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High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders

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Abstract

Background—Eosinophilic esophagitis (EoE) is an emerging chronic inflammatory disease mediated by immune hypersensitization to multiple foods and strongly associated with atopy and esophageal remodeling.

Objective—We provide clinical and molecular evidence indicating a high prevalence of EoE in patients with inherited connective tissue disorders (CTDs).

Methods—We examined the rate of EoE among patients with CTDs and subsequently analyzed esophageal mRNA transcript profiles in patients with EoE with or without CTD features.

Results—We report a cohort of 42 patients with EoE with a CTD-like syndrome, representing 0.8% of patients with CTDs and 1.3% of patients with EoE within our hospital-wide electronic

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medical record database and our EoE research registry, respectively. An 8-fold risk of EoE in patients with CTDs (relative risk, 8.1; 95% confidence limit, 5.1-12.9; $\chi^2_1 = 112.0$; $P < 10^{-3}$) was present compared with the general population. Esophageal transcript profiling identified a distinct subset of genes, including *COL8A2*, in patients with EoE and CTDs.

Conclusion—There is a remarkable association of EoE with CTDs and evidence for a differential expression of genes involved in connective tissue repair in this cohort. Thus, we propose stratification of patients with EoE and CTDs into a subset referred to as EoE-CTD.

Keywords

Eosinophilic esophagitis; eosinophilic gastrointestinal disease; eosinophil; connective tissue disorders; Ehlers-Danlos syndrome; Marfan syndrome; hypermobility syndrome

Eosinophilic esophagitis (EoE) is an emerging worldwide immune-mediated disease characterized by intense eosinophil infiltration of the esophageal mucosal epithelium that is refractory to acid-suppressive therapy and often associated with significant tissue remodeling.[1] First described in the late 1970s, the incidence and prevalence of EoE has been on the increase. It is now a global health disease reported in every continent except Africa and has been shown to affect approximately 1:1000 subjects.[2,3] EoE typically occurs as an isolated disease entity, although it is often associated with concurrent allergic disease, including asthma, eczema, food-induced anaphylaxis, and polysensitization to antigens, especially food allergens. An allergic cause for EoE is supported by the reversibility of the disease after dietary avoidance of specific foods,[4] the reoccurrence of the disease on reintroduction of the removed foods,[5-7] the induction of the disease in mice by exposure to allergens,[8] and genome-wide transcriptome analysis of esophageal tissue having implicated an interplay of innate and adaptive T_H2 immunity.[9] The disease has a strong hereditary component with a large sibling risk ratio ($\lambda_s \sim 80$),[9] and early genetic analyses have identified susceptibility loci in regions that contain candidate genes that are expressed in epithelial cells and strongly implicated in regulating antigen recognition (thymic stromal lymphopoietin *[TSLP]*) and inflammatory cell recruitment and activation (eotaxin-3 *[CCL26]*).[10-12]

Among the many immune-modulating molecules implicated in EoE disease pathogenesis, recent attention has focused on TGF-β1, the levels of which are increased in the esophagus in patients with EoE and localized to eosinophils within the inflamed and fibrotic esophageal lamina propria, along with deeper-lying mast cells found within the esophageal smooth muscle layer.[13-15] TGF-β1 not only promotes smooth muscle contractility and fibrosis, processes that might be involved in eliciting the esophageal dysfunction seen in patients with EoE, but also is a key immunomodulating cytokine that is expressed by and essential for the function of regulatory T cells. Notably, an increased level or imbalance of regulatory T cells occurs in patients with EoE and in animal models of EoE.[16,17]

A series of Mendelian-inherited connective tissue disorders (CTDs) are caused by genetic variants in TGF-β binding proteins (eg, Marfan syndrome [MFS]) and TGF-β receptors (Loeys-Dietz syndrome [LDS]), and excess TGF-β1 levels and pathway signaling have been associated with these 2 disorders.[18,19] Although the Ehlers-Danlos syndromes (EDSs) have not been directly associated with excess TGF-β1 levels, direct protein and regulatory interactions between TGF-β1 and a mutated *COL5A1* collagen protein have been reported.[20-22] It is notable that these disorders are often associated with gastrointestinal symptoms,[23,24] especially dysphagia,[25] which also represents a chief symptom of EoE in adults. Although eosinophilia has not been previously associated with CTDs outside of collagen vascular diseases such as scleroderma, dermatomyositis, and polymyositis,[26,27] we recently began to encounter patients with EoE who had coexisting CTDs without the

features of autoinflammatory collagen vascular disease. Herein, we describe a new syndrome involving the coexistence of EoE with CTD (EoE-CTD). Although some patients with EoE-CTD have known causative mutations in CTD genes, they did not manifest the full phenotype of CTDs but rather had an enrichment of Marfanoid features and extensive hypermobility.

METHODS

Patients

The patients used in these analyses came from 2 primary data sources: an Informatics for Integrating Biology & the Bedside (i2b2) data warehouse and our eosinophilic gastrointestinal disorders (EGIDs) research database. The i2b2 warehouse represents a deidentified database of all patients seen at Cincinnati Children's Hospital Medical Center (CCHMC) whose data are derived from our local implementation of the EPIC electronic medical records (EMRs) containing patients' records from March 2007 through December 2012.[28,29] Our EGID database contains patients with EoE and control subjects. All participants registered in the EGID database have undergone a formal informed consent process approved by the CCHMC Institutional Review Board, with data collection beginning in approximately June 2000 and continuing through December 2012. Data collected include demographics, clinical testing, and past medical, surgical, and family histories, along with samples (blood DNA and esophageal biopsy mRNA). However, data and samples available for participants varied, and thus the specific subjects entering each type of analysis are described below. Importantly, a simple majority of the patients with EoE at our medical center are included in the EGID database (58%). Patient phenotypes have been described previously.[9,30] In brief, patient phenotypes for mRNA analyses are as follows: *control subjects* (n = 12), patients with no EoE diagnosis with normal esophageal histology; *patients with active EoE* (n = 12), peak esophageal eosinophil count of 15 or more per high-power field; *patients with EoE-CTD* (n = 6), peak esophageal eosinophil count of 15 or more per high-power field with a coexisting CTD. The diagnosis of EoE was confirmed based on proton pump inhibitor (PPI) administration before a positive endoscopic result in 47% of patients with EoE-CTD for the mRNA analyses. Control subjects had not been given a diagnosis of EoE or other related gastrointestinal conditions and had normal esophageal histology. For this study, slides of the biopsy specimens obtained at endoscopy that yielded tissue for mRNA extraction (see below) from the patients with EoE-CTD were reviewed by a single pathologist (M.H.C.) and analyzed for peak eosinophil counts and histopathologic features associated with EoE. For analysis of height, weight, body mass index (BMI), and age, the EoE-CTD group (n = 42; male, n = 29; female, n = 13) was identified based on clinical evaluations by physicians in the fields of allergy, gastroenterology, and genetics. Of these patients with EoE-CTD, 10 (24%) had evidence of eosinophilic gastrointestinal disease outside of the esophagus (stomach, n = 7; duodenum, n = 3; and colon, n = 1). This extraesophageal disease is defined as an eosinophil count in excess of that reported in Debrosse et al,[31] along with evidence of architectural destruction (as evaluated by M.H.C.) while also fulfilling the criteria for eosinophilic gastritis, as suggested by Lwin et al.[32]

For the mRNA analysis cohort, subjects had no evidence of extraesophageal eosinophilic gastrointestinal disease, and evidence of active EoE was determined by rereview of available slides or from data previously collected within the EGID database. For comparison with patients with EoE-CTD, 42 control subjects and 42 patients with EoE without CTDs were randomly selected from the EGID database, excluding the 42 patients with known EoE-CTD. These control subjects and patients with EoE without CTDs in the EGID database were assigned a random number derived from a globally unique identifier, sorted by random

number value, and selected to match the same distribution of male and female patients seen for the EoE-CTD patient population.

Thirty-six percent (15/42) of patients with EoE-CTD responded to a variety of dietary treatments based on review of clinical records. No patients in this report underwent esophageal manometry, and a small number of patients (5/42) underwent barium swallow evaluation, none of whom had structural abnormalities. Videos E1 to E4 demonstrating evidence of the joint hypermobility seen in these patients with EoE-CTD can be found in this article's Online Repository at www.jacionline.org. Releases for the use of these videos were obtained from the parents or a single adult subject. This study was approved by the Institutional Review Board of CCHMC.

Comparison of rates of EoE, CTD, and EoE-CTD

To determine the total number of patients and the numbers of patients with EoE, CTD, and EoE-CTD, we used the i2b2 workbench.[28,29] The following specific diagnostic codes were used to identify patients with CTDs: Marfan and Marfanoid-related syndromes, 759.82, 759.82F, 759.82Q, and 759.82R; Ehlers-Danlos and related syndromes, 756.83, 756.86.CQ, 756.86CT, 756.83CU, 756.83.DL, 756.83.DM, 756.83.DN, 756.83EL, and 756.83X; and Loeys-Dietz syndrome, 759.89ALK. The specific diagnostic codes 530.13 and 530.19AQ were used to identify patients with EoE. Using the numbers of patients with EoE, CTDs, and EoE-CTD, we then compared the proportions of patients with and without EoE and CTDs by using 2 × 2 contingency tables to determine whether these 2 conditions occurred independently of each other. Gastroesophageal reflux disease (GERD) searches and diagnostic codes include 530.11J, 530.11AE, 530.11B, 530.11, 530.81BQ, 530.81AP, 530.81T, 530.81BG, 530.81AN, 530.81V, 530.81U, 530.81AV, 530.81Q, 530.81AK, 530.81N, 530.81B, 530.81AL, 530.81AX, 530,81AA, 530.81S, 530.81AZ, 530.81BY, 530.81AH, 530.81CC, 530.81R, 530.81CB, 530.81AM, and 530.81AS. The alphabetic encoding following the diagnostic codes represents additional granularity layered over the SNOMED International Classification of Diseases–ninth revision diagnostic codes from Intelligent Medical Objects.

The EGID database contains 1268 patients with EoE who have undergone a formal informed consent process and maintains information related to patients' demographics, clinical testing, and past medical, surgical, and family histories, along with information regarding a variety of collected samples. However, no formal capture of patients with CTD-type features was initially designed into this database structure, and therefore patients were assigned to a CTD diagnosis as they were identified. The diagnosis of EoE in these patients with EoE-CTD was confirmed by means of PPI administration before a positive endoscopic result in 69% of the patients. We subsequently used our EGID database (a comprehensive dataset of the majority of all patients with EGIDs, including EoE, at our medical center) to identify patients with EoE with CTDs. All of the patients with EoE who were suspected of having a CTD were excluded from the regular EoE and control groups.

Expression levels of representative EoE genes

To examine expression differences in EoE genes, we selected representative patients from each study group: 13 control subjects, 14 patients with EoE, and 6 patients with EoE-CTD. Normal specimens were obtained from patients undergoing evaluation in gastroenterology clinics, whose endoscopic and histologic appearances demonstrated neither gross nor histopathologic abnormalities. For this analysis, extraesophageal disease was excluded from all of the patients with eosinophilic disease, and all patients with EoE and patients with EoE-CTD had active EoE at the time of the analysis (peak esophageal eosinophil counts, 21-268 per high-power field). mRNA extraction was performed, as described previously.[9] The

mRNA was reverse transcribed with the iScript cDNA Synthesis Kit (Bio-Rad Laboratories, Hercules, Calif), according to the manufacturer's recommended protocol. The TaqMan reagents for amplification of major EoE signature genes[9] were obtained from Applied Biosystems, and TaqMan real-time PCR amplification was performed on an ABI 7900HT System (Applied Biosystems, Carlsbad, Calif). The amplification protocol consisted of a hot start of 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. EoE gene expression was normalized to glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) to acquire relative expression for each given gene of interest. A statistical criterion of a corrected *P* value of less than .05 (after a Benjamini-Hochberg multiple comparison correction) and a fold change of greater than 2.0 were applied to screen for genes differentially expressed between patients with EoE and patients with EoE-CTD.

RESULTS

We recently noted an unexpectedly high prevalence of patients with CTDs presenting with EoE symptoms in our general EoE patient population. These patients with CTDs mainly included patients with conditions that resembled MFS, hypermobile EDS, or joint hypermobility syndrome (JHS). By searching our hospital's EMRs (n = 1,339,280 patients) for CTDs (eg, MFS, EDS, and JHS), there was a 1.3% prevalence of EoE in patients with CTDs (Table I). Searching the same EMRs for EoE, 0.8% of the total EoE population was found to have CTDs. Thus using our hospital-based cohort, there was an 8-fold risk of CTDs in patients with EoE (relative risk, 8.1; 95% confidence limit, 5.1-12.9; $\chi^2_1 = 112.0$; $P < 10^{-3}$) compared with the general population. By comparison, there was a 7.7% prevalence of GERD in patients with CTDs when using International Classification of Diseases–ninth revision codes 530.11 and 530.81. Within the general population, EoE is noted to occur with a prevalence of approximately 1:1000 and 1:10 for GERD, whereas the incidence rate for the CTDs is approximately 1:5000 for both EDS and MFS.[33-36] We then examined our well-defined EGID Research Registry (n = 1268 patients with EoE) for evidence of CTDs. For patients with EoE from this database, there was a 3.3% prevalence of CTDs in the EoE group. These results were not driven by patient selection bias because 2.1% of patients with EoE residing in the immediate catchment area of our hospital (n = 420) also had a CTD (Table I).

The patients with EoE-CTD had a syndromic phenotype including a combination of dysmorphic scaphocephalic facial appearances (Fig 1, *A*), hypermobility of the hands and large joints (see Videos E1-E4), and a high rate of atopic diseases (Table II). Esophageal biopsy specimens from patients with EoE-CTD revealed features that were typical of those found in patients with EoE without CTDs (Fig 2). However, approximately 24% (10/42) of this population had evidence of significant and pathologic extraesophageal eosinophilic inflammatory disease affecting the stomach, duodenum, and colon (Fig 2). The presence of extraesophageal disease was specifically excluded from the control EoE cohort by means of review of pathology records. Although not having all of the clinical features associated with formal hypermobile EDS or MFS (see modestly increased Beighton and Ghent scores in Table II),[37,38] evidence of cardiac abnormalities was noted in 4 of the 23 patients subjected to echo-cardiographic evaluation. Cardiac anomalies included aortic root dilatation, mitral valve prolapse and/or insufficiency, atrial septal defect, atrial valve insufficiency, and/or aortic valve defects. One of 42 patients also exhibited a history of pneumothoraces, which are seen in patients with MFS, LDS, and vascular EDS.[39-41] Patients with EoE-CTD had distinct anthropomorphic features compared with patients with EoE and control subjects and were generally lean, with a lower BMI that was statistically different in male subjects (patients with EoE-CTD, −0.9 [SD, 1.5]; patients with EoE, +0.36 [SD, 1.2]; $P < .01$; Table II). Twenty-one of the patients with EoE-CTD were genotyped for well-established causes of CTDs (Table II). Of note, 2 subjects had established disease-causing mutations in

fibrillin-1 (*FBN1*), 1 subject had a likely disease-causing mutation in *FBN1*, 2 had variants of unknown significance in *FBN1*, and 4 had a common variant in *TGFBR1* (*TGFBR1**6A) that has been associated with excessive TGF-β signaling and appears to be a contributing allele to the MFS phenotype (Table II).[42] The remaining 12 genotyped patients had no mutations found in genes typically associated with CTDs.

To further demonstrate that a patient with EoE-CTD had *bona fide* EoE rather than secondary esophageal eosinophilia caused by acid-induced reflux disease or a primary motility disorder, we molecularly characterized the gene expression signature of the esophageal tissue of representative patients with EoE-CTD, focusing on genes representative of the known EoE transcriptome.[9] Notably, patients with EoE-CTD (n = 6) had a remarkable overlap with the EoE transcriptome of nonsyndromic EoE (n = 14, Fig 1); however, patients with EoE-CTD had significant differences ($P < .05$) in the expression of 4 genes, including increased levels of *CD200R1* and *SAMSN1* and decreased levels of *PTGFRN* and *COL8A2* (Fig 1), which encodes for type VIII collagen, which has been shown to modulate TGF-β signaling.[43] Although differences in mRNA expression profile levels could be detected, no differences in histology based on hematoxylin and eosin staining could be discerned among the 3 studied groups in this limited sample.

DISCUSSION

Although our study was retrospective, we would like to emphasize the link between the prevalence of EoE and CTDs. We focused on 2 CTDs, namely MFS and EDS including the JHS. MFS is an autosomal dominant disorder caused by mutations in *FBN1*, and deficiencies in fibrillin-1 alter or preclude matrix sequestration of the large complex of TGF-β.[18] This leads to increased levels of TGF-β in the affected tissue, as well as increased circulating TGF-β levels. These circulating levels correlate with the aortic root dimensions, one of the main complications in patients with MFS.[44,45] LDS (formerly MFS type II), on the other hand, is associated with 2 additional loci, 9q22.33 and 3p25-p24.2, with disruptions in the genes *TGFBR1* and *TGFBR2*, respectively.[46-48] EDS is often idiopathic but can result from mutations in collagen genes, such as *COL5A1* and *COL3A1*. In general, TGF-β signaling is enhanced in patients with CTDs in an effort to compensate for the direct mutations present in this pathway.[49] It is notable that patients with EoE-CTD were enriched in well-established causative mutations for MFS *(FBN1)* and had a remarkable decrease in the expression of *COL8A2*, yet the patients did not manifest the full spectrum of these disorders. *COL8A2* encodes for the collagen α2 (VIII) chain, and mutations in this gene have been associated with defects in the cornea, leading to endothelial metaplasia, hyperplasia, and corneal edema within the Descemet membrane.[50] At our institution, 6Ala *TGFBR1* mutations are part of the MFS genetic panel because this genetic variant has been shown to be enriched in patients with MFS and to be associated with gain of function of TGF-β signaling, which is consistent with other known mutations in patients with CTDs.[42] Thus, it is noteworthy that 4 of the 21 patients with EoE-CTD screened for this genetic variant had positive results. It is notable that increased TGF-β levels in the esophagi of patients with EoE have been reported and localized to eosinophils and mast cells, adding a plausible further link to the association of CTDs and EoE.[51-53]

Although several patients with EoE-CTD did not have formal confirmation of the EoE diagnosis with the use prolonged high-dose PPIs, at least one third of these patients responded to dietary interventions, suggesting an allergic link to this disorder rather than primary acid reflux–mediated eosinophilia. It is interesting to note that patients with CTDs have been known to have a high rate of gastrointestinal problems, mainly attributed to GERD. We propose that patients with CTDs, especially those with allergic diatheses, are more prone to have EoE and that some of these patients with GERD might instead have

EoE. Whether most patients with CTDs have genuine GERD or EoE cannot be ascertained here, and this represents an area for future potential study.

In summary, we have described a new syndrome involving EoE in association with inherited CTDs that represents a new class of this gastrointestinal disorder. These patients with EoE-CTD appear to have a lower BMI and might have an increased risk of extraesophageal eosinophilic gastrointestinal disease relative to their peers with EoE given the unusual preponderance of frank eosinophilic gastritis, duodenitis, and colitis within this population. Although all searches have their limitations, we were able to confirm in 3 independent analyses not only that the prevalence of EoE in the CTD population is 8-fold higher compared with expected rates in the general population but also that there is a higher percentage of patients with CTDs in the EoE population. Furthermore, these data likely underrepresent the number of patients with a concurrent CTD and eosinophilic gastrointestinal disease because it is likely that most of these patients do not typically undergo endoscopy in spite of the known high frequency of gastrointestinal complaints in these patients. Our findings also raise concern that at least some patients with EoE might require physical and occupational therapy for joint disease while also being monitored for cardiac disease. In view of losartan's ability to decrease TGF-β levels[54-56] and reverse MFS-associated tissue remodeling in mice[45,57,58] and the recent development of humanized anti–TGF-β therapeutics,[18,59] our findings have imminent therapeutic applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations used

BMI	Body mass index
CCHMC	Cincinnati Children's Hospital Medical Center
CTD	Connective tissue disorder
EDS	Ehlers-Danlos syndrome
EGID	Eosinophilic gastrointestinal disorder
EMR	Electronic medical record
EoE	Eosinophilic esophagitis
FBN1	Fibrillin-1 gene
GERD	Gastroesophageal reflux disease
i2b2	Informatics for Integrating Biology & the Bedside
JHS	Joint hypermobility syndrome
LDS	Loeys-Dietz syndrome
MFS	Marfan syndrome
PPI	Proton pump inhibitor

Key messages

- Patients with EoE can also have features of CTDs, particularly those involved in hypermobility. We refer to this new subset of EoE as EoE-CTD.
- The risk of EoE is increased 8-fold in a broad CTD population.
- There is evidence of dysregulation of collagen transcription in patients with EoE-CTD that is distinct from that seen in typical patients with EoE or healthy subjects.
- Patients with EoE-CTD might be at greater risk for more diffuse eosinophilic extraesophageal gastrointestinal disease than their peers with EoE without evidence of CTDs.

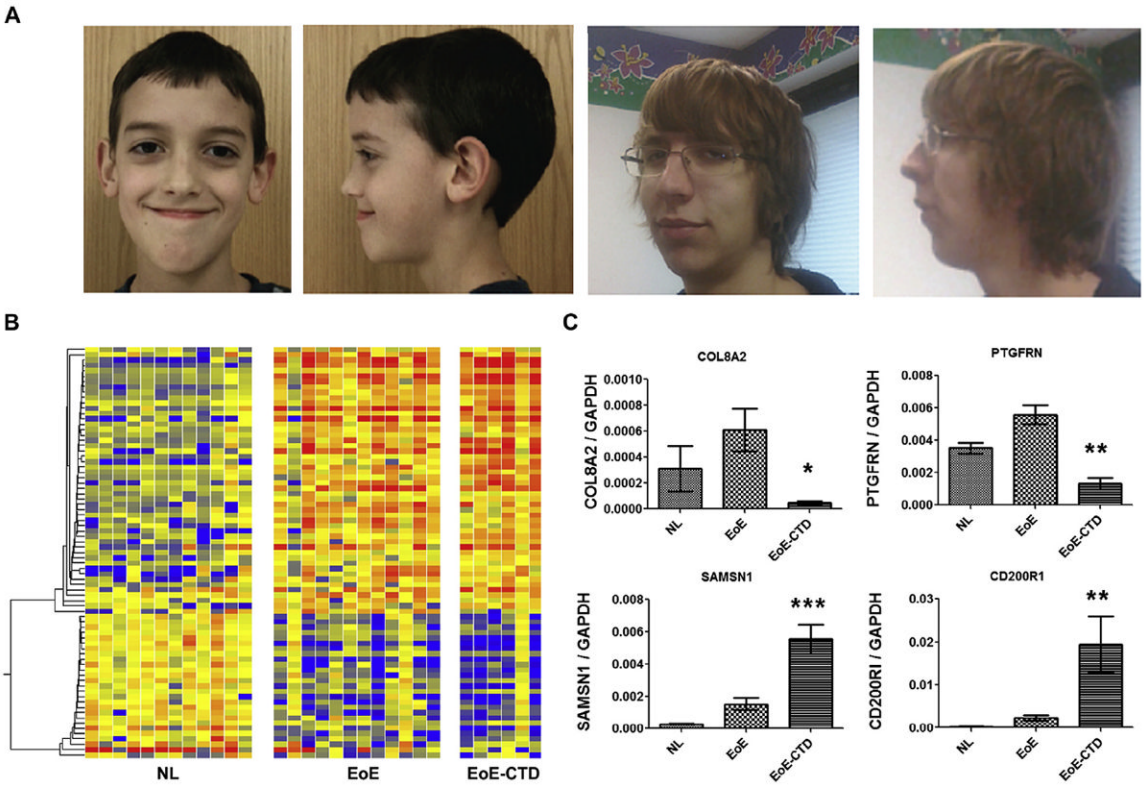
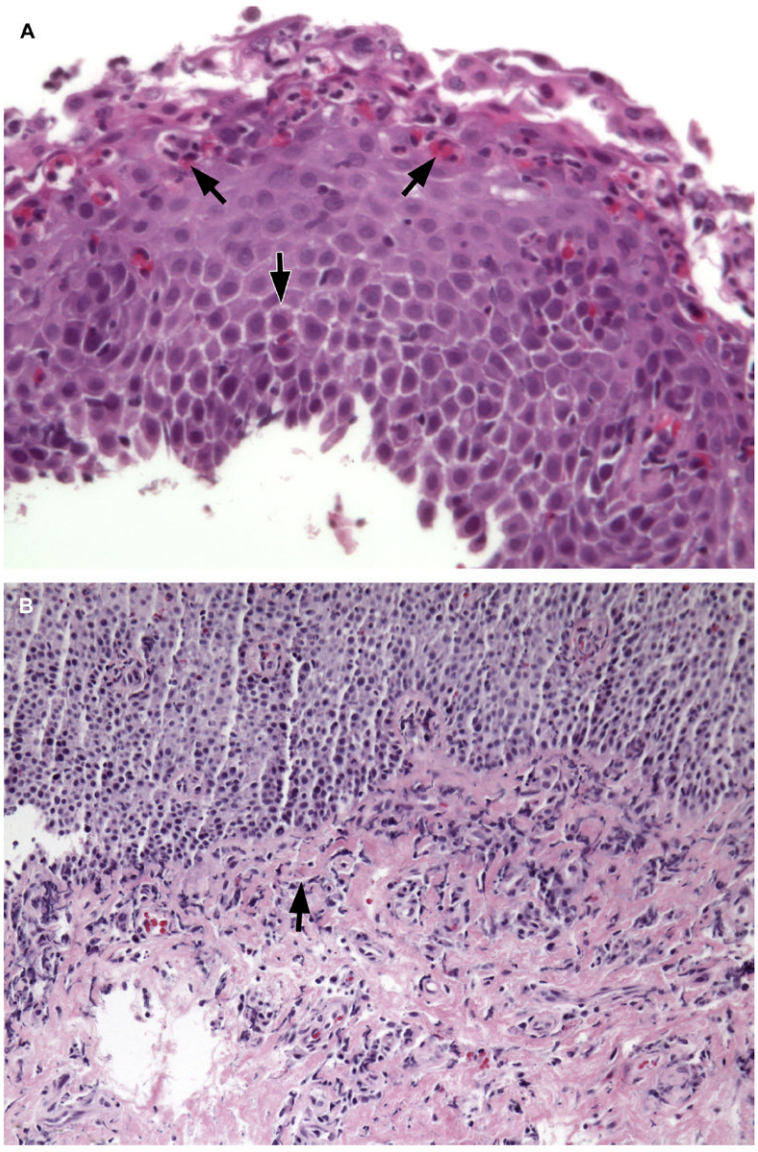


FIG 1.

Phenotypic and genotypic features of EoE-CTD. **A**, Typical facial features seen in 2 patients with EoE-CTD. **B**, Heat *map* from a large panel of differently regulated esophageal genes in patients with active EoE, patients with EoE-CTD, and control subjects *(NL)*. **C**, Quantitative analysis of *COL8A2, PTGFRN, SAMSN1*, and *CD200R1* by means of quantitative PCR, all of which are differentially expressed in patients with EoE versus patients with EoE-CTD. Data are *graphed* as means ± SEMs of the glyceraldehyde-3-phosphate dehydrogenase *(GAPDH)*–normalized relative expression values. **P* < .05, ***P* < .01, ****P* < .001; EoE-CTD versus EoE; 2-tailed, unpaired *t* test.



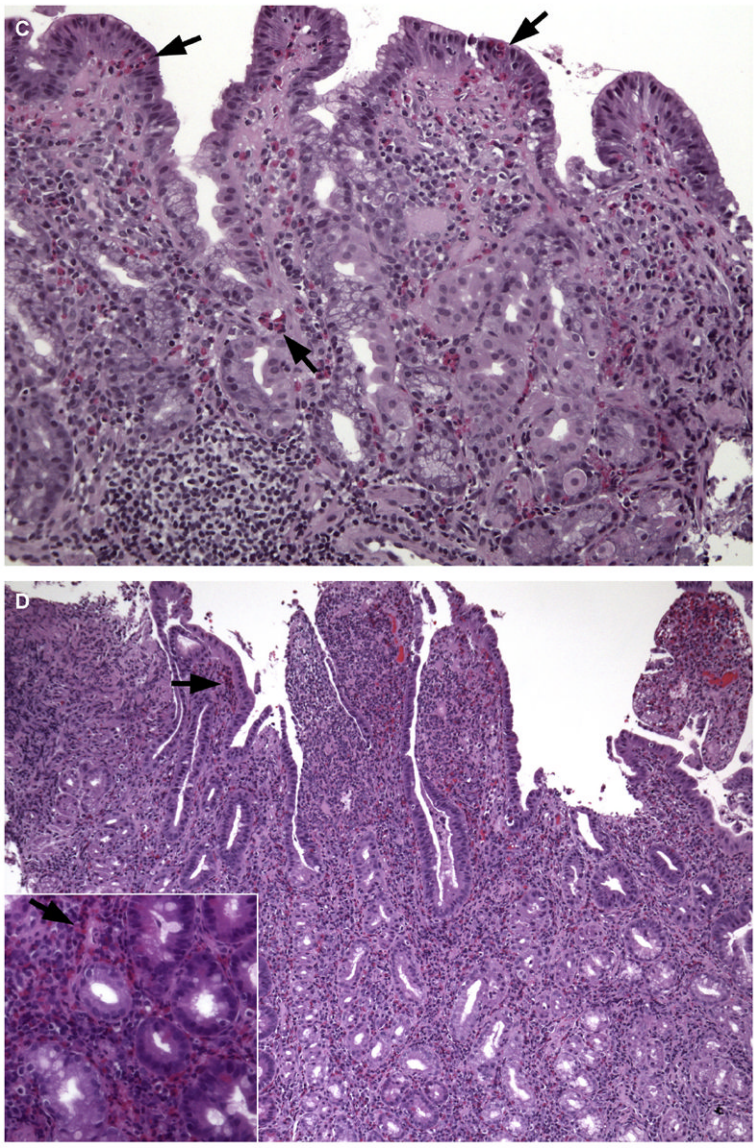


FIG 2.

Esophageal, gastric, and duodenal biopsy specimens from a patient with EoE-CTD. **A**, Numerous intraepithelial eosinophils *(upper black arrows)* align near the surface of this biopsy specimen. The basal epithelial layer is expanded, and intercellular spaces are dilated *(lower black and white arrow)*. **B**, Lamina propria in this biopsy specimen from a different patient with EoE-CTD shows dense fibrosis *(arrow)*. **C**, Numerous eosinophils are found in the lamina propria and epithelium *(arrows)* of this gastric biopsy specimen. **D**, Numerous eosinophils are found in the superficial lamina propria *(arrow)* and crypt epithelium *(inset, arrow)* of this duodenal biopsy specimen, which exhibits chronic architectural damage.

TABLE I

Prevalence of CTDs in the EoE populations

Patient database	Total patients with CTDs (no.)*	Total patients with EoE (no.)	Total patients with EoE-CTD (no.)	% EoE in patients with CTDs	% CTDs in patients with EoE
EMRs	1356	2199	18	1.3	0.8
EGID	42	1268	42	NA	3.3
Local EGID	9	420	9	NA	2.1

Databases used include CCHMC-wide EMRs and the EGID database. The total number and percentages of patients with CTDs and EoE are calculated for the EMRs and EGID databases. For "Local EGID," patients in the EGID database were limited to those with zip codes corresponding to CCHMC's catchment area.

NA, Not applicable.

*CTD searches and diagnostic codes included Marfan and Marfanoid-related syndromes (759.82, 759.82F, 759.82Q, and 759.82R), Ehlers-Danlos and related syndromes (756.83, 756.86.CQ, 756.86CT, 756.83CU, 756.83.DL, 756.83.DM, 756.83.DN, 756.83EL, and 756.83X), and Loeys-Dietz syndrome (759.89ALK). Patients with EoE were identified by using codes 530.13 and 530.19AQ.

TABLE II

Phenotype of the EoE, EoE-CTD, and healthy cohorts

	Control subjects (n = 42)	Patients with EoE (n = 42)	Patients with EoE-CTD (n = 42)	*P* value
Age (y), mean (SD)	10.3 (3.8)	10.1 (5.2)	12.3 (4.1)	.04 *†
Sex (% male)	69	69	69	
Race (no.)	White: 40 African American: 2 Other: 0	White: 41 African American: 1 Other: 0	White: 38 African American: 2 Other: 2	
Height *z* score, mean (SD)	Male: 0.04 (1.0) Female: 0.31 (1.1)	Male: −0.36 (1.6) Female: −0.04 (0.9)	Male: 0.01 (1.5) Female: 0.28 (1.5)	
Weight *z* score, mean (SD)	Male: 0.10 (1.3) Female: 0.81 (1.2)	Male: 0.08 (1.7) Female: 0.14 (0.9)	Male: −0.68 (1.9) Female: 0.68 (1.4)	
BMI *z* score, mean (SD)	Male: 0.06 (1.2) Female: 0.65 (1.4)	Male: 0.36 (1.2) Female: 0.11 (1.2)	Male: −0.9 (1.5) Female: 0.71 (1.1)	Male: <.01 *†
Beighton score, mean (SD)			3.56 (3.0)‡	
Ghent score, mean (SD)			2.10 (2.2)‡	
Sequencing for known CTD genes (21 patients) Variant identified (no. of patients with variant)			*FBN1* c.3208+55_60 delTCTTTA in intron 25 (1) *FBN1* p.Arg2726Trp c.8176C>T in exon 64 (2) *FBN1* p.Glu1584Lys c.4750 G>A in exon 38 (1) *FBN1* p.Ala986Thr c.2956G>A in exon 24 (1) *TGFBR1* p.24_26del AlaAlaAla (6 Ala allele) in exon 1 (4)	
Atopy (%)§	71	86	88	
PPI-confirmed EoE (%)		71	69	
Eosinophilic gastritis			17% (n = 7)	
Eosinophilic duodenitis			7% (n = 3)	
Eosinophilic colitis			2% (n = 1)	

The most recent available height and weight were obtained from EMRs. Healthy subjects and patients with EoE but without CTDs, excluding the known patients with EoE-CTD, were randomly selected from the EGID database to match the overall total of 29 male and 13 female patients with EoE-CTD identified in this study. Age and BMI were calculated for all healthy subjects and patients with EoE and 28 male and 11 female subjects of the 42 patients with CTDs because height and weight data were not available for 3 of the patients with EoE-CTD. The frequency of pathologic extraesophageal disease is reported for the 10 patients described in the text. The total here is greater than 10 because 2 patients had simultaneous eosinophilic gastritis and duodenitis in addition to the esophageal pathology. Where blank, data were either not obtained or no significant differences were noted among the groups. Statistical comparisons between groups were made by using a 2-tailed *t* test with the assumption of equal variances.

[*] Patients with EoE-CTD were statistically different from healthy control subjects.

[†] Patients with EoE-CTD were statistically different from patients with EoE without CTDs.

[‡] Beighton scores were determined for 18 patients, and Ghent scores were determined for 20 patients.

[§] Atopy was defined as any evidence of allergic rhinitis, asthma, or eczema.