

## **Eosinophilic Esophagitis and Gastritis Masquerading as Post Cholecystectomy Syndrome**

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### **Abstract**

Eosinophilic gastroenteritis is not only easy to ignore in clinical practice, but also easy to miss in the process of pathological diagnosis. It is considered an uncommon disease with a low incidence rate that remains as a diagnostic challenge for the clinician, in spite of the fact that seventy years have passed since its original description. It is characterized by focal or diffuse infiltration of eosinophils in the gastrointestinal tract in the absence of secondary causes. The pathogenesis of this condition is not well understood and its clinical presentation depends on the segment and layer of the gastrointestinal tract affected. Hereby we present the case of a 45-year-old female without history of allergies who was evaluated for unspecific gastrointestinal symptoms, without relevant findings on physical examination. Subsequently she received repeated course of helicobacter pylori eradication therapy, anti helminthes therapy and eventually underwent cholecystectomy for cholelithiasis without any improvement of her symptoms postoperatively. Later she was treated by psychiatrists and gastroenterologist as non ulcer dyspepsia for years. On complete blood count (CBC) she had persistent severe eosinophilia. The patient was evaluated and the diagnosis of eosinophilic esophagitis and gastritis was confirmed by histopathological findings. Her symptoms as well as complete blood count improved dramatically within two weeks with oral steroid and montelukast therapy. The relevance of the case resides in highlighting the lack of guidelines or consensus for histological diagnosis being virtually the only one available. To a similar extent, treatment evidence is based on case series with a reasonable number of patients and case reports.

**Keywords:** *Eosinophilic Gastroenteritis; Eosinophilia; Cholecystectomy; Oral Steroid*

### **Introduction**

Eosinophilic gastrointestinal disorders (EGD) are rare conditions characterized by excess eosinophils in the mucosal biopsies of 1 or multiple sites in the gastrointestinal tract in the absence of other known causes of tissue eosinophilia that may lead to organ dysfunction and clinical symptoms [1,2]. EGD include five variants according to their localization on the gastrointestinal tract: esophagitis, gastritis, gastroenteritis, enteritis, and eosinophilic colitis [3]. As to gastroenteritis, stomach and small bowel are the most affected segments by 26% to 81% and 28% to 100%, respectively, often associated with simultaneous infiltration of the esophagus, colon, and rectum with a minor intensity. EGD is a rare disease characterized by focal or diffuse eosinophilic infiltration of the gastrointestinal tract, in the mucosal biopsies of 1 or multiple sites in the gastrointestinal tract in the absence of other known causes of tissue eosinophilia that may lead to organ dysfunction and clinical symptoms in the absence of secondary causes like adrenal insufficiency, medication hypersensitivity

reactions, collagen vascular disease, malignancy, hyper eosinophilic syndrome or parasitic infection. EGD can affect patients of any age, but it is diagnosed most frequently in the third through fifth decade of life [4-6] and is reported to be more common in men [5]. This condition has been associated with a personal or family history of allergic disorders, such as asthma, hay fever or eczema, which are present in 60 - 70% of patients diagnosed with EGD [6,7].

Patients with EG have a variety of problems, including nausea, vomiting, abdominal pain, bloating, ascites, diarrhoea, weight loss and malabsorption [8-10]. These clinical manifestations may vary by the involved organ and by the layer of tissue targeted by the infiltrative process [4,11]. The diagnosis is established by demonstrating eosinophilic infiltration on biopsies obtained on endoscopy, laparoscopy or laparotomy. Multiple biopsies may be required because of the patchy nature of the disease [12]. We present a case of 45 years old female patient with EGD who presented with long standing dyspepsia. Subsequently she underwent cholecystectomy without any improvement of her symptoms post operatively. EGD was diagnosed on the basis of histopathological examination of biopsy sample from esophagus and stomach. She showed significant clinical and hematological improvement after oral steroid and montelukast therapy.

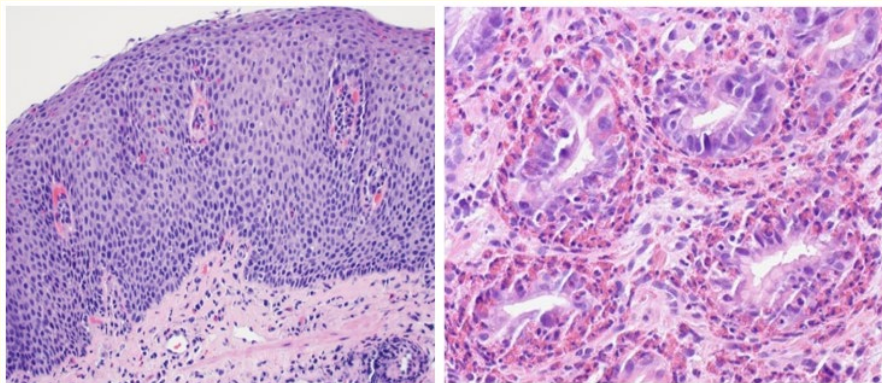
### Case Report

A 45-year-old lady not known to have diabetes, hypertension, bronchial asthma or ischemic heart disease presented with a 6 months history of paroxysmal upper abdominal pain accompanied by the nausea, episodic vomiting. She went to the local hospital where he underwent the following diagnostic investigations: Ultrasonography of whole abdomen, routine blood tests including complete blood count, liver function tests, renal function tests, gastroscopy, and colonoscopy. Multiple gall stones were detected on Ultrasonography. Random blood sugar liver and renal function tests were normal. Complete blood count revealed normal hemoglobin and platelet count but there was marked leukocytosis (74.25 K/mcL- normal 4 - 11 L/mcL) with eosinophilia (85%- normal 1% - 6%). Gastroscopy revealed gastritis, whereas colonoscopy showed a normal colonic mucosa. She was referred to hematologist where bone marrow examination excluded eosinophilic leukemia. She was given 14 days helicobacter pylori eradication therapy, gastric mucosal protective agent with anti helminthic. After two weeks of treatment, her symptoms improved slightly. Repeat complete blood count again revealed leukocytosis (27.05 K/mcL- normal 4 - 11 L/mcL) with eosinophilia (45%- normal 1% - 6%). The she was referred to surgeon where elective laparoscopic cholecystectomy was done. Post operative period was uneventful but there was minimal relief of her symptoms. She underwent CT scan of whole abdomen which was non conclusive. With the suspicion of eosinophilic gastrointestinal disease repeat upper GI endoscopy was done which revealed normal esophagus and stomach (Figure 1 and 2). Multiple biopsies were taken from esophagus and stomach.



**Figure 1 and 2:** Showing normal esophagus and stomach on upper GI endoscopy respectively.

In all biopsy specimens, the pathological findings showed acute and chronic inflammation accompanied by eosinophilic infiltration (> 20 eosinophils/ high-power field [HPF]) (Figure 3 and 4).



**Figure 3 and 4:** Histopathology of biopsy from esophagus and stomach showing massive eosinophilic infiltration of mucosa extending to submucosal layer of esophagus and stomach respectively.

She was started treatment with oral prednisolone 40 mg daily along with montelukast 10 mg daily and ketotifen 1 mg daily. After one month on OPD follow up her symptoms dramatically improved. Repeat complete blood count reveals normal white cell counts (8.04 K/mcL- normal 4 - 11 L/mcL) with normal eosinophil (2.6%- normal 1%-6%). Steroid was started tapering slowing over next 2 months. Montelukast and ketotifen was continues. At the end of 3 months of treatment she was totally symptom free.

### Discussion

EGD is a non frequent primary gastrointestinal disease of which its etiology is not fully understood and characterized by histopathologic eosinophilic infiltrates in one or more segments from esophagus to the rectum [13] where eosinophils are present in excess of 20/HPF in either the mucosal, muscular or subserosal layers [4,14]. EG can was first described by Kaijser in 1937 [15]. It may affect adults as well as pediatric population, preponderance within the male gender has been suggested [16]. Eosinophils are normally present in the lamina propria, except the esophagus, and the number of eosinophils along the GI tract varies, with the highest concentrations found in the caecum and appendix [8]. Eosinophils are involved in the mucosal immune system of the GI tract and play a role in host defense in healthy individuals [12].

It is important to differentiate it from secondary diseases associated with eosinophilia of which eosinophilic accumulation has an identifiable cause, like hypereosinophilic syndrome, inflammatory intestinal diseases, infections particularly by helminthes, vasculitis such as Churg-Strauss or polyarteritis nodosa, connective tissue diseases such as systemic lupus erythematosus, scleroderma, dermatomyositis, neoplasms, graft versus host disease in bone marrow transplant recipient patients, secondary reactions to nonsteroidal anti-inflammatory drugs, interferon, enalapril, carbamazepine, trimethoprim/sulfamethoxazole, clopidogrel, food allergies, *Helicobacter Pylori* infection, all of the above considered as differential diagnosis [17,18].

The incidence of EGD is estimated to be approximately 1 - 30/100 000 [19,20]. All ethnic groups may be affected, between 20 and 50 years of age, commonly around the third decade of life, 70% of the cases have personal and/or family history of allergies such as atopia, eczema, asthma, or allergic rhinitis. Unlike eosinophilic colitis most patients with gastroenteritis variant present elevated total serum IgE concentration [10,12,18].

The pathophysiology of eosinophilic gastroenteritis remains not fully comprehended. A hypersensitivity response is strongly suggested by clinical improvement reported in patients managed with corticosteroids. As part of the innate defense system, the presence of eosinophils in the intestinal lamina propria is a normal finding; however infiltration to deeper layers is considered abnormal. It is known that peripheral eosinophil concentration greater than  $1.5 \times 10^9/L$  can produce tissular damage regardless of the underlying cause [21,22]. The main cytokines involved in the pathogenesis of this condition are IL-3, IL-5, granulocytes, and macrophages colony stimulating factors (GM-CSF); IL-5 plays a major role being the most potent, selective, chemotactic factor along with eotaxin (CCL11) for the migration of eosinophils towards the intestinal mucosa, promoting degranulation and inhibiting their apoptosis, remaining highly activated for any event that alters the intestinal mucosa, even in non inflammatory states [21,23].

The clinical manifestations depend on the affected region of the gastrointestinal tract [11]. For example, with gastric and colonic mucosal disease, the most common symptoms are abdominal pain, nausea, vomiting, early satiety and diarrhea [4]. In contrast, dominant duodenal disease may present with malabsorption, protein-losing enteropathy and failure to thrive. Additionally, the extent of invasion of the eosinophils into the various layers can affect presentation. For instance, eosinophilic invasion of the muscular layer causes muscular wall thickening and impaired motility causing intestinal obstruction, leading to nausea, vomiting and abdominal pain and, in severe cases, perforation or obstruction of the gastric outlet, small bowel or colon [4]. Patients with subserosal EG can suffer from isolated ascites, causing abdominal distention and discomfort. Since jejunal and ileal biopsies are not routinely obtained on endoscopy, we do not know how much these gut segments contributed to the patient's presentation. Up to 80% manifest symptoms for several years, rarely presenting as an acute abdomen or intestinal perforation, all of the above should raise suspicion of a tumor which must be ruled out [10,21].

The classification proposed in 1970 by Klein, *et al.* has been the most employed, based on the depth of the eosinophilic infiltration; it can be divided according to mucous, muscular or serious involvement [4]. The mucous variant is the most common ranging from 25% to 100%, however this is not reliable due to diagnosis bias, being serous samples the least obtained for histopathological assessment. The key manifestations in mucous variant include protein-losing enteropathy, bleeding or malabsorption, nausea, vomit, diarrhea, and dyspepsia that do not respond to anti secretory therapy; the above symptoms can be confused with irritable bowel syndrome, pancreatitis, dyspepsia, appendicitis, or inflammatory intestinal disease. Muscular affection comprehends 13% to 70% of cases, manifested as thickening of the wall and obstructive symptoms such as colic pain, nausea, and vomit; it is rare to find true stenosis and, if present, jejunum is the most common site and less frequent as a caecal mass. Affection of the serosa exists in 14% to 40%, and ascites with predominance of eosinophils are the typical manifestation, along with abdominal distention and a large peripheral blood count of eosinophils, characteristically with good response to corticosteroid therapy [4,21].

The initial workup comprehends a complete medical history and exhaustive physical examination, a CBC and chemistry panel. The hemogram will typically show eosinophilia in 20% to 80% of the cases, with a mean serum count of 2000 eos/ $\mu L$  when the mucosa is involved, 1000 eos/ $\mu L$  and 8000 eos/ $\mu L$  for the muscular wall, and the serosa, respectively. It is possible to find sideropenic anemia and hypoalbuminemia especially in association with the mucous variant and a case has been reported of hypercholesterolemia as a manifestation of gastroenteritis within the duodenal muscularis mucosae as part of a protein-losing enteropathy [21,24]. The production of eosinophils is moderated by a net of cytokines that maintain their normal peripheral blood count between 0.05 and  $0.5 \times 10^9/L$  and their concentration in bone marrow aspiration between 1% and 6%. It is not normal to find eosinophils in the rest of the human economy, except for the thymus, spleen, lymphatic nodules, uterus, and gastrointestinal tract from stomach to rectum as mentioned above; however, it is important to notice that the normal count has not been yet determined [25]. Efforts have been made into establishing the normal eosinophil count throughout different segments of the gastrointestinal tract; nevertheless, it may not be widespread since the evidence is limited to small samples and including just a few ethnic groups in the same way as for pediatric population [14,26].

According to the “2011 Year Working Conference on Eosinophil Disorders and Syndromes” the term hypereosinophilia is defined as a blood count of eosinophils greater than  $1.5 \times 10^9/L$  in two samples, taken 1 month apart and/or hypereosinophilia in tissues defined by (1) eosinophils greater than 20% of all nucleated cell in bone marrow and/or (2) eosinophilic infiltration cataloged as extensive according to pathologist opinion and/or (3) marked deposition of protein granules of eosinophils in presence or absence of important tissue infiltration. Hypereosinophilia must fulfill the above criteria plus evidence of specific organ damage. However eosinophilic gastroenteritis is excluded and categorized as an organ-restricted condition accompanied by hypereosinophilia, reason by which no definitive criteria have been determined for this entity [25]; therefore peripheral eosinophilia is not an universal phenomenon in the context of eosinophilic gastroenteritis [21,25].

The stool analysis will show up to 30% of patients, mild to moderate steatorrhea. In relation to image studies, nodular or irregular thickening of the stomach or small bowel folds can be found on computed tomography [21]. Ultrasonogram is useful in the search for ascites in the variation affecting the serosa and guided paracentesis will result in being sterile with eosinophilic cellular predominance.

Endoscopy is poorly specific showing a friable mucosa, nodular changes or ulcers, occasionally diffuse inflammation with vellus atrophy, submucosa oedema, or fibrosis. Technetium (99mc) exametazime labeled leukocytes single photon emission computed tomography (SPECT/CT) can be useful for evaluating extension but not for establishing the diagnosis [18,21]. Endoscopically, mucosal disease can appear relatively nonspecific with nodularity, polypoid gastric mucosa, erythema or erosions, therefore the diagnosis is made histologically. Because of the nonspecific nature of mucosal disease, biopsies should be taken from both normal- and abnormal-appearing mucosa, as normal-appearing mucosa can also have eosinophilic infiltration [27]. The diagnosis of EGD is made by the presence of more than the number of expected eosinophils seen on a random gastrointestinal tract biopsy [28]. While there is not a designated cutoff number of eosinophils to make a diagnosis, most reports have defined EG when there are  $>20$  eosinophils/HPF [429,30].

In sum, in order to reach a diagnosis the following are required: (1) gastrointestinal symptoms, (2) eosinophilic infiltration in one or more segments of the gastrointestinal tract, by measuring the number of eosinophils under high power field view, without established threshold ranging from more than 20 to even more than 50 eosinophils, and (3) exclusion of other causes that course with eosinophilic intestinal infiltration [8,21,31].

Treatment strategies of EGD focus on either medical or dietary therapy, with the aim of not only controlling symptoms and inflammation but also identifying potential food triggers. Due to the rarity of the disease, there are no established therapeutic strategies for EGD. Hence, treating EGD is challenging. However, approximately 40% of patients will have spontaneous remission [32]. The first step of treatment includes withdraw of common allergens in the diet; nevertheless the therapeutic response is highly variable. The treatment with steroids shows an improvement in up to 90% of cases; however, the duration is not specified, and relapse is not uncommon; hence, treatment tends to extend. There is no consensus about the optimal type or dose of steroid; however, budesonide has the advantage of a local effect and a first step metabolism which entails less risk for adrenal suppression; prednisolone at 20 to 40 mg/day, for 6 to 8 weeks including the tapering, has been the most utilized regimen. Although corticosteroid treatment alone has been reported to result in clinical remission in 50% to 90% of patients with EE, about 20% will still require low-dose prednisone to maintain clinical remission due to corticosteroid dependency. In our case, the patient had good response to steroid treatment, resulting in a good prognosis. Patients who fail to respond to steroids should undergo careful reevaluation to rule out the presence of an underlying infection or alternate diagnoses (e.g. inflammatory bowel diseases). Several other approaches for the treatment of recurrent or refractory symptoms have been described in case reports or small series. Azathioprine has been used with efficacy in patients with EE who are either dependent on, or refractory to, glucocorticoids [32]. In addition, leukotriene inhibitors, mast cells stabilizers, antihistamines ketotifen, and sodium cromoglycate have also been used to treat patients with EE [33-38]. Biological therapies targeting the eosinophilic signaling pathway such as mepolizumab, an anti-IL-5 antibody, or omalizumab, an anti-IgE monoclonal antibody, have also been reported to be potential therapeutic agents for EE

[32]. However, because of the limited data available, none of these agents can be recommended for routine use. Surgery becomes useful in cases of obstructive symptoms lacking improvement with medical treatment. Parental nutrition will be useful in cases where patient co morbidities exclude the enteral route [8,21,31].

Not much is known about the natural evolution and prognosis of this disease, and it is possible that different segments are affected in the course of time or even progress to a complete hypereosinophilic syndrome which entails extra intestinal involvement for which endoscopic and cardiopulmonary follow-up is recommended [18].

### Conclusion

Eosinophilic esophagitis and gastritis is a rare and heterogeneous disease that requires a high degree of suspicion and an endoscopic biopsy for definite diagnosis; hence, the disease may probably be under diagnosed in clinical practice. Since its initial description more than 70 years ago, the efforts for characterizing the pathophysiology process and establishing standard diagnostic criteria for eosinophilic esophagitis and gastritis have been scarce. A non despicable number of cases have been reported, which indicates that clinical suspicion is increasing despite its low incidence. This entity emphasizes the importance of an invasive approach along with a thorough medical history; findings on physical examination are not useful for reaching the diagnosis, hence being fundamentally histological.

### Conflict of Interest

None declared.

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