CASE REPORT

Eosinophilic gastroenteritis: a challenge to diagnose and treat

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SUMMARY

The patient presented with bloody diarrhoea, and crampy abdominal pains. She was diagnosed with eosinophilic gastroenteritis (EGE) after the finding of persistently high peripheral eosinophil counts and histology of endoscopic biopsies. She responded to steroids but became dependent on it and her symptoms recurred on steroid tapering. There was little improvement with alternative treatment such as budesonides, azathioprine and montelukast. Surprisingly her symptoms improved significantly after she was treated with clarithromycin for chest infection and she was continued on clarithromycin. Her eosinophil counts fell dramatically and follow-up CT (thorax, abdomen and pelvic) scan showed the mucosal thickening had improved. She became completely free of the symptoms since she was on clarithromycin and her eosinophils counts fell within the normal range during the follow-up.

BACKGROUND

Eosinophilic gastroenteritis (EGE) is an uncommon disease. There is limited epidemiology data of the disease owing to its rarity. Although the aetiology of the disease is not well understood, there is evidence of IgE-induced hypersensitivity reaction and the current literature strongly suggests the cytokine-mediated eosinophilic inflammation. There are no randomised controlled trials for the treatment of the disease. However, the disease responds well to corticosteroids but relapses are common. Sodium cromoglycate, montelukast, budesonide and immunosuppressants such as azathioprine have been reported to be successful in some case studies. The patient described in this case, whose symptoms relapsed on tapering steroids, surprisingly improved after having treatment for chest infection with clarithromycin.

CASE PRESENTATION

A 44-year-old woman was admitted to the emergency department with 5 weeks history of watery diarrhoea up to 8 times a day with streaks of blood mixed with the stool and crampy abdominal pains. She had a medical history of anaphylactic reaction to aspirin, nasal polyp and asthma (Samter's triad), type 2 diabetes mellitus, epilepsy and food intolerances. She did not have any family history of inflammatory bowel diseases. The drug history included phenytoin, omeprazole, fostair, lacidipine and zonisamide. Clinical examination was unremarkable. She was afebrile and haemodynamically stable on admission.

INVESTIGATIONS

Full blood count was as follows: haemoglobin—148 g/L, white cell count— $10.7 \times 10^9/L$, eosinophil— $1.15 \times 10^9/L$, C reactive protein—0.7 mg/L and albumin—40 g/dL. Her stool culture including *Clostridium difficile* and parasites was negative. We performed stool antigen *Helicobacter pylori* test and it was negative. Sigmoidoscopy and colonoscopy showed confluent inflammation of the colonic mucosa (figure 1). The histology result showed infiltration of inflammatory cells in the mucosa with cryptitis. There is also marked increase in eosinophil count over 100 eosinophils/high-power field in the lamina propria (figures 2 and 3). A CT scan of the thorax, abdomen and pelvis (figure 4) was performed and it did not show any lymphadenopathy or splenomegaly or malignancy but it revealed that there are prominent mucosal folds in the distal stomach. Upper gastrointestinal (GI) endoscopy revealed thickened and erythematous mucosa of the stomach and duodenum. We did not perform a biopsy during the procedure. Hypereosinophilia work up was performed. The bone marrow biopsy showed no evidence of underlying clonal or myeloproliferative disorder. There was no evidence of PDGFRA, BCR-ABL and JAK2 mutation.

DIFFERENTIAL DIAGNOSIS

Symptoms of EGE may mimic other GI diseases such as infective gastroenteritis, inflammatory bowel diseases and irritable bowel syndrome. Radiological appearances of thickened bowel are non-specific and transmural thickening may occur in Crohn's disease and infiltrative conditions such as lymphoma. Eosinophilic infiltration of the

Figure 1 Colonoscopic mucosal appearance showing mild-inflammatory change of loss of vascularity and erythema.

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Figure 2 Histopathology specimen of colonic mucosa showing eosinophilic infiltration of lamina propria $\times 200$.

mucosa of the GI tract may occur in other causes of eosinophilia such as parasitic infestation, haematological malignancies and idiopathic hypereosinophilic syndrome.

TREATMENT

The patient was treated initially with corticosteroids and mesalazine for presumed ulcerative colitis before the histology report was received. She was put on maintenance dose of the steroids and mesalazine was stopped subsequently after the diagnosis of EGE was considered. The patient relapsed on the tapering of the steroids and she was tried on other alternative treatments including oral budesonide preparations, montelukast and azathioprine without any success. She was advised avoidance strategies and was put on the salicylate free diet with the guidance of dietitian. However, the elimination diet was of little help to her the bowel symptoms and she continued to be dependent on steroids. Addition of the steroid sparing agent azathioprine was unsuccessful. She was treated by the chest physician for her asthma and on one occasion a chest infection was diagnosed and she was placed on treatment with clarithromycin. The patient noticed her symptoms markedly improved with restoration of normal bowel movements and cessation of her abdominal pain while she was treated for the chest infection with clarithromycin. When the drug was stopped, the symptoms returned. We therefore placed her on maintenance therapy with

Figure 3 Histopathology specimen of colonic mucosa showing eosinophilic infiltration of lamina propria $\times 400$.

Figure 4 CT scan of the abdomen showing thickened gastroduodenal folds.

clarithromycin 500 mg two times a day and eventually stopped after 3 months as her bowel symptoms remained stable.

OUTCOME AND FOLLOW-UP

During the follow-up, her eosinophil counts fell dramatically ($0.47 \times 10^9/L$) and follow-up CT (thorax, abdomen and pelvic) scan showed improvement in the mucosal thickening (figure 5). She is now in complete remission of the symptoms.

DISCUSSION

EGE is an uncommon disease characterised by eosinophilic infiltration of GI tissue usually associated with peripheral eosinophilia in the absence of the known causes of eosinophilia. Although it was first described in 1937 by Kaijser, data on the prevalence of the disease are limited owing to the rarity of the disease.¹ The estimated prevalence in USA is around 22–28/100 000 individuals.²

The aetiology of the disease is still poorly understood. However, many patients with EGE have a history of seasonal allergy, atopy, food allergies, asthma and elevated serum IgE levels, which may strongly suggest the role of hypersensitivity

Figure 5 CT scan of the abdomen showing some improvement.

reactions in the pathogenesis of EGE.³ A small amount of eosinophils can be found in the mucosa of the GI tract of normal healthy individuals and they play the role in the host defence mechanism. Eosinophils can trigger proinflammatory effects and cellular activation by releasing cytokines interleukin (IL) (IL-3 and IL-4), chemokine (eotaxin) and neuroactive chemicals. The literature suggests that allergens may cross the intestinal mucosa and trigger an inflammatory response by increased expression of eosinophil activating T helper 2 cytokines such as IL5 and granulocyte-macrophage colony stimulating factor (GM-CSF) that causes the recruitment of eosinophils and subsequent degranulation.^{3,4}

Diagnosing the disease can be challenging and may be delayed in some cases as the presentation of the disease may mimic the other GI diseases. Klein *et al*⁵ classified the disease based on the different anatomical layers of tissue involvement determining the varied clinical manifestation of the symptoms. They are mucosal type (non-specific symptoms such as abdominal pain, nausea, vomiting), muscle layer disease (intestinal obstruction) and serosa disease (characterised by the ascites and effusion). The three diagnostic criteria by Talley *et al*⁶ are the presence of GI symptoms and eosinophilic infiltration of the gut or radiological diagnosis with evidence of peripheral eosinophilia in the absence of parasitic infestation or extra intestinal disease. The clinical presentations of our case overlap with other inflammatory GI diseases such as ulcerative colitis; however, high clinical suspicion, histological and radiology guided direct us to reach the accurate diagnosis.

There are no randomised control trials for the treatment of the disease due to its rarity. A trial of elimination diets has been tried although the results are mixed. Steroid is the mainstay treatment as it demonstrates efficacy in many studies. The duration of the steroid treatment is unknown and the relapses are common during treatment tapering and may require the long-term treatment in some cases. Sodium cromoglycate (a mast cell stabiliser), montelukast (a leukotriene receptor antagonist), budesonide, immunosuppressants such as azathioprine are reported to be successful in some case studies.⁷ There are studies evaluating the efficacy of the use of mepolizumab a humanised monoclonal antibody against IL-5 in the treatment of eosinophilic oesophagitis and eosinophilic GI disorders. The result from the studies yields improvement in the eosinophil count and endoscopic findings; however, long-term beneficial effect is still uncertain.⁷ The use of clarithromycin in EGE was reported once earlier and was found to be effective.⁷ The dose of clarithromycin and the duration of the treatment are still unknown.

In our case, the management of the disease was challenging as the patient was dependent on steroids and the symptoms relapsed on its tapering; she did not respond to other treatments (oral budesonide preparations, montelukast and azathioprine). We continued clarithromycin after the patient reported significant improvement of the symptoms with impressive changes in radiological findings and eosinophil counts.

The beneficial effects of the long-term use of macrolides (clarithromycin and azithromycin) in respiratory diseases such as bronchial asthma and cystic fibrosis have long been known. There is extensive discussion about the mechanism of action of macrolides in these diseases. There are studies which suggest that in addition to the antimicrobial effects, macrolides have

anti-inflammatory and immunomodulatory effects.⁷ One study shows that treatment with macrolides significantly reduces the secretion of proinflammatory cytokines, ILs and tumour necrotic factors in both sputum and plasma.⁹ In another study, macrolide triggers the eosinophil apoptosis by the suppression of the IL5-induced prolongation of eosinophil survival.¹⁰

EGE is thought to be related to the cytokines mediated eosinophilic inflammation, it is possible that the antieosinophilic and immunomodulatory mechanism of macrolides may have a role in the treatment of the disease. Therefore, though further studies are needed to validate the use of clarithromycin or other macrolides in the treatment of EGE, it may be useful when the use of steroid is inadvisable and other therapies have failed.

Learning points

- ▶ Consider eosinophilic enteritis as a diagnosis of atypical colitis or enteritis.
- ▶ Cross-sectional imaging may show thickened gastrointestinal tract, anywhere from the oesophagus to the rectum.
- ▶ Treatment with steroids is effective but dependence is a common problem.
- ▶ Clarithromycin may be effective if steroid is inadvisable or other treatments failed.

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