

Clinicopathologic Findings in Eosinophilic Gastroenteritis: A German Case Series

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Abstract

Eosinophilic gastroenteritis (EG) is a rare disease that includes a spectrum of clinical presentations, characterized by eosinophilic gastrointestinal infiltration in the absence of other causes of eosinophilia. The clinical presentation varies according to the intestinal wall layer and the localization within the gastrointestinal tract.

The aim of this pilot study was to assess clinical, imaging and histopathological features of a case series and to develop a questionnaire for prospective follow-up.

The diagnosis was established in 6 patients by endoscopic biopsies and in one case by sonographic imaging in the presence of peripheral eosinophilia and symptomatic response to therapy. Charts were reviewed and patients were contacted.

Since 2010, 7 patients (3 men, 4 women, mean age 44 ± 20 years) were diagnosed with EG. The most common symptom was abdominal pain, followed by bloating, intermittent nausea and diarrhea, but symptoms did not correlate well with disease location. All patients with endoscopic biopsies showed involvement of the mucosa, even in case of normal endoscopic appearance. Two had additional involvement of the muscularis and serosa. A history of allergy was reported in 43%. Peripheral eosinophilia was absent in 43%. Five patients were treated with oral prednisolone and improved within two to four weeks. In two patients no further therapy was necessary. One patient showed recurrence after 2 years and received a second successful treatment. Maintenance therapy was necessary with prednisolone in one and montelukast in another. One patient improved spontaneously and another received budesonide 9mg and an elimination diet with partial improvement.

In summary, clinicians should think of EG in patients with common gastrointestinal symptoms. Biopsies from normal appearing mucosa might increase the diagnostic yield. Most patients had good response to steroid therapy often followed by longer lasting symptom-free periods. However, long-term follow-up is necessary, because relapse frequently occurs and maintenance therapy may become necessary.

Keywords: Eosinophilic gastroenteritis; Eosinophilic colitis, Abdominal pain; Allergy

Introduction

Eosinophilic gastroenteritis (EG) is a rare disease, characterized by eosinophilic infiltration of the intestinal wall. The exact incidence is unknown. The disease affects all races and any age group from infancy to old age, although in adults, it has a peak incidence in the third to fifth decade [1,2]. The etiology and pathophysiology of this disease remain unclear but are suspected to be related to a hypersensitivity reaction because of the association with other atopic disorders and the clinical response to corticosteroid therapy [3]. The clinical presentation varies and is related to the layer and the region affected by the eosinophilic infiltration [4]. It can be classified into mucosal, muscular and serosal subtypes based on the involved layer of the intestinal wall [5].

The most common symptoms are abdominal pain, vomiting/nausea, early satiety and diarrhea. Because these nonspecific symptoms, some of which can overlap with other diseases, including irritable bowel syndrome [2], clinical suspicion of eosinophilic gastroenteritis must remain high in order to make the diagnosis. The endoscopic findings vary from a macroscopically normal mucosa to nodularity, ulceration or stenoses [6] and the treatment remains empiric due to the lack of prospective randomized trials. At the moment, corticosteroids are the mainstay therapy.

This study was designed to evaluate the clinical presentation, diagnostic findings and therapeutic outcome of eosinophilic

gastroenteritis in a series of cases seen by the authors. Furthermore, it was also used to test and modify the systematic questionnaire for future use in a prospective study.

Patients and Methods

Since 2010, all patients who were diagnosed with eosinophilic gastroenteritis at the German Diagnostic Clinic (Deutsche Klinik für Diagnostik) were prospectively registered by the authors. All patients underwent structured interviews at the initial investigation. Questions focused on clinical symptoms such as abdominal pain, diarrhoea, nausea and vomiting, early satiety and diarrhea, as well as on a history of allergies and/or specific food intolerance. Medical records of these patients were now reviewed and patients were contacted by telephone for follow-up.

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EG was defined by a) the presence of gastrointestinal symptoms, b) biopsies showing eosinophilic infiltration (20 or more eosinophils per high-power field (hpf)) of one or more gastrointestinal locations (stomach to colon), in the absence of parasitic disease or other causes of intestinal eosinophilia, or alternatively characteristic radiological findings with peripheral eosinophilia [7,8]. Klein's criteria were followed: 1) mucosal disease was defined as infiltration of the mucosa without involvement of the muscularis or serosa, 2) muscular disease was defined as complete or incomplete intestinal obstruction and eosinophilic infiltration of the muscularis without eosinophilic ascites, and 3) serosal disease was defined as eosinophilic infiltration of the GI tract with eosinophilic ascites, or biopsy proven eosinophilia of the serosal surface [4]. Data collected from the charts included demographic characteristics, presenting symptoms, laboratory testing with a special focus on peripheral eosinophilia and IgE concentrations, as well as signs of malabsorption, endoscopic, sonographic and radiological findings, histological results of biopsies, response to medication, and length of follow-up.

Results

The assessment of basic data (height, weight, age, sex, ethnicity etc.), history, disease location and distribution, laboratory data, symptom scales, physical exam findings, endoscopic and imaging studies, as well as histology and therapeutic management was performed with the use of a structured questionnaire. This questionnaire was modified and improved during the course of this pilot study to account for important data that was initially missing. In the end the modified questionnaire was again applied to all patients. The final questionnaire can be viewed in the appendix. Space for write-in responses was provided in case any additional important information had to be added.

7 patients (2 men, 5 women, mean age 44 ± 20 years) were diagnosed with EG. The diagnosis was made in 6 patients by endoscopic biopsies and additional laparoscopic biopsies in one patient, which were consistent with eosinophilic peritonitis. In one patient EG was diagnosed by sonographic imaging with a thickened wall of the duodenum, in the presence of peripheral eosinophilia and symptomatic response to steroid therapy.

Radiographic techniques including transabdominal and endoscopic ultrasound, computerized tomography and small bowel follow through (Figures 1 and 2). Fifty-seven percent of the patients had positive findings on radiographic imaging. The most common site of involvement was the stomach with thickened walls, especially in the area of the pylorus and antrum.

Half of the patients had histological and/or radiological evidence of gastric involvement (two antrum, one body, one pylorus) and 57% had involvement of the duodenum. These numbers add up to more than 100% due to the fact that some patients had multiple areas of disease. Six patients had colonic and ileum biopsies taken, 83% had colonic involvement (Figure 3) and 50% had ileal involvement, even in the absence of specific symptoms. The sites, where tissue biopsies were obtained in the patients, are summarized in Table 1.

The endoscopic findings were mostly non-specific and sometimes unremarkable. Gastric erythema or "edema" was the most common endoscopic finding (Figure 4). All patients with endoscopic biopsies showed involvement of the mucosa, two of whom had additional involvement of the muscularis and serosa, confirmed by EUS-guided fine-needle aspiration and or laparoscopic biopsy.

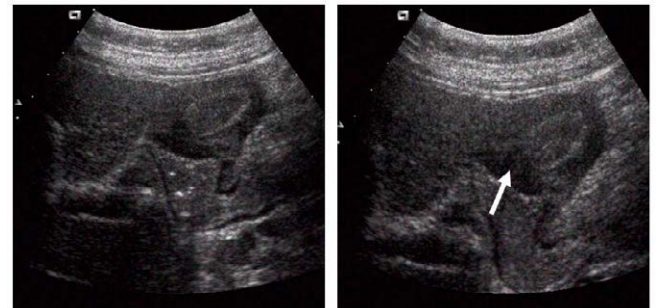


Figure 1: Transabdominal ultrasound of a patient with eosinophilic gastroenteritis showing general thickening of the stomach wall (white arrow).

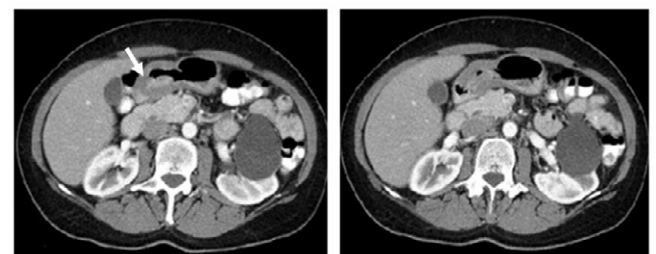


Figure 2: Abdominal computed tomography with intravenous contrast medium showing general thickening in the gastric wall (white arrows), characteristics of the distribution of eosinophilic gastroenteritis.

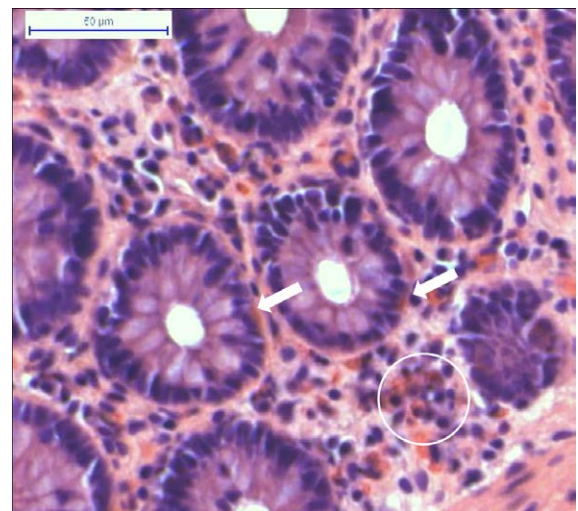


Figure 3: Histological image of a colon mucosal biopsy of a patient with eosinophilic gastroenteritis. Medium power view of dense eosinophilic infiltrates in the lamina propria and mucosa, as well as an infiltration of a crypt (white arrow) (H&E).

The most common symptom was abdominal pain followed by bloating, intermittent nausea and diarrhea. Three (43%) patients had a weight loss of less than 5kg. The symptoms and distribution of the disease are shown in Table 2.

Hypereosinophilia in peripheral blood was noted in 4 (57%) of the 7 patients and in 3 (43%) patients a history of allergy and elevated IgE-levels could be detected, respectively. Two (29%) had iron-deficiency

Site of biopsies	Patients biopsied at each site (n)	Patients with eosinophilic infiltration (n)
Gastric antrum and body	6	3
Duodenum	6	3
Proximal Jejunum	2	0
Ileum	4	3
Colon and rectum	6	5
Esophagus	4	1

Table 1: Sites of biopsies and sites of eosinophilic infiltration.

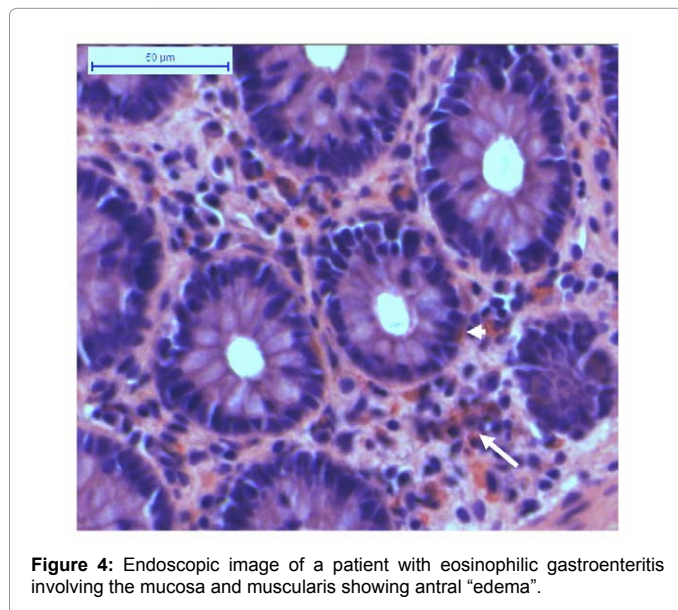


Figure 4: Endoscopic image of a patient with eosinophilic gastroenteritis involving the mucosa and muscularis showing antral "edema".

Age	Gender	Abdominal pain	Nausea/Vomiting	Diarrhea	Weight loss	Bloating/Fullness	Localisation	Layers involved
20	m	+	+	-	-	-	e*, st	muc
55	f	+	+	-	-	+	st, d, i, c	muc, mus, s
59	f	+	+	+	+	-	st,d,c	muc, mus,s
46	m	+	+	+	-	-	i,c	muc
38	f	+	-	-	+	+	i,c,d	muc
49	f	+	-	+	-	+	c	muc
23	m	+	-	+	+	+	st,d	mus

m: male; f: Female; muc: mucosal layer; mus: muscularis layer; e: esophagus; s: serosa; st: stomach; d: duodenum; i: ileum; c: colon
*no dysphagia observed

Table 2: Presenting symptoms and distribution of the disease in 7 patients with eosinophilic gastroenteritis.

anemia and none of the patients showed signs of malabsorption or protein-losing enteropathy.

Treatment included steroids (prednisolone, budesonide), dietary modification and leukotriene receptor antagonists. One patient had mild symptoms and refused treatment. Five patients were treated with oral prednisolone (initially 40 mg/day) which was gradually tapered over 6 weeks. The symptoms improved within two to four weeks to complete clinical remission. One patient who received budesonide 9mg and six food elimination diet, improved only 50%.

The median length of follow up was 14 ± 5.6 months (range 6-48

months). In two patients no further therapy was necessary, after an initial course of prednisolone. Three patients relapsed after discontinuing steroids, two of them were maintained on low dose prednisolone (2.5-10 mg/day) one of them in combination with a leukotriene antagonist. One of the three patients continues to be on monotherapy with a leukotriene antagonist to prevent relapse. One patient showed recurrence of symptoms after 2 years and received a second successful course of prednisolone. Currently, all treated patients are symptom-free. The patient without specific therapy has mild symptoms and two patients remain in remission without any treatment.

Discussion

EG is a rare disease characterized by patchy infiltration of eosinophils in one or more layers of the gastrointestinal wall [8]. After its first description by Kaijser in 1937 [9], approximately 300 cases have been reported in the literature [10]. The pathogenesis is still under debate, although several epidemiologic and clinical features suggest an allergic component.

The clinical presentation has been found vary depending on the localization of eosinophils within the intestinal wall (Klein's classification) and within the gastrointestinal tract (usually stomach to colon) [10]. Although esophageal involvement can occur, the disease must be differentiated from isolated esophageal disease, known as eosinophilic esophagitis. The clinical spectrum of the disease and response to therapy remains somewhat elusive, because most information is based on case reports or retrospective studies. In this pilot study, we aimed to develop a systematic approach to the evaluation of our patients with eosinophilic gastroenteritis and to launch a prospective follow-up investigation.

In the last three years we encountered this diagnosis with an increasing frequency in our institution, probably as a result of better recognition in our group, rather than an increase in true incidence. Because symptoms may be non-specific, the disease may be misdiagnosed, unless clinical suspicion remains high [8].

The common symptoms of the patients in the present investigation were abdominal pain followed by bloating, intermittent nausea and diarrhea. Interestingly, the symptoms were similar in all patients, regardless of the involvement of different layers of the intestinal wall or location. Our series therefore challenges the observation that clinical manifestations can reliably predict involvement of different layers of the intestinal wall or their location. The mucosal type of eosinophilic gastroenteritis has previously been shown to lead to symptoms such as vomiting, abdominal pain, and diarrhea, blood loss in stools, iron-deficiency anemia, malabsorption, and protein-losing enteropathy. The muscularis type is usually characterized by infiltration of eosinophils predominantly in the muscle layer, leading to thickening of the bowel wall, which might result in gastrointestinal obstructive symptoms. The latter phenomenon also occurred in 3 of our patients, all of whom had involvement of the muscularis propria, but also other locations. The serosal type occurs in a minority of patients with EG, and is characterized by exudative ascites with higher peripheral eosinophil counts compared with the other forms [7,4]. In our series, involvement of the serosal surface was noted incidentally in one case during exploratory laparoscopy for abdominal pain, when white exudates were seen on the peritoneum, consistent with eosinophilic infiltrates, whereas ascites only occurred later in the clinical course. The most commonly affected abdominal wall layer was the mucosa in 6 of 7 patients in this series. It has been noted by others that there seems to be a shift towards the mucosal in recent years [1,2]. However, this

higher incidence of the mucosal form might be due to bias, because it is technically easier to make the diagnosis by endoscopic biopsy than by other means, such as EUS-guided fine needle aspiration or laparoscopy [3,11]. In addition, mucosal involvement is often not isolated. Two of our patients had additional involvement of the muscularis (confirmed by EUS-guided fine-needle aspiration) and subserosa (diagnosed by laparoscopy). In one of these patients the primary clinical picture was that of gastric outlet obstruction due to involvement of the gastric muscularis. Although there was no involvement of the gastric mucosa in this case, ileocolonic mucosal involvement was found without evidence of diarrhea or malabsorption. In one patient marked thickening of the muscularis on sonographic imaging and peripheral eosinophilia was noted, but mucosal involvement was not found on biopsies. However, clinical improvement and improvement in imaging occurred after treatment, suggesting the diagnosis of eosinophilic gastroenteritis. Although it is known that EG can involve any part of the gastrointestinal tract, the stomach and duodenum are reported to be the most common site of involvement, whereas esophagus and colon are uncommonly involved [12-16]. In contrast, in our series only half of the patients had evidence of gastric involvement and 4 had duodenal involvement. In addition, a significant proportion (83%) showed colonic involvement and half of those had additional ileal disease. This finding suggests that systematic biopsies from all examined parts of the gastrointestinal tract might increase the diagnostic yield, even in the absence of specific symptoms.

Epidemiological data showed that EG can affect all races and age groups. In adults, it usually presents in the third to fifth decade [1,6,14]. Similar to this observation the median age in the present investigation was 44 years. However, the described male predominance was not confirmed in our small series [15].

Up to 50% of the patients have allergic diseases, such as asthma, drug allergy, food sensitivities, eczema and allergic rhinitis [16-18]. Corresponding to this data, in the present study 43% of the patients had a history of allergy. Though a history of allergy may be of little help in establishing the diagnosis [8,1]. Similarly, it appears that peripheral blood eosinophilia and elevated serum immunoglobulin E (IgE) are not reliable to establish the diagnosis, because they are neither universal, nor specific [8,19]. Consistent to this observation, only half of our patients showed hyper eosinophilia in the peripheral blood and less than half of the patients had elevated IgE-levels.

The treatment of eosinophilic gastroenteritis remains empiric, because until now no prospective randomized therapeutic trials exist as a result of the rarity of the disease.

Data on the natural history are also rare and are limited to case reports and retrospective series [10]. In our series steroids were very effective and all 5 patients, who were treated with prednisolone, responded. Steroids are the mainstay of treatment in EG with a 90% response rate in previous studies [6,8,14]. Some patients have no recurrences or only require periodic steroid treatment. Some patients may require long-term low dose maintenance therapy with 5-10mg prednisolone per day [20,21]. Such treatment was effective in 2 of our patients who relapsed. Several other approaches have been described in small series or case reports such as budesonide (non-enterically coated) for EG involving the gastric antrum and small intestine [22,23], oral cromolyn [8,24] or leukotriene antagonists, such as montelukast [25,26]. In our study, one patient with duodenal, colon and ileum involvement who was treated with budesonide and a six-food elimination diet only had a partial response, which might be related to the limited release of coated budesonide in the upper gastrointestinal tract. Three patients had a

relapse after discontinuing steroids, two of them maintained on low dose prednisolone (2.5-10 mg/day). One of these patients received a combination with a leukotriene antagonist. One patient is in remission on a leukotriene antagonist only, suggesting that this treatment might be a steroid sparing alternative in some.

In the present series, patients were followed up for up to 48 months. Consistent to the known data, no further therapy was necessary in 2 patients with initial steroid response. One patient had a relapse after 2 years and received a second successful prednisolone course. Long term prospective follow-up will be necessary to determine the true incidence of recurrences.

In summary, clinicians should be aware of EG as a diagnostic possibility for patients with common gastrointestinal symptoms. Biopsies should be taken even from endoscopically normal appearing mucosa if EG is suspected in order to increase the diagnostic yield. Symptoms may not always predict location and layer of origin. So far, we encountered 7 cases with a heterogeneous clinical picture and we plan future prospective follow-up of these and subsequent cases. Most patients had good response to steroid therapy often followed by longer lasting symptom-free periods.

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