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Gnathostoma

O. Sanpool, P.M. Intapan, David Blair, Yukifumi Nawa, and W. Maleewong Q0

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80.1 Introduction

Gnathostomiasis, a helminthic zoonosis, is a dangerous foodborne disease caused by spiruroid roundworms of the genus *Gnathostoma*. The disease is endemic mainly in Asia and the Americas (e.g., Mexico, Thailand, Japan, and Vietnam).[1–4] Sporadic cases have been emerging among travelers who have returned from these well-known endemic areas[5,6] and from other tropical regions (e.g., Zambia[7] and Botswana[8]). The possibility of gnathostomiasis occurring in Oceania needs attention, because indigenous cases have recently been reported from Australia[9] and New Zealand.[10]

Humans usually acquire infection by consuming raw or undercooked flesh of the second intermediate and paratenic hosts, especially freshwater fish containing infective third-stage larvae (L3). In endemic areas, popular dishes such as *sashimi* and *sushi* in Japan, *ngar lay chi* in Myanmar, *koi ga* in Vietnam, *koi-pla* in Thailand, and *ceviche* and *callos* in Latin America are prepared using raw or semicooked freshwater fish.[4] A few cases of gnathostomiasis in Japan have been reported following consumption of *sashimi* of snakes.[11]

Upon ingestion, *Gnathostoma* L3 larvae migrate into subcutaneous tissues and cause intermittent migratory dermal swellings or creeping eruption on the skin. Normally, L3 cannot develop further in humans, so the disease is best known for its cutaneous manifestations. Occasionally, the parasite wanders to vital organs, that is, the central nervous system (CNS), eyes, etc., producing serious clinical features, harmful complications, and even death.[2,12–14] There are some records of people becoming infected as a result of handling meat of infected animals (fish, chicken, and pig), presumably by direct skin penetration of larvae.[15] Feto-maternal transmission of *Gnathostoma* advanced third-stage larva (AL3) across the placenta may also occur.[3]

80.2 Classification and Morphology

80.2.1 Classification

Genus *Gnathostoma* Owen, 1836 is classified in the phylum Nematoda, order Spirurida Chitwood, 1933, family Gnathostomatidae Railliet, 1895. Thirteen species are considered valid: *Gnathostoma socialis* Leidy, 1858; *G. turgidum* Stossich, 1902; *G. americanum* Travassos, 1925; *G. procyonis* Chandler, 1942; *G. miyazakii* Anderson, 1964; *G. binucleatum* Almeyda-Artigas, 1991; *G. lamothei* Bertoni-Ruiz et al., 2005; *G. spinigerum* Owen, 1836; *G. hispidum* Fedchenco, 1872; *G. doloresi* Tubangui, 1925; *G. nipponicum* Yamaguti, 1941; *G. malaysiae* Miyazaki and Dunn, 1965; and *G. vietnamicum* Le-Van-Hoa, 1965.[4] Among these, six are in Eurasia, and seven are in the Americas. Four species in Asia and one species in Latin America are recognized as human pathogens.[4] *Gnathostoma spinigerum* is the most common species to cause human disease in Asia. Infections with *G. doloresi*,

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G. hispidum, and *G. nipponicum* are known primarily from Japan, although *G. hispidum* infection in a Korean man returning from China has also been reported.[16] *Gnathostoma binucleatum* is the only species proven to cause human gnathostomiasis in the Americas.[3,4] One Japanese man was reportedly infected with *G. malaysiae*,[17] but the species identification was inadequate, and further confirmation is necessary.

80.2.2 Morphology

Adult *Gnathostoma* parasites generally live in a tumor of the stomach wall of their mammalian hosts. Exceptions are *G. nipponicum*, adults of which live in the esophagus of weasles, and *G. vietnamicum*, adults of which live in the kidneys of rodents.[2,18] Adult *Gnathostoma* worms have a cylindrical body: male worms are about 1–3 cm, and female adult worms are about 2–5 cm in length. Adults of *G. turgidum* are exceptionally large with males 2–5 cm and females 5–10 cm in length. The anterior end of the body has a round head-bulb equipped with 8–10 concentric rows of hooklets and a pair of lips surrounding a mouth in the center. The body surface is covered by rows of cuticular spines varying in size, distribution, and form characteristic to each species. These morphological features are clearly summarized.[4]

Male genitals, located near the posterior end, are surrounded by papillae varying in number, size, and distribution. This area is curved ventrally and houses two spicules of unequal length (0.9–2.1 and 0.4–0.5 mm) (Figure 80.1d). The female has a bluntly rounded tail. The vulva is a slight transverse slit behind the middle of the body connected to a long muscular vagina, which passes anteriorly then posteriorly and dorsally before dividing into two uterine branches filled with eggs at different developmental stages. Eggs are passed to the environment through the vulva. Fertile eggs are oval in shape, usually colored yellow or brown (Figure 80.1a). A fertile egg is about 70 × 40 μm in size; its shell has either some small pits or a smooth surface, with one or two polar bulges, depending on the species.[18,19]

The newly hatched first-stage larva (L1) is cylindrical, covered with a delicate, voluminous, smooth, and transparent sheath, and displays active movements. The anterior part is round and covered with minute solid spines. The second-stage larva (L2) has two unequal transparent lips and gradually increases in size while living in the coelom of copepods (Figure 80.1b). The size of the early third-stage larva (EL3) (Figure 80.1b) is about 300–400 × 50–60 μm. The head-bulb is equipped with four rows of hooklets (except for *G. nipponicum* larvae, which have three rows of hooklets there). A marked constriction is seen between the head-bulb and the body. Four cervical sacs are well developed and extend along both sides of the esophagus down to about the beginning of the intestinal tract. A group of sensory papillae is located at the head and another at the neck portion of the body (cervical papillae). The AL3 is approximately 2–3 mm in length (Figure 80.1c). That of *G. turgidum* is exceptionally large, measuring about 1 cm.[20] AL3s frequently encyst in the liver or muscles of intermediate and paratenic hosts.

In gross appearance, AL3 is divided into lips, head-bulb, and body. The lips have two pairs of papillae and two amphids. The head-bulb of L3 and adults has four chambers, called ballonets, which are independently linked with the four cervical sacs located in the pseudocoel. The ballonet-cervical sac system contains fluid and acts in locomotion. The esophagus extends from the mouth and has a well-developed gland that secretes substances to help migration and external digestion. The intestine ends posteriorly as an anal pore and is formed by a monolayer of cuboidal or columnar cells with one to six nuclei (depending on the species) and numerous brown granules. The body surface of larvae is covered with rows of cuticular spines diminishing in size and number toward the posterior end. Usually, a pair of cervical papillae is located between rows 12 and 14; further down, in rows 30–32, is an excretory pore. The morphological features of larvae such as the number of hooklets in each row on the bulb, shape and distribution of cuticular spines, shape of the intestinal epithelial cells, and number of nuclei in the cells,

FIGURE 80.1 Demonstration of *Gnathostoma spinigerum* eggs (a), the early third-stage larva living in copepods (b), the advanced third-stage larva (c), the female and male adults (d).

are the important landmarks for differentiation of *Gnathostoma* species,[18,21] which are clearly summarized.[4]

80.3 Biology and Life Cycle

The host range of adult gnathostomes seems to be rather narrow depending on the species.[4] All species of the genus *Gnathostoma* exploit copepods in freshwater or brackish water as the first intermediate hosts, perhaps with low species specificity. The second intermediate hosts are amphibians (frogs, newts), crustaceans, and freshwater or brackish-water fish. Several fish-eating fish and birds, reptiles (snakes and turtles), small mammals, etc., can act as paratenic hosts,[18] in which AL3s encyst, remaining infective but unable to grow further.

Adults generally live in a tumor formed through a proliferation of the host connective tissue, which may be followed by calcification of the area surrounding the parasite. Worms lie with their heads buried in the wall of the relevant organ and their tails extending from the tumor into the lumen of the organ. More than one tumor might occur in a host, and each may contain one or more worms of both sexes. Females release fertilized eggs into the stomach (or esophageal) lumen, from which they are eventually voided via the stool (or urine in the case of *G. vietnamicum*). Fertilized eggs embryonate and develop, from L1 to sheathed L2 in water. In the case of *G. spinigerum*, optimum development occurs within a temperature range of 24°C–30°C. The L2 larvae hatch through an operculum and swim in water until they are eaten by copepods. Within the hemocoel of the copepod, they develop into EL3 within 7–14 days.[22] When infected copepods are eaten by the second intermediate host, EL3s move into the muscle tissue or liver of the new host, where they encyst and grow into AL3. When these in turn are ingested by a definitive host, they develop to the adult stage to complete the life cycle within about 100 days.

Despite often being regarded as accidental hosts for *Gnathostoma* worms, recovery of adult worms from humans is rather frequent, suggesting that humans can function as definitive hosts.[4] Most of these cases were infected with a single adult worm; multiple worm infection is uncommon.[15]

80.4 Epidemiology

Species of fish, reptiles, birds, amphibians, and mammals act as second intermediate hosts or paratenic hosts in the endemic areas of Central and South America[23] and Asia.[2,18] Increasing numbers of gnathostomiasis cases have been reported among travelers returning from endemic countries,[6,24] and the disease is regarded as an emerging imported disease in Europe and other Western countries. More than 9,000 cases of gnathostomiasis have been reported in Thailand and in Mexico, and more than 4,000 cases in Japan. Over 600 serologically diagnosed cases have been found in Vietnam.[25] Outside of those endemic countries, more than 2,000 cases have been reported in Ecuador.[26] Areas with high seroprevalence were recently found in Lao PDR.[27] Apart from Asia and Latin America, Africa should be considered as a gnathostomiasis-endemic area, since small group infections were found among travelers who visited Zambia[7] and Botswana.[8] A male dog infected with *Gnathostoma* in the stomach was recently reported from Zambia.[28]

80.4.1 Occurrence in the Americas

Of the seven *Gnathostoma* species identified in the Americas,[4] *G. binucleatum* is the only one proven to cause human gnathostomiasis. Mexico (>10,000 cases), Ecuador (>2,000 cases), and Peru (>18 cases) have the highest incidences of human gnathostomiasis in the Americas.[4] Many countries have reported human gnathostomiasis from autochthonous cases. Among these are Brazil,[29] Ecuador,[26,30–33] Mexico,[34–40] Peru,[41–47] and the United States.[48,49] Cases have also been reported among travelers who have returned from countries in the Americas, such as Brazil.[47]

80.4.2 Occurrence in Asia

Gnathostomiasis occurs across many parts of Asia.[4] The first human case was reported by Levinsen (1889), who found an immature female worm in the breast skin of a young Thai woman in Bangkok. This worm was initially identified as *Cheiracanthus siamensis* but subsequently described as *G. spinigerum*.[2] From then on, human gnathostomiasis cases and animal infections with *G. spinigerum*, *G. hispidum*, *G. doloresi*, *G. nipponicum*, *G. malayanum*, *G. malaysiae*, and *G. vietnamicum* have been reported in several Asian countries, that is, Bangladesh,[5,37,50–54] Cambodia,[2,55] China,[1,16,18,56–62] India,[4] Indonesia,[63–67] Malaysia,[1,37,68–74] Philippines,[75–80] and Sri Lanka.[81]

In Japan, *G. spinigerum*, *G. hispidum*, *G. nipponicum*, and *G. doloresi* were reported as causative agents for human infection.[82] *Gnathostoma spinigerum* was initially imported into Japan[1] when snakehead fish were introduced from China, and its life cycle was established in central to southwestern Japan. Stray dogs and cats act as final hosts there. *Gnathostoma hispidum* was introduced from China by importation of loaches harboring the infective larvae.[82] *Gnathostoma nipponicum* and *G. doloresi* are indigenous species. An extensive review on gnathostomiasis cases in Japan by Ando[83] revealed a total of 3,225 cases during the period 1911–2002, with a peak incidence of about 1,300 patients in Kyushu district in 1950. In addition to indigenous cases, 86 individuals were originally infected in China and 34 in other Asian countries. Most cases in Japan were caused by *G. spinigerum*, 119 by *G. hispidum*, 26 by *G. nipponicum*, 45 by *G. doloresi*, and one by *G. malaysiae*. Males were infected more than twice as often as females. Most patients were 30–40 years old: the youngest was an infant of 1 year and 11 months, and the oldest was aged 76. One interesting gnathostomiasis case in Japan was infected by eating raw snake meat as *sashimi*.[11]

In Korea, *Gnathostoma* larvae were collected from freshwater fish in the southeastern part of the country,[84] and *G. hispidum* and/or *G. nipponicum* larvae were found in snakes and/or frogs.[85,86] Most reported cases were foreigners from endemic areas[87] or Korean travelers who had returned from endemic areas.[88–90] For example, a Korean man who had returned from China was confirmed to be infected with *G. hispidum*.[16] One American man with eosinophilic meningitis might have been infected in Korea.[91] A Korean indigenous case caused by *G. spinigerum* infection has also been reported.[92]

In Lao PDR, the overall prevalence was about 30% according to a seroepidemiological study. The majority of cases were from the central (47%) and southern (38%) provinces: prevalence was very low in the north (3.6%).[27] Adult *G. spinigerum* were found in cats[93] and dogs,[27] and AL3s were found in snakehead fish, swamp eels, and several other fish species and also in frogs.[27] Recently, *G. spinigerum* AL3 from a snake, *Ptyas korros* Schlegel, from Laos was identified using, for the first time, a molecular method.[94] Gnathostomiasis cases among Laotian immigrants have been reported in various countries, for example, the United States,[95–98] France,[99] and Germany.[100]

In Myanmar, *G. spinigerum* adult worms have been found in cats and dogs, and two human cases of intraocular gnathostomiasis have been reported.[73,101] Ocular gnathostomiasis cases in Chinese Burmese in Taiwan have also been reported.[102] Two Japanese men were reportedly infected with *G. malaysiae* in Myanmar,[17] although the identification of the worm was not convincing. An outbreak of gnathostomiasis occurred in 38 of 60 Korean emigrants who consumed raw freshwater fish together in a Korean restaurant in Yangon. The patients were diagnosed by their clinical symptoms and serology (enzyme-linked immunosorbent assay [ELISA]) using *G. doloresi* adult-worm antigen.[88] *Gnathostoma spinigerum* larvae were found in snakehead fish in Myanmar.[103]

In Thailand, *G. spinigerum*, *G. hispidum*, *G. doloresi*, *G. vietnamicum*, and *G. malaysiae* have been found in many hosts. Forty-eight species of animals have been reported as the natural vertebrate hosts of *G. spinigerum* AL3.[15,104] Many human cases have been claimed, but there is no official record of total gnathostomiasis cases. About 100–400 new suspected patients visited the Gnathostomiasis Clinic of the Hospital for Tropical Diseases, Mahidol University, Bangkok, between 1997 and 2002.[104] Recently, *G. spinigerum* worms recovered from humans,[105] dogs,[9] and freshwater swamp eels[106] were identified using a combination of morphological and molecular methods.

In Vietnam, large numbers of gnathostomiasis patients have been found among local residents. Cases among overseas travelers returning from Vietnam have also been reported. *Gnathostoma spinigerum*, *G. hispidum*, *G. doloresi*, and *G. vietnamicum* have been reported from Vietnam in wild animals.[107] Most human cases in Vietnam were diagnosed using a combination of clinical symptoms and serodiagnosis (ELISA).[25,108] Four cases of cerebromyelitis[109] and one of intraocular gnathostomiasis,[110] caused by *G. spinigerum* larvae, have been reported.

80.4.3 Occurrence in Other Localities

Human gnathostomiasis cases and/or animal infections with *Gnathostoma* species have been reported in several areas apart from those discussed above, that is, the African continent,[7–8,111–113] Australia,[9,114–117] Palestinian Territory,[118] Spain,[119–124] Italy,[125] France,[126–129] and New Zealand.[10] The causative species in some cases was tentatively identified as *G. spinigerum*. However, further identification using combined morphological and molecular methods is required in those areas.

80.5 Clinical Features

Gnathostoma larvae, as well as immature and mature adults, cause a variety of clinical manifestations in humans. Their speed of migration varies from 1.8 mm to 3.0 cm/h, and direction is apparently random. After being ingested, *Gnathostoma* AL3 preferentially migrates through the liver and then disperses mainly to the skin (subcutaneous connective tissue) via the bloodstream.[18] The duration of *G. spinigerum* infection in humans varies. Larvae are recorded as persisting for 10[130]–17 years[131] without reaching maturity. Although ingestion of infected intermediate or paratenic hosts is the usual route of infection, percutaneous penetration can also happen when AL3-contaminated meats are used as a poultice.[15] Ingested AL3s penetrate the gastric and/or intestinal wall, causing eosinophilia and nonspecific systemic symptoms, including malaise, fever, urticaria, anorexia, nausea, vomiting, diarrhea, and epigastric pain within 24–48 hours.[15,132] Although uncommon, intestinal obstruction due to severe inflammatory reaction around a worm in the gut wall has been reported.[133–135] Migration to the lungs has only been sporadically reported.[136–140]

Clinical manifestations are divided into two major disease categories, cutaneous larva migrans and visceral larva migrans. Migration into the subcutaneous tissues results in intermittent painful and pruritic migratory swelling. Migration into visceral organs (visceral larva migrans) often causes eosinophilic abscess.[132] Migration into the eyes (intraocular) and the CNS[13] often causes substantial damage. Clinical features of skin lesions caused by *G. binucleatum* infection in Mexico and Ecuador are basically the same as those caused by *G. spinigerum* infection in Asia; intermittent migratory swellings appear on peripheral parts of the body and persist over years.[3] In contrast, patients infected with *G. hispidum*, *G. doloresi*, and *G. nipponicum* mostly show intermittent serpiginous eruptions on the skin (creeping diseases), principally on the abdomen or back, which persist for not longer than 2 months even without treatment.[4,82] A hemorrhagic zone or a pigmented plaque remains in the area, but tends to vanish in 2–5 weeks, after inflammation has faded away.[4,15] Creeping lesions seen in gnathostomiasis are often misdiagnosed as cutaneous larva migrans caused by other helminthic infections, such as *Ancylostoma caninum*, human hookworm, *Strongyloides stercoralis*, etc.[31,82,141]

The prognosis for ocular gnathostomiasis is generally good, but irreversible damage leading to blindness has been reported.[142] An extensive literature review by Nawa et al.[37] covered 73 cases of ocular gnathostomiasis.[90,143–145]

Over a hundred neurognathostomiasis cases have been reviewed, most of which were found in Thailand.[14] Since ocular gnathostomiasis cases have similar prevalences in endemic countries like Japan, Thailand, and Mexico,[37] the high incidence of neurognathostomiasis only in Thailand needs more epidemiological as well as genetic study on both parasites and hosts.

80.6 Pathogenesis

The pathological features of gnathostomiasis consist of inflammation, edema, and tissue destruction along the migration route of the worm. Mechanical damage by the parasite and the effects of its excretory-secretory products are the principal causes of pathological change. Among the excretory-secretory products of *G. spinigerum* are various biologically and immunogenically active substances such as acetylcholine, hyaluronidase, protease, and hemolysin.[1] Horii et al.[146] demonstrated extremely strong

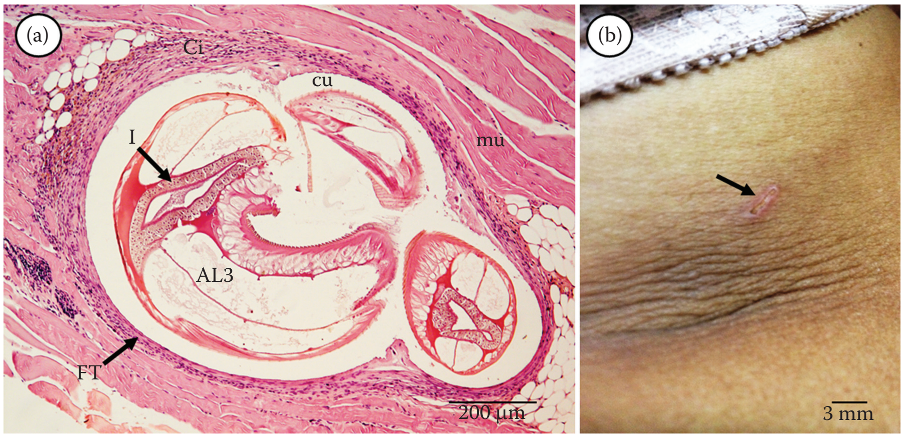

FIGURE 80.2 (a) Hematoxylin-eosin staining section of a *Gnathostoma spinigerum* larva (AL3) in infected mouse muscle (mu) surrounding with fibrous connective tissue (FT). Parasite cyst showing mixed inflammatory infiltration (CI) and the section exhibiting the *G. spinigerum* larva in the center with intestine (I) and cuticle (cu). (b) Lesion on the skin of a gnathostomiasis patient after *G. spinigerum* had emerged (arrow).

eosinophil and neutrophil chemotactic activity in a crude extract of *G. doloresi* adult worms. The tissue reactions could possibly be regarded as allergic, but the number and size of larvae, and the sites through which they migrate, are also important factors (Figure 80.2).

80.7 Diagnosis

Definitive diagnosis of gnathostomiasis can be made by identification of *Gnathostoma* worms that have spontaneously emerged from the body or are found in biopsy specimens. However, worms are infrequently seen. Worm detection rate is far lower in cutaneous cases and visceral cases than in ocular cases.[37,83] Information helpful for supporting diagnosis of suspected patients when actual worms have not been recovered and identified is as follows:

1. History of eating raw meat dishes prepared from fish, amphibians, reptiles, birds, or mammals. These could have been contaminated with infective larvae. More than 90% of suspected patients have a history of eating raw or semicooked freshwater or brackish-water fishes. This information is important in the case of travelers who have visited endemic areas, or of immigrants from endemic areas.
2. History of intermittent migratory swelling in the skin or other skin lesion. Differential diagnosis is essential, since similar clinical manifestations can be due to infections by larvae of several other parasites such as *Ancylostoma caninum* and other dog hookworms, *Strongyloides* spp., *Paragonimus* spp., *Spirometra* spp., etc. Signs and symptoms of visceral larva migrans are variable depending on the organs or tissues affected, and rather nonspecific. The presence of eosinophilia of more than 10% with or without leukocytosis is a supportive criterion.
3. For neurognathostomiasis, the main diagnostic clue is detection of cerebral hemorrhage.[147] Visualization of a hemorrhagic tract by computed tomography and/or magnetic resonance imaging is highly suggestive of neurognathostomiasis.[148] In angiostrongyliasis, another famous zoonotic nematodiasis causing eosinophilic meningitis, almost all patients have normal brain computed tomography findings, and few cases show parenchymal brain lesions. Radioimaging is sometimes helpful to distinguish between *Gnathostoma* and *Angiostrongylus* parasites as causes of eosinophilic meningoencephalitis.[149]
4. Specific antibody detection by ELISA and/or immunoblotting is helpful for the diagnosis of suspected cases without detection of parasite larvae/adults. Many serodiagnostic tests can provide supportive clues.[150] ELISA, based on the detection of human IgG antibody to *Gnathostoma* antigen, has been commonly used.[141,151–153] Skin tests were often used before the development of ELISA,[1] and its field use in developing countries is recommended even now.[154] The diagnostic values of somatic extract and excretory-secretory antigens of AL3 *G. spinigerum* in ELISA have been reported.[155]

Immunoblot analysis identified a 24 kDa polypeptide in *G. spinigerum* larval extract that specifically reacted with IgG antibody in human gnathostomiasis sera.[156] This antigen, partially purified, gave 100% diagnostic sensitivity and specificity in ELISA.[157] Two-dimensional gel electrophoresis of antigenic components (23–25 kDa, pI 8.3–8.5) extracted from *G. spinigerum* larvae, followed by immunoblot analysis, yielded 83.3% sensitivity without cross-reaction to angiostrongyliasis, cysticercosis, or healthy control sera.[158] In a later study, a 21 kDa antigenic band of *G. spinigerum* AL3 extract reacted with IgG_4 antibody in human gnathostomiasis sera with 100% sensitivity and specificity, whereas the 24 kDa band gave only 92.9% sensitivity and 93.4% specificity.[159] Similarly, the 24 kDa antigenic component of *G. spinigerum* AL3 was predominantly recognized by human IgG_4 subclass antibodies.[160] Detection of 21 and 24 kDa bands in the crude somatic AL3 *G. spinigerum* antigen was recognized by IgG antibody in immunoblot, showing also good diagnostic values for neurognathostomiasis.[161]

In addition to crude or partially fractionated worm antigens, recombinant proteins have been tested as antigens for use in immunodiagnosis. Recombinant *G. spinigerum* cyclophilin reacted with human gnathostomiasis sera but not with sera from other parasitosis or healthy control sera.[162] Recombinant matrix metalloproteinase (MMP) of *G. spinigerum* was similarly tested.[163–165] Sanseeha et al.[166] developed an MMP-dot-ELISA, which appears to be a suitable rapid diagnostic test for epidemiological studies. Caballero-García et al.[167] also found that MMP is an immunodominant antigenic component in excretory-secretory products of *G. binucleatum* larvae. A cathepsin L-like cysteine protease was identified and characterized as an immunogenic component of *G. spinigerum*.[168] Recently, type 1 galectin was identified as an immunodominant antigen of *G. binucleatum* and partially purified as the lactose-binding glycopeptide.[169] In spite of such extensive work on immunodiagnosis of gnathostomiasis, it should be noted that the causative species cannot be identified by such methods due to cross-reactivity among *Gnathostoma* species.[37] Recently, Neumayr et al.[170] suggested that *G. spinigerum*–based serodiagnostic assays should be interpreted with caution if the patient is possibly infected with any other species of *Gnathostoma*, especially with *G. binucleatum* in the Americas. Recently, an immunochromatographic test (ICT) kit was developed using a recombinant protein (rGslic18) for a simple and rapid diagnosis of human gnathostomiasis.[171] The ICT method is convenient and easy to implement and expected to provide reliable diagnostic results with high sensitivity (93.8%) and specificity (97%) (Figure 80.3) and is suitable for rapid clinical diagnosis at the bedside and for large-scale epidemiological surveys.

80.8 Treatment

The best treatment for cutaneous gnathostomiasis is surgical removal of the worm. Albendazole was evaluated for the treatment of human gnathostomiasis at a dose of 400 or 800 mg/day for 21 days. Cure rates (i.e., no further appearance of swellings) of 93.9% and 94.1%, respectively, were obtained.[172] However, side effects, including gastrointestinal distress, headache, dizziness, elevated and reversible levels of hepatic enzymes, and transient reduction of the total leukocyte count, were often recorded after albendazole treatment. The efficacy of various drugs against *Gnathostoma* larvae in experimentally infected mice was reviewed by Rusnak and Lucey.[132] Although the exact parasiticidal action of praziquantel remains unclear, it might cause worms to exit the host, improving the chance of surgical extirpation of the worm. Ivermectin is effective against many human tissue parasitic infections. It is somewhat, but not significantly, less effective than albendazole (400 mg/day for 21 days) for treatment of cutaneous gnathostomiasis.[173] There is no clear verification of the effectiveness of albendazole and ivermectin for treatment of human gnathostomiasis.[174] For ocular gnathostomiasis, most cases have been treated by surgical removal of the parasite.

80.9 Prevention

The two anthelmintic drugs, albendazole and ivermectin, currently used for gnathostomiasis treatment give unsatisfactory cure rates. Signs and symptoms often persist after treatment, and infection can be serious if the worm migrates into vital organs. Thus, prevention of infection is better than treatment. The eating habits of people in endemic areas need to be changed, but this is notoriously difficult. Another approach might be to treat uncooked foods to minimize chances of infection. The effects of temperature, chemicals, and radiation on viability of gnathostome larva have been investigated.[3,15]

80.10 Conclusions and Future Prospects

Gnathostomiasis is a harmful foodborne helminthic zoonosis caused by the migration of the *Gnathostoma* worm. In this chapter, we reviewed the biology, epidemiology, clinical features, pathogenesis, diagnosis, treatment, and control of gnathostomiasis. *Gnathostoma spinigerum*, *G. doloresi*, *G. hispidum*, *G. nipponicum*, *G. malaysiae*, and *G. binucleatum* have all been reported as causing human

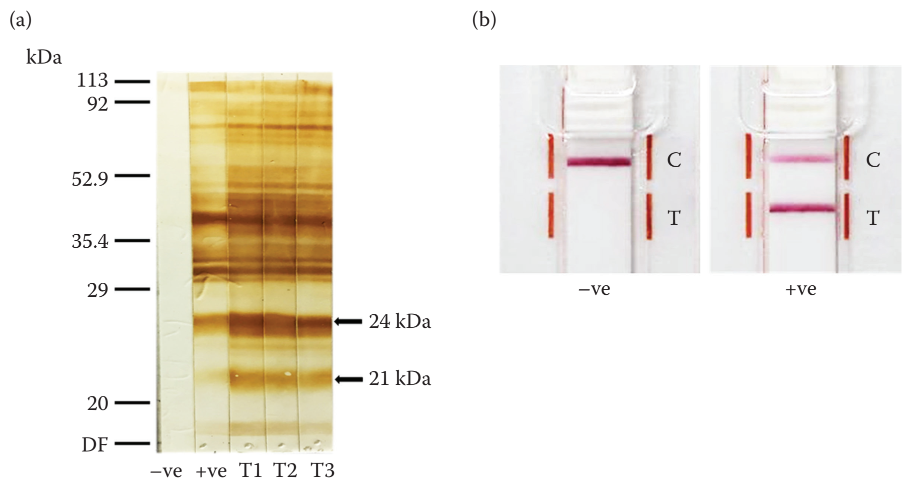

FIGURE 80.3 (a) Representative immunoblot patterns revealing serum antibody reactive to *G. spinigerum* larval extract antigen. Pooled negative reference sera (−ve), pooled positive reference sera (+ve), gnathostomiasis patient sera (T1–T3). The molecular weight markers in kilodaltons (kDa) are located on the left. The positions of the 21 and 24 kDa specific diagnostic bands are indicated on the right side. (b) Demonstration of immunochromatographic assay for the diagnosis of human gnathostomiasis. Representative images of ICT strips on which positive (+ve) and negative (−ve) results are shown.

disease. *Gnathostoma spinigerum* is common in Asia, while *G. binucleatum* is the main causative agent of gnathosomiasis in the Americas. Advanced L3 larvae are the infective stage for humans, ingested with raw or improperly cooked meat contaminated with them. More than 40 species of fish, reptiles, amphibians, birds, and small mammals act as intermediate and paratenic hosts. Human gnathostomiasis commonly presents with a migratory swelling syndrome: vital organs might be infected, resulting in death or serious symptoms. Infection by skin penetration of larvae while handling contaminated flesh, and transplacental transmission, are possible. Diagnosis is dependent on identification of *Gnathostoma* worms recovered from patients, clinical manifestations, and serological tests. Albendazole or ivermectin have been used for the treatment, but their efficacy remains uncertain. Proper cooking of food is the best means of prevention. Gnathostomiasis cases have been increasing among international travelers returning from endemic countries. Clinicians in nonendemic areas therefore need to be aware of the clinical features of gnathostomiasis for early diagnosis and treatment. There are clear needs for research on rapid diagnostic tests, effective therapy, and evaluation of drug efficacy. Proteomic studies will assist the search for candidate proteins for diagnosis and vaccine/drug design and may provide better understanding of the host-parasite relationship in human gnathostomiasis.[175]

To better understand this disease, immunological studies on its pathogenicity and pathology are indispensable. Molecular methodologies are also required to assist taxonomic determinations within the genus and to uncover further details in nematode systematics. Collaborative networks and data sharing between researchers and public health experts should be promoted. To prevent transmission of gnathostomiasis to nonendemic regions, information on its prevention and control must be widely disseminated. A surveillance system needs to be established in endemic Asian and American countries to facilitate rapid diagnosis and treatment.

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REFERENCES

1. Miyazaki I. On the genus *Gnathostoma* and human gnathostomiasis, with special reference to Japan. *Exp Parasitol* 1960;9:338–70.
2. Daengsvang S. Gnathostomiasis in Southeast Asia. *Southeast Asian J Trop Med Public Health* 1981;12:319–32.
3. Waikagul J, Diaz Chamacho SP. Gnathostomiasis. In: Murrell KD, Fried B, ed. *Food-Borne Parasitic Zoonoses. World class parasites*, Vol. 11. New York, NY: Springer, 2007:235–61.
4. Nawa Y, Maleewong W, Intapan PM et al. *Gnathostoma*. In: Xiao L, Ryan U, Feng Y, eds. *Biology of Foodborne Parasites*. New York, NY: CRC Press, Taylor and Francis Group, 2015:405–20.
5. Moore DA, McCroddan J, Dekumyoy P et al. Gnathostomiasis: An emerging imported disease. *Emerg Infect Dis* 2003;9:647–50.
6. Clément-Rigolet MC, Danis M, Caumes E. Gnathostomosis, an exotic disease increasingly imported into Western countries]. *Presse Med* 2004;33:1527–32. (French)
7. Hale DC, Blumberg L, Frean J. Case report: Gnathostomiasis in two travelers to Zambia. *Am J Trop Med Hyg* 2003;68:707–9.
8. Herman JS, Wall EC, van-Tulleken C et al. Gnathostomiasis acquired by British tourists in Botswana. *Emerg Infect Dis* 2009;15:594–7.
9. Jeremiah CJ, Harangozo CS, Fuller AJ. Gnathostomiasis in remote northern Western Australia: The first confirmed cases acquired in Australia. *Med J Aust* 2011;4;195:42–4.
10. Mulroy E, Simpson M, Frith R. Thoracic myelopathy due to gnathostomiasis acquired in New Zealand. *Am J Trop Med Hyg* 2016;95:868–70.
11. Kurokawa M, Ogata K, Sagawa S et al. Cutaneous and visceral larva migrans due to *Gnathostoma doloresi* infection via an unusual route. *Arch Dermatol* 1998;134:638–9.
12. Boongird P, Phuapradit P, Siridej N et al. Neurological manifestations of gnathostomiasis. *J Neurol Sci* 1977;31:279–91.
13. Schmutzhard E, Boongird P, Vejjajiva A. Eosinophilic meningitis and radiculomyelitis in Thailand, caused by CNS invasion of *Gnathostoma spinigerum* and *Angiostrongylus cantonensis*. *J Neurol Neurosurg Psychiatry* 1988;51:80–7.
14. Katchanov J, Sawanyawisuth K, Chotmongkoi V et al. Neurognathostomiasis, a neglected parasitosis of the central nervous system. *Emerg Infect Dis* 2011;17:1174–80.
15. Daengsvang S. *A Monograph on the Genus Gnathostoma and Gnathostomiasis in Thailand*. ~~Tokyo:~~ Southeast Asian Medical Information Center, 1980:85. Q2
16. Kim HS, Lee JJ, Joo M et al. *Gnathostoma hispidum* infection in a Korean man returning from China. *Korean J Parasitol* 2010;48:259–61.
17. Nomura Y, Nagakura K, Kagei N et al. Gnathostomiasis possibly caused by *Gnathostoma malaysiae*. *Tokai J Exp Clin Med* 2000;25:1–6.
18. Miyazaki I. *An Illustrated Book of Helminthic Zoonoses*. Tokyo: International Medical Foundation of Japan, 1991.
19. Koga M, Akahane H, Ishii Y. Surface ultrastructure of adults and eggs of *Gnathostoma spinigerum* (Nematoda, Gnathostomatidae). *Trans Am Microscopical Soc* 1991;110:315–20.
20. Díaz-Camacho SP, Delgado-Vargas F, Willms K et al. Intra-hepatic growth and maturation of *Gnathostoma turgidum* in the natural definitive opossum host, *Didelphis virginiana*. *Parasitol Int* 2010;59:338–43.
21. Akahane H, Sano T, Mako T. Morphological differences of the advanced third-stage larvae of *G. spinigerum, G. hispidum* and *G. doloresi*. *Jpn J Parasitol* 1986;35:465–7.
22. Janwan P, Intapan PM, Sanpool O et al. Growth and development of *Gnathostoma spinigerum* (Nematoda: Gnathostomatidae) larvae in *Mesocyclops aspericornis* (Cyclopoida: Cyclopidae). *Parasit Vectors* 2011;4:93.
23. Pérez-Álvarez Y, García-Prieto L, Osorio Sarabia D, Lamothe-Argumedo MR, Leon Régagnon V. Present distribution of the genus *Gnathostoma* (Nematoda: Gnathostomatidae) in Mexico. *Zootaxa* 2008;1930:39–55.
24. de Górgolas Hernández-Mora M, Fernández Guerrero ML. [Gnathostomiasis: An increasing disease among travellers]. *Med Clin (Barc)* 2005;125:190–2.

25. Xuan LT, Hoa PTL, Dekumyoy P et al. *Gnathostoma* infection in South Vietnam. *Southeast Asian J Trop Med Public Health* 2004;35(suppl 1):97–9.
26. Lazo RF. Gnathostomiasis in Ecuador. *Southeast Asian J Trop Med Publ Health* 2004;35:92–6.
27. Vonghachack Y, Dekumyoy P, Yoonuan T et al. Sero-epidemiological survey of gnathostomiasis in Lao PDR. *Parasitol Int* 2010;59:599–605.
28. Chikweto A, Bhaiyat MI, Mofya S, Sharma RN. Gnathostomiasis in a dog in Rusaka, Zambia. *Int J Vet Med: Res Reports.* 2015;2015:330445.
29. Jeunon de Sousa Vargas T, Kahler S, Dib C et al. Autochthonous gnathostomiasis, Brazil. *Emerg Infect Dis.* 2012;18(12):2087–9.
30. Ollague W. Gnathostomiasis (nodular migratory eosinophilic paniculitis). *J Am Acad Dermatol* 1985;13:835–6.
31. Ollague W, Ollague J, Guevara de Veliz A et al. Human gnathostomiasis in Ecuador (nodular migratory eosinophilic panniculitis: First finding of the parasite in South America. *Int J Dermatol* 1984;23:647–51.
32. Jiménez PJ, Alava JJ. Infección por *Gnathostoma* (Spirurida: Gnathostomatidae) en Hoplias microlepis: Prevalencia, correlación con la talla del pez, huéspedes e implicaciones para salud pública en Ecuador. *Biomedica* 2009;29:591–603.
33. Almeyda-Artigas RJ, Bargues MD, Mas-Coma S. ITS-2 rDNA sequencing of *Gnathostoma* species (Nematoda) and elucidation of the species causing gnathostomiasis in the Americas. *J Parasitol* 2000;86:537–44.
34. Pelaez D, Pérez-Reyes R. Gnathostomiasis humana en América. *Rev Lati- noamer Microbiol* 1970;12:83–91.
35. Tarango Martínez VM, Rojas Castañeda RG, Barba Borrego JA et al. *Dermatología Rev Mex* 2011;55:84–94.
Q3
36. de Peña J, Navarrete G, de Alba L et al. Gnatostomiasis confirmada histológicamente. *Dermatología Rev Mex* 2006;50:31–3. (in Spanish with English abstract)
37. Nawa Y, Katchanov J, Yoshikawa M et al. Ocular gnathostomiasis: A comprehensive review. *J Trop Med Parasitol* 2010;33:77–86.
38. Lamothe-Argumedo R. Gnatostomiasis ocular en México. *Rev Mex Oftalmol* 2005;79:118–20.
39. Diaz-Camacho SP, Willms K, Ramos MZ et al. Morphology of *Gnathostoma* spp. isolated from natural hosts in Sinaloa, Mexico. *Parasitol Res* 2002;88:639–45.
40. Diaz-Camacho SP, Willms K, de la Cruz-Otero MC et al. Acute outbreak to gnathostomiasis in a fishing community in Sinaloa, Mexico. *Parasitol Int* 2003;52:133–40.
41. Costa Alfaro H, Bravo Puccio FG, Valdes L et al. Paniculitis nodular migratoria eosinofílica en el Perú (gnathostomiasis humana). Informe de once casos, posibles causas y revisión de la literature. *Folia Dermatol Peru* 2001;12:21–35. (in Spanish with English abstract)
42. Álvarez P, Morales A, Bravo F. Gnathostomiasis, experiencia en una práctica privada en Lima-Perú. *Folia derm. Perú* 2011;22:67–74.
43. Laga AC, Lezcano C, Ramos C et al. Cutaneous gnathostomiasis: Report of 6 cases with emphasis on histopathological demonstration of the larva. *J Am Acad Dermatol* 2013;68:301–5.
44. Bruno C, Napoli A, González N et al. Gnathosomiasis: Case report and revision. *Prensa Medica Argentina* 2008;95:462–5.
45. Bommer W. Massive subkutane gnathostomiasis nach aufenthalt in Peru—Erfolgreiche therapie mit albendazol. *Wiener Klinische Wochenschrift* 2004;116:61–4. (in German with English abstract)
46. Chappuis F, Farinelli T, Loutan L. Ivermectin treatment of a traveler who returned from Peru with cutaneous gnathostomiasis. *Clin Infect Dis* 2001;33:17–9.
47. Dani CM, Mota KF, Sanchotene PV et al. [Gnathostomiasis in Brazil: Case report]. *An Bras Dermatol* 2009;84:400–4.
48. Jarell AD, Dans MJ, Elston DM et al. Gnathostomiasis in a patient who frequently consumes sushi. *Am J of Dermatopathol* 2011;33:E91–3.
49. Cole RA, Choudhury A, Nico LG et al. *Gnathostoma* spp. in live Asian swamp eels (*Monopterus spp.*) from foods markets and wild populations United States. *Emerg Infect Dis.* 2014;20:634–42.
50. Ahmad R. Some aspects of parasites of East Pakistan. *Agric Pakist* 1962;13:109.
51. Shaikh H, Hug MM, Rahman MS et al. Trial with Promintic in the treatment of gnathostomiasis in cat. *Pakistan J Vet Sc* 1968;2:200.
52. Bashirullah AKM. Occurrence of *Gnathostoma spinigerum* Owen, 1836, in Dacca, Bangladesh. *J Parasitol* 1972;58:187–8.
53. Qahtani F, Deschenes J, Ali-Khan Z et al. Intraocular gnathostomiasis: A rare Canadian case. *Can J Ophpthalmol* 2000;35:35–9.
54. Grobusch MP, Bergmann F, Teichmann D et al. Cutaneous gnathostomiasis in a woman from Bangladesh. *Int J Infect Dis* 2000;4:51–4.
55. Mazaud R, Audebaud G, Brumpt V et al. A case of human gnathostomosis in Cambodia. *Bull Soc Pathol Exot Filiales* 1973;66:320–4. (in French)
56. Morishita K, Faust EC. Two new cases of human creeping disease (gnathostomiasis) in China with a note on the infection in reservoir hosts in the China area. *J Parasitol* 1925;11:158.
57. Andrew MN. The helminth parasites of dogs and cats in Shanghai, China. *J Helminthol* 1937;15:145–52.
58. Li X. Food-borne parasitic zoonoses in the People's Republic of China. *Southeast Asian J Trop Med Public Health* 1991;22:31–5.
59. Li DM, Chen XR, Zhou JS et al. Short report: Case of gnathostomiasis in Beijing, China. *Am J Trop Med Hyg* 2009;80:185–7.
60. Cui J, Wang Y, Wang ZQ. Cutaneous gnathostomiasis with recurrent migratory nodule and persistent eosinophilia: A case report from China. *Korean J Parasitol* 2013;51:467–70.
61. Akahane H, Sano M, Kobayashi M. Three cases of human gnathostomiasis caused by *Gnathostoma hispidum*, with particular reference to the identification of parasitic larvae. *Southeast Asian J Trop Med Publ Health* 1998;29:611–4.
62. Sohn WM, Kho WG, Lee SH. Larval *Gnathostoma nipponicum* found in the imported Chinese loaches. *Korean J Parasitol* 1993;31:347–52.
63. Lie KJ. A case of gnathostomiasis in Indonesia. *Doc Ned Indones Morb Trop* 1949;1:368–70.
64. Miyazaki I. *Gnathostoma doloresi* Tubangui, 1925 from pigs in New Guinea. *J Parasitol* 1968;54:186–7.
65. Margono SS, Indris KN, Brodjonegoro NS. Another case of human gnathostomiasis in Indonesia. *Southeast Asia J Trop Med Public Health* 1978;9:406–8.
66. Hadidjaja P, Margono SS, Moeloek FA. *Gnathostoma spinigerum* from the cervix of a woman in Jakarta. *Am J Trop Med Hyg* 1979;28:161–2.
67. Permadi I, Suratma A, Damriyasa I. Prevalensi Cacing Nematoda pada Babi. *Indonesia Medicus Veterinus* 2012;1: 596–606. (in Indonesia)

68. Adams ARD. Report on a collection of nematodes from the Federation Malay States. *Ann Trop Med Parasitol* 1933;27:1.
69. Miyazaki I, Dunn FL. *Gnathostoma malaysiae* sp. n. from rats on Tioman Island, Malaysia (Nematoda: Gnathostomidae). *J Parasitol* 1965;51:382–4.
70. Kamiya H, Kamiya M, Ohbayashi M et al. *Gnathostoma malaysiae* Miyazaki and Dunn, 1965 from Rattus surifer in Thailand. *Southeast Asian J Trop Med Public Health* 1987;18:121–6.
71. Thuraisingam V, Tan Ewe Aik P, Sandosham AA. A presumptive case of gnathostomiasis in Malaysia. *Med J Malaya* 1969;24:107–12.
72. Bathrick ME, Mango CA, Mueller JF. Intraocular gnat[illegible]omiasis. *Ophthalmology* 1981;88:1293–5.
73. Gyi[illegible]*r J Ophthalmol* 1960;44:42–5.
74. Mokhtar E, Alias A, Abd Ghani Z et al. A live intraocular *Gnathostoma* spp. with diffuse unilateral subacute Neuroretinitis. *Int Med J* 2003;2:C3.
75. Wharton D. The intestinal worms of dogs in the Philippines Islands. *J Parasitol* 1917;4:80–2.
76. Tubangui MA. Metazoan parasites of Philippine domestic animals. *Philip J Sci* 1925;28:11.
77. Africa CM, Refuerzo PG, Garzia EY. Observation on the life cycle of *Gnathostoma spinigerum*. *Phillip J Sci* 1936;59:513–21.
78. Arambulo PV. *A Summary of Zoonoses in th*[illegible]*ilippines*. The American Veterinary Epidemiology Socie[illegible]71:29.
79. Tudor RC, Blair E. *Gnathostoma spinigerum*: An unusual cause of ocular nematodiasis in the Western Hemisphere. *Am J Ophthalmol* 1971;72:185–90.
80. Eduardo SE. Food-borne parasitic zoonoses in the Philippines. *Southeast Asian J Trop Med Publ Health* 1991;22:16–22.
81. Samarasinghe S, Perera BJ, Ratnasena BG. First two cases of gnathostomiasis in Sri Lanka. *Ceylon Med J* 2002;47:96–7.
82. Nawa Y. Historical review and current status of gnathostomiasis in Asia. *Southeast Asian J Trop Med Public Health* 1991;22:217–9.
83. Ando K. Gnathostomiasis in Japan. In: Arizono N, Chai JY, Nawa Y, Takahashi Y, eds. *Asian Parasitology, vol. 1: Food-Borne Helminthiasis in Asia*. Japan: FAP Journal, 2005:231–9.
84. Kim YK. A study on *Gnathostoma* (1) An investigation into the geographical distribution of larvae on the second-third stage in Gyengsang Nam do. *Bull Fusan Natl Univ (Natur Sci)* 1973;15:111–6.
85. Sohn WM, Lee SH. The first discovery of larval *Gnathostoma hispidum* (Nematoda: Gnathostomatidae) from a snake host, *Agkistrodon brevicaudus*. *Korean J Parasitol* 1998;36:81–9.
86. Han ET, Park JH, Shin ER et al. Surface ultrastructure of the advanced third stage larvae of *Gnathostoma nipponicum* found in the republic of Korea. *Proceedings of First International Meeting of Gnathosomosis*, Mexico 2002:78.
87. Lee SH, Hong ST, Chai JY. Description of a male *Gnathostoma spinigerum* recovered from a Thai Woman with meningoencephalitis. *Korean J Parasitol* 1988;26:33–8.
88. Chai JY, Han ET, Shin EH et al. An outbreak of gnathostomiasis among Korean emigrants in Myanmar. *Am J Trop Med Hyg* 2003;69:67–73.
89. Bae EY, Koh BK, Kim JW. A case of human gnathostomiasis successfully treated with ivermectin. *Ann Dermatol (Korea)* 2006;18:33–6.
90. Yang JH, Kim M, Kim ES et al. Imported intraocular gnathostomiasis with subretinal tracks confirmed by western blot assay. *Korean J Parasitol* 2012;50:73–8.
91. Lo Re V 3rd, Gluckman SJ. Eosinophilic meningitis due to *Gnathostoma spinigerum*. *J Infect* 2002;45:117–20.
92. Kim JH, Lim H, Hwang YS et al. *Gnathostoma spinigerum* infection in the upper lip of a Korean woman: An autochthonous case in Korea. *Korean J Parasitol* 2013;51:343–7.
93. Scholz T, Uhlirova M, Ditrich O. Helminth parasites of cats from the Vientiane province, Laos, as indicators of the occurrence of causative agents of human parasitoses. *Parasite* 2003;10:343–50.
94. Jongthawin J, Intapan PM, Sanpool O et al. Molecular phylogenetic confirmation of *Gnathostoma spinigerum* Owen, 1836 (Nematoda: Gnathostomatidae) in Laos and Thailand. *Folia Parasitol (Praha).* 2016;63:002.
95. Stowens D, Simon G. Gnathostomiasis in Oneida County. *N Y State J Med* 1981;81:409–10.
96. Kagen CN, Vance JC, Simpson M. Gnathostomiasis. Infestation in an Asian immigrant. *Arch Dermatol* 1984;120:508–10.
97. Horohoe JJ, Ritterson AL, Chessin LN. Urinary gnathostomiasis. *JAMA* 1984;25:255–6.
98. Norcross WA, Johnson BN, Ganiats TG et al. Urinary gnathostomiasis in a Laotian refugee. *J Am Board Fam Pract* 1992;5:533–5.
99. Chabasse D, Cauchy AC, de Gentile L et al. [Human gnathostomiasis manifested by cutaneous larva migrans syndrome. Apropos of a case]. *Bull Soc Pathol Exot Filiales.* 1988;81:326–31. [Article in French]
100. Hennies F, Jappe U, Kapaun A et al. Gnathostomiasis: Import from Laos. *J Dtsch Dermatol Ges* 2006;4:414–6.
101. Khin T. Intra-ocular gnathostomiasis. *Br J Ophthalmol* 1968;52:57–60.
102. Yu CY, Lin CL, Liu JH. *Gnathostomiatic endophthalmitis-*case report. *Chin J Ophthalmol PRC* 1984;23:374–81.
103. Jung BK, Lee JJ, Pyo KH et al. Detection of *Gnathostoma spinigerum* third-stage larvae in snakeheads purchased from a central part of Myanmar. *Korean J Parasitol* 2008;46:285–8.
104. Rojekittikhun W. Gnathostomiasis in Thailand. In: Arizono N, Chai JY, Nawa Y, Takahashi Y, eds. *Food-Borne Helminthiasis in Asia*. *Asian Parasitology*. Vol 1. Japan: FAP Journal, 2005:241–59.
105. Jongthawin J, Intapan PM, Sanpool O et al. Three human gnathostomiasis cases in Thailand with molecular identification of causative parasite species. *Am J Trop Med Hyg* 2015;93: 615–8.
106. Eamsobhana P, Wanachiwanawin D, Roongruangchai K et al. Genetic diversity of infective larvae of *Gnathostoma spinigerum* (Nematoda:Gnathostomatidae) in freshwater swamp eels from Thailand. *J Helminthol* 2016;28:1–5.
107. Hoa LV, Ai NV, Luyen TV. Gnathostomes et gnathostomose humaine au Viet-Nam. *Bulletin Pathologie Exotic* 1965;58: 118–24.
108. Vinh NQ. Clinical features of gnathostomiasis in adult. *H.C.M.C. Med Magaz* 2001;1:100–2.
109. Hoan NH, Pham Y, Luyen TV et al. Cerebromyelitis caused by *Gnathostoma* sp., a review of 4 cases detected at Choray Hospital. *H.C.M.C. Med Magaz* 2001;1:100–2.
110. Xuan LT, Rojekittikhun W, Punpoowong B et al. Case report: Intraocular gnathostomiasis in Vietnam. *Southeast Asian J Trop Med Public Health* 2002;33:485–9.

111. Le Rouk PL. *Gnathostoma spinigerum* in Northern Rhodesia. *Trans R Soc Trop Med Hyg* 1958;52:14.
112. Chhuon H, Sangkim K, Voeunthal Y. [Mobile edema of the face and neck followed by intraocular localization of *Gnathostoma spinigerum*]. *Bull Soc Pathol Exot Filiales* 1976;69:347–51. (in French)
113. Müller-Stöver I, Richter J, Häussinger D. [Infection with *Gnathostoma spinigerum* as a cause of eosinophilic oesophagitis]. *Dtsch Med Wochenschr* 2004;129:1973–5. (in German)
114. Heydon GM. Creeping eruption or larva migrans in North Queensland and a note on the worm *Gnathostoma spinigerum* (Owen). *Med J* 1929:1(18):583–91.
115. Olds RJ. *Gnathostoma spinigrum* (Owen, 1836) in North Queensland. *Australia Vet J* 1952;29:124.
116. Moorhouse DE, Bhaibulaya M, Jones HI. Suspected human gnathostomiasis in Queensland. *Med J Aust* 1970;2:250.
117. Bussaratid V, Dekumyoy P, Desakorn V et al. Predictive factors for *Gnathostoma* seropositivity in patients visiting the Gnathostomiasis Clinic at the Hospital for Tropical Diseases, Thailand during 2000–2005. *Southeast Asian J Trop Med Public Health* 2010;41:1316–21.
118. Witenberg G, Jacoby J, Steckelmacher S. A case of ocular gnathostomiasis. *Ophtalmologia* 1960;119:114.
119. Anderson RC. *Nematode Parasites of Vertebrates: Their Development and Transmission*. Wallingford: C.A.B. International, 1992:339–42.
120. Montero E, Montero J, Jose Rosales M et al. Human gnathostomosis in Spain: First report in humans. *Acta Trop* 2001;78:59–62.
121. Puente S, Gárate T, Grobusch MP et al. Two cases of imported gnathostomiasis in Spanish women. *Eur J Clin Microbiol Infect Dis* 2002;21:617–20.
122. Górgolas M, Santos-O'Connor F, Unzú AL et al. Cutaneous and medullar gnathostomiasis in travelers to Mexico and Thailand. *J Travel Med* 2003;10:358–61.
123. Oliván-Gonzalvo G. [Gnathostomiasis after a trip to China for international adoption]. *Med Clin (Barc).* 2006;126:758–9. (in Spanish)
124. Godoy-Gijón E, Belhassen-García M, Santos-Briz A et al. Migrating skin lesions in a Thai patient. *Enferm Infecc Microbiol Clin* 2012;30:479–80. (in Spanish)
125. Veraldi S, Carrera C, Pravettoni C et al. A case of suspected cutaneous gnathostomiasis. *G Ital Dermatol Venereol* 2000;135:363–5.
126. 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.
127. Ligon BL. Gnathostomiasis: A review of a previously localized zoonosis now crossing numerous geographical boundaries. *Semin Pediatr Infect Dis* 2005;16:137–43.
128. Del Giudice P, Cua E, Le Fichoux Y et al. Gnathostomiasis: An emerging parasitic disease? *Ann Dermatol Venereol* 2005;132(12):983–5. (in French)
129. Develoux M, Dekumyoy P, Baygon E et al. Imported gnathostomiasis acquired in Myanmar. *Médecine et Maladies Infectieuses* 2006;36:340–2.
130. Taniguchi Y, Hashimoto K, Ichikawa S et al. Human gnathostomiasis. *J Cutan Pathol*, 1991;18:112–5.
131. Komiya Y. "Changchiang edema": The review of research. *Igaku no Ayumi* 1965;52:78–9. (in Japanese).
132. Rusnak JM, Lucey DR. Clinical gnathostomiasis: Case report and review of the English-language literature. *Clin Infect Dis* 1993;16:33–50.
133. Seguchi K, Matsuno M, Kataoka H et al. A case report of colonic ileus due to eosinophilic nodular lesions caused by *Gnathostoma doloresi* infection. *Am J Trop Med Hyg* 1995;53:263–6.
134. Miyaoka Y, Sagawa Y, Harada H et al. Two cases of creeping eruption and ileus by *Gnathostoma doloresi* infection in Kenzan mountain system (in Japanese). *Rinsho Hifuka (Jpn J Clin Dermatol)* 1998;52:325–7.
135. Horino K, Kimura M, Shimokawa Y et al. A case report of small bowel ileus possibly caused by *Gnathostoma doloresi*. *Trop Med Health* 2007;35:351–3.
136. Prijyanonda B, Pradatsundarasar A, Viranuvatti V. Pulmonary gnathostomiasis; a case report. *Ann Trop Med Parasitol* 1955;49:121–2.
137. Miyamoto N, Mishima K, Nagatomo K et al. A case report of serologically diagnosed pulmonary gnathostomiasis. *Jpn J Parasitol* 1994;43:397–400.
138. Elzi L, Decker M, Battegay M et al. Chest pain after travel to the tropics. *Lancet* 2004;363:1198.
139. Parola P, Bordmann G, Brouqui P et al. Eosinophilic pleural effusion in gnathostomiasis. *Emerg Infect Dis* 2004;10:1690–91.
140. Intapan PM, Morakote N, Chansung K et al. Hypereosinophilia and abdominopulmonary gnathostomiasis. *Southeast Asian J Trop Med Public Health* 2008;39:804–7.
141. Diaz-Camacho SP, Ramos MZ, Torrecillas E et al. Clinical manifestation and immunodiagnosis of gnathostomiasis in Culiacan, Mexico. *Am J Trop Med Hyg* 1998;59:908–15.
142. Funata M, Custis P, de la Cruz Z et al. Intraocular gnathostomiasis. *Retina* 1993;13:240–4.
143. Mathews AS, Shafi T, Radhakrishnan N et al. Intraocular gnathostomiasis – A case report. *Kerala J Ophthalmol* 2011;23(3):306–8.
144. Saidul I, Harsha B, Dipankar D et al. *Gnathostoma* and gnathostomiasis in North East India: II. On the occurrence of an advanced third stage larva of *Gnathostoma spinigerum* Owen, 1836 in human eye with a description of its light microscopic morphology. *J Vet Parasitol* 2011;25:18–20.
145. Sujata DN, Renu BS. Intraocular gnathostomiasis from coastal part of Maharashtra. *Trop Parasitol* 2013;3:82–4.
146. Horii Y, Owhashi M, Fujita K, Nakanishi H, Ishii A. A comparative study on eosinophil and neutrophil chemotactic activities of various helminth parasites. *Parasitol Res* 1988;75:76–8.
147. Kanpittaya J, Sawanyawisuth K, Intapan PM et al. A comparative study of neuroimaging features between human neuro-gnathostomiasis and angiostrongyliasis. *Neurol Sci* 2012;33:893–8.
148. Sawanyawisuth K, Tiamkao S, Nitinavakarn B et al. MR imaging findings in cauda equina gnathostomiasis. *AJNR Am J Neuroradiol* 2005;26:39–42.
149. Giudice P, Dellamonica P, Durant J. A case of gnathostomiasis in a European traveller returning from Mexico. *Br J Dermatol* 2001;145:487–9.
150. Herman JS, Chiodini PL. Gnathostomiasis, another emerging imported disease. *Clin Microbiol Rev* 2009;22:484–92.
151. Suntharasamai P, Desakorn V, Migasena S et al. ELISA for immunodiagnosis of human gnathostomiasis. *Southeast Asian J Trop Med Public Health* 1985;16:274–9.

152. Dharmkrong-at A, Migasena S, Suntharasamai P et al. Enzyme-linked immunosorbent assay for detection of antibody to *Gnathostoma* antigen in patients with intermittent cutaneous migratory swelling. *J Clin Microbiol* 1986;23:847–51.
153. Mimori T, Tada I, Kawabata M et al. Immunodiagnosis of human gnathostomiasis in Ecuador by skin test and ELISA using *Gnathostoma doloresi* antigen. *Jpn J Trop Med Hyg* 1987;15:191–6.
154. Maek-A-Nantawat W, Bussaratid V et al. Diagnosis of gnathostomiasis by skin testing using partially purified specific antigen and total IgE levels. *Trans R Soc Trop Med Hyg.* 2014;108:71–6.
155. Maleewong W, Morakote N, Thamasonthi W et al. Serodiagnosis of human gnathostomiasis. *Southeast Asian J Trop Med Public Health* 1988;19:201–5.
156. Tapchaisri P, Nopparatana C, Chaicumpa W et al. Specific antigen of *Gnathostoma spinigerum* for immunodiagnosis of human gnathostomiasis. *Int J Parasitol* 1991;21:315–9.
157. Nopparatana C, Setasuban P, Chaicumpa W et al. Purification of *Gnathostoma spinigerum* specific antigen and immunodiagnosis of human gnathostomiasis. *Int J Parasitol* 1991;21:677–87.
158. Wongkham C, Maleewong W, Ieamviteevanich K et al. Antigenic components of *Gnathostoma spinigerum* recognized by infected human sera by two-dimensional polyacrylamide gel electrophoresis and immunoblotting. *Asian Pac J Allergy Immunol* 2000;18:47–52.
159. Anantaphruti MT, Nuamtanong S, Dekumyoy P. Diagnostic values of IgG4 in human gnathostomiasis. *Trop Med Int Health* 2005;10:1013–21.
160. Laummaunwai P, Sawanyawisuth K, Intapan PM et al. Evaluation of human IgG class and subclass antibodies to a 24 kDa antigenic component of *Gnathostoma spinigerum* for the serodiagnosis of gnathostomiasis. *Parasitol Res* 2007;101:703–8.
161. Intapan PM, Khotsri P, Kanpittaya J et al. Immunoblot diagnostic test for neurognathostomiasis. *Am J Trop Med Hyg* 2010;83:927–29.
162. Laummaunwai P, Intapan PM, Wongkham C et al. *Gnathostoma spinigerum*: Molecular cloning, expression and characterization of the cyclophilin protein. *Exp Parasitol* 2010;126:611–6.
163. Uparanukraw P, Morakote N, Harnnoi T et al. Molecular cloning of a gene encoding matrix metalloproteinase-like protein from *Gnathostoma spinigerum*. *Parasitol Res* 2001;87:751–7.
164. Janwan P, Intapan PM, Yamasaki H et al. Application of recombinant *Gnathostoma spinigerum* matrix metalloproteinase-like protein for serodiagnosis of human gnathostomiasis by immunoblotting. *Am J Trop Med Hyg.* 2013;89:63–7.
165. Janwan P, Intapan PM, Yamasaki H et al. A recombinant matrix metalloproteinase protein from *Gnathostoma spinigerum* for serodiagnosis of neurognathostomiasis. *Korean J Parasitol.* 2013;51:751–4.
166. Saenseeha S, Penchom J, Yamasaki H et al. A dot-ELISA test using a *Gnathostoma spinigerum* recombinant matrix metalloproteinase protein for the serodiagnosis of human gnathostomiasis. *Southeast Asian J Trop Med Public Health* 2014;45:990–6.
167. Caballero-García Mde L, Almeyda-Artigas RJ, Mosqueda-Cabrera MA et al. *Gnathostoma binucleatum*: Excretion-secretion antigen analysis obtained from advanced third-stage larvae in in vitro culture. *Exp Parasitol* 2005;110:140–5.
168. Kongkerd N, Uparanukraw P, Morakote N et al. Identification and characterization of a cathepsin L-like cysteine protease from *Gnathostoma spinigerum*. *Mol Biochem Parasitol* 2008;160:129–37.
169. Campista-León S, Delgado-Vargas F, Landa A et al. Identification of immunodominant peptides from *Gnathostoma binucleatum*. *Am J Trop Med Hyg* 2012;87:888–96.
170. 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.
171. 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;12;9:14.
172. Kraivichian P, Kulkumthorn M, Yingyourd P et al. Albendazole for the treatment of human gnathostomiasis. *Trans R Soc Trop Med Hyg* 1992;86:418–21.
173. Kraivichian K, Nuchprayoon S, Sitichalernchai P, Chaicumpa W, Yentakam S. Treatment of cutaneous gnathostomiasis with ivermectin. *Am J Trop Med Hyg.* 2004;71:623–8.
174. Ruiz-Maldonado R, Mosqueda-Cabrera MA. Human gnathostomiasis (nodular migratory eosonophilic panniculitis). *Int J Dermatol* 1999;38:56–7.
175. Janwan P, Intapan PM, Laummaunwai P et al. Proteomic analysis identification of antigenic proteins in *Gnathostoma spinigerum* larvae. *Exp Parasitol* 2015;159:53–8.