研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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Ⅳ. 研究成果の代表的論文

Eosinophilic gastrointestinal disorder in an infant with feeding dysfunction

Running head: EGID with FD

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Keywords: Eosinophilic gastrointestinal disorders, feeding dysfunction, eosinophils

Established Facts

- A few recent studies have shown that feeding dysfunction (FD), including maladaptive learned behaviors and physical difficulties in eating mechanics, is a prevalent symptoms complex in young children with EGIDs.
- FD that adversely affects development, feeding, and nutrition in affected children does not respond well to the medical treatments that improve eosinophilic inflammation.

Novel Insights

- Not only eosinophilic esophagitis but also other EGID should be considered in the differential diagnosis of an infant with FD.

Abstract

Feeding dysfunction (FD) has recently been considered to comprise a prevalent set of symptoms in eosinophil gastrointestinal disorders (EGIDs) in young children. We report the case of an 8-month-old girl with EGID who visited our hospital due to vomiting, poor weight gain, and feeding difficulties; her condition was discovered during the examination of the symptoms including FD. Tracheal aspiration and reduced esophageal clearance were shown in a barium swallow test and upper gastrointestinal contrast radiography, respectively. Further, delayed clearance from the stomach was detected on gastrointestinal scintigraphy. Gastrointestinal endoscopy and biopsies revealed esophagitis with a few eosinophils and duodenitis with eosinophilic inflammation. She was not likely to be an eosinophilic esophagitis (EoE). On administration of an elemental diet, the patient gained weight. Subsequently, esophageal and stomach clearance improved, although the vomiting and FD persisted to some extent. We concluded that it is important to consider other EGIDs as well as EoE in the differential diagnosis of FD.

Introduction

Eosinophilic gastrointestinal (GI) diseases (EGIDs) are characterized by primary eosinophilic infiltration of the GI tract accompanied by GI symptoms. Clinical studies on EGIDs have demonstrated an obvious association between these conditions and food allergies. Over the past decade, the incidence of primary EGIDs, especially eosinophilic esophagitis (EoE), has increased along with the increase in the incidence of atopic diseases [1]. This may be due to an actual increase in the number of affected patients as well as better disease awareness [2]. EGIDs are classified into 4 groups (EoE, eosinophilic gastritis, eosinophilic gastroenteritis, and eosinophilic colitis) on the basis of the primarily affected GI sites. The symptoms of EGIDs vary by anatomic location and include dysphagia, abdominal pain, cramping, bloating, nausea, vomiting, diarrhea, ascites, and obstruction. In addition to those symptoms, feeding dysfunction (FD), a symptom complex including maladaptive learned behaviors, developmental differences, immature diet selection, dysphagia, oral sensory skills deficits, and oral motor skill deficits, has recently been found to be prevalent in pediatric patients with EGIDs [3]. Significant FD was observed in 16.5% of patients, and not only patients with EoE but also those with other EGID were included in the study. Besides unexplained oral aversion, feeding refusal or difficulty, vomiting, and poor weight gain in patients less than 4 years of age are symptoms of an EGID, EoE [4]. The authors present a case of pediatric EGID that is unlikely to be EoE discovered by the examination of FD including food refusal and exaggerated responses to touch in the mouth or around the face, and poor weight gain.

Case report

An 8-month-old girl presented at our hospital with vomiting, poor weight gain, and feeding difficulties. She was born with a low birth weight of 1,936 g at 35 weeks of gestation. She had been admitted to another hospital because of poor weight gain at 2 months of age. Her weight gain improved after her mother was educated on how to feed her milk. However, after the initial recovery, the amount of feeding decreased gradually, and she began vomiting frequently, resulting again, in poor weight gain. Finally, the infant started refusing oral intake, and tube feeding was started. Therefore, she was referred to our hospital at age 8 months. At this visit, her body weight was 5,360 g (−3 standard deviation [SD]) and her height was 59.8 cm (−3.8 SD). She had severe food refusal and exaggerated responses to touch in the mouth or around the face. A pediatric neurologist found that her motor development was slightly delayed. Laboratory data showed undetectable C-reactive protein (CRP) levels and marginally elevated levels of total and milk-specific IgE (28.7 IU/ml and 0.41 UA/ml, respectively). The eosinophil count was 456 cells/μl, and anemia, hypoproteinemia, and electrolyte imbalance were not found detected. A barium swallow test showed tracheal aspiration. Tube feeding had been continued with rehabilitations, since she had gained a little weight. However, the vomiting and food refusal did not improve much. At 11 months of age, she was admitted to our hospital for further examination. Reduced esophageal clearance was observed in upper GI contrast radiography. GI scintigraphy showed delayed clearance from the stomach. Upper GI endoscopy showed lymphoid hyperplasia (LH) and mucosal erythema in the duodenum (Figure 1A). Esophageal biopsy showed basal zone hyperplasia and papillary elongation with a few eosinophils (Figure 1B). While LH (Figure 1C) with eosinophil infiltration (26 eosinophils per high-power field [HPF], Figure 1D) was observed in duodenal biopsy. EGID was suspected on the basis of the findings. Since elemental diet (ED) is sometimes considered as a therapeutic approach for EGID when any causative foods are not found[1], ED was started. The ED caused rapid weight gain (Figure 2). The amount of vomiting each time reduced, but the frequency of vomiting did not reduce much. In addition, the food refusal and exaggerated responses to touch in the mouth or around the face became milder. At 16 months of age, a reevaluation was performed using the barium swallow test, upper GI contrast radiography and upper GI endoscopy. Tracheal aspiration and esophageal clearance were improved as shown by the barium swallow test and

upper GI contrast radiography, respectively. However, LH and mucosal erythema in the duodenum were still detected on endoscopy. The eosinophil infiltration in the duodenum also persisted. Currently, ED is being continued since the child's symptoms have been improving.

Discussion

Widely accepted diagnostic criteria have not been established for EGIDs, but an increase in the number of eosinophils in biopsy specimens from the GI tract is an indicator [5]. A study that evaluated 14 biopsies showed that the mean number of eosinophils in the lamina propria of the duodenum was 9.6 ± 5.3 per HPF [6]. In adition, a previous review article defined duodenal eosinophilia as >10 eosinophils per HPF in 2 or more locations of the duodenum [5]. Therefore, the 26 eosinophils per HPF observed in the present case was considered to indicate significant eosinophilia. The endoscopic findings for the current patient demonstrated duodenal LH with mucosal erythema indicative of duodenitis as well as eosinophilia. LH is mostly a benign condition in children and usually regresses spontaneously, but it is significantly associated with food allergy when seen in the duodenal bulb [7]. On the other hand, although obvious inflammation was observed histologically in this case, only a few eosinophils were found in the esophagus. Thus, the etiology of the esophagitis could not be determined. Collectively, the findings led us to suspect that the patient had an EGID that is not likely to be EoE.

EGIDs are commonly associated with allergies[1,5]. However, it would be sometimes difficult to identify the specific allergens in EGID since EGID have properties that fall between IgE-mediated and cellular-mediated allergy[1]. In fact, the association of food allergy in this patient has been unclear. In addition, the symptoms of FD made it more difficult to perform further examinations such as challenge tests. Once disease remission has been observed by means of ED, the specific food groups will be slowly reintroduced. This food-reintroduction process may be helpful to identify the causative foods.

The symptoms of FD are generally associated with neurologic diseases, developmental delays, and gastroesophageal reflux disease (GERD). The painful swallowing and heartburn observed in GERD cause FD [8]. Recently, EGIDs including not only EoE but also other EGIDs have been considered as a differential diagnosis of FD. In addition, several distinguishable FD characteristics from GERD are observed in young children with EGIDs [3]. Since the symptoms of EGIDs, especially EoE, and GERD are sometimes similar; GERD is the most important differential diagnosis of EGID [9]. Therefore, the difference of FD characteristics may be useful to distinguish EGID from GERD.

A recent report showed the detailed characteristics of FD and defined it in depth [3]. The characteristics include learned maladaptive behaviors, developmental differences, dysphagia, oral sensory skill deficits, and oral motor skill deficits. The current patient had all 6 characteristics. Notably, learned maladaptive behaviors such as food refusal were more remarkable than other characteristics.

Interestingly, in a previous study, almost half the EGID patients with active FD showed GI eosinophilia that fulfilled the required criteria; however, FD can persist even after the eosinophilic inflammation has subsided [3], whereas dysphagia is exclusively correlated with the histological score [10], suggesting that it is difficult to estimate the severity of eosinophilic infiltration in the tissues on the basis of changes in other symptoms except dysphagia, including FD. Indeed, endoscopic reevaluation after confirmation of weight gain showed poor improvements in the eosinophil inflammations in this patient. However, there may be unfixed time lag between reduction of symptoms and histological improvement since, subsequently, the patient's symptoms has been improving by the continuation of ED despite the presence of duodenal eosinophilia on the re-evaluation.

In summary, the EGID in the current patient was discovered on the basis of FD symptoms. ED was effective for weight gain and improving esophageal clearance as well as symptoms. It is important that not only EoE but also other EGIDs would be considered in the differential

diagnosis in the case of infants with FD.

Acknowledgements
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Figure legends

Figure 1. **Endoscopic and histological findings**
Panel A shows the endoscopic findings of the duodenum. Histopathologic analyses of the esophagus (B) and duodenum (C and D) were performed using hematoxylin and eosin staining (optical magnifications are X 100 in B and C, and X 200 in D, respectively).

Figure 2. **Growth charts of the patient plotted on the Japanese sex-matched standard growth curves (0–24 months)**
The dots represent the actual height and weight. From the top, the lines indicate +2 SD, +1 SD, the mean, −1 SD, and −2 SD. The periods for which each mode of nourishment was implemented are indicated. ED indicates elemental diet.

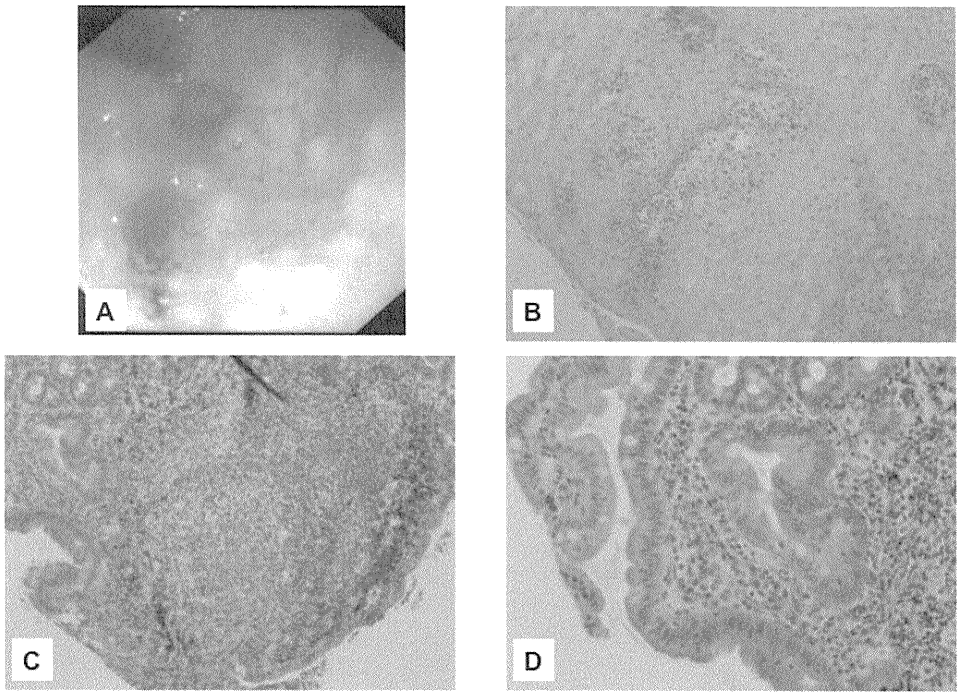

Figure 1

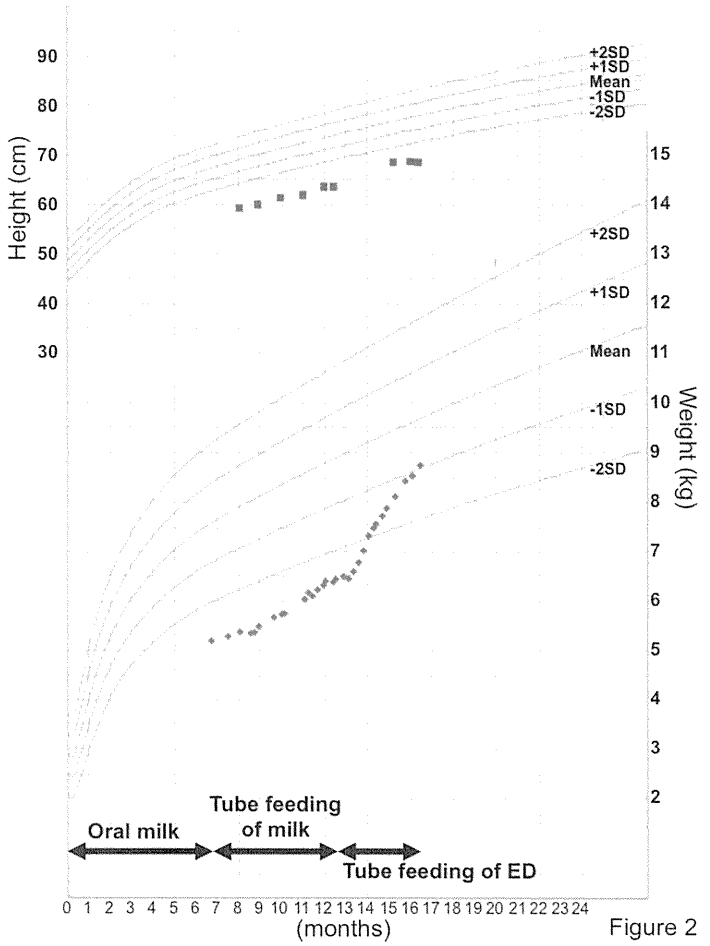

Figure 2

Original Paper

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Eosinophilic Gastrointestinal Disorders in Infants: A Japanese Case Series

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Key Words
Eosinophilic gastrointestinal disorders · Eosinophils · Bloody stool · Allergic colitis · Hypereosinophilic syndrome

Abstract
Background: Eosinophilic gastrointestinal disorders (EGIDs) are disorders characterized by primary eosinophil inflammation in the gastrointestinal tract. There are a small number of reports of eosinophil infiltration in gastrointestinal tracts presenting as EGIDs in infants. In this study, we present Japanese cases of EGIDs in infants. ***Methods:*** Five patients diagnosed with or strongly suspected to have EGIDs in our hospital from 2008 to 2010 were reviewed. Radiographic contrast enema examinations and/or endoscopies were performed in 4 and 3 patients, respectively. ***Results:*** There were patients with eosinophilic colitis (1 suspected and 2 biopsy-proven), a patient who was suspected of having allergic eosinophilic enterocolitis, and a patient with eosinophilic gastroenteritis associated with pediatric hypereosinophilic syndrome. ***Conclusions:*** The causes and clinical findings of patients with intestinal eosinophil inflammation vary. Therefore, deliberate examination and observation are important for patients with infantile EGID.

Introduction

Eosinophilic gastrointestinal disorders (EGIDs), including eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC), were originally defined as disorders that primarily affect the gastrointestinal tract with eosinophil inflammation with the exclusion of secondary diseases caused by drug reactions, parasitic infections, and malignancy [1]. Biopsy is the only way to definitively diagnose EGIDs [1]. Most patients with EGIDs are atopic and EGIDs are considered to have properties that fall between IgE-mediated allergies and cellular-mediated hypersensitivity disorders, although EC occurs mostly through a non-IgE-mediated mechanism [1]. In Western countries, eosinophilic esophagitis is increasingly diagnosed across all age groups and attracts much attention [2]. On the other hand, eosinophil infiltration in the lower gastrointestinal tract is mostly described as a histological finding of allergic diseases such as food protein-induced proctocolitis (FPIP), whose diagnosis is generally made clini-

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cally; therefore, only a small number of series have focused on biopsies [3]. In addition, unlike eosinophilic (procto)colitis, EGE is solely categorized as a disease that generally affects children and young adults, meaning that it is rare in infants [4]. Here, we present a case series of EGIDs in infants, including a rare case associated with pediatric hypereosinophilic syndrome (HES).

Patients and Methods

Patients

During a 2-year period (from June 2008 to May 2010), at Gunma Children's Medical Center, 5 patients were diagnosed or strongly suspected to have EGIDs. The patients were clinically examined by the pediatricians or pediatric surgeons, and blood for the analysis of total and differential white blood cell counts, levels of IgE, allergen-specific IgE, and the allergen-lymphocyte stimulation test (ALST), as well as fecal samples, were obtained. The ALST was performed using LPS-depleted cow's milk proteins at the National Research Institute for Child Health and Development, Tokyo, Japan. Fecal samples were placed on glass slides either directly or using cytospin, and the slides were then stained with May-Giemsa staining [5].

Radiographic Examinations and Endoscopies

Four out of 5 patients had a radiographic contrast enema examination. Upper gastrointestinal endoscopy or colonoscopy was performed on 1 and 2 patients, respectively, under general anesthesia. Biopsy specimens for morphology were fixed in phosphate-buffered formalin and embedded in paraffin blocks using standard methods. Paraffin sections were stained routinely with hematoxylin and eosin and reviewed by a pathologist [6].

Elimination and Provocation Test

Open cow's milk challenge testing was performed after rectal bleeding disappeared during an elimination diet and the subjects had had good daily weight gain with no demonstration of symptoms [7]. We carefully observed the patients for up to 2 weeks while increasing their intake of milk.

Results

Case 1

An 8-month-old boy who had a congenital syndrome characterized by iris coloboma, ptosis, hypertelorism, and mental retardation, described as Baraitser-Winter syndrome (BWS) [8], was admitted to the allergy and immunology department of our hospital for generalized edema and coldness of limbs, along with exacerbation of full-body eczema. The patient had presented with severe eczema and peripheral blood hypereosinophilia and had been treated with supportive measures since he was a newborn infant. He often had vomiting and loose stool. He was a mixed-fed infant and had never been examined in relation to allergy elsewhere. On admission, he had peripheral blood leukocytosis with severe hypereosinophilia and granulocytic immature cells (myelocytes and metamyelocytes), hypoproteinemia, and hyponatremia. Radioallergosorbent tests for major food allergens, except egg white, were negative. A bone marrow biopsy demonstrated an increased number of eosinophil lineage cells and no blasts. The patient's karyotype was normal. Molecular analysis for the Fip1-like1-platelet-derived growth factor receptor, α chain fusion gene [9], was negative. Albumin was administered intravenously because the patient showed oligouresis and hypotension. Administration of prednisolone (PSL) was started at the same time and the patient responded very well. In addition, an elemental diet was used to eliminate multiple allergens. However, when the patient was set on a taper, he required a dose of 1 $mg \cdot kg^{-1} \cdot day^{-1}$ of PSL in order to eliminate the eczema with edema and hypereosinophilia. Despite the dose of PSL, frequent vomiting reappeared and persisted. Therefore, an upper gastrointestinal endoscopy was performed. Endoscopic findings showed erosion in the gastric mucosa and edema in the duodenal mucosa. A biopsy revealed increased eosinophilic infiltration with plasma cells and hyperemic edema in the lamina propria in the duodenal mucosa (fig. 1a) and increased eosinophilic infiltration, interstitial edema, hyperemia, and bleeding in the gastric mucosa. This finding motivated us to increase the dose of PSL to 2 $mg \cdot kg^{-1} \cdot day^{-1}$. The higher dose of PSL reduced the frequency of vomiting and diminished the intestinal eosinophil infiltration according to a reevaluation by endoscopy. Although exacerbation of symptoms and hypereosinophilia were observed when we tapered the steroid, despite more than 1 year of treatment with PSL and an elemental diet, the PSL was tapered slowly and epinastine and suplatast tosilate had a steroid-sparing effect. At the time of reporting, the patient remained completely off steroids and his eosinophil count was within the normal range with these drugs.

Case 2

A 2-month-old girl who had been hospitalized with mild myocarditis that seemed to be associated with a viral infection, since the age of 55 days, presented mucous and bloody stool after improvement of the myocarditis. She was a mixed-fed infant and previously healthy. Although her peripheral blood eosinophil count was within the normal range upon admission, laboratory data showed peripheral blood hypereosinophilia and detectable eosinophils in the mucous and bloody stool at that

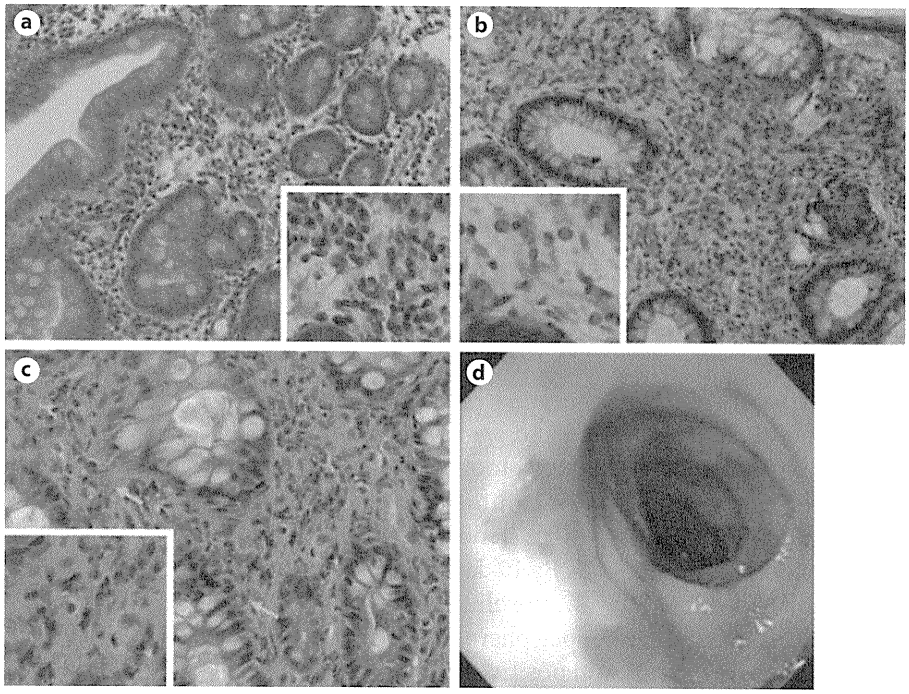

Fig. 1. Histological and endoscopic findings of the patients. Histopathologic analysis of the duodenum in case 1 (**a**) and of the colon in cases 3 (**b**) and 4 (**c**) was performed by hematoxylin and eosin staining (optical magnifications ×200). The arrows point to Charcot-Leyden crystals. **d** Endoscopic findings in case 4. **Insets** represent blowups of the original pictures.

time. The relationship between the bloody stool containing eosinophils and the myocarditis remained unclear. A radiographic contrast enema was performed and presented a finding suggestive of follicular lymphoid hyperplasia. Mucous and bloody stool were the only symptoms. Hydrolyzed formula eliminated the mucous and bloody stool within several days, although spotted blood was detected for a longer time. A normal diet was resumed after confirming that the provocation test was negative. At the time of reporting, the patient had neither mucous nor bloody stool.

Case 3

A 3-month-old boy was admitted to our hospital due to persistent bloody stool that had appeared a month before the visit. He was a mixed-fed infant with good feeding and satisfactory weight gain. Laboratory data showed peripheral blood hypereosinophilia and detectable eosinophils in his stool. The patient was suspected to have a colon polyp and had a colonoscopy. The colonoscopy revealed mucosal edema of the cecal and ascending colon and lymphoid hyperplasia of the rectum and sigmoid colon. The histological findings showed eosinophil and lymhocyte infiltrations with interstitial edema, hyperemia, and bleeding in the lamina propria. The eosinophils were detectable in crypts and seemed to be degranulated (fig. 1b). After switching from mixed feeding to only breast milk feeding, the bloody stool disappeared within a few days.

Case 4

A 2-month-old, mixed-fed baby girl was admitted to our hospital due to sustained bloody stools beginning at 33 days of age, although she was otherwise healthy. Her weight gain had been good despite the bloody stool. Laboratory data showed peripheral blood hypereosinophilia and positive fecal eosinophils. ALSTs of α-lactalbumin and α-, β-, and κ-casein were positive. A radiographic contrast enema presented segmental narrowing with granular mucosa on a serrated wall of the colon. Colonoscopic examination demonstrated several mucosal erythemas of the colon and rectum (fig. 1d). Colonic and rectal biopsies revealed intense eosinophil infiltrations in the crypt epithelium with Charcot-Leyden crystals (fig. 1c). In order to eliminate milk allergens from the breast milk, her mother ingested a strict dairy-free diet. After dairy-free breast milk was used, the bloody stool was resolved within a month. After confirmation of a negative provocation test, the mother was no longer required to eliminate dairy from her diet. Since then, her breast milk has not induced any symptoms.

Case 5

An 8-day-old girl in whom bloody stool was detected just after her first artificial milk feeding at 1 day of age was admitted to our hospital due to exacerbation of the symptom with poor milk feeding. The patient was treated with intravenous fluid without ingesting anything orally. The patient developed vomiting in addition to bloody stool. The next day, milk was resumed and then increased in small increments. Although her daily weight gain and general condition showed some improvement, the symptoms persisted. She was referred to the allergy and immunology department. Her laboratory data showed peripheral blood hypereosinophilia and aggregation of eosinophils in her mucous and bloody stool upon consultation with allergists. A radiographic contrast enema at 17 days of age presented a lead-pipe-like stenosis of the descending and sigmoid colon (fig. 2). By 19 days of age, the symptoms had resolved. On day 27, the elimination of milk allergens was started since her peripheral blood showed persistent hypereosinophila and positive milk-specific IgE. A follow-up radiographic contrast enema at 3 months of age revealed improvement in the narrowing of the sigmoid colon. At 6 months, as the provocation test was negative, the patient returned to normal formula. Although she had often had mild eczema and recurrent wheeze associated with respiratory viral infection, she had neither mucous nor bloody stool at the time of reporting.

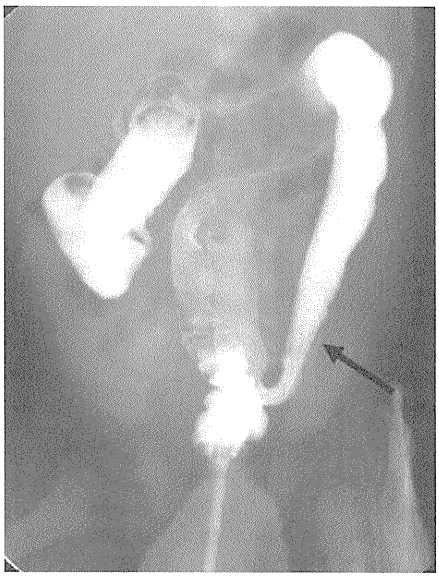

Fig. 2. Radiographic contrast enema examination of the patient. A radiographic contrast enema examination was performed on case 5. The arrow points to the narrowing of the colon.

Discussion

EGIDs are heterogeneous disorders categorized by gastrointestinal eosinophil inflammation [1]. We experienced 5 cases of EGIDs, including secondary EGIDs associated with HES (summarized in table 1). Case 1 was a secondary EGE with HES. The patient presented hypereosinophilia with >1,500 eosinophils/μl for more than 6 months (2,980–31,158 cells/μl in stable condition for the last 6 month before admission) and symptoms of organ involvements in the skin and gastrointestinal tract. He also showed mild mitral and tricuspid valve regurgitation and prolapse of the mitral valve in the heart and stenosis of the ureteropelvic junction. However, a causal linkage between these findings and eosinophilic inflammation could not be confirmed. Elimination of multiple allergens would not be sufficient to improve the symptoms and eosinophilia. Unlike acute allergic reactions, chronic allergy is rarely associated with absolute eosinophil counts of >2,000 cells/μl [10]. Besides, the presence of immature granulocytic cells with hypereosinophila in peripheral blood may imply that the patient has a primary hematopoietic disorder [11]. About 40 pediatric cases of HES have been reported, based on the literature in English [12]. However , infancy onset HES is extremely rare. This patient was also associated with a congenital syndrome, i.e. BWS. However, no report shows the relationships between hematological disorders or allergic disorders and BWS [8, 13]. In addition, although pediatric HES is often associated with chromosomal abnormalities [12], this patient's karyotype was normal. Interestingly, despite 1 $mg \cdot kg^{-1} \cdot day^{-1}$ of PSL, the patient presented symptomatic eosinophilic infiltration of the intestine and a higher dose of PSL was required to resolve the symptom, suggesting that intestinal eosinophil infiltration associated with HES may be more persistent compared to that of primary EGIDs. Another interesting point is that splatast tosilate and epinastine were used since antieosinophilic effects have been reported for these drugs [14, 15]. These drugs could be effective at least for steroid sparing in case 1.

EC shows a bimodal age distribution in infancy and adolescence. Infantile EC presents at a mean age of diagnosis of approximately 60 days [1]. In infants, EC, allergic colitis (AC), and FPIP are significantly overlapping disorders sometimes approached from different points of view [6, 7, 16]. It seems reasonable that EC in infants is considered as histologically proven AC or FPIP. Cases 2–5

Table 1. Characteristics of patients with EGIDs

Patient No.:	1	2	3	4	5
Age (sex):	8 months (male)	2 months (female)	3 months (male)	2 months (female)	8 days (female)
Chief complaint	exacerbation of eczema	bloody stool	bloody stool	bloody stool	bloody stool
Peripheral blood eosinophils cells/μl	22,410	2,136	3,052	3,154	7,375
Total IgE antibody, IU/ml	41.5	14.5	5.09	<2.0	12.6
Positive specific IgE antibody	egg white	–	–	–	milk
CRP, mg/dl	0.1	0.0	0.0	0.0	0.0
Stool examination	n.d.	Eos (+)	Eos (+)	Eos (+)	Eos (+)
ALST	n.d.	n.d.	n.d.	+	n.d.
Barium enema	n.d.	LH	LH	stenosis of colon	stenosis of colon
Endoscopy	edema in duodenum	n.d.	LH and edema in colon	edema and erythema in colon	n.d.
Histology	Eos with PC	n.d.	LH and Eos with Ly	Eos with CLC in crypt Epi	n.d.
Provocation test[1]	n.d.	– (1.2 years)	n.d.	– (5 months)	– (7 months)
Treatment	PSL	elimination	breast milk alone	elimination	elimination
Diagnosis[2]	EGE/HES	EC	EC	EC	AEEC

n.d. = Not done; Eos = eosinophils; Ly = lymphocytes; PC = plasma cells; Epi = epithelium; CLC = Charcot-Leyden crystal; LH = lymphoid hyperplasia; AEEC = allergic eosinophilic enterocolitis; elimination = elimination of cow's milk allergens.

[1] Result of test (age when provocation test was performed). [2] Including suspected cases.

showed bloody stool as an initial symptom. They may be categorized as food protein-induced enterocolitis syndrome or FPIP [4]. Interestingly, case 5 appeared to be distinguishable from the other 3 cases. In fact, case 5 had an earlier and more severe onset of vomiting than did the other 3 patients and tested positive for milk-specific IgE. Milk-specific IgE was mostly negative in patients with AC or EC, which is typically a non-IgE-mediated allergy [1, 4]. Therefore, allergic eosinophilic enterocolitis was suspected in case 5.

Concerning the diagnosis of allergy, in addition to the usual IgE-mediated diagnostic tests, ALST and the atopy patch test are useful as adjunctive diagnostic tests when a non-IgE-mediated allergy is suspected [17]. For a definitive diagnosis, elimination and challenge of allergens are recommended [7]. As a distinctive approach, the histological findings associated with eosinophil infiltrations – for example, >20 eosinophils/HPF (87 and 130 eosinophils/HPF in cases 3 and 4, respectively) – are also reported to be good criteria for the diagnosis of AC [6, 18, 19]. A cluster of eosinophils in mucous and bloody stool may be of diagnostic value. Peripheral blood hypereosinophila could be important since the eosinophil count is often checked routinely as a differential count of leukocytes even in those patients not suspected of having allergies. EC (AC) was suspected in case 2 based on peripheral blood and stool examinations [20] after excluding surgical diseases such as colon polyps and intussusceptions. A definitive diagnosis of EC was made based on the histological findings in cases 3 and 4.

Although there are a limited number of studies showing radiological findings of AC, EC, or eosinophilic enterocolitis, detectable radiological findings are not common [21, 22]. Lymphoid hyperplasia has occasionally been presented but is not always a pathological condition [17]. Surprisingly, a radiographic contrast enema revealed narrowing of the colon in cases 4 and 5. Radiographic examination may be useful as an adjunct to the diagnosis of EC.

Based on the literature, 18% of infants with bloody stool were confirmed by an elimination and provocation test as being allergic to cow's milk [7], whereas another report showed that 64% of patients with rectal bleeding had histological findings-proven AC [6]. The great difference between these 2 groups could be interpreted as follows. First, although cow's milk is the most common cause of AC, milk-associated proteins are not the sole cause of AC since infants become sensitized to the proteins excreted in breast milk [17]. Second, there is the possibility that patients have already become tolerant during elimination [17]. A significant proportion of patients developed tolerance after 1 year of a strict elimination diet [17]. In addition, there are types of EC that do not present any allergic reactions, like neonatal transient EC [23]. Indeed, the elimination and provocation tests were negative in our cases. Therefore, it seems important to carefully observe biopsy-proven AC as well as those patients diagnosed by the elimination and provocation test, which is the gold standard for diagnosis.

Only 18% of patients with AC were allergic to cow's milk, as mentioned above [7]. In addition, AC proved to be benign and self-limiting and, in most cases, cow's milk elimination did not affect the duration of bleeding [7]. Another problem is that the elimination and provocation test for AC is available only in restricted hospitals as compared with the routinely performed provocation test. These facts may discourage pediatricians and pediatric surgeons from further investigating allergies, resulting in missing patients with AC.

In conclusion, intestinal eosinophil infiltration would seem to be a common finding in all of the patients presented here, but the clinical findings and courses vary. To clarify the cause of gastrointestinal eosinophil infiltration, histological analysis as well as the elimination and provocation test would be useful.

Acknowledgements

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Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of this article.

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An 8-Year-Old Boy with Hypereosinophilic Syndrome

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Established Facts

- Hypereosinophilic syndrome (HES) is a heterogeneous group of rare disorders defined by persistent blood eosinophilia, absence of a secondary cause, and evidence of an eosinophil-associated pathology.
- The diagnosis of HES requires exclusion of multitudes of diseases including various myeloid neoplasms and is sometimes very difficult in children because it is extraordinarily rare in this age group.
- The first-line drugs for HES are oral corticosteroids but indication of other drugs including cyclosporine has not been established for corticosteroid-resistant or dependent cases.

Novel Insights

- Although common presenting symptoms in children with HES are fever, arthralgia, and skin rash, this case presented with gastrointestinal symptoms; this is important clinical information alerting us to consider the disease when we see 'common' eosinophilic gastroenteritis.
- The comprehensive diagnostic procedures performed here may be of help, and among them elevated serum TARC was suggestive of corticosteroid responses.
- Cyclosporine was effective for reducing the corticosteroid dose; this was an important therapeutic experience with this rare disease.

Key Words
Hypereosinophilic syndrome · Prednisolone · *Helicobacter pylori*

Abstract
Hypereosinophilic syndrome (HES) is a heterogeneous group of uncommon disorders characterized by the presence of marked peripheral blood eosinophilia and tissue eosinophilia, resulting in a wide variety of clinical manifestations. We present the case of an 8-year-old boy with HES. He complained of recurrent abdominal pain, general fatigue, and diarrhea. Laboratory data showed marked eosinophilia, elevated total IgE with positive specific IgE antibodies to common inhalant and food allergens, and elevated serum CCL17/TARC. A chest CT scan revealed central bronchiectasis, bronchial wall thickening, a mosaic attenuation pattern, and multiple small nodules in lung parenchyma; abdominal CT

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showed a thickened bladder wall. Gastrointestinal endoscopy revealed scarring in the gastric mucosa and mucosal erosion in the duodenum. Immunohistochemical examination demonstrated numerous eosinophil infiltrations with extensive extracellular eosinophil major basic protein deposition in the gastric mucosa. Only high-dose oral steroid was effective and cyclosporine appeared to have a steroid-sparing effect. HES is extraordinary rare in children and the long-term prognosis in pediatric HES is not well known. Comprehensive diagnostic procedures are vital for the early detection and management of complications in pediatric HES.

Introduction

Hypereosinophilic syndrome (HES) is a heterogeneous group of uncommon disorders characterized by the presence of marked peripheral blood eosinophilia and tissue eosinophilia, resulting in a wide variety of clinical manifestations. HES can occur at any age but is very rare in childhood. Uncertainties in classification and lack of prospective studies make therapeutic decisions difficult. The authors present a case of childhood HES which was initially diagnosed and treated as eosinophilic gastrointestinal disorders; only high-dose oral steroid was effective and cyclosporine appeared to have a steroid-sparing effect.

Table 1. Laboratory data

Variable	Normal range	Value	Variable	Normal range	Value
Hemoglobin, g/dl	11.5–15	12.9	Antinuclear antibody	<1:40	<1:40
Hematocrit, %	35–45	39.8	Antineutrophil cytoplasmic antibody		
Leukocyte, /mm^3	4,500–8,500	13,100	Anti PR3 antibody	<10	<10
Differential count			Anti MPO antibody	<10	<10
Neutrophil, %	32–73	22	IL-4, pg/ml		6.0
Lymphocyte, %	18–59	39	IL-5, pg/ml		1.0
Monocyte, %	0–8	4	IL-10, pg/ml		2.9
Eosinophil, %	0–6	35	IL-13, pg/ml		1.0
Basophil, %	0–2	0	TARC, pg/ml	<743	3,647
Platelet, /mm^3	$15–35 \times 10^4$	32.8×10^4	EDN, ng/ml		120
Total protein, g/dl	6.7–8.3	7.3	Specific IgE		
Albumin, g/dl	4–5	3.9	Egg, UA/ml	<0.34	0.60
Creatine kinase, IU/l	45–163	71	Milk, UA/ml	<0.34	1.25
Aspartate aminotransferase, IU/l	13–33	19	Wheat, UA/ml	<0.34	0.93
Alanine aminotransferase, IU/l	6–27	9	Rice, UA/ml	<0.34	0.44
Lactate dehydrogenase, IU/l	119–229	289	Peanut, UA/ml	<0.34	0.64
Total bilirubin, mg/dl	0.3–1.2	0.3	Soy, UA/ml	<0.34	0.57
Gamma glutamyl transferase, IU/l	10–47	11	Tuna, UA/ml	<0.34	0.76
Tryptase, μg/dl	<11.4	1.9	Trachurus, UA/ml	<0.34	<0.34
Vitamin B_{12}, pg/ml	180–914	503	Casein, UA/ml	<0.34	1.06
Brain natriuretic peptide, pg/ml	<18.4	12.9	Gluten, UA/ml	<0.34	<0.34
Troponin T, ng/ml	<0.014	<0.01	Ovomucoid, UA/ml	<0.34	0.38
Immunoglobrin G, mg/dl	870–1,700	2,218	Orchard grass, UA/ml	<0.34	0.68
Immunoglobrin A, mg/dl	110–410	212	Ragweed, UA/ml	<0.34	1.39
Immunoglobrin M, mg/dl	33–190	76	Cedar, UA/ml	<0.34	76.5
Immunoglobrin E, mg/dl	<173	4,437	Mite, UA/ml	<0.34	1.16
Complement total, U/ml	25–48	45.6	Cat, UA/ml	<0.34	6.01
C3, mg/dl	86–160	105	Dog, UA/ml	<0.34	3.85
C4, mg/dl	17–45	36.9			

Case Presentation

An 8-year-old boy was admitted to Mie National Hospital with frequent abdominal pain. He had been well before chronic diarrhea and severe recurrent abdominal pain occurred at the age of 6 years. Because of his gastrointestinal symptoms, the patient was initially admitted to another hospital. Based on profound eosinophilia (peripheral eosinophils 11,773/mm^3) and eosinophil infiltration in the gastric mucosa detected by upper gastrointestinal endoscopy, the diagnosis of eosinophilic gastritis and gastric ulcer was made. He was then treated with oral prednisolone (PSL) at 2 mg/kg/day every day and 0.9 mg/kg/day on alternate days and a proton pump inhibitor for 2 years, resulting in resolution of the symptoms. A 6-month treatment-free interval was followed by recurrence of the abdominal pain, and he was admitted to Mie National Hospital.

On admission, physical examination was normal. Laboratory data showed marked eosinophilia, elevated total IgE with positive specific IgE antibodies to common inhalant and food allergens, and elevated serum TARC (table 1). The sputum culture was negative for *Aspergillus*. Cardiac and lung functions were normal. Chest radiograph showed peribronchial thickening (fig. 1a). Chest CT scan revealed central bronchiectasis, bronchial wall thickening, a mosaic attenuation pattern, and multiple small nodules in lung parenchyma (fig. 1b, c); abdominal CT showed a markedly thickened bladder wall (fig. 1d). Gastrointestinal endoscopy revealed scarring (S2 stage) in the gastric mucosa and mucosal erosion in the duodenum. Macroscopic findings of the esophagus, gastric cardia, and colon were negative. A rapid urease test and Giemsa stain for *Helicobacter pylori* were positive in the biopsy specimen from gastric mucosa. Immunohistochemical examination of gastrointestinal mucosal biopsy specimens for eosinophil major basic protein (MBP) demonstrated numerous eosinophil infiltrations with extensive extracellular MBP deposition in the gastric mucosa (fig. 2) and no significant eosinophil infiltration in the esophagus, the duodenum, or the rectum. Chromosomal analysis did not identify any abnormality, and fluorescence in situ hybridization for *BCR-ABL* and RT-PCR for the *FIP1L1PDGFRA*

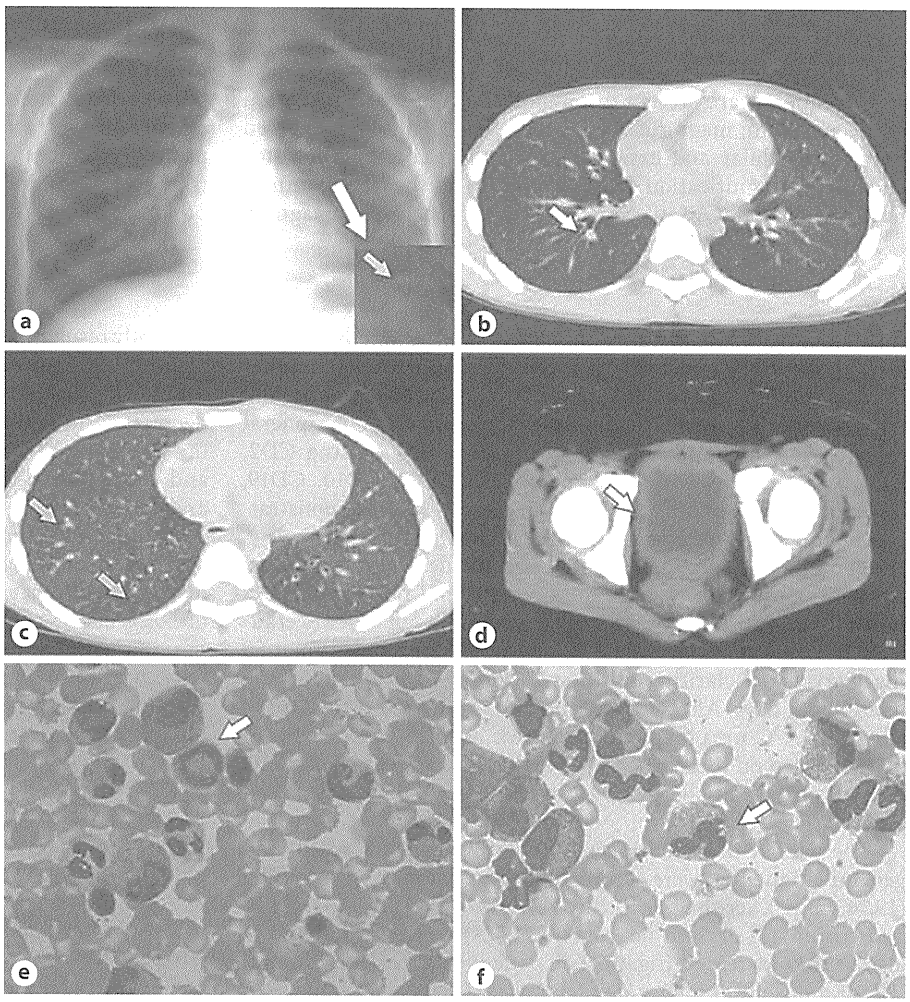

Fig. 1. Chest radiograph (**a**), chest CT scans (**b**, **c**), abdominal CT scan (**d**), and bone marrow. **a** Chest X-ray film showing peribronchial thickening (gray arrow). **b**, **c** Chest CT showing bronchial wall thickness and central bronchiectasis (white arrow), multiple small nodules (gray arrows), and mosaic lung attenuation patterns. Scans were obtained during maximal inspiration. **d** Abdominal CT scan showing a thickened bladder wall (white arrow). **e**, **f** Representative bone marrow smears stained with hematoxylin and eosin; magnification ×1,000. The white arrow points to ringed nuclei of eosinophils, and the black arrow points to a hypersegmented eosinophil, indicating eosinophil dysplasia.

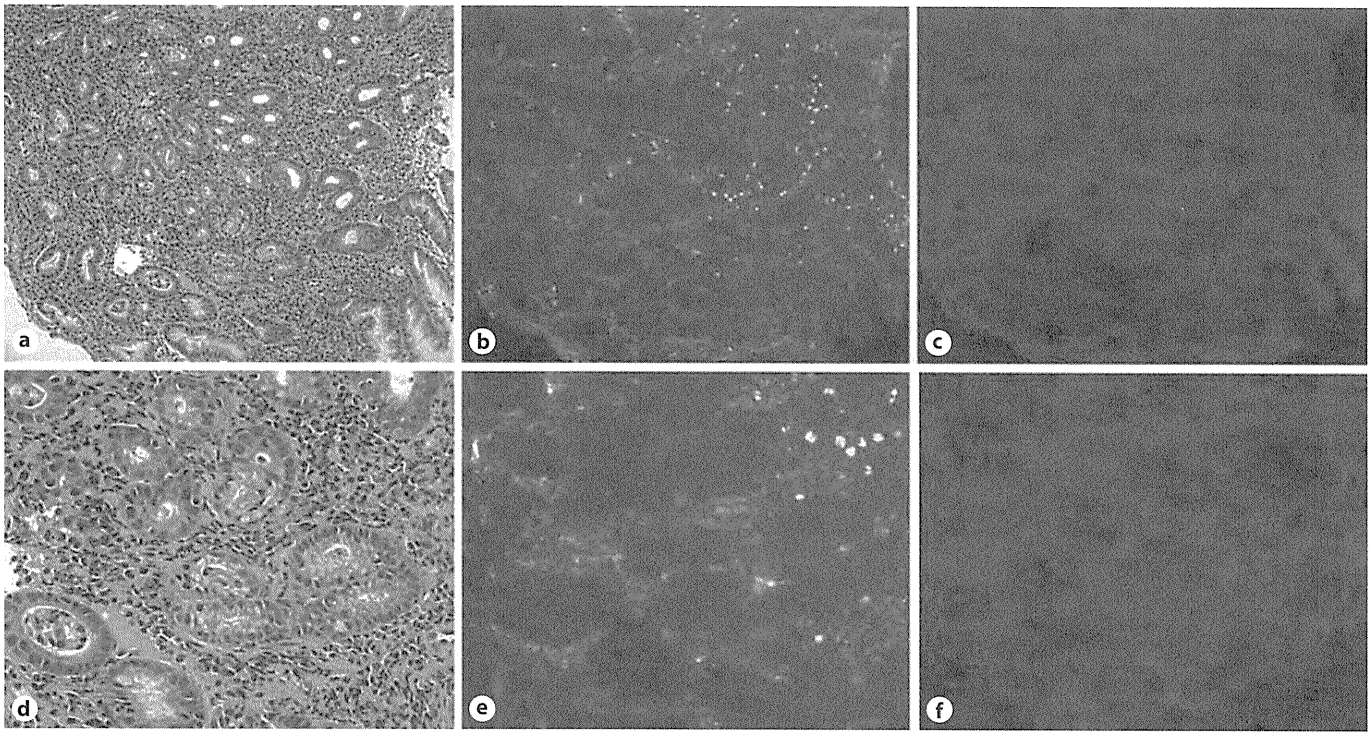

Fig. 2. Histopathology of the gastrointestinal mucosa. **a** Numerous eosinophils are present throughout the biopsy (hematoxylin and eosin stain; magnification ×160). **b** MBP antibody stained both intracellular and extracellular deposition (immunohistochemistry; magnification ×160). **c** Control normal rabbit immunoglobulin (NRIgG) antibody (immunohistochemistry; magnification ×160). **d** Numerous eosinophils are present throughout the biopsy (hematoxylin and eosin stain; magnification ×400). **e** MBP antibody stained both intracellular and extracellular deposition (immunohistochemistry; magnification ×400). **f** Control NRIgG antibody (immunohistochemistry; magnification ×400).

fusion gene in whole blood and bone marrow specimens was negative. Bone marrow examination revealed an increased number of eosinophil precursors, mature but dysplastic eosinophils, and neutrophils (fig. 1e, f). Surface marker analysis of peripheral mononuclear cell and bone marrow aspirates, including CD2, CD3, CD4, CD7, CD8, CD28, CD45, CD45RO, CD10, CD19, CD20, κ-chain, λ-chain, CD34, CD25, and HLA-DR, demonstrated no monoclonal or aberrant B cell or T cell populations.

The patient's initial symptoms were mild despite eosinophilia. An elimination diet of eggs, milk, wheat, and fish for 3 weeks failed to reduce the symptoms and eosinophilia. In order to eradicate *H. pylori*, lansoprazole at 1.5 mg/kg/day, amoxicillin at 50 mg/kg/day, and clarithromycin at 20 mg/kg/day were administered for 14 days. Although the therapy had no effect on the eosinophilia, ^{13}C-urea breath tests became normal (from 14.2‰ to 0.5‰). Based on these results, we excluded reactive eosinophilia secondary to food allergy or *H. pyroli* infection and diagnosed HES.

The patient then had severe abdominal pain, diarrhea, and general fatigue that were accompanied by profound eosinophilia (19,745/mm^3). Serum interleukin (IL)-5, IL-4, IL-10, IL-13, TARC, and eosinophil-derived neurotoxin (EDN) concentrations were also greatly increased (fig. 3). The patient was treated with oral PSL at a dose of 2 mg/kg/day for 2 weeks. His symptoms then promptly resolved and leukocyte and eosinophil counts decreased from 35,900/mm^3 to 10,800/mm^3 and from 19,745/mm^3 to 108/mm^3, respectively. Elevated levels of cytokines and EDN were also decreased in parallel with eosinophil numbers (fig. 3). Tapering of PSL, however, caused significant deterioration in symptoms and eosinophilia. Imatinib mesylate, 100 mg daily for 1 month and 200 mg daily for 1 month, was then added to PSL, but the eosinophilia, abdominal pain, and diarrhea continued; no steroid-sparing effect was observed. The treatment was unintentionally discontinued because of poor family support. After several bouts of exacerbation of abdominal pain, he was transferred to another hospital with the help of city officials. There, cyclosporine with doses to maintain blood levels of 50–200 ng/ml and low-dose PSL at 0.1 mg/kg/day induced remission of the gastrointestinal symptoms despite continuous eosinophilia at around 2,000/mm^3.

Discussion

HES is a heterogeneous group of rare disorders defined by persistent blood eosinophilia $\geq 1.5 \times 10^9$/l, absence of a secondary cause, and evidence of an eosino-