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ORIGINAL ARTICLE

The Changing Faces of Eosinophilic Esophagitis: The Impact of Consensus Guidelines at the University of South Florida

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Abstract

Background and Aims Prior to the consensus guideline conference in 2007, eosinophilic esophagitis (EoE) was uncommon dominated by the fibrostenotic phenotype, but over the past decade has become a common cause of dysphagia with more inflammatory phenotypes diagnosed. We assessed the impact of guideline definitions on the characteristics of EoE phenotypes over the past 26 years at our institution.

Methods We reviewed the electronic health record of 75 consecutive patients meeting guideline definition EoE from 1/1988 to 5/2014. We separated groups based on 5-year intervals of diagnosis and phenotype. For continuous data, results were summarized as mean difference and standard deviation with 95 % confidence intervals.

Results Five groups based on 5-year intervals of diagnosis were identified: group 1—1988–1993 ($n = 7$), group 2—1994–1999 ($n = 7$), group 3—2000–2005 ($n = 4$), group 4—2006–2011 ($n = 35$), and group 5—2012–2014 ($n = 22$). Prior to 2000, all patients were diagnosed with fibrostenotic EoE. After the initial 2007 guideline conference, inflammatory EoE has predominated with only one-third diagnosed with fibrostenotic EoE. Prior to 2011, only two were diagnosed with PPI-REE. In the last 3 years, 8 out of 22 patients (32 %) had PPI-REE. Overall, 8 out of 10 (80 %) PPI-REE were the inflammatory phenotype. When comparing pre- ($n = 18$) and post ($n = 57$)-consensus definitions, there was a significant difference between age of diagnosis (30.710.2 vs. 41.3 ± 14.3; $p = 0.001$), age of symptom onset (18.4 +/15.2 vs. 32.4 ± 15.5), and initial esophageal diameter (10.5 ± 2.7 vs. 14.3 ± 4.2; $p < 0.0001$), respectively.

Conclusions Fibrostenotic EoE has steadily decreased, and inflammatory EoE is now the most recognized form. Across our 26-year experience, there was a decrease in delay in diagnosis and severity of esophageal stricture. The pivotal change occurred around 2007 corresponding to the first EoE guideline emphasizing the impact and importance of early detection of disease.

Keywords Eosinophilic esophagitis · Natural history · Dilation · Steroid naïve · Complications · Follow-up

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Introduction

The historical naming of eosinophilic esophagitis (EoE) has evolved from various aliases over the past several decades including ringed esophagus, corrugated esophagus, feline esophagus, small caliber esophagus, and congenital esophageal stenosis (CES) [1–6]. The term "eosinophilic esophagitis" was first reported into the literature in 1978 with most physicians at the time uncertain whether EoE represented a congenital disease or another form of GERD [7]. Case series thereafter began to differentiate EoE from other diseases and defined distinct characteristics of the

disease. The histologic and phenotypic description of the disease was first described by Attwood [8] and later by Straumann [9]. As larger cohorts reported natural history data [10–14], consensus guideline definitions evolved [15, 16]. The first consensus guidelines published in 2007 distinguished gastroesophageal reflux disease (GERD) from EoE [15]. However, after Ngo et al. [17] reported a case series of three patients responding endoscopically and histologically to PPI therapy, a new form of the disease evolved, termed "PPI-responsive esophageal eosinophilia (PPI-REE)." According to the second EoE consensus statement published in 2011, "EoE is a clinicopathological diagnosis defined as symptoms related to esophageal dysfunction, >15 eosinophils per high-power field, eosinophilia that persists after a trial of PPI therapy, and exclusion of other secondary causes of esophageal eosinophilia" [16].

EoE is currently considered the most common cause of food impaction in young adult and adolescent patients, and second leading cause of chronic esophagitis behind GERD [16]. One prospectively collected study of patients undergoing endoscopy with routine esophageal biopsies reported over 40 % of subjects with dysphagia and 4 % without dysphagia meeting the current histologic definition of EoE (>15 eos/hpf) [18]. One recent review evaluates the previously published epidemiology studies of EoE and estimates the prevalence in the general population to range from 0.5 to 1 case/1,000 persons; the incidence was approximated at 1 out of 10,000 new cases per year and concluded the incidence to be outpacing the increases in recognition [19].

Endoscopically, the features of EoE are quite variable with at least two forms, an inflammatory and a fibrostenotic phenotype [20, 21]. Normal esophageal diameter, edema, whitish exudates, and linear furrows constitute the inflammatory phenotype, whereas fixed rings, narrowing, and esophageal strictures characterize the fibrostenotic phenotype [20–22]. Most patients present with mixed features of these two phenotypes endoscopically [23, 24].

Due to the scarcity in the literature of EoE case series detailing the clinical and phenotypic presentation over time, we retrospectively reviewed our database of EoE patients diagnosed over the past 26 years at the University of South Florida (USF) to assess the potential impact of guideline definitions on disease recognition and separation into inflammatory and fibrostenotic phenotypes.

Methods

Data

For this retrospective cohort study, Institutional Review Board approval was obtained from the University of South Florida (#00008547). All consecutive patients treated between 1988 and 2014 were included from a database of patients who met consensus definition of eosinophilic esophagitis at the University of South Florida Joy McCann Culverhouse Center for Swallowing Disorders in Tampa, Florida. This is a predominantly white patient population found in an urban area serving approximately 2 million people on the central west coast of Florida. All patients experienced the symptoms of esophageal dysfunction, >15 eos/hpf on esophageal biopsy, and did not respond to a 2-month trial of proton pump inhibitor [16]. In addition, other causes of esophageal eosinophilia were ruled out such as GERD, collagen vascular disease, autoimmune processes, or infections. All patients in this database were adults, 18 years or older when first seen in the Swallowing Center.

Data were extracted from patient charts through electronic medical records including patient encounters, endoscopy reports, and pathology records. Information included demographics (age, sex, race), past medical history, age of symptom onset, age of diagnosis, symptom presentation, and time of diagnosis. Delay in diagnosis was defined by subtracting the pre-diagnosis symptom from the time of EoE diagnosis.

Esophageal characteristics during endoscopy were recorded, i.e., edema, exudates, furrows, rings, and narrowing/strictures. As per our Swallowing Center protocols, all patients with any type of dysphagia undergo careful graduated esophageal dilation at their first endoscopy. Esophageal diameter was recorded using the smallest bougie with moderate resistance noted during either Maloney or Savory-Guilliard bougie dilation. We prefer to dilate our EoE patients with bougies rather than through-the-scope balloons and do not look for mucosal tears during or after the procedure. The passage of each dilator is graded for subjective resistance as 0—none, 1—minimal, 2—moderate, and 3—extensive resistance and recorded in the endoscopy record. We chose "moderate" resistance to estimate esophageal diameter realizing it may overestimate stricture size, but eliminates the mild resistance sometimes noted with passage over guide wires or from the bite block. Although subjective, we are confident this technique is more precise than gauging stricture size on the diameter of the endoscope alone.

Pathology reports were reviewed by one of two pathologists experienced with diagnosing EoE and recorded based on location and eosinophil counts (400×, area 0.4 mm^2 per HPF) with the highest density for each biopsy used. Biopsies from patients prior to 2007 EoE guidelines were reviewed retrospectively and previously referenced [25].

Phenotype Definitions

The inflammatory phenotype was defined by an esophageal diameter >17 mm (smallest bougie with moderate

resistance during dilation) and primary endoscopic characteristics of edema, furrows, or exudates [26]. In contrast, the fibrostenotic group had primarily rings/strictures on endoscopy and diameter <17 mm. The cut point for esophageal diameter was set at 17 mm as patients can normally eat a regular diet above this size [27]. PPI-REE was defined using 2011 guideline definitions as patients responding to a PPI dose of 20–40 mg once or twice daily for 8–12 weeks dependent on the patient and chosen PPI [16]. "Responders" were defined as <15 eos/hpf on esophageal biopsy after an 8- to 12-week PPI trial.

Statistical Analysis

The association between dependent and independent variables was assessed using either an independent t test in case of binary and continuous variable and Chi-square test for dichotomous variables comparing pre- and post-first EoE consensus conference diagnosed EoE. For continuous data, the results were summarized as mean difference (MD) and standard deviation (SD). For dichotomous data, results are summarized using odds ratio (OR) and 95 % confidence intervals (CI). The statistical significance was set at 5 %. All data analyses were performed using SPSS version 22.

Results

Population

Seventy-five adult patients met consensus guideline definition for EoE identified between January 1988 and May 2014. The population consisted of 73.3 % males (55/75) with a mean age of 44.2 years and mean age of diagnosis of 38.7 years. The average follow-up on our patients was 5.4 years. Twenty-four percent (18/75) of our patients were diagnosed prior to the first consensus conference meeting.

Patient Characteristics

Table 1 displays the patient characteristics broken into 5-year intervals over 26 years. Of note, there appears to be a linear increase in age of diagnosis with each 5-year increment in decade of diagnosis. In general, age of symptom onset occurred at a younger age in the earlier 5-year intervals compared to the post-consensus years: 14.2 years old (1988–1993) trending upward to 35.7 years old during the more recent time (2012–2014). Delay in diagnosis appeared to decrease overtime with an average delay of 14.2 years (1988–1993) compared to 7.4 years during the 2012–2014 time span. The diameter of the esophagus at the time of diagnosis was less narrowed by 2–3 mm in the more recent time span (2012–2014).

Impact of Consensus Guidelines

There were 18 patients diagnosed prior to the first consensus guideline published in 2007 versus 57 diagnosed subsequently (Table 2). There was a statistically significant change in age of symptom onset when comparing pre- and post-consensus guideline diagnosed patients 18.4 ± 15.2 versus 32.4 ± 15.5 MD 14.0 (95 % CI 5.5–22.4); $p = 0.002$), respectively. Similarly, age of diagnosis was also significantly different between the two groups 41.3 ± 14.3 versus 30.7 ± 10.2 MD 10.6 (95 % CI 4.4, 16.7; $p = 0.001$), respectively. Delay in diagnosis was longer in the pre-consensus group, although this did not reach statistical significance 12.3 ± 7.7 versus 8.2 ± 8.9 MD -4.1 (-8.5, 0.34; $p = 0.07$). The average esophageal diameter of patients diagnosed prior to 2006 was 10.5 ± 2.7 versus 14.3 ± 4.2 mm after recommendations MD 3.8 (95 % CI 2.1–5.5; $p < 0.0001$). Neither BMI nor eosinophil count/hpf (initial or highest count) appeared to change significantly after initial guidelines.

Evolution of Frequency of EoE Phenotypes and PPI-REE

Prior to 2000, all patients seen in our clinic were diagnosed with the fibrostenotic phenotype. The inflammatory phenotype increased from 25 % in year 2000–2005 to 45.7 % in year 2006–2011 after the initial guideline definitions.

Similarly, PPI-REE was not diagnosed prior to 2006, only appearing in a small percentage 8.6 % from 2006 to 2011 compared to 31.8 % after 2012 (see Fig. 1). The trend was statistically significant for all comparisons ($p < 0.0001$). Overall, 8 out of 10 (80 %) of PPI-REE were of the inflammatory phenotype.

Discussion

The standard definition of a "Clinical Practice Guideline" was first described by Field and Lohr in 1990 as: "Systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances." [28] The purpose of guidelines was to help focus appropriate management, highlight the inappropriate variations in standard practices, and bring forth short comings in the existing literature to generate future research.

For eosinophilic esophagitis, the most problematic delay in forming initial diagnostic and treatment guidelines was the limited understanding, sparse recognition, and lack of uniform criteria to define the disease. The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition held the First International Gastrointestinal

Table 1 Demographic and clinical characteristics of patients divided into 5-year intervals from 1988 to 2014

	1988–1993 (N = 7)	1994–1999 (N = 7)	2000–2005 (N = 4)	2006–2011 (N = 35)	2012–2014 (N = 22)
BMI	24.3 ± 2.9	26.2 ± 4.4	26.0 ± 3.0	25.1 ± 6.3	27.3 ± 4.7
Age of symptom onset	14.2 ± 12.5	22.7 ± 18.4	18.3 ± 15.4	30.3 ± 15.6	35.7 ± 15.2
Age of diagnosis	26.1 ± 6.4	35.3 ± 13.4	30.8 ± 7.1	40.2 ± 14.8	43.0 ± 13.4
Delay in diagnosis (years)	11.9 ± 8.0	12.6 ± 8.2	12.5 ± 8.9	8.8 ± 7.1	7.4 ± 11.5
Initial eosinophils/HPF	25.5 ± 0.71	39.7 ± 35.4	63.3 ± 35.1	31.5 ± 36.1	22.2 ± 14.7
Highest eosinophils/HPF	25.5 ± 0.71	61.3 ± 31.3	63.3 ± 35.1	40.1 ± 32.7	39.8 ± 29.4
Esophageal stricture diameter (mm)	11.0 ± 2.3	9.8 ± 2.4	11.0 ± 4.1	13.7 ± 4.2	15.1 ± 4.2

Separation of pre- and post-EoE consensus guidelines; displayed as mean ± standard deviation

BMI body mass index

Table 2 Demographic and clinical characteristics of patients divided into pre- and post-consensus recommendations

	Pre-2006 consensus guidelines (n = 18)	Post-2006 consensus guidelines (n = 57)	MD (95 % CI)	P value
BMI	25.6 ± 3.3	26.0 ± 5.8	0.37 (−2.4,3.1)	0.78
Age of symptom onset	18.4 ± 15.2	32.4 ± 15.5	14.0 (5.5,22.4)	0.002
Age of diagnosis	30.7 ± 10.2	41.3 ± 14.3	10.6 (4.4,16.7)	0.001
Delay in diagnosis (years)	12.3 ± 7.7	8.2 ± 8.9	−4.1 (−8.5,0.34)	0.07
Initial eosinophils per HPF	51.5 ± 34.1	27.7 ± 29.4	−23.8 (−59.5,11.8)	0.15
Highest eosinophils per HPF	54.0 ± 30.6	40.0 ± 31.2	−14.0 (−38.4,10.4)	0.23
Esophageal stricture diameter (mm)	10.5 ± 2.7	14.3 ± 4.2	3.8 (2.1,5.5)	<0.0001

Displayed as mean ± standard deviation

MD mean deviation, *BMI* body mass index

Fig. 1 Phenotype incidence at diagnosis separated in 5-year intervals
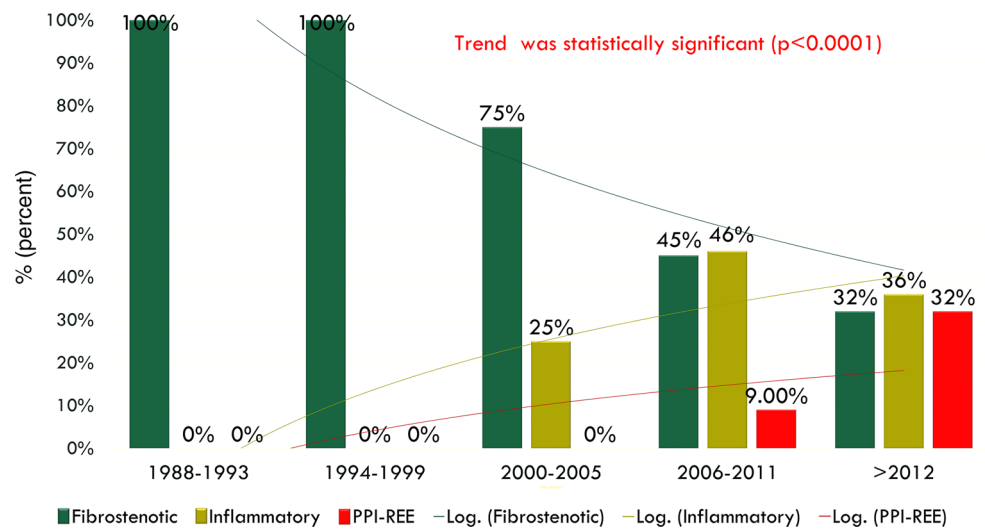
Eosinophil Research Symposium in 2006 at Digestive Disease Week in Orlando, Florida. Later, in 2007, the first consensus recommendations were published, focusing on the clinical experiences of a multidisciplinary team of experts, both clinicians and scientists [15]. Since then, many large prospectively collected studies were published, as well as clinical drug trials strengthening the knowledge of a chronic progressive disease with limited treatment options. After the initial recommendations in 2007, three more guidelines were published based on well-designed prospective studies with fewer flaws and biases [16, 29, 30].

Isolated endoscopic case reports of patients with an EoE like syndrome were first reported as early as the 1960s and 1970s [7, 31, 32]. In 1989, Attwood et al. [33] published an abstract in *Gut* reporting on a group of 15 adults presenting with dysphagia and normal pH tests displaying markedly elevated eosinophil counts, which they named "esophageal asthma." The histologic and phenotypic description of the disease was first described and published by Attwood et al. [8] in 1993 and later by Straumann et al. [9] in 1994. Straumann called this new disease "idiopathic EoE."

As the primary esophageal center in Florida, we began to see along this same time line a similar group of patients (mostly white men) with complaints of debilitating dysphagia, frequent food impactions, and endoscopic findings characterized by multiple rings, generalized narrowing, and strictures. Dr H. Worth Boyce called these patients "congenital esophageal stenosis." Their endoscopic/X-ray features resembled a known pediatric disease associated with fixed esophageal strictures and trachealization, the result of residual tracheobronchial tissue remaining in the esophagus from incomplete esophageal and tracheal separation [1]. During this period, biopsies were primarily obtained from the distal esophagus looking for BE and dysplasia and selectively from ringed/strictured areas. Our pathologists consistently read these biopsies as histology compatible with "reflux esophagitis" or "reflux esophagitis with eosinophilia." [14, 25] Therefore, patients were treated like complicated GERD strictures with PPIs and esophageal dilation, as other options in adult patients were unknown with no guidelines.

We believe the key to early detection of EoE in adults evolved from the 2007 EoE guidelines where the histologic number of eosinophils required for diagnosis (>15 eosinophils/HPF) and multiple biopsies became a part of standard practice [15, 16]. Prior to this time, the common teaching was that eosinophils were a marker of severe GERD [34, 35]. This was based on the investigation published in 1982 by Winters et al. [36] showing in a cohort of patients undergoing esophageal pH testing that prolonged acid reflux correlated with the proximal extent of eosinophils.

Pediatric gastroenterologists began in the early 1990s to take random biopsies from the proximal and distal esophagus, recognizing that inflammatory diseases could be found despite normal appearance to the mucosa [11, 37]. Likely, this contributed to this earlier recognition of EoE than their adult colleagues [11, 12]. After the consensus guidelines in 2007, adult gastroenterologists began to follow the same practice, and simultaneously pathologists increasingly made the diagnosis of EoE. Our review at USF of biopsies from the pre-2006 era confirmed the histologic criteria for EoE in all our patients with "congenital esophageal stenosis" [14] and subsequently the delay in

diagnosis decreased by over 4 years after the consensus guidelines (Table 2).

Many articles in the early 2000s began to focus on the clinicopathological characteristics of EoE. Endoscopic features associated with EoE were described including exudate, furrows, crepe paper esophagus, fixed rings, strictures, and narrowed caliber esophagus [38–40]. Subsequently, the features of EoE began to be described as two phenotypic forms: one with primary endoscopic features of esophageal edema, exudates, and linear furrows defining the inflammatory phenotype, and the second termed fibrostenotic, which was associated with esophageal strictures and fixed rings [20, 41].

At USF, we primarily recognized the fibrostenotic phenotype prior to 2005. This phenomenon may have been a referral bias as many physicians did not know how to treat these patients as well as the inflammatory features of EoE were poorly defined and probably confused with reflux esophagitis. However, the inflammatory phenotype evolved as a common presentation after the 2007 guidelines with recognition of these endoscopic features confirmed by multiple biopsies and histology. The inflammatory phenotype increased from 26 % in those diagnosed with EoE from 2000 to 2005 to around 46 % over the 2006–2011 time span with a reciprocal drop in the percentage of patients presenting with the fibrostenotic phenotype. As shown in Fig. 1, both trends were significant. This is similar to the experience at the University of North Carolina where unpublished data showed only 12 % of patients after 2011 were diagnosed with the fibrostenotic phenotype, 29 % inflammatory, and 59 % mixed compared to 2001 when the fibrostenotic form represented 50 % of cases [42].

Owing to the EoE guidelines, patients are now being recognized earlier with shorter delays in diagnosis. As shown in our 26-year experience, this had a major impact on the severity of esophageal strictures at presentation in our EoE patients. The average esophageal diameter was approximately 10 mm prior to the first consensus guidelines. Over the last 8 years, the average esophageal diameter significantly increased to over 14 mm, despite the degree of mucosal eosinophilia not significantly changing (Table 2). As first suggested by Schoepfer, early diagnosis and treatment interrupts the chronic sequela of eosinophilia inflammation with resulting subepithelial fibrosis [43].

The first consensus guidelines in 2007 distinguished GERD from EoE, but after Ngo et al. [17] first reported a case series of three patients responding endoscopically and histologically to PPI therapy in 2006, the coexisting relationship between the two diseases began to evolve. Several later studies confirmed the existence of patients with clinical symptoms of dysphagia and food impaction and eosinophilia responsive to PPI BID therapy highlighting

this newly recognized form of EoE termed "PPI-responsive esophageal eosinophilia." [44–46] Before 2006 at USF, these patients were given the diagnosis of GERD. Over the next 7 years, patients with PPI-REE tripled from 9 to 32 % after 2012. This is similar to the histologic remission rates currently reported in the literature after a trial of PPI therapy ranging between 33 and 61 % [18, 46–51].

Limitations of this study include the retrospective nature of this study, as well as the difficulty in separating true changes in the disease presentation of EoE (i.e., a shift from fibrostenotic to inflammatory) from changes related to different reporting of previously existing findings based on increased awareness and, potentially, on improved scope optics/imaging/technology. Strengths include a 26-year observation period of EoE and the steady change in phenotype over this time frame.

Conclusions

Before the consensus guideline recommendations in 2007, early detection of EoE prior to severe esophageal stricturing was uncommon. Over the past decade, EoE has become a common cause of dysphagia with the inflammatory disease predominating as the primary phenotype seen at the time of diagnosis. Treatments have improved, and one-third of patients experienced resolution of their eosinophilia with BID PPIs. Our study has assessed the impact of guideline definitions on EoE patients over the past 26 years at our institution and demonstrates the success of the immense research focused on a relatively new disease.

Conflict of interest None.

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