EDUCATION IN PRACTICE

A hard act to swallow: modern management of eosinophilic oesophagitis

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ABSTRACT

Eosinophilic oesophagitis (EO) is now established as an important cause of oesophageal symptoms. It is presumed to result from eosinophilic activation to dietary antigens, which is limited to the oesophagus. Inflammatory strictures and secondary dysmotility are common and contribute to symptomatology. Current management involves food exclusion diets and swallowed topical steroid. Strictures may require endoscopic dilatation. Relapse is common but strategies for maintaining remission are not well described. Here we describe a patient with severe stricturing EO, whose symptoms were significantly exacerbated by secondary oesophageal spasm. His symptoms were refractory to dietary, endoscopic and medical therapy including parenteral corticosteroid but responded dramatically to diltiazem. Remission was eventually achieved and maintained with azathioprine, and he was able to discontinue the other therapies and relax his dietary restrictions. We discuss the evidence for dietetic, endoscopic and pharmacological interventions for this disease.

CASE REPORT

A 36-year-old male professional musician presented to the emergency department with a 3-week history of progressive dysphagia to solids more than liquids, localised to the mid-sternum. There was associated severe odynophagia, chest pain and marked weight loss (5.5 kg or 7% of baseline body weight). Further questioning revealed that he had needed to eat slowly since childhood, but had grown accustomed to this.

Past medical history was significant for atopy (seasonal allergic rhinitis, mild predominantly seasonal asthma and oral allergy syndrome). He was otherwise fit and well and on Salbutamol inhalers only.

Oesophagogastroduodenoscopy (OGD) showed features suggestive of EO with

longitudinal furrowing, concentric ridged folds and micro-abscesses (figure 1). A smooth impassable mid-oesophageal stricture was also noted. Oesophageal and stricture biopsies were consistent with EO, with spongiotic squamous epithelium and >25 eosinophils per high power field.

A water-soluble contrast swallow showed a smooth 3.5 cm long mid-oesophageal stricture that was causing mild narrowing only, which was not causing any hold-up. Motility could not be assessed as the patient was reluctant to take adequate mouthfuls.

He was started on swallowed fluticasone (500 mcg twice daily) and high dose proton pump inhibitor (PPI). His symptoms and oral intake failed to improve and he was admitted 2 weeks later with complete dysphagia for nutritional support and further investigation and management.

On admission, he was started on oral corticosteroid (prednisolone 40 mg once daily) and a six food elimination diet (SFED: cow's milk protein, soya, wheat, egg, nuts and seafood) after being assessed by a dietician. Skin prick testing was negative for all common food groups and specific immunoglobulin (Ig)E was positive for wheat only. He was given supplementary elemental feeding by nasogastric tube to meet his daily nutritional requirements. These interventions resulted in only mild symptomatic improvement. He consequently underwent endoscopic balloon dilatation 10 days into his admission, when he was also started on parenteral corticosteroid (hydrocortisone 100 mg four times a day). This also failed to provide any significant sustained improvement.

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Figure 1 Initial oesophagogastroduodenoscopy demonstrating classic ringed and furrowed oesophagus with eosinophilic microabscesses (arrows).

He then underwent oesophageal physiology studies, which showed features consistent with oesophageal spasm (figure 2). He was started on diltiazem

(Tildiem Retard 120 mg twice daily) which resulted in dramatic symptomatic improvement, allowing him to eat and drink a semisolid diet within 3 days. Before discharge he also underwent endoscopic Botox injection since his lower oesophageal sphincter pressure was elevated and did not appear to relax fully, which resulted in some further improvement. On discharge he was managing a soft diet and had regained 1.8 kg in weight. He was discharged on a tapering course of prednisolone, diltiazem, PPI and swallowed fluticasone. He was maintained on SFED with elemental liquid food supplements.

Over the next 3 months, he was followed up closely in both the gastroenterology and dietetic outpatient clinics. His prednisolone, fluticasone and diltiazem were weaned after 4 weeks. One week later, he re-introduced dairy foods to his diet and his dysphagia returned, although he was able to meet his dietary requirements and was continuing to gain weight. Endoscopic and histological reassessment 3 weeks after restarting dairy confirmed moderately severe active disease. There was some symptomatic improvement after re-excluding dairy after his endoscopy, when he was started on another course of swallowed

Figure 2 High resolution oesophageal manometry showed low amplitude simultaneous contractions (arrows) as well as long duration, high amplitude propagated contractions. The lower oesophageal sphincter pressure was elevated and did not appear to fully relax on some of the swallows (arrowheads). Manometric findings are suggestive of a spasm variant found in patients with eosinophilic oesophagitis.

fluticasone. After this again failed to control his symptoms he was restarted on diltiazem, which again resulted in prompt improvement.

A month later his symptoms remained inadequately controlled on diltiazem and fluticasone, and he was unable to wean himself off the swallowed steroid, despite strict adherence to his exclusion diet. He was therefore started on azathioprine at a dose of 2 mg/kg.

Over the next 2 months, his symptoms improved to such an extent that he was able to stop his swallowed steroid and diltiazem, and was gradually able to relax his exclusion diet. He has now been symptomatically in remission with an unrestricted diet for almost 2 years on azathioprine. Interestingly, his hay fever and asthma are now also much less problematic since starting azathioprine.

DISCUSSION

Our patient highlights several points in the management of EO. He was initially tried on first line medical and dietary therapy, which was unsuccessful. Endoscopic dilatation was also ineffective. The presence of stricturing disease suggests that he had been suffering from the condition for many years prior to his presentation; consistent with this he had learned to live with poor swallowing. He was shown to have significant oesophageal dysmotility (possibly due to refractory underlying inflammation) which responded rapidly to diltiazem, suggesting that dysmotility was the predominant cause of his symptoms during this presentation. Given the severity of his disease and the difficulties in controlling his symptoms he was started on immunosuppressive therapy, which has resulted in long-term remission and apparently improved his allergenic tolerance.

Evidence for exclusion diets

Standard treatment of EO consists of food exclusion diets with or without pharmacological therapy. Most evidence for dietary restriction is from retrospective paediatric cohorts, with a few small prospective studies in adults. Studies in children suggest that SFED and strict elemental diets are similarly efficacious, although SFED is significantly more palatable and results in better compliance.¹ A prospective study in adults has shown excellent symptomatic and histological response following SFED.² This study also demonstrated symptomatic and histological relapse following the re-introduction of dietary triggers. Elemental diets in adults have not been studied. Close dietetic care and follow-up are essential to ensure compliance and adequate nutritional intake as well as directing dietary elimination and re-introduction of unoffending foods.

Tests for food allergy triggers

This case highlights the problems with trying to create a rational dietary exclusion diet. A panel of food allergy tests was positive for wheat only, whereas he

was symptomatically sensitive to milk. Identifying triggering dietary allergens would allow rational dietary therapy, limit poor compliance due to poor palatability and limit potential protein-energy malnutrition due to restricted food group intake. Unfortunately, no good test for dietary triggers exists, and the best 'test' remains a trial of dietary elimination +/- re-introduction.² Endoscopy with repeat biopsies can be considered for objective confirmation if appropriate. Skin prick testing is positive in less than 15% patients with causal food identified.² Specific IgE and patch testing are similarly insensitive and non-specific due to unrelated coexisting food/environmental allergies that are commonly present.³

Strictures and their management in EO

There is evidence that duration of disease is associated with stricture development.⁴ Inflammatory strictures may respond to dietary and pharmacological therapy. Endoscopic dilatation is however commonly required because of symptom severity and/or lack of response to first line therapy. Initial case series suggested a very high rate of deep mucosal tears or oesophageal perforation associated with endoscopic dilatation or even simple diagnostic endoscopy. Modern case series and meta-analyses however confirm that complications following dilatation are similar to dilatation for other benign diseases (0.1%–0.2%).⁵ Superficial tears are characteristic because of the friable mucosa, as in this case (figure 3), but not a concern. As with dilatation for other diseases, dilatation should be performed cautiously, no more than 3 mm per session.

Second line treatments and maintenance of remission

Pharmacological therapy has also been better studied in children. The majority of patients respond to dietary modification and/or swallowed topical

Figure 3 Superficial mucosal tear after balloon dilatation.

steroid.⁶ Our patient was refractory to first line therapy, and was sequentially treated with oral and then intravenous corticosteroid. In children, systemic corticosteroid may be marginally more effective than topical preparations, and results in greater histological improvement.⁷ There is no benefit in relapse rates, however, and is associated with the normal side effects of systemic steroid administration. There are no published data on the efficacy of parenteral as opposed to oral corticosteroid, although our patient did not appear to benefit from intravenous hydrocortisone.

EO as a rule recurs after treatment (dietary and/or pharmacological) withdrawal.⁷⁻⁸ There is some evidence that topical steroid maintains symptomatic remission, although it fails to fully suppress eosinophilic inflammation.⁹ Azathioprine has previously been successfully used in steroid dependent EO.¹⁰ There are however no published data on pharmacological treatment in steroid resistant/refractory EO, and to our knowledge this is the first successful use of azathioprine in steroid refractory EO. Biological therapies targeting the underlying immunological pathway, such as the IL-5 antagonists mepolizumab and reslizumab, result in histological but not symptomatic improvement.¹¹⁻¹² Similarly, the leukotriene antagonist montelukast has been studied in small case series only, and has not been shown to be effective.¹³

Dysmotility in EO

Our patient demonstrates a common finding in EO, namely that dysmotility may be a major contributing factor to symptoms. Dysmotility may be present in up to 60% of cases, and may only be transient, explaining the intermittent nature of symptoms in many patients. Manometric improvement mirrors symptomatic, histological and endoscopic resolution following treatment of the underlying oesophagitis.¹⁴⁻¹⁵

Symptoms of chest pain, dysphagia and food bolus obstruction can exist in the absence of obstructing pathology, and are then likely to be due to associated dysmotility. Dysmotility may be under-recognised, because it tends to improve with treatment of eosinophilic inflammation. Our patient's symptoms were initially attributed to his stricture; however, endoscopic therapy failed to result in any significant improvement and manometry confirmed significant dysmotility. He had dramatic symptomatic improvement with treatment for his dysmotility, although this would not have treated the underlying cause of it. It is likely that thiopurine therapy improved the eosinophilic inflammation, resulting in less dysmotility and allowing him to come off his diltiazem.

The mechanisms underlying dysmotility in EO are poorly understood, but may relate to pathological thickening of the mucosa due to inflammatory eosinophilic infiltrates and/or abnormal smooth muscle and fibroblast contraction due to eosinophilic activation.

SUMMARY AND RECOMMENDATIONS

A recent consensus statement¹⁶ supports the use of dietary exclusion and/or topical steroid for induction and maintenance of remission. Dietary exclusion can be considered as a first line intervention if there is good dietetic support and the patient is motivated. First line pharmacological therapy consists of topical steroid, with systemic steroid reserved for severe cases. Recurrence after treatment cessation (dietary or pharmacological) is invariable and maintenance therapy with topical steroid and/or carefully managed exclusion diet should be considered.

At present, there are no data to support the routine use of immunosuppressive agents or biological treatments in inducing or maintaining remission. However, thiopurine therapy has been used successfully and should be considered in difficult or refractory cases.

Symptomatic strictures can be safely treated by conventional endoscopic methods, if standard precautions and protocols are followed. Patients without significant strictures may be predominantly symptomatic from oesophageal dysmotility secondary to eosinophilic inflammation.

Oesophageal physiology studies or empirical treatments for oesophageal dysmotility should be considered for patients without stricturing who do not gain satisfactory improvement with standard medical therapy or as an early adjunct in patients with severe symptoms.

Learning points

- ▶ The symptoms and underlying inflammation of eosinophilic oesophagitis can usually be managed with well coordinated dietary modification and/or courses of topical steroid, but will generally recur on treatment withdrawal.
- ▶ Symptoms may be due to secondary dysmotility and may respond to empirical treatment, controlling symptoms while diet or anti-inflammatory therapy reduces underlying inflammation.
- ▶ Dietary restriction is effective in maintaining remission but adherence may be difficult. Pharmacological therapies for maintaining remission are imperfect and understudied. There is most experience with topical steroid. Second line immunosuppressants such as thiopurine therapy may be considered in severe or refractory cases.
- ▶ Specialist dietetic support is important to identify possible food triggers, supervise dietary restriction and/or re-introduction, and ensure healthy nutritional intake.
- ▶ Strictures can be safely treated endoscopically.

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