

Idiopathic eosinophilic esophagitis is associated with a T_H2-type allergic inflammatory response

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Background: Idiopathic eosinophilic esophagitis (IEE) is a chronic-inflammatory disorder of the esophagus of unknown origin. The established cornerstone of diagnosis is a dense infiltration of the esophagus with eosinophils, but neither the precise pattern of inflammatory cell infiltration nor the mechanisms that likely contribute to induction and maintenance of the inflammatory response have been described.

Objective: The intention of this study was to characterize the esophageal inflammatory infiltrate and the expression of cytokines in the esophagus in this disease. In addition, we searched for immunologic abnormalities of blood leukocytes to exclude major primary hyporeactive and hyperreactive conditions of the immune system.

Methods: Infiltration of inflammatory cells in the esophagus, stomach, and duodenum was analyzed by immunohistochemistry through use of mAbs against lineage-associated molecules. Cytokine expression was measured by ELISA and immunohistochemical analysis. Lymphocyte subpopulations in blood were determined by means of flow cytometry.

Results: High eosinophil infiltration into the esophageal squamous epithelium was observed in patients with IEE but not in control subjects. Interestingly, increased T-cell and mast cell numbers were also found within the epithelium in these patients. In contrast, the numbers of inflammatory cells were not increased in the stomach and duodenum in patients with IEE, suggesting a specific inflammatory process within the esophagus. Moreover, increased expression of IL-5 and TNF- α was observed in esophageal epithelial biopsy specimens. The distribution of lymphocyte subsets in the peripheral blood and their capacity to generate cytokines did not reflect the changes observed at the inflammatory site.

Conclusions: IEE is a selective inflammatory response of the esophagus. T cells, IL-5, eosinophils, and IgE-mediated mechanisms appear to be involved, giving rise to the possibility that allergic reactions might play a role in the pathogenesis of the disease. (*J Allergy Clin Immunol* 2001;108:954-61.)

Key words: Allergy, eosinophil, cytokines, idiopathic eosinophilic esophagitis, immunohistochemistry, inflammation, IL-5, mast cells, T cells, T_H2-type inflammatory response

Idiopathic eosinophilic esophagitis (IEE) is a rare chronic-inflammatory disorder of the esophagus of unknown origin. The only presenting symptom is acute and recurrent dysphagia, there being great variability in the intensity, frequency, and duration of attacks.¹ IEE is characterized by large numbers of intraepithelial eosinophils in esophageal biopsy specimens.^{2,3} The dysphagia appears to be due to an inflammatory response and does not appear to be a consequence of anatomic obstruction.

Other diseases associated with eosinophilic inflammation of the esophagus are eosinophilic gastroenteritis with esophageal involvement⁴ and gastroesophageal reflux disease.⁵ IEE can be diagnosed by histology only, because most patients have endoscopically unremarkable mucosal alterations.^{1,2}

Little is known about the pathogenesis of specific eosinophil infiltration of the esophagus in patients with IEE. However, it appears that eosinophilic granulocytes might play a role in the development of the dysphagia, inasmuch as patients with IEE can successfully be treated with antieosinophil therapies.^{6,7} Moreover, in some patients, IEE was associated with allergic manifestations and a family history of allergy.^{2,8} IgE-mediated allergies, eosinophilic infiltration, and spastic motility disturbance, as well as response to steroid therapy, are also observed in many patients with bronchial asthma.⁹ We therefore hypothesized that similar immunopathogenic mechanisms might account for the inflammatory process in asthma and IEE. We examined a group of patients with IEE and observed many immunologic features, typical of allergic inflammatory responses, that have previously been described in asthmatic patients.

METHODS

Study population

Eight patients (7 men and 1 woman; mean age, 46.5 years; age range, 22-63 years) with clinically, endoscopically, and histologically diagnosed IEE were investigated (Table I). The average duration of the disease was 10.4 years. The only presenting symptom was acute recurrent dysphagia with food impaction. Gastroesophageal reflux disease was excluded by (1) a lack of clinical and histologic response to acid blockade, (2) normal pH probe monitoring of the distal esophagus, and (3) esophageal eosinophilia of

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TABLE I. Clinical characteristics of 8 patients with IEE and 3 controls

	Sex	Age (y)	Duration of IEE (y)	Dysphagia		Total IgE* (kU/L)	Endoscopic findings†
				Frequency (no. of events/y)	Duration (min)		
Patient no.							
1	M	48	17	25	2-30	27	Minimal
2	M	22	14	25	1-5	797	Minimal
3	M	46	14	25	1-30	22	Minimal
4	M	54	9	50	2-60	5	Minimal
5	M	57	8	50	1-5	847	Obvious
6	M	63	10	15	1-30	145	Minimal
7	M	54	2	100	1-5	957	Minimal
8	F	28	9	10	2-120	355	Obvious
Control no.							
1	M	36	—	—	—	18	Normal
2	M	43	—	—	—	5	Normal
3	F	17	—	—	—	9	Normal

*Although 5 patients had elevated serum IgE levels, only patients 2 (asthma), 6 (atopic dermatitis), and 8 (asthma) had IgE-mediated allergic disease.

†Endoscopic findings were classified as minimal or obvious.

Abbreviations used

ECP: Eosinophilic cationic protein
IEE: Idiopathic eosinophilic esophagitis
PHA: Phytohemagglutinin

both the proximal and the distal esophagus. All 8 patients were from the northwestern part of Switzerland, a mixed urban/rural area with a total population of approximately 750,000; each patient had undergone a diagnostic work-up in 1999. At that time, 6 of the 8 patients were symptomatic but no abdominal symptoms were noticed. None of the patients had been receiving treatment with corticosteroids, antihistamines, or mast cell stabilizers at the time of the study. The results of physical examination and routine laboratory tests, usually performed in patients with inflammatory diseases, were normal in all patients.

Controls included 3 patients (2 male and 1 female; mean age, 32 years; age range, 17-43 years) with untreated functional dyspepsia in whom gastroscopy was performed as part of the diagnostic evaluation. Selection criteria were (1) no history of reflux-disease or allergies, (2) no evidence of systemic diseases, (3) no abnormalities (as determined endoscopically) in the upper gastrointestinal tract and a negative urease test result for *Helicobacter pylori* (CLO-Test, Delta West Ltd, Perth, Australia), and (4) no histologic abnormalities in the esophageal, gastric body, gastric antrum, and duodenal mucosa. An additional control group of 6 healthy individuals was included for functional T-cell tests in vitro.

Informed consent was obtained from all patients and control subjects, and the study was approved by the Swiss Academy of Medical Science, represented by the Medical Ethics Committee of Davos.

Analysis of leukocytes and lymphocyte subsets

Blood leukocyte and differential count were determined in all patients by automatic blood count analysis (Technicon H1, Technicon, Tarrytown, NY). In a subgroup of 5 patients, immunofluorescence analysis of peripheral blood T cells was performed to exclude abnormal clones of T cells in the pathogenesis of esophageal eosinophilia.^{10,11}

Lymphocyte proliferation test

PBMCs at a concentration of 10^6 /mL were cultured in complete culture medium (RPMI 1640 supplemented with 10% FCS, 2 mmol/L L-glutamine, 200 IU/mL penicillin, and 100 µg/mL streptomycin [all from Life Technologies, Basel, Switzerland]) in the presence or absence of 10 µg/mL phytohemagglutinin (PHA) for 48 hours (96-well plates in triplicates). [³H]-thymidine incorporation was measured after a 4-hour incubation period with 1 µCi/well of [³H]-thymidine by liquid scintillation counting.

Measurements of cytokine levels in stimulated PBMCs

To determine the capacity to generate T_H1-type (IFN-γ) and T_H2-type (IL-5, IL-13) cytokines after pan-T-cell stimulation, PBMCs were stimulated with PHA as described above for 24 hours. Supernatants were harvested and frozen at -80°C until analysis. Cytokine concentrations were measured by ELISA through use of commercial kits according to the manufacturer's instructions (R&D Systems, Abingdon, United Kingdom). The assay sensitivities were 1.8 pg/mL for IL-5, 15.0 pg/mL for IL-13, and 0.7 pg/mL for IFN-γ.

Endoscopy and tissue samples

Upper gastrointestinal endoscopy was performed in all patients with IEE and control individuals through use of a standard instrument (Pentax FG 29, Asahi Optical Co, Tokyo, Japan) after administration of light sedation with intravenous diazepam (0.05 mg per kilogram of body weight) and tramadol (0.5 mg per kilogram of body weight). Biopsy specimens were obtained from esophageal, stomach, and duodenal mucosa with standard forceps. The specimens were immediately fixed in 4% paraformaldehyde solution. Formaldehyde-fixed biopsy specimens were embedded in paraffin. Paraffin blocks were sectioned at 4 µm for immunohistochemical examination.

Characterization of the inflammatory cell infiltrate

Inflammatory cells were identified through use of mAbs against lineage-associated molecules and immunohistochemistry.¹² Briefly, paraffin sections were deparaffinized in xylene and rehydrated through graded concentrations of ethanol before use. Antigen retrieval was achieved by the microwave oven heating procedure.

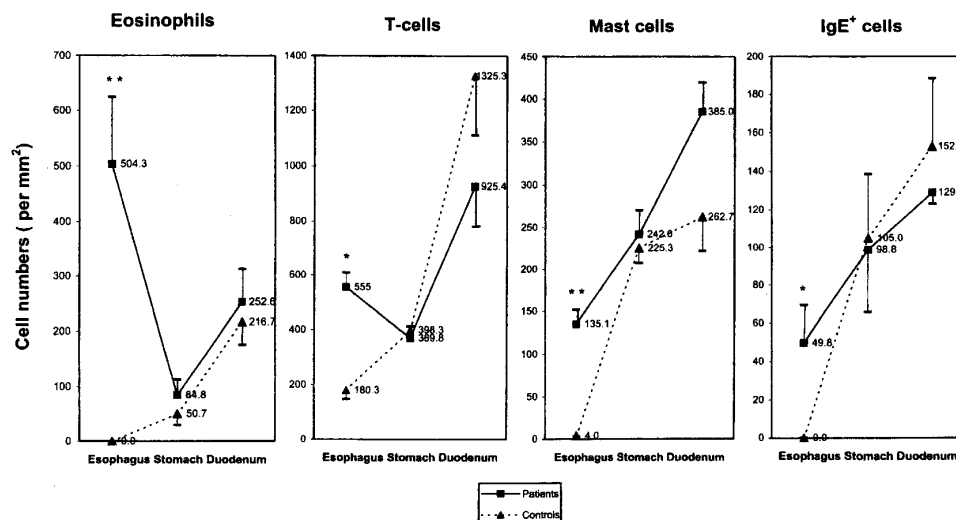


FIG 1. Numbers of eosinophils, T cells, mast cells, and IgE⁺ cells (most likely mast cells) in esophageal epithelium compared with gastric and duodenal mucosa in patients with IEE and control subjects. Patients with IEE present increased numbers of all investigated cell types in esophageal epithelium but not in gastric or duodenal mucosa. Normal esophageal epithelium is infiltrated by T cells but not by eosinophils or mast cells. Numbers indicate mean levels. Identification of cells was performed by means of immunohistochemistry. **P* < .05. ***P* < .01.

TABLE II. Proliferative response and cytokine production by PBMCs after pan-T-cell stimulation

Patient no.	Lymphocyte proliferation test (PHA) (cpm)	Cytokine release of PHA-stimulated PBMCs (pg/mL)		
		IL-5	IL-13	IFN- γ
1	105,236	38	108	662
2*	16,589	65	309	389
4	52,291	87	188	311
6*	59,984	99	309	389
7	130,332	63	259	303
Controls (n = 6): mean $\pm$ SEM	33,877 $\pm$ 8,740	69 $\pm$ 36	136 $\pm$ 62	243 $\pm$ 195

PHA, Phytohemagglutinine.

*Patients 2 (asthma) and 6 (atopic dermatitis) had IgE-mediated allergic disease.

Eosinophils were identified with anti-eosinophil cationic protein (ECP) mAb and through use of the alkaline phosphatase–antialkaline phosphatase (APAAP) method with a commercial kit (Dako, Glostrup, Denmark), used according to the manufacturer's instructions. Mast cells were identified through use of mAb against α -tryptase (Dako). An antihuman IgE mAb (Dako) was used to determine IgE-bearing cells; most of them were most likely mast cells. T cells were identified by anti-CD3 (Novocastra Laboratories, Newcastle, United Kingdom), and B cells were identified by anti-CD20 (Dako) mAbs. All of these stainings were performed through use of the Zymed Lab-SA System (Zymed Laboratories, South San Francisco, Calif) according to the manufacturer's instructions. Sections were lightly counterstained with hematoxylin, mounted, and examined by means of conventional light microscopy (Zeiss Axioscope) at a magnification of $\times 400$ or $\times 1000$. The cells were counted, and results were expressed as numbers of cells per square millimeter.

Expression of inflammatory mediators

Expression of IL-5, IFN- γ , eotaxin, RANTES, and TNF- α was determined by immunohistochemistry through use of the APAAP

technique, as previously described.^{11,12} The following primary mAbs were used at 50 μ g/mL: anti-IL-5 and anti-IFN- γ (R&D Systems), anti-eotaxin (Repro Tech, Rocky Hill, NJ), and anti-RANTES and anti-TNF- α (R&D Systems). For negative controls, monoclonal mouse IgG1 (Dako) was used at 50 μ g/mL.

The stainings were evaluated by 2 independent investigators as follows: –, there was no staining; (+), either <10% of the infiltrating cells were positive or there was weak staining intensity of the epithelial cells; +, either 10% to 49% of the infiltrating cells were positive or there was medium staining intensity of the epithelial cells; ++, either 50% to 90% of the infiltrating cells were positive or there was strong staining intensity of the epithelial cells; +++, either more than 90% of the infiltrating cells were positive or there was very strong staining intensity of the epithelial cells.

Statistical analysis

Single data or means $\pm$ SEMs are presented. Statistical analysis was performed through use of the Student *t* test. Probability values for statistically significant differences are indicated as follows: **P* < .05; ***P* < .01.

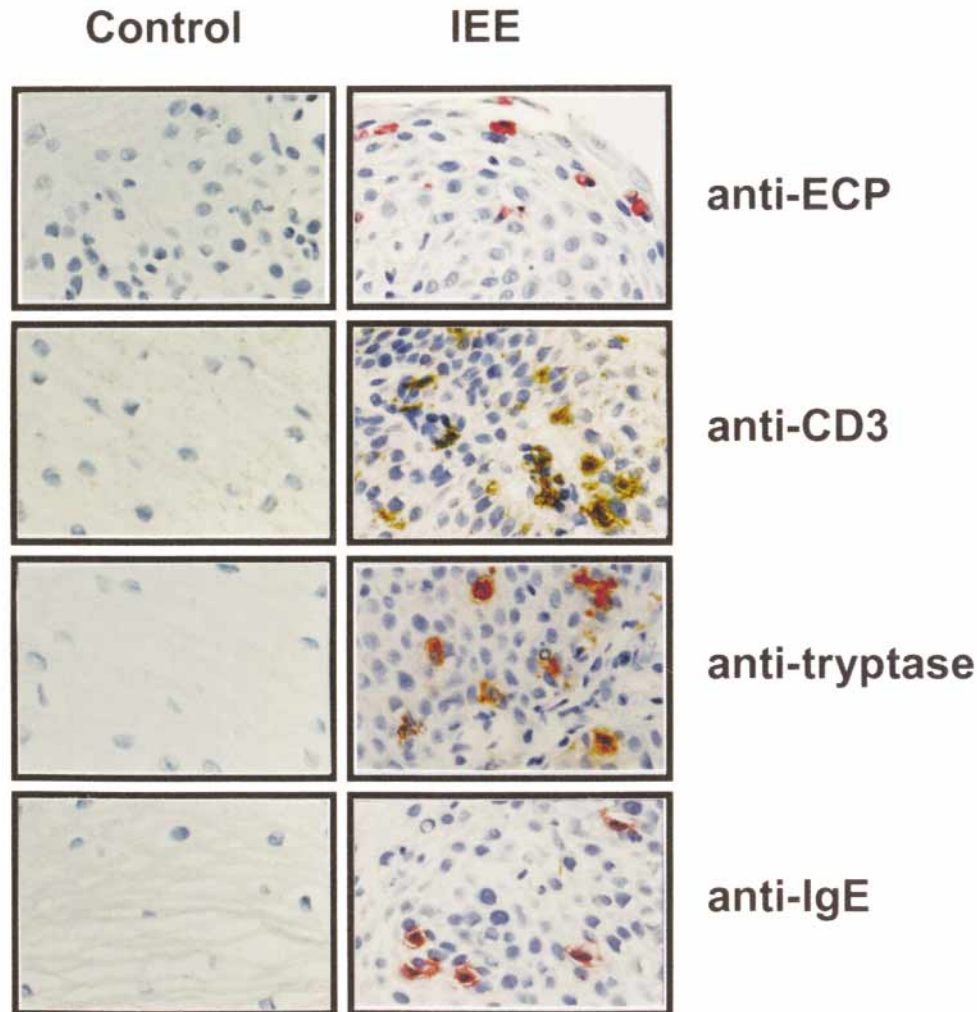


FIG 2. Identification of eosinophils (anti-ECP), T cells (anti-CD3), mast cells (anti-tryptase), and IgE⁺ cells (anti-IgE) in esophageal epithelium, as assessed by means of immunohistochemistry. In IEE, esophageal epithelium is strongly infiltrated by eosinophils, T cells, mast cells, and IgE-bearing cells (most likely mast cells). Original magnification: $\times 1000$.

RESULTS

Patients

The clinical features of the 8 patients with IEE and the 3 control patients are shown in Table I. Patients reported that the dysphagia events had lasted between 1 minute and 2 hours. The duration of the events varied considerably in most of the patients. Only patients 2, 5, and 7 had brief events (not exceeding 5 minutes). Most of the patients had had IEE for many years, suggesting that it is a chronic disease. Physical examination of all patients revealed no abnormalities. In 6 patients with IEE, only minimal alterations of the esophageal mucosa with whitish reticular or nodular structures were found. The abnormalities were present throughout the whole length but were more prominent in the upper and middle third of the organ. Two patients had more pronounced abnormalities (pseudomembranelike and plaquelike lesions), and in 3 patients we observed a mucosal ring. No abnor-

malities were found in the stomach and duodenum, and none of the patients demonstrated evidence of reflux disease. Serum IgE levels were higher than normal in 5 of the 8 patients with IEE (range, 5-957 kU/L). Patients 2 and 8 had bronchial asthma, and patient 6 had atopic dermatitis. None of the patients with IEE had a detectable parasitic infection. All 3 control patients had normal endoscopic findings in the upper gastrointestinal tract as well as normal histology of the esophagus, gastric body, antrum, and duodenum. Their total IgE levels were within normal range.

Some but not all patients with IEE present increased blood eosinophils and increased IL-13 production of T cells in vitro

To better understand the pathogenic mechanisms driving eosinophilic inflammation in patients with IEE, we examined numbers of leukocyte subpopulations and func-

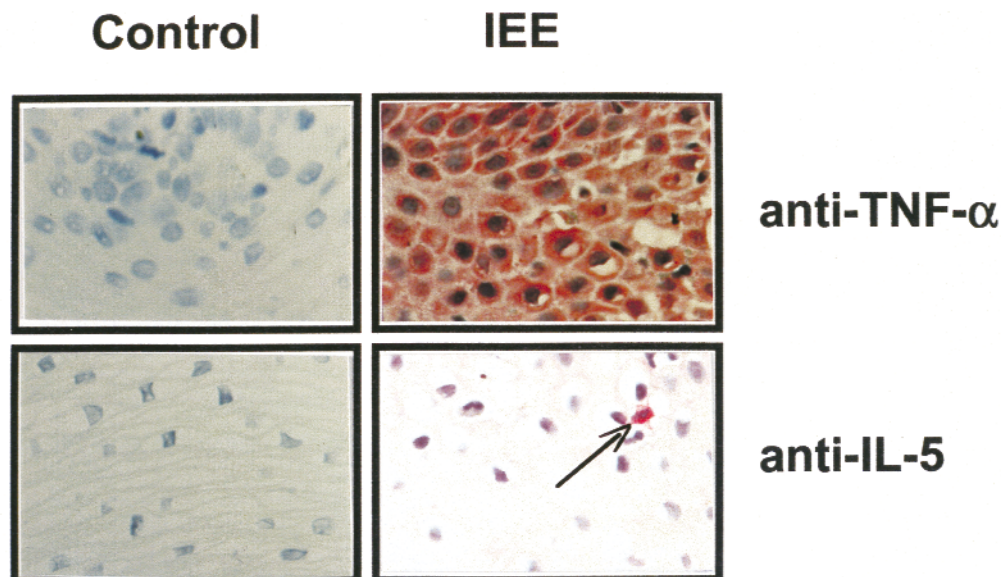


FIG 3. Expression of TNF- α and IL-5 in esophageal epithelium is associated with IEE. Cytokine expression was assessed by means of immunohistochemistry. TNF- α is strongly expressed by epithelial cells. In contrast, IL-5 expression appears to be restricted to infiltrating inflammatory cells (*arrow*). Original magnification: $\times 1000$.

TABLE III. Cellular inflammatory infiltration in esophageal mucosal tissues as assessed by immunohistochemistry

	Infiltrate (no. of cells/mm ²)				
	Eosinophils (ECP ⁺)	T cells (CD3 ⁺)	B cells (CD20 ⁺)	Mast cells (tryptase ⁺)	IgE ⁺ cells
Patient no.					
1	789	803	3	226	40
2	543	636	3	170	42
3	195	509	8	122	102
4	1090	469	3	93	0
5	733	435	6	68	20
6	220	387	11	144	40
7	246	455	8	122	20
8	218	746	17	136	175
Mean $\pm$ SEM	504 $\pm$ 199.7	555 $\pm$ 54.6	7.4 $\pm$ 1.7	135 $\pm$ 17.0	54.9 $\pm$ 20.1
Control no.					
1	0	201	0	6	0
2	0	204	0	3	0
3	0	136	0	3	0
Mean $\pm$ SEM	0	180 $\pm$ 22.2	0	4 $\pm$ 0.9	0

tional T-cell responses in vitro. Blood eosinophil counts exceeded the normal value of 350 cells/mm³ in 4 of the 8 patients with IEE (mean, 404 cells/mm³; range, 135–660 cells/mm³). In 5 of the patients with IEE, we determined the distribution of T cells, B cells, natural killer cells, and T-cell subpopulations. With the exception of patient 6, who demonstrated an elevated CD4/CD8 ratio, no abnormalities were observed (data not presented).

The capacity of T cells to proliferate and generate cytokines was investigated by means of PHA stimulation. The results were compared with those in the group of 6

normal healthy control individuals. As shown in Table II, the T cells of patients 2, 6, and 7 had an increased capacity to generate IL-13 in comparison with those of the other patients with IEE and the control individuals. The 2 patients with the highest IL-13 production had IgE-mediated allergic diseases. Increased production of IL-5 and/or deficient IFN- γ generation was not observed in any of the patients with IEE. The proliferative response varied considerably between patients and control individuals. Nevertheless, the latter data prove that in each case significant stimulation of the T cells was achieved.

IEE is characterized by increased eosinophil, T-cell, and mast cell numbers in the esophagus but not in other parts of the gastrointestinal tract

To identify the inflammatory cells present in the esophageal epithelium, we performed immunohistochemistry using biopsy specimens from patients with IEE and control patients. Eosinophils were identified with anti-ECP mAb, T cells with anti-CD3 mAb, mast cells with anti-tryptase and anti-IgE mAbs, and B cells with anti-CD20 mAb. As shown in Table III and Figs 1 and 2, patients with IEE exhibited an infiltration of the esophageal epithelium with high numbers of eosinophils, T cells, and mast cells. B cells were also detected, though at much lower numbers. Normal esophageal epithelium contains some T cells but is otherwise free of inflammatory cells. This is in contrast to observations made in tissue biopsy specimens from lower parts of the gastrointestinal tract. Gastric and duodenal tissues demonstrated physiological occurrence of eosinophils and mast cells. Moreover, as seen in the esophagus, T cells were also present in gastric and duodenal mucosa under noninflammatory conditions. In general, it appears that the number of eosinophils, T cells, and mast cells is higher in more distal parts of the gastrointestinal tract, at least until one reaches the duodenum. The number of these cells in gastric and duodenal mucosa did not differ between patients with IEE and control patients, suggesting that the inflammatory process in the gastrointestinal tract in patients with IEE is restricted to the esophagus.

Increased expression of IL-5 and TNF- α in esophageal epithelium of patients with IEE

Cytokine expression at the inflammatory site was investigated by means of immunohistochemistry through use of biopsy specimens from patients with IEE and control patients. As demonstrated in Fig 3 and Table IV, most of the inflammatory cells infiltrating the esophageal epithelium, but not the epithelial cells themselves, expressed IL-5. In contrast to IL-5, TNF- α was highly expressed in epithelial cells. Whereas IL-5 and TNF- α were not detectable under noninflammatory conditions, eotaxin and RANTES were expressed in some of the infiltrating cells found in normal, noninflamed esophageal epithelium. Although high numbers of infiltrating eosinophils were present, increased eotaxin expression was not observed in patients with IEE. However, RANTES expression appeared to be slightly increased in IEE esophageal tissues compared with control tissues (Table IV). Epithelial cells did not express detectable levels of eotaxin and RANTES either in patients with IEE or in control patients.

DISCUSSION

Esophageal eosinophilia has been observed in several diseases, including reflux esophagitis,⁵ eosinophilic gastroenteritis,⁴ parasitic infection,¹³ and drug-induced reac-

TABLE IV. Expression of IL-5, TNF- α , eotaxin, and RANTES in esophageal mucosal tissues as assessed by immunohistochemistry

	IL-5	TNF- α	Eotaxin	RANTES
Patient no.				
1	+++	++	(+)	(+)
2	++	+++	+	+
3	+	+++	+	+
4	(+)	+++	++	+
5	+	+++	(+)	+
6	++	+++	+	+
7	+	+++	+	—
8	+	+	(+)	ND
Control no.				
1	—	(+)	+	(+)
2	—	—	+	(+)
3	—	—	—	—

IL-5, eotaxin, and RANTES were expressed in infiltrating cells only. TNF- α was mostly expressed by epithelial cells. Evaluation was performed as described in the Methods section.

ND, Not determined.

tions.¹⁴ These diseases must be ruled out before the diagnosis of IEE can be established. In agreement with previous reports,¹⁻³ we note that IEE was mostly found in male individuals. The primary symptom of IEE is dysphagia. All of the patients in this study had exclusively esophageal symptoms with uniform attacks of dysphagia, including a typical on-off phenomenon. The events lasted from a few minutes to several hours, sometimes leading to long-lasting episodes of food impaction. These clinical symptoms, which obviously involve smooth muscle contraction within the esophagus, are reminiscent of the bronchoconstriction that is seen in patients with asthma. Moreover, recent studies in allergic mice have suggested an association between the eosinophilic inflammatory response in the airways and that in the esophagus.¹⁵ We therefore investigated whether some of the immunologic features known to be important within the pathogenesis of asthma are also found in patients with IEE.

In agreement with previously published work,^{2,3} we observed high numbers of intraepithelial eosinophils in biopsy specimens of the esophagus from patients with IEE. We also confirmed that normal esophageal tissues are not infiltrated by eosinophils either in human beings^{2,3} or in mice.¹⁶ Interestingly, eotaxin, a specific chemotactic factor for eosinophils,¹⁶ was expressed under normal circumstances and was not found in increased amounts under inflammatory conditions. This suggests that eotaxin alone is not sufficient for eosinophil infiltration into the esophagus. The same appears to be true for RANTES. An additional factor required for the eosinophilic infiltration might be IL-5.¹⁵ This assumption is confirmed by the fact that IL-5 transgenic mice have strong eosinophil accumulation within the esophagus.¹⁶ Although our findings are in agreement with these mouse studies, it should be noted that we studied the expression of cytokines and chemokines within the

epithelial cell layer only. We cannot exclude the possibility of higher eotaxin and/or RANTES levels in subepithelial esophageal tissues of patients with IEE.

IL-5 is a specific eosinophil differentiation and survival factor generated by T-helper cells, eosinophils, and mast cells in chronic allergic reactions.¹⁷ In this study, IL-5 was expressed by inflammatory cells, most likely by T cells and eosinophils infiltrating the esophageal epithelium. Given that some of our patients had also increased eosinophil numbers in blood, it is possible that IL-5 produced at the site of inflammation "spills over" into the blood and reaches the bone marrow, where it can induce further eosinophil differentiation.

In addition to eosinophils, we found increased numbers of T cells and mast cells in esophageal epithelium. The role of T cells in regulating eosinophils in allergic disorders is well established.¹⁸ Given that some of the patients with IEE had allergic diseases, such as bronchial asthma and atopic dermatitis, it is possible that IEE is part of a general allergic condition in these patients. A role for IgE-mediated mechanisms is also suggested by the observation that large numbers of mast cells, and perhaps of other IgE-bearing cells, were found in the epithelial layer of the esophagus in patients with IEE. TNF- α might be an important factor, inasmuch as it determines tissue infiltration of inflammatory cells by increased expression of adhesion molecules on endothelial cells. However, it remains unclear which mechanisms are responsible for the induction of the TNF- α gene in esophageal epithelial cells. Future studies should pay more attention to the role of allergens in triggering esophageal symptoms.

Although the pathophysiologic role of eosinophils in asthma is still under debate, there is evidence that eosinophils are involved in bronchial mucosal alteration by the release of toxic mediators. Previous work on IEE suggests that eosinophilic inflammation of the esophagus is not associated with epithelial defects as assessed by endoscopy and histologic analysis.^{1,2} In our patients, we observed endoscopically in 6 cases minimal mucosal alterations with whitish reticular or nodular structures. Two patients had a pronounced pattern with pseudomembranes, plaquelike lesions, and ring formations. These results suggest that the inflammatory response damages the epithelium in patients with IEE.

Because 2 of the 8 patients with IEE had more pronounced esophageal lesions than the other 6, we compared the numbers of infiltrating eosinophils among patients. We found no correlation between eosinophil number and severity of endoscopic findings (data not presented), suggesting that the presence of eosinophils alone does not cause epithelial damage. It is more likely that the amount of eosinophil degranulation, a mechanism requiring eosinophil activation,¹⁹ correlates with tissue damage. Eosinophil degranulation might also be involved in the dysphagia observed in patients with IEE. For instance, it has been shown that major basic protein can act as an antagonist at the muscarinic M2 receptor and directly increases smooth muscle reactivity.²⁰ In

addition, eosinophils generate large amounts of lipid mediators, such as leukotrienes, which are potent stimulators of smooth muscle contraction.²¹ It therefore seems reasonable to suggest that activation of eosinophils might contribute, at least partially, to dysphagia attacks in IEE.

Our study demonstrates that high numbers of mast cells infiltrate into the esophagus. Like eosinophils, mast cells store potent mediators in their granules. Antigen-mediated cross-linking of high-affinity IgE receptors or nonimmunologic activation mechanisms induce rapid degranulation of mast cells, resulting in the release of histamine, leukotriene C4, platelet-activating factor, and other activators of smooth muscle contraction.²² Accordingly, mast cells as well as eosinophils might participate in the scenario leading to dysphagia.

Taken together, our results indicate that IL-5-producing inflammatory cells are present within the esophageal epithelium in patients with IEE. Increased eosinophil, T-cell, and mast cell numbers are selectively observed in the esophagus but not in further distal parts of the gastrointestinal tract. The presence of eosinophils in esophageal epithelium remains an important cornerstone in IEE diagnosis.²³ Although the investigated peripheral markers do not correlate with disease activity, at least 2 findings suggest that IEE is not necessary a local disease. First, increased blood eosinophil numbers are observed in many patients, suggesting stimulation of the bone marrow. Second, some patients demonstrate evidence of inflammatory responses in other organs—in particular, the bronchi and skin—implying that the events in the esophagus are part of a systemic allergic disease. Clearly, future studies should pay more attention to potential IgE-mediated mechanisms.

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