Eosinophilic Gastroenteritis : Brief Review

Hong-Mou Shih[1], Ming-Jong Bair[2], Huan-Lin Chen[2], I.-Tsung Lin[2]

(1) Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan ; (2) Division of Gastroenterology, Department of Internal Medicine, Mackay Memorial Hospital, Taitung Branch, Taiwan.

Abstract

Eosinophilic gastroenteritis (EGE) is a rare disease which belongs to primary eosinophilic gastrointestinal disorders (primary EGIDs), characterized by an accumulation of eosinophils in the gastrointestinal (GI) tract and is strongly associated with atopy and allergy. The clinical presentations vary depending on the site and depth of eosinophilic intestinal infiltration. Radiology pictures may show irregular thickening of the folds, but these findings can also be present in other conditions like inflammatory bowel disease and lymphoma. The endoscopic appearance is also nonspecific. The definite diagnosis requires biopsy for histological evidence of GI eosinophilic infiltration and clinicians make the diagnosis in correlation with and by exclusion of other possible causes of eosinophilic infiltration. Because EGE is a rare disease, the treatment is based on limited case reports and clinicians' experience. Corticosteroids are the mainstay of therapy. The prognosis of EGE is relatively good when patients receive timely and proper treatment. (Acta gastroenterol. belg., **2016**, 79, **239-244**).

Key words : allergy, eosinophil, atopy.

Introduction

Primary eosinophilic gastrointestinal disorders (primary EGIDs) constitute a group of disease characterized by the accumulation of eosinophils in the gastrointestinal (GI) tract. These disorders include eosinophilic esophagitis (EoE), gastritis, gastroenteritis, enteritis, and colitis (1). Primary EGIDs are known to be strongly associated with atopy and allergy in the absence of other causes of eosinophilic infiltration (2). EGIDs can occur secondarily in systemic disease such as idiopathic hypereosinophilic syndrome (3), inflammatory bowel disease (4), parasite infections (5), drug reactions, and malignancies. The term "eosinophilic gastroenteritis" refers to one of the primary EGIDs and therefore, other secondary causes of eosinophilic infiltration should be excluded before a diagnosis is made. Eosinophilic gastroenteritis (EGE) is an uncommon disease and presents with various GI symptoms. A definite diagnosis requires histological evidence of eosinophilic infiltration and the exclusion of other possible causes. In general, EGE responds well to corticosteroid treatment. Clinicians should be aware of this treatable disease because of its rarity and should be considered if a patient has unexplained GI symptoms.

Epidemiology

Since the first case of EGE was identified in 1937, cases have been described worldwide. However, less than 300 cases are reported in the literature and the largest case series by Talley *et al*. only included 40 patients (6). Therefore, the exact incidence and prevalence are still unknown. Spergel *et al*. published results from a United States nationwide survey that estimated a prevalence of EGE and eosinophilic colitis (EC) of 28/100,000 population ; however, the results also revealed geographical variation within the United States and suggest that prevalence may also vary in other countries (7). The disease can occur over a wide range of ages from infants to the elderly, but the peak age of onset is in the third decade of life. Both sexes can be affected, but there is a slight male predominance (2).

Pathogenesis

Although the pathogenesis of the EGE is still not well understood, it is thought to be related to a hypersensitive reaction. Eosinophils are involved in this reaction. The eosinophils are formed in bone marrow from pluripotent stem cells and can be found in peripheral circulation. Normally, eosinophils reside in the lamina propria of the GI tract and are regulated by chemoattractants. One of the most specific eosinophil chemoattractants is eotaxin (8), which is critical for the recruitment of eosinophils. Animal studies have demonstrated that a deficiency of eotaxin may impair eosinophil recruitment and protects from gastrointestinal allergic hypersensitivity which induces cachexia (9). Another important factor that regulates eosinophil trafficking to the GI tract is the production of cytokines by Th-2 cells (10), of which the most specific is Interleukin-5 (IL-5). During allergic reactions, IL-5 has been shown to promote eosinophil migration from the bone marrow to the circulation and then trafficking to tissue (11). Clinical studies have also revealed high levels of IL-5 in the peripheral blood of patients with EGE (12). Eosinophils contain various factors such as major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophilic cationic protein (ECP) and

Correspondence to : Ming-Jong Bair, No. 1, Lane 303, Changsha Street, Taitung, Taiwan. E-mail : a5963@mmh.org.tw

Submission date : 02/11/2015
Acceptance date : 18/01/2016

eosinophilic peroxidase (EPO). These substances are cytotoxic to the intestinal epithelium. Once eosinophils are activated, the release of these mediators initiates tissue damage, which triggers the degranulation of mast cells and the release of cytokines (2). Other cytokines generated by Th-2 cells such as IL-4 and IL-13 may also play an important role in eosinophilic inflammation. IgE is produced by B cells and can be influenced by IL-4 and IL-13. IgE further triggers the degranulation of basophils and mast cells (13-15). In addition, IL-1, IL-4, IL-13, and TNF-α also promote adhesive interactions of eosinophils with the endothelium (1). It is proposed that food allergens may trigger these inflammatory responses via eosinophils and that this is the main pathogenesis of EGE.

Clinical manifestations

Klein *et al*. classified EGE into three subtypes according to the different layers of eosinophilic infiltration : mucosal, muscularis, and subserosal (16). The clinical presentations vary depending on the site and depth of eosinophilic intestinal infiltration (6). However, this classification only refers to the primary layer of tissue involvement because most diseases involve multiple layers and have multiple presentations.

The most common symptoms are abdominal pain (70-100%), vomiting (60-100%), diarrhea (40-65%), nausea (50-60%), and weight loss (40-60%). Others include protein-losing enteropathy, steatorrhea, generalized malabsorption, melena, bloody stools, heart burn, dysphagia, and early satiety (17-20). Occasionally, some cases may have intestinal obstruction requiring surgical intervention (21). Rarely, eosinophilic infiltration may involve the gallbladder and biliary tract presenting with obstructive jaundice and biliary pancreatitis (22-24).

The mucosal predominant form of EGE has been reported to be the most common subtype ; there was more body weight loss, malabsorption, steatorrhea and protein losing enteropathy compared with the other two subtypes. Previous food intolerance or allergy was also reported in more than 50% of cases with this subtype. However, these data may have reporting bias due to the small number of patients included (6).

The muscularis form of EGE shows predominant eosinophilic infiltration into the muscle layer, which often causes bowel wall thickening, and therefore may result in gastrointestinal obstruction. Documented complete or incomplete bowel obstructive symptoms may be present in this subtype of disease (6,19,21).

Ascites can also be present in EGE and was thought to be related to subserosal involvement. A high ascites eosinophil count can be noted in ascites analysis. High blood eosinophil count was also observed in comparison with the other two subtypes of disease in study. Some suggested that this subserosal predominant form of EGE had the best response to steroids (6,19,25,26).

Evaluation

History and physical examination

History must be focused on food and allergies from the environment as identifying certain allergens triggering this disease is crucial. In case reports, secondary causes of eosinophilic gastrointestinal disorders, such as enalapril (27) and gemfibrozil (28) have been proposed and possible culprit drugs must be carefully investigated. Parasite infections should also be considered, especially in patients at risk, e.g. patients who work on a farm, eat undercooked meat and those who live in or have emigrated from underdeveloped countries. Clinicians should be aware that these secondary EGIDs are suspected and exclude them in order to make the correct diagnosis of primary EGID. Signs of atopy such as dermatitis, rhinitis and wheezing may be noted on physical examination.

Laboratory findings

A complete blood count with differential must be acquired. Some patients may have hypereosinophilia which may be a useful clue for the diagnosis of EGE. However, it should be noted that the peripheral eosinophil count was normal in at least 20% of patients and the disease should not be excluded in patients without hypereosinophilia (6,19,29). Therefore, peripheral eosinophilia may be present as a useful clue for EGE but is not necessary to make the diagnosis. Furthermore, examination of stool ova and parasites to rule out parasite infections is recommended. If ascites is present, paracentesis can be performed and sterile eosinophilic peritoneal fluid can provide the clue for diagnosis.

Radiology

Image findings also depend on different layers of eosinophilic infiltration and the location of the GI tract involvement. Radiographic appearance is variable and nonspecific because of its rarity.

Abdomen sonography is an easy way to detect ascites ; therefore, paracentesis can be performed. In addition, sonography may also reveal a thickened bowel wall. This finding, together with eosinophilic ascites and clinical symptoms, support the diagnosis of EGE (19,30). Barium studies and abdomen computed tomography may demonstrate mucosal fold and wall thickening, which are the most common findings in the mucosal subtype of EGE (Fig. 1). In the muscularis subtype, lumen narrowing with irregularities may be present in addition to findings in the mucosal subtype ; also, areas of reduced distensibility and intestinal obstruction may be noted in this subtype of disease. In the subserosal subtype, radiological studies may detect ascites, eosinophilic lymphadenopathy, eosinophilic pleural effusion, adherent loops of bowel and mesenteric thickening. However, it should be emphasized that these findings are nonspecific and may occur in other inflammatory bowel diseases such as

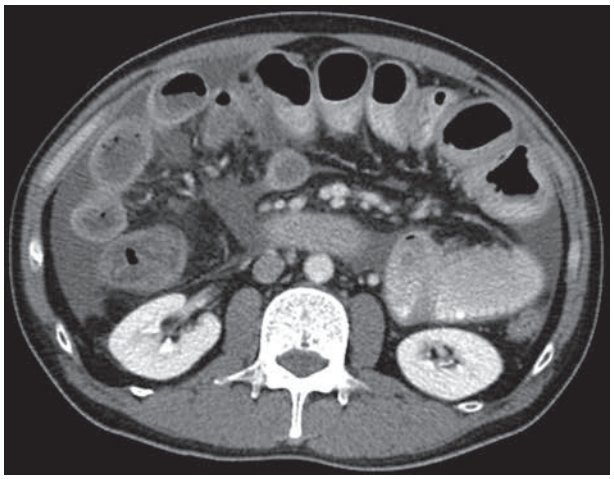

Fig. 1. — Diffused irregular wall thickening of small intestine and colon in abdominal computed tomography due to EGE.

Crohn's disease and ulcerative colitis. In addition, about 40% of patients may not have these radiographic changes (31-34).

Endoscopy and biopsy

There is also no specific endoscopic appearance of EGE. It may show erythema changes, and friable, nodular and occasional ulcerative changes (19) (Fig. 2). Edema and polyp appearance have also been reported (35). Endoscopic biopsy is necessary to aid in the diagnosis, especially in peripheral eosinophilia patients with GI symptoms and should be taken in both normal and abnormal regions. However, the diagnosis may still be missed because of the patchy distribution of disease (6). It is important to interpret the mucosal eosinophil content in biopsy specimens. Despite a lack of precise histological criteria for diagnosis, an upper normal limit of > 20 eosinophils per 400 × high power field is generally accepted and a higher eosinophil density above this range is considered EGE if there is a clinical correlation (36) (Fig. 3).

Diagnosis

No clear standards exist for the diagnosis of eosinophilic gastroenteritis. It is generally accepted that the diagnosis should include : [1] the presence of GI symptoms, [2] eosinophilic infiltration over the GI tract, and [3] no evidence of parasite diseases along with an absence of other systemic involvement outside the GI tract (6).

A definite diagnosis requires biopsy for histological evidence of GI eosinophilic infiltration ; clinicians make the diagnosis correlated with clinical symptoms and after excluding other causes of eosinophilic infiltration. However, as mentioned previously, patients with subserosal involvement may have ascites and paracentesis reveals high eosinophil count in peritoneal fluid. Biopsy is not necessarily required in these patients (19,25). A high index of suspicion in a patient with relevant clinical symptoms is essential to help clinicians avoid missing the diagnosis during evaluation.

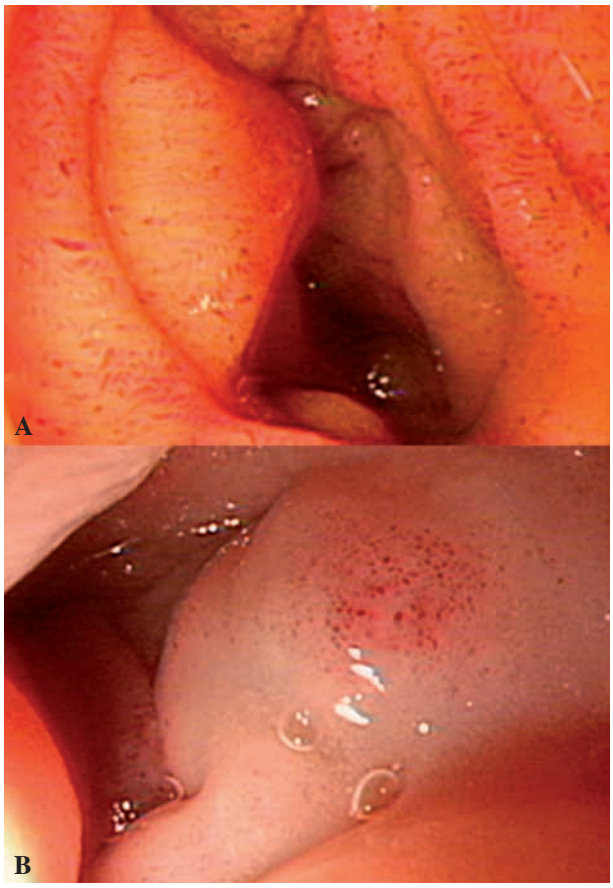

Fig. 2. — (A) Mucosal swellings with multiple reddish spots upon upper endoscopy in a patient with eosinophilic gastroenteritis. (B) Mucosal edema and erythema change in the colon.

Treatment

Due to the rarity of this disease, there have been no large controlled trials for the evaluation of treatment efficacy. The current treatment is based on limited case reports and experience. It is generally accepted that steroids are the main treatment for this disease.

Diet

Some case reports have shown that an elimination diet may provide successful treatment if a food allergy is identified (19). However, only a small number of patients may achieve remission with an elimination diet alone and relapses have been reported in some patients (37). Fewer case reports suggested that an elementary diet can improve clinical symptoms and steroid-dependent disease (37,38).

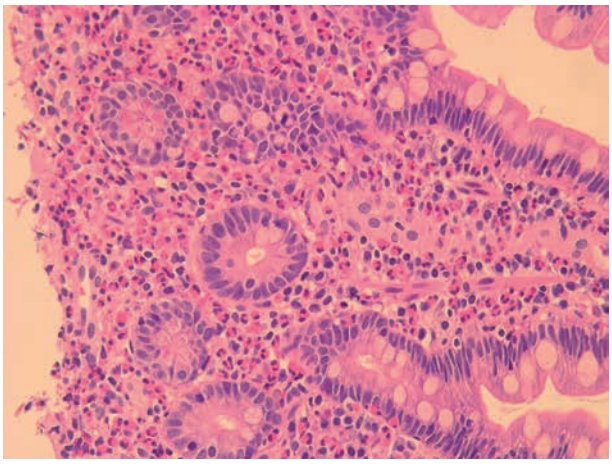

Fig. 3. — Many Eosinophils infiltrate in duodenum (H&E stain).

Steroids

Corticosteroids remain the main treatment of choice. Different steroid regimens have been proposed. Most commonly, daily oral prednisone (about 40 mg/day) was suggested as an initial dose ; the symptoms usually improve within two weeks (17). The duration of steroid treatment remains unknown, but tapering within the next two weeks has been suggested. Some patients may relapse during steroid tapering and require long-term maintenance steroids (5-10 mg/day). Budesonide, a locally acting corticosteroid with extensive first-pass metabolism, has been studied in Crohn's disease and fewer side effects have been reported than for conventional systemic corticosteroid such as prednisone (39,40). Only a few case reports using budesonide to treat EGE have been reported ; most of them were using it for patients with relapsing disease or for those who cannot tolerate the side effects of systemic steroids, and promising results were reported (41-43). Despite the advantages of fewer adverse effects compared with systemic corticosteroids, more experience is still needed to evaluate the efficacy of this medication in severe disease.

Other medications

Sodium cromoglycate, a mast cell membrane stabilizer, has been described in the successful treatment of EGE in case report. The dose of sodium cromoglycate was 300 mg, 4 times daily, for four to five months (44,45). Patient who failed to respond to steroids but had a response to sodium cromoglycate were reported (46). Ketotifen, an anti-H1 drug and mast cell stabilizer, has also been used in the treatment of EGE in case reports. These results showed that ketotifen may be an alternative to steroids in the treatment of disease (47,48). Montelukast, a selective, competitive leukotriene receptor antagonist, can reverse the inflammatory process mediated by leukotrienes. Successful treatment by Montelukast was noted in some reports (49) ; however, other groups reported that it only reduced peripheral blood eosinophilia but not tissue eosinophilia or the associated symptoms (50). As previously described, cytokines produced by Th-2 cells may be involved in EGE (10). Suplatast, an anti-allergic medication targeting Th-2 cytokines, has been studied in the treatment of steroid-dependent asthma in a controlled trial which reported a decrease in corticosteroid dosage with improved pulmonary function and symptom control (51). Successful treatment with Suplastast in a patient with asthma and EGE has also been described (52). 6-Mercaptopurine (6-MP) and its prodrug, azathioprine, are conventional immunomodulators and have been previously used in inflammatory bowel disease. 6-MP undergoes intracellular metabolism and is converted to 6-thioguanine (6-TG) nucleotides, which accumulate in tissue. These active metabolites inhibit purine synthesis and therefore DNA and RNA synthesis, resulting in decreased circulating B and T lymphocytes. Several patients with EGE who experience relapses under corticosteroid treatment have maintained remission with azathioprine (53).

Novel biologics targeting inflammatory pathways such as IL-5, IL-4/ IL-13, TNF-α and IgE are being explored in the treatment of EGE and may provide new therapeutic options in the future. Reslizumab (formerly SCH55700) and Mepolizumab, both of which are humanized anti-IL-5 monoclonal antibodies, have been proposed for use in eosinophilic disorders. In EoE, one randomized, double-blind, placebo-controlled study revealed that Mepolizumab reduced tissue eosinophils in adult patients with active EoE compared with placebo, but failed to significantly demonstrate the improvement of clinical symptoms (54). A similar result was found in another trial using Reslizumab (55). Unlike EoE, EGE cases treated with these drugs were only investigated in case series. Four patients with EGE treated with Reslizumab showed symptomatic improvement with an initial decrease in eosinophilia. However, eosinophil counts elevated above the baseline levels were observed between 60 and 90 days after treatment, accompanied with worsening symptoms. Therefore, the safety and efficacy of these medications must be further clarified thoroughly for the long-term management of EGE (56).

IL-4 and IL-13 are critical in allergic disease. IL-4 binds to type I and type II IL-4 receptors, whereas IL-13 only binds to the type II IL-4 receptor. These two types of receptor have the same IL-4 receptor α-chain (IL-4Rα) polypeptide (57). Pitrakinra, an IL-4 mutein, binds to the IL-4Rα subunit, and dupilumab, a fully human monoclonal antibody to the IL-4Rα subunit, theoretically prevent inflammation induced by IL-4 and IL-13. These drugs are currently undergoing investigation in the treatment of asthma and may have some role in EGE (58,59).

Infliximab, a chimeric monoclonal antibody, is a potent inhibitor of TNF-α. Despite the fact that increased expression of TNF-α was observed in esophageal epithelial biopsy specimens, a study using infliximab in three patients for the treatment of severe corticosteroid-dependent adult EoE did not show promising results. These

data demonstrate that eosinophilic infiltration in esophageal tissue and symptoms cannot be ameliorated by infliximab using a standard induction dosage schedule (60,61). Another study of eight pediatric cases of refractory eosinophilic enterocolitis were treated with infliximab and six of them clearly responded (62). However, there is currently no established protocol for the treatment of EGE and whether it is more effective when used in combination with other medications remains unknown. Further investigation is still warranted.

Omalizumab, a humanized monoclonal antibody that targets circulating IgE, blocks the binding of IgE to IgE receptors on mast cells and basophils, therefore preventing these cells from undergoing degranulation and releasing cytokines. Guidelines for the management and prevention of asthma, issued by the Global Initiative of Asthma (GINA) recommended that omalizumab should be considered an add-on therapy for severe persistent allergic asthma (63). However, only a few case studies investigating omalizumab treatment in EGID have been reported. In one case series, omalizumab significantly decreased peripheral eosinophilia, improved gastrointestinal symptom scores and was associated with a decrease in tissue eosinophil numbers in the gastric antrum and duodenum, but there was an upward trend in the esophageal eosinophils (64). Whether omalizumab treatment is more efficient in EGE than in EoE therefore requires more clinical evidence.

Prognosis

Due to the limited number of cases, the clinical course of EGE is still not clear and the prognosis is also difficult to determine. Despite acute complications such as intestinal obstruction existing, the prognosis appears to be good if the patient is treated properly. Mortality is rare ; however, the disease is still a chronic condition and flare-up after remission has been observed (17). De Chambrun *et al*. identified three different courses of EGE (65). According to Klein's classification (16), predominant subserosal disease usually presents a single flare course, predominant mucosal disease mostly presents a continuous course, and predominant muscle layer disease presents a recurring course. These data provide clinical clues for prediction of recurrence and whether long-term maintenance therapy is warranted.

Conclusion

Despite the rarity of EGE, an increasing number of cases have been described in the literature. Recognition of its clinical manifestations, endoscopic appearance and image findings help clinicians to make the diagnosis. The correct diagnosis requires a strong suspicion of the disease and can avoid unnecessary surgery intervention in patients with unexplained and severe symptoms because of its relatively good response to medical treatment. Until now, corticosteroid treatment remains the main therapy. Recently, a better understanding of its pathogenesis has provided novel drugs of choice to treat the disease. However, it should be emphasized that these steroid-sparing agents are only described in case reports and large clinical trials are still required to confirm their efficacy.

References

1. ROTHENBERG M.E. Eosinophilic gastrointestinal disorders (EGID). *J. Allergy Clin. Immunol*., 2004, **113** (1) : 11-28 ; quiz 29.
2. KHAN S. Eosinophilic gastroenteritis. *Best Pract. Res. Clin. Gastroenterol*., 2005, **19** (2) : 177-198.
3. WELLER P.F., BUBLEY G.J. The idiopathic hypereosinophilic syndrome. *Blood*, 1994, **83** (10) : 2759-2779.
4. WALSH R.E., GAGINELLA T.S. The eosinophil in inflammatory bowel disease. *Scand. J. Gastroenterol*., 1991, **26** (12) : 1217-1224.
5. BEHM C.A., OVINGTON K.S. The role of eosinophils in parasitic helminth infections : insights from genetically modified mice. *Parasitol. Today*, 2000, **16** (5) : 202-209.
6. TALLEY N.J., SHORTER R.G., PHILLIPS S.F., ZINSMEISTER A.R. Eosinophilic gastroenteritis : a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut*, 1990, **31** (1) : 54-58.
7. SPERGEL J.M., BOOK W.M., MAYS E., SONG L., SHAH S.S., TALLEY N.J. *et al*. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. *J. Pediatr. Gastroenterol. Nutr*., 2011, **52** (3) : 300-306.
8. MISHRA A., HOGAN S.P., LEE J.J., FOSTER P.S., ROTHENBERG M.E. Fundamental signals that regulate eosinophil homing to the gastrointestinal tract. *J. Clin. Invest*., 1999, **103** (12) : 1719-1727.
9. HOGAN S.P., MISHRA A., BRANDT E.B., ROYALTY M.P., POPE S.M., ZIMMERMANN N. *et al*. A pathological function for eotaxin and eosinophils in eosinophilic gastrointestinal inflammation. *Nat. Immunol*., 2001, **2** (4) : 353-360.
10. MISHRA A., HOGAN S.P., BRANDT E.B., ROTHENBERG M.E. IL-5 promotes eosinophil trafficking to the esophagus. *J. Immunol*., 2002, **168** (5) : 2464-2469.
11. ROTHENBERG M.E., MISHRA A., BRANDT E.B., HOGAN S.P. Gastrointestinal eosinophils. *Immunol. Rev*., 2001, **179** : 139-155.
12. TAKAHASHI T., NAKAMURA K., NISHIKAWA S., TSUYUOKA R., SUZUKI A., MURAKAMI M. *et al*. Interleukin-5 in eosinophilic gastroenteritis. *Am. J. Hematol*., 1992, **40** (4) : 295-298.
13. BABU K.S., POLOSA R., MORJARIA J.B. Anti-IgE--emerging opportunities for Omalizumab. *Expert. Opin. Biol. Ther*., 2013, **13** (5) : 765-777.
14. STONE K.D., PRUSSIN C. Immunomodulatory therapy of eosinophil-associated gastrointestinal diseases. *Clin. Exp. Allergy*, 2008, **38** (12) : 1858-1865.
15. DE VRIES J.E., CARBALLIDO J.M., AVERSA G. Receptors and cytokines involved in allergic TH2 cell responses. *J. Allergy Clin. Immunol*., 1999, **103** (5 Pt 2) : S492-496.
16. KLEIN N.C., HARGROVE R.L., SLEISENGER M.H., JEFFRIES G.H. Eosinophilic gastroenteritis. *Medicine (Baltimore)*, 1970, **49** (4) : 299-319.
17. LEE C.M., CHANGCHIEN C.S., CHEN P.C., LIN D.Y., SHEEN I.S., WANG C.S. *et al*. Eosinophilic gastroenteritis : 10 years experience. *Am. J. Gastroenterol*., 1993, **88** (1) : 70-74.
18. VENKATARAMAN S., RAMAKRISHNA B.S., MATHAN M., CHACKO A., CHANDY G., KURIAN G. *et al*. Eosinophilic gastroenteritis – an Indian experience. *Indian J. Gastroenterol*., 1998, **17** (4) : 148-149.
19. CHEN M.J., CHU C.H., LIN S.C., SHIH S.C., WANG TE. Eosinophilic gastroenteritis : clinical experience with 15 patients. *World J. Gastroenterol*., 2003, **9** (12) : 2813-2816.
20. GUAJARDO J.R., PLOTNICK L.M., FENDE J.M., COLLINS M.H., PUTNAM P.E., ROTHENBERG M.E. Eosinophil-associated gastrointestinal disorders : a world-wide-web based registry. *J. Pediatr*., 2002, **141** (4) : 576-581.
21. YUN M.Y., CHO Y.U., PARK I.S., CHOI S.K., KIM S.J., SHIN S.H. *et al*. Eosinophilic gastroenteritis presenting as small bowel obstruction : a case report and review of the literature. *World J. Gastroenterol*., 2007, **13** (11) : 1758-1760.
22. SHETH A., PALMER R., JORDAN P.A., MANAS K., BHALODIA A. Eosinophilic gastroenteritis of the pancreas : an unusual cause of obstructive jaundice. *J. Clin. Gastroenterol*., 2006, **40** (7) : 623-625.

23. WHITAKER I.S., GULATI A., MCDAID J.O., BUGAJSKA-CARR U., ARENDS M.J. Eosinophilic gastroenteritis presenting as obstructive jaundice. *Eur. J. Gastroenterol. Hepatol.*, 2004, **16** (4) : 407-409.
24. POLYAK S., SMITH T.A., MERTZ H. Eosinophilic gastroenteritis causing pancreatitis and pancreaticobiliary ductal dilation. *Dig. Dis. Sci.*, 2002, **47** (5) : 1091-1095.
25. SANCHEZ-FAYOS M.P., MIRANDA R., RENEDO L., PORRES J.C., HERNANDEZ GUIO C. [Eosinophilia and ascites as an expression of a subserous form of eosinophilic gastroenteritis]. *Rev. Clin. Esp.*, 1992, **191** (1) : 30-34.
26. SALGUEIRO P., MAGALHAES R., LAGO P. Cramping pain and eosinophilic ascites : what is the diagnosis ? *Gastroenterology*, 2013, **144** (7) : 1353, 1577.
27. BARAK N., HART J., SITRIN M.D. Enalapril-induced eosinophilic gastroenteritis. J. Clin. Gastroenterol., 2001, **33** (2) : 157-158.
28. LEE J.Y., MEDELLIN M.V., TUMPKIN C. Allergic reaction to gemfibrozil manifesting as eosinophilic gastroenteritis. *South Med. J.*, 2000, **93** (8) : 807-808.
29. KAMAL M.F., SHAKER K., JASER N., LEIMOON B.A. Eosinophilic gastroenteritis with no peripheral eosinophilia. *Ann. Chir. Gynaecol.*, 1985, **74** (2) : 98-100.
30. MAROY B. Nonmucosal eosinophilic gastroenteritis : sonographic appearance at presentation and during follow-up of response to prednisone therapy. *J. Clin. Ultrasound*, 1998, **26** (9) : 483-486.
31. MAC CARTY R.L., TALLEY N.J. Barium studies in diffuse eosinophilic gastroenteritis. *Gastrointest. Radiol.*, 1990, **15** (3) : 183-187.
32. VITELLAS K.M., BENNETT W.F., BOVA JG., JOHNSON J.C., GREENSON J.K., CALDWELL JH. Radiographic manifestations of eosinophilic gastroenteritis. *Abdom. Imaging*, 1995, **20** (5) : 406-413.
33. SHANBHOGUE A.K., PRASAD S.R., JAGIRDAR J., TAKAHASHI N., SANDRASEGARAN K., FAZZIO RT. *et al*. Comprehensive update on select immune-mediated gastroenterocolitis syndromes : implications for diagnosis and management. *Radiographics*, 2010, **30** (6) : 1465-1487.
34. HORTON K.M., CORL F.M., FISHMAN E.K. CT of nonneoplastic diseases of the small bowel : spectrum of disease. *J. Comput. Assist. Tomogr.*, 1999, **23** (3) : 417-428.
35. PARK H.S., KIM H.S., JANG H.J. Eosinophilic gastroenteritis associated with food allergy and bronchial asthma. *J. Korean Med. Sci.*, 1995, **10** (3) : 216-219.
36. LOWICHIK A., WEINBERG A.G. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. *Mod. Pathol.*, 1996, **9** (2) : 110-114.
37. KATZ A.J., TWAROG F.J., ZEIGER R.S., FALCHUK Z.M. Milk-sensitive and eosinophilic gastroenteropathy : similar clinical features with contrasting mechanisms and clinical course. *J. Allergy Clin. Immunol.*, 1984, **74** (1) : 72-78.
38. JUSTINICH C., KATZ A., GURBINDO C., LEPAGE G., CHAD Z., BOUTHILLIER L. *et al*. Elemental diet improves steroid-dependent eosinophilic gastroenteritis and reverses growth failure. *J. Pediatr. Gastroenterol. Nutr.*, 1996, **23** (1) : 81-85.
39. BAR-MEIR S., CHOWERS Y., LAVY A., ABRAMOVITCH D., STERNBERG A., LEICHTMANN G. *et al*. Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. *Gastroenterology*, 1998, **115** (4) : 835-840.
40. SCHOON E.J., BOLLANI S., MILLS P.R., ISRAELI E., FELSENBERG D., LJUNGHALL S. *et al*. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. *Clin. Gastroenterol. Hepatol.*, 2005, **3** (2) : 113-121.
41. TAN A.C., KRUIMEL J.W., NABER T.H. Eosinophilic gastroenteritis treated with non-enteric-coated budesonide tablets. *Eur. J. Gastroenterol. Hepatol.*, 2001, **13** (4) : 425-427.
42. SIEWERT E., LAMMERT F., KOPPITZ P., SCHMIDT T., MATERN S. Eosinophilic gastroenteritis with severe protein-losing enteropathy : successful treatment with budesonide. *Dig. Liver Dis.*, 2006, **38** (1) : 55-59.
43. GONNELLI S., TANZILLI L., BURRONI L., CAFFARELLI C. New-onset hypercholesterolemia as an unusual presenting manifestation of eosinophilic gastroenteritis. *J. Clin. Lipidol.*, 2013, **7** (3) : 229-233.
44. DI GIOACCHINO M., PIZZICANNELLA G., FINI N., FALASCA F., ANTINUCCI R., MASCI S. *et al*. Sodium cromoglycate in the treatment of eosinophilic gastroenteritis. *Allergy*, 1990, **45** (3) : 161-166.
45. VAN DELLEN R.G., LEWIS J.C. Oral administration of cromolyn in a patient with protein-losing enteropathy, food allergy, and eosinophilic gastroenteritis. *Mayo Clin. Proc.*, 1994, **69** (5) : 441-444.
46. MOOTS R.J., PROUSE P., GUMPEL J.M. Near fatal eosinophilic gastroenteritis responding to oral sodium chromoglycate. *Gut*, 1988, **29** (9) : 1282-1285.
47. SUZUKI J., KAWASAKI Y., NOZAWA R., ISOME M., SUZUKI S., TAKAHASHI A. *et al*. Oral disodium cromoglycate and ketotifen for a patient with eosinophilic gastroenteritis, food allergy and protein-losing enteropathy. *Asian Pac. J. Allergy Immunol.*, 2003, **21** (3) : 193-197.
48. MELAMED I., FEANNY S.J., SHERMAN P.M., ROIFMAN C.M. Benefit of ketotifen in patients with eosinophilic gastroenteritis. *Am. J. Med.*, 1991, **90** (3) : 310-314.
49. QUACK I., SELLIN L., BUCHNER N.J., THEEGARTEN D., RUMP L.C., HENNING B.F. Eosinophilic gastroenteritis in a young girl – long term remission under Montelukast. *BMC Gastroenterol.*, 2005, **5** : 24.
50. DAIKH B.E., RYAN C.K., SCHWARTZ R.H. Montelukast reduces peripheral blood eosinophilia but not tissue eosinophilia or symptoms in a patient with eosinophilic gastroenteritis and esophageal stricture. *Ann. Allergy Asthma Immunol.*, 2003, **90** (1) : 23-27.
51. TAMAOKI J., KONDO M., SAKAI N., AOSHIBA K., TAGAYA E., NAKATA J. *et al*. Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependent asthma : a double-blind randomised study. Tokyo Joshi-Idai Asthma Research Group. *Lancet*, 2000, **356** (9226) : 273-278.
52. SHIRAI T., HASHIMOTO D., SUZUKI K., OSAWA S., AONAHATA M., CHIDA K. *et al*. Successful treatment of eosinophilic gastroenteritis with suplatast tosilate. *J. Allergy Clin. Immunol.*, 2001, **107** (5) : 924-925.
53. BAGHERI M., ASHRAFI M., MOHAMADNEJAD M., ABDOLLAHZADEH HOSSEINI L., NASSERI-MOGHADDAM S., MERAT S. *et al*. Eosinophilic gastroenteritis : a case series from iran. *Middle East J. Dig. Dis.*, 2011, **3** (2) : 115-118.
54. STRAUMANN A., CONUS S., GRZONKA P., KITA H., KEPHART G., BUSSMANN C. *et al*. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis : a randomised, placebo-controlled, double-blind trial. *Gut*, 2010, **59** (1) : 21-30.
55. SPERGEL J.M., ROTHENBERG M.E., COLLINS MH., FURUTA G.T., MARKOWITZ J.E., FUCHS G., 3rd. *et al*. Reslizumab in children and adolescents with eosinophilic esophagitis : results of a double-blind, randomized, placebo-controlled trial. J. Allergy Clin. Immunol., 2012, **129** (2) : 456-463, e451-453.
56. KIM Y.J., PRUSSIN C., MARTIN B., LAW M.A., HAVERTY T.P., NUTMAN T.B. *et al*. Rebound eosinophilia after treatment of hypereosinophilic syndrome and eosinophilic gastroenteritis with monoclonal anti-IL-5 antibody SCH55700. *J. Allergy Clin. Immunol.*, 2004, **114** (6) : 1449-1455.
57. WILLS-KARP M., FINKELMAN F.D. Untangling the complex web of IL-4- and IL-13-mediated signaling pathways. *Sci. Signal.*, 2008, **1** (51) : pe55.
58. WENZEL S., WILBRAHAM D., FULLER R., GETZ E.B., LONGPHRE M. Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients : results of two phase 2a studies. *Lancet*, 2007, **370** (9596) : 1422-1431.
59. WENZEL S., FORD L., PEARLMAN D., SPECTOR S., SHER L., SKOBIERANDA F. *et al*. Dupilumab in persistent asthma with elevated eosinophil levels. *N. Engl. J. Med.*, 2013, **368** (26) : 2455-2466.
60. STRAUMANN A., BAUER M., FISCHER B., BLASER K., SIMON H.U. Idiopathic eosinophilic esophagitis is associated with a T (H)2-type allergic inflammatory response. *J. Allergy Clin. Immunol.*, 2001, **108** (6) : 954-961.
61. STRAUMANN A., BUSSMANN C., CONUS S., BEGLINGER C., SIMON H.U. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *J. Allergy Clin. Immunol.*, 2008, **122** (2) : 425-427.
62. TURNER D., WOLTERS V.M., RUSSELL R.K., SHAKHNOVICH V., MUISE A.M., LEDDER O. *et al*. Anti-TNF, infliximab, and adalimumab can be effective in eosinophilic bowel disease. *J. Pediatr. Gastroenterol. Nutr.*, 2013, **56** (5) : 492-497.
63. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2015. Available from : http://www.ginasthma.org/.
64. FOROUGHI S., FOSTER B., KIM N., BERNARDINO L.B., SCOTT L.M., HAMILTON R.G. *et al*. Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. *J. Allergy Clin. Immunol.*, 2007, **120** (3) : 594-601.
65. PINETON DE CHAMBRUN G., GONZALEZ F., CANVA J.Y., GONZALEZ S., HOUSSIN L., DESREUMAUX P. *et al*. Natural history of eosinophilic gastroenteritis. *Clin. Gastroenterol. Hepatol.*, 2011, **9** (11) : 950-956 e951.