Intestinal Anisakiasis

First Case Report from North America

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The first case of intestinal anisakiasis in North America is described. This parasitic disease is recognized as a public health hazard in Japan and Europe. Man becomes infected with a larval form of the nematode Anisakis by consuming raw or undercooked fish containing the parasite. Typically, patients present with acute abdominal syndromes. Clinical and roentgenographic features may cause confusion with regional enteritis. Histologically, a striking eosinophilic granulomatous reaction occurs. Anisakiasis is most effectively prevented by discouraging the consumption of raw fish.

Anisakiasis, sometimes called "herring worm disease," has been recognized as a public health problem in Japan [1] and the Netherlands [2] for about 10 years. An acute abdominal syndrome may occur after the ingestion of raw marine fish containing nematode larvae of the genus Anisakis. Migration of the parasite into the wall of the stomach, small intestine or, less commonly, the colon elicits a striking eosinophilic granulomatous tissue response. Although some raw fish are consumed in the United States and anisakid larvae have been identified in market fish [3], no prior cases of intestinal anisakiasis have been reported in this country. However, sporadic descriptions of "eosinophilic granuloma" or similar gastrointestinal lesions of undetermined etiology, have appeared in the literature [4].

We describe a case of intestinal anisakiasis which occurred in Boston; this represents the first fully documented occurrence of this disorder in North America.*

CASE REPORT

A 32 year old Swedish born housewife was admitted to the Peter Bent Brigham Hospital on July 20, 1972. The onset of her illness was difficult to assess. She had been in good health except for occasional, nonradiating pain in the right lower abdominal quadrant which she had noted for more than 2 years and which she disclaimed as relating to her menstrual cycle. During the previous year, the pain had become increasingly severe. Four days prior to admission she experienced intermittent cramping abdominal pain of increasing severity, associated with fever and diarrhea. An appendectomy had been performed at age 7.

Since childhood it had been the patient's custom to eat raw herring and salted salmon. The latter were prepared at home. After coming to the United States in 1967, she had continued to prepare salted fish for her family during the 4 years she lived in California and, more recently, in Massachusetts where she had lived for about 6 months. She routinely sampled pieces of fish during the salting process and recalled doing this at Easter time, about 3 months prior to admission.

* This case has been reported previously in the radiology literature. The similarity of the roentgenographic features of anisakiasis to those of regional enteritis have been discussed in detail in the article by Richman and Lewicki [5].
Physical examination revealed a well developed, well nourished woman in no acute distress, complaining of pain in the right lower abdominal quadrant. Temperature was 99.6°F, pulse rate 100 beats/min, respirations 20/min and blood pressure 125/90 mm Hg. Bowel sounds were normal. There was no abdominal rigidity or rebound tenderness, but there was tenderness and guarding, and a palpable mass in the right lower quadrant. Pelvic and rectal examinations were not remarkable except that the right ovary was not felt.

Laboratory data included a normal urinalysis and negative urine culture. Hematocrit value was 35 per cent, hemoglobin level 12.1 g/100 ml and white cell count 19,000/mm³ with 72 per cent neutrophils, 2 per cent eosinophils, 25 per cent lymphocytes and 1 per cent basophils. Blood urea nitrogen, blood glucose, electrolytes, amylase, lactic dehydrogenase (LDH) and serum glutamic oxaloacetic transaminase (SGOT) were within normal limits. Chest roentgenogram and electrocardiogram were normal. Films of the kidney, ureter and bladder were suggestive of a right lower quadrant mass. An x-ray series of the upper gastrointestinal tract followed by a barium enema showed the terminal ileum, cecum and ascending colon to be narrowed, fixed and distorted, but not obstructed. The ileocecal valve appeared thickened. Cecal distention was not evident. The roentgenologic changes resembled those seen in regional enteritis, i.e., Crohn's disease (Figure 1), and have been described in greater detail in another report [5].

Following admission the patient's temperature rose to 101°F, and on the 2nd hospital day she underwent laparotomy. Preoperative diagnoses included ruptured ovarian or mesenteric cyst, and regional enteritis. At operation, the abdominal cavity appeared normal except in the area of the cecum where a large hard mass was fixed posteriorly. Operative findings suggested either a malignant tumor or inflammatory changes, possibly related to granulomatous colitis. A right colectomy and ileocolostomy were performed. A frozen section demonstrated an inflammatory process of the cecum involving the submucosa, muscularis and pericolic fat with necrotizing granulomas and a prominent eosinophilic infiltrate.

The postoperative course was uneventful except for a transient temperature elevation. The patient was discharged on the 8th postoperative day. Six months after discharge she remarked that she felt well; in fact, better than at any time during the 2 years prior to surgery. She had abandoned the practice of eating raw fish.
Pathologic Findings

The resected specimen consisted of terminal ileum, cecum and proximal ascending colon. The mucosa of the terminal ileum, ileocecal valve and cecum was edematous, with obliteration of mucosal folds. There was no mucosal ulceration or hemorrhage. In the area of the cecum, there was an indurated mass which measured 9 cm in greatest dimension (Figure 2). The cecal wall was firm and nonresilient, measuring up to 2.8 cm in thickness. Upon sectioning, the layers of colonic wall were somewhat indistinct and contained scattered abscesses (Figure 2, insert). Within the pericolic fat there was prominent induration with areas of abscess formation measuring up to 1 cm in the greatest dimension. A thin fibrinous exudate was present on the serosal surface.

Microscopically, the most striking feature was necrotizing eosinophilic granulomatous inflammation which involved the wall of the cecum and extended from the submucosa through the muscularis, into the pericolic tissue (Figure 3). In the latter area, there was prominent fibroblastic proliferation. The mucosa of the ileum and cecum was intact but contained small foci of acute inflammation and abundant eosinophils in the lamina propria. The granulomas present in the colonic wall were characterized by irregular areas of central necrosis which contained eosinophils and eosinophilic material with peripheral palisading histiocytes and occasional multinucleated giant cells (Figure 4). Focally, a granulomatous response with occasional foreign body giant cells also involved lymphatics. One of the four regional lymph nodes showed necrotizing eosinophilic granulomatous inflammation, most marked in the subcapsular areas. Elsewhere, there was an intense eosinophilic infiltrate with a predilection for vessel walls and perivascular areas. The parasite was found in the pericolic tissue in the midst of the inflammatory response, located 5 mm or more below the serosal surface (Figure 5).

Material from the surgical specimen was submitted to one of us (M.D.L.) for further study and identification of the parasite. Portions of the parasite were found in two of many blocks of tissue taken from the resected portion of intestine. These blocks were sectioned completely, and the entire anterior part of the worm as well as portions of the posterior part were obtained in serial sections. Although the worm was obviously dead, the distinctive features of the body wall and digestive tract were evident. The larva was in the process of molting to the fourth stage and at some levels, the molted cuticle of the third stage could clearly be seen surrounding the body (Figure 6).

Following the criteria of Oshima [1] the worm resembled an Anisakis type I larva. At mid-body the worm was approximately 0.4 mm in diameter and there were about 60 to 90 muscle cells in each quadrant. The lateral chords were large, Y-shaped, with the nuclei extending to the base of the narrow stem (Figure 7). Although the intestine had obviously undergone degeneration, in some sections, it could be seen that it was composed of numerous tall columnar cells each of which had its nucleus located near the base. A ventriculus was present between the muscular portion of the esophagus and the anterior end of the intestine (Figure 8), but there was no evidence of an intestinal cecum or an esophageal appendix. At the level of the upper intestine the excretory cell was large and had a "banana-like" shape in cross section.

COMMENTS

In recent years numerous cases of acute abdominal syndrome caused by nematode larvae of the family Anisakidae have been recognized in man. The nematode larva responsible for some of these infections was initially identified as Eustoma rotundatum, but later was established as belonging to the genus, Anisakis [6]. In nearly all the cases reported from Japan and the Netherlands the etiologic agent has been identified as Anisakis type I larva [1,6]. Oshima [1]...
Figure 4. A, necrotizing eosinophilic granuloma in pericolic fat. Periphery of granuloma is comprised of palisading histiocytes with occasional multinucleated giant cells. In the necrotic central portion, there are abundant eosinophils, many of which are fragmented. Hematoxylin and eosin stain; original magnification X 80, reduced by 33 per cent. B, higher magnification of multinucleated giant cells at periphery of granuloma. Original magnification X 500, reduced by 33 per cent. C, higher magnification of palisading histiocytes at periphery of granuloma. The necrotic central portion of the granuloma is in the upper part of the photo. Original magnification X 500, reduced by 33 per cent.

Figure 5. Anisakis larva in pericecal fat. Eosinophilic infiltrate and organizing fat necrosis are present in surrounding tissue. Hematoxylin and eosin stain; original magnification X 90.
has concluded that the adult stage of this type of larva is A. simplex. In addition to the cases caused by Anisakis, larvae of the genus Terranova were recently identified as the etiologic agents in six cases of acute abdominal syndrome in Japan [7,8], and a larva of Contracaecum osculatum was reported to be the causative agent of eosinophilic granuloma of the intestine in one case in Germany [9].

The Anisakis type I larva, the one probably responsible for the present case, has been found in a much greater variety of fish in the North Pacific than has the larva of any other anisakid species. Fish known to harbor the larval parasite include chum, mackerel, cod, pollack, herring, whiting, bonito and pike. The parasite has also been found in squid. This larve is also common in fish making pelagic migrations in the North Atlantic and North Sea, particularly herring.

The life-cycle of A. simplex as described by Oshima [1] is as follows: Adult worms live in the stomach of various marine mammals, e.g., dolphins, porpoises, seals, sea lions and odontocete whales. Eggs of the nematode are passed in the feces of the host and develop to second-stage larvae in sea water. They are then eaten by crustaceans in which the larvae develop to the third stage. When fish or squid ingest the infected crustaceans, the larvae migrate into their tissues and develop to the advanced third stage in the body cavity or muscle. These larvae can be serially passed from one fish to another. The advanced third-stage larvae recovered from fish fillets and squid are usually 18 to 36 mm in length and 0.34 to 0.69 mm in width. When an infected fish is eaten by an appropriate marine mammal the larvae attach to the wall of the stomach and then undergo development to the fourth and finally to the adult stage.

In man, infections are acquired by eating raw fish containing the third-stage anisakid larvae. In Japan, raw (sashimi) or pickled (sunomono) marine fish are frequently eaten and provide a means of transmitting anisakid larvae. Raw or slightly salted herring ("green herring") represent the most common source of the infection in the Netherlands. Although anisakid larvae have been identified in marine fish marketed in the United States [3], no previous documented case of intestinal anisakiasis has been reported here. In three instances, anisakid larvae (of Phocanema or Terra-
nova type) have been recovered from man in North America, but in none was the abdominal syndrome typical of intestinal anisakiasis observed. In two cases, the worm was "coughed up" or removed from the throat following ingestion of raw or undercooked fish [10, 11]. In the third case, the worm was submitted as an unidentified intraperitoneal body which was noted incidental to the resection of an iliac artery aneurysm [12].

Infection rates and the incidence of anisakiasis appear to be low in relation to the number of larvae consumed. Host factors influencing the course of larvae have not been clearly defined. However, in Japan, where gastric achlorhydria is relatively common, gastric lesions with peripheral eosinophilia account for more than half of the cases [1]. The acute gastric syndrome is characterized by epigastric pain, nausea and vomiting 4 to 6 hours after ingestion of infected fish. Through the gastroscope, larvae may be seen penetrating the stomach mucosa and can sometimes be removed [13]. A more chronic form may last about 2 years and has been treated with partial gastric resection when conservative measures failed. In Europeans, the small intestine has been the site most frequently penetrated by the larvae [2]. An abdominal condition requiring surgery may be simulated as in the case we describe. Nausea, vomiting and lower abdominal pain usually occur about 7 days after ingestion of larvae. Abdominal tenderness is not well localized, and fever may be an inconsistent finding. Peripheral eosinophilia is not characteristic but leukocytosis is common. Laparotomy has usually been performed within a week of the onset of symptoms. The colon is less frequently involved, and a few cases have been described in which larvae migrated to the liver, pancreas, greater omentum or gallbladder [13].

The prognosis in intestinal anisakiasis is generally good in the absence of perforation and peritonitis. If the diagnosis can be established, conservative therapy consisting of hydration, antibiotics and possibly steroids has been recommended [1]. Immunologic diagnostic technics are not yet available. Laparotomy with resection of the involved area may be necessary, both for diagnostic and therapeutic purposes. In several instances, serious postoperative complications have occurred. Van Thiel et al. [2] described two patients who died with staphylococcal enteritis following partial ileal resection, and one patient who recovered after the development of peritonitis due to suture breaks forming through an edematous wall at the anastomotic site.

The pathologic features in reported cases of anisakiasis have been similar. Grossly, the mucosa of the stomach or intestine is generally intact, although small foci of hemorrhage or ulceration may occur. The intestinal wall is thickened and indurated due to edema and inflammation, simulating changes seen in regional enteritis. The parasite has most frequently been identified in the submucosa of the involved area of the gastrointestinal tract, but it may also penetrate the entire wall [1,14]. In the absence of histologic studies, it is possible that cases regarded clinically and roentgenologically as regional enteritis may actually represent intestinal anisakiasis. In Japan, a review of 1,531 cases of "acute and chronic regional enteritis" demonstrated histologic changes of necrotizing eosinophilic granulomatous inflammation compatible with intestinal anisakiasis in half the cases [1]. In a review of the world literature prior to 1964, Ashby et al. [4] found 89 cases of "eosinophilic granuloma" of the gastrointestinal tract and described two additional cases. The histologic features were similar to those found in anisakiasis. In most instances, an etiologic agent was not apparent.

The most striking pathologic features in anisakiasis are the marked edema, eosinophilia and granuloma formation which appear out of all proportion to the small size of the worm. These have been considered to be the consequence of a hypersensitivity reaction, and several reported cases suggest repeated infection [1]. In the case documented here, there was ample opportunity for prior infection with Anisakis larvae and possible sensitization. However, in other cases only one exposure was known, and the pathogenesis of the flare-up in Anisakis lesions has not been settled.

Another mechanism which may be important in producing the characteristic tissue response is that of a spreading lymphangitis. Of particular note in our case was the involvement of lymphatic channels, including the regional lymph nodes, by the eosinophilic and granulomatous response. Possibly, antigens released by the degenerating larva may be carried through the lymphatics of tissue which already had been sensitized by materials from the live parasite. As these substances progress along the course of lymphatics, they may elicit an eosinophilic granulomatous thrombolympthangitis. Obstruction of lymphatic channels by this mechanism may contribute to the marked edema. These features are reminiscent of those described in filariasis. In that parasitic disorder only mild change is produced by the intact worms. However, as the worms disintegrate a spreading type of thrombolympangitis which tends to be granulomatous occurs in the tissues near the degenerating worms [15]. Further studies of the pathogenesis of intestinal anisakiasis are indicated [16].

Prevention of anisakiasis is probably best affected by alerting the public to the hazards of eating raw fish. The evisceration of marine fish immediately
after being caught is probably of little practical value in preventing infection in man since most fish have larvae in the muscles as well as in or on the visceral organs [1]. The third-stage larvae of Anisakis can remain viable under various adverse conditions. For example, larvae can survive 51 days in vinegar, and 6 days in 10 per cent formalin at room temperature, 50 days at 2°C, and about 2 hours at -20°C. At 60°C, however, larvae survive only 1 second. Therefore, it has been recommended that prior to consumption, fish should be heated to at least 60°C, or frozen at -20°C for 24 hours. These measures have markedly reduced the number of cases of anisakiasis in the Netherlands.

With attention focused on the recognition of lesions in man and the investigation of the prevalence of pathogenic nematodes in market fish, it should be possible to define the public health importance of anisakiasis in the United States more precisely and to undertake measures for its control [17].

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REFERENCES