

Acute Abdominal Pain with Hypereosinophilia in Two Patients

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Abstract

Two cases of previously healthy young adults presented with acute severe epigastric pain, malaise, low grade fever and enlarged and tender liver. The most striking laboratory abnormality was hypereosinophilia, leading to leukocytosis. Both of them had history of frequently eating raw or undercooked fresh water fishes. The diagnosis of visceral larva gnathostomiasis were made by the typical clinical manifestations and hypereosinophilia supported by a dietary history. This syndrome is different from the other well known forms of adult gnathostomiasis because it is caused by visceral migration of many infective larvae of *G. spinigerum*. Albendazole and prednisolone were given with a satisfactory result. Gnathostomiasis is not uncommon in Thailand and neighbouring countries. Unaware clinicians and surgeons may misdiagnosed hence the patients may be subjected to inappropriate treatment including unnecessary operations. (*J Infect Dis Antimicrob Agents* 1999;16:73-7.)

First case presentation (HN 186859)

A previously healthy 22-year-old Thai woman was admitted to Vichaiyut Hospital on March 4, 1998 with complaint of acute abdominal pain for 5 days prior to the admission. The epigastric pain was rather sudden, severe, continuous and sharp in character. It was not related to meal nor position. The patient experienced anorexia, nausea and vomiting, associated with loose stool 2-3 times a day. She also had low grade fever and extreme malaise.

The patient came from Ubon Ratchathani province in the Northeast of Thailand to work in Bangkok in the last 3 years. She frequently eats raw or undercooked animal flesh, such as, Pla Ra (raw fresh water fish), Nam (raw pork), Nam Tok (raw beef), Som Fuk (raw fresh water fish). She just ate "Som Fuk" and "Nam" 1 week prior to this illness. She denied previous history of cutaneous migratory swelling and abdominal pain.

Physical examination revealed an oral temperature of 37.5°C, blood pressure 120/80 mmHg, pulse rate 100/min and respiratory rate 16/min. She

looked weak and moderately distress, well conscious, not pale and no jaundice. The only positive physical findings were moderately tenderness at the epigastrium and 1 FB enlarged liver below right costal margin with mild tenderness. The spleen was not palpable.

Laboratory investigation showed hemoglobin 11.5 g/dl, hematocrit 34.9 percent, white blood cell count 35,000 cells/mm³, neutrophil 8 percent, lymphocyte 15 percent, monocyte 1 percent, eosinophil 76 percent, platelet 210,000 cells/mm³, blood urea nitrogen 8 mg/dl, alkaline phosphatase 164 U/L (control <104 U/L), SGOT 27 U/L (control <40 U/L), SGPT 56 U/L (control <40 U/L), GGT 52 U/L (control 6-32 U/L), negative HIV antibody and negative stool examination. Chest X-rays and ultrasound of upper abdomen were negative. The diagnosis of visceral larva gnathostomiasis was made and she was treated with albendazole 400 mg twice daily plus prednisolone 60 mg a day. All symptoms subsided within few days and she was discharged on March 6, 1998. Peripheral blood test on March 25,

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1998 revealed hematocrit 39 percent, hemoglobin 12.5 g/100 ml wbc 6,000 mm³, neutrophil 28 percent, lymphocyte 60 percent, monocyte 2 percent and eosinophil 10 percent. The treatment was continued for 2 weeks and she has been asymptomatic up to August 20, 1998.

Second case presentation (HN 198741)

A previously healthy 23-year-old Thai man came to Vichaiyut Hospital on March 16, 1998 because of acute epigastric pain for one day. The pain was rather severe, continuous and sharp in character associated with nausea without vomiting. It was not related to the meals nor position. He had some loose stools 2-3 times per day. The initial diagnosis of acute peptic ulcer was made and appropriate drugs were given. Two days later, he again came to the clinic with the same symptoms and this time he was given an analgesic injection. The pain was improved only temporarily and he had to come 3 more times to get analgesic injections. On March 24, 1998 he was referred to a gastroenterologist for further investigations. During this period he complained of coughing, low grade fever and malaise. He however had normal appetite and had no weight loss. Physical examination revealed an oral temperature of 36.9°C, pulse rate 80/min, blood pressure 110/70 mmHg and respiratory rate 16/min. The patient is thin, good consciousness, not pale and no jaundice. The only positive finding was soft and mild to moderate tenderness at the epigastrium. Bowel sound was normal. Liver and spleen were not palpable.

Laboratory investigation revealed hemoglobin 14.8 g/dl, hematocrit 43.4 percent, white blood cell count 22,400 cells/mm³, neutrophil 28 percent, lymphocyte 13 percent, monocyte 2 percent, eosinophil 57 percent, platelet 199,000/mm³, Hb typing showed HbAA₂ (HbA 95.9, HbA₂ 4.1, HbF 1.2), blood urea nitrogen 9 mg/dl, cholesterol 153 mg/dl, alkaline phosphatase 47 U/L (control <110 U/L), SGOT 45 U/L (control <40 U/L), SGPT 23 U/L (control <40 U/L), GGT 16 U/L (control <11-50 U/L), amylase 65 U/L (control <90 U/L) urinalysis was normal, stool examination revealed positive occult blood with few white blood cells and red blood cells. Parasitic ova was not found. Serum HIV antibody was negative, urine porphyria was negative. Chest X-rays and upper GI study were normal. Ultrasound of upper abdomen showed abnormal liver parenchyma without focal

mass but spleen was prominent.

After the above investigations were made this patient discussed his illnesses with the first patient who has been working in the same institute. He realized that their symptoms were most similar. He then came to the out patient clinic on April 10, 1998 and requested to be treated similarly. He was then referred to an infectious disease specialist who treated the first case and the diagnosis of visceral larva gnathostomiasis was confirmed.

Additional epidemiological information revealed he is a native of Chiang Mai province in the North of Thailand who has come to work in Bangkok for 2 years. He has been eating raw or undercooked animal flesh especially raw fresh water fishes so frequent that he could not remember the specific dates. He denied previous history of migratory cutaneous swelling nor similar abdominal pain. He was then treated with 400 mg twice daily of albendazole plus 60 mg of prednisolone a day for 2 weeks. All the symptoms subsided. Subsequent blood tests on April 15, 1998 showed hematocrit 44 percent, hemoglobin 14.4 g/dl, white blood cell count 10,000 cells/mm³, neutrophil 34 percent, lymphocyte 61 percent, atypical lymphocyte 1 percent, monocyte 3 percent and eosinophil 1 percent. He had been followed at the clinic up to August 15, 1998 and he was asymptomatic through out.

DISCUSSION

Eosinophilia is the presence of eosinophil more than 500 cells per microliter of blood. It is commonly seen in many clinical settings such as allergic diseases and allergic reaction to drugs, helminthic infections, collagen vascular diseases and some malignancies.¹ Hypereosinophilic syndrome is an uncommon features of eosinophilia which is usually presented with absolute eosinophil count as high as 20,000 cells per microliter or above. It represents a group of disorders, including loeffler's endocarditis, eosinophilic leukemia and idiopathic hypereosinophilic syndrome. The hypereosinophilic syndrome presents with prolonged hypereosinophilia of unknown etiology and it usually associates with various organs dysfunction including the heart, central nervous system, kidneys, lungs, gastrointestinal tract and skin.

In Thailand and other tropical countries, the most common cause of eosinophilia is probably helminthic infections. Hookworm, strongyloidiasis,

toxocariasis, gnathostomiasis, trichinosis, trichuriasis, filariasis, schistosomiasis, echinococcosis and cysticercosis are commonly associated with some degree of eosinophilia. However the extreme eosinophilia that leads to leukocytosis is well documented in some tissue parasitism such as toxocariasis (visceral larval migrans), gnathostomiasis, trichinosis, strongyloidiasis as well as filariasis (tropical pulmonary eosinophilia or eosinophilic lungs).

These two reported cases were previously healthy young adults who presented with symptoms of acute severe epigastric pain, low grade fever and malaise. Physical examination revealed tenderness at the epigastrium and hepatomegaly. The most striking laboratory abnormality was a marked increase in eosinophil counts leading to leukocytosis. The degree of eosinophilia in the second case is less pronounced than the first patient because the blood test was done at the later date of illness. Both patients had history of frequently eating undercooked flesh, particularly fresh water fishes. The first patient was properly treated at the first week of symptoms therefore no pulmonary symptoms was observed. The second case experienced pulmonary symptoms but the chest X-rays was initially negative and it has not been repeated. Both patients responded well to the anthelmintics and corticosteroid. These features were the important clues in the diagnosis of visceral larva gnathostomiasis. The differential diagnosis of other causes of hypereosinophilia were rule out by history of acute onset of symptom, no persistent pulmonary involvement (tropical pulmonary eosinophilia), negative stool examination (i.e., strongyloidiasis, schistosomiasis), no myalgia or myositis (trichinosis) and no history of intimate contact with dogs or cats (toxocariasis).

Gnathostomiasis is a disease caused by larvae or immature adult of *G. spinigerum*.^{2,3} In nature other species of *Gnathostoma* namely *G. hispidum*, *G. nipponicum* and *G. doloresi* have been found in different animal hosts. Their roles in human infection are most unusual. Many countries in Asia especially Thailand^{3,4} and Japan⁵ are endemic areas of this disease. The disease has also been reported from some countries of the nonendemic areas, i.e., America, Europe and Australia, but most of the patients were asian immigrants.

Dogs and cats are the definitive hosts of *G. spinigerum*.²⁻⁴ The mature adult worms reside in

stomach of the definitive hosts and they pass eggs into water and soil. Copepods or Cyclops is the first intermediate hosts. Man is an accidental host, typically acquires the infection by eating raw or undercooked flesh of second intermediate hosts. There are great varieties of second intermediate and transported hosts in nature, mostly aquatic and amphibian such as fishes, shrimps, snails, copepods, frogs, snakes etc. It had been found also in birds, pigs, chicken, bears etc. The favorite dishes of raw fishes namely "Som Fuk" or "Pla Ra" in Thailand and "Sashimi" in Japan are accounted as common infective sources for most reported cases of human gnathostomiasis. Transmission also possibly occurs *via* skin penetration when the skin contacts with infected flesh. Ingestion of copepods infected with third stage larvae in the natural pond or canal water may also transmit the parasite.

A well known clinical manifestation of gnathostomiasis is migratory swelling of the skin and underlying soft tissue. The other clinical presentation is an internal organ involvement presented as migrating pneumonia or pleural effusion,^{6,7} tumor mass in internal organs such as bowel wall,⁸⁻¹¹ urinary bladder,^{12,13} ocular^{14,15} and cerebrospinal involvement.¹⁶⁻²⁰ Only a single immature or mature adult worm was recovered from these patients.

The syndrome of visceral larva gnathostomiasis (VLG) caused by many infective larvae is not generally known. In 1967, Punyagupta S. and Juttijudata P. first reported the VLG as abdomino-pulmonary hypereosinophilic syndrome,²¹ by presented a group of five patients who developed symptoms after sharing the same dish of "Som Fuk". They presented with rather severe acute epigastric pain, low grade fever and malaise similar to our patients. Some patients had vomiting or hematemesis. One had symptom and sign of partial intestinal obstruction. Two of them had enlarged and tender liver. Pulmonary involvement including chest pain, non productive cough and abnormal chest X-rays either pleural effusion or transient migrating pneumonia mostly on the right lung were seen in 3 out of 5 patients. In the second case of this report, he also had non productive cough but the single chest X-rays was negative. If the X-rays was repeated at an interval prior to the treatment we might detect some abnormalities. Those five patients had leukocytosis (upto 65,000/mm³) and hypereosinophilia (ranged from 40-60%). In these 2 cases they had leukocytosis;

35,000 and 24,000/mm³ and extreme eosinophilia of 76 percent and 56 percent respectively.

The diagnosis of VLG bases on the characteristic clinical syndrome, hypereosinophilia in peripheral blood, and a recent dietary history of raw or undercooked fleshes of intermediate hosts.^{22,23} The immunological tests include immediate skin hypersensitivity, precipitin, radioimmunoassay, gel diffusion, indirect hemagglutination, immunoprecipitation reaction and immunozyme test, using extract of *G. spinigerum*, are not routinely done because of the limitation by the cross reactions to other parasites.²⁴⁻²⁶ The diagnosis of VLG is not always easy if the clinician is not aware of this syndrome. This usually leads to unnecessary investigations and delayed treatment similar to the second case. Some patient may be subjected to improper treatment including unnecessary operation for the treatment of acute abdomen. In fact based on the life cycle of *G. spinigerum* visceral larval migration occurs in every gnathostomiasis patient but it may be mild and unrecognized because they are infected by just one or few larvae.

The curative treatment of gnathostomiasis is by surgical removal of the worm but it is rarely feasible. The evaluation of the effect of anthelmintic drugs in the treatment of gnathostomiasis is quite difficult because the disease is self limited and it may take months or years before another episodes will develop. Besides it may be a new infection because it is less likely for most patients to change their eating habit. Several anthelmintic drugs including diethyl carbamazine, metronidazole,²⁷ thiabendazole,²⁸ quinine,²⁹ chloroquine, bithinol, levamisole,^{30,31} mebendazole,³² praziquantel³³ have been on trial without success. The only drug that had undergone double blind-placebo control trial and showed unique but unexplainable effect is albendazole at a dosage of 400 mg twice daily for two to three weeks.³⁴⁻³⁶ During the treatment the adult worm tends to migrate outward to the superficial part of the skin and it may be removed by an excisional biopsy or by fishing with a needle.³⁵ However there has been no information on the effectiveness of albendazole to the infective third stage larvae. It may kill the larvae in the tissue. In these 2 cases, albendazole 400 mg twice daily plus high dose of prednisolone 60 mg per day were used for 2 weeks with a satisfactory clinical outcome. In the untreated cases

from the previous report²¹ all clinical symptoms subsided spontaneously in about 6-12 weeks. Two out of their 5 patients developed migratory cutaneous swelling 4 and 6 months later. The eosinophilia gradually decreased but persisted as long as 4 months. In these 2 reported cases, after starting the treatment all symptoms subsided within few days and extreme eosinophilia returned to normal within 2 weeks. During the 4-5 months of follow-up these patients are still doing well without any manifestations of gnathostomiasis. This strongly suggests the effectiveness of the treatment regimen.

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