

Presumptive pulmonary toxocariasis in a patient affected by acute myeloid leukemia and Hodgkin lymphoma: case report and review of the literature in immunocompromised hosts

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SUMMARY

Toxocariasis is a zoonosis transmitted by the nematode *Toxocara* spp. Immunocompromised hosts are more susceptible than general population to bacterial, viral, fungal and parasitic infections. In this population toxocariasis may present as exacerbation or reactivation and could have severe or atypical manifestations being a diagnostic challenge for healthcare providers. We report a case of a presumptive pulmonary toxocariasis during chemotherapy in a patient affected by acute myeloid leukaemia (AML) and Hodgkin lymphoma and we summarize current evidence of pulmonary involvement in immunocompromised population with *Toxocara* spp infection in a narrative review. The aim of this work is also to revise the current literature on pulmonary involvement during *Toxocara* spp infection in immunocompromised hosts to improve knowledge on clinical presentation, treatment and outcome. A 66 years old man who had undergone to a cytarabine and idarubicin chemotherapy induction scheme for AML, complained of febrile neutropenia and dry cough. At the chest computed tomography (CT) there were multiple nodular pulmonary lesions with subpleural consolidations. The lung biopsy revealed inflammatory infiltration with diffuse small granulomas with minor eosinophil component. The laboratory analysis showed

high immunoglobulin E (IgE) count with normal peripheral eosinophils, among the extended parasitological analysis, *Toxocara* immunoblot assay resulted positive. In the most accepted hypothesis of a pulmonary toxocariasis infection, the patient was treated with a combination of albendazole plus corticosteroids for four weeks, with a positive outcome. Infection complications during chemotherapy are not uncommon, however, this is the first reported case of pulmonary toxocariasis during cytarabine and idarubicin treatment in AML. The revised literature shows male gender and younger age as possible risk factors, nevertheless the majority of cases of seropositivity for *Toxocara* was reported in solid organ malignancies. In this case, the suspect was mainly based on laboratory total elevated IgE, confirmed by serological, anatomo-pathological and radiological findings. Hypereosinophilia is often not present in chronic infection. In conclusion, pulmonary toxocariasis should be ruled out in patients with pulmonary involvement and high IgE titre, with or without peripheral eosinophilia, especially in those with known immunocompromised status.

Keywords: *Toxocara*, pulmonary toxocariasis, haematological diseases, pneumonia, immunoglobulin E.

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■ INTRODUCTION

Toxocara canis and *Toxocara cati* are the two main helminthic species that cause human toxocarasis in tropical and subtropical latitudes [1]. The global seroprevalence for this anthrozoosis is around 19% and varies widely among countries and between rural or urban areas [2]. Infection occurs when a person accidentally ingests the eggs of *Toxocara*, usually through contaminated soil, water, or food. Once ingested, the eggs hatch in the intestine and the larvae can migrate to various organs and tissues in the body, including the liver, lungs, eyes, and central nervous system. The larvae do not develop into adult worms in humans, but their presence and movement can cause tissue damage and provoke an immune response. Therefore, humans are considered non-definitive hosts and the parasite larvae are unable to mature into adults and complete their life cycles after ingestion of viable eggs from a contaminated source (especially dog and cat faeces) [3-6]. Instead, the larvae of *Toxocara* spp. are capable of invading almost all organs in humans, especially the liver, lungs, spleen, brain and eyes [3-6].

Toxocarasis can present unique challenges in immunocompromised patients, as exacerbation or reactivation during chemotherapy in immunocompromised hosts has been reported rarely in the literature and most cases have occurred in non-haematological malignancies [7]. Generally speaking, individuals with weakened immune systems, such as those with HIV/AIDS, organ transplant recipients, or individuals undergoing chemotherapy, may be more susceptible to severe and disseminated forms of toxocarasis. Importantly, it has to be considered that immunocompromised patients are more susceptible to a range of infectious and parasitic diseases, and that host-immune-parasite interactions are unique [8, 9]. In particular, it has been reported that solid organ and bone marrow transplantations, blood transfusions and immuno-suppressive treatment are associated with a small but real risk of parasitic infections in Europe [10]. Immunocompromised individuals may include those with HIV/AIDS, organ transplant recipients, cancer patients undergoing chemotherapy, individuals on immuno-suppressive medications, and those with congenital immune deficiencies. Parasitic infections that can pose specific significant risks in immunocom-

promised patients include Toxoplasmosis, Cryptosporidiosis, Strongyloidiasis, Leishmaniasis, Trypanosomiasis (i.e., African sleeping sickness and Chagas disease), and Paragonimiasis among others. Amidst these, Strongyloidiasis has been more extensively described and present peculiar features such as an auto-infective cycle [11, 12].

Broadly, global climate change and demographic changes are modifying the natural eco-system, and travel across continents have resulted in an increase in the transmission of parasites to human beings. Specifically, parasitic lung infections are being increasingly recognized and patients with immunodeficiency syndromes and acute or subacute chest symptoms should be evaluated for early detection of these pathogens [13].

As already pointed out, in immunocompromised individuals these infections can have severe and atypical manifestations, and clinicians may lack awareness in diagnosis. It is important for health-care providers to be vigilant in assessing and managing parasitic infections in immunocompromised patients before any new therapy to be introduced, as the range of biological therapies is increasing, and a widespread use of newer immunosuppressive therapies, the growing population of individuals with immuno-compromised states as well as the prolonged survival of these patients have altered the pattern of parasitic infection [8, 9].

In immunocompromised patients, the larvae of *Toxocara* can migrate more extensively throughout the body, leading to widespread infection and potentially affecting multiple organs. Laboratory tests such as serological assays to detect specific antibodies may be helpful, although cross-reactivity with other nematodes (specifically *Ancylostoma* sp.) is possible. In some cases, a biopsy of affected tissues may be necessary to confirm the presence of larvae [3-6].

Special consideration should be made for immunocompromised returning travellers, or when immunocompromised are traveling to foreign regions where there are greater health risks than their home country [14, 15]. Moreover, transplant tourism, travel with the intent of receiving or donating a transplanted organ, has grown immensely in the past decade and appropriate epidemiological screening and diagnostic testing, may help to reduce the risk of transmission and disease of endemic pathogens [16]. An increase in donors who have emigrated from tropical areas and more

transplant recipients traveling to endemic areas have led to a rise in parasitic infections reported among SOT recipients [17].

Here, we report the case of a presumptive pulmonary toxocariasis exacerbation during chemotherapy in a patient recently diagnosed with acute myeloid leukaemia (AML). Moreover, we have revised the literature describing cases of pulmonary toxocariasis in the immunocompromised population affected by onco-haematological diseases.

■ MATERIALS AND METHODS

The current narrative review followed the Scale for the Assessment of Narrative Review Articles (SANRA) flow-chart (Figure 1) [18].

The main aim of this work was to summarize current evidence on pulmonary involvement during *Toxocara* spp. infections in immunosuppressed adults patients to understand clinical characteristics, treatment, and outcome.

A search was run on Cochrane, PubMed, and Google Scholar using the terms ('Toxoxara' [Mesh] AND ('Lung' [Mesh] OR ('Pulmonary' [Mesh] OR ('Pneumonia'), ('Toxocarasc' [Mesh]) AND ('Immunocompromised' [Mesh]), ('Toxocara' [Mesh]) AND ('Malignancy' [Mesh]), ('Toxo-

carasc' [Mesh]) AND ('Tumor' [Mesh]) and ('Toxocara' [Mesh] AND ('Haematological' [Mesh]) in English. Results were limited to those published between 1 January 1990 and 1 July 2023. Studies were filtered for practice guidelines, guidelines, meta-analyses, systematic reviews, narrative reviews, case series, and case reports. Therefore we have filtered results including only humans and adults patients.

Our search strategy permitted the identification of 818 papers, of which 789 were excluded by title and abstract evaluation. Then, the reviewers studied titles and abstracts. Subsequently, 29 papers were included. Finally, quality assessment of full-text studies was performed by two independent reviewers (EC and TL). Researchers reviewed the summary of all articles sought and ultimately used data from full articles to compile this review paper. Researchers assessed the inclusion of all titles and abstracts without language limitations in English. We duplicated other studies previously included and excluded papers with no methods described, along with papers not strictly related to the aim of the study and according to journal importance and the number of references.

Full-text papers were then assessed for eligibility according to the above criteria, and the results are included in Table 1.

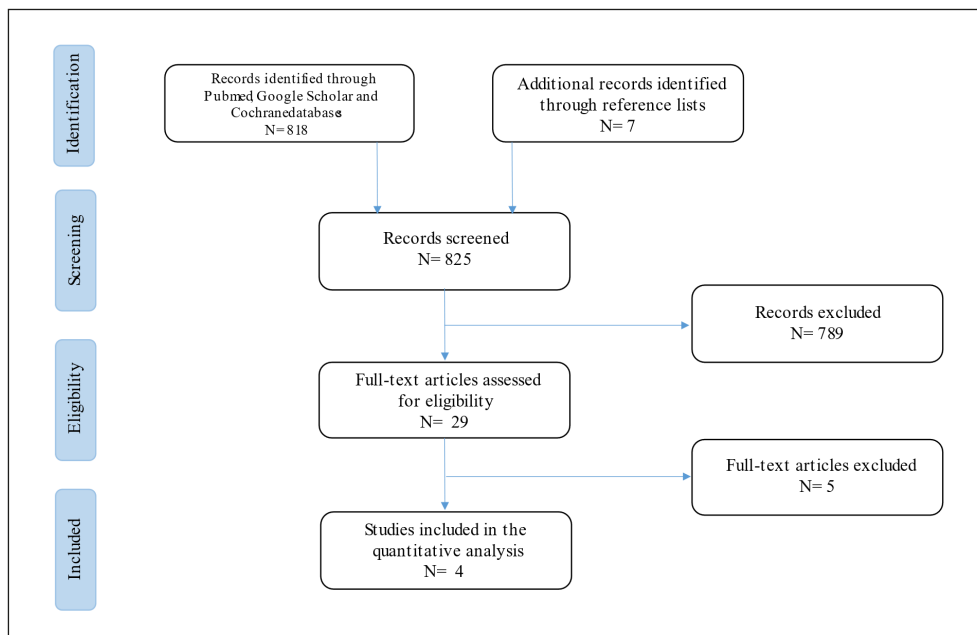


Figure 1
Flow-chart of the studies revised in the narrative review.

Table 1 - Manuscripts collected for the narrative review.

First Author et al. (year) [ref]	Type of study	Origin of patient(s)
Park et al. (2011) [19]	Case Series	2, Korea
Krcmery et al. (1992) [20]	Case Report	1, Slovakia
Park et al. (2014) [21]	Case Report	1, Korea
Hanslik et al. (1998) [22]	Case Report	1, France

Abbreviations: NA: not available; U.S.: United States.

We performed descriptive statistics on the entire study population. Data were analyzed using standard statistical methods. Variables were described with medians, absolute values, and rates.

■ CASE REPORT

A 66-year-old male patient, living in an urban area with no history of recent travel, was admitted to hospital for a "7-3" cytarabine and idarubicin chemotherapy induction scheme for AML. His medical history included a bowel resection for acute appendicitis three months earlier, arterial hypertension, insulin-dependent diabetes mellitus, chronic pulmonary obstructive syndrome and concomitant classic Hodgkin lymphoma diagnosed three years prior. After chemotherapy induction, the patient presented with a long-lasting neutropenia of 18 days complicated by febrile neutropenia and a bloodstream infection (BSI) due to *Stenotrophomonas maltophilia*, which was treated effectively with intravenous cotrimoxazole and cefiderocol. Four weeks after the BSI, the patient developed a second episode of febrile neutropenia complicated by a new-onset dry cough. During this febrile episode, chest computed tomography (CT) was done, revealing multiple nodular pulmonary lesions and sub-pleural consolidations, without cavitation and characterized in part by surrounding ground-glass halos (Figure 2).

At the time of evaluation, the patient did not have fever and pulse oximetry was 96% while breathing room air. Laboratory examination revealed a white blood cell count of 3,950 cells/uL with a normal eosinophil count (300 cells/uL). Other results included haemoglobin (8.2 g/dL), platelets (12,000), lactate dehydrogenase (330 U/L) and C-reactive protein (47 g/dL) (Table 2).

Broncho-alveolar lavage was also performed; bacterial, viral, fungal and mycobacterial microbio-

logical analyses were negative. After a pulmonary and radiological consult, a lung biopsy was carried out, which revealed diffuse inflammation infiltrated with small diffuse granulomas with a minor eosinophil component. In addition, bacterial, fungal and mycobacterial microscopy and cultures on biopsy samples were negative. Serological analysis showed a high immunoglobulin E (IgE) count (5,677 kUA/L; normal value <0.5) with a normal eosinophil count. After an infectious disease consultation, a *Strongyloides* spp., *Trichinella* spp., HTLV-1 serological analysis and an extended parasitological analysis of faeces on three consecutive samples were performed, with negative results. In addition, an immunoblot assay (*Toxocara* western blot IgG [LDBIO Diagnostics, Lyon, France]) was performed and had a strongly positive result. The biopsy was revised, but no larvae were seen in the sample. After an eye examination

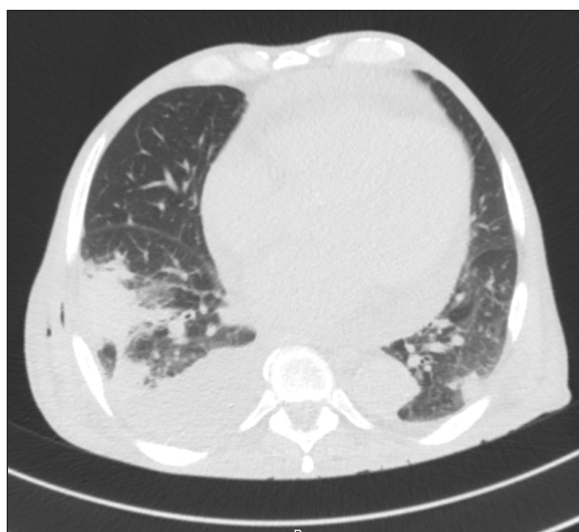


Figure 2 - Chest computed tomography revealing pulmonary involvement during the second episode of febrile neutropenia.

Table 2 - Laboratory Features from diagnosis to clinical and radiological resolution.

	At diagnosis	Treatment start	2 wks of Albendazole	4 wks of Albendazole	4 wks after treatment
WBC ($10^9/L$)	3.95	2.43	3.58	4.17	NA
Neutrophils (N)	0.89	0.33	1.47	1.75	NA
Lymphocytes (N)	2.64	2.03	1.77	1.84	NA
Eosinophils (N)	0.3	0.8	1.1	1.4	NA
RBC ($10^{12}/L$)	3.13	2.53	2.74	2.47	NA
Hb (g/dL)	8.2	8.0	8.9	8.2	NA
PLTS ($10^9/L$)	12.00	21.00	24.00	36.00	NA
AST (U/L)	26.00	17.00	24.00	NA	NA
ALT (U/L)	42.00	25.00	18.00	NA	NA
IgE (kU/L)	NA	5677.00	4620.00	4246.00	3740.00
C-RP (mg/dL)	47.0	1.03	1.78	NA	NA

Abbreviations: WBC: White Blood Cell; RBC: Red Blood Cell; Hb: Haemoglobin; PLTS: Platelets; C-RP: C-Reactive Protein; IgE: Immunoglobulin E; ALT: Alanine amino-transferase; AST: Aspartate amino-transferase; Wks: Weeks; NA: Not Available.

to exclude ocular involvement and due to the compatible CT findings, treatment with albendazole 400 mg every day for four weeks in combination with 50 mg of prednisone progressively de-escalated during the first week was started. The CT scan was repeated four weeks after the end of anti-helminthic treatment and revealed a complete regression of lung involvement (Figure 3). Interestingly, the total IgE count had a descent up to 3,740 kUA/L after anti-helminthic treatment.

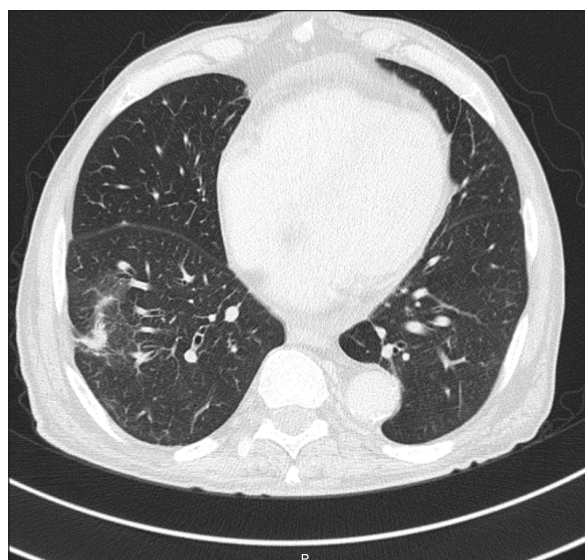


Figure 3 - Chest computed tomography after four weeks from the end of albendazole treatment.

Because of the persistence of a detectable IgE count, an immunological consultation was made that excluded a Hyper IgE syndrome but revealed a concomitantly high anti-staphylococcal toxin A IgE count (1.84 kUA/L; normal value <0.1). We conclude that the patient had a multifactorial high IgE count due to haematological disease (i.e., Hodgkin lymphoma and AML), recent anthroponosis and the staphylococcal IgE component.

■ DISCUSSION

Pulmonary toxocariasis is an uncommon presentation of *Toxocara* spp. infestation in the haematological population and this is, to our knowledge, the first case reported in an AML/LH patient. Therefore we have reviewed the previously reported cases of pulmonary toxocariasis in immunocompromised patients presented in the literature (Table 3).

Most of the cases presented in this review occurred in males (Table 3) as in our patient. Raissi and colleagues reported an interesting sero-epidemiological study on human toxocariasis in individuals with blood disorders and cancer patients in Iran. Raissi and colleagues have founded a higher prevalence of seropositivity in female patients in all the groups (i.e., white cell disorders, blood cell disorders and cancer from all types), despite the lack of statistical significance between differences [7]. According to a review of studies on toxocariasis in the United States, Lee et

Table 3 - Cases collected from the narrative review of the literature performed.

Author	Type of article	N of patients included	Gender/ Age	Type of immuno-suppression	Immuno-suppressant	Involvement	Type of pulmonary involvement	Eosino-phils	IgE	Toxocara isolation	Treatment	Complication	Outcome
Krcmery et al. [20]	Case report	1	M/55	Mycosis fungoides	Corticosteroids; cytotoxic chemotherapy	Pneumonia, Liver, Spleen	Pulmonary infiltrates	No data	No data	N.A.	Mebendazole	<i>Enterococcus</i> pneumonia superinfection	Death
Hanslik et al. [22]	Case report	1	No data	Lung cancer	No data	Pneumonia	No data	No data	No data	N.A.	No data	No data	No data
Park et al. [19]	Case series	1/2	M/52	Gastric adenocarcinoma	No	Pneumonia; Liver	Bilateral, multiple nodules with ground glass attenuation	Increased	Increased	N.A.	Mebendazole	Not reported	Complete response
Park et al. [19]	Case series	2/2	M/58	Rectum adenocarcinoma	No	Pneumonia; Liver	Several areas of ground glass opacity	Increased	Increased	N.A.	Mebendazole	Not reported	Complete response
Park et al. [21]	Case Report	1	M/45	Ulcerative colitis	Azathioprine; mesalazine	Pneumonia	Multifocal large consolidations	Increased	No data	N.A.	Albendazole	Not reported	Complete response

Abbreviations: M: male. N.A.: not available. N: number.

al. discovered that 73% of the studies showed a higher prevalence in males compared to females, whereas 27% of the studies revealed no significant differences between genders [24]. The prevalence of *Toxocara* infection was not observed to be substantially greater in females compared to males in any study. Interestingly, Rostami and colleagues in a global meta-analysis have showed that being male (odds ratio [OR], 1.27; 95% CI, 1.17-1.39) represent a possible risk factors for seropositivity to *Toxocara* worldwide [2]. Corresponding to the larger collections of pulmonary toxocariasis cases reported by Ranasuriya et al., most of the patients (8/12) were males [25]. Moreover, Ranasuriya and colleagues in their review on pulmonary toxocariasis without mention of immunocompromising reported younger ages than reported in our review with a median of 38 vs 53 but with a wider range of ages (20 to 75 vs 45 to 58) of patients included [25]. Therefore, in the global meta-analysis of Rostami et al., younger

age was reported among possible risk factors for positive serology of *Toxocara*, despite that patients aged between 41-60 vs ≥ 60 presented similar prevalence (17.4 vs 18.1) in their analysis [2]. Immunocompromised cohort presented in this review showed a single patient affected by haematological disorders (i.e., mycosis fungoides). Moreover, most of patients presented solid organ malignancies. Interestingly, Raissi and colleagues in their epidemiological analysis in immunocompromised hosts reported out of 101 individuals an higher seropositivity for *Toxocara* in cancer patients (11.06%) respect to white blood cell disorders (5.94%) [7]. Interestingly, we reported a case of pulmonary toxocariasis that occurred and was exacerbated after chemotherapy induction. Moreover, only two patients among five collected had undergone immunosuppressive regimens before diagnosis of pulmonary toxocariasis. At our knowledge no cases of toxocariasis were reported after or during

cytarabine and idarubicin treatment for AML, on the other hand infections events are not uncommon during this regimen in AML patients with 186 events among 810 patients (22.9%) in randomized clinical trials according to Wang and colleagues meta-analysis [26]. Therefore, other helminthic infection reactivations during anti-neoplastic regimens, such as *Strongyloides* infections, were reported.

In our patients radiological suspected involvement by toxocariasis was uniquely pulmonary. Despite that three patients of five reported other organ involvement, notably hepatic. Moreover, we reported the CT pattern of pulmonary involvement with sub-pleural nodules and consolidations at diagnosis and after treatment (Figures 2 and 3), respectively. Lee et al. reported a more comprehensive collection of CT findings in pulmonary toxocariasis (N=63 patients) [27]. In this report, sub-pleural lesions were reported in 81% of cases. Moreover, solid nodules and patchy consolidations on CT were reported in 29% and 21% of cases, respectively [27]. These CT patterns were also reported in pneumonia involving of patients reviewed in this work (Table 3).

As a specific feature, migratory nodular shadows with halos are important chest computed tomographic findings in human toxocariasis, and can also be unexpectedly found in other parasitic disease in specific vulnerable population [28]. Projects exist to implement integrated multidisciplinary programs to prevent, diagnose and treat zoonotic or parasitic infections in the immunocompromised host [29]. Awareness is increasing regarding the different parasitic infections that may be evaluated prior to immune-modulatory therapies and guidelines have been produced accordingly [30, 31].

We therefore reported data regarding presence of hyper-eosinophilia and IgE. Contrary to our case with isolated hyper IgE most of patients collected reported both higher eosinophils and IgE. According to Park and colleagues, 20-30% of patients with toxocariasis do not have eosinophilia. In general, eosinophilia in helminth infection is more frequent and more pronounced in acute or early infection and in the paediatric population [3-6, 32-34]. In fact, in chronic infection, chemotactic stimulation is reduced, and the migration of eosinophils presenting as peripheral blood eosinophilia is diminished [3-6, 32, 33]. For these rea-

sons, the role of eosinophilia in subacute or chronic toxocariasis diagnosis may be less consistent [3-6, 32, 33]. Interestingly, in our patient the diagnosis was driven by the high total IgE count and confirmed by compatible serological, anatomopathological and radiological patterns paired with the exclusion of other microbial aetiologies. The serum IgE count correlates well with pulmonary infiltration and the level of toxocariasis activity, and this trend could be a useful surrogate to evaluate treatment efficacy [35].

In addition, Takamoto and colleagues [36] described the production of eosinophils and IgE in mutant mice deficient in CD4⁺ T cells and their normal and heterozygous littermates after *T. canis* infection. Eosinophil counts slowly decreased after a peak on day 10; in contrast, total IgE counts increased rapidly on days 7-14 and less rapidly on days 14-42 after *T. canis* infection [36]. Furthermore, Boldiš and colleagues reported that high IgE counts in human toxocariasis were more frequent in patients coming from urban areas, as was the case with our patient [32].

Histopathological findings of larvae in lung biopsies are rarely reported in humans and biopsies are performed in only a small percentage of suspected pulmonary toxocariasis cases [4, 5, 32]. Moreover, cases collected from the literature did not report histopathological isolation of *Toxocara* spp. as happened in our experience.

Albendazole treatment was continued for up to 4 weeks according to extent of lung involvement, immunological status of the patients and accordingly previous reported cases. In their literature review, Ranasuriya et al. reported a treatment duration for pulmonary toxocariasis between 5 and 56 days [26]. The treatment was well tolerated for the entire duration of therapy.

Treatment of toxocariasis in immunocompromised patients usually involves a combination of anthelmintic drugs, such as albendazole or mebendazole, and close monitoring for potential drug interactions with other medications. The treatment duration may be prolonged compared to immunocompetent individuals, and the response to therapy may vary based on the degree of immunosuppression [6]. Moreover, alongside anthelmintics, corticosteroids are currently indicated for patients with severe symptoms. Corticosteroids are effective in decreasing inflammation and managing hypersensitivity responses

induced by deteriorated larvae after ntelmintics therapy [37].

Pulmonary toxocariasis should be ruled out in patients with pulmonary involvement and high IgE counts with or without eosinophilia, and in patients from urban areas, especially those with known immunocompromised status.

This narrative review presents different limitations. First, this is a narrative revision of the literature and lacks a systematic methodology or meta-analysis of the data. Secondly, cases reported are uncommon in literature and the whole population is small respect to other more frequent pulmonary parasitic infections (i.e., Strongyloidiasis) in haematological population.

This review highlights the importance of continuing raising awareness and surveillance. In fact, increased awareness among healthcare professionals about pulmonary toxocariasis, particularly in immunocompromised populations, can lead to earlier diagnosis and appropriate management. Surveillance systems can help public health authorities monitor the prevalence and trends of this infection, enabling them to take timely preventive measures. In this perspective, we should not forget the zoonotic transmission nature of this infection. Therefore, public health efforts should focus on educating the public about the risks of exposure to contaminated soil and the importance of good hygiene practices, such as handwashing after contact with animals, to prevent infection. As clinicians we should promote integrated locally led multidisciplinary programs. This would enhance the prevention, diagnosis, and treatment of parasitic infections in immunocompromised hosts at the capillary level. These programs can also bring together healthcare providers, public health officials, and researchers to collaboratively address the challenges associated with these infections, providing an update body of literature for patient care. Particularly, at a global scale data we retrieved are suggesting possible risk factors for *Toxocara* seropositivity, including gender and age, and highlights the need for international collaboration in studying and addressing parasitic infections. Public health efforts should extend beyond national borders to tackle zoonotic infections effectively. By understanding and addressing the factors influencing pulmonary toxocariasis in immunocompromised individuals, healthcare

professionals and public health authorities can improve patient outcomes, enhance surveillance and monitoring, and implement preventive measures to protect vulnerable populations. Possibly, enhanced diagnostic methods, both immune and parasite-based assays, coupled with imaging software, could overcome the difficulties in diagnosing and screening immune-compromised patients. Characterization and discussion of these challenges can be informed by data presented in the present work.

Author contributions

Each authors contributed equally to this work respect to study drafting and critical revision of the manuscript intellectual content.

Conflict of interest disclosure

All the authors declare no conflict of interest.

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