Eosinophilic oesophagitis: from the trenches to the frontline

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Idiopathic eosinophilic oesophagitis has been described throughout the world, with the exception of Africa. Although the prevalence of eosinophilic oesophagitis within the general population remains low (0.4–0.7%¹), it appears to be increasing. It is unclear if this is due to increased recognition among gastroenterologists or a true epidemic. A recent database study done within the USA, receiving data from 26 states, reported an increase in prevalence from 0.1% to 1.9% over a 4 year period.² Despite these statistics, eosinophilic oesophagitis is still underdiagnosed. One reason might be that most of the studies on eosinophilic oesophagitis have been published in journals of gastroenterology and allergy and immunology. In this issue of *Frontline Gastroenterology*, Lamb and colleagues³ nicely bring to light this disease with presentation of three characteristic cases and a discussion of the literature (see page 25). The basic characteristics of the disease are discussed and convey an excellent background for the internist on which to make this diagnosis.

There is no question that allergy is a key component in the aetiology of this disease, as supported by several types of data. For example, in children, we know that using an elemental formula (ie, a nutritional formula devoid of food antigens) is virtually 100% effective in this disease, supporting the concept that this disease is mediated by food allergy.^{4,5} It is also becoming more clear through animal models that there may be a two hit hypothesis to this disease, first involving a priming of the allergy pathway with either respiratory or dermatological antigens followed by development of oesophagitis later in life.⁶ Indeed, in patients with this disease, activation of eosinophilic oesophagitis can be preceded for years by respiratory allergies and may precipitated acutely during seasonal allergy season.⁷ Further data supporting an allergic aetiology derive from both animal and human data

demonstrating both an early and delayed hypersensitivity reaction in oesophageal mucosa, the former mediated by a Th-2 pathway.⁸ There are also important data supporting a genetic aetiology. Some of this is derived by the common finding of more than one family member with the disease, in some series supporting an autosomal recessive aetiology.⁸ The most compelling information comes from the laboratory of Dr Marc Rothenberg where an abnormality in the eotaxin-3 gene has been described in close to 50% of children with this disease. This finding may not only be important for identification of the disease but also in understanding its pathophysiology where expression of eotaxin-3 has been shown to be central to eosinophil attraction to the oesophageal mucosa.⁹

The epidemiology of the disease has been further understood from recent US data. Work from the Children's Hospital of Philadelphia has demonstrated that its prevalence is evenly distributed throughout urban, suburban and rural areas that surround a major city. Similarly, data from a generally urban environment such as Chicago¹¹ match closely with data from a mostly rural area such as Southern Minnesota.¹² It is not surprising then that US national data documents occurrence of eosinophilic oesophagitis in almost every state without respect to central or coast or Northern or Southern location.¹³ It is truly a disease indigenous to most environments. It is also becoming clear that although eosinophilic oesophagitis is dominant in white men, larger population studies show this disease occurring commonly in women and in multiple ethnicities, including the Asian population and in African Americans.¹³

Diagnosis of eosinophilic oesophagitis has become more complicated with time. As opposed to the originally proposed standard definition of greater than 15 eosinophils per high power field, it is

clear that this histological definition is neither completely sensitive nor specific for the disease. The lack of sensitivity stems from recent data demonstrating that with extensive eosinophil activation and degranulation, the most demonstrative pathological evidence of eosinophilic oesophagitis may be in finding evidence of eosinophil derived proteins in the oesophageal mucosa rather than eosinophils themselves.¹⁴ The lack of specificity is demonstrated by the finding that other diseases, most commonly reflux, may cause eosinophilic infiltration of the oesophageal mucosa. Ruling out reflux as a cause has become problematic in some cases. Recent guidelines from the American Gastroenterological Association¹⁵ recommended either an empiric trial of proton pump inhibitors twice daily for 2 months followed by repeat endoscopy and biopsy, or performance of ambulatory pH monitoring, although each of these methods have their limitations. Classic endoscopic signs such as linear furrowing (referred to as 'tram track' lesions by Lamb and colleagues) and ring formation have also been found in reflux. Whereas a personal and/or family history of allergy is helpful, they by no means ensure diagnosis. As a result, until perhaps a reliable genetic test is available, it is becoming clear that the diagnosis of eosinophilic oesophagitis will rest on finding a set of compatible clinical, demographic, endoscopic and histological criteria.¹⁶

Treatment for eosinophilic oesophagitis is well described by Lamb and colleagues³ with either a topical or systemic steroid being the mainstay of therapy.^{17–20} Unfortunately, other therapies have not been shown to be clearly as effective. One promising treatment is mepolizumab. This medication seems ideal for the disease for two reasons. The first is that it is specifically an antibody to interleukin 5, an interleukin which has been shown to be central to the pathophysiology of this disease. The second is that it has been shown to be an effective treatment of eosinophilic gastroenteritis, perhaps a sibling or at least a cousin of eosinophilic oesophagitis. Unfortunately, results so far with this drug have been promising but not better than steroids.^{21–22} Certainly, more investigation of this drug is needed. Theoretically, the ideal treatment is the use of an elemental diet. It is almost 100% effective in

children and some data suggest that it helps the oesophagus develop a tolerance to previously identified food allergens.^{4–5} Unfortunately, this diet is not tenable in adults as it is barely palatable, socially isolating and expensive. Another dietary approach might be to avoid food antigens identified on allergy testing to cause the disease in specific patients. Unfortunately, standard skin and serum testing for allergens does not necessarily correspond well with the specific foods that trigger the esophagitis.²³ Furthermore, a multitude of food allergens are commonly identified in individual patients making complete avoidance of them impractical.²⁴

As outlined by Dr Lamb and colleagues, one of the great concerns of this disease is that we do not know the natural history as the longest follow-up trial in adults is 11 years.²⁵ We do know from this and other studies that this is a disease of progressive fibrosis and persistent eosinophilic infiltration of the oesophagus when untreated and perhaps even when treated. As a result, we do not know how aggressive we need to be in monitoring or treating this disease. Is the endpoint control of symptoms or histological remission. Although these might seem one in the same, the long history of this disease in specific patients commonly leads to behavioural adaptation and minimisation of symptoms, despite progression of disease.

As with any new disease, there are many questions and concerns that need to be addressed. For example, there is no evidence of premalignant potential of eosinophilic oesophagitis although one worries about this with any chronic inflammatory disease. It is hoped that the eotaxin gene either alone or in combination with other genetic abnormalities may become the sine qua non for diagnosing this disease but for now we rely on perhaps a scoring system based on numerous criteria. It is an exciting time for oesophagologists and allergists but with articles such as this by Lamb and his colleagues, the gauntlet of challenge in eosinophilic oesophagitis is thrown on the floor of the internist. We welcome your participation in understanding this exciting new disease.

Competing interest None.

Provenance and peer review Commissioned; not externally peer reviewed.

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