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Research Paper

Eosinophilic Infiltration in Surgically Resected Gastrointestinal Tissue of Children With Non-traumatic Gastrointestinal Pathologies: A Descriptive Analysis

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ABSTRACT

Background: Considering that non-eosinophilic esophagitis eosinophilic gastrointestinal disorders (EGIDs) could mimic serious surgical conditions, including hypertrophic pyloric stenosis, intussusception, and bowel perforation, this study investigates these disorders as major causes of gastrointestinal surgery in children.

Materials and Methods: Children who had undergone gastrointestinal surgery between March 2017 and March 2018 at Mofid Children's Hospital in Tehran City, Iran, were randomly selected to perform a rigorous and complete re-evaluation of the pathology to determine the presence of eosinophils or eosinophil-related inflammation in the tissue samples collected after surgery. Traditional hematoxylin and eosin staining was used to quantify eosinophils and their footprints. Trichrome staining was also applied to measure the tissue fibrosis.

Results: A total of 72 pediatric patients with a median age of 2.5 years, suffering from constipation and abdominal pain were studied. The majority of patients were primarily diagnosed with Hirschsprung's syndrome (38.9%), followed by imperforated anus (34.7%) and ileal atresia (16.7%). Among the studied patients ten (13.9%) were confirmed to have tissue eosinophilia, compatible with the conventional method of non-EoE-EGID diagnosis. More evidence supporting the presence of tissue eosinophils was infiltration of 1-26 eosinophils in the muscular and subserosal layers of more than 97% of samples, degranulated eosinophils and multi-nucleated cells in 6(8.3%) tissue samples, and different levels of tissue fibrosis in 37 patients (51.4%).

Conclusion: Non-EoE EGIDs should be considered in the context of severe relapsing gastrointestinal complications requiring urgent or emergent surgical interventions, particularly in subjects without a convenient response after surgery.

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Introduction

Eosinophilic gastrointestinal disorder (EGID) is a rare group of disorders characterized by gastrointestinal symptoms and pathologically extensive eosinophil infiltration of the gastrointestinal tract. Eosinophilic infiltrations in patients with eosinophilic esophagitis (EoE) are only found in the esophagus, while non-EoE-EGID patients have gastrointestinal eosinophilic infiltration regardless of esophageal involvement. Depending on the gastrointestinal tract segments involved, non-EoE-EGIDs can be also referred to as eosinophilic gastritis, eosinophilic enteritis, eosinophilic gastroenteritis, and eosinophilic colitis [1-5].

Eosinophils are innate immune cells traditionally associated with allergic diseases and parasitic infections [4]. Non-EoE-EGID is a chronic type 2 inflammatory disease activated by T-helper type 2 (Th2) cells; therefore, Th2 cytokines are crucial for the infiltration and activation of eosinophils [6].

Since food allergens are mostly known as potential triggers of eosinophilic inflammation in the gastrointestinal tract of the affected children, the elimination of these kinds of food may significantly improve their clinical conditions [7, 8]. Allergic diseases and comorbidities, including food allergy, asthma, and allergic rhinitis have been widely reported in patients with EGIDs [9]. In addition, these patients have a constellation of unmet needs, which could significantly impact their lives [3]. More than half of these patients experience delays in diagnosis often due to transition through multiple health providers [3].

Considering the different levels of gastrointestinal tract involvement, EGIDs are categorized into four groups comprising EoE, eosinophilic gastritis, eosinophilic gastroenteritis, and eosinophilic colitis. Meanwhile, the location of the gastrointestinal involvement is responsible for specific symptoms appearing in each patient. For example, the involvement of the muscle layer mainly causes bowel obstruction, and subserosal layer involvement is also predominantly associated with eosinophilic ascites [10]. Some studies have reported that non-EoE EGIDs could mimic serious surgical conditions, including hypertrophic pyloric stenosis (HPS), intussusception, and bowel perforation, leading to surgical complications, especially in pediatric patients, whereas the removal of the probable allergen or administrating immunosuppressive drugs could simply resolve the symptoms [11-13]. Considering that 11% to 85% of the total global burden of all disorders is attributable to surgically-treated diseases [14], and knowing that patients with non-EoE EGIDs tend to undergo more surgical procedures due to the higher chance of recurring symptoms as well as diagnostic difficulties [15], achieving a better understanding of this disease is of paramount importance. At present, no guidelines exist for diagnosis or treatment of non-EoE EGIDs [2].

Accordingly, this study investigates what proportion of the pediatric patients who had undergone gastrointestinal surgery were suffering from non-EoE EGIDs. Meanwhile, this study outlines how the timely diagnosis of non-EoE EGIDs may prevent unnecessary surgery to improve the patient's clinical conditions by eliminating food allergens and/or immunosuppressive medications.

Material and Method

Study patients

The patients were randomly selected from the children who had undergone gastrointestinal surgery between March 2017 and March 2018 at the Surgical Department of Mofid Children's Hospital (Tehran, Iran) affiliated with Shahid Beheshti University of Medical Sciences. Patients who were older than 18 years at the time of surgery, were operated on secondary to trauma, had inadequate tissue samples, or were affected by other known secondary causes of eosinophilia were excluded from the study. Finally, a total of 72 patients fulfilled the criteria and underwent subsequent analyses.

Samples collection and demographic data

After the evaluation of the gastrointestinal pathologic specimens of the patients, an appropriate form was developed to collect the demographic data from the patient's medical records or by direct interviews and medical examinations. The form included age, sex, family history of allergy, present and prior allergic diseases comorbidities (asthma, allergic rhinitis, or atopic dermatitis), and clinical pre- and post-surgery gastrointestinal surgery, non-gastrointestinal surgery, and allergic manifestations. This form was designed according to the National Institute for Health and Care Excellence (NICE) (2018) guidelines for food allergy symptoms [16]. Complete blood count values were obtained from the patient's medical records at the time of admission and were compared to normal age-adjusted ranges. Skin prick test for food allergens including cow's milk, meat, egg, sesame, nuts (walnut, peanut, hazelnut, pistachio), barley, and wheat was subsequently performed on all of the patients.

Histological assessment

Gastrointestinal biopsy specimens, previously collected from the patients during surgery, were reassessed by a pathologist with special attention to eosinophil infiltration or its footprints, such as fibrosis, degranulated eosinophils, and multinucleated cells, in different layers of gastrointestinal specimens. The number of eosinophils per high-power field (HPF), as the main and conventional criterion for diagnosis of EGID, was measured and compared with normal pediatric values in each part of the gastrointestinal tract described by DeBrosse et al. [16]. Hematoxylin and eosin staining was employed as the conventional approach to quantify eosinophils and their footprints. Trichrome staining was also used to measure the tissue fibrosis in patients.

Statistical analysis

All statistical analyses were performed using the SPSS software, version 26 (Chicago, IL). Median and interquartile ranges (IQR) were calculated for quantitative variables with abnormal distribution. Qualitative data were interpreted using numbers and percentages.

Results

Demographic data

The data evaluation of 72 pediatric patients (41 males, 31 females) who underwent gastrointestinal surgery at a median (IQR) age of 2.5 (1.2-11.0) years showed that 28 patients were operated due to Hirschsprung syndrome (38.9%), followed by 25 imperforated anus (34.7%) and 12 ileal atresia cases

Clinical presentations

Constipation, abdominal pain, and vomiting were the most common reported pre-surgical symptoms with 62.5% (45 patients), 40.3% (29 patients), and 13.9% (10 patients), respectively. After comparing these clinical symptoms in each diagnostic group, constipation and abdominal pain were more common in Hirschsprung syndrome, and mucus/or blood in stool was frequently found in surgically-repaired imperforated anus after operation (Table 1).

The recurrence of gastrointestinal symptoms after surgery, including constipation (31 cases, 43.1%), abdominal distension (30 cases, 41.7%), obstipation (28 cases, 38.9%), and vomiting (9 cases, 12.5%), were observed in all the patients, even after the initial surgical interventions (Table 2), suggesting another underlying disorder other than the initial diagnoses.

Peripheral blood cells findings and allergic lab data

The complete blood counts of the 68 pediatric patients who underwent gastrointestinal surgery are summarized in Table 3.

Normal white blood cell count, platelet, and lymphocyte count with low hemoglobin levels were found in 88.4%, 73.5%, and 48.8% of the patients, respectively. However, most patients (46 out of 72) were reported to have blood eosinophilia (63.9%).

The skin prick test yielded positive results in 31 patients (43%), although there was no significant difference between the patients undergoing different types of surgery. Only 6.9% of the patients (5 out of 72) mentioned having a family history of allergies. Milk and eggs were the most common food allergens (in 19 and 14 individuals, respectively). Two of the ten patients with obvious tissue eosinophilia, indicating non-EOE EGIDS (14% of the total), had negative skin tests. Meanwhile, 6 patients (60%) tested positive for eggs, four (40%) for cows' milk, one for almonds, and one for wheat.

Histologic findings

Except for 2 patients (2.8%), a range of 1-35 eosinophils/HPF, not normally found in healthy children, was detected in the muscular or serosal layers of the patient's specimens. Additionally, 1-26 eosinophils/HPF were reported in the subserosal layers of specimens in 70 patients (97.2%) (Figures 2, 3, 4, and 5). Six specimens (8.3%) revealed degranulated eosinophils and multinucleated cells. Also, 10 patients revealed tissue eosinophilia compatible with EGID according to conventional diagnostic criteria (13.9%).

Four of these patients underwent surgery for Hirschsprung disease (40%), three for imperforated anus (30%), and one for ileal atresia (10%), intussusception (10%), and necrotizing enterocolitis (NEC, 10%) each. However, tissue eosinophilia was not taken into consideration initially in any of the aforementioned conditions before the surgery. Almost half of the patients (37 of 72, 51.4%), including all of those with tissue eosinophilia, had different levels of tissue fibrosis in the collected specimens. Furthermore, due to hemorrhagic mucosa in two specimens, it was not pathologically possible to become certain about the existence of eosinophilic infiltration.

Table 1. Pre-operation clinical symptoms of 72 pediatric patients with gastrointestinal surgeries

Clinical Symptoms	No. (%)					
	Initial Diagnosis					
	GERD Symptoms	Colic	Abdominal Pain	Sialorrhea	Food Aversion	Constipation
Hirschsprung syndrome (n=28)	1(3.6)	1(3.6)	14(50)	1(3.6)	2(7.1)	25(89.3)
Annus imperforus (n=25)	2(8)	2(8)	3(12)	1(4)	2(8)	9(36)
Atresia (n=12)	2(16.7)	1(8.3)	7(58.3)	1(8.3)	3(25)	8(66.7)
Intussusception (n=2)	0(0)	0(0)	1(50)	0(0)	0(0)	0(0)
Reflux (n=1)	1(100)	0(0)	1(100)	0(0)	1(100)	0(0)
NEC (n=1)	0(0)	0(0)	1(100)	0(0)	0(0)	1(100)
Appendicitis (n=1)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)
Colon stenosis (n=1)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)
Gastrostomy (n=1)	0(0)	0(0)	1(100)	0(0)	0(0)	1(100)
Total (n=72)	6(8.3)	4(5.6)	29(40.3)	3(4.2)	8(11.1)	45(62.5)

Clinical Symptoms	No. (%)							
	Initial Diagnosis							
	Diarrhea	Obstipation	Mucus/ Blood In Stool	Vomiting	Fatigue	Eczema	Wheezing	Bruxism
Hirschsprung syndrome (n=28)	1(3.6)	1(3.6)	0(0)	1(3.6)	1(3.6)	1(3.6)	0(0)	0(0)
Annus imperforus (n=25)	2(8)	4(16)	4(16)	3(12)	0(0)	2(8)	1(4)	1(4)
Atresia (n=12)	2(16.7)	0(0)	2(16.7)	5(41.7)	0(0)	1(8.3)	0(0)	0(0)
Intussusception (n=2)	0(0)	0(0)	0(0)	1(50)	0(0)	0(0)	0(0)	0(0)
Reflux (n=1)	1(100)	0(0)	1(100)	0(0)	1(100)	0(0)	0(0)	0(0)
NEC (n=1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Appendicitis (n=1)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	0(0)
Colon stenosis (n=1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Gastrostomy (n=1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Total (n=72)	6(8.3)	5(6.9)	8(11.1)	10(13.9)	2(2.8)	4(5.6)	1(1.4)	1(1.4)

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Abbreviations: n: Number; GERD: Gastroesophageal reflux; NEC: Necrotizing enterocolitis.

Table 2. Post-operation clinical symptoms of patients with gastrointestinal surgery

Clinical Symptoms	No. (%)			
	Initial Diagnosis			
	Constipation	Abdominal Distension	Obstipation	Vomiting
Hirschprung syndrome (n=28)	12(42.9)	13(46.4)	9(32.1)	3(14.3)
Imperforated anus (n=25)	10(40.0)	10(40.0)	13(52.0)	3(12.0)
Atresia (n=12)	4(33.3)	5(41.7)	3(25.0)	2(16.7)
Intususception (n=2)	1(50.0)	0(0)	1(50.0)	0(0)
Gastroesophageal reflux (n=1)	1(100)	1(100)	0(0)	0(0)
Necrotizing enterocolitis (n=1)	1(100)	0(0)	1(100)	0(0)
Appendicitis (n=1)	1(100)	0(0)	0(0)	0(0)
Colon stenosis (n=1)	1(100)	1(100)	1(100)	0(0)
Gastrostomy (n=1)	0(0)	0(0)	0(0)	0(0)
Total (n=72)	31(43.1)	30(41.7)	28(38.9)	9(12.5)

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Table 3. Complete blood counts of the 68 pediatric patients undergoing gastrointestinal surgery

Initial Diagnosis	Median (IQR)						
	CBC						
	WBC ($\times 10^3$ cell/µL)	Hemoglobin (g/dL)	Platelets ($\times 10^3$)	Neutrophils % (Cells/µL)	Lymphocytes % (cells/µL)	Eosinophils % (cells/µL)	Monocytes % (cells/µL)
Hirschsprung syndrome (n=25)	10.5 (8.5-12.3)	11.2 (10.1-12.4)	385.0 (301.5-452)	33 (22.5-41)	60 (52-70.5)	4.8 (2.5-6.5)	2 (0-2.6)
Imperforated anus (n=24)	11.8 (8.4-16.3)	11.7 (9.9-15.4)	320.5 (234-383.2)	57 (32.7-72)	36.5 (20.2-58)	3.5 (2-8)	1 (0-3)
Atresia (n=12)	11.3 (8.6-14.3)	11.6 (9.3-12.3)	375.0 (293.5-462.5)	41 (31.2-54.5)	50.5 (36.7-62.7)	5 (3.2-7)	1 (0-3.7)
Intususception (n=2)	12.4 (6.5-18.40)	9.6 (7.8-11.50)	461.5 (390-533)	76.6 (65.3-88)	21 (12-30)	2.3 (0-4.6)	0
Reflux (n=1)	9.6	12.0	738.0	63.4	30.4	6.2	0
NEC (n=1)	10.8	10.3	88.0	68	30	1	1
Appendicitis (n=1)	12.6	12.5	271.0	80	16	3	1
Colon Stenosis (n=1)	10.6	10.4	525.0	24	70	2	4
Gastrostomy (n=1)	12.9	11.6	308.0	58	36	6	0
Total (n=68)	10.9 (8.7-13.4)	11.5 (10.1-13.1)	358 (278.7-443.5)	42 (25.7-60)	50 (31.3-67)	4.3 (2-7)	1 (0-3)

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Abbreviations: CBC: Complete blood counts; WBC: White blood cells; NEC: Necrotizing enterocolitis; IQR: Interquartile range (percentile 25^{th}-75^{th}).

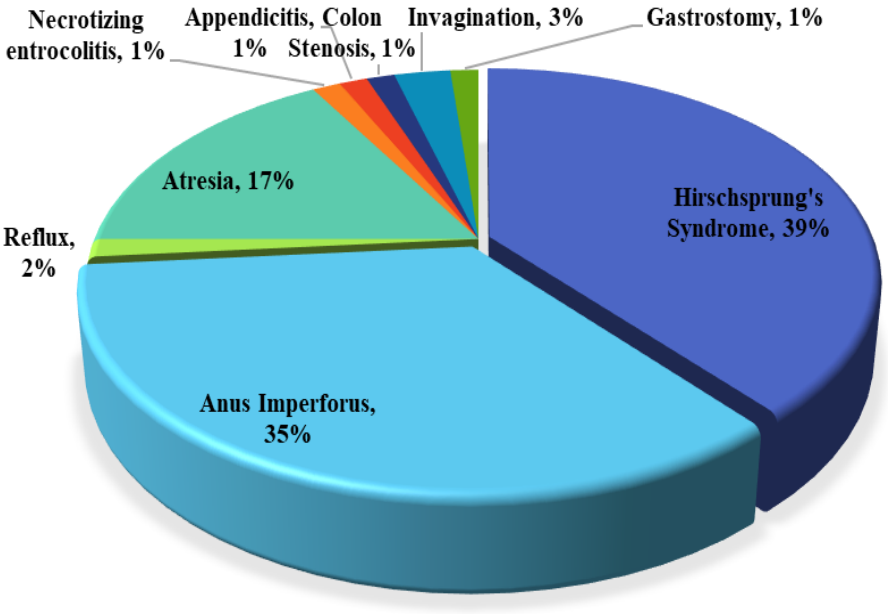

Figure 1. An illustration of the causes of gastrointestinal surgery in pediatric patients

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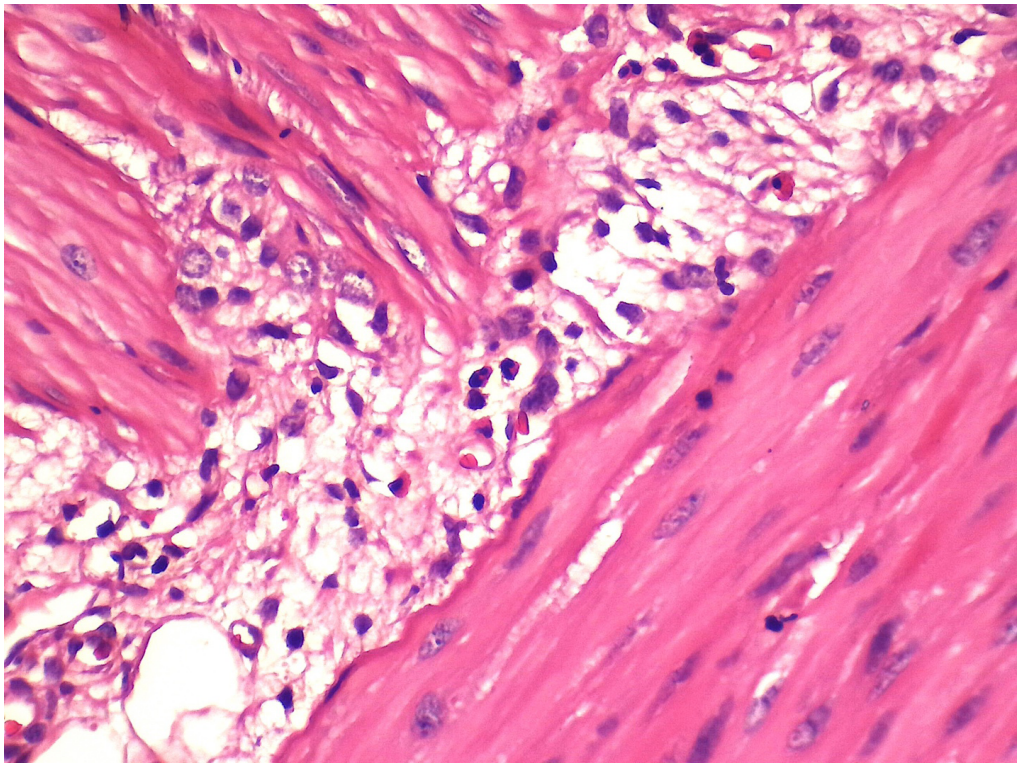

Figure 2. Eosinophilic infiltration in muscularis properia and intermuscular nerve bundles (H&E, ×400)

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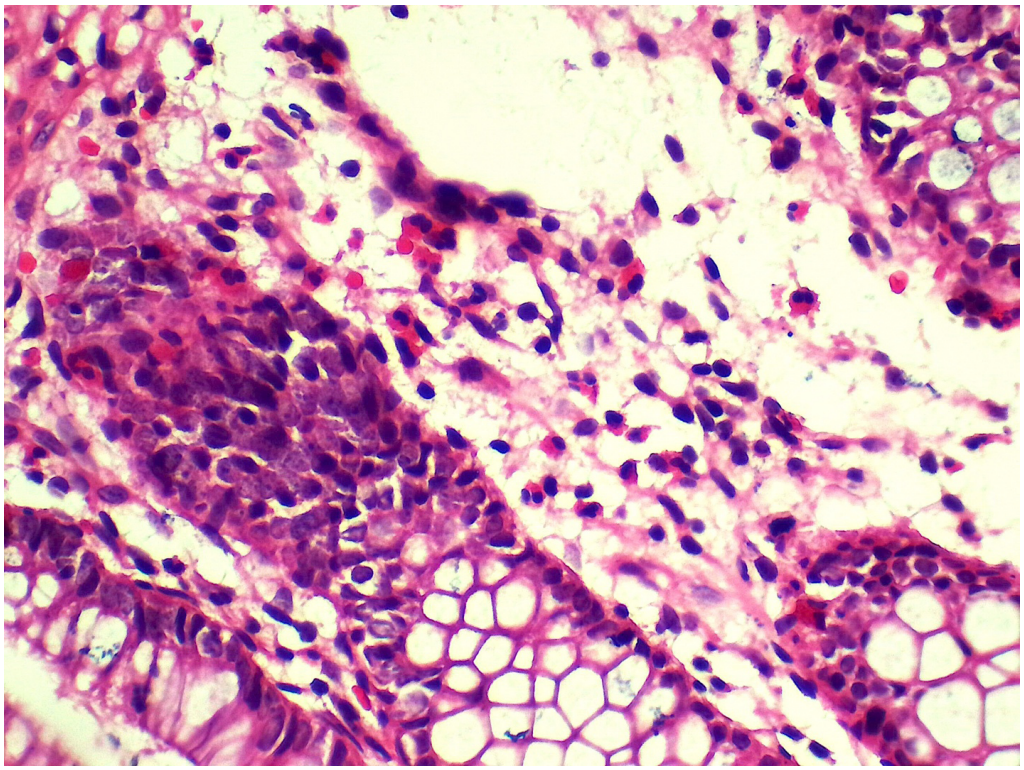

Figure 3. Marked eosinophilic infiltration in the mucosa with permeation into glands (H&E, ×400)

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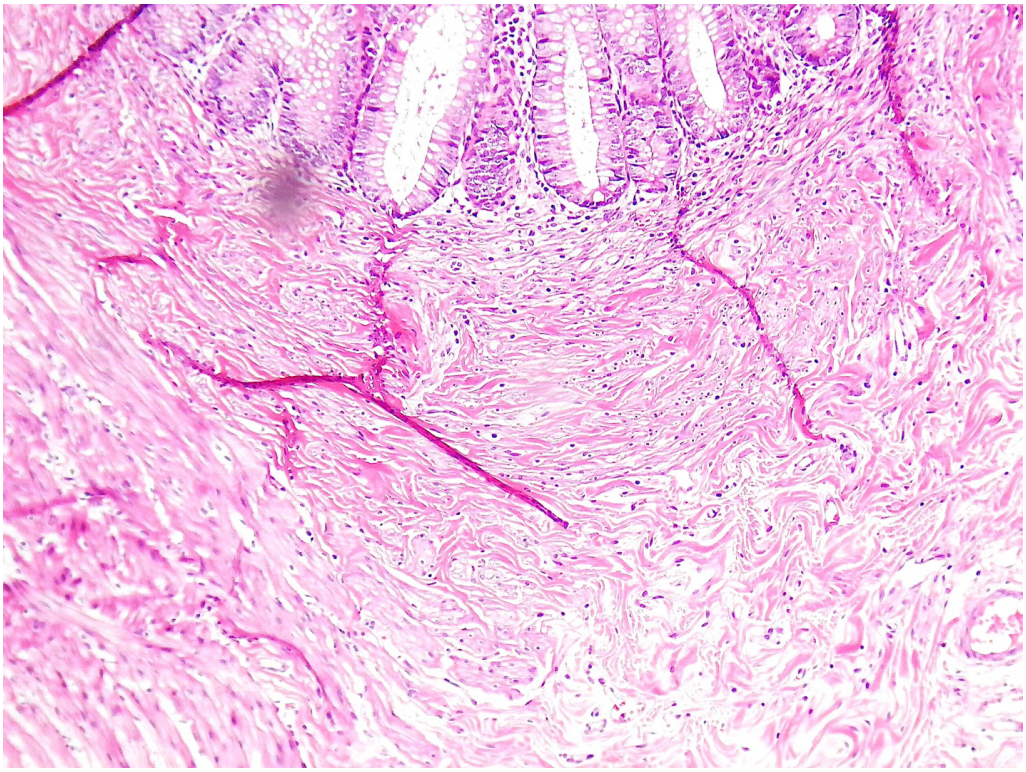

Figure 4. Submucosal fibrosis and deposition of pink collagen bundles (H&E, ×100)

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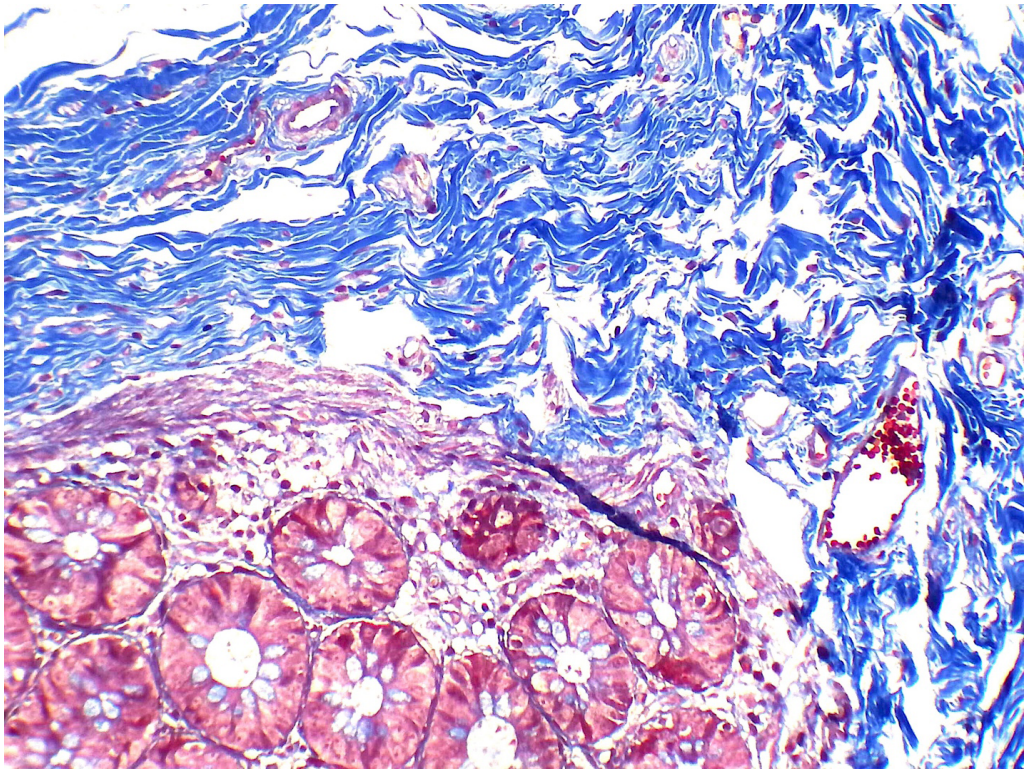

Figure 5. Submucosal fibrosis highlighted with special staining (Trichrome, ×200)

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Constipation, vomiting, and abdominal pain were the most common presentations. Peripheral blood eosinophilia was present in 70% and 63.2% of the patients with and without tissue eosinophilia (according to conventional diagnostic criteria), respectively. The skin prick test was positive in 8 out of 10 patients whose tissue eosinophilia exceeded the cut-off limit. The results of egg and cow's milk skin prick tests were positive in 6 and 4 of these patients, respectively.

Discussion

In this study, 72 patients who had undergone intestinal surgery were recalled for further interviews as well as skin prick tests. An expert pathologist also reexamined the patients' histopathology specimens for the second time. Additionally, their histopathologic specimens were evaluated again. This evaluation aimed to detect tissue eosinophilia, caused by non-EoE EGID as the underlying disease, leading to surgical operations in the course of the disease. The allergic background of these patients was also evaluated.

Almost 14% of the patients' specimens matched the conventional diagnostic criteria for non-EoE EGID, which mainly relied on the number of eosinophils in the tissue [17, 18]. The post-operative diagnoses in the majority of these patients were congenital gastrointestinal developmental disorders, including Hirschsprung's disease followed by imperforated anus and ileal atresia. Interestingly, all the patients experienced recurrent gastrointestinal symptoms (mainly constipation and abdominal pain) before and even after the surgery. Relying on the classical diagnosis method of non-EoE EGID (i.e. counting tissue eosinophils alone), it was diagnosed in 13.9% of the patients in the present study, which is 5000 times more than the general population (2.5/100000) [18].

In light of the two findings presented above (recurrent gastrointestinal symptoms and a higher prevalence rate of non-EoE EGIDs), we developed an innovative hypothesis of an etiological relationship between non-EOE EGIDs and pediatric intestinal surgery, raising the question as to whether the origin of non-EoE EGIDs could be from an early intrauterine onset with possible evolution to surgical conditions in the natural course of the disease. However, this is not to be verified by this study alone and further research is needed before confirming such a presumption.

On the other hand, further evidence was found that corroborated the presence of tissue eosinophils in the study

population. More than half of the patients had different levels of tissue fibrosis in their obtained intestinal tissue. Since the presence of eosinophils leads to the secretion of transforming growth factor-beta and several other related cytokines which, in turn, cause fibrosis as the final stage of chronic inflammation [19, 20], fibrosis might stem from previous eosinophilic inflammations and non-EoE EGID. Additionally, the histological assessments of six patients (8.3%) revealed degranulated eosinophils and multi-nucleated cells, known as suggestive diagnostic criteria of non-EoE EGIDs [21]. Eosinophils were also detected in the muscular and serosal layers of the surgically excised tissues in more than 97% of the patients. Muscular and serosal layers are considered abnormal tissues in case of the existence of eosinophils in the gastrointestinal tract, indicating the presence of non-EoE EGID [22].

Due to the normal presence of hemostatic eosinophils in the lower parts of the gastrointestinal tract as well as the lack of consensus on the cut-off number of tissue eosinophils, non-EoE EGIDs, cannot still be diagnosed with high levels of certainty [22]. Favorably, a histological system has been developed for EoE that scores eight pathological signs including eosinophil density, eosinophil abscess (accumulation of more than 4 eosinophils), and basal cell hyperplasia [23]. Establishing such a scoring system for pathological tissue changes, as well as accumulation of eosinophils in the tissue is essential for more accurate and timely diagnosis of the disease.

Additionally, it is safe to assume that only counting the number of tissue eosinophils does not seem to be sufficient for diagnosis, and therefore more clinical and pathologic studies are required to elucidate the diagnosis. Apart from the challenges in identifying tissue eosinophilia [24], such as the problems with measuring eosinophils in the acute diagnosis of non-EoE EGID, our recommendation is considering a combination of the patient's chronic and recurrent clinical symptoms, the subtle evidence of the presence of eosinophils in tissues (in forms of fibrosis, fistula, presence of eosinophils in layers other than mucosa), macroscopic features of gastrointestinal tissues (such as nodular lymphoid hyperplasia and eosinophilic abscess) along with the measurements of eosinophil cytokines (such as major basic protein, eosinophilic cationic protein, Eotaxin) for a precise diagnosis.

Remarkably, the frequency of non-EoE EGID in the patients diagnosed by the conventional method in the present study was about 13.9% which is far more than the prevalence of non-EoE EGID in the general population (with a prevalence of 2.5/100 000) [18]. This higher prevalence of non-EoE EGID in our study population along with other evidence confirming tissue eosinophilia (in more than 97% of the patients) raises this question as to whether there was a real cause and-effect relationship between non-EoE EGID and abdominal surgical conditions. In addition, peripheral blood eosinophilia in more than 63% to 70% of the patients as well as positive skin prick test results with "egg" as the most common food allergen in 43% of the patients may indicate other supportive evidence of this causality, and highlight the role of allergy as an etiopathological factor in our study population.

The allergic nature of non-EoE EGIDs has been earlier expressed by Spergel et al. [25], and the immunological mechanism in delayed food allergic reactions are predominantly non-immunoglobulin E-mediated [26].

A few studies have reported the allergic basis of some surgical conditions such as recurrent NEC (e.g. in a boy secondary to allergic enterocolitis due to cow's milk protein allergy) [27] and intussusception in both pediatric and adult patients resulting from eosinophilic enteropathy [28, 29]. In one study, Yamada et al. [30] recommended screening and treatment of EoE in patients with esophageal stenosis/or atresia.

Due to the above-mentioned nature of allergy in inducing non-EoE EGIDs, non-invasive interventions including dietary elimination and elemental diets have shown promising effects in both children and adults with non-EoE EGIDs [7, 31, 32]. Elemental and six-food-eliminating diets are the most effective treatments in 90.8% and 72.1% of the patients with EGID, respectively [31]. This mode of therapy alongside systemic and topical corticosteroids may reduce surgical interventions and their potential complications as well as the burden of the disease on both the patients and the health system.

As with most studies, the design of the current study is also subject to limitations. Firstly, there was no other choice but to re-evaluate the patients' tissues that were previously collected during the operation. This might negatively have influenced the finding of eosinophils by taking the sample from inappropriate necrotic sites leading to inaccurate and inconclusive pathologic results regarding eosinophils and other inflammatory cells. In addition, immunohistochemistry assay as a reliable method to trace the presence of eosinophil-related proteins and cytokines [33] was not implemented in this study either. Another possible source of error was taking biopsies from fibrotic tissues lacking eosinophils because of their

fibrotic nature, which was reported in more than 50% of the patients as a sign of chronic eosinophilic inflammation, bleeding, or necrosis.

Conclusion

Currently, there are no consensus guidelines, pathognomonic symptoms, or laboratory tests for the diagnosis of non-EOE EGIDs. However, clinical manifestations, positive family history of allergies, and positive skin prick tests for food allergens may provide useful clues in the diagnosis of non-EoE EGIDs. Our work has led us to conclude that non-EoE EGIDs should be considered in the context of severe relapsing gastrointestinal complications requiring urgent and/or emergent surgical interventions (except traumatic and cancerous indications), particularly in those without a convenient response after surgery. Under such circumstances, tissue samples obtained from gastrointestinal surgery should be reviewed and scrutinized for eosinophils. Other abnormal, additional findings in the histological assessment of non-EoE EGIDs may include the presence of eosinophils in muscular and serosal layers, degranulated eosinophils, and fibrosis. Samples that are positive for eosinophils may indicate non-EoE EGID in patients, so if treated appropriately in terms of food allergy and timely use of anti-inflammatory medications, it may potentially result in the relief of the symptoms, without further need for surgical procedures.

This study is the first step towards suggesting the surgical complications of delayed diagnosis and management of non-EoE EGIDs in the natural course of this group of disorders, so if diagnosed and treated promptly, such surgery might not ever be required in some patients. Further studies need to be carried out prospectively in larger populations with specific laboratory studies enabling statistical analysis. Immunohistochemistry staining as well as detection of the eosinophil-driven cytokines, eosinophil specific or secondary granules in addition to direct eosinophil counts, are needed to increase the probability of identification of tissue eosinophilia.

Ethical Considerations

Compliance with ethical guidelines

All the experiments were approved by the local Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Code: IR.SBMU.MSP.REC.1398.501 in accordance with the Declaration of Helsinki. Written informed consents were obtained from the patients and/or their caregivers/parents for their participation and article publication.

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Authors' contributions

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Conflicts of interest

The authors declared no conflict of interest.

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