Eosinophilic ascites - a rare presentation of eosinophilic gastroenteritis with spontaneous remission and relapse in an adolescent

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\textbf{ABSTRACT}

Eosinophilic ascites is a severe form of eosinophilic gastroenteritis presenting as unexplained ascites with normal liver function tests. Our patient had a window period of spontaneous remission making the diagnosis difficult during the early stage. Eosinophilic gastroenteritis can present in children as nonspecific gastrointestinal (GI) symptoms such as diarrhoea and abdominal distension, making it clinically indistinguishable from other causes of chronic diarrhoea.

\textbf{Key words:} Ascites, Diarrhoea

\textbf{INTRODUCTION}

A 15 year old previously well Caucasian girl presented with a six-week history of nausea and vomiting, diarrhoea, abdominal pain and abdominal distension. She reported 2-3 episodes of watery diarrhoea a day, associated with urgency; there was no blood or mucus in the stool. The vomiting was not blood or bile stained, and was not associated with food. The abdominal pain was diffuse with localised stabbing pains in the flanks, exacerbated by eating. She described appearing pregnant during the initial stages of her illness due to gross abdominal distension, however her menses were regular and a pregnancy test was negative.

There was no history of fever, dysuria, increased urinary frequency, rash, joint pain/swelling, or abdominal surgery. There was no significant travel history, and no known food or drug allergies. The patient was known to have eczema but not asthma, and was not on any medication. There was no family history of inflammatory bowel disease, and her siblings and parents were well. She was treated with Mebendazole and Metronidazole for suspected parasitic infection at local hospital in view leucocytosis with eosinophilia on routine blood tests and referred to our unit for further assessment in view of 7.3 kg weight loss since she became unwell.

On inspection, she looked systemically well and she was 151.2 cm in height and 50.02kg in weight and BMI 21.8. Surface body piercings were noted on both lower abdominal quadrants, which had been made two months prior to the patient becoming unwell. The abdomen was mildly distented (admitted an improvement prior to referral to our unit). Cardiovascular, respiratory and oral examinations were normal and there was no pedal oedema.

One week later, the patient reported a global improvement. Abdominal ultrasound showed mild ascites. An endoscopy was performed due to the suspicion of eosinophilic GI disease, but was unremarkable both macroscopically and microscopically.

A week later the patient reported spontaneous remission of symptoms. However, 5 months later she presented to Accident and Emergency with a five day history of severe sharp abdominal pain radiating to the back with bloody diarrhoea. This was associated with a three week history of non-bilious, non-bloody vomiting with reduced appetite.

The abdominal pain was exacerbated by eating and was not alleviated by defecation, paracetamol, buscopan, gaviscon or ranitidine. The patient was passing 1-2 watery stools per day, occasionally with blood but no mucus. The patient’s mother reported a weight loss of 2.5 kg.

On examination the patient was alert and not in distress. She was afebrile, warm and well perfused with no jaundice or pallor. The abdomen was distended, with present shifting dullness. There was a generalised mild tenderness, but no peritonism.
There was no organomegaly, palpable mass or lymphadenopathy. Bowel sounds were present. Cardiovascular examination was unremarkable.

**INVESTIGATIONS**

Full blood count (table 1) showed a high white cell count with raised eosinophils and neutrophils. White cell morphology showed eosinophilia and neutrophils with toxic eosinophilic granules. Inflammatory markers were raised with a CRP of 7.8 mg/L and ESR 75 mm/hr. Coagulation screen showed a raised APTT ratio of 1.20, with a normal INR.

Serum electrolytes, renal and thyroid function tests were unremarkable. Liver function tests were normal except for globulin which was low at 24 g/L. Amylase and the lipid profile were normal.

Faecal alpha 1 anti-trypsin was raised at 0.85 mg/g faeces [<0.49 mg/g]. Stool culture for pathogens, ova cysts, parasites and norovirus were negative. Faecal calprotectin was normal. Amoebiasis, Lyme disease serology and Toxoplasma IgG were negative.

IgG was low, IgA and IgM were within normal range and coeliac screen was negative. Vitamin A was low at 0.7μmol/L (0.9-2.5μmol/L). Food allergy test was unremarkable. Autoantibodies and ANCA test were negative. Alpha-feto protein was normal. Hepatitis, CMV and EBV tests were negative.

**Table 1: Full blood count taken on A&E admission, comparing normal values with the patient's result. Abnormal levels are in bold - H = high, L = low.**

<table>
<thead>
<tr>
<th>Test (normal range)</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>WBC [4.00-11.00 10^9/L]</td>
<td>16.08 H</td>
</tr>
<tr>
<td>RBC [3.8-5.8 10^12/L]</td>
<td>5.72</td>
</tr>
<tr>
<td>Hb [11.5-15.5 g/dL]</td>
<td>15.5</td>
</tr>
<tr>
<td>PCV [0.370-0.470 L/L]</td>
<td>0.504 H</td>
</tr>
<tr>
<td>MCV [77.0-95.0 fl]</td>
<td>88.1</td>
</tr>
<tr>
<td>MCH [25-34 pg]</td>
<td>27.1</td>
</tr>
<tr>
<td>MCHC [32.0-37.0 g/dL]</td>
<td>30.8 L</td>
</tr>
<tr>
<td>RDW [11.0-15.0 %]</td>
<td>13.0</td>
</tr>
<tr>
<td>PLT [150-450 10^12/L]</td>
<td>314</td>
</tr>
<tr>
<td>MPV [7.4-10.4 fl]</td>
<td>11.7 H</td>
</tr>
<tr>
<td>Neutrophils [2.2-6.3 10^9/L]</td>
<td>7.22 H</td>
</tr>
<tr>
<td>Lymphocytes [1.3-4.0 10^9/L]</td>
<td>2.43</td>
</tr>
<tr>
<td>Monocytes [0.2-1.0 10^9/L]</td>
<td>0.39</td>
</tr>
<tr>
<td>Eosinophils [0-0.4 10^9/L]</td>
<td>6.00 H</td>
</tr>
<tr>
<td>Basophils [0-0.1 10^9/L]</td>
<td>0.05</td>
</tr>
<tr>
<td>NRC</td>
<td>&lt;0.02 %</td>
</tr>
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</table>

**IMAGING**

Abdominal ultrasound showed moderate ascites in the upper abdomen and pelvis. The spleen was enlarged with a length of 13.3cm, a 2.5cm increase since an ultrasound four months previously. The stomach wall and peritoneum had a thickened appearance. The liver, kidneys, uterus and ovaries were unremarkable. Chest X-ray was normal, although a colon MRI ten days later detected traces of fluid in the pleural spaces.

Paracentesis extracted cloudy yellow-orange fluid, consisting of abundant neutrophils, small lymphocytes, histiocytes, a few eosinophils and reactive mesothelial cells. No malignant cells were seen. The total peritoneal fluid protein was 42 g/L, containing <2 kIU/L of alpha-feto protein, albumin 28 g/L, LDH 167 IU/L, and triglycerides 0.7 mmol/L. Peritoneal fluid culture had no growth. Ascitic fluid was negative for acid fast bacilli and mycobacterium, and the T-spot test was negative.

Liver MRI with contrast confirmed significant ascites, mild splenomegaly and thickened gastric antrum. MRI colonogram demonstrated thickened walls of the oesophagus, gastric antrum and jejunal folds of the proximal duodenum. There was no lymphadenopathy.

Laparoscopy revealed erythematous bowel and peritoneal surface and a fibrinous exudate on the stomach wall and spleen. There were adhesions on the lateral abdominal wall from the caecal surface. The appendix, ovaries and fallopian tubes appeared normal. Cell block analysis of the ascitic fluid showed a heavy infiltrate of eosinophils 70%, with neutrophils 15%, lymphocytes 10% and reactive mesothelial cells 5%. No malignant cells were seen.

Bone marrow trephine biopsy demonstrated hypereosinophilia. Erythroid, myeloid and lymphoid cells were represented, with 80% of the myeloid series being dominated by eosinophils. Megakaryocytes were increased. There was no evidence of lymphoma, with a reticulin stain of grade 1. Immunophenotyping of the bone marrow revealed a hypercellular aspirate, with mild dyserythropoiesis. Eosinophils and their precursors were increased and contributed to 26% of total nucleated cells.

Oesophagogastrroduodenoscopy showed an erythematous oesophagus with a mid-oesophageal ulcer. The gastric antrum was erythematous and the stomach rugae were prominent. From duodenum to jejunum the bowel was erythematous with white patches on friable tissue.

Upper GI biopsies of the duodenum, jejunum, antrum, oesophagus, and fundus were obtained. The oesophageal and gastric biopsies were heavily infiltrated with eosinophils, with...
minimal eosinophilic infiltration of the small bowel mucosa and colon fragments. Eosinophils in the gastric mucosa had infiltrated the lamina propria and muscularis mucosae. There was no evidence of parasites, vasculitis, intestinal metaplasia or malignancy, and CLO test for H. Pylori was negative. In light of these negatives, and the histologically characteristic biopsies, a diagnosis of eosinophilic gastroenteritis (EGE) was confirmed.

**PROGRESS**

Prednisolone (20mg/od) and ketotifen (1mg/bd) settled the eosinophilia. The patient was also started on sodium cromoglicate (200mg/bd), spironolactone (20mg/bd), omeprazole (20mg/od), Montelukast (10mg/od), and Calci chew (1250mg/od). She was put on elemental feeds of 2500mls/day.

Three months after presenting in A&E the patient reported no GI symptoms. On examination shifting dullness was not present. The patient’s weight had increased by 3.6kg since discharge. She had not been adherent to the dairy-elimination diet, which was deemed no longer necessary as she was asymptomatic. Azathioprine was suggested in the event of symptoms returning.

**DISCUSSION**

**Pathophysiology**

Eosinophilic gastroenteritis (EGE) is an inflammatory process involving eosinophilic infiltration anywhere in the GI tract, including the oesophagus, pancreatic and biliary tree.

EGE is classified by the extent to which eosinophils have infiltrated the layers of the gut wall, or by the layer predominantly affected: mucosal, muscularis or subserosal.

Klein’s classification attributes specific symptoms to each subtype of EGE. However, the literature frequently reports symptoms overlapping between EGE subtypes, as usually more than one gut layer is affected.

Subserosal eosinophilic infiltration is thought to be the rarest subtype of EGE, although Bleibel et al. state that current data is insufficient to quantify the prevalence of EGE subtypes.

Freeman hypothesises as to how eosinophils may cause cellular damage. One potential mechanism is the release of damaging cytotoxic proteins such as eosinophil peroxidase by eosinophil degranulation. Eosinophilic production of inflammatory mediators including leukotriene C4 may also be responsible for direct damage to the gastric mucosa, while indirect damage could be caused by eosinophils activating mast cells.

Since the presentation of EGE covers a wide range of possible symptoms; a high index of suspicion is required to prevent missing the diagnosis.

**Aetiology**

The aetiology and incidence of EGE remain unclear. A controversial topic is the potential significance of atopy and allergy in recruiting eosinophils to the GI tract. Talley et al. found that 20 of 40 patients with EGE had a reported history of allergy (including asthma, nasal polyps, hayfever), while Hepburn et al. cite the association of atopy with EGE in 80% of cases, with 62% involving food allergy.

Food hypersensitivity has been proposed as a cause of EGE, but with limited evidence, as hypoallergenic diets have not significantly benefited patients in EGE treatment.

**Signs and symptoms**

EGE can present with a multitude of symptoms, predominantly GI. Talley et al. compared the presenting symptoms of EGE in 40 patients by Klein’s classification. They concluded that subserosal disease - which frequently presents with ascites, is most likely to present with abdominal pain, bloating and diarrhoea. Pleural effusions may also occur with subserosal disease. Muscle and mucosal layer disease are more likely to present with nausea, vomiting and weight loss.

Severe disease can cause malabsorption, weight loss, protein-losing enteropathy and anaemia due to blood loss. A mildly elevated level of peripheral eosinophilia occurs in some, but not all patients with EGE; therefore the absence of peripheral eosinophilia does not exclude EGE.

Rare presentations of EGE have been reported; citing the importance of having a high index of suspicion of EGE. Hepburn et al. report the unusual case of EGE precipitated by pregnancy and delivery in a 20 year old woman, while Shin et al. report the first known case of EGE presenting as intussusception in an adult.

The natural history of the disease is still largely unknown. This case study highlights the ability of signs and symptoms to spontaneously resolve and relapse.

Complications include growth retardation in preadolescent patients, intussusception and obstruction. Although morbidity can be significant, mortality from intestinal perforation is very low.

**Investigations**

Talley et al. defined three criteria for confirming a diagnosis of EGE (figure 1). The gold standard test is endoscopy, biopsy and histological assessment, as for IBD. Patchy involvement of EGE can occur, making it possible to miss areas of classical eosinophilic infiltration on biopsy, therefore systematic multiple biopsies are recommended.

Findings in the small bowel may include nodular or polypoid gastric mucosa, erythema, erosions, intraluminal masses, superficial ulcerations, a sawtooth mucosal pattern and a diffuse eosinophilic infiltration of the mucosa.

**Differential diagnosis**

Differential diagnoses are multiple due to the wide range of nonspecific symptoms which may present (table 2). EGE should be considered in patients with relapsing and/or unexplained GI symptoms.
Treatment

Treatment may involve dietary regulation and pharmacological measures. Surgical intervention is not indicated as resection of the bowel is not curative.\textsuperscript{11}

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Similar features to EGE</th>
<th>Distinguishing features from EGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper-eosinophilic syndrome\textsuperscript{11,9}</td>
<td>Diffuse GI involvement; peripheral eosinophilia; eosinophilic organ infiltration\textsuperscript{11}</td>
<td>Systemic involvement of multiple organs\textsuperscript{2,10}</td>
</tr>
<tr>
<td>Parasitic infection (excluding protozoal infections)\textsuperscript{11}</td>
<td>Diarrhoea; abdominal pain; peripheral eosinophilia\textsuperscript{11}</td>
<td>History of travel; positive stool examination for parasites\textsuperscript{11}</td>
</tr>
<tr>
<td>IBD\textsuperscript{2}</td>
<td>Diarrhoea; abdominal pain; nausea; vomiting; malabsorption\textsuperscript{11}</td>
<td>Increased eosinophils histologically;\textsuperscript{11} erythema nodosum; clubbing; stigmata of liver disease (oral inflammation and perianal disease in Crohn's)\textsuperscript{3}</td>
</tr>
<tr>
<td>IBS\textsuperscript{10,7}</td>
<td>Diarrhoea; abdominal pain; nausea; vomiting\textsuperscript{10}</td>
<td>Absence of characteristic EGE histology\textsuperscript{7}</td>
</tr>
</tbody>
</table>

Corticosteroids are beneficial as they inhibit eosinophil growth factors.\textsuperscript{1} Most patients experience remission after 7-10 days of 20-40mg of oral corticosteroids such as prednisone or budesonide.\textsuperscript{1,11} Steroids can then be tapered over two weeks.\textsuperscript{2} A minority of patients may require long term steroid treatment.\textsuperscript{2,8} The subserosal type of EGE responds best to steroids.\textsuperscript{10}

To avoid adverse effects of steroids on growth and bone health in the paediatric population, the antihistamine ketotifen is an alternative.\textsuperscript{3,1} Freeman\textsuperscript{4} reports the case of a man with EGE for over 20 years, who was symptom free providing he took ketotifen, with discontinuation precipitating recurrence. Interestingly, during the asymptomatic periods the disease process itself continued, showing progressive changes on endoscopy. This suggests that ketotifen alone can provide symptomatic relief but may not prevent the evolution of inflammatory changes in the gastric mucosa.\textsuperscript{4}

Immunosuppressant drugs such as azathioprine and 6-mercaptopurine inhibit eosinophil recruitment to the GI tract, thereby alleviating symptoms.\textsuperscript{3} Other pharmacological therapies include leukotriene receptor antagonists such as Montelukast, and monoclonal antibodies, which work against the action and production of inflammatory mediators respectively.\textsuperscript{1}

Short term elemental and elimination diets may be trialled to identify if a food allergy is associated with the EGE.\textsuperscript{1} However, adherence is poor due to the inconvenience of a limited diet,\textsuperscript{1} and have had limited success.\textsuperscript{2} However, patients with severe disease who do not respond to steroids may require total parenteral nutrition\textsuperscript{11} to eliminate the risk of an allergic reaction to food.\textsuperscript{5}

CONCLUSION

- The disease course of EGE may follow a relapsing and remitting pattern.
- EGE may present in paediatric patients as nonspecific gastrointestinal symptoms, therefore clinicians should maintain a high index of suspicion.
- Diagnostic confirmation requires multiple biopsies of the GI tract as EGE can have a patchy distribution.

Competing interests: none.

REFERENCES