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Ascites and Pleural Effusion as the Leading Symptoms of Eosinophilic Gastrointestinal Disease: A Case Report and Review of the Literature

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1. Summary

Eosinophilic gastrointestinal diseases (EGIDs) are rare, immune-mediated disorders characterized by eosinophilic infiltration of one or more areas of the gastrointestinal (GI) tract, various gastrointestinal symptoms depending on the affected tract region, as well as depth and extent of eosinophilic infiltration, and the absence of other known causes of eosinophilia. A case of a patient who had ascites, pleural effusion, and abdominal pain as the leading signs of the disease, is presented. The pathohistological finding of eosinophil-rich ascitic fluid on diagnostic paracentesis and eosinophilic infiltration of the esophageal, duodenal, and ileal mucosa directed the differential diagnosis to EGID. Under glucocorticoid therapy, all subjective complaints withdrew and laboratory parameters were normalized. EGID can easily remain undiagnosed and should be suspected in patients with gastrointestinal problems, in whom standard examinations cannot detect the cause of symptoms. A pathohistological finding of eosinophilic infiltration in affected segment specimens, obtained by endoscopic biopsies, is a cornerstone of confirming the diagnosis if carried out with excluding other causes of eosinophilia.

2. Introduction

Eosinophilic gastrointestinal diseases (EGIDs) are rare diseases of unknown etiology characterized by eosinophilic infiltration of the gastrointestinal tract (GIT) wall. This nosological unit was first described by Kaijser in 1937 [1], and more than 400 cases of EGID with varying clinical presentations have ever since been reported worldwide.

The incidence and prevalence of the disease in the world are growing due to lifestyle and dietary habits, but also due to more frequent recognition. The disease most often occurs in the age group of 20-50 years. The etiology and the pathophysiological mechanisms of EGE are only partially clarified, with both genetic and environmental factors considered to be involved. Many patients have a history of hypersensitivity responses like asthma, seasonal allergies, eczema, and food sensitivities.

Primary pathophysiological mechanism is the Th2-eosinophil allergic reaction caused mainly by food allergens. It induces overproduction of the cytokines eotaxin, IL-3, IL-4, IL-5, IL-13, and GM-CSF, resulting in increased eosinophils recruitment, activation, and survival, combined with antigen-specific IgE production and the eosinophilic inflammation of the gastrointestinal tract [2]. In this complex process the synergistic action of IL-5 and eotaxin is more pronounced.

The signs of this disease and the physical finding include loss of appetite, weight loss, dysphagia, heartburn, food impaction, nausea, vomiting, abdominal pain, diarrhea, melena, bloating, and

ascites, depending on the segment affected by eosinophilic infiltration and the depth of the infiltration into the organ wall. Regarding laboratory findings, these patients have elevated serum IgE, erythrocyte sedimentation is usually moderately accelerated, the number of leukocytes is slightly increased with eosinophilia values of 20-80% in differential blood count, and there is often moderate sideropenic anemia. Depending on the layer of the GIT wall that is most infiltrated with eosinophils, mucosal, muscular, subserous, and mixed types of the disease are distinguished [3]. The symptoms of the disease are non-specific and not easy to recognize because they overlap with many other more common diseases of the digestive system.

In this article, we want to present a case of ascites and pleural effusion, which led to the diagnosis of EGID.

3. Case Report

A 37-year-old female patient presented to the Emergency Department of the Infectious Diseases Clinic, complaining of progressive and painful abdominal distension and watery stools up to 15 times a day, both lasting for the last 2 weeks. No elevated body temperature was recorded until arriving at the hospital. Past medical history included: chronic bronchial asthma under intermittent long-acting beta-2-agonist and topical steroid treatment, regular medical controls due to local scleroderma (morphea) of the forehead, which was surgically removed at the age of 19, as well as nasal polyposis for which the patient had undergone three surgical interventions in 15 years. The patient denied alcohol or nicotine consumption habits.

There were no chronic liver disease stigmata or skin rash. Physical examination pointed to a remarkably distended abdomen with a positive fluid wave test, while no peripheral edema was detectable. The patient had decreased breath sound with dullness on percussion of the lower half of the right hemithorax. Her vital parameters were: RR 140/90 mmHg; pulse rate 100 beats/min; respiration rate 18/min; and body temperature, 37.6°C. The initial workup confirmed leukocytosis (22.6 x 109/L) with eosinophilia (44.3%), elevated C-reactive protein level (22.0 mg/L), potassium 3.5 mmol/L, with all other parameters unremarkable. The pregnancy was excluded, as well as viral, parasitic, or bacterial infection of the GI tract. Abdominal ultrasound showed voluminous ascites with normal liver, spleen, and kidney parenchyma. Chest x-ray revealed mild right pleural effusion and normal appearance of the heart and mediastinum. Hospital admission to the Department of Internal Medicine was chosen because gastrointestinal malignancy was suspected.

MSCT of the abdomen revealed abundant ascites with mild right pleural effusions and eccentrically thickened small intestine wall, predominantly duodenal and ileal, with soft post-contrast imbibition (Figure 1). Ascites was analyzed and described as slightly turbid, colorless fluid, WBC count 5.1 x 10^9/L, eosinophils 89%, and negative for gram and AFB stain. Eosinophilic leukemia was ruled out using cytological analysis of bone marrow smear and measurement of alkaline phosphatase concentration in leukocytes.

Preliminary diagnosis of eosinophilic gastroenteritis (EGE) was made. Esophagogastroduodenoscopy showed edema and hyperemia of the descending duodenum. Colonoscopy showed segmental mucosal edema, hyperemia, and erosions in the distal ileum. Histopathology exam found eosinophil infiltration through the stroma of the esophagus (eosinophil count >15/HPF), duodenum (eosinophil count >25/HPF), and ileum (eosinophil count >50/HPF), confirming the diagnosis of EGID (Figure 2).

After just a few days of treatment with 64 mg of methylprednisolone, diarrhea stopped, ascites significantly decreased, and the patient's general condition improved markedly. The blood eosinophil count was decreased to 430/μL, and CRP to 4.5. She was discharged from the hospital with nutritional advice on the Mediterranean diet and avoiding food rich in allergens, and with a gradual reduction of the corticosteroid dose until the first follow-up examination. After 6 weeks, the patient had no signs or symptoms of EGID, and corticosteroids were completely discontinued. During the one-year follow-up, there was also no recurrence of the disease and the patient remained only on asthma medications.

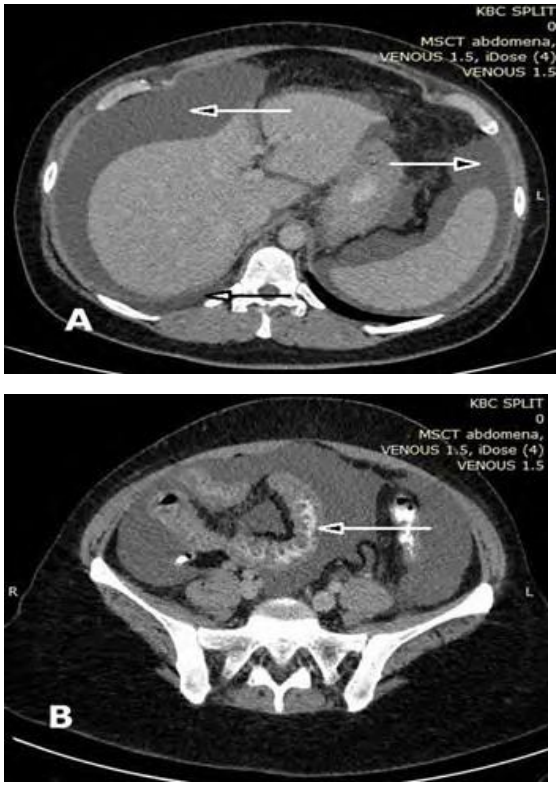

Figure 1: MSCT of the abdomen revealed abundant ascites (white arrows) with mild right pleural effusion (black arrow) **(scan A)**, and eccentrically thickened small intestine wall ("saw-tooth" mucosa), predominantly duodenal and ileal, with enhanced post-contrast imbibition **(scan B)**. Muscular involvement is indicated by an irregular narrowing of the lumen filled with barium contrast. Stratification, haziness, and increased enhancement of the surrounding mesentery and fat tissue suggest serosal infiltration of the bowel wall.

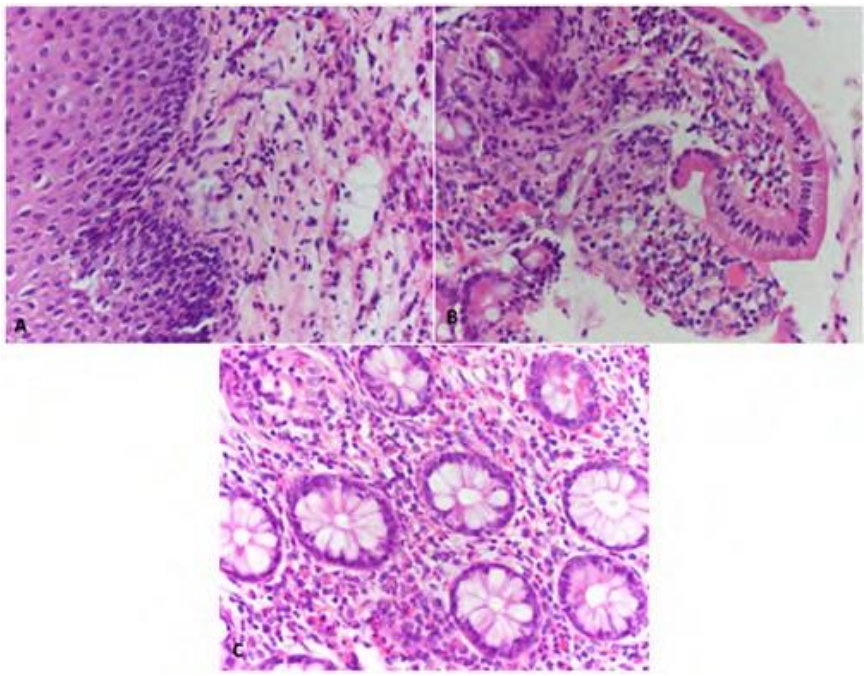

Figure 2: Histological examination of biopsy specimens from EGID patient demonstrates a dense eosinophilic infiltration in the esophageal (A), duodenal (B), and ileal (C) mucosa (hematoxylin-eosin stain, magnification ×40); the eosinophils are seen in red with a lobulated nucleus, predominantly located within the lamina propria, and showing signs of degranulation (red coloration outside cells).

4. Discussion

The eosinophilic gastrointestinal diseases (EGIDs) remain underdiagnosed, due to the insufficient understanding of EGE, the variety of symptoms and endoscopic presentations, the poor communication between clinicians and pathologists, and the lack of clarity in the terminology previously used to describe these diseases. The diagnosis is often delayed several years after the first visit to the doctor [4]. Because of all mentioned, the nomenclature of these diseases is revised in 2022. by an international consensus. Eosinophilic gastrointestinal disease (EGID) has since been a collective name for eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), eosinophilic enteritis (EoN), and eosinophilic colitis (EoC). The earlier term «eosinophilic gastroenteritis» (EGE), which was often used as a comprehensive phrase for all non-EoE EGIDs, was abandoned [5]. The patients may have concomitant eosinophilic infiltration of multiple segments of the gut and the final diagnosis should reflect all of the involved areas. It is also practical to distinguish between EoE and non-EoE EGID.

Recent studies and case reports have demonstrated that these rare diseases' incidence has been increasing, which can be explained by diet and lifestyle, but also by greater knowledge and a better understanding of this disease. According to an American study [6], EoE is the most common form of EGID (52/100,000 population), while EoG, EoN, and EoC together occur in 28/100,000, with the prevalence decreasing distally and EoC occurring only in 3/100,000 population. In a retrospective-prospective study, Abassa KK, et al. revealed that more than 4.3% of cases were missed diagnoses of EGID in patients whose upper and lower GI endoscopy and histopathology results showed only chronic inflammation [7]. Endoscopy with biopsy of the mucosa with histological confirmation of eosinophilic infiltration is an indispensable criterion for making a diagnosis. The reason for such a large number of unrecognized cases is that pathologists often do not accurately determine the level of infiltration of certain segments of the GI tract if they are not warned by the clinician [8]. In addition to the increased number of eosinophils in intestinal mucosal biopsy specimens, the diagnosis is additionally indicated by histological changes such as the grouping of eosinophils into clusters, their presence in the epithelium and lamina propria, and the formation of eosinophilic cryptitis and crypt abscesses with consequent gland destruction [9].

We suspected eosinophilic enteritis due to anamnestic data on asthma and the patient's atopic constitution, which is characteristic of 50-70% of patients with EGIDs [10]. A high level of IgE and high eosinophils count in the serum is also a very common finding [11], but the most important indicator was a high concentration of eosinophils in ascites, as well as wall thickening in the duodenum and ileum, visualized in an MSCT scan. For this reason, endoscopic examinations were performed and eosinophilic infiltration of the mucous membrane was proven in almost all segments of the intestine, which is a mandatory finding for establishing the diagnosis, after ruling out other causes of eosinophilia.

All gastrointestinal symptoms associated with eosinophilic gastroenteritis are not specific and can be found, in different combinations, in many other common organic and/or functional disorders, such as food intolerance, irritable bowel syndrome, inflammato-

ry bowel diseases, celiac disease, and alimentary infections. The diagnosis can therefore only be confirmed based on endoscopic findings and histopathological criteria, which is also not a simple process because endoscopic findings are non-specific and vary from a completely normal appearance of the mucosa to very significant changes such as edema, hyperemia, erosions, ulcerations, and bleeding. In addition, it is difficult to assess eosinophilic infiltration of intestinal segments due to uneven involvement of the intestinal wall. Therefore, when EoE is suspected, it is necessary to take multiple random biopsies, according to most authors at least 5-6 from each segment of the digestive tract. (12) Frequent watery diarrhea is the most common symptom of EGID ranging from 25% to 100%. It was the first symptom of the disease in our patient because the mucosa is almost always affected either as an isolated mucosal type or as part of a mixed form of the disease. If the muscular layer is dominantly affected (13% to 70% of cases), obstructive symptoms such as colic pain, nausea, and vomiting may occur, as well as obstructive jaundice if the biliary tree is involved [13]. Ascites, pleural effusions, and a CT finding of wall thickening indicated eosinophilic infiltration of the entire wall, including the serosa. Pleural effusion in EGID patients is also characterized by an elevated number of eosinophils and can be massive, causing respiratory insufficiency. The dominant findings of ascites and the thickening of the intestinal wall spoke in favor of the subserous infiltration subtype, the least common form of the disease (exists in 14% to 40% of cases), usually present when the entire intestinal wall is infiltrated with eosinophils [14]. A very rare form of EGID is eosinophilic infiltration limited to the serous and subserous layer of the intestinal wall. In that case, neither endoscopic changes nor increased eosinophilic infiltration of the mucosa is seen, which further complicates the diagnosis. Sometimes it is necessary to obtain samples of the outer layer of the intestinal wall laparoscopically because clinical and radiological presentations of a serosal form of eosinophilic gastroenteritis can be atypical and mucosal biopsies may appear normal [15]. In our patient, the entire intestinal wall was affected, but predominantly the outer layers, as shown by the histological findings of mucosal samples with an increasing number of eosinophils towards the distal parts of the digestive tract, as well as a large number of eosinophils in ascites. Also, the symptoms indicated that all layers of the intestinal wall were affected - diarrhea as a sign of mucosal and submucosal infiltration, and ascites and pleural effusion as signs of serous and subserous infiltration.

After excluding intestinal and systemic infectious diseases as possible causes of the symptoms and with a strong suspicion that it is the EoE with the outer layers of the intestinal wall being dominantly affected, we started treatment with methylprednisolone following generally accepted guidelines, which resulted in rapid reduction of ascites and pleural effusion with regular stools and an improvement in the general condition. This also represented an additional confirmation of the diagnosis. Chambrun et al. analyzed the files of 43 patients who were diagnosed with EGID and were then followed for 21 years. Out of 27 patients who were treated with medication, 20 of them (74%) received oral corticosteroids. Only 1 patient did not achieve remission. Patients with subserous type of disease had the lowest percentage of relapses, while the majority of patients who presented a recurring or chronic type of disease had predominant mucosal and/or muscle layer disease [16].

Early recognition and treatment of these diseases is very important because of possiblle complications depending on the affected layers of the digestive tract wall. Diffuse involvement of the mucosal layer can lead to malabsorption, peripheral edema, ulcers with acute or chronic GI bleeding, iron deficiency anemia, and even failure to thrive, involvement of the muscular layer can cause wall thickening and intestinal obstruction, and when the subserosa is affected often develop ascites and pleural effusion, which, if massive, can lead to respiratory failure [17].

5. Conclusions

This reported case indicates the difficulties in establishing the diagnosis, assessing the spread of the disease, and choosing the optimal treatment of eosinophilic gastrointestinal disorders. We emphasized the importance of anamnestic data on the allergic constitution, clinical and laboratory parameters correlation, diagnostic criteria based on ordinary and specific diagnostic procedures, and personalized therapeutic approaches. An important step is the recent international consensus about the classification of EGID, and in the same way, better standardization of diagnostic criteria, evaluation, monitoring and treatment of these diseases should be done.

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