Anisakis simplex and urticaria. What we know about its real incidence and management in dermatological settings?

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Abstract

Acute or chronic infections have been described among causes of chronic urticaria (CU). Anisakidosis is a human disease caused by the ingestion of larval nematodes of the family Anisakidae. The infestation is acquired by eating raw seafood or undercooked fish and squid. There are considerable variations in the frequency of underlying causes in the different studies and in different countries, such as differences in diets and the prevalence of infections. *Anisakis simplex* has been recognized as a trigger of both acute and CU manifestations. However, there is still a lack of evidence about its management and treatment in dermatology. We, therefore, reviewed some biologic properties of *Anisakis simplex* in order to understand the relationship between its biology and the mechanism it uses to establish chronic dermatological conditions such as urticaria and cause late complications. In addition, we herein report some concerns about the effectiveness of systemic treatment in preventing complications and management in dermatological settings.

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Introduction

A wide diversity and number of different urticaria subtypes have been described with an improvement in understanding causes and eliciting factors of urticaria as well as the molecular and cellular mechanisms involved in its pathogenesis. Urticaria is characterized by the development of wheals, angioedema, or both. Chronic spontaneous urticaria is defined as the recurrent development of transient wheals, angioedema, or both for >6 weeks due to known or unknown causes.[1] In more than 90% of chronic urticaria (CU) cases seen in routine clinical practices, the search for underlying causes is usually unsuccessful.[1] The EAACI/GA²LEN/EDF/WAO guideline provides recommendations for diagnostic and therapeutic approaches in common subtypes of urticaria.[2] Acute or chronic infections have been described among causes of CU, Helicobacter pylori as well as streptococci, staphylococci, *Yersinia*, *Giardia lamblia*, *Mycoplasma pneumoniae*, hepatitis viruses, norovirus, parvovirus B19, *Anisakis simplex*, *Entamoeba spp*, *Blastocystis spp*.[2] Anisakidosis is a human disease caused by the ingestion of larval nematodes of the family Anisakidae, especially A. simplex. The adult worm parasitizes sea mammals, like whales, seals, dolphins, and sea lions, but, during its different larval stages, it is able to colonize several intermediate hosts. In sea fish or cephalopods, the worm develops to the third larval stage. The infestation is acquired by eating raw seafood or undercooked fish and squid.[3] However, there are considerable variations in the frequency of underlying causes in the different studies and in different countries, such as differences in dietary regimens and in the prevalence of infections. *Anisakis simplex* has been recognized as a trigger of both acute and CU manifestations. However, there is still lack of evidence about its management and treatment in dermatology.

Materials and Methods

All the English-written articles have been searched in bibliographic databases and we reviewed some biologic properties of

Anisakis simplex in order to understand the relationship between its biology and the mechanism that may lead to chronic dermatological conditions such as urticaria and late complications. In addition, we analyzed some concerns about the effectiveness of systemic treatment in preventing complications. All the English-written articles available in bibliographic databases (MEDLINE, PubMed, Google Scholar) were included in the present review.

Results

Epidemiology

The real burden of anisakidosis is still not completely known. Worldwide sensitization rates in patients with food allergy reported a seroprevalence of 27.4% in Spanish general population and 29.8% in Japan. These numbers are even higher among patients with CU diagnosis, ranging between 14% and 63% as reported in the literature.[4] In countries with a high burden due to raw seafood ingestion the true allergy to anisakis is probably underestimated, ranging from 4.5% to 15% of suspected cases of seafood allergy,[4] but these data differ significantly among different populations. In Italy, a recent study of Hospital Discharge Records from 2005 to 2015 evidenced a higher number of cases reported from central and southern regions, than in north Italy, especially in populations inhabiting the coastal territories.[5] Around 40% of studied patients presented allergic manifestations and half of them showed serious allergic reactions. The multivariate analyses used in the study showed an independent association between allergic manifestations and characteristics of subjects living in southern regions and female gender,[5] while anaphylaxis was independently associated only with the female gender.[5] Moreover, from 10,570 subjects screened from October to December 2010 in a total of 34 Italian allergy centers, 474 (4.5%) scored positive for anisakis skin prick test and 66 of these (14% of those sensitized, 0.6% of the studied population) had a history of *Anisakis simplex* allergy.[6] Sensitization rate showed marked geographic differences (range: 0.4-12.7%), being highest among Adriatic and Tyrrhenian coasts. The same study showed that about 60% of sensitized subjects from northern cities came from southern Italy or non-European countries.[6] Although more than 1000 cases are reported annually in Japan, intestinal anisakiasis could be considered a rare disease with a prevalence of diagnosis less than 10 cases in the United States.[7] The real incidence is probably underestimated due to non-specific abdominal symptoms.

There is a trend towards increasement of anisakis sensitization worldwide but the real incidence is probably higher than reported in literature. According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, from 1996 to February 2017, including 41 studies comprising 31,701 participants from eleven countries, general asymptomatic population resulted sensitized to anisakis in 0.4 to 27.4% of cases detected by indirect ELISA or ImmunoCAP specific immunoglobulin (Ig)-E detection, and between 6.6% and 19.6% by skin prick test. Occupationally exposed workers such as fishermen and workers of fish-processing industries documented specific IgE between 11.7% and 50% of cases, whereas skin prick test positivity ranged between 8% and 46.4%.[8]

Clinical aspects and pathogenesis

Anisakidosis clinical presentation can be gastric, intestinal, ectopic (*i.e.*, involving the oral cavity, lungs, peritoneal cavity) and allergic.[9,10] Gastric anisakidosis is characterized by the onset of epigastric pain, nausea, vomiting and low-grade fever usually 1-12 hours after consumption of raw fish. The acute phase usually resolves in a few days but abdominal pain, nausea and vomiting can last longer. Intestinal anisakidosis is characterized by abdominal involvement with a duration ranging from 5 to 7 days after ingestion. The intestinal infection can be complicated by ascites, and peritoneal signs, small bowel obstruction, and perforation. Larval penetration of stomach or intestine and their subsequent migration in the peritoneal or pleural cavity determine ectopic anisakidosis. Chronic infection may present with mesenteric masses. Anisakis can penetrate mucosae by releasing proteases. Local innate immune response contributes to the formation of an eosinophilic and/or neutrophilic granuloma surrounding the larvae.[4] Adaptive immunity with peculiar attention to the Th1/Th2 balance plays a central role in the pathogenesis of the disease. Patients with a less adapted, strictly Th1-driven, immune response manifest pure gastrointestinal disease and can require surgical or endoscopic removal of parasites. On the contrary, a more Th2-driven immune response induces release of polyclonal IgE, which further activates mast cells causing a rapid constriction of gastrointestinal and bronchial smooth muscles and intense vomiting, diarrhea and cough in order to eliminate larvae. It is possible that patients with disregulation of Th2 response may also present with allergic symptoms such as urticaria, angioedema or even anaphylaxis due to massive mast cell activation. Such response may recur during subsequent re-exposure, suggesting a chronic rather than relapsing acute urticaria/angioedema, or anaphylaxis.[4] Only a few IgE binding components are known as allergens because the human production of IgE against helminths is a normal protective response elicited during infection when specific IgE in response to a great number of antigens is produced.[11] Some of IgE binding antigens are able to induce an allergenic activity and IgE mediated inflammation have been clinically or experimentally demonstrated.[11] Therefore, the IgE response documented by skin prick tests and specific IgE levels are to be interpreted as type I hypersensitivity reaction, as well as the physiologic response against parasite invasion.[12] Studies from Japan describe urticaria in about 10% of patients affected by gastric anisakiasis.[12] Daschner *et al*.[13] proposed that in the model of *A. simplex* sensitization-associated urticaria, immediate-type urticaria in gastro-allergic anisakiasis (GAA) is immunologically different from prolonged acute urticarial (PROL), that shows characteristic more typical of CU than to GAA. The same authors defined PROL as urticaria with a duration between 3 days and 6 weeks and GAA lasting less than 48 h.[13] In this study, specific IgE were present in all patients with gastroscopically confirmed gastroallergic anisakiasis. Thus, the presence of specific IgE is a marker not only of acute parasitism but also indicates the responsible pathogenic mechanism of the hypersensitivity reaction. A study performed by Daschner *et al*. showed a difference in time interval between fish intake and abdominal symptoms or hypersensitivity symptoms: 15 minutes to 7,5 hours (mean 3.2±2.3 hours) and 20 minutes to 26 hours (mean 5.4±6.3 hours), respectively. Another study showed that hypersensitivity reactions may present up to 36 hours after ingestion.[3] This finding supports the difficulty of a diagnosis because, especially in long time interval, patients do not relate allergic symptoms to previous intake of fish.[12]

Management of the infected patients: diagnosis and treatment

In case of acute onset of urticaria/angioedema or CU, the investigation about the consumption of raw or undercooked fish or squid correlated to the onset of gastric and/or intestinal symptoms

may direct the clinical suspicion on anisakidosis.

For gastric anisakidosis, gastroscopic or surgical removal of the larva provides the diagnosis. Although larvae can be found up to 6 days, if endoscopy is further delayed, the larvae may be absent due to physiological elimination or migration through the mucosa thus leaving its inflammation as the unique detectable sign. Chronic infection can cause abscess and/or granuloma formation. Intestinal infection can result in irregular bowel wall thickening and luminal narrowing. Computed tomography can show lymphadenopathy, focal masses, and ascites. Gastric infection is frequently associated with leukocytosis; eosinophilia is more commonly described in gastric than intestinal infection.[13]

Suspected sensitization to *Anisakis simplex* can be investigated by skin prick test and specific IgE assay. However, the evaluation of clinical relevance of *Anisakis simplex* sensitization associated with CU and possible previous parasitism is difficult. In fact, skin prick tests and IgE testing with anisakis whole extracts have shown low specificity as they are not always related to symptomatic allergy and can produce false positive results because of cross-reactivity between different nematode species, *e.g.*, Ascaris, or other allergen sources such as mites, insects, shellfish, cockroach.[14] In order to discriminate genuine allergy from molecular cross-reactivity, specific IgE against recombinant allergens are currently the best option for diagnosis in terms of sensitivity and specificity. So far fourteen *Anisakis simplex* allergens are recognized by the World Health Organization (WHO)/International Union of Immunological Societies allergen nomenclature subcommittee.[15] According to their origin, they are divided into allergens from dead parasites (somatic and cuticular) and from living larvae (excretory/secretory). Somatic allergens Ani s 2 (paramyosin) and Ani s 3 (tropomyosin) show high cross reactivity to house dust mites and crustacean homologous. Moreover, they relate to sensitization but not necessarily to allergic reactions.[16,17] Cuticular allergens are involved in a chronic stimulus leading to granulomas and other chronic lesions. Excretory allergens are hystolitic enzymes that facilitate the parasite penetration through the digestive mucosa.[18,19] Among them, Ani s 1, Ani s 7 and Ani s 13 are considered as major allergens. They lack homology with other allergens and, as a consequence, they have good diagnostic value to identify true *Anisakis simplex* allergy.[20,21] Ani s 1 specific IgE seems to be associated with severe allergic reactions. Caballero *et al*. showed that recombinant allergen such as Ani s 1, Ani s 3, Ani s 5, Ani s 9 and Ani s 10 have the same diagnostic sensitivity as A. simplex ImmunoCAP for the diagnosis of A. simplex-allergic patients but they increase diagnostic specificity. Specifically, Ani s 9 showed the highest specificity (98.99%) despite a low sensitivity (42.86%) and the major allergen, Ani s 1, had the highest sensitivity (85.71%) with a good specificity (90.91%).

Cuéllar *et al*. showed that Ani s 7 is present in over 90% of both patients with GAA and CU related to A. simplex previous sensitisation, whereas Ani s 1 is frequent only in GAA but it presents a frequency under 50% in A. simplex sensitisation-associated CU, thus mining its strict concept of major allergen. Moreover, they confirmed the combined evaluation of Ani s 1 and Ani s 7 determination as the best choice for serodiagnosis of human anisakiasis, with a 100% sensitivity in GAA and 95% sensitivity in A. simplex sensitisation-associated CU.[14]

Recently, anisakis haemoglobin was described as a major allergen (Ani s 13) responsible for primary sensitization and presenting clinical relevance. Gonzalez-Fernandez *et al.*, in their study, showed that it was detected by 72.1% of anisakis sensitised patients measured by indirect ELISA.[22] Recent studies tried to identify further possible parasitic molecular markers in order to improve the diagnosis of unknown urticaria aetiology such as the levels of specific IgG (sIgG) and IgE (sIgE) antibodies against crude extracts and isolated components from whole larvae of *Anisakis simplex* (Ani s 1, Ani s 3 and Ani s 7) using immunologic and molecular diagnostic methods.[1]

The diagnosis of allergy to A. simplex should be suspected in the presence of 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.[23]

The most effective measure for the prevention of anisakiasis is prophylaxis, that is currently regulated by the European Union.[24] Because larvae cannot survive at a temperature higher than 60°C for 10 minutes or lower than –20°C for 24 hours, patients should be told to eat only well-cooked or deep-frozen fish.[12]

The Centers for Disease Control and Prevention guidelines recommend the administration of antielmintic drugs or the endoscopic removal of worms to treat gastric anisakiasis. Enteric anisakiasis can generally be managed without removal of the worms because it will eventually die. Surgery may be required for intestinal or extraintestinal infections when intestinal obstruction, appendicitis, or peritonitis occurs. Successful treatment of anisakiasis with albendazole 400 mg orally twice daily for 6 to 21 days has been reported in cases with presumptive (highly suggestive history and/or serology) diagnoses.[25] Particular attention should be paid on albendazole usage in pregnancy because the drug belongs to category C. Data on the use of albendazole in pregnant women are limited, though the available evidence suggests no difference in congenital abnormalities in the children of women who were accidentally treated with albendazole during mass prevention campaigns compared with those who were not. The WHO has determined that the benefit of treatment outweighs the risk and allows use of albendazole in the 2nd and 3rd trimesters of pregnancy.[25]

Discussion

The diagnosis of urticaria is based primarily on a detailed clinical history and physical examination. Dermatologist should be aware of the existence of different clinical scenarios when approaching patients with urticaria having an acute or chronic *A. simplex* infection in order to prevent the complications and choose the best management for their patients. Furthermore, also in the absence of gastrointestinal symptoms in patients with positive medical history for raw fish intake, skin prick tests and specific IgE assay should be performed to confirm the suspect of *Anisakis simplex* exposure. Some authors suggest that the presence of specific IgE is a marker not only of acute parasitism but also indicates the responsible pathogenic mechanism of the hypersensitivity reaction.[13] In these patients, a gastroenterological evaluation should be recommended. Skin prick tests and specific IgE measured by the ImmunoCAP system are two methods with good sensitivity,[26] but with low specificity due to complete parasite extracts use. For these reasons, researchers are focusing on improving diagnostic methods using molecular diagnosis that should be available worldwide.

Conclusions

In conclusion, in dermatologic context anisakiasis should be considered in differential diagnosis of acute and CU. Both clinical

and diagnostic evaluations are important in anisakiasis because they have been shown to be associated with a strong allergic response,[26] with clinical symptoms ranging from isolated swelling to urticaria, angioedema and life-threatening anaphylactic shock, that could be prevented.

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