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Case Report

Anisakiasis, Accidental Helminthiasis in Humans Due to Ingestion of Seafood

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Abstract

Worldwide, 56 million people acquire anisakiasis caused by members of the *Anisakidae* family, an emerging helminthiasis that affects humans who consume raw or undercooked fish products.

The objective: is to concisely but sufficiently gather up-to-date knowledge about this parasitic infection.

Method: A narrative bibliographic review of scientific articles from scientific databases using search engines or keywords was used.

Results: the information found was distributed into six chapters for ease of reading: discovery of anisakiasis, etiological agent, life cycle, pathogenesis, clinical manifestations, diagnosis and treatment, and an introduction and discussion were also included. Conclusions: anisakiasis is an important human disease described in different regions of the world as an emerging zoonosis, with reports increasing in most countries, as well as the number of investigations conducted on the subject. The L3 larvae of *Anisakis simplex*, responsible for 97% of human cases of anisakiasis, have been included among the group of food allergens and even caused anaphylaxis. Studies have led to significant advances in understanding the pathogenesis and life cycle of great value to the healthcare sector in individual and collective settings for the prevention, diagnosis, treatment, and control of this accidental human helminthiasis.

Keywords: Anisakiasis, *Anisakis simplex*, helminthiasis, allergy, fish.

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Introduction

It is estimated that approximately 56 million people worldwide acquire parasitic infections with severe clinical manifestations caused by the consumption of fish products containing a significant proportion of helminths from the *Anisakidae* family, which are widely distributed worldwide and have been reported on all continents. Infection arises as a consequence of consuming marinated or raw fish in Asian (e.g., Japan) and European (e.g., Italy) cuisines, and recently in the United States. Ninety percent of anisakiasis cases are reported in Japan, with approximately 20,000 cases per year. Furthermore, sensitization rates appear to be increasing worldwide, reaching a seroprevalence of 27.4% and 29.8% (1-3). Members of the *Anisakidae* family (parasitic worms that infect marine animals that feed on fish and cephalopods, which are considered their intermediate hosts), specifically their genera *Anisakis*, *Hysterothylacium*, *Pseudoterranova*, and *Contracaecum,*

cause the zoonotic disease known as anisakiasis (primarily the first genus). However, human infection is caused by only three species of the *Anisakis* genus: *A. simplex sensu stricto*, *A. pegreffii*, and *A. physeteris* (1, 4).

Humans become infected and ill by consuming raw or undercooked fish meat containing live *Anisakis* spp. larvae, presenting with a clinical picture known as acute abdomen or eosinophilic gastroenteritis, as well as IgE-mediated hypersensitivity allergy to live or dead larvae, whose allergens are resistant to digestion and are not denatured by heat or cold. The diagnosis of this pathology focuses on a thorough clinical history, the identification of specific IgE, and the visualization of parasitic larvae by endoscopy (5, 6).

Anisakidosis or anisakiasis is an emerging, cosmopolitan disease that until a few decades ago was underdiagnosed. However, due to greater public awareness of the infection and the development of sophisticated diagnostic techniques, reports of this parasitic infection have increased worldwide. Therefore, the objective of the following narrative literature review is to provide updated and condensed information on this important scourge.

Method

The literature review method was used to obtain information and is presented in this article in narrative format. Data were extracted from the main collections of PubMed, Medline, and Scielo, and clinical trials, meta-analyses, editorials, reviews, and letters to the editor were included in the study. The search was conducted over a three-month period, between January and March 2025. The following search engines were used: *Anisakis*, anisakiasis, and parasite allergy. The majority of articles selected were articles no older than 10 years, but relevant studies published previously were also cited.

The retrieved publications were exported as text or PDF files. All publications related to the topic, in English or Spanish, were included, and were appropriately written and conducted with scientific rigor. Those that lacked these principles were excluded.

Results

Discovery of Anisakiasis

The presence of *Anisakis* larvae in fish has been known since at least the 13th century. Galen (129–216 AD) referred to *Anisakis* larvae encapsulated in fish viscera as "fish worms," considering them to be encysted nematodes. Linnaeus erroneously described a herring worm larva as Gordius marinus. Rudolphi named the larvae and adults he discovered in porpoises in 1809 *Ascaris simplex* (7, 8).

Dujardin, in 1845, created the subgenus *Anisakis* within the genus *Ascaris*, which by then included this species. The first case of anisakiasis (a term more frequently used in the scientific literature instead of anisakidosis) was reported in 1876 by Leuckhart. It was Baylis in 1920 who finally elevated *Anisakis* to the genus (9).

Between 1955 and 1959, Dr. Straub (in the Netherlands) established the relationship between the consumption of raw herring and the presence of L3 larvae of *A. simplex* (initially identified as Eustoma rotundatum) and the development of violent abdominal cramps with fever in healthy men, despite the fact that the presence of *Anisakis*-like larvae had been determined in the feces of an Alaskan Inuit since 1959 (10, 11).

The first case of anisakiasis was reported in the 1960s by Van Thiel of the Leiden Institute of Tropical Medicine in the Netherlands. Although the etiologic agent was initially identified as *Eustoma rotundatum*, it was only in 1962 that Van Thiel and his team recognized that it was actually *Anisakis* spp. larvae. Since then, this parasitic infection has been known as anisakiasis. Given this epidemiological situation in the Netherlands, the government implemented prevention and control measures such as freezing, salting, marinating, or smoking herring. These measures, but primarily freezing, have drastically reduced the incidence of human cases (1, 6, 7, 12).

Etiological Agent

Anisakiasis is caused in 97% of cases by third-stage (L3) larvae of the A. *simplex sensus lato* species complex, specifically the species *A. simplex sensu stricto*, *A. pegreffii*, and *A. berlandi*. *A. simplex* larvae are cylindrical, pinkish-white, and measure 20 to 30 mm in length, making them visible to the naked eye. The parasite in humans rarely evolves to the fourth larval stage (L4), but never to the adult stage, because its definitive hosts are cetaceans (8,13).

Life Cycle

Human infection begins with the accidental ingestion of third-stage larvae of parasitic nematodes of the *Anisakidae* family, genus *Anisakis* and *Pseudoterranova* (rarely of the *Contracaecum* genus), through the consumption of raw or undercooked fish or cephalopods (herring, sardine, anchovy, salmon, haddock, hake, monkfish, horse mackerel, blue whiting, turbot, and squid) that are infected with larvae. The parasites have two life cycles: one in definitive hosts, marine mammals (cetaceans such as whales, dolphins, orcas, among others) and piscivorous birds, and another in intermediate hosts, crustaceans, cephalopods, and fish. It is worth noting that *Hysterothylacium aduncum* of the *Raphidascarididae* family produces clinical pictures very similar to anisakiasis (8, 13).

Pathogenesis

The L3 larvae of *Anisakis* spp. attach to the wall of the digestive tract and release enzymes that produce tissue lysis, with local eosinophilia, accompanied by eosinophilic granuloma (induced by the local immune response), intestinal perforation, or severe allergic reactions. Regarding allergic reactions, Japanese researchers in 1990 first identified the involvement of these larvae in the context of acute parasitism with urticarial and anaphylactoid syndromes (1, 14).

A few days after infection, the parasites tend to die due to the harmful effects of major basic protein, nitric oxide synthase, and eosinophil peroxides. The most important role against *Anisakis* spp. larvae corresponds to the adaptive Th2 immune response, as it induces the release of polyclonal IgE, which further activates mast cells, whose mediators induce a massive and rapid constriction of the gastrointestinal and bronchial smooth muscle, which generates intense vomiting, profuse diarrhea and cough, which contribute to the elimination of the larvae (2). The pathogenesis of *Anisakis* L3 larvae is poorly understood. Therefore, as a model to mimic the inflammatory response triggered by *Anisakis* larvae in the human intestine, human colorectal adenocarcinoma cell lines (Caco-2) have been used. These cells have been exposed to the parasite, specifically to the L3 larvae (initial contact with the host), to extracellular vesicles released by the larvae (*Anisakis*-host communication), and to their crude extract (dead) (8, 15-17).

These models have shown that the parasite's L3 larvae have, on the one hand, an immunomodulatory effect that allows them to survive in the human digestive tract. On the other hand, when dead, they induce an aggressive immune response that leads to their expulsion from the intestine, generating eosinophilia and granuloma formation, as mentioned earlier in this section. Likewise, research using this model has allowed the identification of excretory-secretory proteins related to parasite-host interaction, including the allergens Ani s 1, Ani s 4, Ani 547, and the Ani s 11-like protein (Ani s 11.0201) (2, 8, 16, 17).

The dilemma of the role of Ani s in the human allergic response to the live or dead parasite is attempted to be elucidated by the description of anaphylaxis using puncture tests with *Anisakis* extracts, which confirms that *A. simplex* allergens are potent enough to cause allergies. In this regard, allergic responses in the host without larval infection have been reported, due to the simple presence of parasitic antigens in the edible muscle of the fish, based on the existence of traces of *A. simplex* allergens in fish muscle areas adjacent to the larva (1). Prolonged inflammatory reactions due to continuous activation by *Anisakis* spp. antigens can lead to chronicity, which favors a tumor microenvironment characterized by the inactivation of suppressor genes, the activation of oncogenes, and somatic mutations. Polypoid colonic lesions and gastric and colon tumors have been reported in the context of anisakiosis. In this regard, research has shown decreased regulation of EPHB2 and LEFTY1 and increased regulation of the NUPR1 genes, known for their association with colorectal cancer (18-20). Clinical Manifestations

Clinical symptoms vary depending on the degree of mucosal penetration, whether noninvasive (luminal, more common with the genus *Pseudoterranova*) or invasive (more common with the genus *Anisakis*), as well as the segment of the digestive tract affected. Symptoms can be gastric or intestinal (with mild to severe abdominal pain, hours or days after ingestion of live larvae), and even ectopic (oral cavity, lungs, and peritoneal cavity) (1).

Gastrointestinal symptoms, although severe, do not last more than two weeks due to the death or expulsion of the parasite. Strict gastric involvement is characterized by acute epigastric pain, nausea, and vomiting, with or without fever, in the first 24 hours after consumption of undercooked or raw fish. Intestinal anisakiasis appears 48 hours to one week after exposure with abdominal pain, diarrhea with mucus or blood, and fever. The main complications are intestinal obstruction, appendicitis, and peritonitis due to peritoneal migration, which can also occur in the pleural cavity. In addition, allergic manifestations ranging from mild (urticaria, rhinitis, and conjunctivitis) to severe allergic reactions are common as a result of human sensitization to *Anisakis* after primary infection. Parasites from the same family (*Pseudoterranova* and *Contracaecum*) or phylogenetically related (*Hysterothylaciu*m) can also cause allergic symptoms (2, 8, 21, 22).

Generally, allergic symptoms are not associated with fish consumption, so the clinical history of *A. simplex* allergy is not as clear as with other food allergies. Because the parasite has been tolerated for decades, it has been considered a hidden allergen. However, the allergic reaction occurs between 15 and 30 hours, and up to 2-6 hours after consuming fish products, with a clinical picture that can progress to anaphylactic shock, which can lead to intensive care. Allergic symptoms are most frequently described in people between 40 and 70 years of age, with symptoms that, in order of frequency, are cutaneous (100%), respiratory (39%), and hypotension/syncope (23%). Reactive arthritis (with its positive acute-phase reactants) is reported in a few cases (1).

Diagnosis and Treatment

As a diagnostic and treatment strategy for anisakiasis in humans, the combination of upper gastrointestinal

endoscopy and colonoscopy is recommended. This allows for the location of larvae and reliable treatment with their elimination, as they can be found anywhere in the digestive tract. This prevents chronic inflammation caused by the damage caused by the parasite, resulting in a rapid and safe recovery of the affected patient. Furthermore, some authors suggest using albendazole at a dose of 400–800 mg daily for 6 to 21 days (2, 23, 24).

In the diagnosis of allergy due to *Anisakis* spp., the basophil activation test (BAT) is recommended, which has a sensitivity of 92.5% and a specificity of 100% in the detection of *Anisakis*-specific IgE. Skin prick tests are currently used to detect hypersensitivity to Anisakis simplex, with results in 15–20 minutes. A considerable increase in specific and total IgE levels has been demonstrated in the days following larval infection, which remain elevated for months or even years (1, 23–26).

Discussion

Cases of anisakiasis are reported worldwide, as well as a trend toward increasing quantitative and qualitative research on this parasitic disease, although with particular emphasis on seafood-consuming countries due to its health and economic impact. In this regard, health experts strongly recommend epidemiological studies on fish for human consumption to update knowledge about the risk of human anisakiasis and as a basis for developing strategies for the prevention and control of this infection in humans(6).

The recommendation to carry out studies on the epidemiological behavior of anisakiasis is based on the fact that the consumption of fish marketed with *Anisakis* parasites poses a potential risk of infection and disease, and because of its negative commercial and economic implications in aquaculture and fishing (thus, occupational diseases such as rhinoconjunctivitis and asthma have been described in those who handle fish, including housewives due to sensitization to *A. simplex*), because research, despite its limitations, provides a good basis for the development of clinical guidelines for the diagnosis and treatment of this helminthiasis (1, 26).

Field research has led to significant progress in understanding the life cycle and pathogenesis of *A. simplex*. The former has led to the establishment of health policies such as freezing fish (at -35°C for 24 hours or at -20°C for more than 72 hours, or deep-freezing overseas), cooking fish for at least 10 minutes at 60°C, and avoiding the consumption of smoked or marinated fish, all of which contribute to substantially reducing the incidence of human cases of anisakiasis. The latter has allowed for the development of simple, rapid, and specific diagnostic techniques for detecting the parasite or its proteins in both humans and infected fish in the coming years (1, 2, 8).

The clinical characteristics of anisakiasis, including its potential to induce allergic reactions, are only partially described, as many of the in vivo and in vitro studies conducted to date lack standardized working methods, making comparison of results extremely difficult. Hence, the use of three-dimensional organoids is recommended, as they are rarely used in the field of parasitology and would avoid fragmentation of information as they reflect the complexity of the host (18, 27).

Another aspect to consider in research on anisakiasis is fluorescent labeling, which allows the study of extracellular vesicles due to their participation in the communication and interaction between the parasite and the host. This tool could provide key information on relevant aspects of cellular life, such as post-transcriptional gene regulation and its role in the host's immune and inflammatory responses, with the aim of generating better therapies against the parasite (18, 19, 28).

Finally, it is noted that health professionals need to be informed and constantly update their knowledge of anisakiasis due to the economic importance of countries and the health risks posed by this emerging parasitic zoonosis, which are largely neglected in many countries. In some, epidemiological surveillance is not even carried out. This occurs with this and other parasitic diseases in low-income countries, which limits investment in policies and programs for the prevention and control of parasitic diseases that affect humans (29-33).

Conclusions

Anisakiasis, described since the 13th century, is a major human disease described in different regions of the world as an emerging zoonosis. Reports have increased in most countries, as has the number of studies conducted on the subject. The L3 larvae of A. simplexs, responsible for 97% of human cases of anisakiasis, have been included among the group of food allergens and even caused anaphylaxis.

Due to the growing trend toward consuming raw or undercooked fish, progress is needed toward comprehensive evaluations of idiopathic allergic reactions related to the ingestion of these foods. These studies have led to significant advances in understanding the pathogenesis and life cycle of great value to the health sector in individual and collective countries for the prevention, diagnosis, treatment, and control of this accidental helminthiasis in humans. Hence the need to constantly update knowledge on the subject.

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