Eosinophilic Gastrointestinal Disease: Analysis of Sixteen Cases from Ten Years Experience in Thailand

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Objective: *To study eosinophilic gastrointestinal disease (EGIDs) in children concerning the clinical presentations, diagnostic methods and results of treatment.*
Material and Method: *A retrospective study of EGIDs was done from January 2000 to December 2009. All patients diagnosed as EGIDs according to gastrointestinal symptoms combined with eosinophilic infiltration in mucosal, muscular or serosal layer of involvement. Exclusion of extraintestinal eosinophilic involvement and parasitic infestations were done. Analysis of clinical presentations, diagnostic methods and results of treatment were reviewed.*
Results: *Sixteen children fulfilled criteria of EGIDs. Mucosal type was the most common finding type (12 out of 16 cases) (75%). Muscular and serosal type was found in equal numbers (2 of each in 16 cases) (12.5% each). Ages ranged from 6 months to 13 years. The male: female ratio was 1: 1.2. Abdominal pain was the most common presenting symptom followed by diarrhea. Allergic history was detected in 68.75% of all patients. Peripheral eosinophilia was found in only 37.5% of all cases. Radiographic findings showed non-specific findings. Endoscopy was performed in 14 out of 16 cases (87.5%). Lymphoid hyperplasia was the most common endoscopic finding especially in mucosal type. Eosinophil (more than 20 per high power field) was found from biopsied tissues obtained from the esophagus, stomach, colon or from ascitic fluid. Prednisolone was used in 13 out of 16 cases with satisfactory results in 11 cases. The two resisted cases responded to ketotifen in one and the other in combination with montelukast. One out of 16 cases subsided with only proton pump inhibitor. The last two cases improved by allergic food elimination.*
Conclusion: *Eosinophilic gastrointestinal disease in children presents with varieties of gastrointestinal symptoms. Biopsied tissues or ascitic fluid are required to demonstrate significant eosinophilic infiltration or presence of eosinophil. Allergic history seems to play an important role in more than half of the patients. Specific dietary elimination is the most important treatment in allergic cases. Corticosteroid is the treatment of choice in the non-allergic group or for those who did not improve with food elimination.*

Keywords: *Eosinophil, Eosinophilic gastrointestinal disease*

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Eosinophilic gastrointestinal disease (EGIDs) is an uncommon disease characterized by diffuse thickening of one or more segments of the gastrointestinal tract[1]. The disease can affect any age group but commonly presents in the third to fifth decades of life[2]. Clinical manifestations are variable depend on the region of the GI tract and the depth of bowel wall involvement. The Klein classification describes clinical manifestation into mucosal, submucosal (muscular) and serosal subtypes[3]. The most common presenting symptom is abdominal pain followed by nausea, vomiting and diarrhea[4].

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Material and Method

A retrospective study of EGIDs admitted at Queen Sirikit National Institute of Child Health from 2000 to 2009 was done. Sixteen cases were diagnosed as EGIDs by using diagnostic criteria[5]:

1. Gastrointestinal symptoms manifestation;
2. Eosinophilic infiltration in GI tract tissues or in ascitic fluid defined as 20 or more eosinophils per high power field;

3. No evidence of parasitic infestation;

4. No extraintestinal eosinophilic disease.

Demographic data, clinical manifestations, clinical course, diagnostic methods and treatment were reviewed.

Results

Sixteen patients (7 male, 9 female), ages ranged from 6 months to 13 years, were diagnosed as EGIDs according to Klein's criteria over a ten year period. Table 1 shows subtypes of EGIDs which were divided into 12 cases of mucosal type, 2 cases of muscular type and 2 cases of serosal type. Peripheral eosinophilia ($> 500/mm^3$) was found in 6 cases (37.5% of all cases). Symptoms and signs are listed in Table 2.

Allergic histories were noted in 11 cases of mucosal type (68.75% of all patients). Specific IgE for mixed food was done in cases 6-10. The result was positive in only case 8. Patch test was positive for cow's milk and shrimp in case 8 and cow's milk, soy milk and egg in case 12. Barium studies were done in some cases (Table 2) which showed compatible findings with the pathologic types in cases 1, 14, 16. The others showed non-specific findings.

Fourteen patients underwent GI endoscopy (Table 3) and all were positive for eosinophil (more than 20 per high power field) in biopsied tissues. The other two patients (cases 15, 16) who presented with abdominal pain and abdominal distention had a significant amount of absolutely eosinophil in the ascitic fluid. Exclusion of parasitic disease and abdominal lymphoma were done by negative stool concentration for parasites plus clinical findings.

Thirteen patients were treated with prednisolone and 11 cases responded well. The two resisted cases improved with ketotifen in one case and combined with montelukast in the other case. One case improved with only proton pump inhibitor. Two cases of mucosal type improved by food elimination with no medication. All cases were followed-up on at least three-month periods up to 5 years. Only one case (case 16) relapsed after 3 years but responded well to oral steroid.

Discussion

Eosinophilic gastrointestinal disease (EGIDs) is a disease of unknown etiology known to be partly allergic in origin from eosinophilic findings in GI tract tissues or ascitic fluid[6]. There are no definite criteria to diagnose this disease except eosinophilic esophagitis. Gastrointestinal symptoms combined with peripheral eosinophilia are useful diagnostic clues of this disease. Findings of peripheral eosinophilia ranged from 5-35% with an average eosinophil count of 2,000 cells/ul[7]. Allergic histories are present in 60 to 70% of the patients[8]. From this report the authors found history of allergies in 68.75% (11/16 cases) and peripheral

Table 1. Demographic data of patients classified by Klein's criteria

Group	Case	Sex	Age (years)	WBC/ul	Eosinophil count (cells/ul)
I	1	M	9	8,600	172
	2	M	10	19,600	10,388*
	3	F	4	8,600	304
	4	M	8.25	8,800	704*
	5	M	8.25	8,490	170
	6	F	13.75	12,490	2,623*
	7	F	12.5	6,600	132
	8	M	8.75	6,360	64
	9	M	2.25	7,700	0
	10	F	9.5	8,200	0
	11	F	0.5	6,830	273
	12	F	1.75	5,830	0
II	13	M	10.5	6,540	195
	14	M	4.4	20,300	3,451*
III	15	F	10	30,900	16,995*
	16	F	12	13,300	4,522*

Group I: mucosal, Group II: muscular, Group III: serosal, *eosinophilia

Table 2. Symptoms and signs and Radiographic findings

Group	Case	Symptoms and signs	Radiographic findings	Allergy
I	1.	Abdominal pain	Diffuse mucosal swelling of duodenum and jejunum	+
	2.	Abdominal pain/Nausea/Weight loss	-	-
	3.	Abdominal pain/Vomiting/Hematochezia	-	+
	4.	Abdominal pain/Diarrhea/Hematochezia	Irritable duodenum Normal barium enema	+
	5.	Abdominal pain/Diarrhea	Gastric dilatation	+
	6.	Abdominal pain/Vomiting	Gastric dilatation	+
	7.	Hematemesis	-	+
	8.	Abdominal pain/Vomiting	-	+
	9.	Abdomonal pain/Diarrhea/Urticaria	-	+
	10.	Hematochezia	Normal Barium enema	+
	11.	Hematochezia/Diarrhea	-	+
	12.	Diarrhea	-	+
II	13.	Abdominal pain	Unremarkable study	-
	14.	Abdominal pain/Vomiting/Weight loss	Diffuse infiltrative process in gastric antrum causing antral narrowing	-
III	15.	Abdominal pain/Abdominal distention/ Diarrhea	-	-
	16.	Abdominal pain/Vomiting/Abdominal distention/Diarrhea	CT - massive ascites - marked thickening of mucosa from stomach to large intestine	-

eosinophilia in 37.5% of all cases which were comparable to many reports. Eotaxin-1 which acts as an eosinophil specific chemoattractant produced by intestinal epithelial cells at inflammatory site contributes to eosinophil accumulation and activation. Cytotoxic proteins contained in their secondary granules are released including eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil peroxidase and major basic protein[9]. The following results have the ability to cause tissue damage and destroy parasitic infections.

Symptoms and signs depend on organ and depth of eosinophilic infiltration in the bowel wall. The most common presenting symptom is abdominal pain followed by nausea, vomiting and diarrhea[7]. The mucosal type is the most common type of EGIDs (25%-100%) manifesting with abdominal pain, nausea, vomiting, diarrhea, occult GI bleeding, weight loss and protein losing enteropathy[10]. The authors found 12 cases of mucosal type in this report (75%), half of these manifested with hematochezia and abdominal pain. Biopsied tissues from the colon and/or terminal ileum in cases 3, 9, 10, 11, 12 and surgical tissues from jejunum and colon in case 4 proved to be eosinophilic enterocolitis (Fig. 4-6).

Muscular type associated with obstructive symptoms was diagnosed in 13% to 70% of all cases as in cases 13, 14 in this report (12.5%). Serosal type involvement in 12% to 40% of cases of EGIDs presents with abdominal distention and ascites which the authors found in equal numbers with muscular type (12.5%) (cases 15, 16).

Radiographic findings were non-specific and not helpful in diagnosis but barium studies may show many different signs such as irregular thickening of folds, polyps, ulceration, stenosis, rigidity or omental and mesenteric thickening depend on type or layer of involvement[6,11]. Intense infiltration deep into small bowel loops may produce pictures of small bowel lymphoma or adenocarcinoma in the differential diagnosis[12]. In the present study, three cases of the mucosal type underwent barium studies which showed diffuse mucosal swelling of duodenum and jejunum in case 1, irritable duodenum in case 4 (Fig. 1) and normal barium enema in case 10. From the two cases of the muscular type, one (case 3) showed normal study and the other (case 14) had pictures of diffuse infiltrative process and narrowing of gastric antrum. Massive ascites and marked mucosal thickening of mucosa from the stomach to large the intestine were found from

Table 3. Endoscopic findings and Histology

Group	Case	Endoscopic findings	Site	Histologic Eosinophilic infiltration
I	1.	Erythematous mucosa	Gastric antrum	Gastric body Gastric antrum Duodenum
	2.	Erythematous mucosa	Gastric body Gastric antrum	Duodenal bulb Second part of duodenum
		Aphtous ulcer	Duodenal bulb	
	3.	Normal mucosa	Gastric body Gastric antrum Colon	Terminal ileum Colon
	4.	Lymphoid hyperplasia Normal mucosa	Gastric antrum Colon	Colon
	5.	Erythematous mucosa	Gastric antrum Duodenum	Gastric antrum
	6.	Whitish nodule	Distal end esophagus	Esophagus
		Erythematous mucosa	Gastric antrum	
	7.	Multiple hemorrhagic spots Erythematous mucosa Lymphoid hyperplasia	Gastric body Gastric antrum	Gastric antrum
	8.	Erythematous mucosa	Gastric body Gastric antrum	Gastric body Gastric antrum Duodenum
	9.	Lymphoid hyperplasia	Transverse colon Cecum Ileum	Colon Ileum
	10.	Lymphoid hyperplasia	Colon Ileum	Colon Ileum
	11.	Lymphoid hyperplasia	Colon Ileum	Colon Ileum
	12.	Lymphoid hyperplasia	Colon Ileum	Colon
II	13.	Lymphoid hyperplasia	Gastric antrum	Gastric body Gastric antrum
	14.	Gastric rugal hypertrophy Lymphoid hyperplasia	Gastric body Gastric antrum	Gastric body Gastric antrum

computed tomography in case 16 of the serosal type (Fig. 2, 3).

Endoscopic findings may be normal or non-specific including erythema, friability, erosions, ulceration and nodularity[13,14]. In the present report the findings in mucosal and muscular types varied from normal mucosa, erythematous mucosa and small duodenal ulcer in case 2. Eight cases (6 mucosal, 2 muscular) had nodular or lymphoid hyperplasia in the gastric antrum or ileum or colon.

Corticosteroids and dietary therapy are two popular treatment interventions[2]. Elimination of suspected allergic food is the most important for those with proven food allergies[9]. However, food allergy has been reported in only 50% of cases[15,16]. In the present series two cases in mucosal type improved with only allergic food elimination. For corticosteroid therapy, symptom responses were nearly 80 to 100% in both children and adults[7,17]. Improvement occurs rapidly usually within two weeks in all types of the disease[18]. Some patients can rapidly be tapered off steroid but some require prolonged therapy[19]. In the present series, 11 out of 13 cases responded well to steroid with the duration of treatment varying from two to six months. Ketotifen is similar to sodium cromoglycate as mast cell stabilizers and both are

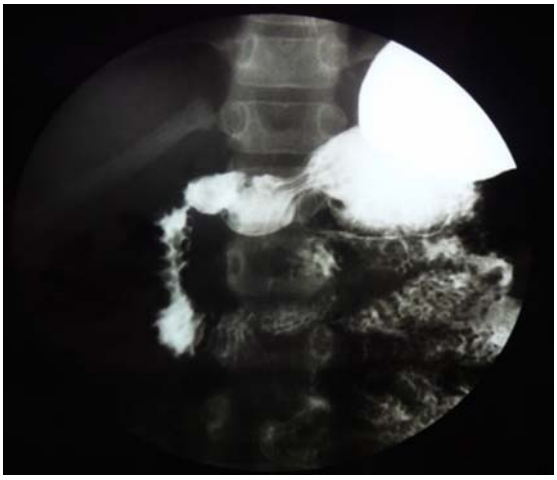

Fig. 1 Case 1 Upper GI study showed prominent mucosal folds of duodenum compatible with duodenitis

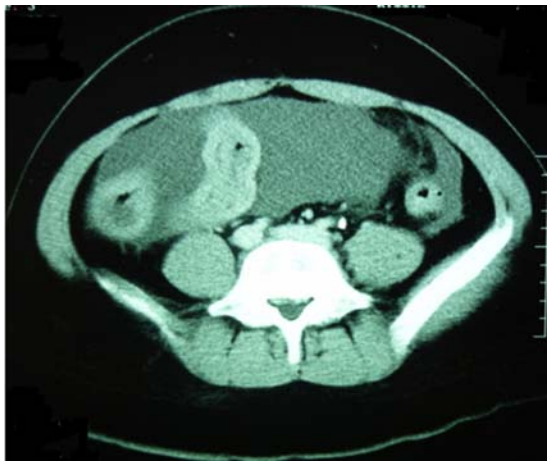

Fig. 3 Case 16 CT scan abdomen showed thickened mucosa of small bowel and ascites

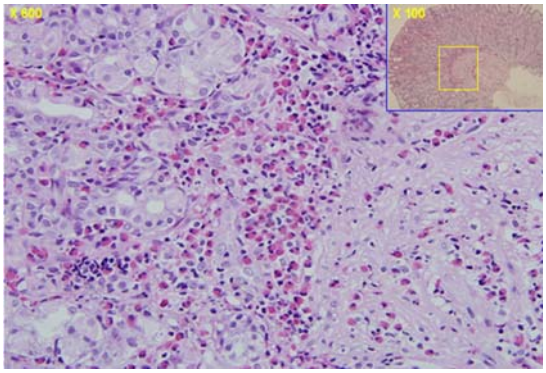

Fig. 5 Case 13 Multiple foci of eosinophilic infiltrate in the lamina propria with extension into muscularis mucosae

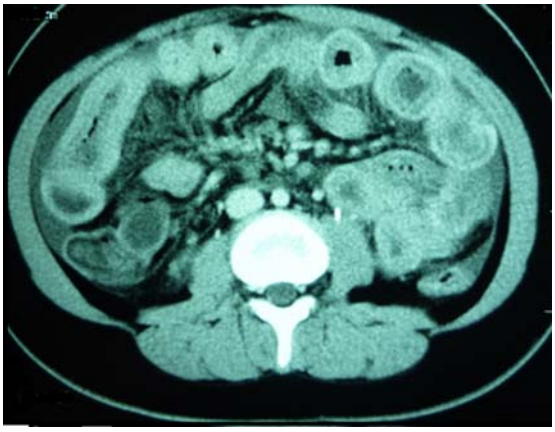

Fig. 2 Case 16 CT scan abdomen showed thickened mucosa of stomach to colon

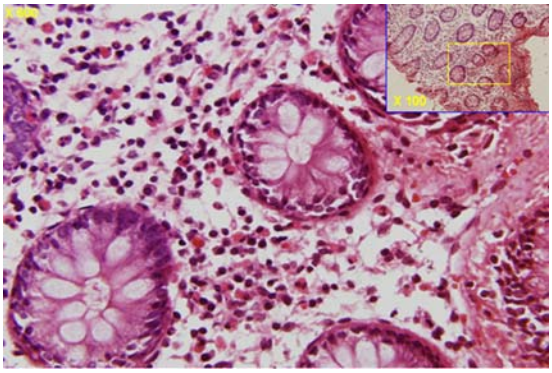

Fig. 4 Case 4 Colonic mucosa showed increased numbers of eosinophilic infiltrate in the lamina propria with extension into the submucosa

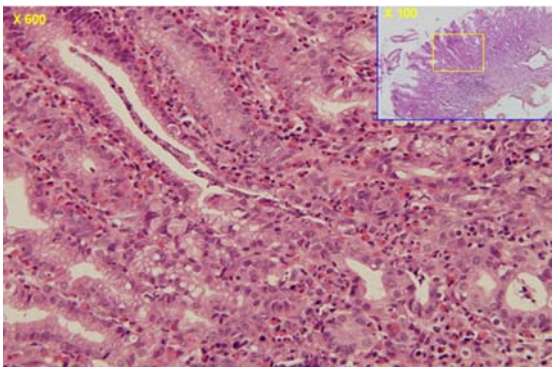

Fig. 6 Case 14 Biopsied tissues from stomach showed eosinophils aggregate in lamina propria with cryptitis

beneficial in some cases[20]. Montelukast works as leukotriene receptor antagonist is one effective drug[21]. The two cases in the mucosal type did not improve

with steroid, but the symptoms were successfully controlled with mast cell inhibitor (ketotifen) in one case and the other case combined with leukotriene receptor antagonist (montelukast). One case in the muscular type was treated with only proton pump inhibitor and the abdominal pain subsided in 4 weeks. One case of the serosal type (case 16) which was the only one in the present report who had hypoalbuminemia (3.14 g/dl) showed remission of the disease in a short time (4 weeks). Relapse occurred once after 3 years follow-up but responded well to steroids.

Conclusion

Eosinophilic gastrointestinal disease is a rare, problematic and challenging disease. Diagnostic clues of allergic histories and peripheral eosinophilia present in only half of the cases. The depth of eosinophilic infiltration in the bowel wall as well as location causes different clinical manifestations. The final diagnosis requires histological confirmation and exclusion of other causes of eosinophilia. Role of allergens, eosinophils, Th-2-type cytokines and eotaxin-1 in mediating tissue inflammation are involved in the pathogenesis of EGIDs. Specific dietary antigen elimination or elemental diet is the effective treatment in some patients. Corticosteroids remain the treatment of choice, but relapses can occur in some cases. Novel pharmacologic agents are used in steroid resistant cases such as mast cell stabilizer and leukotriene receptor antagonists. Although this disease is characterized by a waxing and waning course, the authors' experiences found only one case of relapse, which responded well to steroids.

Potential conflicts of interest

None.

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Eosinophilic Gastrointestinal Disease: วิเคราะห์รายละเอียดของผู้ป่วย 16 ราย จากประสบการณ์ 10 ปี ในประเทศไทย

นิยะดา วิทยาศัย, ศิริลักษณ์ เจนนุวัตร, อัญชลีรัตน์ เลิศสถิตย์,

วัตถุประสงค์*: เพื่อศึกษาโรค Eosinophilic gastrointestinal disease เกี่ยวกับอาการทางคลินิก, การวินิจฉัยโรคและผลการรักษา*

วัสดุและวิธีการ*: เป็นการศึกษาย้อนหลังในผู้ป่วยเด็กที่ได้รับการวินิจฉัยว่าเป็น Eosinophilic gastrointestinal disease ตั้งแต่เดือนมกราคม พ.ศ. 2543 ถึงเดือน ธันวาคม พ.ศ. 2553 ผู้ป่วยได้รับการวินิจฉัยโรคนี้จากอาการทางระบบทางเดินอาหารร่วมกับการพบเม็ดเลือดขาวชนิด eosinophil ในชั้นเยื่อบุผิวทางเดินอาหาร, ชั้นกล้ามเนื้อหรือชั้น serosa รวมทั้งการตรวจไม่พบเม็ดเลือดชนิดนี้นอกระบบทางเดินอาหาร และไม่พบว่ามีพยาธิในร่างกาย ได้ทำการศึกษาวิเคราะห์อาการทางคลินิก, วิธีการวินิจฉัยและผลการรักษาโรค*

ผลการศึกษา*: มีผู้ป่วย Eosinophilic Gastrointestinal Disease 16 ราย ชนิดของโรคที่พบมากที่สุดคือ ชนิดเยื่อบุผิวทางเดินอาหาร (12 ใน 16 ราย) สำหรับชนิดกล้ามเนื้อและ serosa พบเท่ากันชนิดละ 2 ราย อายุของผู้ป่วยจากการศึกษาคือ 6 เดือน ถึง 13 ปี อัตราส่วน ชาย:หญิง = 1:1.2 อาการที่พบมากที่สุด คือปวดท้องและอุจจาระร่วง ประวัติภูมิแพ้พบ 68.75% เม็ดเลือดขาว eosinophil สูงในเลือดพบเพียง 37.5% ของผู้ป่วย ลักษณะทางรังสีวิทยาไม่มีลักษณะที่เฉพาะของโรค ผู้ป่วยได้รับการส่องกล้องตรวจทางเดินอาหาร 14 ราย ลักษณะความผิดปกติจากการส่องกล้องทางเดินอาหารที่พบมากที่สุด คือ ต่อมน้ำเหลืองนูนแดง และปริมาณ มากกว่าปกติ โดยเฉพาะชนิดโรคที่เป็นที่เยื่อบุผิวทางเดินอาหาร พบเม็ดเลือดขาวชนิด eosinophil มากกว่า 20 ตัวต่อการตรวจด้วยกล้องจุลทรรศน์ หัวที่มีกำลังขยายสูง โดยตรวจพบจากชิ้นเนื้อที่ตัดจาก ผิวเยื่อบุหลอดอาหาร กระเพาะอาหาร, ลำไส้ใหญ่ หรือการตรวจน้ำในช่องท้อง เพรดนิโซโลนเป็นยาที่ใช้ในการ รักษาผู้ป่วย 13 ใน 16 ราย และได้ผลดีใน 11 ราย ผู้ป่วย 2 ราย ที่ไม่ตอบสนองต่อเพรดนิโซโลน ได้รับการรักษาด้วยยากลุ่มอื่น เช่น คีโตติเฟนและมอนเตลูคาส มีผู้ป่วย 1 ราย ในการศึกษาที่อาการดีขึ้น ด้วยยาห้ามการหลั่งกรดชนิดโปรตอนปั๊มเพียงอย่างเดียว ผู้ป่วยอีก 2 ราย ในการศึกษานี้ได้รับการรักษา ด้วยการหลีกเลี่ยงชนิดอาหารที่แพ้ โดยไม่ต้องใช้ยาใดๆ*

สรุป*: Eosinophilic Gastrointestinal Disease มีอาการแสดงได้หลายชนิดแตกต่างกันไป การวินิจฉัยโรคจำเป็นต้องได้เนื้อเยื่อหรือน้ำในช่องท้องที่พบปริมาณเม็ดเลือดขาวชนิด eosinophil ในปริมาณที่มีนัยสำคัญ ผู้ป่วยมากกว่าครึ่งที่พบว่ามีประวัติภูมิแพ้จึงน่าจะมีความสำคัญกับโรคนี้ ดังนั้น การรักษาด้วยการหลีกเลี่ยงอาหารที่แพ้จึงมีความสำคัญมากในผู้ป่วยซึ่งมีสาเหตุจากการแพ้อาหาร ส่วนในกลุ่มซึ่งไม่เกี่ยวข้องกับการแพ้อาหารหรือการรักษาด้วย การหลีกเลี่ยงอาหารที่แพ้แล้วไม่ดีขึ้นก็อาจจำเป็น ต้องใช้ยาในกลุ่มของคอติโคสเตียรอยด์*