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Eosinophilic Esophagitis Through the Flexible Endoscope and the Lens of a Photographer in the Amazon

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Abstract

Eosinophilic esophagitis (EoE) is a disorder that has been identified recently, thus knowledge about it, its pathogenesis, and potential etiologies has spread in an era where the medical community and the public are receiving the information and discussing it as it appears in the medical literature. Because physiology, pathology, and pathophysiology are difficult to explain in layman terms, the author has used photographs taken in remote areas of the Amazon to create visual similes within a narrative that brings the scientific and medical concepts of the knowledge on EoE to a level that allows both medical and non-medical persons to grasp and discuss their significance. This set of photographs when presented to audiences has generated interest in the disorder as well as in the Amazon and its natural flora and fauna. The author hopes that this pictorial introduction sets the stage for the multiple novel topics reviewed and presented in this issue.

Keywords Eosinophilic esophagitis · Eosinophils · Mast cells · Macrophages · Interleukin 5 · Eotaxin · Allergens · Diet · Amazon · Anaconda · Camen · Piranha · Dart frog

The esophagus is an interesting organ that has been thought of as only a conduit of food between the mouth and the stomach. Dysfunction of the esophagus has shown that it is an immunologic organ whose physiologic function is affected by histopathologic abnormalities. Thus, the normal esophagus is more like the body of a snake, or an Amazonian anaconda, distensible, and with peristaltic motion that propels even large bites of food forward (Fig. 1). This normality is maintained by an orderly mucosa which microscopically has short papillae, one layer of basal cells lining the papillae, and being devoid of eosinophils. This normal mucosa when seen during an endoscopy is smooth and transparent, showing the underlying vessels, much like a fresh leaf from the Amazonian forest shows it variegations (Fig. 2). When eosinophilic esophagitis (EoE) sets in, the esophageal mucosa becomes filled with eosinophils (the peak number per high power field required to make a diagnosis has varied from 15 to 24); the basal layers divides and becomes disorderly and the papillae lengthen. When seen endoscopically, the mucosa looks more like a dried leaf with deep furrows (Fig. 3) and the esophagus become stiff like a trunk of a giant tree [1] (Fig. 4). The esophagus functionally now moves slowly more like a sloth than the agile snake and the food gets stuck, generating the symptom of food impaction (Fig. 5). The eosinophils cannot be missed in this disorder, much like the Amazonian giant lily pads, and have imparted their name to the disorder (Fig. 6). The eosinophils, like a piranha, are by their nature destructive, through the release of major basic protein, eosinophil-derived neurotoxin, and eosinophil cationic protein (Fig. 7). Like the dart frogs that release their poison when provoked, the mast cells may release histamine and tryptase and add to the symptomatology (Fig. 8). There are cells lurking in the background, like a camen in the darkness of the Amazonian

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Fig. 1 The normal esophagus is as malleable as an anaconda

night, that contribute to the pathogenesis of EoE. The macrophages release TGF B thought to cause fibrosis and ultimately strictures that lead to dysphagia and food impaction (Figs. 9 and 10).

The symptoms of EoE have been characterized depending on age, being mostly difficulty feeding or food refusal in early infancy, recurrent vomiting in toddlers, abdominal pain in school age children, and food impactions in teenagers and adults. The peculiar issue about EoE diagnosis is that, similar to a raft's engine malfunction in a remote area like an Amazon tributary, help is slow to come. In other terms, there is a distinct delay in diagnosis either because of the symptoms are sporadic and vague or because of a lack of general knowledge about the disorder [2] (Fig. 11).

The question that is hotly debated is: what is the driving force behind all these pathogenic changes in the

Fig. 2 A normal esophagus, seen in endoscopy, is like a fresh leaf, it shows its variegations

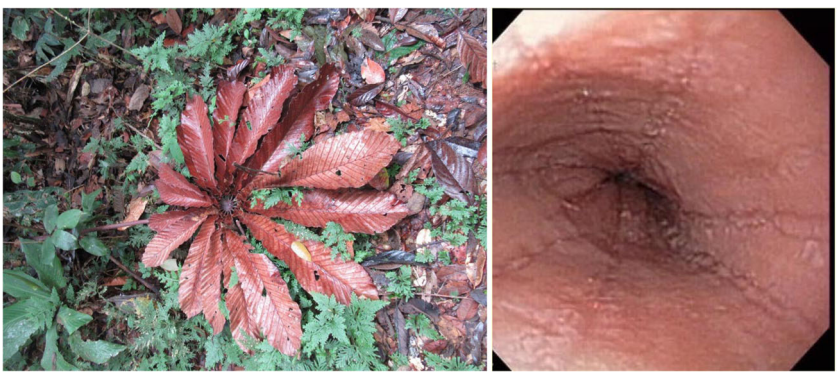

Fig. 3 In eosinophilic esophagitis, the esophagus, seen in endoscopy, looks like this dried leaf

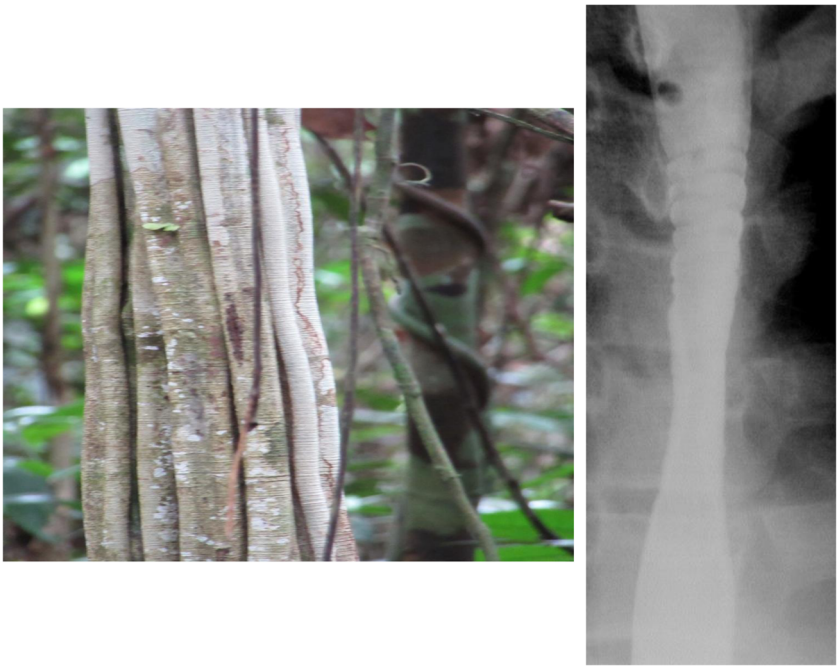

Fig. 4 In eosinophilic esophagitis, the esophagus becomes stiff like the trunk of this giant tree

esophagus? The initial thoughts have been that allergenic triggers coax the eosinophils to the esophagus. The research has concentrated on environmental allergens, for example pollen as seasonal triggers of EoE. Subsequent research redirected the search of a culprit towards food allergens that led to implications on management that will be discussed below.

Whether it is environmental or food allergens, or an endogenous imbalance towards atopy, many of the mediators that lead to tissue eosinophilia have been elucidated. The list is long, but the first contender has been eotaxin 3 which plays a large role in eosinophil development and chemotaxis. Blanchard et al. have shown that, of the eotaxins, only CCL26 is upregulated in patients with EoE, and its expression correlates with eosinophil (and mast cell) levels within esophageal biopsy specimens, indicating a specific contribution in the disease. The levels

Fig. 5 In eosinophilic esophagitis, the esophagus functionally moves slowly more like a sloth, and the food gets stuck

Fig. 6 Much like the Amazonian giant lily pads, the eosinophils cannot be missed, and have imparted their name to the disorder

Fig. 7 The eosinophils, like a piranha, are by their nature destructive, through the release of major basic protein, eosinophil-derived neurotoxin, and eosinophil cationic protein

of CCL26 transcript in a single biopsy specimen are highly sensitive (89%) in distinguishing EoE from control populations [3, 4]. IL-5, which is the main eosinophil chemotactic factor, was also implicated and in fact is one of the few cytokines that has been blocked by a cytokine blocker and the results studied as a proof of concept. In the multicenter trial of the anti-IL 5 mepolizumab, Assa'ad et al. showed that blocking IL-5 results in a remarkable decrease in the peak and mean counts of eosinophils found in esophageal biopsies of children with EoE

Fig. 8 Like a camen lurking in the darkness of the Amazonian night, other cells contribute to the pathogenesis of eosinophilic esophagitis, e.g., macrophages

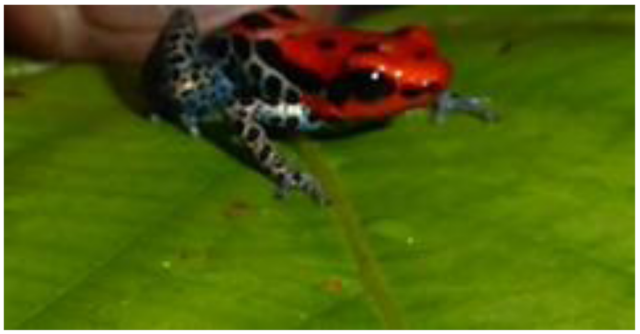

Fig. 9 The Amazonian dart frog releases poison when provoked similar to the mast cell that releases mediators when stimulated

[5]. Subsequently, other cytokines have been shown to play a role, including IL-13 through its effects on CCL26. Sherrill et al. have shown that after IL-13 stimulation ex vivo, epithelial cells production of CCL26 in patients with EoE was upregulated by 279-fold [6]. The cytokine IL-18 was found to be upstream and in vitro stimulated iNKT cells and endothelial cells and induced the eosinophil active cytokines IL-5 and IL-13 [3]. The eosinophils that jump from the circulation to the esophagus are much like the monkeys in the Amazon jumping from one tree to the next (Fig. 12).

The role of foods in EoE and the progression of thinking about it deserves a special attention. Patients with EoE tend to be atopic and testing for food allergens that was done extensively initially led to multiple positive in the majority of patients. From there, the test-directed diets

Fig. 10 Food impaction is one of the most common symptoms of eosinophilic esophagitis

Fig. 11 Help is slow to come in eosinophilic esophagitis and for a broken raft on the Amazon

Fig. 12 Eosinophils moving from the circulation to the esophagus in response to chemotactic factors are like monkeys in the Amazon jumping from one tree to the next

originated, where any food associated with a positive test was eliminated from the diet. Elaborate pathways to re-introduce the eliminated foods were devised to allow a determination of which foods should continue to be eliminated from the diet, and which can be re-introduced. A little while later, the thinking changed to common things are common, and rather than the wide sweep of elimination, and without testing, the six-food elimination diet emerged. These were compared in a retrospective study by Henderson et al., where the performance of the six food elimination diet surpassed the directed diet. Current thinking now is that one or two foods may be the only ones associated with EoE [7]. If we return to our Amazon trip, this would be likened to a flock of birds that gets reduced to a few on the branch and eventually one large bird dominating the tree tops (Fig. 13).

Finally, an important part of the etiology and pathogenesis of EoE is genetic predisposition, first noted by the clinical observation by Collins et al., that multiple members of the same family have EoE. Alexander et al. has shown that among 914 pediatric probands (within 2192 first degree family members), relative risk ratios for EoE in family members range from 10 to 64, depending on the relationship, with higher values for: brothers (64-fold), compared with sisters, fathers (43-fold), compared with mothers, and men (51-fold), compared with women [8]. Much work has been done to identify genes associated with EoE. Hakonarson et al. found four novel-loci significantly associated with EoE. Two of them, STAT6 and c11orf30, previously were found in association with both allergies and autoimmune diseases. Two other gene loci, ANKRD27 and CAPN14, were specific to EoE [9].

In summary, EoE is a multifactorial disorder with varied etiologies and pathogenesis and it is likely that, like all other atopic disorders, patients will in the future be phenotyped according to their genetic and inflammatory profile as well as their sensitizing agents. This patient characterization will be crucial for directed therapies.

Fig. 13 The role of foods in eosinophilic esophagitis is like a the flock of birds that was reduced to only six and finally to only one

Compliance with Ethical Standards

Conflicts of Interest The author declares that she has no conflict of interest.

Ethical Approval and Informed Consent There were no ethical approvals or informed consents needed for this type of work.

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