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Early Gastric Cancer Superimposed on Infestation of an Anisakis-Like Larva: A Case Report

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This report describes a 73-year-old male with early gastric cancer (type IIc) superimposed on infestation of a parasitic larva. Eosiophilic granulomas surrounding a dead worm were seen in the submucosa just beneath the intramucosal tubular adenocarcinomatous lesion measuring 1 × 1cm at the anterior wall in the acid-secreting area. The cancer cells showed lowered and altered mucin production in comparison with the surrounding non-cancerous fundic mucosa. The parasite was identified as an Anisakis-like larva by the presence of typical lateral chords. An immunohistochemical examination revealed that the cancer cells were more strongly positive for IgA and secretory component than the surrounding non-cancerons mucosa, and that IgG, IgA and IgM were detected in plasma cells around the granulomas but IgE and IgD were not. The possibility that the Anisakis-like larva preferentially infested the cancerous mucosa because of the change in mucin, local defect in acid secretion and /or other structural alterations in the area is discussed.

(Key Words: Early gastric cancer, Eosinophilic granuloma, Gastric anisakiasis, Indirect immunoperoxidase method)

INTRODUCTION

The Anisakis is a kind of roundworm or Ascaris. Its final hosts are dolphins and/or whales. Over 1,200 cases of human anisakiasis have been reported so far, mostly from Japan but also from other countries (3, 4, 6). The disease is acquired by eating infected raw, pickled, smoked or salted fish such as herring, haddock, cod, mackerel, bonito, tuna, salmon, pike, flat fish or squid (4, 7). Recently, we experienced a case of gastric anisakiasis confined to the area just beneath a small early mucosal cancer. This is only the second report of infestation of an Anisakis-like worm associated with early gastric cancer. In this article, histological details of the case are presented with the aid of the immunoperoxidase technique, and the pathogenesis of the concomitant occurrence of these two lesions is discussed.

CASE REPORT

A 73-year-old male was referred to Tokai University Hospital on December 7, 1982 because of irregular folds in the gastric mucosa, which had been pointed out in a mass screening for gastric cancer. The patient had had no complaints. Physical findings were essentially normal except for mild hypertension (160/90 mmHg). Past and family histories were uncontributory. Laboratory data including carcinoembryonic antigen and α-fetoprotein were all within normal limits. The patient said that he was in

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the habit of eating seafood, especially raw squid. The gastric biopsy confirmed histological features of tubular adenocarcinoma. Subtotal gastrectomy was performed on January 6, 1983. The postoperative course of the patient was uneventful.

The resected stomach showed irregular mucosal folds with a shallow depression (type IIc) measuring 1 × 1cm at the anterior wall along the greater curvature of the body (Fig. 1). The cut surface of this lesion showed localized submucosal fibrosis. Histologically, the carcinomatous lesion was located in the fundic gland area, and was confined to the mucosa in the range indicated by the arrows in Figure 2. In the submucosa through the muscle layer just beneath the cancer, there was a S-shaped canalicular space, around which fibrosis was formed in association with a number of lymphoid follicles (Fig. 2). In a high power view, the intramucosal cancer revealed a well-differentiated tubular structure (Fig. 3). Neither infiltration into the submucosa nor lymph node metastasis was found. With Alcian blue (pH 2.5)-periodic acid Schiff staining, the surface coat of the cancer cells was slightly positive for alcianophilic mucin, while the surrounding non-cancerous epithelial cells contained abundant neutral mucin in the cytoplasm (Fig. 4). Figure 5 shows the submucosal lesion where a dead parasitic worm surrounded by necrotic substances and granulomas with giant cells was seen. Outside the granulomas, a number of eosinophils intermingled with lymphocytes and plasma cells were present (Fig. 5).

Careful observation of the parasite clarified various organs and tissues of the worm, such as the cuticle, thick muscular coat and intestine as well as a lateral chord (Fig. 6), which is known to be a characteristic clover-shaped structure of the Anisakis species. Because of the presence of a very thick muscular coating, however, this worm did not appear to be a common Anisakis. Its true scientific name could not be determined owing to severe autolytic changes.

To determine the local immune reactions against the worm, the indirect immunoperoxidase method after Nakane was performed using formalin-fixed paraffin-embedded sections. Rabbit antibodies against human γ, α, μ or δ chain and lysozyme were purchased from DAKO Immunoglobulins, Denmark. Rabbit antisera against human ϵ chain and secretory component (SC) were obtained from Behringerwerke, West Germany. Horseradish peroxidase-labeled goat IgG Fab fragment against rabbit IgG was prepared in our laboratory. Incubation and rising times in each step were 30 minutes. Endogenous peroxidase was inactivated by 0.5% periodate oxidation for 10 minutes.

In the areas surrounding granulomas, there were scattered plasma cells containing IgG, IgA and IgM (Fig. 7a-c) as well as many lysozyme-positive granulocytes. Necrotic substances around the worm were also positive for these immunoglobulins and lysozyme. Neither IgE- nor IgD-containing plasma cells were detected in these areas (Fig. 7d). In an examination of the local immune system in the mucosa, the cancerous glands showed positive immunostaining for IgA and SC, while the surrounding non-cancerous fundic mucosa revealed weak or even no staining for IgA and SC except for scattered intestinalized glands (Fig. 8).

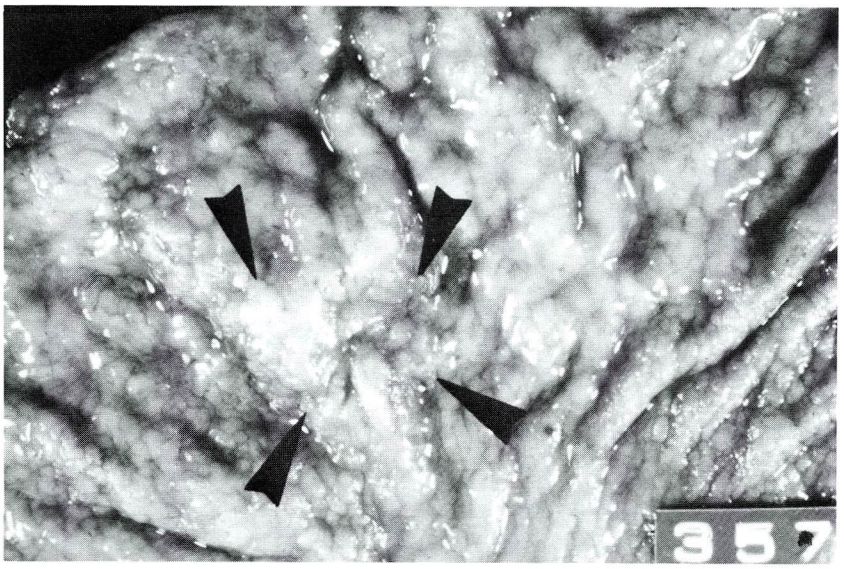

Fig. 1 A close-up view of the resected stomach shows a 1 × 1cm mucosal lesion with a shallow depression located at the anterior wall of the body (arrowheads).

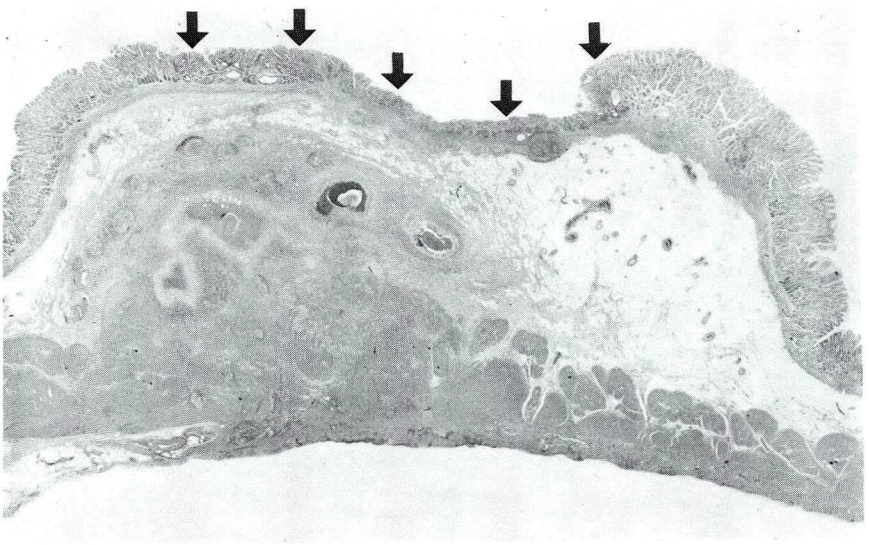

Fig. 2 Low power histology reveals intramucosal cancer (arrows) and submucosal fibrosis containing a S-shaped canalicular space which extends into the muscle layer. A number of lymphoid follicles are present in the submucosal lesion. H & E, ×4.8

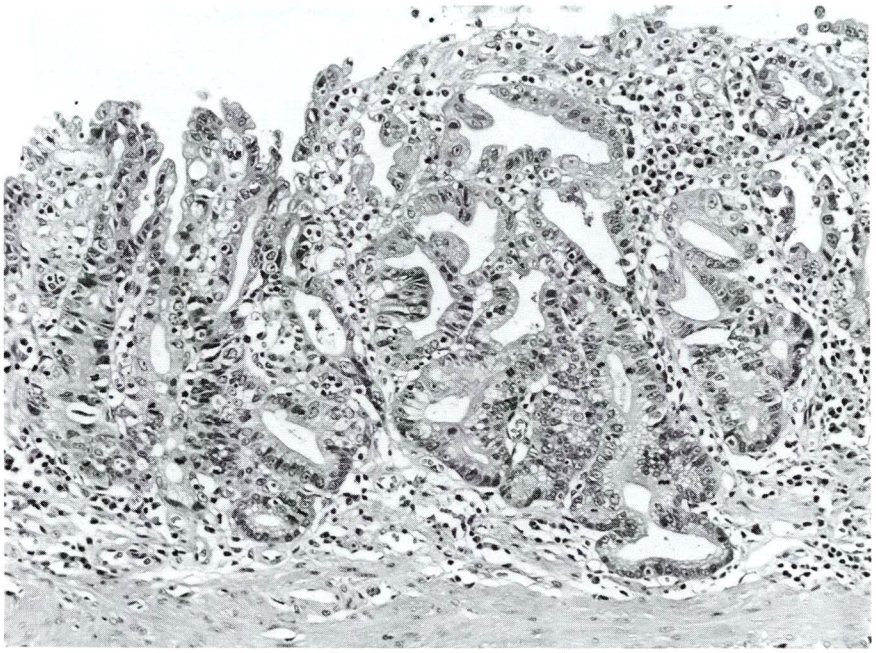

Fig. 3 In a high power view, a well-differentiated tubular adenocarcinoma is noted exclusively in the mucosa. H & E, ×150

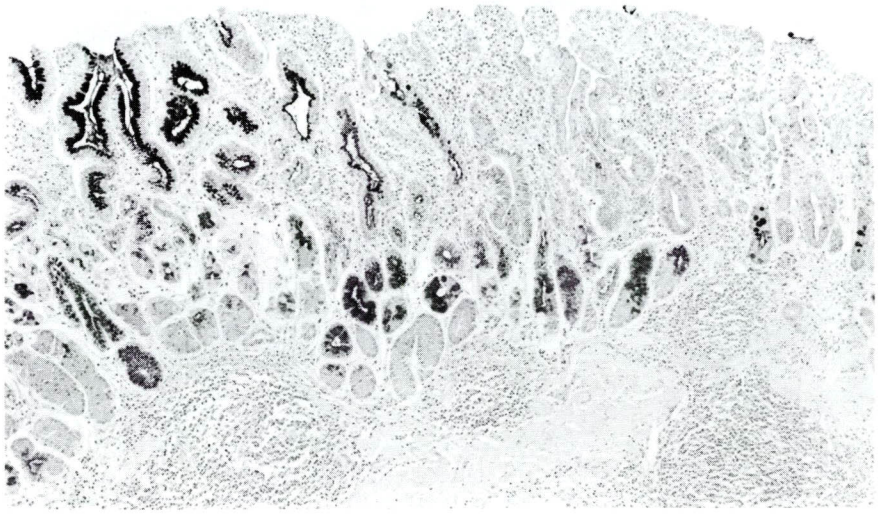

Fig. 4 The cancer cells (right half) show an evident decrease of mucin contents in comparison with the surrounding non-cancerous fundic mucosa (left half). Alcian blue (pH 2.5)—periodic acid Schiff staining, ×60

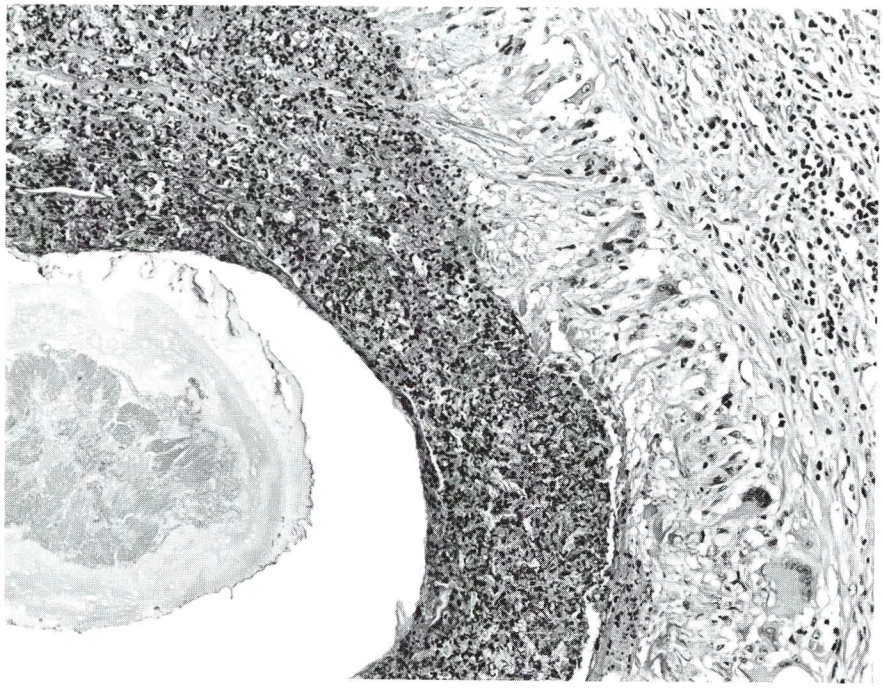

Fig. 5 The submucosa just beneath the cancer shows a foreign body-type granuloma containing a dead parasite. Exudative changes and granulomatous reactions are noted around the worm. Many eosinophils and plasma cells are present outside the granuloma. H & E, ×150

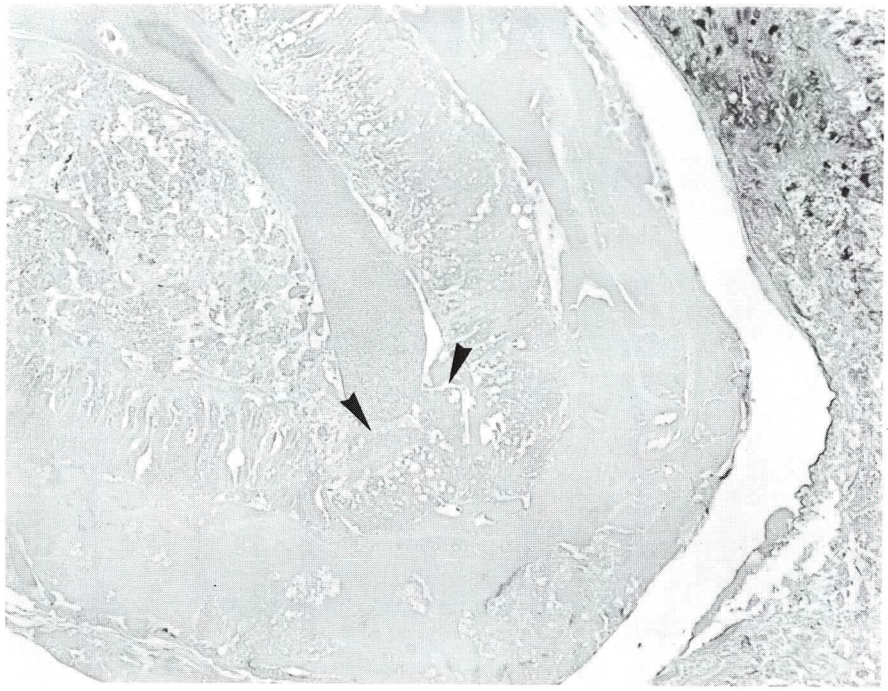

Fig. 6 Careful observation of the dead parasite revealed the presence of a clover-shaped lateral chord (arrowheads) which is characteristic of the Anisakis species. H & E, ×300

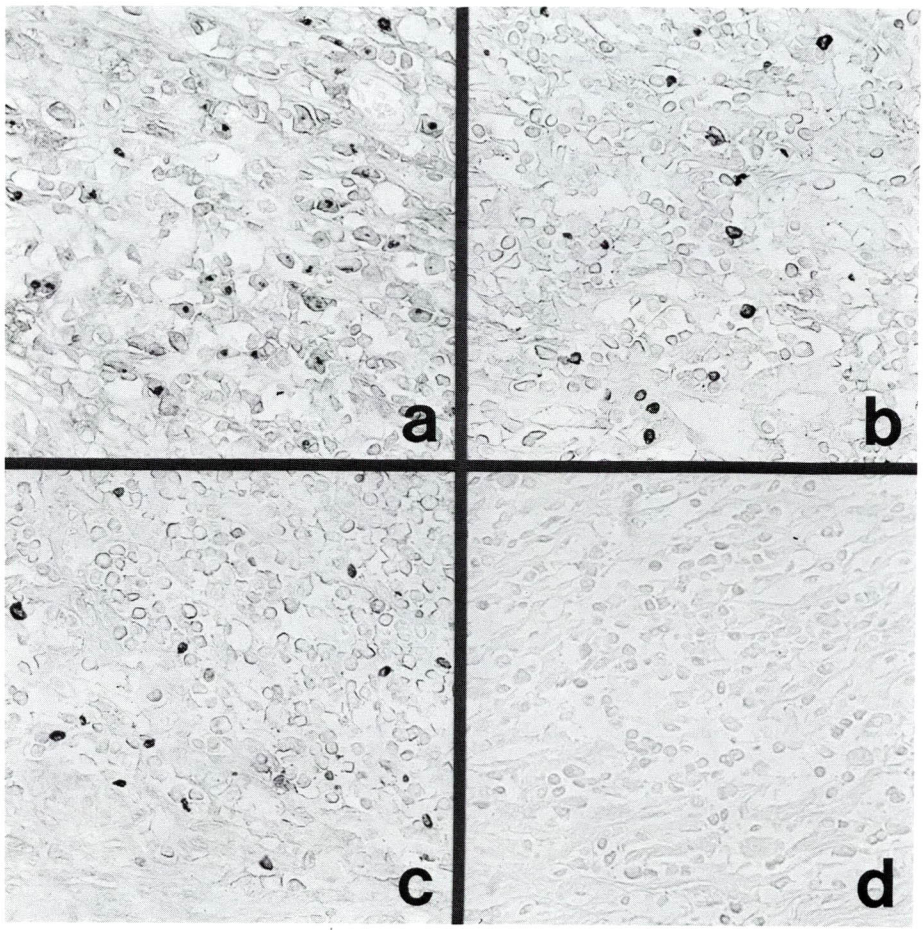

Fig. 7 An immunohistochemical examination revealed scattered IgG (a)-, IgA (b)- and IgM (c)-containing plasma cells in the inter-granulomatous area, while IgE (d) containing cells were absent. Indirect immunoperoxidase method with 1% methylgreen counterstaining, ×150

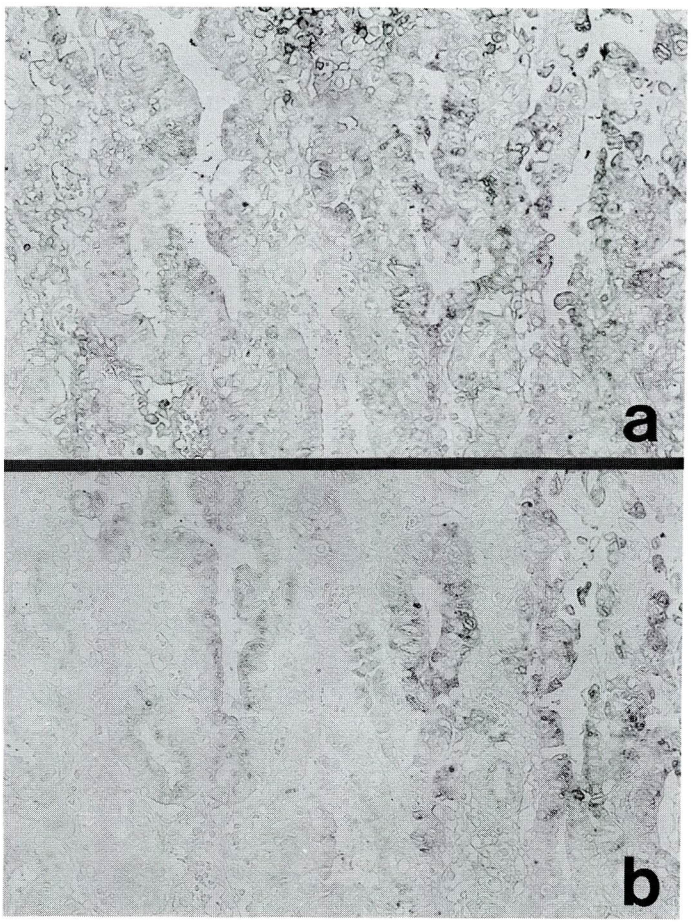

Fig. 8 The cancer cells (right half) show enhanced immunoreactivities of IgA (a) and secretory component (b) compared with the non-cancerous fundic epithelium (left half) in which these immunoreactivities are weak. Indirect immunoperoxidase method, ×150

DISCUSSION

Over 1,200 cases of human anisakiasis have been reported so far, mostly from Japan where raw fish is regularly eaten, but also from Europe, Scandinavia and North America (3, 4, 6). In 496 Japanese cases studied by Totsuka in 1973, the lesions caused by Anisakis larvae occurred in the stomach in three fourths of the cases and in the intestine in one fourth (7). Gastric anisakiasis was most commonly seen in the greater curvature of the body, while intestinal anisakiasis was most common in the ileum (7). In 1970, Suzuki *et al.* classified the clinicopathological changes of gastrointestinal human anisakiasis into two types (Table) (5): a fulminant form and a mild form. The fulminant form is characterized histopathologically by a massive eosinophilic phlegmon. Eosinophilic abscesses and/or granulomas are seen in the mild form. If the patients are previously sensitized by Anisakis antigens, drastic clinical symptoms occur by means of an Arthus-type allergic reaction. This is the fulminant form. If the worm infests a non-sensitized person, the mild form follows with a foreign body host reaction in which the clinical symptoms are mild or absent. Almost all intestinal anisakiasis is of the fulminant form, while both forms have been recorded in gastric anisakiasis (5, 7). Our patient can be categorized as the mild form. The absence of IgE-positive plasma cells around the eosinophilic granulomas suggests the non-allergic nature of the host reactions in this case.

Table Subtypes of Human Anisakiasis

Subtype	Sensitization	Host reaction	Symptoms	Histology	Site
Fulminant	+	Arthus-type allergy	+	Phlegmon	Stomach/ Intestine
Mild	−	Foreign body reaction	−	Abscess/ Granuloma	Stomach

(Suzuki *et al.* 1970, See Ref. 5)

This is only the second report of gastric anisakiasis associated with early mucosal cancer. Hayakawa *et al.* reported a similar case of gastric anisakiasis associated with early mucosal cancer classified as type IIa in 1970 (2). Possible etiological relationships between anisakiasis and gastric cancer are as follows: 1) The cancer presented an entry site for an Anisakis larva. 2) The cancer was induced by infestation of an Anisakis larva. 3) The concomitant occurrence was merely incidental.

The second possibility is most unlikely. The granulomatous lesion caused by the Anisakis larva is assumed to be formed within a few months (7), while several or more years should be necessary for the formation of a clinically detectable cancer (1). The third notion is possible. However, we would like to consider the first possibility. The susceptibility of entry of the Anisakis larva in the cancerous mucosa was not due to the lowered local immunity through the secretory immune system since enhanced immunoreactivities of IgA and SC were demonstrated in the cancer cells. Instead, the

susceptibility may have been induced by a local decrease or change in the mucin coating in the cancerous area. The cancer was located in the acid-secreting fundic mucosa, and a local defect of acid-secreting parietal cells was evident in the cancerous lesion. The cancerous mucosa might be structurally more fragile than the non-cancerous mucosa. Hence, it is possible that the worm selectively infested the cancerous mucosa because of the change of mucin, local defect of acid secretion and/or other structural alterations in the area. Statistical and experimental confirmation of this assumption must be attempted.

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