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平成23年度

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VI. 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.

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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.

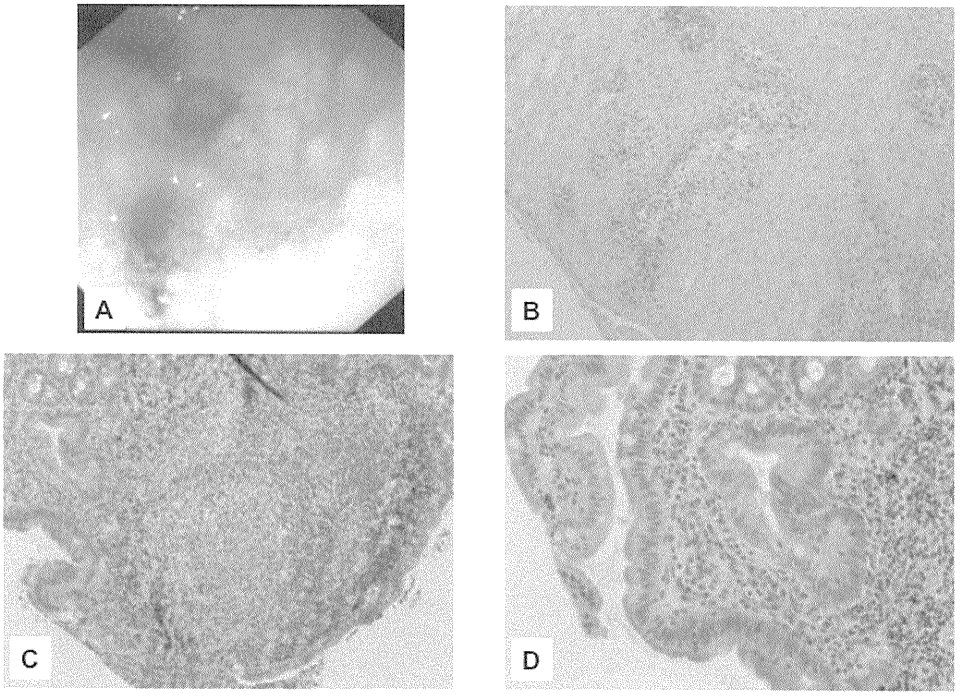

Figure 1

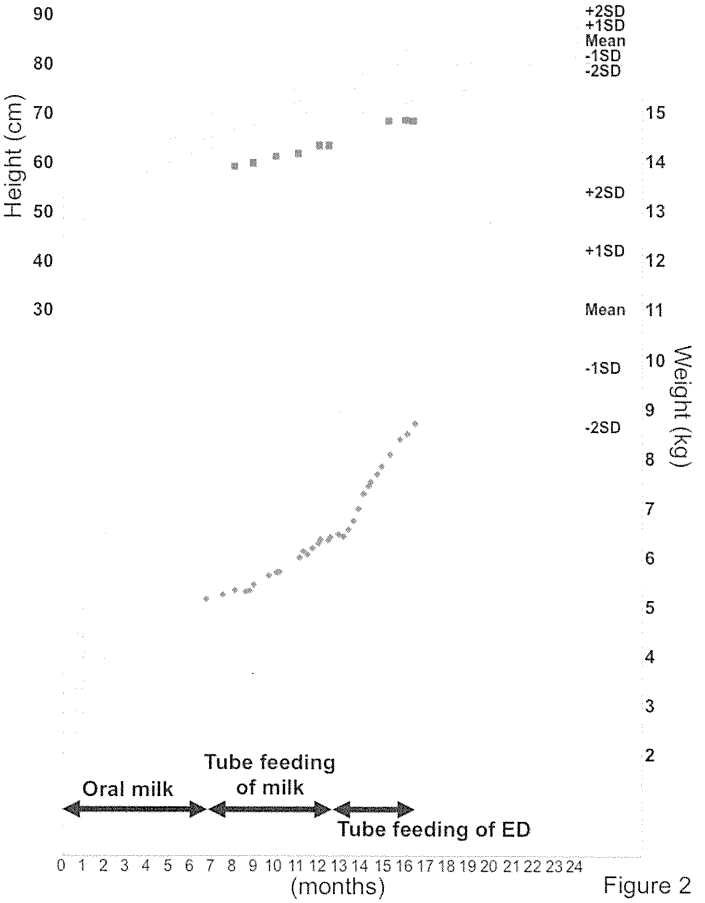

Figure 2

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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 × 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*

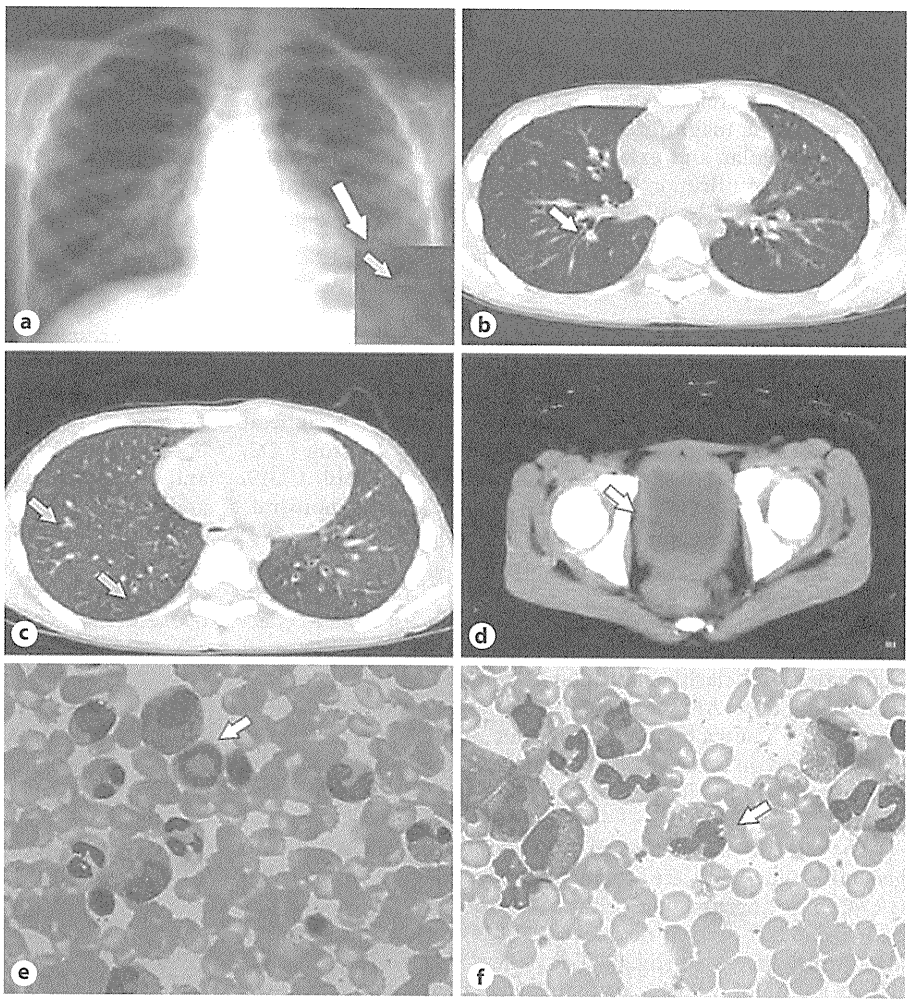

Fig. 1. Chest radiograph (**a**), chest CT scans (**b**, **c**), abdominal CT scan (**d**), and bone marrow. **a** Chest X-ray film showing peribronchial thickening (gray arrow). **b**, **c** Chest CT showing bronchial wall thickness and central bronchiectasis (white arrow), multiple small nodules (gray 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.

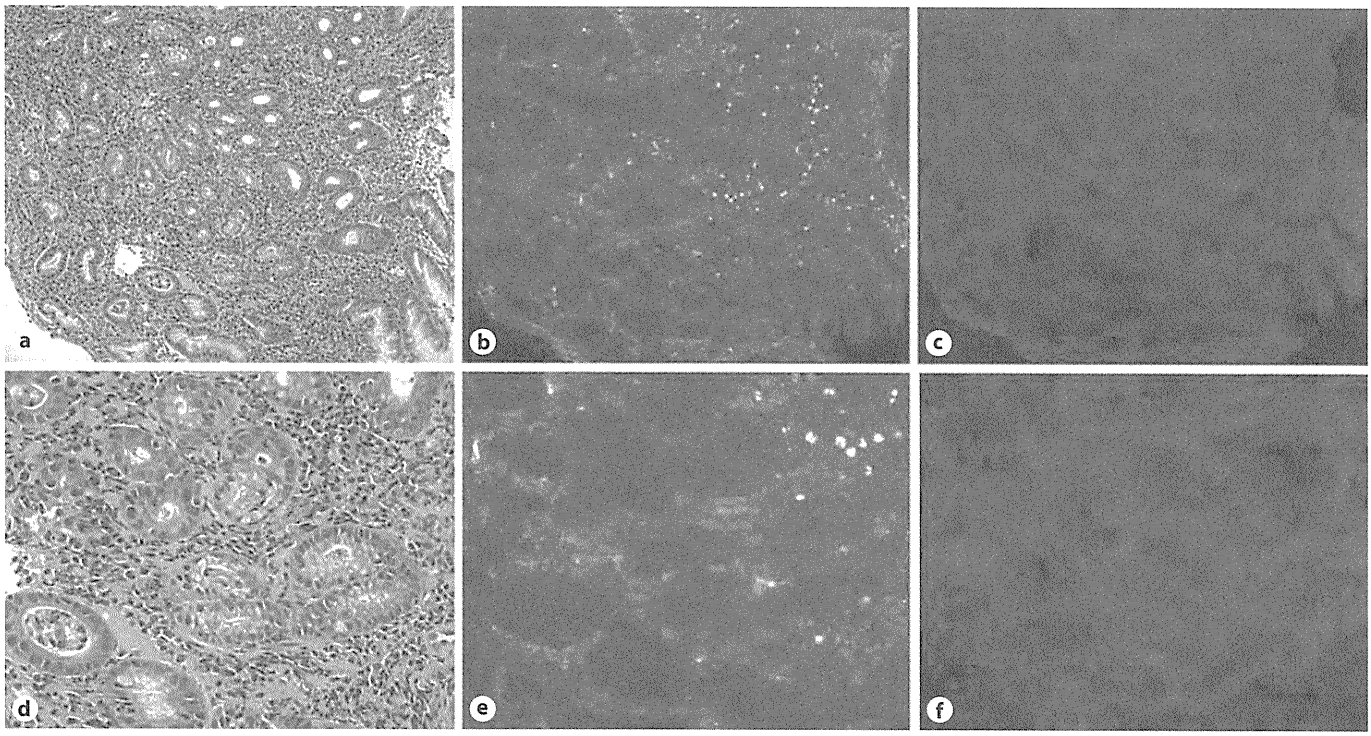

Fig. 2. Histopathology of the gastrointestinal mucosa. **a** Numerous eosinophils are present throughout the biopsy (hematoxylin and eosin stain; magnification ×160). **b** MBP antibody stained both intracellular and extracellular deposition (immunohistochemistry; magnification ×160). **c** Control normal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