Case 2-2013: Eosinophilic Ascites (EA); Pathophysiology, Differential Diagnosis and Therapeutic Challenges

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Eosinophilic ascites (EA) is a rare disorder of unknown etiology that has been reported in both adult and pediatric patients. It is a part of the eosinophilic gastroenteritis (EGE) syndrome, which is characterized by the presence of non specific abdominal complaints in association with eosinophil-driven inflammation of any or all layers of the gut wall. Peripheral eosinophilia may or may not be present. Here, we report a case of EA, a rare presentation of the serosal variant of EGE that developed in a thirty years old Egyptian female. She complained initially from nonspecific GI symptoms associated with diffuse abdominal pain and distention for several weeks. Her physical examination was significant for moderate ascites. Initial work-up demonstrated: very high peripheral eosinophilia, normal liver function tests, thickening of the small and large bowel walls, and normal total serum IgE. Upper endoscopy and extensive testing for malignancy and parasitic infections failed to establish a diagnosis. Ascetic fluid analysis showed significant eosinophilia. Further, a duodenal biopsy showed marked eosinophilic infiltration of the lamina Propria. This report adds to the scarce data on serosal involvement, "the rarest form of presentation" and illustrates that EGE complicated by ascites can be effectively treated with a combination therapy of steroids and the leukotriene receptor antagonist "Montelukast" after other systemic disorders associated with peripheral eosinophilia have been ruled out. The pathophysiology, differential diagnosis as well as therapeutic challenges associated with EGE are discussed.

INTRODUCTION

Eosinophilic gastrointestinal disease (EGE) is a rare chronic inflammatory bowel condition of unknown etiology that was originally described by Kajiser in 1937 [1]. EGE is a spectrum of gastrointestinal (GI) disorders characterized by inflammation rich in eosinophils without evidence of other known causes of eosinophilia (i.e., parasitic, infectious, drug reaction, or malignancy) [2]. The disease can affect one segment or several segments of the GI tract from the esophagus to the rectum, giving rise to various clinical presentations. Three distinct subtypes of EGE are recognized. The most common "mucosal" form (58% of cases) typically presents with nausea, vomiting, abdominal pain, diarrhea and malabsorption, while involvement of the muscularis (30% of cases) may manifest with symptoms of obstruction. Serosal involvement is rare, occurring in less than 13% of cases of EGE, and can result in abdominal pain and eosinophilic ascites (EA) [3]. Most reported cases of EA are idiopathic, often accompanied by an atopic condition, such as asthma, food or medication allergy. Peripheral eosinophilia is a usual finding in most cases of EA [4,5]. EGE is primarily a polygenic allergic disorder involving mechanisms that fall between IgE-mediated food allergy and cellular-mediated hypersensitivity disorders [2]. Steroids are the main therapy for cases in which diet restriction is not feasible or has failed. The recent researches suggest a similar pathophysiology to asthma. Cysteinyl leukotrienes are known to have potent chemo- attractant properties for eosinophils. Together with interleukins 3 and 5 they play a major

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role in the recruitment of eosinophiles into the tissue causing damage. Disrupting this vicious circle provides the rationale for treating EGE patients with the leukotriene receptor antagonists (LTRA) [6, 7].

Case report

We present a 30-year-old single female working as a school teacher from a rural area not known to have any previous chronic medical illness. She experienced intermittent nausea, non-bloody vomiting and diarrhea for several weeks, accompanied by upper abdominal pain and distention which was increased after meals. There was no obvious aggravating or relieving factors for her abdominal pain. She received nonspecific treatment in the form of domperidone, omeprazole, and an anti-flatulent without improvement. However, her abdominal distention was worsening and associated with severe bloating. She denied any history of fever, night sweats, weight loss, blood transfusion, recent travel, respiratory symptoms, rash, allergies, or ill contact. There was no history of liver or heart disease. She was not consuming alcohol or any illicit drug, and was taking neither medications nor supplements. She had a regular menses with no gynecologic troubles. She had no family history of liver disease, atopy or coagulation disorders. On physical examination, the patient was alert, well built, and showed no signs of distress. She was afebrile and hemodynamically stable and her skin and mucosa were anicteric and clear without spider angiomata, no lymphadenopathy or pedal edemas were detected. The cardiovascular and thyroid examinations were normal. Chest examination revealed; dullness to percussion over the right lower lobe, with auscultation we demonstrated decreased breath sounds over the right lower lobe, no wheezing or crackles but increased egophony was detected. The abdomen was distended and diffusely tender with active bowel sounds and positive bilateral shifting dullness; no caput medusae, rebound or guarding were observed, no hepatosplenomegaly were detected. Her investigations were as follow: Hgb 12.9 g/dL, Htc 38, PLT 415,000/mL, WBC 11,800/mL, differential: segmennonuclear neutrophils 48%, lymphocytes 9%, monocytes 1%, eosinophils 42% (absolute count, 7200). ESR was 9 mm/hour. Serum electrolytes, urine analysis, renal functions, serum amylose &lipase, coagulation studies, thyroid and liver tests were all normal. HIV (human immunodeficiency virus) ELISA, hepatitis markers (HbsAg & HcvAb) as well as autoantibody screen were all negative. Cancer Antigen-125 (CA-125), CEA, CA19-9, and alpha feto-protein were all negative. She had a positive tuberculin (purified protein derivative or PPD) skin test of 12 mm induration diameter after 48 hours. Total IgE was normal: 147 U/ml (range 5 to 200). Parasitic infestations were excluded by repeated negative stool studies and negative serology for Echinococcus, Strongyloidiasis, and Toxocariasis. However, we gave her a precautionary course of oral albendazole (400 mg twice a day for 5 days) with no change in her current state for almost two weeks until the investigations were completed. On abdominal ultrasonography, the liver was normal in size and echogenicity, and all vessels were patent. There was a moderate amount of pelvic and abdominal ascites and a mild right-sided pleural effusion. Chest x was normal apart from the mild RT sided pleural effusion. Computed tomography (CT) of the abdomen and pelvis revealed moderate volume ascites with no solid organ tumors, lymphadenopathy, or omental deposits but with thickening of the small intestinal and colonic walls. Diagnostic ascitic aspirate revealed straw colored fluid with no cytological signs of malignancy, with protein level 5.5 g/dL, albumin 3.4 g/dL, (low SAAG of 0.8), RBC 1200/mL, WBC 1.780/mL with eosinophilic predominance of 73%. Ascitic fluid for bacterial culture and for tuberculosis had no growth, ascetic adenosine deaminize (ADA) as well as PCR for tuberculosis were negative. Ascitic Glucose, amylase, and LDH had normal values. Bone marrow biopsy demonstrated an increased myeloid-to-erythroid ratio with an increase of eosinophilic component (up to 35% of the myeloid precursors); there was no evidence of dysplasia. Upper GI endoscopy demonstrated patchy erythema in the lower esophagus and gastric antral regions, and duodenal edema. Mucosal biopsies were obtained, and were consistent with mild reflux esophagitis and antral gastritis manifested as mild nonspecific acute inflammation predominantly lymphocytic but no eosinophilic infiltration could be detected. However the duodenal biopsies demonstrated eosinophilic infiltration in the lamina propria of more than 20 eosinophils/high power field. Unfortunately, the patient refused colonoscopy or laparoscopy which would have been the next steps in the clinical work-up of eosinophilic gastroenteritis. The constellation of clinical
features, eosinophilic ascites, thickening of intestinal and colonic walls, eosinophilic infiltration in the lamina propria of the duodenum and peripheral eosinophilia were all consistent with the diagnosis of EGE after exclusion of other possible causes of such condition. She was empirically treated with a combination regimen of prednisone (40mg/day) plus montelukast (10 mg/day) for two weeks. The dose of steroid was tapered off over the following 2 weeks and the patient was left on montelukast alone to avoid the serious long term adverse effects of steroids. After completion of steroids, the patient’s abdominal pain and physical finding of ascites had completely resolved and peripheral blood count revealed an absolute eosinophil count of 378/μl (N < 450). Furthermore, chest x was normal with complete resolution of the RT sided pleural effusion. CT imaging of the abdomen and pelvis showed disappearance of the ascites and small and large bowel thickening. Four months have elapsed since treatment was initiated and the patient remained asymptomatic on montelukast alone. As there is no clear treatment end point for montelukast in the literature, we intend to keep our patient on this safe drug for one year to avoid the commonly met with relapses after cessation of steroids.

DISCUSSION

Eosinophilic gastroenteritis (EGE) is a rare condition characterized by recurrent [8] eosinophilic infiltration of portions of the gastrointestinal tract presenting with nonspecific GI symptoms in association with peripheral eosinophilia in most of the cases [9, 10]. In a study conducted on 15 patients with EGE, Chen et al. reported that abdominal pain and diarrhea were the most common presenting symptoms. Our patient complained of similar presentations for several weeks with no response on nonspecific treatment. One-third of the patients in Chen et al study, had history of allergy and more than 80% were found to have peripheral eosinophilia [8]. Peripheral eosinophilia was marked in our patient, with 42% eosinophilic predominance (normal range 1-3%). Although profound peripheral eosinophilia in EGE is usually associated with the serosal form, it should be noted that eosinophil count can be normal at presentation in up to 23% of EGE patients in general, which may further obscure the diagnosis and require an extensive and invasive work up and surgery [3, 12]. EA is a rare presentation of EGE and should be considered when facing a patient with ascites in the absence of liver disease, and with refractory gastrointestinal symptoms, especially in the presence of a concomitant allergic condition [29, 30]. The most common classification of EGE based on the involved layer of the GI tract is known as Klein’s classification. Subsequently, there are three subtypes of EGE (mucosal, muscular, and subserosal), with some degree of overlap [3, 9]. Data are insufficient in regard to the true prevalence of EGE and each of its subtypes. However, the mucosal form is the most common followed by muscular and lastly subserosal [2]. The stomach and duodenum are the most commonly affected sites in EGE, with colonic involvement being less common. However it is unclear whether this represents bias related to accessibility to endoscopic biopsy [3, 27]. The etiology and pathogenesis of EGE remain unclear. The role of allergy in recruitment of eosinophils to the GI tract remains controversial. Several studies have shown that half of the patients with EGE had a preexisting history of atopy [3, 11]. Moreover, Alfadda, et al; confirmed the presence of strong association with atopy in 80% of EGE patients reporting a personal history of asthma, eczema, allergic rhinitis or drug allergy. The association with atopy suggests a genetic component and unsurprisingly approximately 16% of patients with EGE have a family member with a similar condition. They added that activated eosinophils release an array of cytotoxins by degranulation, including Major Basic Protein (MBP), Eosinophil Cationic Protein (ECP) and others, producing tissue damage both directly and by downstream production of cytokines and leukotrienes. Eosinophil degranulation also triggers the release of histamine from mast cells, further perpetuating inflammation and cell damage [27]. In addition, serum IgE levels were elevated in some patients; which was not the situation in our case as she denied any history of allergy or food intolerance and her IgE level was normal. Although rarely IgE antibodies are directed against identified food allergens, yet in an interesting case report presented by B. Rodriguez et al, they found that Skin prick tests and patch tests with different allergens were all negative in their EGE confirmed patient. The patient’s eosinophil cationic protein (ECP) level was very high. Given that one of the most common causes of this condition is allergy to cow’s milk, ECP levels were determined during
a diet with and without cow’s milk. ECP levels were considerably elevated during the diet with milk, although it returned to normal values several months after milk was withdrawn. The favorable clinical outcome and normalization of ECP levels point to a very probable association with cow’s milk in EGE presented in that patient. On the other hand, hypoallergenic diets have not been shown to be of significant benefit in treating EGE specially the serosal variant of the disease. Regardless of the initial trigger, activated tissue eosinophils are known to release various chemo-attractive cytokines resulting in recruitment of more eosinophils into the affected tissues [2, 10, 12, 21]. Symptoms of EGE are nonspecific and overlap with many other GI and systemic diseases. Mucosal subtype of EGE often presents with abdominal pain, nausea, vomiting, and/or diarrhea. Eosinophilic infiltration of the tunica muscularis results in a thickened rigid gut that produces symptoms of intestinal obstruction [6, 8]. Finally, patients with the exceedingly rare serosal EGE have ascites as the source of their symptoms [2, 9–11]. Furthermore, this subgroup is clinically distinct in having abdominal bloating, higher eosinophil counts, and dramatic response to steroid therapy [3, 29]. Eosinophilia is a distinguishing feature of ascites in patients with serosal EGE. Further characterization of 42 patients with this subtype of EGE by Durieu et al. revealed female predominance with 75% of the patients being females 40 years and older. Moreover, the study showed that 69% of these patients had peripheral eosinophilia and 11% had pleural effusion which was almost similar to our case. The diagnosis of EGE is established on high clinical suspicion in conjunction with suggestive histopathologic findings. Although peripheral eosinophilia is very common in all subtypes of EGE, it can be absent in as high as 23% of cases. In addition, 25% of the patients may have moderately elevated erythrocyte sedimentation rate (ESR) which was not the case in our patient [3]. Thus, tissue samples are essential for confirming the diagnosis and classical findings include sheaths of eosinophils in the involved layer [12]. Nevertheless, this is not always an easy task as multiple endoscopic biopsies may be required due to the patchiness of the disease and diagnosis can be missed in up to 25% of cases [3]. Moreover, in cases where the diagnosis remains uncertain, CT imaging can help in localizing areas of thickened bowel suitable for surgical full thickness biopsy [12, 14]. In contrast to the other two types, serosal EGE may be confirmed by ascetic fluid analysis, which in the majority of cases reveals predominant eosinophilia reaching up to 99% of the white cells [15, 16]. No test specific for EGE is available and prior to establishing such a diagnosis, a number of GI and systemic diseases should be excluded. Many of these disorders have similar presentations and may be associated with eosinophilia. The differential diagnosis should include parasitic infections with Visceral larva migrans as "Toxocariasis, Strongyloides, Trichinosis, Echinococcus, Ascaris suum, Capillaria hepatica, and Anisakis” [17, 22]. In any case, it is essential that parasitic infection is completely out-ruled prior to treatment of EGE, as initiation of corticosteroid therapy in the presence of occult parasitic infection may result in catastrophic disseminated disease [25]. Other differential diagnosis include, malignancies such as "intestinal lymphoma; gastric cancer; colon cancer and ovarian malignancy". Para neoplastic eosinophilia, inflammatory bowel disease, and more rarely connective tissue diseases as SLE with overlap syndrome [24,25, 26], systemic vasculitides such as polyarteritis nodosa and Churg-Strauss syndrome. The distinctive histologic features of EGE are absent in these diseases. Another major differential diagnosis of EGE is idiopathic hypereosinophilic syndrome (HES), a condition associated with marked peripheral eosinophilia and gastroenteritis. In addition to possible involvement of the GI tract, this systemic entity may involve the heart, lungs, brain, and kidneys and frequently has a progressive course, while EGE lacks any extraintestinal manifestations [2, 3]. Further investigations to exclude the HES may be indicated in certain cases, and investigations should assess for each of several pathogenetically distinct variants of the HES. For example, clonality of eosinophils on phenotyping implies a diagnosis of chronic eosinophilic leukemia. A subset of these patients has F/P-associated HES, in which a sporadic hematopoietic stem cell chromosomal rearrangement occurs, producing the F/P fusion gene on 4q12. The F/P fusion gene can be detected using reverse transcription polymerase chain reaction or fluorescent in situ hybridization for surrogate markers of the chromosomal abnormality. In contrast, lymphocytic-HES occurs when a proliferating T cell population overproduces interleukin-5 resulting in reactive polyclonal hypereosinophilia. Analysis of T cell
subsets to detect a phenotypically aberrant T cell population, and assessment of T cell receptor gene rearrangement patterns to assess for clonality may reveal an underlying primary T cell disorder as a cause for eosinophilia [28]. These investigations are essential in suspected HES cases as certain variants; in particular F/P-associated HES demonstrate dramatic therapeutic response to the tyrosine kinase inhibitor imatinib. Finally, when EGE presents as a part of HES, patients should be referred for appropriate hematological evaluation, since eventual malignant transformation is a possibility [28]. Available data on the natural history and therapy of EGE remains scarce. Untreated patients can remit spontaneously [22] or progress to develop severe malabsorption. In most cases, the disease is essentially benign and pharmacologic therapy is not always indicated [14]. Many patients have been reported to spontaneously recover over a period of days however; others have a relapsing-remitting course and require long-term treatment with steroids, usually at a low dose of prednisone (5 to 10 mg/day). [13, 18, 19]. The outcome of EA in particular was favorable in 90% of patients while relapses occurred in 26% of 42 cases studied by Durieu et al. [11]. More symptomatic patients require therapy with prednisone (20 to 40 mg/day) which is considered the current standard treatment. A two-week course produces dramatic clinical improvement regardless of the histological subtype of EGE. Rapid tapering over another two weeks is sufficient to keep the majority of patients in remission [2, 12, 19]. For localized disease or where systemic corticosteroid treatment is not well tolerated, topical corticosteroid therapy in the form of swallowed fluticasone or non-enteric coated budesonide may be of benefit. It is unclear whether topical corticosteroid treatment is as efficacious in serosal EGE as compared with the mucosal variant [25, 31]. In cases that fail to respond to corticosteroids, treatment with azathioprine or 6-mercaptopurine should be considered [20]. Multiple therapeutic strategies have been tried in order to avoid steroid side effects (steroid sparing regime). Novel approaches in the treatment of patients with EGE include the use of sodium cromoglycate for its mast cell stabilizing properties, especially in individuals with a strong history of atopy or elevated serum IgE and mucosal predominant disease [32]. Another therapeutic option is the leukotriene receptor antagonists " Montelucast" which has been successfully used in treatment of serosal EGE with EA [33]. Moreover, Monoclonal antibodies directed against IgE and IL-5 (omalizumab and mepolizumab respectively) as targeted treatments for EGE and other eosinophilic conditions show some promise in early clinical studies [34, 35]. In addition to the above pharmacological approaches, it may be possible to significantly reduce steroid dependence in patients with documented food allergies through elimination, oligoantigenic or elemental diets [27]. These medications offer a steroid-sparing approach to treatment of EGE which aids in avoiding the serious side effects of steroid therapy. The latter is especially important in the younger patient population.

CONCLUSION

EGE is a rare condition characterized by recurrent eosinophilic infiltration of portions of the GI tract and presenting with nonspecific GI symptoms in association with peripheral eosinophilia. Its etiology and pathogenesis remain obscure and its symptoms overlap with many GI and systemic diseases. Thus, the diagnosis of this readily treatable and easily missed disease requires a high index of suspicion accompanied by the judicious application of tests. We presented a case of EA which is considered one of the rare presentations of EGE and is typically associated with the serosal variant of the disease; also it behaves in a manner distinct from the more common mucosal EGE. Our patient was a thirty years old female who presented with non-specific abdominal symptoms. Investigations revealed large volume eosinophil-rich ascites and a markedly elevated peripheral eosinophil count. Histopathological diagnosis is essential and is usually complicated by the patchy nature of mucosal disease and the paucity of mucosal infiltration in the serosal predominant form. In our patient, we could not perform colonoscopy or laparoscopy due to patient's refusal. However, duodenal biopsies; markedly elevated peripheral eosinophilia; and eosinophilic ascites as well as bowel thickening by imaging studies and, otherwise, negative workup for TB, parasitic infections and malignancy confirmed the diagnosis of EGE. So she was put on a combination regimen of prednisone (40mg/day) plus montelukast (10 mg/day) for two weeks. The dose of steroid was tapered off over the following 2 weeks and the patient was left on montelukast alone. Four months after her initial presentation, the patient is asymptomatic with a normal absolute
eosinophilia. Fortunately, novel targeted pharmacologic therapies provide promise for steroid-free remission for patients with EGE. As there is no clear treatment end point for montelukast in the literature; we intend to keep our patient on this safe drug for one year.

REFERENCES


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