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TREATMENT OF CUTANEOUS GNATHOSTOMIASIS WITH IVERMECTIN

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Abstract. In a randomized open study, we compared the efficacy of a single dose of oral ivermectin (200 μg/kg) and oral albendazole (400 mg/day for 21 days) for the treatment of cutaneous gnathostomiasis. Thirty-one patients were randomly assigned to receive ivermectin (n = 17) or albendazole (n = 14). Thirteen of 17 patients who received ivermectin responded, 3 relapsed, and 1 was unresponsive (cure rate = 76%). Thirteen of 14 patients who received albendazole responded very well and did not relapse. Only one patient was unresponsive (cure rate = 92%; $P > 0.05$). No major side effects were observed in both groups. We concluded that a single dose of ivermectin (200 μg/kg) is less effective than albendazole (400 mg/day for 21 days) for treatment of cutaneous gnathostomiasis, but there was no statistically significant difference ($P > 0.05$).

INTRODUCTION

Gnathostomiasis is a disease in humans caused by the larval stage of roundworms in genus *Gnathostoma*. The disease has been commonly reported in China, Japan, Malaysia, India, Israel, Vietnam, the Philippines, and Thailand. It has also been frequently reported in South America and Mexico.[1–3] Thailand is the country that is most heavily infected, both in human and reservoir hosts.[4,5] Levinsen found the first case of human gnathostomiasis in 1889 in a Thai woman in Bangkok.[6]

In Thailand, the incidence of human gnathostomiasis is high. Each year, approximately 100–150 patients with suspected gnathostomiasis come to the Parasitology Clinic at Chulalongkorn Memorial Hospital in Bangkok. The worm usually migrates in subcutaneous tissue and causes an intermittent migratory swelling. In most cases, the symptoms are not serious, but the worm may migrate to vital organs such as the brain or eye, producing serious pathology, which may lead to serious complications and death.[7–10]

Surgical removal of the worm is considered the best treatment for cutaneous gnathostomiasis. However, it is rather difficult to obtain the parasite. Although various drugs have been tested, they have been shown to be ineffective against the worm.[11–14] A clinical study of albendazole for treatment of human gnathostomiasis was conducted with a dose of 400–800 mg/day for 21 days. This regimen showed cure rates (with no further swelling) of 93.9% and 94.1%.[15] However, side effects noted often after albendazole administration include gastrointestinal distress, headache, dizziness, increasing and reversible levels of hepatic enzymes, and transient reduction of the total leukocyte count.[16]

Ivermectin, the 22, 23-dihydroavermectin B1 derivative of avermectin B, is a semisynthetic macrocyclic lactone derived from the actinomycete *Streptomyces avermitilis*. Avermectin B results in the paralysis of nematodes by acting on the ion channels in cell membranes. Specifically, ivermectin causes an influx of negatively charged ions, leading to hyperpolarization of the affected cells and resulting in muscle paralysis.[17–19] This drug has been shown to be effective against many human tissue parasitic infections. During past decade, approximately six million people with onchocerciasis in more than 30 countries have been successfully treated with ivermectin. The drug is also extremely safe in humans.[20–23] A single dose (150–200 μg/kg) of ivermectin is also highly effective in the treatment of cutaneous larva migrans (creeping eruption), with cure rates of 100%. No major adverse effects have been observed.[24] The efficacy of ivermectin against larvae of *Gnathostoma* in rabbits and rats have shown more efficacy than other anthelmintic drugs.[25,26]

The main objective of this study was to compare the safety and efficacy of a single dose (200 μg/kg) of ivermectin with albendazole (400 mg), twice a day for 21 days, for the treatment of cutaneous gnathostomiasis.

MATERIALS AND METHODS

Patients. Thirty-one patients from the outpatient clinic of the Department of Parasitology at Chulalongkorn Memorial Hospital participated in the study. Informed consent was obtained from each individual. This study was reviewed and approved by the Ethics Committee of the Faculty of Medicine at Chulalongkorn University (Bangkok, Thailand). The criteria for a diagnosis of cutaneous gnathostomiasis were based on 1) presence of migratory swelling lasting at least two days; 2) absolute eosinophil counts > 500/mm^3; 3) stool examination results negative for other parasites; 4) presence of antibodies against a specific 24-kD antigen for *Gnathostoma spinigerum* by Western blot analysis; 5) a history of eating raw freshwater fish, crab, snake, bird, or chicken; and 6) a positive skin test result for *G. spinigerum*. A person was diagnosed with cutaneous gnathostomiasis if he or she satisfied criteria 1, 2, 3, and 4, plus criteria 5 or 6.

Patients were excluded if they 1) were less than 15 or more than 60 years old); 2) were pregnant or lactating; 3) had a chronic illness (such as liver disease, renal disease, diabetes, or were in an immunocompromised state); 4) were sensitive to benzimidazole or ivermectin; or 5) had taken any anthelmintic drug during the previous 14 days. After inclusion in the study, this information was obtained for each patient.

After providing informed consent, each patient was randomly assigned to receive either 200 μg/kg of ivermectin in a single dose, or 400 mg of albendazole, twice a day for 21 days. Clinical assessment, blood examination, and serology were evaluated before treatment and on days 14, 30, 60, 90, and 120. The response to treatment was defined as the complete disappearance of all signs and symptoms and the return of absolute eosinophil values to normal levels during the 60 days follow-up period. Relapse was defined as a reappearance of signs and symptoms following an initial response within 60 days after treatment. Unresponsive was defined as no im-

provement of all signs and symptoms, and an absolute eosinophil count that did not decrease within 14 days after treatment.

Patients who did not respond or relapsed after receiving ivermectin were subsequently given a double dose of ivermectin (200 μg/kg for two consecutive days). Patients who did not respond or relapsed after receiving albendazole were subsequently given a single dose of ivermectin (200 μg/kg). Surgical removal of the parasite was performed if possible.

Western blot. *Gnathostoma spinigerum* advanced third-stage larvae (L3) were obtained from livers of infected freshwater eels obtained from a local market in Bangkok. The worms were washed in 0.9% NaCl until free of blood and tissue debris and were pooled. A crude aqueous L3 extract was prepared by grinding the worms with alumina (Sigma, St. Louis, MO) in distilled water containing 0.1 mM phenylmethylsulfonylfluoride (Sigma), 0.1 mM tosyl-amide-2-phenylethyl-chloromethyl ketone (Sigma), and 10 mM EDTA at 4°C. After the alumina was removed by centrifugation at 250 × *g* for five minutes at 4°C, the worm suspension was extracted twice with ether at 4°C. The worm extract was centrifuged at 10,000 × *g* for 30 minutes at 4°C and the supernatant was removed. The sediment was resuspended in distilled water, sonicated at 4°C for 10 minutes, and centrifuged as in the previous step. The supernatants were pooled, dialyzed with distilled water, and kept at −20°C for further analysis.

Electrophoresis was performed in a vertical slab gel apparatus using the method of Laemmli and Favre[27] with some modifications. Briefly, a 4% acrylamide stacking gel and a 10% acrylamide separating gel were used. Samples containing approximately 30 μg of the L3 extract were boiled at 100°C for three minutes in 12% sodium dodecyl sulfate and 10% 2-mercaptoethanol before loading onto the gel. The separated protein bands were visualized by staining with Coomassie brilliant blue R (Sigma). For Western blot analysis, the resolved components were electroblotted onto a 0.45-μm nitrocellulose membrane (Bio-Rad Laboratories, Hercules, CA). After blotting, the unreacted sites on the membrane were blocked by soaking the strips in phosphate-buffered saline (PBS), pH 7.4, containing 0.5% gelatin, 3% bovine serum albumin (BSA) and 0.04% NaN_3 at 26°C for two hours with gentle rocking. The strips were then washed twice (10 minutes per wash) with washing buffer (0.05% Tween 20 in PBS) and treated with patient sera diluted 1:200 in PBS containing 0.2% gelatin, 0.2% BSA, and 0.04% NaN_3 (PBS-BSA) at 26°C for one hour with gentle rocking. The strips were washed four times (20 minutes per wash) with washing buffer and incubated with ^{125}I-labeled sheep anti-human immunoglobulins (Amersham International Pty, Little Chalfont, United Kingdom) in PBS-BSA ($2–5 \times 10^5$ cpm/mL) at 26°C for 30 minutes. The strips were washed with washing buffer, dried, and exposed to X-Omat RP films (Eastman Kodak, Rochester, NY) with light intensifying screens at −70°C for 24–28 hours.[28]

Skin test. A skin test for gnathostomiasis was performed for all patients. A crude somatic extract of L3 of *G. spinigerum* isolated from eels was used to prepare the test antigen.[29] Each patient was injected with 50 μL of antigen intradermally. The protein concentration of the antigen used was 50 μg/mL. A positive result was an immediate intradermal reaction.

RESULTS

Patient enrollment. The trial was a randomized open study. Thirty-one patients were enrolled in the study: 17 in the ivermectin group and 14 in the albendazole group. The characteristics of the patients are shown in Table 1. All statistical comparisons between these two groups at baseline were not significantly different. A flow diagram following the progress of the patients through the trial is shown in Figure 1. All patients were followed-up for 120 days.

Clinical outcomes. *Ivermectin group.* In this group, lesions disappeared after treatment in 13 (76.47%) of 17 patients. No recurrence occurred in these patients (Figures 1 and 2). However, of the remaining four patients, three relapsed on days 7, 11, and 35 (mean time = 17.8 days), respectively. Although the lesion disappeared in the fourth patient, he had persistent eosinophilia until day 60. All four patients received the second double dose of ivermectin (200 μg/kg for two consecutive days). After receiving the second treatment, one patient developed a creeping eruption at another site different from the previous lesion, and showed an erythematous plaque with linear lesion on the flexure area of the right wrist (Figure 3). A skin biopsy was performed. The section showed dense superficial and deep mixed inflammatory cell infiltration composed of lymphocytes, plasma cells, and eosinophils. A deeper biopsy was also performed; however, the parasite could not be detected. The histologic findings were supportive of the parasitic infection (Figure 4). The lesions disappeared within three days in all patients after the second treatment.

TABLE 1

Characteristics and clinical response of the two patient groups receiving ivermectin or albendazole for treatment of cutaneous gnathostomiasis

Characteristics	Ivermectin	Albendazole	Statistical significance (*P*)
No. of patients	17	14	
Age, years, mean (range)	27.53 (17–46)	32.79 (22–47)	NS (0.09)
No. of males	4	7	NS (0.22)
No. of females	13	7	NS (0.36)
Mean time since onset, days (mean duration of skin manifestation)	8.71	8.21	NS (0.89)
Number of episodes of symptoms before treatment	4.18	3.21	NS (0.88)
Clinical response in treatment groups, no. (%)			
Responsive	13 (76.48)	13 (92.86)	NS (0.21)
Unresponsive	1 (5.88)	1 (7.14)	NS (0.57)
Relapsed	3 (17.64)	0	NS (0.09)

NS = not significant.

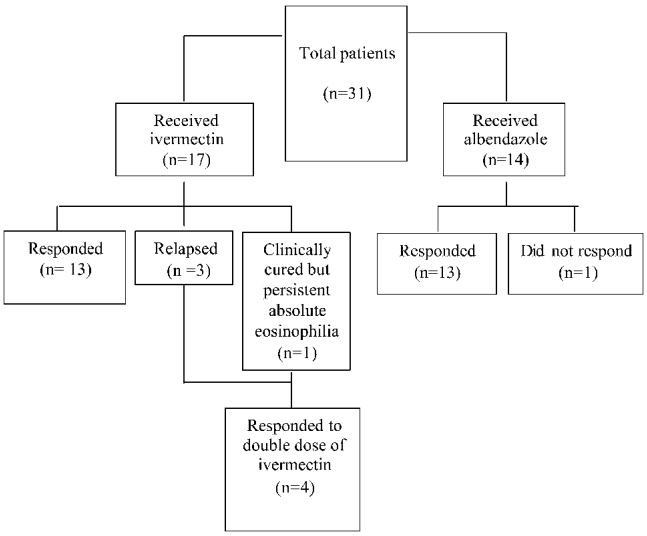

FIGURE 1. Flow diagram of the allocation of gnathostomiasis patients in the groups that received ivermectin or albendazole.

Albendazole group. In this group, lesions disappeared after treatment in 13 (92.8%) of 14 patients. No relapses occurred until day 120 after the first treatment. A lesion was persistent in one patient, with no decrease in the absolute eosinophil counts until day 14.The lesion in this patient was an erythematous plaque on right side of the mid-back (Figure 5). A skin excision biopsy was performed, and an immature adult worm of *G. spinigerum* was found at the edge of lesion (Figure 6). After removal of the worm, the lesion disappeared within two weeks. The histologic findings in this patient were supportive of parasitic infection. The effects of treatment are shown in Figure 1 and Table 1.

Duration of lesion clearance. In the responsive patients receiving ivermectin, the shortest duration of lesion clearance was 3 days and the longest was 40 days (mean = 6 days, mode = 3 days, 61.54%). The patient who had the longest lesion clearance time was better at each follow-up visit, and exhibited complete clearance at day 40. There was no relapse in this patient. For those who received albendazole, the shortest duration of lesion clearance was 3 days and the longest was 30 days (mean = 6.8 days). However, there was no statistically significant difference between the two treatment groups (P = 0.44). More than 50% of the patients receiving ivermectin showed no symptoms within three days of treatment, while symptoms were not observed until after five days in those who received albendazole ($P > 0.5$).

Local skin reactions after treatment. At the follow-up, 10 (58.8%) of 17 patients in the ivermectin group and 4 (28.5%) of 14 in the albendazole group showed local skin reaction after treatment by the first week. The reactions included more swelling, more erythema, more pain, or more itching at the previous lesion, and new lesions such as creeping eruption and migratory swelling. However, the occurrence of reactions after treatment in both the ivermectin and albendazole groups did not show a correlation with the clinical outcomes. There was no statistically significant difference (P = 0.21) between two treatment groups.

Absolute eosinophil counts. The mean ± SD absolute eosinophil count before treatment was 1.49 ± 0.24 (range = 0.6–4.25) × $10^3/\mu l$ in the ivermectin group and 1.06 ± 0.26 (range = 0.6–4.14) × $10^3/\mu l$ in the albendazole group. However, these results did not show a statistically significant difference (P = 0.25). In the group receiving ivermectin, the mean absolute eosinophil counts showed a statistically significant decrease on the first visit after treatment and decreased further to normal levels within a month ($P < 0.05$). The same result was found in the group receiving albendazole ($P < 0.05$). However, the mean absolute eosinophil counts in both groups were not significantly different at all times after treatment. The mean absolute eosinophil counts before and after treatment are shown in Figure 7.

Serology. Arithmetic means of enzyme-linked immunosorbent assay (ELISA) optical density (OD) values for detection of specific IgG antibody to *G. spinigerum* in both groups decreased slowly after treatment ($P > 0.05$). The mean OD values of both groups before and after treatment (at day 60 and 120) were not significantly different ($P > 0.05$).

Side effects. No major adverse effect was reported during interviews or at any follow-up visit in both groups.

DISCUSSION

We studied 31 cases of cutaneous gnathostomiasis at Chulalongkorn Memorial Hospital. Detection of the worm in the skin, although rarely found, is important to confirm the diagnosis of cutaneous gnathostomiasis. During 1986–1990, 127 patients were diagnosed with cutaneous gnathostomiasis but only 17 patients (13.39%) were found to have cutaneous worms (Kraivichian P, Yingyaud P, unpublished data). Thus, in most cases, only a presumptive diagnosis is made based on the clinical ground alone when the worm cannot be identified. In this study, diagnostic criteria were derived from our previous study, with some modifications to ensure more accuracy. First, cutaneous swelling should persist at least two days so that urticaria and angioedema can be readily be ruled out.[30] Second, absolute eosinophil counts > 500/mm^3 were used instead of eosinophil percentage since eosinophil percentages can give a false-positive result.[31] Recently, IgG subclasses have been shown to provide high sensitivity and specificity in the diagnosis of infection with *G. spinigerum* infection.[32] However, immunoblotting for specific *Gnathostoma* antigens was used. This test has a specificity and sensitivity of 100% and is currently the gold standard for the diagnosis of cutaneous gnathostomiasis.[33]

It was less likely that the clinical diagnosis could be other helminthic infections (e.g., strongyloidiasis, toxocariasis) since the skin manifestation from these parasites is a creeping eruption, and not subcutaneous migratory swelling, and the lesions will disappear within 12–18 hours.

The majority of the study population were women. It is still unclear why more women were infected in this study than men. However, Thai women tend to consume more uncooked fish products than men. In addition, since Thai women usually do the cooking, they have a greater chance of exposure to fish infected with *G. spinigerum* and infection via penetration of the skin.

Gnathostoma larvae can enter the human host via skin route; thus, merely skin contact with fish carrying the larvae may cause cutaneous gnathostomiasis.[33] Residence of central and northeastern Thailand were more commonly infected

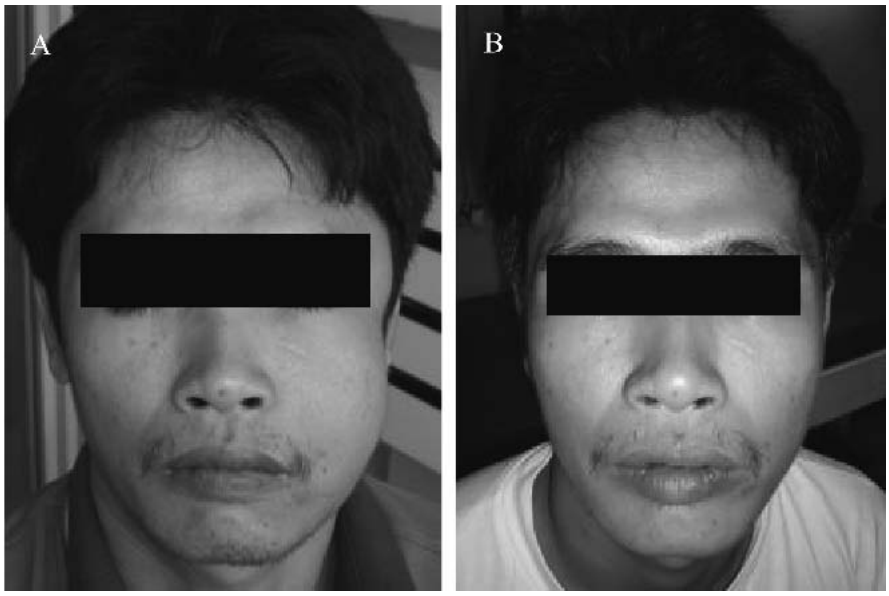

FIGURE 2. **A**, A 36-year-old man with gnathostomiasis who presented with subcutaneous migratory swelling in the left cheek for nine days. **B**, After treatment with ivermectin, the symptoms improved and cleared in three days without any recurrence.

with *Gnathostoma* than those from other regions of the country because of the habit of consuming raw or inadequately cooked freshwater fish or other intermediate hosts, such as chicken, snail, or frog, which contain infective larvae of the parasite. Almost all patients reported a history of consuming raw or partially cooked fish, especially a kind of fermented food called Pla-ra or Pla-som. The food has been found to be contaminated with many living infective larvae of *G. spinigerum*.[34] More than 70% of the cutaneous lesions were on the extremities, especially the upper extremities, possibly because the worm usually inhabits in the bulky muscular parts the human body. A similar finding was also reported in a study from Mexico.[35]

In terms of treatment, clinical cure of cutaneous gnathostomiasis is not defined only by the disappearance of the cutaneous lesion. In a previous report,[15] disappearance of cutaneous swelling was found in both the albendazole treatment and placebo groups with a similar duration (mean duration = 6.8 days), which is comparable to that found in this study. Therefore, serologic tests and absolute eosinophil counts were also important indicators of clinical cure in this study. An animal study showed that 2–4 weeks after infection, rats containing *Gnathostoma* L3 showed elevated peripheral eosinophil counts that gradually returned to normal after five weeks because the larvae were encysted in rat muscles and thus caused no eosinphilic stmulation.[36] However, data in humans is lacking, and *Gnathostoma* larva encystment has never been observed in human host. *Gnathostoma* worm infested in human tissue can cause eosinophilia throughout the course of infection. Therefore, increases and deceases in absolute eosinophil counts can be used as accurate markers in following-up treated patients. Despite one patient who was treated with ivermectin and had persistent elevation of the absolute eosinophil counts until day 60, the clinical symptoms eventually disappeared. One explanation is that the migration of worm

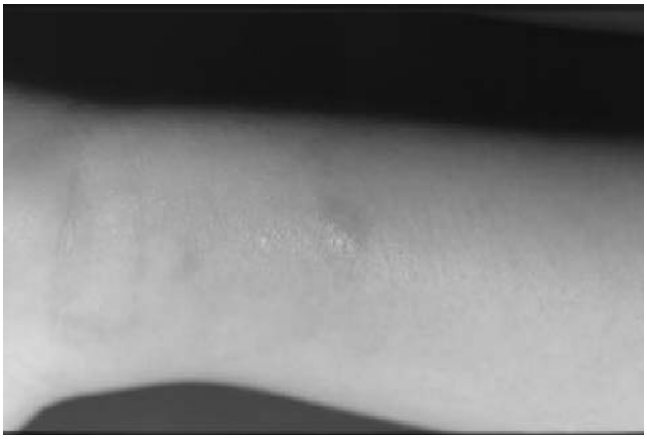

FIGURE 3. Creeping eruption that developed in a patient with gnathostomiasis after receiving a second treatment with ivermectin.

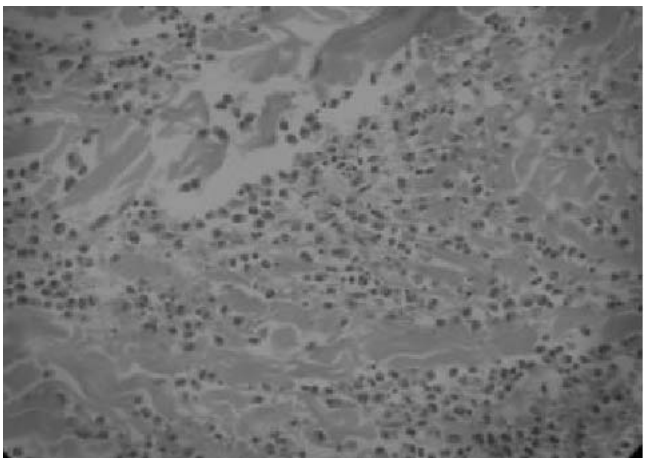

FIGURE 4. High-power view of the infiltration of eosinophils in a patient with gnathostomiasis (hematoxylin and eosin stained, original magnification × 40).

FIGURE 5. Erythematous plaque on the right side of the mid-back of a patient with gnathosotomiasis.

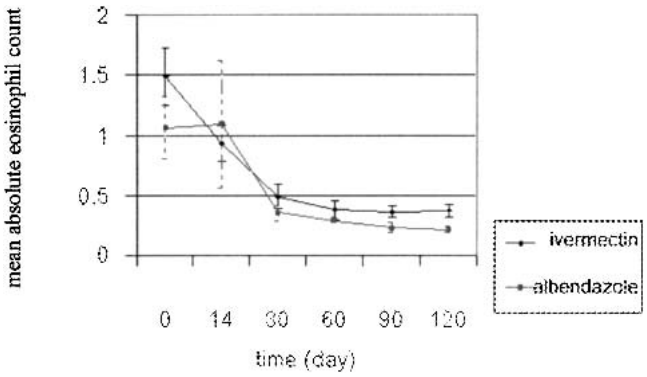

FIGURE 7. Mean ± SD absolute eosinophil counts ($\times 10^3/\mu l$) before and after treatment in both groups of patients.

into the deeper tissue may continue to activate eosinophils, but without any evidence of cutaneous manifestation. The ELISA titer was not appropriate for short term follow-up because a change in the test result takes longer to obtain, as found in our study. It is possible that the absence of a decrease in the titer can predict clinical failure. However, our data failed to demonstrate such a prediction.

Treatment with ivermectin showed a lower cure rate than treatment with albendazole (76% versus 92%), but this difference was not statistically significant ($P > 0.05$). Major side effects from drug treatment were not reported during the interview or at any follow-up sessions. Patients who received ivermectin experienced more flaring of the cutaneous lesions (aching, itching, creeping, and swelling) than those who received albendazole (58% versus 28%). However, cutaneous flares did not show a correlation with cure of the disease ($P < 0.05$). Two patients in the albendazole group and one patient in the ivermectin group showed migration of worms to the upper dermis. This indicated that the drugs were able to stimulate worm migration, which is consistent with a previous report showing that 3 of 41 patients treated with albendazole had migration of worms to the upper dermis.[37] The explanation for this phenomenon is still unknown. One hypothesis involves the effect of the drug in changing the worm millieu in the skin, causing them to migrate. A similar mean duration of clearance of six days was found in both groups. Sixty percent of the patients who received ivermectin showed clearance in three days (8 of 17) while 50% of the albendazole group showed clearance in seven days.[38]

FIGURE 6. Whole body of an immature adult worm of *Gnathostoma spinigerum* removed from the edge of lesion from a patient with gnathosotomiasis.

Although ivermectin showed a lower cure rate than albendazole, it has some advantages over albendazole and appears to be safer. Ivermectin could be given once a day at a lower dosage than albendazole and therefore provided better compliance. Side effects of ivermectin were expected to be lower since a lower dosage was required. Increasing the ivermectin dosage to 200 μg/kg/day was likely to result in a better cure rate and was presumably a better oral medication for gnathostomiasis than albendazole.

The results of our study were similar to those of a previous study,[39] but our cure rate with ivermectin was lower (76% versus 92%). This may be due to the different inclusion criteria. We also used absolute eosinophil counts instead of percentage of eosinophils because it would provide more accurate values. In addition, we used a different definition of response to treatment (cure). Since our previous data showed that eosinophil counts would decrease to normal levels within day 60 after treatment in curative patients, we used 60 days as the cut-off point.

In conclusion, we observed that cutaneous gnathostomiasis could be treated with a single dose of ivermectin (200 μg/kg/day) or albendazole (400 mg/day) for 21 days. Single-dose ivermectin is as safe and effective for treatment of cutaneous gnathostomiasis as albendazole. Slightly more relapses were observed in the ivermectin group, but this result was not statistically significant. Treatment with ivermectin seemed to be associated with more disease flaring than with albendazole, but this observation was also not statistically significant. A comparable duration of clearance of six days was found in both groups, and no major side effect was found in either group. Patients who failed to respond to single-dose ivermectin (200 μg/kg/day) or had relapses responded well to double-dose ivermectin (200 μg/kg/day for two days). Better compliance can be expected for treatment with ivermectin and dose adjustments may improve cure rates. We expect that a larger sample size will verify the efficacy of ivermectin. Individualized dosages of ivermectin (e.g., a second double dose) may increase the cure rate to near 100%, thus making ivermectin a good drug of choice for treatment of gnathostomiasis. Al-

though we have concerns that treatment with ivermectin might worsen occult ocular and neurologic gnathostomiasis, there has had no report of such finding. However, in suspicious cases, ocular and neurologic examinations should be performed.

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