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ORIGINAL ARTICLE

EOSINOPHILIC ENTERITIS CAUSED BY *Angiostrongylus costaricencis*: OCCURRENCE AT THE NORTHERNMOST BORDER OF THE MAIN ENDEMIC AREA IN BRAZIL

Leticia Karolini Walger[1,2], Rubens Rodriguez[3], Clairton Marcolongo-Pereira[1,4], Maria Carmen Lopes Ferreira Silva Santos[5], Carlos Musso[5], Leyva Cecilia Vieira de Melo[6] and Carlos Graeff-Teixeira[1]

ABSTRACT

Abdominal angiostrongyliasis (AA) is endemic in southern Brazil. Few cases have been reported in other countries in South America. The eosinophilic ileocolitis typical of AA has also been detected in southeastern Brazil, including one patient from the State of Espirito Santo (ES). We aimed to investigate a possible northern limit for the occurrence of AA in Brazil and raise awareness and improve the diagnosis of this zoonotic infection. A retrospective survey was conducted using the database from the pathology service of a University Hospital in ES. A prospective study was also conducted to identify blood eosinophilia, a marker for AA, in samples analyzed in clinical laboratories in Santa Maria de Jetibá (SMJ) and Ibatiba (IBA), between October 2021 and June 2022. Cases with eosinophilic lesions in the gastrointestinal tract and/or liver were identified. Of 12,284 reports, 53 cases with moderate to severe eosinophilia were submitted to detailed microscopic evaluation. No case of suspected or confirmed AA was detected. In total, 684/17,228 (3.97%) and 1,025/17,832 (5.75%) cases in IBA and SMJ, respectively, had eosinophil counts > 7%. Serological (Dot-ELISA) results were positive for 2/10 index and 7/14 secondary cases. Possibly active *Angiostrongylus costaricensis* transmission occurs in ES, at the northern limit of the most important endemic area in Brazil and South America. Increased awareness among health personnel and systematic prospective surveillance are needed for the optimized diagnosis and management of AA cases in southeastern Brazil and other less known transmission areas in South America.

KEY WORDS: Abdominal angiostrongyliasis; eosinophilic gastroenteritis; eosinophilic ileocolitis; eosinophilic hepatitis; eosinophilia.

1. Universidade Federal do Espírito Santo, Departamento de Patologia, Núcleo de Doenças Infecciosas, Centro de Ciências da Saúde, Vitória, Espirito Santo, Brazil.
2. Escola Superior São Francisco de Assis, Curso de Biomedicina, Santa Teresa, Espirito Santo, Brazil.
3. Hospital Mãe de Deus, Diagnósticos da América S.A, Departamento de Patologia, Porto Alegre, Rio Grande do Sul, Brazil.
4. Centro Universitário do Espírito Santo, Curso de Medicina, Colatina, Espirito Santo, Brazil.
5. Hospital Universitário Cassiano Antonio Moraes, Unidade de Anatomia Patológica, Universidade Federal do Espírito Santo, Vitória, Espirito Santo, Brazil.
6. Instituto Adolfo Lutz, Seção de Enteroparasitoses, São Paulo, Brazil.

Leticia Karolini Walger ORCID: https://orcid.org/0000-0003-2307-1314; Rubens Rodriguez ORCID: https://orcid.org/0000-0001-5213-1094; Clairton Marcolongo-Pereira ORCID: https://orcid.org/0000-0002-5593-3110; Maria Carmen Lopes Ferreira Silva Santos ORCID: https://orcid.org/0000-0003-4564-1859; Carlos Musso ORCID: https://orcid.org/0000-0003-4928-1280; Leyva Cecilia Vieira de Melo ORCID: https://orcid.org/0000-0002-2014-8614; Carlos Graeff-Teixeira ORCID: https://orcid.org/0000-0003-2725-0061

Corresponding author: Carlos Graeff-Teixeira. E-mail: graeff.teixeira@gmail.com

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INTRODUCTION

Angiostrongylus costaricensis is an intra-arterial nematode in rodents but accidentally infects humans through the ingestion of the third-stage larvae (L3) in the mucous secreted from terrestrial mollusks, the intermediate host. Ingested L3 penetrates the intestinal wall and migrates into the mesenteric arteries, especially their ileocecal branches, to become adult worms (Morera, 1967; Mota & Lenzi, 2005; Rojas et al., 2021). Intense eosinophilic granulomatous inflammation develops around worms and their eggs in the intestinal wall of humans, with the potential complication of intestinal obstruction or perforation. Less commonly, larvae develop in the porta-mesenteric veins, leading to eosinophilic hepatitis (Graeff-Teixeira et al., 1991b; Rodriguez et al., 2023).

A causative agent of abdominal angiostrongyliasis (AA), *A. costaricensis*, has been documented in definitive vertebrate hosts and intermediate mollusk hosts in the southern United States down to northern Argentina (Romero-Alegría et al., 2014). In Brazil, most of the published AA cases were in the south and southeastern States (Pena et al., 1995). Only one case of AA has been documented in the State of Espírito Santo, in the highland municipality of Ibatiba (IBA) bordering the State of Minas Gerais (Pena et al., 1995).

The aim of the present study was to investigate the endemic status of AA in the municipalities of Ibatiba (IBA) and Santa Maria de Jetibá (SMJ), Espírito Santo, Brazil, through surveillance including the retrospective review of histopathological reports of eosinophilic granulomatous lesions in biopsy and surgical specimens from the database of the pathology service of the University Hospital, while prospective survey for blood eosinophilia was performed in the two clinical laboratories in IBA and SMJ, in ES.

MATERIAL AND METHODS

Retrospective survey to identify eosinophilic inflammatory lesions

The Cassiano Antônio de Moraes University Hospital, Espírito Santo, is a reference hub for Brazil's national health system (SUS). It is a medium- and high-complexity healthcare facility with 277 beds and 129 ambulatory units. We reviewed all histopathological reports on biopsy and surgical specimens from the jejunum, ileum, colon, and liver stored in the hospital's computerized database for the period 2008–2023. Case selection and data (date, patient sex and age, anatomical lesion location, and any conclusion on etiology) collection were performed using sequential inclusion criteria: 1) any degree of tissue eosinophilia (cut-off 1) and 2) moderate/severe eosinophilia, defined by eosinophil counts > 20 per microscope field at 400× magnification (cut-

off 2). Cases with parasitic structures, eosinophilic granuloma, and moderate/severe eosinophilia were selected for extensive microscopic evaluation of all available slides with the full appraisal of histopathological findings.

Prospective survey for blood eosinophilia detection and serological testing for AA

The blood samples processed at two clinical analysis laboratories in the municipalities of IBA (20° 21′ 00″ S, 41° 31′ 50″ W) and SMJ (20° 02′ 27″ S, 40° 44′ 45″ W) between October 2021 and June 2022 were surveyed to identify patients with blood eosinophilia. Serum samples were collected from a few individuals with relative eosinophil counts > 7% (primary index cases) and cohabitants (secondary cases) for Dot-ELISA to detect anti-*Angiostrongylus* antibodies at the Adolfo Lutz Institute, São Paulo, the Brazilian reference laboratory for angiostrongyliasis (Melo et al., 2022).

The Ethics Committee of the Cassiano Antônio de Moraes University Hospital reviewed and approved the retrospective and prospective survey protocols (CAAE 53085021.0.0000.5071).

RESULTS

Eosinophilia in the gastrointestinal tract and liver tissues

The retrospective survey led to the identification of 12,284 reports that mentioned tissue eosinophilia, localized in the small intestine (*n* = 105; 8.2%), large intestine (*n* = 136; 2.8%), liver (*n* = 45; 1.9%), and appendix (*n* = 14; 0.5%). Fifty-three cases with parasitic structures, eosinophilic granuloma, and moderate/severe tissue eosinophilia were examined further in detail. The largest proportion (*n* = 16; 30.2%) of these 53 patients was aged 50-59 years, and 39 of them had received resection of more than one gastrointestinal tract portion, most commonly the ileum (*n* = 30), followed by the rectum (*n* = 25) and colon (*n* = 22). The following parasitic structures were found: *Schistosoma mansoni* eggs in the liver and colon (*n* = 2), *Strongyloides* larvae (*n* = 2), adult *Enterobius vermicularis* worms in the ileal lumen (*n* = 1), actinomycosis/nocardiosis grains (*n* = 1), and an unidentified worm was detected in the liver (*n* = 1). Other microscopic findings are presented in Table 1. No characteristic structure (egg, larva, or adult worm) of *A. costaricensis* was detected.

Table 1. Main microscopic findings of the cases with gastrointestinal tract/liver eosinophilia from the Pathology Unit of Cassiano Antônio de Moraes University Hospital, Espírito Santo, Brazil, selected for histological review, 2008–2023.

Microscopic findings according to the original histopathological report	*n* =
Eosinophilia N/E[1]	8
Eosinophilia with up to 30 Eo/HPF[2]	2
Eosinophilia with 35 to 60 Eo/HPF	23
Eosinophilia with 65 to 90 Eo/HPF	5
Sparse eosinophilia N/E[1]	1
Moderate eosinophilia N/E[1]	2
Intense eosinophilia N/E[1]	14
Granuloma without eosinophilia	1
Eosinophilic granuloma	9
Granuloma	3

[1]N/E: unclassified eosinophilia; [2]Eo/HPF: eosinophils/high power field, 400×

Blood eosinophilia in two municipalities in Espírito Santo

In IBA and SMJ, blood eosinophilia (> 7%) was observed in 684/17,228 (3.97%) and 1,025/17,832 (5.75%) blood samples examined, respectively. Approximately 95% of the patients had mild (< 20%) blood eosinophilia, and only 4.3% of these patients in SMJ and 3.5% in IBA had eosinophil counts higher than 20% (Table 2).

Table 2. Distribution of eosinophilia according to relative eosinophil counts in two municipalities of Espírito Santo, Brazil, October 2021–June 2022.

Relative eosinophil (%Eo) counts	Santa Maria de Jetibá	Ibatiba
%Eo ≥ 30	5 (0.4%)	6 (0.8%)
20 ≤ %Eo ≤ 29.9	39 (3.8%)	18 (2.6%)
10 ≤ %Eo ≤ 19.9	374 (36.4%)	233 (34.0%)
7 ≤ %Eo ≤ 9.9	607 (59.2%)	428 (62.4%)

Serological findings

Anti-*Angiostrongylus* antibodies were detected in 2 of 10 individuals with primary eosinophilia and 7 of 14 individuals with secondary cases; details of these cases are provided in Table 3.

Table 3. Detection of anti-*Angiostrongylus* antibodies (Dot-ELISA) in 10 primary (P) cases and 14 cohabitants (C), any clinical manifestation (at the time of blood counts for primary cases and at the time of serology study for cohabitants) percentual blood eosinophilia, elapsed time since blood examination and place of residence: Santa Maria de Jetibá (SMJ) or Ibatiba (IBA), State of Espírito Santo, October 2021 to June 2022.

Local	Case	Clinical manifestations	Eosinophilia (%)	Elapsed Time (months)	DOT ELISA
IBA	P	Abd[a] pain; Diarrhea	9.8	8	N[c]
IBA	P	Fever	8.5	4	N
IBA	P	Asymptomatic	19.7	3	N
IBA	P	Urticaria	33.5	3	N
IBA	P	Abd pain; Fever	9.8	4	N
IBA	P	Abd pain; Vomiting	8.8	7	N
IBA	P	Abd pain; Fever; Diarrhea; Abd dist[b]	39.9	17	Pos[d]
SMJ	P	Abd pain; Fever; Diarrhea; Abd dist	28.0	11	N
SMJ	P	Asymptomatic	22.0	5	N
SMJ	P	Abd pain	15.0	6	Pos
IBA	C	Asymptomatic	ND[e]		Pos
IBA	C	Asymptomatic	ND		N
IBA	C	Asymptomatic	ND		N
IBA	C	Abd pain; Diarrhea	ND		Pos
IBA	C	Asymptomatic	ND		N
IBA	C	Asymptomatic	ND		Pos
IBA	C	Diarrhea; Abd dist	ND		N
SMJ	C	Abd pain; Diarrhea; Abd dist	ND		N
SMJ	C	Asymptomatic	ND		N
SMJ	C	Asymptomatic	ND		N
SMJ	C	Asymptomatic	ND		Pos
SMJ	C	Asymptomatic	ND		Pos
SMJ	C	Asymptomatic	ND		Pos
SMJ	C	Asymptomatic	ND		Pos

[a]Abd: abdominal; [b]dist: distention; [c]N: Negative; [d]Pos: Positive; [e]ND: blood counts not done.

DISCUSSION

A few AA isolated cases have been reported at latitudes higher than 20° S (the northern limits of the States of São Paulo and Rio de Janeiro) in Brazil. One resident of Unaí, Minas Gerais (16° 21′ 50″ S, 46° 54′ 15″ W), underwent surgery for complicated AA in Brasília (Barbosa et al., 1980). The only reported case of AA in the State of Espírito Santo was an individual from IBA (Pena et al., 1995). Unaí and IBA are not far from each other in terms of latitude: 16° and 20°, respectively, and these two cases could indicate a northern limit for the most relevant AA-endemic area in Brazil. AA also occurs at latitudes lower than 20° S: an unpublished report described an isolated case in the State of Tocantins, which extends north from latitudes 12°-9°. Additionally, a few cases of *A. costaricensis* infection have been reported in the less-densely populated Amazon region, where the transmission dynamics of this nematode are probably less intense (Sly et al., 1982; Calvopiña et al., 2022).

Costa Rica and the southern States of Brazil are the two hotspots for *A. costaricensis* transmission in the Americas. In addition to the potentially greater intensity of transmission in these regions, the awareness of medical personnel, especially pathologists, may explain the current distribution of diagnosed cases across Latin America. The data presented here, derived from a university hospital in Espírito Santo, which serves as a reference pathology service, had no suspected or confirmed case of AA. This result may reflect the low endemicity of AA in the State, and it supports the identification of southern Brazil as the most relevant endemic area.

Like many zoonotic infections, AA has a focal spatial and seasonal distribution (Graeff-Teixeira et al., 1991a). Although outbreaks can occur, severe disease is rare, as demonstrated in a prospective field study conducted in Nova Itaberaba, Santa Catarina, Brazil, and by an investigation of an outbreak in Guatemala (Kramer et al., 1998). Additional surveillance and prospective studies are needed to further clarify the occurrence of AA in Brazil and other countries in South America.

Blood eosinophilia is a good marker for the screening of undiagnosed AA, provided that proper differential diagnosis, especially the consideration of other helminthic infections and allergic diseases, is integrated. *Angiostrongylus costaricensis* infection is marked by huge eosinophilic recruitment and infiltration into tissues adjacent to parasitic structures (worms and eggs) (Graeff-Teixeira et al., 1991b). As eosinophils transit through the blood on their way to tissues, their numbers in the blood are not necessarily always large. Waves of blood eosinophilia may be accompanied by counts within the normal range. Although blood eosinophilia is a valuable marker of potential infection, several other signs and symptoms should be considered in individual clinical diagnoses (for criteria and case definitions, see Walger et al., 2024).

The use of serological methods for antibody detection has the main limitation of cross-reactivity, which is especially relevant when crude or semi-crude antigens are employed. Because of the limited specificity and the persistence of antibodies, the use of serology alone to evaluate individual patients is also insufficient; serological findings should never be taken as the sole criterion for suspicion, and certainly not as confirmation. Serological screening for potential infection at the population level is valuable. In the present study, serologically positive individuals were asymptomatic; ideally, such individuals should be followed clinically, and surveys should be conducted to investigate the presence of *A. costaricensis* in mollusks as well as in definitive host rodents in the areas of probable exposure.

In conclusion, there are indications of active *A. costaricensis* transmission in two municipalities in the highlands of Espírito Santo, Brazil, although probably at a low-endemicity level. These results prompt the recommendation that physicians and healthcare personnel raise their awareness of this etiology of abdominal disease, especially when associated with severe blood eosinophilia. Although no effective anthelmintic treatment is available, the suspicion of AA should trigger close follow up for the early detection and proper management of severe complications, such as intestinal obstruction and perforation.

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CONFLICTS OF INTEREST

None is declared.

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