Case Report: Clinical Features of Intermittent Migratory Swelling Caused by Gnathostomiasis with Complete Follow-up

Chollasap Sharma,¹ Watcharapong Piyaphanee,² and Dorn Watthanakulpanich^{3*}

¹Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; ²Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; ³Department of Helminthology, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Abstract. A 15-year-old Thai girl was referred to the Hospital for Tropical Diseases of Mahidol University with a 3-week history of an intermittent migratory mass on the forehead. She was diagnosed with cutaneous gnathostomiasis. The patient was treated with albendazole 400 mg orally twice a day for 3 weeks, with good compliance. She revisited the hospital after 3 months and was seen to have been unresponsive to the initial treatment. There was intermittent swelling in her right upper eyelid along with mild redness around her right upper and lower eyelids. Another attempt of treatment was made with ivermectin 0.2 mg/kg/day for two consecutive days. This is a case of gnathostomiasis in full sequence, with complete follow-up. The case report starts from the beginning of the symptoms until the antibodies against *Gnathostoma spinigerum* decline to negative, confirmed by the western blot test. It took around 18 months to see the western blot test change to a negative result. The resolved clinical symptoms were possibly due to the responsiveness of the patient to ivermectin or the albendazole and ivermectin combination or even the coadministration of antibiotics afterward.

INTRODUCTION

Gnathostomiasis is commonly caused by *Gnathostoma spinigerum*, a food-borne zoonotic nematode found in Asia, particularly Southeast Asia (Thailand, Laos, and Vietnam).^{1,2} The first case of human gnathostomiasis was reported in Bangkok, Thailand; the diagnosis was obtained from a swelling in the breast of a woman half a century after *G. spinigerum* was first discovered.^{3,4} The route of transmission most commonly involves consuming infective larvae within undercooked meat of various animal hosts such as freshwater fish, swamp eels, frogs, snakes, chicken, and other birds. Patients with serious gnathostomiasis may develop complications due to severe damage of important organs, especially when the infection is related to brain or eye invasion.⁵ The diagnosis of gnathostomiasis is confirmed by detecting the specific 24-kDa reactive band on western blot analysis; this band represents the *G. spinigerum* antibody.⁶ Treatment recommendations include albendazole at 400 mg orally twice a day for 3 weeks or ivermectin at 0.2 mg/kg orally for two consecutive days.^{7,8} In 2016, approximately 485 patients suspected to have gnathostomiasis were tested at the Parasite Clinic of the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University. Among these patients, 15 were non-Thai who had spent time traveling throughout Southeast Asia, including Thailand. Transmission of *G. spinigerum* to humans was recently reported in Africa among travelers from Botswana, Tanzania, and Zambia.^{9,10} Infection in tourists from nonendemic countries tends to occur within endemic countries that have few or no regulations for the sourcing and storage of fish destined for consumption in restaurants.¹¹

CASE REPORT

A 15-year-old Thai girl from Thamuang District, Kanchanaburi Province, Thailand was studying in a secondary school

in Nakorn Pathom Province, a border province near Bangkok at the time of her presentation. She had a 3-week history of intermittent migrating erythematous edema at her right ear with mild pruritus but no piercing pain. Each time the swelling recurred, it took days to weeks to subside and finally resolve. She received antihistamines and antibiotics from a local drug store and nearby private clinic. However, her symptoms did not seem to improve. She then visited a local private hospital and underwent a complete blood count (CBC). At that point, she was referred to the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University because of a suspected parasitic infection. She did not receive any additional medication from the referring local hospital.

The patient's medical history included underlying allergic rhinitis and frequent bouts of urticaria since childhood. The intermittent migratory erythematous edema had first occurred at her right shoulder, then moved behind her right ear and finally to her face as detailed in Table 1. She had a history of regularly consuming food from street vendors, particularly fried freshwater scaled fish such as tilapia, snake-headed fish, and catfish. She favored raw watercress but denied having consumed any raw or undercooked meat with the exception of her favorite papaya salad with salty fermented freshwater crabs. She denied any animal contact, use of poultices, or drinking unclean water. She also denied any travel outside Nakorn Pathom Province and her home, Kanchanaburi Province.

Her first physical examination (December 1, 2014) at the Hospital for Tropical Diseases revealed normal vital signs and a painless, nonreducible subcutaneous swelling behind her right ear. A preliminary diagnosis of cutaneous gnathostomiasis was made based on her clinical history of a subcutaneous migratory swelling. Blood was taken to perform a CBC and western blot analysis to detect the specific 24-kDa reactive band indicative of *G. spinigerum*.⁶ A routine stool examination was performed to identify any other parasites. The results of the CBC showed an eosinophil concentration of 5.9% and the absolute eosinophil count (AEC) was 601.8 cells/ μ L (Table 2). She was prescribed oral albendazole at 400 mg twice a day for 3 weeks. On January 27, 2015, she was sent to the dermatological clinic at the Hospital for Tropical

* Address correspondence to Dorn Watthanakulpanich, Department of Helminthology, Faculty of Tropical Medicine, Mahidol University, 420/6 Ratchawithi Road, Bangkok 10400, Thailand. E-mail: dorn.wat@mahidol.ac.th

TABLE 1
Summary of patient's clinical course

Date	Duration from	Affected site(s)	Symptoms
November 9, 2014	Start of clinical symptoms	Right shoulder	Intermittent erythematous edema at right shoulder
November 30, 2014	20 days	Right ear	Migrating intermittent erythematous edema at right ear with mild pruritus but no piercing pain
December 1, 2014	1 day	Right ear, face	Painless, nonreducible subcutaneous swelling behind right ear migrating toward face (Treatment: albendazole 2 × 2 for 3 weeks)
January 27, 2015	58 days	Right eye, nose, and forehead	Right periorbital swelling sporadically radiated from nose and forehead with erythematous nodule; no invasion into the eyes (Treatment: cetirizine 1 × 1 for allergic dermatitis)
February 12, 2015	16 days	Face	Intermittent swelling affecting face; no migratory swelling and no parasitic tract found; the episode subsided and resolved.
March 3, 2015	19 days	Right eye, nose, and forehead	Conspicuous erythematous swelling of left forehead radiating to nose, followed by right periorbital swelling within 3 hours without piercing pain or pruritus (Treatment: ivermectin 2 × 1 for two consecutive days)
March 19, 2015	16 days	—	No migratory swelling
June 23, 2015	95 days	—	No migratory swelling
December 9, 2015	150 days	—	No migratory swelling
May 24, 2016	137 days	—	No migratory swelling

Diseases because of a suspicion of allergic dermatitis and the persistence of the intermittent migratory swelling despite having completed her medication for gnathostomiasis. The same swelling patterns occurred on her face, from the right side of her forehead to her nose and right eyelid; however, the swelling-free period (approximately 2 months) was longer than before. No blood tests were repeated, in line with the gnathostomiasis guidelines of the hospital. She was prescribed one 10-mg tablet of an antihistamine (cetirizine) twice daily. A 2-week follow-up was performed at the Parasite Clinic of the hospital, and she was reassured that she was cured because no signs of skin lesions such as swellings or serpiginous tracts were present on that day.

On March 3, 2015, she revisited the hospital because there were swelling tracks that had migrated about 3 cm from her left

forehead to her right upper eyelid within 2 hours. By the time she reached the hospital, the swelling in her right upper eyelid had increased and she was hardly able to open her right eye. The eye was not painful at rest or with movement, and no infectious-appearing eye discharge was present (Figure 1). Her visual acuity and field were within normal limits. The CBC and western blot for gnathostomiasis were repeated. The number of eosinophils was within the normal limit (1.9%), the AEC was 214.7 cells/ μ L, and the western blot result was weakly positive. We suspected that the initial treatment with albendazole was unsuccessful although there was an improvement in the laboratory findings compared with the previous tests. As the patient still had problematic clinical symptoms, we assumed that the initial treatment with albendazole had failed. The gnathostomiasis guidelines of the

TABLE 2
Laboratory investigations for gnathostomiasis

Pretreatment	Post-treatment				
Parameters	First examination (December 1, 2014)	First follow-up (March 3, 2015)	Second follow-up (June 23, 2015)	Third follow-up (December 9, 2015)	Fourth follow-up (May 24, 2016)
Complete blood count					
Hemoglobin (12.0–16.0 g/dL)	13.4	13.0	13.5	13.3	14.4
Hematocrit (37.0–47.0%)	40.6	38.7	41.4	39.4	43.1
White blood cells (5,000–10,000 cells/mm ³)	10,200	11,300	9,200	9,900	8,200
Eosinophils (0–7%)	5.9 (AEC = 601.8)	1.9 (AEC = 214.7)	2.2 (AEC = 202.4)	2.1 (AEC = 207.9)	1.2 (AEC = 98.4)
Stool examination	Parasite not found	—	—	—	—
Liver function testing					
Aspartate transaminase (0–32 U/L)	18 U/L	18 U/L	—	—	—
Alanine transaminase (0–33 U/L)	19 U/L	19 U/L	—	—	—
Western blot analysis	Positive band at 24 kDa	Positive band at 24 kDa	Weakly positive band at 24 kDa	Weakly positive band at 24 kDa	Negative band at 24 kDa

AEC = absolute eosinophil count.

FIGURE 1. Migratory swellings of *Gnathostoma spinigerum* on March 3, 2015 (A) Erythematous swelling on left forehead, (B) Radiation of swelling to right periorbital region, (C) Obvious right periorbital swelling during physical examination at the outpatient department of the Hospital for Tropical Diseases, Bangkok. This figure appears in color at www.ajtmh.org.

hospital state that local tissue swelling/edema is possible in the first 3 months after treatment as a reaction to the parasite and a new course of drugs is not required. However, ivermectin at 0.2 mg/kg/day for two consecutive days was prescribed after 3 months. The patient was also referred to the eye clinic on the same day for evaluation of the eye complications. No parasites were found by an ophthalmologist, and the probable diagnosis was periorbital cellulitis. The patient, therefore, received a prescription of one 1-g tablet of amoxicillin/clavulanic acid twice daily for 1 week along with tobramycin and terramycin eye ointments. A 1-week follow-up appointment was made at the eye clinic, at which time her symptoms had completely resolved with no eyelid swelling. Three- and six-month follow-up appointments at the parasite clinic (June 23, and December 9, 2015, respectively) revealed no remarkable signs or symptoms, her AEC was < 500 cells/ μ L, and her western blot was weakly positive. On May 24, 2016, her final follow-up examination revealed an AEC of 98.4 cells/ μ L with a negative western blot result. No additional follow-ups were performed, and she was considered cured of cutaneous gnathostomiasis (Figure 2).

DISCUSSION

In most cases, the larvae of *G. spinigerum* cannot be detected. Therefore, a presumptive diagnosis is usually made based on the clinical manifestations of a migratory swelling combined with a history of consumption of freshwater fish and other paratenic hosts in an endemic area. Humans are accidental hosts and may be infected by ingesting uncooked

meats of certain animals such as fish-eating reptiles and birds.¹² The herein described patient had risks of infection because she lived in an endemic area in Thailand where 48 species of animals have been reported as reservoir hosts for transmission of infective *Gnathostoma* larvae to humans.¹³ Although raw or improperly cooked fish dishes were favored, the patient denied having consumed any improperly cooked meats. It must be remembered that a patient's recall of what they have eaten is not always accurate and they may not always know the cooking process involved. At-risk food consumption was one of the minor criteria contributing to the diagnosis in this case.¹⁴ The patient's favorite dish was papaya salad, which she usually ordered with sticky rice, larb, or koi pla (a traditional dish made of various kinds of meat, including chopped fish flesh), grilled chicken, and popular grilled freshwater fish such as catfish, snake-headed fish, and tilapia. The larval and immature stages of *Gnathostoma* spp. are hardy and can likely tolerate the heat beneath the deep flesh or internal organs of improperly grilled fish. Hence, this mode of transmission, via grilled fish, is one explanation for infection in patients who are well educated regarding the mode of transmission and prevention of gnathostomiasis but still become infected with *G. spinigerum*. For safe cooking, fish should be submitted to enough heat and time to ensure that the parasite is killed before consumption; e.g., boiling water and steaming for a few minutes can kill encysted larvae that are located 2 cm deep within fish.¹⁵ In one study, freely encysted larvae completely lost their infectivity when subjected to freezing temperatures (-2°C to -4°C) for 2 days, while encysted larvae retained 20% infectivity in experimental mice.¹⁵

FIGURE 2. No swelling was present on May 24, 2016, (A) Anteroposterior view, (B) Right lateral view. This figure appears in color at www.ajtmh.org.

The clinical symptoms in the present patient were periodic migratory nonpitting edematous swellings in the right shoulder, a site that these nematodes usually inhabit.^{16,17} The patient also had an increased AEC of > 500 cells/ μ L, and her western blot result was positive for gnathostomiasis; this allowed for confirmation of the diagnosis of cutaneous gnathostomiasis with ocular involvement. *G. spinigerum* is reported to be the only significant causative agent of human gnathostomiasis in Thailand. In our experiment, the test and control strips were compared, looking at a specific band of 24 kDa which is the antibody against *G. spinigerum*. This way we ensured it was not a cross reaction with other parasitic diseases. However, the patient was also referred to an ophthalmologist to rule out ocular gnathostomiasis and other eye complications. Approximately 69 cases of ocular gnathostomiasis, including four cases involving the eyelids, were reported in the literature from 1937 to 2009; most of these cases occurred in Japan, Thailand, India, and Mexico.¹⁸ Blurred vision, floaters, iritis, uveitis, subretinal hemorrhage, and tracts were the most frequent presentations of this disease.¹⁹ The diagnosis of ocular gnathostomiasis normally confirmed by detection of *Gnathostoma* larvae in the anterior chamber or vitreous fluid. When larvae are not found and the patient has no eye invasion, as in the present case, serological tests such as western blot or enzyme-linked immunosorbent assay can be performed and may play an important role in the diagnosis.¹⁸ A reliable laboratory is useful for providing diagnostic services and advice for clinicians in nonendemic countries so that imported cases can be effectively managed.²⁰

In the present case, periorbital cellulitis secondary to bacterial infection is another possible explanation for the patient's symptoms because of the swelling and mild erythema. She was also treated for this condition after referral to the eye department. However, we think it is most likely the patient was infected with gnathostomiasis only. The detailed clinical manifestations observed and photographed were of gnathostomiasis. The migratory swelling tract of the immature worm reached the eye and caused periorbital swelling. There was also the corresponding positive result in the 24-kDa specific reactive band during western blotting. The medical ophthalmologist who met the patient after the diagnosis and treatment gave the patient antibiotics to resolve the periorbital swelling when the parasite was not observed in the eye. Noninfectious conditions such as allergy-induced angioedema are unlikely in this case because they usually present with bilateral involvement and persist for < 2 days.²¹ Other autoimmune syndromes such as systemic lupus erythematosus or dermatomyositis are also unlikely because the patient had no other signs of systemic involvement. Albendazole as well as ivermectin monotherapy or a combination of these drugs have been used with good outcomes in patients with initial treatment failure.^{22–24} The present patient switched to ivermectin for two consecutive days with a successful outcome; the tissue swelling improved and then disappeared. A practical criterion with which to determine that a patient has been cured is that the patient has been asymptomatic for > 1 year, especially when improvements are observed in eosinophilia and the antibody level.¹⁷ Our patient met this criterion.

Reinfection was considered unlikely because the cutaneous manifestations did not occur until about 4 weeks after infection. Strady et al.¹⁴ reported the relapse of gnathostomiasis at an interval of 7 months, and in one patient with

central nervous system involvement, the period between relapses was 15 months. Therefore, follow-up at 6–12 months is recommended for patients with gnathostomiasis.¹⁴ Drug readministration should be considered in patients who develop relapse.⁹ In the present case, the western blot result was negative at the last follow-up, and the patient was determined to be cured of gnathostomiasis.

Received March 24, 2017. Accepted for publication June 7, 2017.

Published online August 7, 2017.

Acknowledgments: We thank Vorapot Supsiriravatt, Piyawan Ngamomgard, and Yupin Sa-ngiempong for their help with the data collection. We also thank Paron Dekumyoy and Wallop Pakdee for their laboratory support.

Authors' addresses: Chollasap Sharma, Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, E-mail: chollasap.sha@student.mahidol.edu. Watcharapong Piyaphanee, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, E-mail: watcharapong.piy@mahidol.ac.th. Dom Watthanakulpanich, Department of Helminthology, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, E-mail: dom.wat@mahidol.ac.th.

REFERENCES

1. Dekumyoy P, Watthanakulpanich D, 2013. Gnathostomiasis. Magill AJ, Hill DR, Solomon T, Ryan ET, eds. *Hunter's Tropical Medicine and Emerging Infectious Diseases*, 9th edition. London, United Kingdom: Saunders, 853–855.
2. Dekumyoy P, Yoonuan T, Waikagul J, 2012. Gnathostoma. Liu D, ed. *Molecular Detection of Human Parasitic Pathogens*. Boca Raton, FL: CRC Press Taylor & Francis Group, 563–570.
3. Daengswang S, 1983. The world's first-story of *Gnathostoma spinigerum* infection in the young Thai woman. *J Parasitol Trop Med Assoc Thailand* 6: 1–10.
4. Miyasaka I, 1991. *An Illustrated Book of Helminthic Zoonosis*. Tokyo, Japan: International Medical Foundation of Japan.
5. Daengsvang S, 1986. *Gnathostoma spinigerum* and human gnathostomiasis. A review. Sucharit S, ed. *The 25th Anniversary of the Faculty of Tropical Medicine, Mahidol University*. Bangkok, Thailand: Krung Siam Press, 124–147.
6. Nopparatana C, Setasuban P, Chaicumpa W, Tapchaisri P, 1991. Purification of *Gnathostoma spinigerum* specific antigen and immunodiagnosis of human gnathostomiasis. *Int J Parasitol* 21: 677–687.
7. Kraivichian K, Nuchprayoon S, Sitichalerchai P, Chaicumpa W, Yentakam S, 2004. Treatment of cutaneous gnathostomiasis with ivermectin. *Am J Trop Med Hyg* 71: 623–628.
8. Nontasut P, Claesson BA, Dekumyoy P, Pakdee W, Chullawichit S, 2005. Double-dose ivermectin/albendazole for the treatment of gnathostomiasis. *Southeast Asian J Trop Med Public Health* 36: 650–652.
9. Hale DC, Blumberg L, Frean J, 2003. Case report: gnathostomiasis in two travelers to Zambia. *Am J Trop Med Hyg* 68: 707–709.
10. Herman JS, Wall EC, van-Tulleken C, Godfrey-Faussett P, Bailey RL, Chiodini PL, 2009. Gnathostomiasis acquired by British tourists in Botswana. *Emerg Infect Dis* 15: 594–597.
11. Nawa Y, Hatz C, Blum J, 2005. Sushi delights and parasites: the risk of fishborne and foodborne parasitic zoonosis in Asia. *Clin Infect Dis* 41: 1297–1303.
12. Dekumyoy P, Watthanakulpanich D, Waikagul J, 2014. Helminth-nematode: *Gnathostoma spinigerum*. Motarjemi Y, ed. *Encyclopedia of Food Safety*. Waltham, MA: Academic Press, 94–98.
13. Daengsvang S, 1980. *A Monograph on the Genus Gnathostoma and Gnathostomiasis in Thailand*. Tokyo, Japan: Southeast Asian Medical Information Center (SEAMIC), International Medical Foundation of Japan.
14. Strady C, Dekumyoy P, Clement-Rigolet M, Danis M, Bricaire F, Caumes E, 2009. Long-term follow-up of imported gnathostomiasis shows frequent treatment failure. *Am J Trop Med Hyg* 80: 33–35.

15. Rojekittikhun W, Buchachart K, 2002. The infectivity of frozen *Gnathostoma spinigerum* encysted larvae in mice. *J Trop Med Parasitol* 25: 79–82.
16. Ogata K, Nawa Y, Akahane H, Diaz Camacho SP, Lamothe-Argumedo R, Cruz-Reyes A, 1998. Short report: gnathostomiasis in Mexico. *Am J Trop Med Hyg* 58: 316–318.
17. Kraivichian K, Nuchprayoon S, Sitichalerchai P, Chaicumpa W, Yentakam S, 2004. Treatment of cutaneous gnathostomiasis with ivermectin. *J Trop Med Parasitol* 71: 623–628.
18. Nawa Y, Katchanov J, Yoshikawa M, Rojekittikhun W, Dekumyoy P, Kusolsuk T, Watthanakulpanich D, 2010. Ocular gnathostomiasis: a comprehensive review. *J Trop Med Parasitol* 33: 77–86.
19. Biswas J, Gopal L, Sharma T, Badrinath SS, 1994. Intraocular *Gnathostoma spinigerum*. Clinicopathologic study of two cases with review of literature. *Retina* 14: 438–444.
20. Waikagul J, Diaz Chamacho SP, 2007. Gnathostomiasis. Darwin KD, Fried B, eds. *Food-Borne Parasitic Zoonoses: Fish and Plant-Borne Parasites (World Class Parasites)*. New York, NY: Springer, 235–261.
21. Kaplan AP, 2012. Urticaria and angioedema (Chapter 38). Goldsmith LA, Katz SI, Gilchrist BA, Paller A, Leffell DJ, Wolff K, eds. *Fitzpatrick's Dermatology in General Medicine*, 8th edition. New York, NY: McGraw-Hill.
22. Chappuis F, Farinelli T, Loutan L, 2001. Ivermectin treatment of traveler who returned from Peru with cutaneous gnathostomiasis. *Clin Infect Dis* 33: E17–E19.
23. Moore DA, McCroddan J, Dekumyoy P, Chiodini PL, 2003. Gnathostomiasis: an emerging imported disease. *Emerg Infect Dis* 9: 647–650.
24. Parola P, Bordmann G, Brouqui P, Delmont J, 2004. Eosinophilic pleural effusion in gnathostomiasis. *Emerg Infect Dis* 10: 1690–1691.