

Eosinophilic gastroenteritis and *Anisakis*

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Background The differential diagnosis of eosinophilic gastroenteritis (EG) includes, among other diseases, parasitic infections such as anisakiasis, which has acquired worldwide importance.

Methods We reviewed all patients referred to our allergy service who had been diagnosed as having primary EG to determine the possible role of *Anisakis simplex* in the etiopathology of the disease. All patients ($n=10$) were studied and diagnosed as having primary EG between 1989 and 1996, inclusive. Two different groups of subjects were used as controls: group A (149 subjects without digestive disorder) and group B (10 subjects with digestive disorder different from EG). Cutaneous prick tests were performed with the main foods, aeroallergens, and commercial extract of *A. simplex*. Total and specific serum IgE was measured in all patients. Gastric or gut histologic specimens were re-examined in five cases.

Results Peripheral eosinophilia was detected in 40% of the patients with EG, and sensitization to *A. simplex* was detected in 80% of these. In both control groups, the rate of sensitization to *A. simplex* was 10%. Sensitization to *A. simplex* in EG patients with respect to control groups A and B showed odds ratios (OR) of 36 and 40, respectively. In one case, serialization of the histologic section allowed us to observe a whole *Anisakis* larva.

Conclusions Immunologic methods to detect specific antibodies against *Anisakis* should be used routinely before diagnosing EG as primary disorder. Preventive measures are of capital importance.

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Eosinophilic gastroenteritis (EG) was first described by Kaijser in 1937 (1). It is characterized by infiltration of the wall of the digestive tract (mainly the stomach and small intestine) by eosinophils, frequently in association with peripheral blood eosinophilia and nonspecific digestive symptoms. Histologic examination is the only method to confirm the diagnosis (2).

Although its cause is unknown, findings such as a positive history of allergic disease, high total serum IgE levels, and symptoms related to the ingestion of certain foods point to the possibility of a food allergen response. Nevertheless, in more than 50% of the cases, data supporting this diagnosis were not found (3). Thus, a differential diagnosis must take into account those diseases which produce peripheral eosinophilia, eosinophilic infiltration of the digestive tract, and gastrointestinal symptoms; e.g., parasitic intestinal infections, systemic vasculitis, and hypereosinophilic syndrome, among others (3).

With regard to parasitic intestinal infections, anisakiasis, produced by eating raw, partially

cooked, or semipreserved fish or cephalopods (mollusks belonging to the class Cephalopoda) containing the third-stage *Anisakis simplex* larvae, has acquired worldwide importance. The first cases, reported in The Netherlands (4, 5), were followed by several Japanese authors' reports (6–9) and have been related to Japanese dietary habits (eating raw fish or cephalopods). Nevertheless, anisakiasis seems to be widespread, and cases from the USA (10, 11), the UK (12, 13), France (14), and Spain (15) have also been reported. The per capita fish consumption in Spain (85 g of fish per person per day) is among the highest in the world. Evidence of Anisakidae infection has been found in various markets in Spain; 31.7% of all samples in Madrid (16) and 17 out of 19 species in Galicia (17) were found to be infected. In Navarre, all 46 samples of hake tested were found to be infected (18). Increasingly, cases of anisakiasis have been diagnosed in Spain, perhaps in relation to the recent trend toward lightly cooked fish.

A. simplex is a nematode of the superfamily

Table 1. Digestive tract symptoms in 10 patients diagnosed as having primary eosinophilic gastroenteritis

Patient no.	Symptoms	Parasites in feces	Abdominal radiograph	Barium enema
1	Recurrent abdominal pain and constipation	No	Normal	Thickening of duodenal folds
2	Urticaria and recurrent abdominal pain	No	Normal	Thickening of gastric folds
3	Recurrent and diffuse abdominal pain	No	Normal	Thickening of gastric folds
4	Diarrhea and recurrent abdominal pain	No	Air-fluid levels	ND
5	Epigastric pain and nausea	No	Normal	Normal
6	Acute abdominal pain, nausea, and vomiting	ND	Gas increased with air-fluid levels in small bowel	ND
7	Acute abdominal pain, nausea, and vomiting	ND		ND
8	Acute abdominal pain, nausea, and vomiting	ND		ND
9	Acute abdominal pain, nausea, and vomiting	ND		ND
10	Acute abdominal pain, nausea, and vomiting	ND		ND

ND: not done.

Ascaridae, family Anisakidae. The genus *Anisakis*, as well as genera such as *Pseudoterranova* (*Phocanema*, *Terranova*, *Porrocaecum*) and *Contracaecum* (19), belong to the subfamily Anisakinae. All of them have been reported to cause human disease. Infection by *Phocanema* and *Contracaecum* larvae are generally asymptomatic, and are diagnosed only by the identification of the parasites in vomitus and stools (11).

Depending on the level of the gastrointestinal tract where the larvae penetrate the mucosa, human anisakiasis can present several clinical pictures. Gastric forms cause gastritis and epigastric pain, which become chronic if the parasite is not removed. Intestinal forms may mimic intestinal obstruction, acute appendicitis, or ileitis (7, 10, 15, 20). This parasite may also act as an allergen able to induce IgE-mediated reactions, with several clinical manifestations ranging from urticaria-angioedema to anaphylaxis (21–24).

To determine the role of *A. simplex* in the pathology of gastrointestinal disease, we reviewed the records for all patients who had been diagnosed during the previous 8-year period as having primary EG.

Material and methods

Subjects

We studied all 10 patients who had been diagnosed as having primary EG and referred for allergologic study to our department during the period from

1989 to 1996. The mean age was 50 years, and four of the patients were women.

Two different groups of subjects were used as controls:

- group A: 149 consecutive patients who were seen in our department for another reason
- group B: 11 patients who had presented acute or chronic digestive symptoms, and whose diagnoses were as follows: four acute appendicitis, two duodenal ulcer and inflammatory bowel disease, two Crohn's disease, and three ulcerative colitis.

Methods

Before being referred to our allergy department, all patients underwent digestive system evaluation. This study included clinical anamnesis, hemogram, biochemical parameters, parasites in feces (three specimens of feces obtained over 3 consecutive days were examined fresh and with Gram staining), abdominal radiography, barium enema, and upper gastrointestinal tract endoscopy. Five patients were diagnosed as having acute abdomen and required emergency surgery.

The allergy study consisted of allergologic anamnesis, including history of atopia, dietary habits and clinical symptoms related to the ingestion of fish or other foods, simple hemogram to detect peripheral eosinophilia, and immunologic testing. Skin prick tests (SPT) were done according

Table 2. Endoscopic and histologic findings in 10 patients diagnosed as having primary gastroenteritis

Patient no.	Upper gastrointestinal endoscopy	Histologic findings
1	Superficial gastritis and small nodule in duodenum	Eosinophilic infiltration of duodenal submucosa
2	Thickened and hyperemic pylorus	Atrophic gastritis; eosinophilic infiltration of gastric mucosa
3	Thickening of gastric folds	Eosinophilic infiltration of gastric mucosa
4	Inflammation of gastric folds	Atrophic gastritis; eosinophilic infiltration of gastric and duodenal mucosa
5	Diffuse gastritis	Eosinophilic infiltration of colonic mucosa
6	Not done	Transmural infiltration of
7	Not done	eosinophils and edema in
8	Not done	small bowel
9	Not done	
10	Not done	

to the European Academy of Allergology and Clinical Immunology guidelines with the main foods and aeroallergens in our environment, and with a commercial extract of *A. simplex* at 1 mg/ml (International Pharmaceutical Immunology SA, Madrid, Spain). Becton Dickinson lancets were used. Histamine 10 mg/ml and saline solution were used as positive and negative controls, respectively. The results were measured at 15 min as the diameter of the wheal expressed in millimeters. A diameter equal to or greater than 3 mm was considered positive in the presence of a negative response to the saline control (25). Control groups A and B were skin prick tested by the same method, with *A. simplex* extract as a negative control.

Total and specific serum IgE to *A. simplex*, *Ascaris lumbricoides*, and those foods or aeroallergens which had been positive in skin tests were

measured by the CAP method (Pharmacia CAP System, Uppsala, Sweden). In accordance with the manufacturer's instructions, specific IgE values equal to or higher than 0.35 kU/l were considered positive.

The chi-square and Fisher tests were used to compare the results of SPT with *A. simplex* extract and specific IgE values in the three groups.

Stored histologic samples were reviewed macro- and microscopically. Serial sections of paraffin blocks from the cases 6, 7, 8, 9, and 10 were cut, and the slides were stained with hematoxylin and eosin and periodic acid-Schiff (PAS) staining.

Results

The results of the digestive system study are presented in Table 1. All 10 subjects presented abdominal symptoms; in five of them, symptoms were chronic or subacute, and in the other five, they were acute.

Left-shift leukocytosis was present in five out of the 10 patients. Parasites were not found in stools. The simple radiograph was normal except in those cases in which acute abdomen was the main symptom, and in patient 4.

Of the four patients who underwent barium enema, thickening of the gastric or duodenal folds was found in three, and the findings were normal in one.

Inflammatory signs and thickening of the wall at several levels of the gastrointestinal tract were detected in five patients during upper gastrointestinal tract endoscopy (Table 2).

Histologic examination of the specimen obtained by endoscopic biopsy or of surgical fragments from subjects 6, 7, 8, 9, and 10, who required emergency

Table 3. Results of allergologic study

	Patient no.									
	1	2	3	4	5	6	7	8	9	10
T (months)	29	25	5	3	1	24	29	28	63	84
Atopic antecedents	+	—	—	—	—	+	—	—	—	—
Peripheral eosinophilia	+	+	+	—	+	—	—	—	—	—
Total IgE (kU/l)	1900	27	264	149	71	300	26.3	18.4	49.3	95.2
SPT <i>Anisakis</i>	+	+	+	—	—	+	+	+	+	+
IgE <i>Anisakis</i> (kU/l)	> 100	4.95	0.954	—	—	14.6	8.41	1.20	19.4	12.4
IgE <i>Ascaris</i> (kU/l)	5.05	—	—	—	—	0.654	—	—	0.565	2.53
Review of histologic samples	ND	ND	ND	ND	ND	Eosinophilic transmural infiltration, intense edema, and giant cells phagocytizing slightly PAS-positive cuticles; patient 9: whole larva in mucosa				

T: period of time between digestive study and allergologic study.
+ positive; — negative; ND: not done.

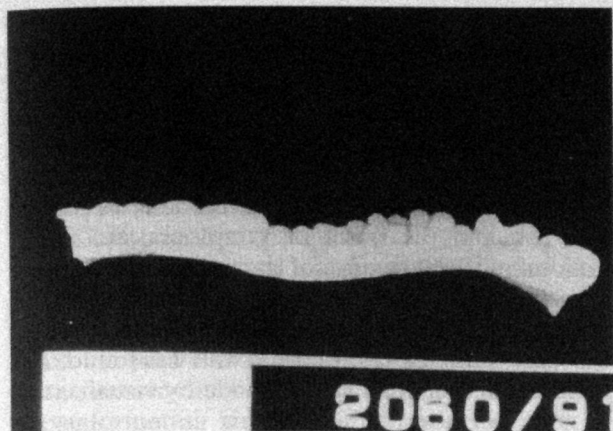


Fig. 1. Macroscopic appearance of surgical specimen. Note edematous thickening of intestinal wall.

surgery, showed inflammatory infiltration consisting mainly of eosinophils. At that moment, there was no evidence of parasites. It was noteworthy that the small bowel was affected in five of the 10 patients, four of whom needed surgery.

The results from the allergologic study are presented in Table 3. Mean fish consumption among our patients and control groups A and B was two to three times a week. No significant findings related to dietary habits or to the presence of symptoms after the ingestion of fish or some other food came to light on allergic anamnesis. Only patient 2 reported generalized pruritus and abdominal pain after eating seafood (hake and crayfish).

Peripheral eosinophilia was detected in 40% of the patients.

Skin tests with foods and aeroallergens were positive in subjects 1 and 6. Subject 1 was sensitive to mites and cereals, and subject 6 was sensitive to Rosaceae fruits, although neither subject reported any relation to symptoms.

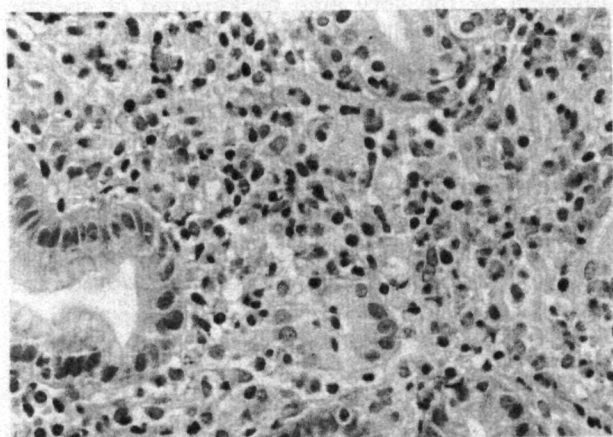


Fig. 2. Diffuse eosinophilic infiltration in submucosa.

Sensitization to *A. simplex* was detected in both *in vivo* and *in vitro* tests in 80% of the subjects with EG. A rate of sensitization to *Ascaris lumbricoides* of 40% was also found. To determine the specificity of *A. simplex* sensitization, we carried out skin tests with *A. simplex* extract in 149 consecutive subjects seen in our department who did not have digestive symptoms. A rate of 90% negative results was found. The findings in group B were also negative except in one case: one of the patients with ulcerative colitis.

Statistical analysis showed a higher frequency of sensitization to *A. simplex* in EG patients (80%) with respect to both control groups (10% sensitization in groups A and B) ($P < 0.05$, Fisher's test). Sensitization to *A. simplex* in EG patients showed an odds ratio of 36 ($6.11 < OR < 271.31$) in comparison with group A and 40 ($2.27 < OR < 1692$) in comparison with group B. No significant differences between groups A and B were found ($P > 0.05$).

Surgical specimens from cases 6, 7, 8, 9, and 10 were available for histologic study. Macroscopically, in three cases, the surgical specimen consisted of a 10–21-cm segment of jejunum (cases 6, 7, and 9). Patient 10 had undergone resection of two fragments of the small bowel (6.5 and 33 cm). The resected specimen from patient 8 consisted of the terminal ileum and appendix. (Patient 9 also underwent appendectomy.) All specimens showed considerable edematous thickening of the intestinal wall (Fig. 1), and white dots were present on the serosal surface.

Microscopically (Fig. 2), there was transmural infiltration of eosinophils reaching and extending through the serosa and the adipose tissue. Microscopic abscesses formed by eosinophils were frequent, and giant cells could be seen phagocytizing a slightly PAS-positive cuticle. In patient 9, serial histologic sections revealed the place where an *Anisakis* larva had passed through the mucosa. The larva was clearly identifiable, as shown in Figs. 3 and 4.

Discussion

As reported, abdominal pain, vomiting, and diarrhea are the most frequent symptoms of EG. Pain is usually colic and recurrent and can even simulate acute abdomen syndrome. Dysphagia is associated with esophageal involvement (3). These symptoms are nonspecific and can be found in many different diseases.

Peripheral blood eosinophilia is the most common laboratory abnormality. However, blood eosinophilia is not present in a relatively high proportion of cases, and is not considered a



Fig. 3. Histologic section showing whole larva that had penetrated mucosa.

diagnostic criterion for EG (3). Other blood parameters are usually normal except when a malabsorptive syndrome develops; in such cases, iron deficiency, anemia, or hypoproteinemia can be found.

Peripheral eosinophilia was present in four out of the 10 subjects, and no significant alteration in the other parameters was found. Abdominal radiography, which can reveal intestinal bowel dilation, edema, thickening of the folds, nodes, rigidity, or stenosis, is usually nonspecific, as all of these features are also observed in other diseases (3, 27). These signs were also present in most of our patients.

A definitive diagnosis of EG is obtained by the histologic demonstration of eosinophils infiltrating the gastrointestinal tract. Pathologic study of the biopsy samples or surgery specimens showed such infiltration, but, initially, no evidence of parasitic infection was found, and patients were diagnosed as having primary EG.

When patients were referred to our allergy department, the chance that anisakiasis was involved in their pathogenesis was considered.

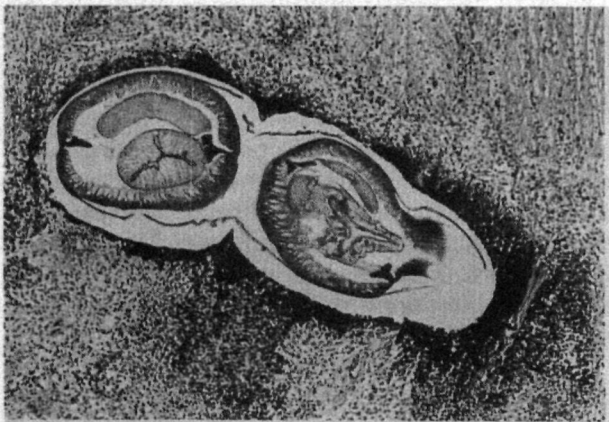


Fig. 4. Typical large lateral chords in parasite (patient 9).

Symptoms due to anisakiasis (2, 6, 28) overlap with those described in EG, with peripheral blood eosinophilia a common finding.

On the other hand, radiography studies are also nonspecific except in those cases in which barium enema shows filiform defects in folding. This finding, together with the antecedent of eating raw fish and the onset of symptoms and/or the endoscopic visualization of the parasite, makes the diagnosis possible (6, 8, 9).

In both EG and anisakiasis, an eosinophilic infiltrate of the gastrointestinal wall was found. The differential diagnosis can be made by visualization of the parasite, although this is not easy in histologic sections and is thus not always considered.

In our series of patients, dietary habits of fish consumption and the temporal relationship between ingestion of fish and the onset of symptoms (except in patient 2) did not give rise to a suspicion of anisakiasis. However, most of the subjects did not remember what they had eaten in the hours previous to the onset of symptoms. This is important, because anamnesis can lead to a firm suspicion, as shown in many reported cases (6–8, 10, 20).

With regard to immunologic findings, the existence of antibodies against *Anisakis* is important in the diagnosis. Sakanari and colleagues, using three immunologic methods (RAST, ELISA, and IFA), detected high levels of serum IgE, IgG, and IgM specific to *Anisakis* and confirmed the diagnosis of intestinal anisakiasis (29, 30). We demonstrated specific IgE to *A. simplex* with *in vivo* and *in vitro* tests in 80% of the subjects. There was a very good correlation (100%) between the *in vivo* and *in vitro* findings, and we detected a sensitization rate of only 10% in control subjects with and without digestive symptoms in whom cutaneous tests were done. In endemic areas (as shown in a Japanese study), the immunologic diagnosis could be a problem by the very high background of specific anti-*Anisakis* antibodies in asymptomatic individuals (31). Nevertheless, the sensitization rate in the general population in our area is not as high (10%).

The detection of serum-specific IgE to *Ascaris lumbricoides*, always at much lower titers than to *A. simplex*, could be explained by a cross-reactivity due to the taxonomic proximity of the worms (22, 29, 32). Previous infestation by *Ascaris* would be a more remote possibility.

In view of these findings, we decided to review carefully the stored pathology specimens in five of the cases in which this was possible. In one of the specimens, we noted a groove in which the typical large lateral chords (26), which are useful in

identifying the parasite in paraffin sections, were visible. In the other specimens, we found the remains of PAS-positive cuticles, which together with the immunologic data, led us to assume that they belonged to *Anisakis*. Therefore, immunologic tests to detect specific antibodies (IgE, IgG, IgM) to *Anisakis* should always be done before diagnosing EG as primary.

Endoscopic removal of the larvae is the preferred treatment for the gastric forms of anisakiasis; however, this is necessary only for intolerable pain. Once the pain is controlled by analgesics, damage to the gastric mucosa can be cured with antacids (ulcer formation is rare) (6). Surgical resection of the involved areas is not necessary in most patients with intestinal anisakiasis because of its good prognosis with conservative treatment (analgesics, antacids, antihelminthics, etc.) (8, 33). However, in some cases, its resemblance to other diseases makes surgical treatment unavoidable. One of the best preventive rules is to avoid eating raw or poorly cooked fish. Another prophylactic measure is the evisceration of fish to avoid the massive passage of larvae from the viscera to muscle, although several authors think that this measure is probably of little practical value, because in most fish larvae are present in the muscle as well as in or on the viscera (10). Smoked fish must reach 60°C for at least 10 min, and salad, pickled, or raw fish must be frozen at -20°C for 24 h to be safe.

We conclude that routine immunologic assessment to rule out the existence of anisakiasis should be stressed in the differential diagnosis of EG. The introduction of preventive measures is of capital importance to avoid a disease which, in its acute forms, often leads to surgical treatment.

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