in any future work on *Toxocara*-egg embryonation, as control steps.

In respect of the larval recovery rate, Kassai [25] stated that after ingestion of infective larvae, histopathological changes occured in the small intestine. The lungs and small intestines were found to have the largest numbers of larvae in the early stages of infection (7 and 14 dpi) in the current study. The recovery of the larvae from the intestines peaked at 14 dpi. Recovered larvae from the lungs showed a higher recovery at 7 and 21 dpi, also present at 14 and 28 dpi. Throughout the current study, recovery of *T. cati* larva in the lungs suggest that lungs could be a favorable site of *T. cati* migration. This in consistent with the results of Santos et al. [26] they found a higher concentration of larva in the lungs at 60 dpi. This is due to the larva's easy access to the lungs through circulation, as well as the suitability of lung tissues and

environment for these larvae.

The number of larva retrieved from the liver, brain, kidneys, and heart did not differ significantly between 7, 14, 21, and 28. This demonstrate the persistence and accumulation of *T. cati* larva depending on the animal model used to study its migratory patterns [11,13,15–18,27]. In comparison to other studies, Cardillo et al. [18] found that the liver contained the highest number of larva on days 1 and 2 dpi; the lungs on 2 dpi and the brain on 28 dpi; muscle recovery was high at 3 dpi with the maximum obtained on day 28, respectively. According to Hrckova et al. [28] and Azizi et al. [16] *T. cati* larvae migration pattern in mice (C57BL6) showed that higher concentration in the liver, lungs, and kidney was found at 5 dpi although, Zaibae et al. [18] noted encapsulated larvae in the liver tissue of experimentally infected chicken at 14 dpi.

The current study finds no larvae in the brain, in contrasts with the findings of Zibaei et al. [18] they studied neurological toxocarosis in Mongolian gerbils and Wister rats, and found that the larval recovery from the brain happened late (i.e. after 70 dpi) and lasts until the 92nd dpi. However, since our study only lasted for 28 dpi and no further examinations were conducted; this may be the reason for the lack of larval recovery from the brain in this study. As a result, it can inferred that larval migration into brain takes longer time than its migration to other organs, this might due to nature of blood supply into brain, which could prevent larva from quickly accessing its tissues. In order to assess the larval migration pattern of *T. cati,* a general interpretation cane be concluded. It mostly depends on the infective dose, animal model used, type of tissue/organ examined, and the period of examination.

Toxocara cati larval migration in the current study was characterized by a multi tissues reaction. The histolopathological details of the different organs examined herein are quite similar to those found in other works. Sloughing of the epithelium of intestinal villi's tips was observed in the intestine, which may be due to larvae migration. Notable cellular infiltration of eosinophil in submucosa and between the intestinal glands was observed, which could be related to the host immune response [28]. The lesions progressed to necrosis of the tips of intestinal villi, eventually encomasing the entire villus, other areas displayed entire necrosis of the villi, which then vanished. The virulence of *T. cati* larvae, which contain a toxic material and the lyso enzyme, which lyses cells and villi, may be the cause of these changes [28–31].

After penetrating the intestinal wall, larvae are transported to the liver and other parenchymatic organs by the circulatory system. Hepatocytes with a pyknotic nucleus and eosinophilic cytoplasm showed congestion, slight fatty changes, and eosinophilic cytoplasm. The bile ducts had a diffuse pervascular invasion and hyperplasia, which tended to be a local response to the migrating larvae After that, the lesions progressed to multiple small focal areas of hepatic necrosis, accompanied by mononuclear cells which is a tissue reaction to disrupted larvae [32].

In renal lesions, congestion, diffuse tubular necrosis, and inflammatory reaction have been observed, likely as a result of larval migration. The pulmonary lesions had diffuse perivascular mononuclear cell infiltration. Bronchial epithelium degeneration and desquamation were persent in the lumen, along with peribronchial cellular infiltration, which was most likely caused by larval migration via lung tissue as same as findings of previous studies [32]. Macrophages were the most abundant peribronchial inflammatory cells, and they were primarily involved in the destruction of parasite larvae [32]. Other areas showed expansion of alveoli causing disruption of inter-alveolar septa and resulting in alveolar emphysema, as well as thickening of the alveolar interstitium, inflammatory cell invasion, and collapsing of the alveolar lumen, resulting in atelectasis, other areas showed expansion of alveoli causing destruction of inter-alveolar septa and resulting in alveolar emphysema. Ali [29] recorded similar emphysematous changes.

The myocardium showed vacuolar degenerative changes of cardiomyocytes with inflammatory reaction to focal necrotic areas. In accordance with Cardillo et al. [17], during experimental inoculations of *T. cati* larval eggs in 18 BALB/c mice, inflammatory infiltrates observed in the muscle and degenerated muscle, particularly around the larva. The same lesions were present in the myocardium and pericardium. Lymphocytes, neutrophils, and a few eosinophils were among the inflammatory cells. The lesions in the brain ranged from edema to ischemic neuronal damage. Ali [29] discovered that *T. cati* larvae cause lymphocyte infiltration in the brain, which is a sign of larval migration. However, Ali [29] reported that in another study, Al-Rubaie [34] infected mice with 1016 egg and found no larvae in the brain after 20 days of infection as

compared to other organs. In fact, there is still poor understanding of neurological toxocarosis and much information are required to help highlight this phenomenon.

Despite that fact that no or less than one larva has been recovered in the organs examined in the current study (i.e. kidney, brain, and heart). In these organs, a patho-immunological responses have been observed. This can be attributed to host immune response to the migratory larva [8,31], the excretory-secretory products of these larvae trigger an immune response that characterized by marked eosinophilia and production of different cytokines. This immune response could not be restricted to a specific migration site, but could be generalized in different organs and tissues. Therefore, even organs without larvae are affected, which might explains the histopathological results of the current study.

The results of the present study could contribute to the understanding of the migratory behavior of *T. cati* in different paratenic hosts. Also, it shows that *T. cati* larva are capable to migrate through diverse tissues of rats, causing pathological changes. This study comes alongside other studies seeking to clarify the host-*T. cati* relationships through studying hitsopathological pictures. Additional studies on *T. cati* and other agents of larval migrans are recommended to highlight the nature of the disease.

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