Anisakidosis: Perils of the Deep

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Anisakidosis, human infection with nematodes of the family Anisakidae, is caused most commonly by Anisakis simplex and Pseudoterranova decipiens. Acquired by the consumption of raw or undercooked marine fish or squid, anisakidosis occurs where such dietary customs are practiced, including Japan, coastal regions of Europe, and the United States. Severe epigastric pain, resulting from larval invasion of the gastric mucosa, characterizes gastric anisakidosis; other syndromes are intestinal and ectopic. Allergic anisakidosis is a frequent cause of foodborne allergies in areas with heavy fish consumption or occupational exposure. Diagnosis and treatment of gastric disease is usually made by a compatible dietary history and visualization and removal of the larva(e) on endoscopy; serologic testing for anti–A. simplex immunoglobulin E can aid in the diagnosis of intestinal, ectopic and allergic disease. Intestinal and/or ectopic cases may require surgical removal; albendazole has been used occasionally. Preventive measures include adequately freezing or cooking fish.

The ocean is a wilderness reaching round the globe, wilder than a Bengal jungle, and fuller of monsters.

—Henry David Thoreau, Cape Cod [1, p 188]

Anisakidosis, also known as whale worm, herring worm, seal-worm, and codworm disease, is the result of accidental human infection with the larval stage of several nematodes found in raw or undercooked marine fish or squid [2]. The first case of a young child vomiting an “ascarid” was described in 1876, but it was not until 1960 that the nematode was identified by Van Thiel in a patient from the Netherlands who had consumed raw herring [3–6]. More recently, anisakidosis has been increasingly identified as the cause of gastric, intestinal, and allergic syndromes in humans who have occupational exposure to or consume uncooked seafood.

Most human infections are caused by Anisakis simplex and Pseudoterranova decipiens (previously known as Phocanema decipiens). Other members of the family Anisakidae less commonly responsible for human infections include additional members of the A. simplex complex (eg, Anisakis pegreffi) and Pseudoterranova complex, as well as A. physeteris, Contra caecum species, and Thynnascaris species [7, 8]. The term anisakidosis refers to disease caused by any member of the family Anisakidae, whereas anisakiasis is caused by members of the genus Anisakis and pseudoterranovosis by the genus Pseudoterranova [8].

**EPIDEMIOLOGY**

Infection with these seafood-associated parasites occurs most commonly where people consume raw or inadequately cooked saltwater fish or squid [2]. Of the ~20,000 reported cases worldwide, >90% occur in Japan, primarily among adult men in coastal regions [8–10]. Most other cases have been described in coastal areas of Europe (especially the Netherlands, Germany, France, and Spain) [2, 9]. Although it has likely been greatly underdiagnosed and underreported, ~60 cases of anisakidosis have been described in the United States. During the past 2 decades, there have also been increasing reports from New Zealand, Canada, Brazil, Chile, and Egypt [8, 9, 11]. The rising incidence can be attributed to larger populations of the definitive hosts (as a result of greater regulatory controls over marine...
mammal exploitation), increased consumption of raw or lightly cooked food, and improved endoscopic diagnostic techniques [9].

Anisakid-infected marine life has been reported to exist in all major oceans and seas. One study found that 98% of the mackerel (Scomber species) and 94% of the cod (Gadus species) from a wholesale fish market in Japan carried the parasite [12]. In a fish market in Spain, 39.4% of fish were found to have anisakid infection; high rates also occur in fish off the coast of Scotland, Italy, and France [13, 14]. In the United States, there is a high prevalence of infection in wild salmon (Oncorhynchus species) [15]. Pseudoterranovosis rarely occurs in Japan and Europe. By contrast, it occurs more frequently in the United States and Canada, where P. decipiens is mainly transmitted by the Atlantic or Pacific cod, Pacific halibut (Hippoglossus stenolepis), and red snapper (Lutjanus campechanus) [8]. A substantial proportion of cod harvested in the Atlantic and Pacific Oceans is infected with P. decipiens (Figures 1 and 2) [8].

The particular source of human infection varies according to the fish-eating culture of the country [8]. In Japan, although sushi and sashimi are potentially high risk, fish commonly served in sushi bars tend to be less contaminated or even free of Anisakid nematodes, and sushi chefs are experts in identifying larval infestation [16]. The risk of infection is greater with less expensive marine fish (eg, cod, herring, and mackerel), and squid that are more frequently consumed in local restaurants or at home and not in sushi bars [16]. In the United States, one study found that there was a 1 in 13 chance of consuming an anisakid larva in salmon sushi (albeit all were dead from freezing) [17]. Other than sushi, high-risk dishes include salted and smoked herring in the Netherlands, Scandinavian gravlax, Hawaiian lomi-lomi (raw salmon), South American ceviche, and pickled anchovies (boquerones en vinagre) and raw sardines in Spain [8, 10].

**LIFE CYCLE**

Marine mammals serve as the primary host for A. simplex and P. decipiens. Although studies from the North Sea have demonstrated that A. simplex is able to select the host species with relatively low specificity, the primary hosts for Anisakis are cetaceans (dolphins, porpoises, and whales), whereas pinnipeds (seals, walruses, and sea lions) are the primary hosts for P. decipiens (Table 1) [9, 18, 19]. Adult worms in the primary host gastric mucosa release eggs that are passed in the feces; in seawater, the eggs are embryonated and form first stage (L1) and then free-living stage II larvae (L2) (Figure 3). Ingested by small crustacean first intermediate hosts (eg, krills), the parasite matures into L3 larvae that are subsequently consumed by marine fish or squid (second intermediate hosts). The L3 larvae migrate into the viscera and peritoneal cavity; the degree of migration into the fish musculature may depend on environmental conditions and/or the species of parasite and fish [9, 20]. They are often transferred from fish to fish along the food chain, and as a result, piscivorous fish may amass large numbers
of larvae [9, 21]. Ultimately, ingestion of infected fish or squid by a marine mammal (final host) leads to development of fourth-stage larvae and then adults. Human consumption of raw or undercooked second intermediate hosts results in infection. Although possible, larvae rarely develop in these accidental hosts; instead, by means of proteolytic enzymes, they usually become embedded in the gastric or intestinal mucosa and die [8, 20, 22].

CLINICAL FEATURES

The 4 major clinical syndromes in humans who experience symptomatic anisakidosis include gastric, intestinal, ectopic (or extra-gastrointestinal), and allergic disease. Gastric anisakidosis is heralded by the abrupt onset (generally 1–12 h after ingestion of raw fish) of severe epigastric pain, nausea, vomiting, and low-grade fever (Figure 4); occasionally, patients may have a rash [24]. Esophageal involvement has been reported [25]. The acute symptoms resolve within a few days, but infected persons may report persistent vague abdominal pain, nausea, and vomiting for weeks to months afterwards [2]. Untreated gastric disease may lead to chronic, ulcer-like symptoms possibly lasting for months and can be more difficult to diagnose [26]. Intestinal anisakiasis is characterized by intermittent or constant abdominal pain that starts 5–7 days after ingestion of the anisakid larvae. Infected individuals may develop ascites and/or peritoneal signs [7]. Intestinal infection and the subsequent inflammatory response predominantly occur in the terminal ileum, and colonic or jejunal involvement is less common [27]. Rare complications include small bowel obstruction, ileal stenosis, intussusception, intestinal perforation, and pneumoperitoneum [26, 28, 29].

Ectopic, extra-gastrointestinal, or intraperitoneal anisakiasis—less common complications—result from larval penetration of the stomach or intestine. This can lead to migration in the peritoneal cavity and, less commonly, the pleural cavity, mesentery, liver, pancreas, ovary, and subcutaneous tissue with pneumoperitoneum from gastrointestinal tract perforation [16, 26]. Chronic infection may present with mesenteric masses [30].

Anisakidosis is also associated with a strong allergic response. In reports primarily emerging from Spain, frequent fish consumption and occupational exposure (eg, fish processing) are associated with increased risk of an allergic response to *A. simplex* [8, 10, 31]. In fact, this pathogen is one of the more important causes of food allergies in the region and is particularly associated with anchovy consumption [8]. Generally ≤5 h (range, <1 h to >24 h) after the ingestion of infected fish, allergic symptoms develop [32, 33]. Manifestations range from urticaria and isolated angioedema to anaphylaxis, sometimes accompanied by gastrointestinal symptoms [32]. Allergic gingivostomatitis has also been reported [34].

The clinical manifestations of anisakidosis vary depending on where the person was infected and which anisakid caused infection. In Japan, gastric infection primarily occurs, whereas intestinal disease is more common in Europe [7]. Such differences may reflect reporting bias or differences in diagnostic methods [2, 10]. Infection with *P. decipiens* usually involves only the stomach and tends to be milder than disease due to *Anisakis* species. Infected persons experience the “tingling throat syndrome” from a worm crawling in the upper esophagus or oropharynx [35]. One of the primary symptoms is cough [36]. Asymptomatic infections with *Pseudoterranova* species may first come to medical attention when the patient coughs or vomits up a living or dead worm, often ≤48 h after the ingestion of infected fish.

DIAGNOSIS AND PATHOLOGIC FINDINGS

A history of recent consumption of raw or incompletely cooked fish or squid followed by the acute onset of epigastric or right lower quadrant abdominal pain provide important clues for the diagnosis of anisakidosis. Gastroscopic or surgical removal and examination of the larva provides a definitive diagnosis.

Table 1. *Anisakis simplex* and *Pseudoterranova decipiens*: Geographic Distribution, Host Species, Common Sources of Infection, and Clinical Syndromes

<table>
<thead>
<tr>
<th>Nematode</th>
<th>Geographic distributiona</th>
<th>Primary host species</th>
<th>Predominant second intermediate host species</th>
<th>Common food dishes</th>
<th>Clinical syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>A. simplex</em> complex</td>
<td>Japan, the Netherlands, northern Europe, United States, Korea</td>
<td>Dolphins, porpoises, whales</td>
<td>Pacific salmon, herring, anchovies, scad, hake, mackerel</td>
<td>Sushi, sashimi, salted or smoked herring, gravelax, boquerones, Hawaiian lomi-lomi, ceviche</td>
<td>Gastric, intestinal, ectopic, allergic</td>
</tr>
<tr>
<td><em>P. decipiens</em> complex</td>
<td>United States, Canada, Japan, Korea, Chile</td>
<td>Seals, walruses, sea lions</td>
<td>Atlantic and Pacific cod, Pacific halibut, red snapper, hake</td>
<td>Ceviche, cod</td>
<td>Oropharyngeal</td>
</tr>
</tbody>
</table>

* This list is not exhaustive but represents countries and regions where cases are more common. Predominant oceanic distribution for *A. simplex* includes the northern Atlantic, the northern Pacific, southern waters (below 30°N), and the Mediterranean Sea; the predominant oceanic distribution for *P. decipiens* complex includes northern Atlantic, Norwegian Sea, Baltic Sea, and Japanese waters.
Anisakid larvae are characterized by the presence of 3 bilobed lips, a ventral boring tooth, and large anterior excretory glands [37]. Most commonly, *A. simplex* larvae are white or milky colored, 19–36 mm in length, and 0.3–0.6 mm in width and have a blunt tail, long stomach, Y-shaped lateral cords, and no cecum. Compared with *A. simplex*, the larvae of *P. decipiens* are yellow-brown in color, longer (length, 25–50 mm), and wider (width, 0.3–1.2 mm); they have an anteriorly directed cecum [2].

Besides directly visualizing the worm(s) embedded in the gastric mucosa, endoscopy may reveal erythema, edema, severe erosive gastritis, a tumor-like nodule, or ulcerations (Figure 4) [38]. The burrowing or dead larva precipitates an intense Th2 immune response, and biopsy can show an early inflammatory infiltrate of eosinophils and lymphocytes in the mucosa and submucosa as well as phlegmon formation [8, 39, 40]. Although larvae may be found up to at least 6 days after consumption of seafood, if endoscopy is delayed, the worm may degenerate, be eliminated, or pass through the mucosa (resulting in ectopic disease) and no longer be visualized; the only signs may be thickened gastric folds and inflammation [24]. Chronic infection can result in abscess and/or granuloma formation in response to degenerating larvae [2, 7].

Radiographic findings depend on the site of infection. Thread-like filling defects and mucosal edema can be seen on barium studies in gastric infection. Intestinal infection can cause nonspecific, irregular bowel-wall thickening with a disappearance of Kerckring folds, mucosal edema, and luminal narrowing [16, 27, 41]. Computed tomography findings include lymphadenopathy, focal masses, and/or ascites [42]. Ascitic fluid obtained by paracentesis may demonstrate an eosinophilic predominance [27]. Gastric infection is frequently accompanied by leukocytosis; eosinophilia is seen more commonly in gastric than intestinal infection—particularly if the worm remains in place [8, 24, 27].

Although extraction of the larva(e) is the most direct method of diagnosis, serologic evaluation can be useful in intestinal, extra-intestinal, and allergic cases. Anti-*A. simplex* antibody detection can be performed by enzyme-linked immunosorbent assay (ELISA), latex agglutination, or other immunoassays [43].
Development of anti–A. simplex antibodies follows a typical progression in infected patients, starting with immunoglobulin (Ig) M to development of other isotypes (IgG, IgA, and IgE) during the first month after initial infection. Persons with allergic anisakidosis often have high levels of anti-A. simplex IgE. The results of such assays may be difficult to interpret, however, given that some crude assays are cross-reactive with other parasites, including Ascaris species, Toxocara canis, and nonrelated animals, such as insects (eg, German cockroach) or crustaceans (eg, shrimp) [5, 44, 45]. Furthermore, asymptomatic persons who frequently consume raw fish may also have elevated anti-A. simplex IgE levels, as can those with intestinal (but not allergic) anisakid infection [33, 44]. More specific tests are under investigation [46, 47]. In light of the existing limitations with the assays, it has been suggested that the diagnosis of allergy to A. simplex should be based on the following criteria: a compatible history of allergic reactions after consumption or exposure to fish, a positive immediate-type hypersensitivity skin-prick test result, elevated specific anti-A. simplex IgE levels, and a lack of reaction to fish proteins on skin testing [10]. Multiplex polymerase chain reaction methods have been developed for identification of specific marine nematodes species in fish, but these are not available for human use [48, 49].

DIFFERENTIAL DIAGNOSIS

Given the acute presentation, gastric anisakidosis can be misdiagnosed as peptic ulcer disease, gastritis, or a vanishing “gastric tumor” [7]. Because of the vague symptoms associated with intestinal infections, the differential diagnosis is broad and includes appendicitis, ileitis, diverticulitis, eosinophilic gastroenteritis (from systemic vasculitides and hyper eosinophilic syndrome), cholecystitis, colonic tumor, and inflammatory bowel disease. Infected persons may be diagnosed at the time of appendectomy for presumed appendicitis, and intestinal obstruction from anisakidosis can mimic other obstructive lesions [50]. Extraintestinal infections can be confused with acute peritonitis, tuberculous peritonitis, and pancreatic cancer.

TREATMENT

Early endoscopic extraction is the preferred treatment of gastric anisakidosis unless the larva is spontaneously regurgitated; delayed removal may result in larvae embedding into the submucosa. Surgical removal of the larvae is occasionally required for management of intestinal or extraintestinal infections, especially if complications such as intestinal obstruction, appendicitis, or peritonitis occur. If the diagnosis of intestinal anisakidosis can be established without the need for an invasive procedure, then conservative, supportive therapy will often lead to clinical resolution. Limited evidence suggests that albendazole (400–800 mg daily for 6–21 days) is effective therapy [16, 51, 52].

PREVENTION

The best protection against anisakidosis is to educate the public about the dangers of eating raw fish and to recommend avoiding consumption of raw or inadequately cooked, marinated, or salted marine fish or squid [10]. The risk of human infection can be reduced by visual examination of fish, extraction of visible parasites, and elimination of heavily parasitized fish [10]. Furthermore, eviscerating fish immediately after catch may potentially decrease the number of larvae in the fish flesh by preventing possible migration from the intestinal tract into the edible musculature; however, this approach deserves further study [9]. Larvae are killed by heating to temperatures of >60°C (>140°F) for at least a minute; smoking is not effective if adequate temperatures are not reached [5, 9]. Although salting fish can kill anisakid larvae, concentrations must be quite high for a prolonged period of time [53].

For fish that will be consumed raw, the key to prevention is freezing. The US Food and Drug Administration’s food code recommends that fish intended for raw consumption should be frozen at −20°C (−4°F) for 7 days or blast frozen to −35°C (−31°F) for ≥15 h [54]. Shorter durations of freezing might be effective; the European Union Hazard Analysis and Critical Control Points recommend freezing at less than −20°C (−4°F) for...
CONCLUSIONS

Given the growing popularity of sushi and sashimi worldwide and the increasing availability of what were regionally specific raw or smoked fish dishes (such as ceviche and gravlax), the risk of anisakidosis is widespread. With a range of possible gastrointestinal and allergic syndromes and broad differential diagnosis, a detailed food history will often be the key to the diagnosis. Endoscopic removal is the definitive treatment for gastric infection; intestinal infection may be treated conservatively. Adequate cooking, freezing (at $-20^\circ C$ for 7 days) or salting will prevent infection.

Acknowledgments

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