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Philip E. Putnam

Children who have eosinophilic esophagitis require comprehensive evaluation before treatment and ongoing assessment during treatment. When completed at the appropriate times and under well-controlled circumstances, investigation yields the correct diagnosis, assures recognition of sequelae or recurrence of the inflammation, or confirms whether therapy has been effective. Proper management of each child depends on compulsive follow-up until all of the therapeutic goals have been achieved and the child is on a stable regimen without esophageal inflammation. This article summarizes the issues facing the patient and the physician during this process.

Clinical Evaluation of the Adult who has Eosinophilic Esophagitis 11

Alex Straumann

Eosinophilic esophagitis (EoE) is a rapidly increasing, chronic, T helper 2–type inflammatory disease of the esophagus characterized by esophagus related symptoms and a dense esophageal eosinophilia, both of which are refractory to proton pump inhibitors. The adult patient presents with a typical history of dysphagia for solids and has often experienced food impactions. However the general appearance shows an apparently healthy individual; the physical examination is usually unremarkable. The endoscopic findings are often subtle and misleading. The diagnosis is therefore based on the histologic finding of a dense eosinophilic infiltration of the esophageal mucosa. In adult patients, topical and systemic corticosteroids, leukotriene receptor antagonists, immunomodulators, and dilation have proven efficacy, whereas therapy with diet is still under evaluation.

Eosinophilic Esophagitis

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James P. Franciosi and Chris A. Liacouras

Eosinophilic esophagitis is specific disease that involves an isolated esophageal eosinophilic inflammation and clinical symptoms that do not respond to acid-suppression therapy or are associated with normal esophageal pH monitoring. To establish the diagnosis, upper endoscopy with esophageal biopsies is required. Referral to an allergist and food allergen testing is recommended. Dietary and topical corticosteroid therapies are commonly used and are effective in the majority of patients.

Mechanism of Eosinophilic Esophagitis

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Anil Mishra

Eosinophilic esophagitis (EoE) is a newly recognized disease and is an emerging entity throughout developing and developed countries, including the United States. Therefore, understanding the causes, natural history, diagnosis, and management is important for future therapeutic interventions. The pathogenesis of EoE is still not clear, but a growing body of evidence has established that this condition represents a T-cell-mediated immune response involving several proinflammatory mediators and chemottractants known to regulate eosinophilic accumulation in the esophagus, such as IL-4, IL-5, IL-3 and eotaxin-1, -2, and -3. Determining the mechanism or mechanisms through which human esophageal-derived factors ultimately induce the functional abnormalities observed, and to which antigens patients who have EoE are sensitized that lead to the manifestation of symptoms, is of significant interest.

Putting the Puzzle Together: Epidemiological and Clinical Clues in the Etiology of Eosinophilic Esophagitis

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Peter A.L. Bonis

The cause of eosinophilic esophagitis remains unknown, but its epidemiology and clinical features provide pieces to the puzzle. Eosinophilic esophagitis probably emerged in the 1950s or early 1960s, has an increasing incidence, occurs in most developed countries, is related to food allergies, affects adults and children, has a strong male predominance, clusters in families, and is commonly associated with other allergic and atopic disorders. Several theories have been proposed to explain its evolution, but none has been convincingly demonstrated.

Eosinophilic Gastrointestinal Diseases

Evaluation of the Patient with Suspected Eosinophilic Gastrointestinal Disease 53

David M. Fleischer and Dan Atkins

This article focuses on the evaluation and management of eosinophilic gastrointestinal diseases other than eosinophilic esophagitis. Those diseases include eosinophilic gastritis, gastroenteritis, enteritis, and colitis. The diagnosis of eosinophilic gastrointestinal disease is primarily dependent on the clinical history and histopathology of multiple biopsy specimens after ruling out other causes of intestinal eosinophilia. The diagnosis of eosinophilic gastrointestinal diseases other than eosinophilic esophagitis is complicated by the lack of uniformly accepted diagnostic criteria. Treatment involves evaluation for food sensitivity, elimination diets, and the use of anti-allergy and anti-inflammatory medications with varying degrees of success. Little is known about the natural history of eosinophilic gastrointestinal diseases, underscoring the need for long-term follow-up studies of patients with these disorders.

Clinical Presentation of Feeding Dysfunction in Children with Eosinophilic Gastrointestinal Disease 65

Angela M. Haas and Nancy Creskoff Maune

Feeding issues may affect many aspects of a child's health, development, growth, nutrition and overall well-being. There is a developmental continuum for the acquisition of feeding skills, which includes motor skills, sensory systems, behavioral/emotional components and communication. Food refusal, dysphagia, reduced volume and reduced variety of intake are common complaints associated with eosinophilic gastrointestinal diseases in children. As the understanding of this disease process evolves, clinicians are recognizing that feeding difficulties are a prevalent characteristic of children with eosinophilic gastrointestinal disease and the difficulties can disrupt a child's progress along the typical developmental feeding continuum. Despite effective medical treatment, the residual effects on feeding can persist and need to be addressed. Collaboration regarding the medical, nutritional, and developmental plan of care optimizes outcomes for the well-being of children and families affected by this disease.

Nutritional Management of Children who have Food Allergies and Eosinophilic Esophagitis 77

Catherine M. Santangelo and Emily McCloud

Over the past decade, eosinophilic esophagitis has become increasingly prevalent in the United States. One of the effective treatment approaches

is dietary management, which aims to eliminate exposure to food allergens. Approaches to dietary management include the use of elemental diets, elimination diets, and tailored elimination diets, each of which poses potential nutrition risks. The benefits and potential downsides of each treatment are discussed in detail. Regardless of the diet therapy selected, a complete nutrition assessment by a registered dietitian with expertise in the management of food allergies is recommended for all patients diagnosed with eosinophilic esophagitis.

Association of Eosinophilic Gastrointestinal Disorders with Other Atopic Disorders 85

Soma Jyonouchi, Terri A. Brown-Whitehorn, and Jonathan M. Spergel

Eosinophilic esophagitis is a chronic disease that leads to either persistent symptoms or, at times, intermittent “flares.” It shares many features with other atopic diseases (asthma, allergic rhinitis, and atopic dermatitis), including the following: T helper 2 cells and eosinophils play a critical role in the pathogenesis of the disease; avoidance of allergens promotes remission of disease and symptom control; and locally applied corticosteroids provide control. Finally, most patients who have eosinophilic gastrointestinal disorders have an associated atopic disease.

Psychological Impact of Eosinophilic Esophagitis on Children and Families 99

Mary D. Klinnert

Because eosinophilic esophagitis (EoE) has only recently been recognized and described, systematic research regarding the natural history of the disease and the short- and long-term effects of treatment is in its infancy. Clinical experience indicates that disease symptoms and treatments can have profound effects on the quality of life of affected children and their families. The responses of children and adolescents are variable, and are dependent on developmental level, temperament, and pre-existing psychological adjustment. Although parents of chronically ill children typically experience increased burden and stress, it is possible that the uncertainties currently associated with EoE contribute to even higher levels of anxiety. Research studies are needed to investigate the impact of EoE symptoms and of current treatments on quality of life and psychological adjustment in children and their families.

Histopathology Associated with Eosinophilic Gastrointestinal Diseases 109

Margaret H. Collins

Eosinophilic gastrointestinal diseases (EGIDs) are broadly defined as diseases that characteristically exhibit excessive numbers of eosinophils, in normal and abnormal locations, in one or more gastrointestinal tract

segments. EGIDs have multiple possible etiologies. Pathologists must avoid overdiagnosis of EGIDs by applying site-specific criteria for eosinophil density to mucosal biopsy specimens. Gastroenterologists must avoid contributing to overdiagnosis by submitting biopsy samples from each segment of the gastrointestinal tract separately, especially from the colon where the maximum mucosal eosinophil density in the right side normally exceeds that of the more distal colon. More studies of normal tissue and tissue from patients who are known or suspected to have EGIDs, with clinicopathologic correlations, are required to more fully define the spectrum of histopathology in EGIDs.

Biomarkers for Nononcologic Gastrointestinal Diseases

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Rohit Katial

Biomarkers are objectively measured indicators of normal and abnormal biologic processes and may vary with therapeutic interventions. In the area of gastrointestinal diseases, biomarker research is primarily in the area of cancer biology. Little is known about biomarkers in connection with other gastrointestinal disorders. This article reviews biomarker data for nononcologic gastrointestinal processes with a focus on allergic disorders.

Functional Role of Eosinophils in Gastrointestinal Inflammation

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Simon P. Hogan

Eosinophilic gastrointestinal (GI) diseases (EGIDs) are characterized by a rich eosinophilic inflammation of the GI tract. Clinical and experimental studies suggest that eosinophils have a pathogenic role in EGIDs; however, the function of eosinophils in these diseases remains an enigma. This article describes eosinophil immunoregulatory and effector function and discusses the possible involvement of these pathways in EGIDs.

Chemotactic Factors Associated with Eosinophilic Gastrointestinal Diseases

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Carine Blanchard and Marc E. Rothenberg

The gastrointestinal (GI) tract is in constant negotiation with the microbial flora present in the lumen. Resident hematopoietic cells (ie, lymphocytes, mast cells, and eosinophils) are part of this ongoing and silent homeostatic battle. Eosinophilic GI diseases are characterized by an increased number of eosinophil infiltrates with no identified cause. This article describes the past and present knowledge regarding the chemotactic factors involved in GI eosinophilia.

The Role of Lymphocytes in Eosinophilic Gastrointestinal Disorders

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Mirna Chehade and Hugh A. Sampson

Eosinophilic gastrointestinal diseases (EGIDs) encompass a variety of disorders including eosinophilic esophagitis (EE), eosinophilic gastroenteritis (EG), and eosinophilic colitis. Although the pathogenesis of EGIDs is still poorly understood, dietary food antigens have been shown to cause EGIDs through several short-term clinical studies. The relationship of EGIDs with food allergy points to a potential breach of oral tolerance in EGIDs and to a potentially important role played by lymphocytes in responding to the oral food antigens. This article discusses the concept of oral tolerance, the available evidence for the role that lymphocytes play in the induction and pathogenesis of EGIDs, and the evidence for a potential breach in oral tolerance in EGIDs.

The Role of the High-Affinity IgE Receptor, FcεRI, in Eosinophilic Gastrointestinal Diseases

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Eleonora Dehlink and Edda Fiebiger

Primary eosinophilic gastrointestinal diseases (EGIDs) are a heterogeneous group of diseases including eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis. The unifying hallmark and diagnostic marker of EGIDs is an eosinophil-rich inflammatory infiltrate of the GI mucosa, in the absence of known causes for eosinophilia. The etiology of EGIDs is not yet fully understood. The pathogenesis however seems to involve a complex interplay of genetic predisposition, exposure to food- and environmental allergens and IgE-mediated activation of the immune system. Accumulating evidence relates EGIDs to the group of T-helper (Th) 2 mediated immune disorders, like IgE-mediated allergy. In this article we discuss a possible role of IgE-mediated immune-activation via the high affinity receptor for IgE, FcεRI, in the pathogenesis of primary EGIDs. Beyond its defined role in type I allergic reactions, we here hypothesize that activation of tetrameric FcεRI on mast cells and basophils as well as trimeric FcεRI on human eosinophils and antigen presenting cells in the gastrointestinal mucosa is critically involved in the pathology of EGIDs. We also discuss how IgE-independent triggering of FcεRI could be a mechanisms responsible for activation of the immune system in patients with EGID.

Epithelial Function in Eosinophilic Gastrointestinal Diseases

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Sophie Fillon, Zachary D. Robinson, Sean P. Colgan, and Glenn T. Furuta

Eosinophilic gastrointestinal diseases (EGIDs) are characterized by a wide variety of gastrointestinal symptoms that occur in conjunction with increased numbers of eosinophils in intestinal tissues. With the precise

role or roles of eosinophils in gastrointestinal dysfunction incompletely understood, this subject remains an area of intense investigation. Most studies suggest that the intimate anatomic association of eosinophils with the intestinal epithelium implicates participation in the pathophysiology of EGIDs. This article reviews the limited evidence suggesting that the epithelium and eosinophils interact in the gastrointestinal tract and in other organ systems and describes how the epithelium and eosinophils might participate in gastrointestinal inflammatory diseases.

Role of Tolerance in the Development of Eosinophilic Gastrointestinal Diseases 179

Pooja Varshney and A. Wesley Burks

Although the precise link is not completely understood, eosinophilic gastrointestinal diseases have been shown to be highly associated with atopy. Oral tolerance describes the specific suppression of immune responses to an antigen by prior administration of the antigen by the oral route. Like other allergic gastrointestinal diseases, eosinophilic gastrointestinal disorders may result from a loss of oral tolerance or a failure in the induction of tolerance. Further study to clarify the role of tolerance in the development of eosinophilic gastrointestinal diseases can help identify potential prevention strategies and therapeutic targets.

Exploring the Role of Mast Cells in Eosinophilic Esophagitis 189

Barry K. Wershil

The mast cell plays a critical role in allergic responses in the gastrointestinal tract and other sites. Emerging evidence indicates that mast cells also participate in the pathogenesis of eosinophilic esophagitis, although their precise role has not been defined. This article reviews the biology of mast cells and examines the potential involvement of the cell as an effector of the inflammatory response and tissue remodeling, and as a cell that has the potential to function as an immunomodulator and limit inflammation.

Relationships Between Eosinophilic Inflammation, Tissue Remodeling, and Fibrosis in Eosinophilic Esophagitis 197

Seema S. Aceves and Steven J. Ackerman

The clinical and pathologic features of eosinophilic esophagitis (EE) include extensive tissue remodeling. Increasing evidence supports a key role for the eosinophil in multiple aspects of the esophageal remodeling and fibrosis seen in this allergic disease. This article reviews the clinical implications of esophageal remodeling and fibrosis in EE and discusses the possible pathogenic mechanisms inducing and regulating these

responses. The focus is specifically on eosinophil and cytokine interactions with the esophageal epithelium, vascular endothelium, resident fibroblasts, and smooth muscle. Current and potential therapeutic interventions are discussed that may impact the development or resolution of chronic esophageal remodeling and fibrosis in EE.