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▣ CASE REPORT

Cutaneous Gnathostomiasis with Recurrent Migratory Nodule and Persistent Eosinophilia: a Case Report from China

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Abstract: The present study reports a human case of cutaneous gnathostomiasis with recurrent migratory nodule and persistent eosinophilia in China. A 52-year-old woman from Henan Province, central China, presented with recurrent migratory reddish swelling and subcutaneous nodule in the left upper arm and on the back for 3 months. Blood examination showed eosinophila (21.2%), and anti-sparganum antibodies were positive. Skin biopsy of the lesion and histopathological examinations revealed dermal infiltrates of eosinophils but did not show any parasites. Thus, the patient was first diagnosed as sparganosis; however, new migratory swellings occurred after treatment with praziquantel for 3 days. On further inquiring, she recalled having eaten undercooked eels and specific antibodies to the larvae of *Gnathostoma spinigerum* were detected. The patient was definitely diagnosed as cutaneous gnathostomiasis caused by *Gnathostoma* sp. and treated with albendazole (1,000 mg/day) for 15 days, and the subsequent papule and blister developed after the treatment. After 1 month, laboratory findings indicated a reduced eosinophil count (3.3%). At her final follow-up 18 months later, the patient had no further symptoms and anti-*Gnathostoma* antibodies became negative. Conclusively, the present study is the first report on a human case of cutaneous gnathostomiasis in Henan Province, China, based on the past history (eating undercooked eels), clinical manifestations (migratory subcutaneous nodule and persistent eosinophilia), and a serological finding (positive for specific anti-*Gnathostoma* antibodies).

Key words: *Gnathostoma spinigerum*, gnathostomiasis, migratory subcutaneous nodule, serodiagnosis, albendazole, China

INTRODUCTION

Gnathostomiasis is a food-borne parasitic zoonosis caused by the third stage larvae of the genus *Gnathostoma*. Human beings are an accidental and abnormal host for *Gnathostoma*. Human infection is mainly resulted from eating raw or undercooked intermediate hosts (e.g. fish, eels, and loaches) or paratenic hosts (e.g. crustaceans, freshwater fish, and mammals) containing the third-stage (L3) larvae [1]. The larvae cannot mature in humans and keep migrating in the skin, subcutaneous tissues, or other organs. Gnathostomiasis is characterized by intermittent creeping eruptions and/or migrating swellings and eosinophilia; larval migration to other tissues (visceral larva migrans) can result in a serious consequence [2]. If untreated, gnathostomiasis may remit and recur several times until death of the larvae up to 12 years after infection [3].

The endemic foci of gnathostomiasis have been predominantly distributed in Japan and Southeast Asia, particularly Thailand, but the disease is also endemic in Cambodia, Laos, Myanmar, Indonesia, the Philippines, and Malaysia [4]. Human cases have also been reported in India, Australia, Brazil, and parts of South Africa, and it has been regarded as an emerging disease [5]. Imported human cases of gnathostomiasis were also reported in the Republic of Korea [6,7]. Recently, it has been known that this disease is endemic in the Pacific region of Mexico [8]. In China, gnathostomiasis occurred sporadically in 23 Provinces, Autonomous regions, or Municipalities. Until the year 2012, 57 cases of gnathostomiasis have been reported in the Chinese literatures [9]; however, only 1 case was reported in English [10]. Also, to our knowledge, no human cases of gnathostomiasis have been reported in Henan Province, China [11]. Accordingly, the present study reports for the first time a human case of cutaneous gnathostomiasis in Henan Province, China.

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CASE RECORD

A 52-year-old lady from Zhengzhou city of Henan Province, central China, presented to the Parasitology Department of Zhengzhou University on 22 August 2011. She had a 3-month history of recurrent appearance of migratory reddish swelling in the upper arm and on the back. The initial lesions appeared on the left side of the back and subsequent lesions were observed in the left upper arm. These swellings were characterized by a migrating edema with a cord-like shape and pruritic nodules. The swellings reappeared in a different area close to the previous one after about 10-15 days of subsidence of the initial lesion. She was an officer, denied a history of travel abroad, and never had any pets, nor had a history of intimate exposure to stray cats, dogs, or other domestic animals. On physical examination, the migratory linear subcutaneous nodule was observed on the left side of her back.

Initial laboratory testing revealed a normal white blood cell count of 4,900, but with high eosinophilia (21.2%, 1,040 eosinophils/ml). The chemistries, including liver function tests, were within normal limits. The serum specific antibodies against tissue-dwelling parasites (*Paragonimus skrjabini*, *Schistosoma japonicum*, metacestode of *Taenia solium*, and *Trichinella spiralis*) were assayed by ELISA or immunofluorescence test (IFT), and shown to be negative. However, anti-sparganum antibodies were positive by ELISA using excretory-secretory (ES) antigens of *Spirometra erinacei* spargana [12]. The optical density (OD) of the serum samples from this patient was 0.46, whereas the positive (patients with sparganosis) and negative (normal persons) controls were 0.55 and 0.21, respectively. A fecal examination was negative for parasites. Serum samples were sent to the Third Affiliated Hospital of Sun Yat-Sen University and anti-sparganum antibodies were also positive. Skin biopsy was performed at 1 cm of the anterior end of the nodule near the axilla on the left side of the back on 28 August 2011. Worms were not observed during the operation. Histopathologic examination of the biopsy samples revealed a dense superficial and deep dermal infiltrate of eosinophils and neutrophils but did not show any parasites. One day after the skin biopsy, multiple migrating subcutaneous nodules reappeared on the patient's back (Fig. 1A). Subcutaneous sparganosis was diagnosed on the basis of clinical manifestations and results of serologic tests, and the patient was treated with praziquantel (75 mg/kg/day in 3 doses for 3 days) [13]. However, 1 day after the treatment, new migratory swellings occurred in the left upper arm

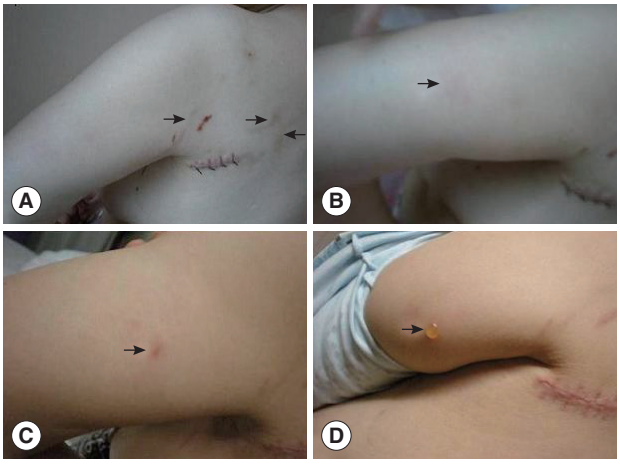

Fig. 1. Cutaneous gnathostomiasis in a 52-year-old woman from Henan Province, central China. (A) Multiple migrating subcutaneous nodules (arrows) on the back, occurring 1 day after skin biopsy. The suture wound is visible. (B) Migrating swellings (arrow) in the left upper arm, occurring 1 day after treatment with praziquantel (75 mg/kg/day in 3 doses for 3 days). (C) The subsequent papule (arrow) emerging 1 day after beginning of the treatment with albendazole (1,000 mg/day, twice daily). (D) The subsequent blister (arrow) developing on the 9th day of treatment with albendazole.

(Fig. 1B); anti-sparganum antibodies were re-assayed and remained positive. On further inquiring, she recalled that she had eaten undercooked eels. Thus, gnathostomiasis was highly suspected on this history, together with symptoms such as recurrent migratory subcutaneous nodule and eosinophilia. The serum sample was sent to the Institute of Parasitic Diseases of Zhejiang Academy of Medical Sciences, dot immunogold filtration assay (DIGFA) using soluble antigens of the third stage larvae (L3) of *G. spinigerum* presented by Mahidol University in Thailand showed that anti-*Gnathostoma* antibodies were strongly positive, and anti-sparganum antibodies were only weakly positive.

The patient was treated with albendazole (1,000 mg/day, twice daily for 15 days). One day after the beginning of the treatment, the migrating swellings in the left upper arm tended to be confined and a papule developed (Fig. 1C); subsequent blister emerged on the 9th day of treatment (Fig. 1D). However, parasites were not found by examination of the puncture samples of the blister. Two days after the treatment, the papule disappeared but anti-*Gnathostoma* antibodies were still positive; Laboratory testing revealed a white blood cell count of 5,800, with 5.5% eosinophils. After 1 month, laboratory findings showed an almost normal eosinophil count (3.3%). At her final follow-up at 18 months, the patient had no further symp-

toms and anti-*Gnathostoma* antibodies became negative.

DISCUSSION

Although 13 species of the genus *Gnathostoma* have been reported to date, 5 of them such as *Gnathostoma spinigerum*, *G. nipponicum*, *G. hispidum*, *G. doloresi*, and *G. binucleatum* infect humans [5,6]. Out of these species, *G. binucleatum* is a major etiologic agent of gnathostomiasis in endemic areas of America, especially in Mexico and Venezuela. *G. spinigerum* is the most common and important agent of gnathostomiasis in China. Out of 57 cases with gnathostomiasis reported in China during 1918-2012, 54 cases were caused by *G. spinigerum*, 2 by *G. hispidum* and 1 by *G. doloresi* [9]. A previous survey showed that 23 species of animals (6 cyclops, 13 fish, 2 frogs, and 1 each of snake and bird) served as the first or second intermediate host, or a paratenic host of *G. spinigerum* in 3 provinces (Jiangsu, Anhui, and Jiangxi) of China [14].

The triad of eosinophilia, migratory lesions, and obvious exposure risk are highly suggestive of the diagnosis of gnathostomiasis. The exposure risk usually include consumption of raw or undercooked fish (in particular, swamp eels and loaches), or meat of intermediate or paratenic hosts. The definite diagnosis was established by isolation of larvae from the lesions, but this is often difficult in migratory skin lesions. The detection rate of larvae in skin biopsy specimens was only 24-34% of the cases [15]. The skin biopsy in our patient reported failed to show the worms. Treatment with albendazole may promote outward migration of the larvae to the dermis, and stimulate development of a papule or pseudo-furuncle containing the larva. Biopsy of a papule or pseudo-furuncle subsequent to treatment increases the likelihood of demonstrating the larva on skin biopsy specimens [16]. Regrettably, our patient disagreed with a second skin biopsy. With introduction of antigens from L3 larvae of *G. spinigerum*, the serodiagnosis of gnathostomiasis became more convenient and efficient, although cross-reactivity with other parasitic infections remained a problem. Our patient was first misdiagnosed as sparganosis because of a cross-reactivity with in *S. erinacei* sparganun antigens. Tapchaisri et al. [17] found that a specific L3 antigen with a molecular mass of 24 kDa had the greatest specificity and reacted only with sera from the patients with gnathostomiasis sera and not with those from other parasitic infections. Hence, immunoblot is now regarded as the most valuable serologic test and can be used as a confirmatory test of gnathostomiasis when specific antibodies to 24 kDa component of *G. spinigerum* L3 larvae were detected. Although recommended dose of albendazole for gnathostomiasis is 400 mg/day for 21 days [18], our patient was cured with a shorter course of albendazole (1,000 mg/day for 15 days) treatment.

Although *Gnathostoma* larvae were not found in the skin biopsy of our patient, the patient was diagnosed as cutaneous gnathostomiasis according to the following evidences: the history of eating undercooked eels, typical clinical manifestations (recurrent migratory subcutaneous nodule), persistent eosinophilia, specific anti-*Gnathostoma* antibodies, and a cure by albendazole. The excellent therapeutic response to albendazole can differentiate it from sparganosis because albendazole has no obvious efficacy for treating sparganosis [19]. This case is most likely be caused by *G. spinigerum* which is the predominant agent of gnathostomiasis in China. Because clinicians outside of high endemic areas are unfamiliar with the disease, and therefore diagnosis is often missed or prolonged. The classic triad of intermittent migratory swellings, persistent eosinophilia, and a history of eating raw freshwater fish should alert physicians to the possible diagnosis of gnathostomiasis.

Recently, some Chinese people have the habit of eating raw fish; sashimi was often served in restaurants and hotels. In addition, some inhabitants like to eat quick-fried eels or scalded eel fillets. If the fillet was too large and the time of scalding was insufficient, the temperature in the fillet center would not be sufficient to kill the larvae. Recently, L3 of *Gnathostoma* spp. have also been detected from wild swamp eels sold at the market in Henan and Zhejiang Provinces (http://zjnews.zjol.com.cn/05zjnews/system/2011/10/28/017949925. shtml). In Thailand, the infection rate of farmed and wild eels with *G. spinigerum* was 10.2% and 20.4%, respectively [20]. Moreover, swallowing live loaches have become a folk remedy in some areas of China since some inhabitants believe the live loaches to have a medicinal role for treating diseases. Gnathostomiasis caused by swallowing live loaches was reported recently in Taiwan [21]. Gnathostomiasis cases resulted from ingestion of native loaches or loaches imported from Korea or mainland China were also reported in Japan [22]. *Gnathostoma* larvae were found in imported Chinese loaches in Korea [23]. To prevent human *Gnathostoma* infection, the government, public health officials, and medical practitioners should be aware of misdiagnosis of zoonotic gnathostomiasis. The best strategies for preventing gnathostomiasis are to educate people to only consume fully cooked meat, especially avoiding raw and un-

dercooked freshwater fish and loaches in endemic areas.

In conclusion, we report here a case of cutaneous gnathostomiasis in Henan Province, China based on the history of eating undercooked eels, recurrent migratory subcutaneous nodule, persistent eosinophilia, specific anti-*Gnathostoma* antibodies, and cure by albendazole. Our study presents a risk of *Gnathostoma* infection by consumption of undercooked freshwater fish; therefore, fish inspection for *Gnathostoma* larvae should be carried out for ensuring food safety and public health.

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