

Correlation between eosinophilic oesophagitis and aeroallergens

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SUMMARY

Background

Aeroallergens have been implicated in the pathogenesis of eosinophilic oesophagitis.

Aim

To determine whether a seasonal variation exists in the diagnoses of eosinophilic oesophagitis and whether there is a correlation with seasonal pollen count.

Methods

A retrospective review was performed from January 2006 to November 2008 to identify eosinophilic oesophagitis patients. Cases were classified by endoscopic date. Daily pollen counts for grass, trees and weeds were obtained from a certified counting station. Per cent of eosinophilic oesophagitis cases were collated seasonally and compared with mean pollen counts for grass, trees and weeds during the same time period.

Results

A total of 127 eosinophilic oesophagitis cases were identified (median age 41, range 19–92 years, 84% men). The highest percentage of cases (33.0%; Binomial $P = 0.022$) was diagnosed in the spring, while the least percentage (16%; Binomial $P = 0.010$) occurred in the winter. There was a significant association between per cent eosinophilic oesophagitis cases diagnosed seasonally and mean grass pollen count ($r_s = 1.000$, $P < 0.01$), but not with trees ($r_s = 0.400$, $P = 0.600$) or weeds ($r_s = 0.800$, $P = 0.200$).

Conclusions

A seasonal variation was seen in the diagnosis of eosinophilic oesophagitis which correlated with pollen counts. These findings have important implications regarding the pathogenesis of eosinophilic oesophagitis, suggesting a potential role for aeroallergens.

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INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic inflammatory disorder characterized by dense eosinophilic infiltration of the oesophageal mucosa.¹ The pathogenesis is incompletely understood; however, an association with allergic disorders such as food allergies, allergic rhinitis, asthma and atopic dermatitis has been well described.^{1–3} Data supporting the relationship with food allergies come predominantly from the paediatric literature where a vast majority of children with EoE have a positive reaction to various foods on skin prick testing.^{2, 4, 5} Additionally, clinical and histological improvement has been reported with elimination and allergy-free diets.^{6–8}

Aeroallergens have also been implicated as a contributing factor in the development of EoE. One study noted that oesophageal eosinophilia developed in a mouse following intranasal introduction of the allergen, *Aspergillus fumigatus*.⁹ Subsequently, Fogg *et al.*¹⁰ described a case report of a young woman with EoE, whose symptoms were exacerbated during pollen season with resolution of symptoms and oesophageal eosinophilia during the winter months. This seasonal distribution in clinical presentation was supported in larger paediatric and adult populations.^{11, 12} If this seasonal variation during times of peak pollen counts is confirmed, this would suggest a role for aeroallergens, such as pollen, in the pathogenesis of EoE.

The purposes of our study were to determine (i) whether a seasonal variation in the diagnosis of EoE exists in our patient population and (ii) whether peak diagnoses correlate with peak tree, grass and weed pollen concentrations in the Washington, DC area.

METHODS

Identifying EoE patients

A retrospective review of our endoscopic database was performed to identify patients with suspected EoE. The database was searched from January 2006 to November 2008 for the key terms 'eosinophilic oesophagitis, dysphagia, food impactions, concentric rings, longitudinal furrows'. Peak oesophageal eosinophil counts of these patients were obtained through review of their pathology report. Inclusion criteria consisted of patients who were 18 years of age or older, with symptoms suggestive of EoE (predominantly dysphagia or food impaction), and oesophageal biopsies

demonstrating a peak eosinophil count of at least 15 eosinophils per 40 times high powered field, which measured 0.19 mm². Cases were classified by season using the date of upper endoscopy. Data regarding demographics and co-existing atopic disorders (allergic rhinitis, food allergies, asthma and atopic dermatitis) was obtained from a detailed chart review of their electronic medical records using ICD-9 codes. This study was approved by the Walter Reed Army Medical Center Institutional Review Board (WU No. 09-7076).

Pollen sampling and obtaining pollen count

Atmospheric sampling for pollen aeroallergens was performed using a volumetric rotating-arm impaction sampler (Model 40 Rotorod Sampler; SDI Company, Plymouth Meeting, PA, USA) according to standards outlined by the National Allergy Bureau, American Academy of Allergy, Asthma and Immunology. The sampler is situated on the roof of a two-storey building, at an elevation of 25 ft above ground level, at the US Centralized Allergen Extract Laboratory, Walter Reed Army Medical Center in Silver Spring, Maryland. The site is in a suburban location surrounded by representative area tree, weed and grass species found in the mid-Atlantic (Table 1).

Two sampling polystyrene 'I' rods (1.52 mm wide × 32 mm long) coated with adhesive silicone grease, were placed in the fixed retracting head of the Rotorod sampler and sampled the air at 274 g. The Rotorod sampling exposure time was set for a 10% sampling period (i.e. 60-s exposure time each 10-min period). Total exposure time for a 24-h period is 144 min. At the end of a 24-h collection period, the sampling rods were removed, mounted on a grooved stage adapter slide and stained with Calberla's solution, a fuchsin pollen stain (glycerol 16.0% vol/vol, ethyl alcohol 33.0% vol/vol and basic fuchsin 0.02% vol/vol). The rods were examined by light microscopy for pollen grains at 400× magnification by a National Allergy Bureau, American Academy of Allergy, Asthma and Immunology certified counter. The sampler was returned yearly to the manufacturer for calibration.

We obtained daily atmospheric pollen concentrations over the same time period (January 2006 to November 2008). Atmospheric pollen concentrations were determined in a standard fashion by dividing the 'raw' pollen count, obtained microscopically from the collecting surfaces of the rods, by the volume of air sampled for the

Table 1. Common area trees, grass and weed species for pollens observed in the Washington, DC area

Family	Area species (common name)
Trees	
Betulaceae	Alder, birch, hazelnut, hornbeam, hop-hornbeam
Cupressaceae	Cedar, cypress, juniper
Fagaceae	Oak, beech
Hamamelidaceae	Sweetgum
Juglandaceae	Hickory, walnut, pecan
Moraceae	Mulberry
Oleaceae	Ash
Pinaceae	Pine, fir, spruce
Platanaceae	Sycamore
Salicaceae	Poplar, cottonwood, aspen, willow
Sapindaceae	Maple, box elder
Tiliaceae	Linden
Ulmaceae	Elm, hackberry
Grass and grass like	
Poaceae	Sweet vernal, grama, brome, bermuda, orchard, bent, fescue, velvet, rye, timothy, june, johnson, crab
Cyperaceae	Sedge
Typhaceae	Cattail
Weeds	
Amaranthaceae/ Chenopodiaceae	Pigweed, lambs quarters
Asteraceae	Ragweed, sage, cocklebur, queen annes lace
Plantaginaceae	Plantain
Polygonaceae	Dock, sorrel
Urticaceae	Nettle

24-h period. The daily pollen count for trees, weed and grass species was reported as the average number of pollen grains per cubic metre (grains/m³) of air for each 24-h sampling period. The mean monthly pollen count for each species was calculated and the results were further collated into four quarters to reflect the four seasons. The distribution was as follows: winter (January to March), spring (April to June), summer (July to September) and fall (October to December).

Statistical analysis

Statistical software package, SPSS version 13 (SPSS Inc., Chicago, IL, USA), was used to collate and analyse the data. Continuous data are expressed as means (standard deviations, s.d.) and categorical data as

percentages. The correlation between the percentage of EoE patients diagnosed monthly and quarterly and the respective mean pollen counts for grass, trees and weeds was analysed with Spearman rank correlation coefficient (r_s). The binomial test was used to evaluate the deviations in distribution of observed EoE patients diagnosed within a time interval (monthly or quarterly) to a theoretically expected distribution, assuming a probability of 0.25. Analysis of variance was used to compare differences in mean eosinophilic counts in proximal and distal oesophagus, mean total number of upper endoscopies and mean total number of clinic visits among the four seasons. A probability value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 127 EoE cases were identified during the study period. Patient demographics, primary indication for upper endoscopy, and history of atopic disorders are listed in Table 2. There were significantly fewer cases identified in the winter months ($P = 0.010$) and significantly more cases identified in the spring time ($P = 0.023$) based on the binomial test assuming equal distribution for each season, i.e. $P = 0.25$). There were no significant differences in the observed versus

Table 2. Demographics, indications for endoscopy and atopic history

Gender, <i>n</i> (%)	
Male	106 (84)
Female	21 (16)
Race, <i>n</i> (%)	
White	104 (82)
Black	13 (10)
Hispanic	9 (7)
Other	1 (1)
Age	
Median (range), years	41 (19–92)
Indications for endoscopy, <i>n</i> (%)	
Dysphagia	88 (69)
Food impaction	18 (14)
Heartburn	17 (13)
Dyspepsia	2 (2)
Nausea	1 (1)
Atypical chest pain	1 (1)
Concomitant atopic disorders, <i>n</i> (%)	
Allergic rhinitis	42 (33)
Food allergies	17 (13)
Asthma	15 (12)
Atopic dermatitis	8 (6)

expected frequency of cases identified in the summer or fall seasons (Figure 1).

Grass pollen was undetectable in the winter. Peak weekly average concentrations for grass pollen are recorded from the third week in May through the first week in June. Seventy-seven per cent of the total annual grass pollen count is observed April through June in the Washington, DC area. Lesser concentrations of grass pollen are noted through October with a small secondary peak noted in September. This secondary peak coincides with the flowering of area weed species. A positive significant correlation was noted between mean grass pollen count and percentage of EoE cases ($P < 0.01$, $r_s = 1.000$), both peaking in the spring time (Figure 2).

Atmospheric concentration of tree pollen was minimal during the winter. Considerable overlapping of flowering periods for numerous area tree species is noted by mid-March. Highest weekly average concentrations for area tree species are generally recorded in the second and third weeks in April. Eighty-four per cent of total annual tree pollen production is noted in the months April–May coinciding with the peak percentage of EoE cases. However, this was not statistically significant ($P = 0.600$, $r_s = 0.400$) (Figure 3). The most abundant allergenic tree pollens observed during the peak months of tree season were from oak, cedar/cypress/juniper, mulberry, birch and maple species.

Weed pollen was undetectable in the winter. While area weed species begin to pollinate in late spring, the highest weekly average concentrations are noted in the August to September time frame. Peak weekly

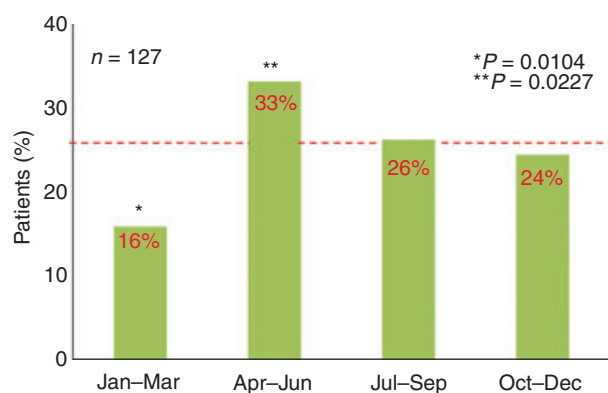


Figure 1. Distribution of eosinophilic oesophagitis (EoE) cases by seasons. Significantly more EoE patients were identified in the spring ($P = 0.02275$) and significantly fewer EoE patients were identified in the winter ($P = 0.0104$).

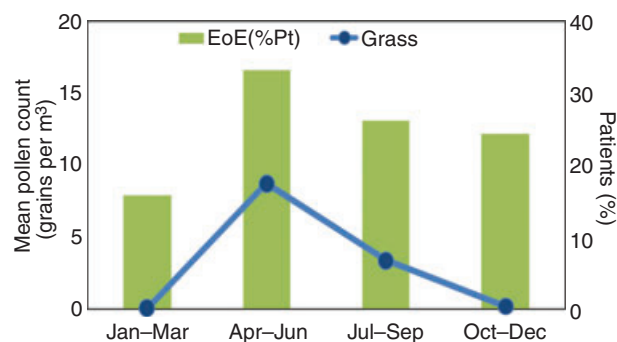


Figure 2. Peak grass pollen count (line graph) significantly correlates with peak percentage of eosinophilic oesophagitis (EoE) patients ($r_s = 1.000$, $P < 0.010$).

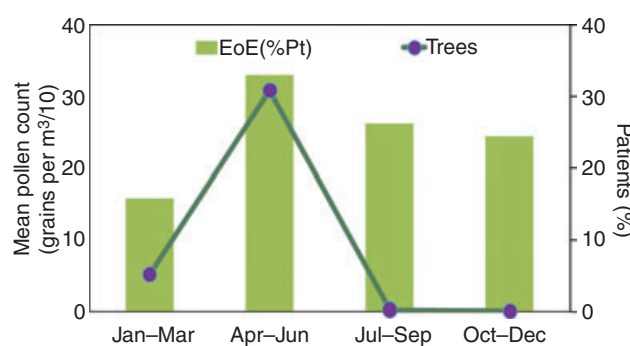


Figure 3. Peak tree pollen count (line graph) in the second quarter coincided with peak percentage of eosinophilic oesophagitis (EoE) cases ($r_s = 0.400$, $P = 0.600$).

average concentrations for ragweed, the area's most prolific weed pollen producer, is recorded from the third week in August to the second week in September. Eighty-five per cent of total annual weed pollen production is observed in the months from July through September in our region. This coincided with the second highest percentage of EoE cases, which was not statistically significant ($P = 0.200$, $r_s = 0.800$; Figure 4).

Interestingly, a greater number of EoE patients with seasonal allergies and atopic dermatitis presented in the spring time. In contrast, asthmatics with EoE more frequently presented in the summer months. The diagnosis of EoE in patients with food allergies was constant throughout the year (Figure 5).

Mean eosinophil counts in the proximal and distal oesophagus were compared across all four seasons. There was no significant difference in mean eosinophil count in the proximal or distal oesophagus among the

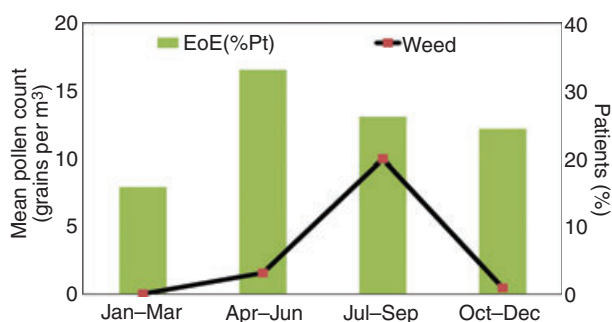


Figure 4. Peak weed pollen count (line graph) occurred in the third quarter and coincided with the second highest percentage of eosinophilic oesophagitis (EoE) cases ($r_s = 0.800$, $P = 0.200$).

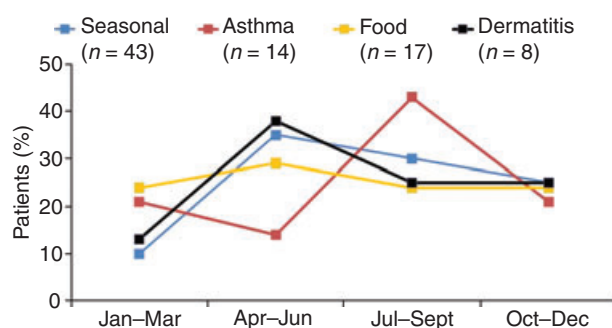


Figure 5. Per cent eosinophilic oesophagitis (EoE) cases diagnosed each quarter based on the type of patient allergies. EoE patients with seasonal allergies and atopic dermatitis were most likely to present in the spring time. Asthmatic EoE patients were more likely to present during the summer months. EoE in patients with food allergies was constant throughout the year.

four seasons. The mean $\pm$ s.d. eosinophil count (units) in the proximal oesophagus was 43 ± 33 , 36 ± 31 , 31 ± 28 , 34 ± 26 ; $P = 0.501$ and in the distal oesophagus was 42 ± 28 , 34 ± 22 , 34 ± 24 , 37 ± 32 ; $P = 0.757$, for the winter, spring, summer and fall seasons respectively (Figure 6).

The monthly variation in the number of upper endoscopies and clinic visits was examined to determine whether this would impact diagnoses of EoE within a season. There was no significant difference in the mean $\pm$ s.d. total number of endoscopies (winter 145 ± 19 , spring 148 ± 12 , summer 137 ± 20 and fall 143 ± 29 ; $P = 0.687$) and clinic visits (winter 589 ± 62 , spring 611 ± 60 , summer 618 ± 75 and fall 575 ± 91 ; $P = 0.591$) among the four seasons.

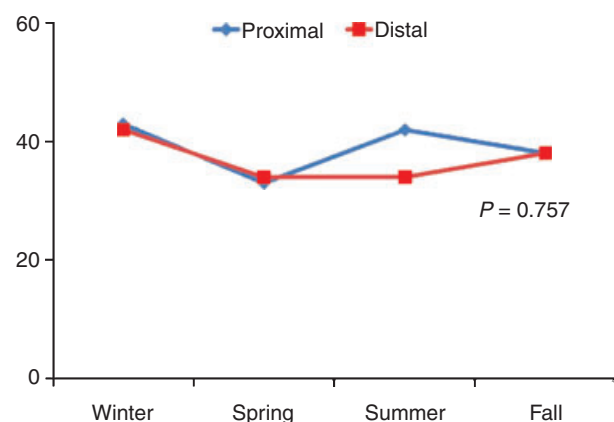


Figure 6. Mean proximal and distal eosinophil counts in the proximal compared across all four seasons. $P = 0.757$.

DISCUSSION

Our study demonstrates that the diagnosis of EoE varies with seasons with most cases diagnosed in the spring months. This is consistent with two previous studies which reported similar findings. The first was a retrospective review of 234 children and young adults (mean age 7 years, range 0.2–19.5 years) over a 6-year period in a paediatric population with EoE.¹¹ Significantly more patients were diagnosed in the spring ($n = 65$, $P = 0.0008$), summer ($n = 69$, $P = 0.0001$) and fall ($n = 58$, $P = 0.0118$). More recently, a seasonal distribution of EoE was noted in an adult population over a 1-year period with significantly more cases ($18/41$, $P < 0.019$) diagnosed during the spring and summer months.¹² In addition to noting the seasonal variation in EoE diagnoses, our study was able to correlate this with the timing of peak atmospheric concentrations for grass pollen in our region. A trend was also seen with tree and weed pollen, but this did not reach statistical significance.

This correlation of high pollen levels with EoE diagnoses suggests that aeroallergens may contribute to the aetiology of this disorder. It remains unclear whether patients with EoE presenting during peak periods for atmospheric pollen concentrations have pre-existing subclinical disease with exacerbation of symptoms during outdoor seasons or may represent entirely new diagnoses of EoE. Although our database does not have information regarding the duration of symptoms, we suspect that several patients' symptoms follow a fluctuating course with exacerbation of symptoms during high pollen months.

A recent study in paediatric EoE patients reported that the intensity of oesophageal eosinophilia was significantly less in the winter months compared with other seasons.¹¹ This suggests that the intensity of oesophageal eosinophilia correlates with severity of symptoms, which has not been supported by other studies. To test this hypothesis further, we also examined oesophageal eosinophilia in EoE patients across the four seasons and found no significant difference in mean eosinophil counts based on the season of diagnosis. Although EoE is a patchy disease,¹³ these results are unlikely to reflect sampling error as it is our practice to take between 5 and 8 oesophageal biopsies from the proximal and distal oesophagus.

Interestingly, EoE was still diagnosed during periods of lower atmospheric pollen concentrations and in patients without a history of atopic diseases, which suggests a multi-factorial pathogenesis. In the paediatric literature, food allergies have been implicated in the pathogenesis of EoE.^{4, 5, 14} In our study, adult EoE patients were more likely to have seasonal allergies than food allergies. This sequential progression of food allergies to allergic rhinitis and asthma over time has been described as the 'atopic march'.^{2, 15} Our data indicate that those with food allergies do not have significant seasonal variation in the diagnosis of EoE. This may be for reasons of minimal change in diet over the course of a year.

In addition to a seasonal variation, our study demonstrates a correlation between the diagnosis of EoE and particular pollen counts in the Washington, DC area. Specifically, grass and tree pollen may be responsible for the peak in diagnoses in the spring months, and weed pollen may contribute to the peak seen during the summer months. These findings support aeroallergen involvement in the pathogenesis of EoE. The idea of allergen sensitization inducing oesophageal eosinophilia was first described in a murine model.⁹ This has also been supported by our study and others that observed adult EoE patients present more frequently during the outdoor or pollen seasons.^{11, 12}

One possible mechanism in the development of EoE from aeroallergens results from deposition of pollen in the nares and pharynx with subsequent swallowing of secretions and introduction into the oesophagus.¹⁰ These aeroallergens bind to antigen presenting cells and activate the cell-mediated immune system. In turn, the bone-marrow upregulates its production of eosinophils via the release of cytokines, particularly, interleukin-5. The eosinophils then migrate exclusively into the oesophagus

and degranulate causing mucosal injury through the release of inflammatory mediators.^{16–20} Another explanation of the development of EoE in allergic patients may be related to the systemic immune response in patients with atopic disorders.^{21, 22} In this hypothesis, the upregulated eosinophils migrate to the nares, airway, skin and oesophagus as part of the same re-circulating pool and are responsible for many of the atopic symptoms.

An association between EoE and atopic disorders has been well described.^{2, 23, 24} Approximately 50% of EoE patients in this study had coexisting atopic diseases (allergic rhinitis, food allergies, asthma, atopic dermatitis). This finding was based on chart review and ICD-9 codes, which may limit the accuracy of this finding. In other studies, 41% (288/709) of subjects with EoE had an atopic disorder.² Most of these patients were children and atopic history was obtained by query. In a recent study in adult patients with EoE, 82% (19/23) had atopic diseases as determined by IgE testing specific to food allergens.³ Interestingly, patients with atopy were less likely to respond to medical treatment in two studies.^{25, 26}

There are several limitations that are inherent in this retrospective study. Our chart review may underestimate the true prevalence of coexisting atopic diseases in patients with EoE; however, approximately 50% of EoE patients in our study were found to have such coexisting diseases, which is consistent with other studies in adult EoE patients.^{1, 12} For patients with a history of atopic disorders, allergy sensitization profile through skin prick testing, atopic patch testing or serum-specific IgE testing was not available. Another limitation is the classification of cases by the date of index endoscopy. This date may not represent the true onset of symptoms. Patients' symptoms may have been present for several days, months or even years prior to undergoing consultation in our clinic and upper endoscopic examination. Exacerbation of symptoms, however, during peak pollen season, may have prompted patients to seek medical attention.

In summary, our study was able to identify a seasonal variation in the diagnosis of EoE in our region. We were also able to correlate the peak number of EoE cases diagnosed during the outdoor months with increased atmospheric pollen concentrations most clearly for grass pollen and, to a lesser degree, with trees and weed pollen concentrations. These findings have important implications regarding the pathogenesis of this disease, as it suggests a distinct role of aeroallergens in the development of this disorder. Future

prospective studies with allergen sensitization testing may help further elucidate the exact relationship between aeroallergens and EoE.

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