

Association between urticaria and nematode infections

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ABSTRACT

Background: The association between parasites and urticaria was first suggested in the last century. A wide range, 0–75.4%, of the prevalence of parasitic infection has been reported with chronic urticaria (CU). Moreover, urticaria may be detected in patients with parasitosis. Nematodes are a type of helminth that infect hundreds of millions of people throughout the world.

Objective: The aim of this work was to collect and review the published studies and cases of urticaria associated with nematode infections.

Methods: A search of scientific literature data bases from January 1960 until May 2017 was carried out.

Results: Numerous nematode infections have been associated with urticaria and/or angioedema: *Anisakis simplex*, *Ascaris* species (spp.), *Dirofilaria* spp., *Enterobius vermicularis*, *Gnathostoma* spp., *Loa loa*, *Mansonella streptocerca*; *Necator americanus*, *Onchocerca volvulus*, *Strongyloides stercoralis*, *Toxocara* spp., *Trichinella* spp., and *Wuchereria bancrofti*. The pathogenesis of urticaria in these infections generally remains unexplained. In some cases, skin manifestations were caused by the presence of the worm in the skin (*Filaria*, *Gnathostoma*); in other cases, such as *A. simplex* and *S. stercoralis* infections, there was a clear immunoglobulin E-mediated mechanism that led to allergic reactions, and infection and allergy coexisted; for other nematodes, the association was anecdotal and only a few cases were reported.

Conclusion: It is difficult to detect a certain causal effect, except when urticaria improves or disappears after infection treatment. Cases of isolated urticaria not associated with other symptoms rarely may be caused by helminths. In the current guideline for urticaria, parasitosis is considered to be a rare possible cause of CU in developed industrial countries. Therefore, although a routine screening of parasitic infection in CU is not recommended, in our opinion, testing a patient with urticaria for parasites is a physician's choice based on the characteristics of the patient, such as associated symptoms, dietary habit, provenance country and previous travel.

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Nematodes (roundworms) are a large group of helminths. They can inhabit both intestinal and extraintestinal tissues in humans and animals, and any organ can be affected.¹ The human immune reaction to helminth infections is associated with elevated levels of type 2 T-helper (Th2) cytokines and immunoglobulin E (IgE), and tissue eosinophilia, which are physiologic responses to eliminate the parasite. Furthermore, helminths actively regulate host immune responses, which induces regulatory T (Treg) and B cells; modulates Th cell differentiation; and blocks T-cell cytokine production, epithelial cell alarmin, and dendritic cell antigen presentation.^{2,3} The immune response can vary according to the type of infection: subjects without symptoms have a prevalent Th2 and Treg response,

subjects with symptomatic infection show a failure of tolerance, with a prevalent of Th1 and Th17 responses.³

Individuals who are infected may have allergic inflammatory responses to parasites and parasite antigens. Usually, helminth infections in endemic areas are associated with a low allergy rate.⁴ However, some infections are associated with increased allergy.⁵ Different factors may influence the relationship between helminths and allergy, such as the time of first infection and its duration: later or limited infections may induce allergy as a host response against the parasite, whereas early and chronic infections may induce immune modulatory responses by stimulating Treg responses with interleukin-10 production and antigen-specific IgG4, which may block IgE-mediated allergic responses to helminth. Therefore, in endemic areas, subjects with chronic infections may present a Th2-modified response with few allergic-type reactions and a strong Th2 response. Other factors are the intensity of infection, the genetic predisposition to allergic diseases, and the nature of the parasite.^{2,4}

In the past few years, an interesting breakthrough was made on the pathogenesis of urticaria and the possible causes linked to its different subtypes.⁶ In the European Academy of Allergology and Clinical Immunology (EAACI), Global Allergy and Asthma Euro-

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pean Network (GA2LEN), European Dermatology Forum (EDF) and World Allergy Organization (WAO) Guideline for urticaria,⁷ acute or chronic infections have been described as possible causes. Many infectious agents among bacteria, viruses, parasites, and fungi are hypothesized to trigger urticaria; this subject has been a matter of debate for >100 years.^{8–10} In particular, the association between parasites and urticaria was first suggested in the last century.¹¹ The rate of parasitic infections in urticaria varies widely by country and by study type, ranging between 0 and 75.4%.¹² Moreover, patients with parasitosis may exhibit urticaria (range, 1–66.7%).¹²

The mechanism of urticaria during parasitic infection is still unclear; there may be multiple factors involved. The release of histamine and other mediators by skin mast cells (MC) may be triggered by the interaction between parasite-specific IgE and its high-affinity IgE receptors. Moreover, products released by helminths, together with the tissue damage during invasion of parasites cause alarmin production that can induce skin MC degranulation. Furthermore, eosinophil recruitment to the skin and activation of the coagulation and complement systems can also induce MC activation and urticaria development.¹² The aim of this work was to review the published studies and cases of urticaria associated with nematode infections because hundreds of millions of people throughout the world are infected by these parasites.¹³

METHODS

The search was performed by using PubMed and ScienceDirect (Elsevier Science Publisher B.V., Amsterdam, The Netherlands). We referred to the nematodes presented in the book, "Principles and Practice of Infectious Diseases,"¹⁴ and added to the search some other nematodes that rarely cause human infection. The etiologic agents searched were the following: *Ancylostoma* species (spp.), *Angiostrongylus* spp., *Anisakis* spp., *Ascaris* spp., *Baylisascaris procyonis*, *Brugia* spp., *Capillaria philippinensis*, *Diectophyme renale*, *Dirofilaria* spp., *Dracunculus medinensis*, *Enterobius vermicularis*, *Gnathostoma* spp., *Loa loa*, *Mansonella streptocerca*, *Necator americanus*, *Oesophagostomum* spp., *Onchocerca volvulus*, *Phocanema* spp., *Strongyloides stercoralis*, *Ternidens deminutus*, *Thelazia* spp., *Toxocara* spp., *Trichinella* spp., *Trichuris trichiura*, *Trichostrongylus* spp., and *Wuchereria bancrofti*. The PubMed search was carried out by using the following Medical Subject Headings: urticaria, angioedema, and exanthema combined with each one of the etiologic agents mentioned above. The search of the ScienceDirect data base was performed with the following queries: urticaria or angioedema, and the same etiologic agents mentioned above. We included all research articles and case reports published from January 1960

through May 2017 in peer-reviewed scientific journals that describe the association between urticaria and/or angioedema with nematodes. The reference lists of these articles were also checked for relevant articles, including review articles. A study was considered eligible if it reported data on patients with nematode infection who had signs of urticaria and/or angioedema. Duplicate articles and articles in languages other than English were eliminated from the review.

RESULTS

The literature search identified 1354 records about the following genera of helminths associated with urticaria and/or angioedema: *Anisakis simplex*, *Ascaris* spp., *Dirofilaria* spp., *E. vermicularis*, *Gnathostoma* spp., *L. loa*, *M. streptocerca*, *N. americanus*, *O. volvulus*, *S. stercoralis*, *Toxocara* spp., *Trichinella* spp., and *W. bancrofti*. A total of 821 records were discarded: 369 had an unrelated title, 236 were duplicates, 193 were not English language, and 23 were studies on animals. Of 533 records, 499 were discarded because the abstract or the full text was not relevant to the topic in question; 34 records were considered eligible and were included in the review. The main studies that reported the association between urticaria and nematodes are presented in Table 1.

A. simplex

A. simplex is a nematode usually found in marine fish and cephalopod. It infects humans accidentally after the intake of raw or undercooked contaminated fish. The human parasitosis is an acute and transient gastrointestinal infection,^{15,16} sometimes associated with mild-to-severe IgE-mediated reactions. In this form, named gastroallergic anisakiasis, patients simultaneously exhibit clinical manifestations of allergy and infections. Some patients may experience hypersensitivity reactions, without gastrointestinal symptoms.^{15–18} Hypersensitivity to *A. simplex* is indicated by the rapid increase of serum-specific IgE levels immediately after infection and their long persistence. To make the diagnosis of *A. simplex*, hypersensitivity skin-prick, specific IgE, and basophil activation testing can be used.¹⁵ Up to now, 14 kinds of proteins have been identified as *A. simplex* allergens (Ani s 1–14).¹⁹ Ani s1 is considered the major allergen, together with Ani s2, Ani s7, Ani s12, and Ani s14.¹⁹ Ani s1 was present in 67–86% of patients with gastroallergic anisakiasis and was absent in nonsensitized individuals^{20,21}; Ani s7 was found in 100% of patients with *Anisakis* allergy.²²

Besides acute IgE-mediated urticaria,²³ chronic urticaria (CU) also has been associated with *A. simplex* infection, especially in areas where raw fish is consumed.^{24–26} In two studies, the prevalence of *A. simplex* sensitization in patients with CU who were regular

Table 1 Characteristics of the published studies on the association between urticaria and nematodes

Nematode	Study, y	Level of Evidence*	Type of Urticaria	Study Design	Study Group	Rate of Parasitosis in Patients with CU, %	Rate of Urticaria in Patients with Parasitosis, %	Clinical End Point
<i>Anisakis simplex</i>	Daschner <i>et al.</i> , ²⁵ 2005	4	CU	Case control	Adults	52.6	n/a	To estimate the prevalence of specific IgE against <i>A. simplex</i> in patients with CU
	Ventura <i>et al.</i> , ²⁶ 2013	4	CU	Case control	Adults	49.7	n/a	To estimate the prevalence of CU in an area where marinated fish is frequently eaten
	Gracia-Bara <i>et al.</i> , ²⁷ 2001	3	CU	Prospective study	Adults	n/a	64.7	Follow-up of patients with CU and positive specific IgE levels to <i>A. simplex</i> with a fish-free diet
<i>Ascaris</i> spp.	Varga <i>et al.</i> , ³² 2001	4	CU, angioedema	Case series	Adults	69	n/a	Investigate which parasites are more frequently related to the skin manifestations
	Nettis <i>et al.</i> , ³³ 2003	3	CU	Cross-sectional	Not specified	0.16	n/a	To analyze the prevalence of various forms of urticaria according to an etiologic and clinical classification
	Du Toit <i>et al.</i> , ³⁴ 2006	3	CU	Cross-sectional	Children	2.5 (positive stool examination) 29 (positive specific IgE)	n/a	To investigate the frequency of specific IgE to <i>Ascaris lumbricoides</i> in children with CU
	Kaji <i>et al.</i> , ³⁵ 2007 Clark, ⁴¹ 1961	5 5	AU AU	Case report Case report	Adult Children	n/a n/a	n/a n/a	n/a n/a
<i>Enterobius vermicularis</i>	Nettis <i>et al.</i> , ³³ 2003	3	CU	Cross-sectional	Not specified	0.16	n/a	To analyze the prevalence of various forms of urticaria according to an etiologic and clinical classification
	Arik Yilmaz <i>et al.</i> , ⁴² 2016	3	CU	Cross-sectional	Children	1.4	n/a	To investigate the prevalence of parasitic infection-related CSU in children
<i>Dirofilaria immitis</i>	Patrizi <i>et al.</i> , ⁴³ 2012	5	Urticaria pigmentosa	Case report	Child	n/a	n/a	n/a
<i>Dirofilaria repens</i>	Rubin <i>et al.</i> , ⁴⁵ 1975	5	Episodic swelling	Case report	Adult	n/a	n/a	n/a
	Pónyai <i>et al.</i> , ⁴⁶ 2006	5	Localized urticaria and subcutaneous swelling	Case report	Adult	n/a	n/a	n/a
	Fontanelli Sulekova <i>et al.</i> , ⁴⁷ 2016	5	Transient edematous swelling	Case report	Adult	n/a	n/a	n/a

Table 1 Continued

Nematode	Study, y	Level of Evidence*	Type of Urticaria	Study Design	Study Group	Rate of Parasitosis in Patients with CU, %	Rate of Urticaria in Patients with Parasitosis, %	Clinical End Point
<i>Loa loa</i>	Gobbi <i>et al.</i> , ⁵⁴ 2014	4	Urticaria	Case series	Not specified	n/a	8	To compare clinical and parasitologic manifestations of loiasis between subjects born in endemic areas and expatriates and travelers
	Gantois <i>et al.</i> , ⁵⁵ 2013	4	Urticarial rash	Case series	Adults	n/a	14	To describe the clinical and biologic patterns, and the treatment of cases of imported loiasis
	Churchill <i>et al.</i> , ⁵³ 1996	4	Urticaria/rash	Case series	Adults and Children	5	n/a	To assess differences between subjects from endemic areas and expatriates with loiasis
<i>Wuchereria bancrofti</i>	Singh <i>et al.</i> , ⁶¹ 2011	5	Urticarial rash	Case report	Adult	n/a	n/a	n/a
<i>Gnathostoma</i>	Chai <i>et al.</i> , ⁶² 2003	4	Urticaria	Case series	Adults and children	n/a	31	To analyze the characteristics of gnathostomiasis in a group of subjects from an area previously unrecognized as endemic
	Sangchan <i>et al.</i> , ⁶³ 2006	5	AU	Case report	Adult	n/a	n/a	n/a
<i>Necator americanus</i>	Diemert <i>et al.</i> , ⁶⁴ 2012	2	AU	Randomized, double-blind, controlled phase I trial	Adult	n/a	42.85#	To assess the safety and immunogenicity of vaccination with Na-ASP-2 in subjects previously infected with <i>N. americanus</i>
<i>Strongyloides stercoralis</i>	Grove, ⁷¹ 1980	4	Recurrent urticaria	Cross-sectional	Adults	n/a	66	To assess the prevalence of strongyloidiasis in an unselected sample of ex-prisoners of war in southeast Asia and delineate the clinical manifestations of the infection
	Khieu <i>et al.</i> , ⁷² 2013	4	CU	Cross-sectional	Adults and children	n/a	66.7	To analyze the clinical manifestations of patients with strongyloidiasis
	Ramirez-Olivencia <i>et al.</i> , ⁷³ 2014	4	CU	Retrospective study	Adults	n/a	18	To assess the epidemiologic, laboratory, and clinical features of imported strongyloidiasis
	Rampur <i>et al.</i> , ⁷⁴ 2016	4	Urticaria and/or angioedema	Case series	Adults	n/a	41.6	To assess the prevalence of strongyloidiasis in subjects with allergy-type symptoms
	Myers <i>et al.</i> , ⁷⁵ 2000	5	CU	Case report	Adult	n/a	n/a	n/a
	Pelletier and Gabre-Kidan, ⁷⁶ 1985	5	CU	Case report	Adults	n/a	n/a	n/a

Table 1 Continued

Nematode	Study, y	Level of Evidence*	Type of Urticaria	Study Design	Study Group	Rate of Parasitosis in Patients with CU, %	Rate of Urticaria in Patients with Parasitosis, %	Clinical End Point
<i>Toxocara</i>	Humbert <i>et al.</i> , ⁷⁹ 2000	4	CU and/or angioedema	Case control	Adults and children	19.5	n/a	To assess the risk of <i>Toxocara</i> infection in patients with different cutaneous symptoms
	Demirci <i>et al.</i> , ⁸⁰ 2003	4	CU	Case control	Adults	29	n/a	To assess the seroprevalence of <i>Toxocara</i> in patients with CU
	Dal <i>et al.</i> , ⁸² 2013	4	CU	Case control	Adults	14.5	n/a	To assess the seroprevalence of <i>Toxocara canis</i> in patients with CU
	Burak Selek <i>et al.</i> , ⁸³ 2015	4	CU	Case control	Adults	17.8	n/a	To assess the seroprevalence of <i>T. canis</i> in patients with CU
	Van Den Broucke <i>et al.</i> , ⁸⁴ 2015	4	Urticarial rash	Case series	Adults	n/a	28.5	To assess the frequency, presentation, and outcome of toxocariasis among travelers and migrants
	Matos Fialho <i>et al.</i> , ⁸⁵ 2017	4	CU	Cross-sectional	Children	16	46.5	To assess the prevalence of IgG class antibodies against <i>Toxocara</i> spp. and their association with urticaria in 2- to 12-year-old children
<i>Trichinella</i>	Renner <i>et al.</i> , ⁸⁷ 2008	5	CU and/or angioedema	Case report	Adult	n/a	n/a	n/a

CU = Chronic urticaria; n/a = not applicable; IgE = immunoglobulin E; spp. = species; AU = acute urticaria; Na-ASP-2 = *N. americanus* Ancylostoma-secreted protein-2.

*According to Ref. 90.

#Urticaria rate after vaccination with Na-ASP-2.

consumers of raw fish was 49.7²⁶ and 52.6%,²⁵ compared with 16–20% in a control population.^{25,26} In another study, the CU rate in patients with *A. simplex* sensitization was 64.7%.²⁷ Moreover, a fish-free diet in these patients clearly improved urticaria^{25–27} whether compared with patients with CU without sensitization to *A. simplex*²⁵ or compared with patients who did not change their dietary habits.²⁶ The patients involved in the studies had a history of recurrent or persistent wheals and/or angioedema. In some cases, the patients were regular consumers of marinated fish (4–6 times per week), this could explain the persistence of urticaria.²⁶ To explain the presence of symptoms when the patients were not in contact with the antigen, some investigators hypothesized that, after an acute parasitism and the parasite dead, specific IgE against thermo-stable antigens of the larvae could maintain the reaction in habitual fish consumers.²⁵

Ascaris spp.

Ascaris is one of the most common human parasites worldwide, especially in developing countries. *Ascaris* causes a chronic disease of the small intestine, usually asymptomatic or with mild symptoms.^{28,29} Patients with *Ascaris* infection present with increased allergic manifestations, especially asthma, linked to cross-reactivity between worm proteins, as tropomyosins, and highly similar molecules in dust-mites.^{30,31} There were only a few studies on the association of *Ascaris* infection and urticaria.^{32–35} A Romanian study showed that 69% of the patients with CU or angioedema had *Ascaris lumbricoides* infection, with more-severe skin symptoms compared with patients infected with other parasites. The correlation between infection and CU and/or angioedema was confirmed by remission of symptoms after antiparasitic treatment.³² On the contrary, an Italian study reported the association between the parasite and urticaria in only 1 patient among 562 patients with urticaria.³³ Another study, on children with CU, reported a positive result for *A. lumbricoides* of a stool examination in 2.5% of the patients and a high specific IgE titer to the nematode in 29% of the children.³⁴ A single case of acute urticaria (AU) was reported in a patient with acute *A. lumbricoides* infection.³⁵ Urticaria during *A. lumbricoides* infection was due to the migration of larvae through the body.³⁶

E. vermicularis

E. vermicularis is one of the most widespread human helminths worldwide³⁷; however, patients who are infected are usually asymptomatic. The only known host is human.³⁸ Despite the large distribution and its association with an increased risk of atopic dermatitis and allergic rhinoconjunctivitis,^{39,40} this parasite is rarely associated with urticaria. In 1961, two cases of local-

ized AU of the buttocks were reported in two children.⁴¹ CU was associated with *E. vermicularis* infection in 1 of 562 patients with urticaria³³ and in 3 of 211 children with CU.⁴² CU was associated with *E. vermicularis* infection in one adult³³ and three children.⁴² Moreover, an exacerbation of urticaria pigmentosa associated with *E. vermicularis* infection was observed in a child affected by cutaneous mastocytosis; the infection treatment led to a rapid regression of skin manifestations.⁴³

Filaria

Dirofilaria, *L. loa*, *Mansonella* spp., *O. volvulus*, and *W. bancrofti* are responsible for filariasis and have been grouped together.

Dirofilaria spp. *Dirofilaria* causes an endemic zoonosis in many tropical regions and in a few southern European countries. The two species *Dirofilaria repens* and *Dirofilaria immitis* recognize dogs as definitive hosts, but the parasite can also infect wild carnivores and humans. *D. immitis* causes pulmonary dirofilariosis; *D. repens* causes ocular and subcutaneous dirofilariosis.⁴⁴ In 1975, a woman presented with episodic swelling, itch, and pain in one wrist; her serologic and immediate skin test results were positive for *D. immitis* and the presence in blood of *Acanthocheilonema perstans* microfilariae; the clinical manifestation subsided after specific treatment.⁴⁵ *D. repens* was detected in subcutaneous nodules in two patients: one patient had localized urticaria and subcutaneous swelling⁴⁶; in the other patient had transient edematous swelling, creeping eruption, and arthralgias.⁴⁷ After treatment, the first patient⁴⁶ recovered, whereas the second patient⁴⁷ continued to occasionally have urticaria and arthralgia.

L. Loa. *L. loa* causes a rare filariasis, termed loiasis. Humans are infected through the bite of female flies.⁴⁸ The infection of *L. loa* is often asymptomatic. The clinical manifestations are usually due to hypersensitivity reactions to the worm and differ in subjects from endemic and nonendemic areas. In endemic areas, subjects who were infected presented with pruritus; hyper-eosinophilia; a temporary localized edema, called Calabar swelling; and skin lesions described as urticarial rash^{49,50} or urticarial vasculitis.⁵¹ In the subjects from nonendemic areas, the symptoms were more severe and mainly of an allergic type.⁵² These patients showed a marked immunologic hyperresponsiveness with severe pruritus and angioedema and with very high titers of antibody to filariae, increased serum IgE levels, and severe hypereosinophilia.^{50,52} Three articles showed different urticaria rates in patients with imported loiasis: 5% in the U.K. study,⁵³ 8% in the Italian study,⁵⁴ and 14% in the French study.⁵⁵ Most of these patients were from nonendemic areas.

Mansonella spp. Three types of *Mansonella* are known to infect humans: *Mansonella perstans*, *M. streptocerca*, and *Mansonella ozzardi*. The three species have a similar life cycle and the same transmission vector (flies) but are present in different geographic areas. The infections of all three species are usually asymptomatic.⁵⁶ Symptoms usually associated with the *M. perstans* infection include transient upper abdominal pain and allergic reactions that resemble the “Calabar swellings” seen in *L. loa* infections. The swelling is accompanied by pruritus, with or without urticaria, and by hypereosinophilia.⁵⁷ The other two types of *Mansonella* spp. may cause various skin lesions, but urticaria and/or angioedema cases have not been described.

O. volvulus. *O. volvulus* is transmitted to humans by black flies. There are two forms of *O. volvulus* disease, called onchocerciasis, one is characterized by blindness, the other is characterized by a broad range of skin lesions associated with a spectrum of increasing generalized Th2-type responses.^{58–60} The host response to parasitic infection is demonstrated by the so-called Mazzotti reaction, which is caused by the killing of the microfilariae after treatment in individuals who are heavily infected. The reaction is characterized by pruritus, papular or urticarial skin lesions, ocular complications, lymphadenitis, musculoskeletal pain, headache, vertigo, and cardiovascular symptoms.⁵⁸ Among filariasis, a single case of a patient with *W. bancrofti* infection who presented with urticarial rash was reported.⁶¹

***Gnathostoma* spp.**

The genus *Gnathostoma* contains at least 12 distinctive species, but the most important species that causes human infection is *Gnathostoma spinigerum*. Humans usually acquire the infection, called gnathostomiasis, through the ingestion of raw or undercooked meat of a paratenic host that contains the infective larva. Migration of larva causes cutaneous larva migrans syndrome, characterized by a migratory edema and by creeping and mobile erythematous eruption.⁶² In a study from Korea, urticaria was reported in 31% of the patients with signs and symptoms of gnathostomiasis.⁶² In a report, a woman with hepatitis C virus infection showed painful swelling nodules and AU that occurred in every cycle of interferon therapy, until worms, identified as *G. spinigerum*, migrated out of the skin nodule. Symptoms resolved after parasite removal; therefore, the immunomodulatory effect of interferon stimulated the external worm migration.⁶³

N. americanus* and *Ancylostoma duodenale

N. americanus and *Ancylostoma duodenale* are two species of hookworm found exclusively in humans. The

infection is usually asymptomatic. During larvae migration to the intestinal tract, there occasionally may appear a pruritic erythema.^{64,65} To our knowledge, no reports of urticaria and/or angioedema associated with *N. americanus* or *A. duodenale* infection are present in the literature. However, Diemert *et al.*⁶⁴ reported three cases of generalized urticaria after vaccination with *N. americanus* Ancylostoma-secreted protein-2 (Na-ASP-2); the subjects were three healthy adults previously infected with *N. americanus*. They showed pre-vaccination IgE levels to Na-ASP-2 to be 21 times higher compared with levels found in subjects who were vaccinated and were without urticaria; two of the three patients presented immediate hypersensitivity skin testing results for Na-ASP-2 at 18 months after vaccination; the third subject was not tested.⁶⁴

S. stercoralis

S. stercoralis, a soil-transmitted nematode, is responsible for one of the most neglected tropical diseases. Although it affects millions of people worldwide, the prevalence of *S. stercoralis* is often underestimated.⁶⁶ *S. stercoralis* may cause three types of infection: acute, chronic uncomplicated, and complicated and disseminated. The first two forms are characterized by gastrointestinal and pulmonary symptoms. The complicated form is characterized by severe pulmonary symptoms and by secondary concomitant bacterial and/or opportunistic infections.^{67,68} Chronic infection is also characterized by skin manifestations. “Larva currens” is the pathognomonic rash and may represent an allergic response to the migrating larvae. It is a rapidly moving urticarial eruption most often localized to the perianal area, with a linear or serpiginous pattern. The manifestations typically last hours to a few days but could recur for weeks to years because of autoinfection cycles.^{67–69}

Temporary local urticaria, recurrent urticaria, and CU have also been described.^{68,70} In a group of ex-prisoners of war in southeast Asia, nonspecific urticaria was reported in 66% of subjects with strongyloidiasis, with larva currens in 30%.⁷¹ A similar rate of urticaria was reported in a group of Cambodian patients with *S. stercoralis* infection.⁷² A lower rate of urticaria (18%) was reported in a Spanish study on imported strongyloidiasis.⁷³ A retrospective study showed that 8.8% of patients with allergy-type (cutaneous and respiratory) symptoms had positive serologic test results for *S. stercoralis*; 41.6% of subjects who were infected reported urticaria and/or angioedema, and 39% of them improved after treatment of infection.⁷⁴ *Strongyloides* infection may persist for a long time. Three cases of urticaria that persisted for ~20 years were reported in patients infected with *S. stercoralis* who had served in southeast Asia during World War II and during the Vietnam war.^{75,76}

***Toxocara* spp.**

The genus *Toxocara* includes *Toxocara canis* and *Toxocara cati*, two nematodes that cause a zoonotic disease. Clinical symptoms depend on the number and location of the encysted larvae and on the sensitivity of the immune system of the host. There are different forms of toxocariasis: visceral and ocular larva migrans, common toxocariasis, and covert toxocariasis.^{77,78} Today, the relationship between toxocariasis and CU is well established.⁷⁸ The presence of *Toxocara* infection in patients with urticaria ranges from 14.5 to 29% in different studies^{79–83} and sometimes skin symptoms may be the only symptoms of the disease.⁷⁹ Urticarial rash was reported in 28.5% of patients with toxocariasis.⁸⁴ A population-based study on children found that 16% of patients with urticaria had positive serology for *Toxocara* and that 46.5% of children with a positive serology test result for *Toxocara* had urticaria.⁸⁵

***Trichinella* spp.**

Trichinella spp. are widespread parasites that infect mammals all over the world. Among the 10 species identified, *Trichinella spiralis* is the most common. The infection is acquired by the ingestion of raw or inadequately cooked infected meat products.^{86,87} Symptoms may be absent or mild, but larval migration may cause severe and sometimes fatal lesions.^{87,88} Skin manifestations in trichinosis are heterogeneous and include nonspecified rash and periorbital edema.^{87–89} Only a case of severe relapsing urticaria, facial and pharyngeal angioedema, and a deteriorated general condition associated with elevated antibody levels to *T. spiralis* was reported; the patient significantly improved after anti-helminthic and corticosteroid treatment.⁸⁷

CONCLUSION

Several nematode infections have been associated with urticaria manifestation; however, the association can vary according to the pathogens. The pathogenesis of urticaria in these infections is still unclear. In some cases, skin manifestations, described as urticaria or urticarial rash, are caused by the presence of the worm in the skin (*Filaria*, *Gnathostoma*), in other cases, there was a clear IgE-mediate mechanism that led to allergic reactions, and helminth infection and allergic manifestations can coexist (*A. simplex*, *S. stercoralis*); for other nematodes, the association was anecdotal and only a few cases were reported.

There were several limitations with this review: nematodes are a large family, therefore, the method used to select the agents may limit the search. Moreover, it is difficult to detect a certain causal effect, except when urticaria improves or disappears after infection treatment. Furthermore, the studies found in the literature have a weak level of evidence. Cases of isolated urticaria

not associated to other symptoms rarely may be caused by helminths. In the current guideline for urticaria,⁷ parasitosis is considered to be a rare possible cause of CU in developed industrial countries. Therefore, although a routine screening of parasitic infection in CU is not recommended, in our opinion, testing a patient with urticaria for parasites is a physician's choice based on the characteristics of the patient, such as associated symptoms, dietary habit, provenance country, and previous travel. Further studies are needed to strengthen the evidence of the association between parasitic infection and CU.

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