Journal of Travel Medicine

International Society of Travel Medicine
Established 1991
Promoting healthy travel worldwide

Journal of Travel Medicine, 2016, 1–4
doi: 10.1093/jtm/taw074
Brief Communication

Brief Communication

Gnathostomiasis in Brazil: an emerging disease with a challenging diagnosis

Julian Cornaglia[1,*], Maxime Jean[1], Kevin Bertrand[1], Hugues Aumaître[1], Melisande Roy[1], and Beatrice Nickel[2,3]

[1]Infectious and Tropical Diseases Departement, Perpignan Hospital Center, Perpignan, France, [2]Swiss Tropical and Public Health Institute, Basel, Switzerland and [3]University of Basel, Basel, Switzerland

*To whom correspondence should be addressed: E-mail: julian.cornaglia@ch-perpignan.fr

Submitted 16 June 2016; revised 21 September 2016; Accepted 29 September 2016

Abstract

This case report describes the second reported case of gnathostomiasis acquired in Brazil. The French traveller returned from a sport fishing trip from Tocantins where he was repeatedly consuming raw freshwater fish marinated with lemon juice. *Gnathostoma* infection was diagnosed based on clinical symptoms, dietary record and by detection of specific antibodies in the blood.

Key words: Human gnathostomiasis, *Gnathostoma spinigerum*, *Gnathostoma binucleatum*, serodiagnosis, cutaneous larva migrans

Introduction

Human gnathostomiasis is a foodborne parasitic zoonosis acquired after consumption of raw or undercooked freshwater fish, shrimp or crabs containing third-stage larvae of the nematode *Gnathostoma*. It is mainly endemic in Southeast Asia but in recent years has also become an increasing problem in Central and South America. Due to increased international travel to tropical countries and changes in dietary habits, i.e. consumption of raw freshwater fish, the disease is repeatedly imported by travellers to countries where it is not endemic.[1] Currently, there are six human-pathogenic *Gnathostoma* species known with different geographic distribution.[2] Two major clinical manifestations of infection are observed: cutaneous and visceral larva migrans syndrome, the former by far the most common, the latter the more severe affecting viscera and CNS. This case report describes the second reported case of cutaneous gnathostomiasis acquired in Brazil. A French traveller was infected and diagnosed by detection of specific antibodies by western blot. This represents a sentinel case showing emergence of *Gnathostoma* infections in Brazil.

Case Report

A 67-year-old Caucasian man from France with an unremarkable medical history presented to the Service Center for Infectious and Tropical Diseases of the Hospital Center of Perpignan, France, on 23 September 2015, 6 days after return from a recreational trip to Bananal's island in Tocantins district, Brazil (Figure 1A), where he had practiced sport fishing from 4 September 2015 through 17 September 2015. First symptoms started 3 days after return from the trip on 20 September 2015, with onset of a pruritic swelling nodule in the left submammary area. At the initial presentation neither fever nor other associated or systemic symptoms were present. He reported about multiple insect bites during his stay in Brazil and a treatment with a local corticoid cream was initially prescribed. A general blood exam was normal at that time, with no signs of eosinophilia.

Five days after his first consultation the patient developed a deep swelling nodule in the abdominal wall (Figure 2A). At the subsequent consultation he reported that he had repeatedly consumed Tahitian-mode raw freshwater fish marinated in lemon juice starting from the second day of his stay at the sport fishing site, namely *Cichla* spp. (Figure 1B) and *Phractocephalus hemioliopterus*. A skin biopsy revealed eosinophilic panniculitis without any detectable larvae, and a new blood test showed hypereosinophily (1220/mm^3, 14%) and elevated IgE concentration. Cutaneous gnathostomiasis was highly suspected and albendazol, 800 mg/day for 21 days, was prescribed. On the third day of treatment, a serpiginous lesion appeared on the back (Figure 2B). At the end of treatment, the

Figure 1. (A) Tocantins area in Brazil. (B) *Cichla* sp. (peacock bass) fished in Tocantins.

Figure 2. (A) Extensive swelling nodule in the abdominal wall. (B) Serpiginous lesion in the back on the third day of albendazol treatment.

patient presented new swelling skin lesions and one dose of ivermectin, 0.2 mg/kg, was administered with total improvement until now.

A sample of plasma was sent on 5 October 2015 (2 weeks after onset of symptoms) to the Diagnostic Centre of the Swiss Tropical and Public Health Institute (Swiss TPH) for serologic testing of gnathostomiasis by immunoblot. At that time the serodiagnostic test was negative. On 3 December 2015 (3 months after travel) a new plasma sample was tested by immunoblot for gnathostoma antibodies at Swiss TPH and then the test was positive showing the specific 24 kDa-diagnostic band.

The immunoblot for gnathostomiasis is routinely performed at the Swiss TPH with antigen from the most widely distributed species in Asia, *Gnathostoma spinigerum*. In recent years, several serum/plasma samples from patients who had acquired a gnathostoma infection in the Americas have additionally been tested at the Swiss TPH with antigen prepared from *G. binucleatum*, the New World *Gnathostoma* species. All tested samples showed reactivity with the *G. binucleatum* antigen on the immunoblot, but in most cases did not show cross-reactivity with the *G. spinigerum* antigen.[2] The first, negative immunoblot test of the reported case had been performed with antigen from the Asian species *G. spinigerum*, whereas the second, positive test was performed with two antigen preparations in parallel, antigen from *G. spinigerum* and from *G. binucleatum*. The plasma showed a positive reactivity on both antigens. A serologic screening test covering seven other tissue helminth infections (echinococcosis, fasciolosis, strongyloidiasis, toxocariasis, trichinellosis, filariasis and schistosomiasis) was performed in addition and was negative for all antigens.

Discussion

We report a case of cutaneous gnathostomiasis of a traveller returning to France from Brazil. According to literature this is the second reported case of gnathostomiasis acquired in Brazil. The first reported case was acquired in the same region of Tocantins, Brazil, and was published by Vargas *et al.*[3] Gnathostomiasis is known to be endemic in Japan and Southeast Asia, Cambodia, Laos, Myanmar, Indonesia, the Philippines and Malaysia.[4] Some cases have also been reported in India, Sri Lanka, China and more recently in Zambia, Botswana, Australia and Korea.[5,6] But in more recent years, it has become an increasing problem in Central and South America, particularly in Mexico, Guatemala, Peru, Ecuador and Colombia due to the consumption of raw fish marinated in lime (Ceviche).[7,8] Most human infections are caused by *G. spinigerum* in Asia and by *G. binucleatum* in the Americas.

Travellers returning from endemic countries might get infected by consumption of raw fish and bring the disease back to their home countries.[9–11]

Diagnosis can be difficult as only few clinicians outside of endemic areas are familiar with gnathostomiasis, and hence

corresponding diagnostic tests are not requested or diagnosis is delayed. The classic triad of epidemiological exposition, migratory panniculitis and eosinophilia leading to a high index of suspicion is rarely followed up by identification of larvae or by serology. Only few laboratories offer serological tests for gnathostomiasis i.e., the Hospital for Infectious Diseases, Mahidol University, Bangkok, Thailand, and the Swiss Tropical and Public Health Institute, Basel, Switzerland. Definitive diagnosis of gnathostomiasis is only possible by direct identification of larvae. But biopsy or surgical removal of larvae is only feasible in cases of very superficial migration. It appears that albendazol and possibly also ivermectin treatment stimulates the outward migration of the larvae in ~10% of treated cases.[12,13]

It is generally considered that subcutaneous migration of the *Gnathostoma* larva starts 3–4 weeks after ingestion, but the first symptoms can start much later.[10] Our patient showed first symptoms already 3 days after returning from a 2-week trip to Brazil, with a pruritic swelling nodule in the left submammary area followed by a deep swelling nodule in the abdominal wall 5 days later. A biopsy revealed eosinophilic panniculitis and hypereosinophily in the blood. In general, eosinophilia develops in association with larval penetration but not in all cases.[9,11] Moore *et al.* reported peripheral eosinophilia in 44% of treated gnathostomiasis patients and concluded that peripheral eosinophilia could not be applied as reliable screening tool for gnathostomiasis, but could serve as a biomarker of relapse in cases with eosinophilia at baseline. This would only be applicable for regions without endemicity of other helminth infections, since these could also cause eosinophilia.

There are four cutaneous signs associated with gnathostomiasis: migratory panniculitis, creeping dermatitis, oedema and nodules. Our patient presented with deep swelling nodules, eosinophilic panniculitis and creeping dermatitis. In combination with the diet history he was diagnosed with cutaneous larva migrans (CLM) syndrome, most likely caused by *Gnathostoma* infection. This has been confirmed by the serological test. It has to be considered that CLM syndrome can also be caused by other invasive nemathode larvae like animal hookworm, *Strongyloides stercoralis* or *Toxocara* sp.[14]

Currently, a number of serological tests are available for diagnosis of gnathostomiasis. Immunoblot for detection of the specific 24-kDa band is regarded as the most reliable in terms of sensitivity and cross-reactivity to other helminth infections.[15,16] Recently, an immunochromatographic test based on a recombinant protein resulting from a *G. spinigerum* cDNA library has been published with high sensitivity and specificity for detection of *G. spinigerum* specific antibodies.[17] The most widely used diagnostic assay is a *G. spinigerum*-larval-antigen-based immunoblot, but its sensitivity for detection of antibodies directed against other *Gnathostoma* spp. is not clear. The Swiss TPH routinely performs *Gnathostoma* serology with antigen prepared from larvae of the Asian species *G. spinigerum* but holds a second immunoblot in place with antigen from the American species *G. binucleatum*. In the current reported case of gnathostomiasis acquired in Brazil, reactivity of the plasma was negative after 3–4 weeks of potential infection. The diagnostic immunoblot had initially been performed with *G. spinigerum* antigen, but was later repeated with *G. binucleatum* antigen as well. Both blots with the plasma from 5 October 2015, yielded a negative result. The time point for serology was definitively too early for detection of sufficient IgG on the immunoblot. Seroconversion takes several weeks after exposure to parasites and detectable levels of IgG are therefore not measured in the early phase of infection.

Two and a half months later, and after treatment with albendazol and subsequent treatment with ivermectin, the *Gnathostoma* serology was positive with both antigen preparations, *G. spinigerum* and *G. binucleatum*. In other reported cases with infections acquired in Chile, Peru and Central America the *G. spinigerum*-based-immunoblot failed to detect South American gnathostomiasis, presumably caused by *G.* binucleatum.[2] The current case from Brazil is therefore of special interest, as the plasma of the patient was reactive on the antigen preparations of both species, *G. spinigerum* and *G. binucleatum*.

Treatment with albendazol may not be successful and might require a subsequent or combined treatment with ivermectin.[10,11,18] In the current case, 800 mg albendazol for 21 days appeared to be inefficient, as reflected by new swelling skin lesions at the end of treatment. A single dose of ivermectin, 0.2 mg/kg was finally effective. Due to the good tolerability and the incomplete efficacy of either drug, some experts recommend combination or sequential therapy with both drugs.[9,18]

In a review of fishborne diseases in Brazil from 2011[19] the authors were not aware of the occurrence of *Gnathostoma* spp. in freshwater fish like *Cichla* sp. or possibly in *P. hemiliopterus*. Cichlids are freshwater bass species also known as peacock bass and are widely consumed in Brazil due to the excellence of the flesh. Cichlids live very territorial and *Cichla piquiti*, as well as *P.hemioliopterus*, are found in the Amazon basin of Tocantins area.[20,21] Our patient consumed both species as raw fish dish in Tocantins, and acquired gnathostomiasis during his sport fishing trip. The source of infection could be one or even both fish species.

According to our patient, another member of the same fishing team had symptoms of CLM syndrome and swellings but this person has never been tested for the infection. In addition to our reported case, another suspicious case was identified retrospectively. This person returned with the same clinical presentation from a recreational sport fishing trip from Tocantins. A dermatologist in France treated him twice after his travel in 2011 and in 2012 for CLM syndrome with ivermectin. Unfortunately, no serological test was performed for detection of tissue helminth infections.

The accumulation of cases of travellers returning from the same area in combination with consumption of raw fish dishes suggests a substantial infection rate of freshwater fish in the Amazonas basin. We think that a survey for *Gnathostoma* spp. in the mentioned fish specimens at Tocantins would be of highest zoonotic and epidemiologic interest.

Conclusions

We describe the second reported case of confirmed gnathostomiasis in a traveller returning from Brazil. Gnathostomiasis might be more widely present and underestimated not only in Brazil, but also in other South-American countries due to lack of awareness and poor diagnostics. Besides the consultation in travel medicine on recommended vaccinations and preventive

measures, the advice of doctors to travellers to avoid consumption of raw meat (fish and other meat) during the trip is paramount. The awareness of a possibly acquired gnathostomiasis should be considered for all returning travellers fulfilling epidemiological and clinical conditions.

Acknowledgements

We thank Karin Stoll-Rudin from the Diagnostic Centre, Swiss TPH, for expert technical assistance and Pascal Mäser for critical reading.

Conflict of interest: None declared.

References

1. Herman JS, Chiodini PL. Gnathostomiasis, another emerging imported disease. *Clin Microbiol Rev* 2009; **22**: 484–92.
2. Neumayr A, Ollague J, Bravo F *et al*. Cross-reactivity pattern of Asian and American human Gnathostomiasis in western blot assays using crude antigens prepared from *Gnathostoma spinigerum* and *Gnathostoma binucleatum* third-stage larvae. *Am J Trop Med Hyg* 2016; **95**: 413–6.
3. Vargas TJS, Kahler S, Dib C *et al*. Autochthonous gnathostomiasis in Brazil. *Emerg Infect Dis* 2012; **18**: 2087–9.
4. Diaz JH. Gnathostomiasis: an emerging infection of raw fish consumers in gnathostoma nematode-endemic and nonendemic countries. *J Travel Med* 2015; **22**: 318–24.
5. Herman JS, Wall EC, van-Tulleken C *et al*. Gnathostomiasis acquired by British tourists in Botswana. *Emerg Infect Dis* 2009; **15**: 594–7.
6. Jeremiah CJ, Harangozo CS, Fuller AJ. Gnathostomiasis in remote northern Western Australia: the first confirmed cases acquired in Australia. *Med J Australia* 2011; **195**: 42–4.
7. Jurado LF, Palacios DF, López R *et al*. Gnatostomiasis cutánea, primer caso confirmado en Colombia. *Biomédica* 2015; **35**: 462–70.
8. Vanegas ES, Cendejas RF, Mondragón A. Images in clinical tropical medicine, a 41-year-old woman with migratory panniculitis. *Am J Trop Med Hyg* 2014; **90**: 786–7.
9. Moore DAJ, McCroddan J, Dekumyoy P, Chiodini PL. Gnathostomiasis: an emerging imported disease. *Emerg Infect Dis* 2003; **9**: 647–50.
10. Ménard A, Dos Santos G, Dekumyoy P *et al*. Imported cutaneous gnathostomiasis: report of five cases. *Trans R Soc Trop Med Hyg* 2003; **97**: 200–2.
11. Strady C, Dekumyoy P, Clement-Rigolet M *et al*. Long-term follow-up of imported gnathostomiasis shows frequent treatment failure. *Am J Trop Med Hyg* 2009; **80**: 33–5.
12. Suntharasamai P, Riganti M, Chittamas S, Desakorn V. Albendazole stimulates outward migration of *Gnathostoma spinigerum* to the dermis in man. *Southeast Asian J Trop Med Public Health* 1992; **23**: 716–22.
13. Rojas-Molina N, Pedraza-Sanchez S, Torres-Bibiano B *et al*. Gnathostomiasis, an emerging foodbourne zoonotic disease in Acapulco, Mexico. *Emerg Infect Dis* 1999; **5**: 264–6.
14. Caumes E, Danis M. From creeping eruption to hookworm-related cutaneous larva migrans. *Lancet Infect Dis* 2004; **4**: 659–60.
15. Tapchaisri P, Nopparatana C, Chaicumpa W, Setasubun P. Specific antigen of *Gnathostoma spinigerum* for immunodiagnosis of human gnathostomiasis. *Int J Parasitol* 1991; **21**: 315–9.
16. Nopparatana C, Setasuban P, Chaicumpa W, Tapchaisri P. Purification of *Gnathostoma spinigerum* specific antigen and immunodiagnosis of human gnathostomiasis. *Int J Parasitol* 1991; **21**: 677–87.
17. Janwan P, Intapan PM, Yamasaki H *et al*. Development and usefulness of an immunochromatographic device to detect antibodies for rapid diagnosis of human gnathostomiasis. *Parasit Vectors* 2016; **9**: 14.
18. Neumayr A. Gnathostomiasis. In: *Antiparasitic Treatment Recommendations. A Practical Guide to Clinical Parasitology*, 1st edn. Hamburg: Tradition GmbH, 2016, pp. 54–5.
19. Lima dos Santos CAM, Howgate P. Fishborne zoonotic parasites and aquaculture: a review. *Aquaculture* 2011; **318**: 253–61.
20. Moura MAM, Kubitza F, Cyrino JEP. Feed training of peacock bass (*Cichla* sp.). *Rev Brasil Biol* 2000; **60**: 645–54.
21. Amazon sport fishing: http://www.asf.tur.br/index.asp