A 20-year-old woman presented to the emergency room of the Pordenone Hospital with a sensation of food impaction after meat ingestion. Over the prior 4 months she had experienced episodes of dysphagia unresponsive to acid-suppressant treatment. Emergency upper gastrointestinal endoscopy revealed a small-caliber esophagus with concentric mucosal rings and the presence of meat bolus in the distal esophageal tract. It was difficult to pass, and resulted in a long and apparently superficial esophageal tear. The meat bolus was broken up with the diathermic loop and pushed into the esophagus. Biopsies were made of the proximal and distal esophageal mucosae. One hour after removing the obstruction, the patient manifested signs of pneumomediastinum, confirmed by the Computed Tomography, which showed a diffuse thickening of the esophageal wall with a small longitudinal tear.

The patient was hospitalized in the Surgery Department, where she recovered quickly and was discharged after ten days. Since the histological exam of the esophageal mucosae had revealed an intense eosinophilic infiltration (> 30 eosinophils (eos)/high power field (HPF)) with the presence of aggregates or microabscesses (aggregate of 4 or more contiguous eosinophils) (Fig. 1), the patient also was evaluated for allergies.

From the medical history it was clear that the patient, from age three to age eight, had suffered allergic bronchial asthma, with house dust mites hypersensitivity, for which subcutaneous immunotherapy had been started, but was suspended after a few months due to the appearance of significant adverse reactions. Subsequently, the patient presented only rhinitis, but for the last two years had been again experiencing dyspnoea, especially during the spring months. Moreover, for at least three years, she experienced oral allergic syndrome (OAS) after eating kiwi, apple, peach, cherry; and also...
had abdominal pains, and vomiting after ingesting walnuts and banana. Skin prick tests (SPT) for aeroallergens showed hypersensitivity to Graminaceae (4+), Compositae (4+), Plantago lanceolata (3+), Betulaceae (4+), Dermatophagoides pteronissinus (3+), rabbit epithelium (3+) and cat epithelium (4+). The SPT for foods showed hypersensitivity to walnuts (3+), banana (3+) and kiwi (3+). All these hypersensitivities were confirmed by measuring the specific IgE (CAP-FEIA, Phadia, Sweden).

After the diagnosis of eosinophilic esophagitis (EE) was done, the patient was placed on a diet free of the foods to which hypersensitivity had been shown, in addition to the fruit that resulted in OAS, and she was treated with methylprednisolone at the dosage of 1.5 mg/Kg/day divided into twice-daily doses for 3 weeks; then she was tapered off this medication over four weeks. At the end of the therapy with steroids, the patient was treated with montelukast 20 mg/day and over two months her digestive symptoms disappeared completely. After seven months from the first episode, she was submitted to a new endoscopic evaluation and the biopsies, conducted at various levels, confirmed the presence of a eosinophilic infiltration (15 eosinophils/HPF). The 24-hour esophageal pH monitoring was normal and the esophageal manometry testing showed normal esophageal motility.

The patient continued the treatment with montelukast for one year and then suspended this therapy. After the course of three years she remained asymptomatic.

The clinical case reported here represents a good paradigm of EE, for its clinical presentation, the co-presence of allergies, the histo-morphological characteristics, its complication, and its response to therapy. It provides, therefore, a valid introduction to a review of the most recent acquisitions relative to an emerging pathology, which has become an important and simulating field of interest for gastroenterologists and allergists alike.

**Definition**

EE as disease entity was first described in 1978 (1) and it is defined as a clinico-pathological disease characterized by esophageal symptoms and dense esophageal eosinophilic infiltration (> 20 eosinophils/HPF) both of which persist despite prolonged treatment with proton pump inhibitors (2). Furthermore it is important to exclude other disorders associated with similar clinical, histological, or endoscopic features, especially gastroesophageal reflux disease (GERD).

**Epidemiology**

The epidemiology of EE has not yet been well defined. At first considered very rare, in the last decade over 100 works have been published on this type of pathology and cases described world-wide include 1000 pediatric cases and 250 cases in adults (3). It is unclear whether this represents heightened awareness and increased testing or a true escalation in incidence. To confirm the first hypothesis is the fact that, with greater awareness of the clinical and histopathological characteristics of this pathology, patients with multiple esophageal rings with intraepithelial eosinophils previously diagnosed as affected by GERD, but who didn't respond to standard acid suppression therapy, can now be classified as possible EE cases (3).

On the other hand, there is some evidence that demonstrates a true escalation in the disease incidence and prevalence. Noel et al. (4) reported a four-fold increase in prevalence among children from Ohio from 2000 to 2003. Straumann and Simon (5) prospectively followed adult patients with EE in Switzerland for a period of 15 years and reported a three-fold increase in the incidence of EE.

There are few epidemiological studies on EE, and they are not definitive, especially due to the absence of well-es-
established diagnostic criteria. Fox et al. (6) estimated that 6.8% of children with esophagitis had EE, while Lia-couras et al. (7) reported EE in 3.4% of children with re-flux symptoms.

Noel et al. (4) suggested in a pediatric population an incidence of 1 per 10,000 and a prevalence of 4.2 per 10,000 children. In adults, one report from Australia (8) identified EE in 19 patients from a population of 198,000 over a 21-month period. Recently, in a study conducted in Sweden on a random population-based sample of 1000 adults with or without esophageal symptoms the prevalence of EE was 0.1% (9).

EE appears to have a male predominance (about 2/3 of cases) both in children (10-13) and adults (8, 14-16) and occurs in all age groups. When EE affects adults, it is usually diagnosed in the third or fourth decade of life (8, 14).

**Pathogenesis**

The pathogenesis of EE is poorly understood, but there is an increasing body of clinical and basic evidence that EE is a disease related to an immune-mediated response triggered by exogenous allergens. Spergel et al. (13) found that 73% of EE patients had positive skin prick tests and 81% had positive patch tests (19% in patients with skin prick test negative). Recently, Sugnanam et al. (17) reported that younger patients with EE showed more IgE and patch sensitization to food, while older patients showed greater IgE sensitization to inhalant allergens. In the same study the prevalence of atopic eczema (55.6%), allergic rhinitis (93.3%) and asthma (66.7%) was significantly increased in the EE cohort as compared with the general Australian population.

If it is clear that there is an association between EE and other forms of atopic diseases, it is not well known as the antigen initiates the inflammatory response (3). There is some evidence that antigen exposure in the esophagus (i.e. foods) may serve as a trigger in some patients. The best support for this theory is that a number of patients will have symptomatic improvement when a food allergen is identified and then eliminated from the diet or when an amino acid-based formula is administered in children (12). On the other hand, there is evidence that antigens outside the esophagus (e.g. aeroallergens) can result in an immune reaction within the esophagus. Mishra et al. (18) developed a murine model of esophageal eosinophilia in which nasal and bronchial sensitization and challenge with the ubiquitous aeroallergen *Aspergillus fumigatus* led to esophageal but not gastric or small intestinal eosinophilia. In humans, there is often an historical and clinical association between environmental allergens and EE (19). Fogg et al. (20), in addition, reported a case of EE that occurred in a patient affected by asthma and rhinoconjunctivitis with pollen hypersensitivity, which presented both symptomatic and histologic exacerbations of EE during high pollen season with resolution during winter months.

Other than the clinical correlation between EE and atopy, evidence is now being accumulated that EE is associated with TH-2 type immuno-response. In particular, increased levels of eosinophil-active TH-2 cytokines (e.g. IL-4, IL-5, IL-13) as well as mast cells are present in the esophagus of patients with EE (21-23) and in addition, experimental models of EE can be induced in mice by means of overexpression of TH-2 cytokines (IL-5, IL-13) (18, 24).

IL-5 is a critical cytokine for differentiation and activation of eosinophils and likely plays a central role in trafficking eosinophils into the esophagus in patients with EE. Indeed, mice devoid of IL-5 or lacking the receptor for IL-5 have a significant reduction in gastrointestinal eosinophils, whereas overexpression of IL-5 can promote eosinophilic accumulation (25).

IL-13, a key mediator of eosinophilic inflammatory pathways, also seems to be important in the recruitment of eosinophils to the esophagus. Mishra et al. (26) and Blanchard et al. (27) demonstrated that direct delivery of murine or human IL-13 into the pulmonary tree induced esophageal eosinophilia, an effect that was blocked with antihuman IL-13 antibody (27). IL-13 induction of EE seems to be dependent on IL-5, eotaxin, and STAT-6 (26).

IL-4, also, has been implicated in eosinophilic accumulation, regulating trafficking and promoting adhesion to endothelium surfaces (28). Taken together, these studies support a role for TH-2 cytokines in the development of EE.

Finally, it has been recently found that the gene encoding eotaxin-3 is highly induced in patients with EE compared with its expression in healthy controls, and there is a single nucleotide polymorphism in the human eotaxin-3 gene associated with disease susceptibility (22). These results suggest that eotaxin-3 is not only an important molecule in the pathogenesis of EE, but that in EE patients there is an alteration in the gene that encodes eotaxin-3, thus implying a genetic susceptibility.
for the development of EE, both in atopic and non-atopic patients (3).

Given that it is not possible to demonstrate a concomitant atopy in all patients with EE, however, it is interesting to report that which emerged from a recent study by Quaglietta et al. (29). Studying a group of 17 youth with EE, they found that 6 were affected by celiac disease, all of whom went into remission after following a gluten-free diet. In addition, a normalization in the eosinophilic count was reported. This association, in part unexpected since celiac disease, in contrast with EE, is a TH-1-type disease, requires additional confirmation and additional histochemical studies. If these associations are confirmed by further studies, it might be possible to conclude that, at least a subgroup of patients with EE and CD have the same initial pathological trigger event. Gluten, by immunological dysregulation, could stimulate both TH-1 and TH-2 reaction and be responsible for two different disorders, characterized by a common esophageal phenotype (29).

Clinical features

The clinical features and the presenting symptoms of EE may be different between children and adults. In children the predominant feature could be one of GERD-like symptoms including heartburn and regurgitation, nausea, vomiting, abdominal pain, dysphagia, and failure to thrive; food impaction is uncommon (11, 30). The characteristic symptoms of EE in adult patients is dysphagia, often accompanied by food impaction that may be the initial symptom. Dysphagia is often noted to be longstanding and resistant to management with acid-reducing medications (15, 16, 31). In adults, although less common than in children, GERD-like symptoms were also reported (range, 7%–100%) as were chest pain (range, 1%–58%) and abdominal pain (range, 3%–25%). Diarrhea and weight loss were reported in some patients. Defining EE presents some problems because the presenting symptoms are similar to those of GERD. However, a subset of patients has obstructive symptoms related to strictures (6). In adults, although less common than in children, GERD-like symptoms were also reported (range, 7%–100%) as chest pain (range, 1%–58%) and abdominal pain (range, 3%–25%). Diarrhea and weight loss were reported in some patients. Defining EE presents some problems because the presenting symptoms are similar to those of GERD. However, although GERD may coexist with EE, acid reflux is likely not important both in children and in adults with EE, and the symptoms and pathologic features intrinsic to EE do not respond to acid suppression treatment (32). The results of 24-hour esophageal pH monitoring are normal in > 90% of children (7) and in 85% to 100% of adults with EE (8, 15, 16). Although basal cell hyperplasia of esophageal mucosa often occurs in EE, as it does in GERD, the distinguishing primary histologic feature of EE is a striking eosinophilia of esophageal mucosa, often with eosinophil microabcesses.

As mentioned previously, the majority of patients with EE have a history of atopic conditions, such as asthma, allergic rhinitis, eczema, atopic dermatitis and food allergy. Recently, Sugnanam (17) demonstrated an age-specific sensitisation profile transition from food allergen sensitivity to inhalant allergen sensitivity as age increases in EE. Interestingly, the same Authors also reported an increased prevalence (10%) of anaphylaxis in the EE population.

Diagnosis

At present EE is diagnosed when suggestive symptoms and endoscopic features are supported by biopsy specimens demonstrating abnormal eosinophilic infiltration of the esophageal mucosa.

Endoscopic features

During endoscopic evaluation, several features characteristic of EE are found in the majority of patients. In one relatively large series (33) the most common endoscopic findings were, in order of frequency: mucosal transient or fixed rings (81%), vertical furrows (74%), strictures (31%), whitish nodules (15%), small calibre (10%) and oedema (8%). Fragile mucosa, or the so called “crêpe paper mucosa” is also found (34).

Esophageal rings have been reported as both radiographic and endoscopic findings in patients with dysphagia and seem to be correlated with the inflammatory process. Gupta et al. (35), indeed, found a high correlation between the endoscopic appearance of vertical lines and the presence of eosinophils on histological examination of esophageal biopsies.

Whitish exudates occurring in patches or distributed along the length of the esophagus (36, 37) resemble mild superficial *Candida albicans* infection. Biopsies from these areas identify the histological correlate of the whitish area as eosinophils located superficially in the esophageal mucosa (6).

The mucosa of EE patients may be unusually fragile, with lesions appearing after minimal trauma. A characteristic feature is extensive longitudinal tears appearing after di-

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lation of EE-mediated strictures, or merely the endoscopy itself (38).
Small-caliber esophagus represents another frequent endoscopic finding, and it is a complication of chronic inflammation associated with esophageal remodelling characterized by increased fibrosis, vascularity, vascular activation linked to eosinophil-derived TGF-β (39, 40, 41).
However, it is important to note that the above-mentioned extensive changes in esophagus structure occur in the absence of mucosal erosion or ulceration and it distinguishes EE from peptic disease.
Finally, it should be emphasised that EE may present with no or minimal macroscopic changes and that the endoscopic appearance is helpful but not diagnostic without a confirmatory biopsy. Therefore, all patients with endoscopic features of EE should have distal and proximal esophageal biopsies to confirm the EE diagnosis.

Histology

The esophagus is normally devoid of eosinophils (42, 43). Even if eosinophilic infiltration of the esophagus is found in other diseases (Tab. 1), it occurs at a lower density than in EE (< 10 eos/HPF). On the contrary, EE is characterized by a dense accumulation of eosinophils in the superficial layer of the esophageal wall and, in same cases, formation of eosinophilic microabscesses. However, the number of eosinophils required for diagnosis remains a matter of debate. Lee (44) was the first to empirically define “marked esophageal eosinophilia” as >10 eos/HPF demonstrated in at least two separate HPF. When Attwood and coworkers (31) reported their case series of EE as a “distinct clinicopathologic syndrome” they defined “high grade” EE as >20 eos/HPF and “low grade” EE as ≤ 20 eos/HPF, but again this was an empiric definition. Since then, their serial study has frequently been used as justification for a diagnostic cut-off point of 20 eos/HPF.

In a recent systematic review of the literature, Dellon et al (45) reported significant variability in diagnostic criteria for EE and concluded that, because of the lack of a common disease definition, conclusions drawn from the cumulative EE literature should be viewed with caution and that a consensus research-quality standard for diagnosis of EE is needed. Another critical point is that the area of an HPF may differ by microscope type from 0.12 to 0.44 mm². This is problematic, because eosinophil density (in eos/mm²) can vary 23-fold when considered in the contest of the range of reported eosinophil count cut-off points (45). However in clinical practice, the diagnosis of EE can be made when suggestive symptoms and endoscopic findings are corroborated with a “significant” (putatively > 20 eos/HPF) esophageal eosinophil infiltration on biopsy, even if, according to rigorous research methodology, such diagnostic imprecision is not acceptable (45).

Since eosinophil infiltration in the esophagus in EE cases may not be homogeneous [i.e, segmental, (46) patchy, (34) or even fluctuating (20)] multiple biopsy specimens from different levels of the esophagus are required. It is important, also, for the differential diagnosis with GERD where the eosinophilic infiltration (< 10 eos/HPF) is present only on the distal esophagus.
Other histological features that are helpful but not essential for the diagnosis include basal zone hyperplasia, increased papillary size, and superficial layering of eosinophils with aggregates or microabscesses.

Treatment

As in diagnosis of EE, also for therapies there is no consensus. In general, the decision on the type of treatment to undertake is based on various factors, such as the age of the patient, the impact of the symptoms and of the treatment on the quality of life, and possible co-morbidity. Treatments determined to be successful in EE are nutritional treatment (specific elimination diet, elemental diets), systemic or topical corticosteroids, leukotriene receptor antagonist, and esophageal dilatation.
Furthermore, important differences in the clinical presentations of eosinophilic esophagitis in children and adults point toward the possible need for different treatment approaches in the two patient populations.

Nutritional treatment

The premise of an elimination diet is the hypothesis that food allergens are the stimulus for the inflammatory re-
sponse, particularly in the pediatric population. Kelly et al. (47) first reported that 10 children with EE documented long-term improvement in their symptoms with an amino acid-based elemental diet. Subsequent studies have confirmed the effectiveness of this intervention in larger groups of pediatric patients. Markowitz et al. (12), indeed, reported that 49 of 51 patients following an elemental diet showed significant improvement of symptoms within 8.5 days, and Spurgel et al. (48) reported that, of 51 children with EE treated with an amino acid-based formula, all but two showed a clinical response. The Authors also demonstrate the utility of the atopy patch test (APT) in addition to the SPT to identify potential allergenic foods. In the largest series to date, Liacouras et al. (49) in a retrospective study reported their findings on 381 patients. Dietary restriction or complete dietary elimination using an amino acid-based formula significantly improved both the clinical symptoms and esophageal histology in 75 and 172 patients, respectively.

There are few data available regarding the efficacy of dietary restrictions in adults. Straumann et al. (14) in a preliminary trial including six adult patients with active EE sensitized to several foods, reported that the elimination diet failed to reduce disease activity.

Nutritional treatments, therefore, seem to be more efficacious in children, where close collaboration between the pediatrician and allergist is essential to identify the presence of potentially allergenic foods. However, in some cases an elemental diet formula is required to induce a remission. A later reintroduction of foods must take into account the results of SPT, APT, and possible measures of specific IgE. Additional studies are needed in adults with the end of establishing the role of the diet in improving symptoms and in reducing eosinophilic infiltration.

Corticosteroids

Corticosteroids, either systemic or topical, have proven to be effective in the treatment of EE.

Liacouras et al. (7) studied a population of 20 children with EE (mean age, 5.8 years). Thirteen patients became asymptomatic and 6 showed marked improvement after a 4-week treatment period of methylprednisolone 1.5 mg/kg/twice daily. At follow-up biopsy, the number of eosinophils per HPF decreased from 34.2 to 1.5. After 12 months, 10 patients required a second course of systemic steroid treatment. Because repeated courses of systemic corticosteroids are associated with an increased risk of adverse effects, some investigators have assessed the efficacy of topical steroids in EE. Faubion et al. (50) treated 4 boys (age 12-13 years) with EE (> 50 eos/HPF) by swallowed fluticasone (220 µg, one puff four times daily). The treatment was given by an inhaler without a spacer and the patients were instructed to swallow after inhalation. The therapy induced a resolution of symptoms within a week. Teitelbaum et al. (11) used fluticasone propionate with marked improvement in symptoms and disappearance of eosinophilic infiltration in the esophagus, as well as of the number of CD3+ and CD8+ cells, in 11 children with EE. The only side effect was esophageal candidiasis (2 patients). Arora et al. (16) evaluated swallowed fluticasone in adults who had had solid food dysphagia for at least 6 years. Therapy for 6 weeks resulted in complete dysphagia relief for a minimum of 4 months. There were no cases of candidiasis and the only adverse effect was a transient dry mouth. Three patients had a relapse of dysphagia after 4 months and they responded well to a repeat topical corticosteroid treatment. Recently, a group of investigators (51) presented their experience with a topical corticosteroid specifically designed for use in EE: topical viscous budesonide (budesonide mixed with sucralose). This suspension may be used in younger or neurologically impaired children who are not able to perform an inhaler puff-and-swallow sequence. They used doses of 1-2 mg per day in 14 pediatric patients with EE. Histologic improvement was documented in 86% of patients following 3-4 months of therapy.

The efficacy of topical versus systemic corticosteroids has been evaluated in a controlled trial in pediatric patients (52). All 20 patients in the prednisone group were asymptomatic at the end of the treatment period compared with 19 of the 22 patients who received fluticasone, implying a slightly better efficacy for prednisone. However, twenty weeks after patients stopped therapy, there was similar relapse (35%) in the two groups. These data suggest that it is preferential to use topical corticosteroid in an attempt to limit side effects.

Leukotriene Receptor Antagonist

Attwood et al. (15) treated eight patients with Montelukast, a selective inhibitor of the leukotriene D4 receptor, at a starting dose of 10 mg/day that was increased if required up to a total of 100 mg daily. They found that 88% of EE patients had complete resolution of their symptoms. Once symptoms relief had been achieved the dose was then reduced to maintenance levels (20-40 mg/day). The patients continued the treatment for 14...
months and no relapse of symptoms has been described while continuing the medication but six patients had recurrence within three weeks of cessation or reduction in medication. Intriguingly, the treatment with Montelukast for more than four months did not change the density of eosinophils, but by blocking the D4 receptor the inflammatory action of these cells is reduced. Therefore, the use of leukotriene receptor antagonist in EE is promising, but needs evaluation in larger controlled studies, to define also the appropriate dosing schedule and the duration of treatment.

Esophageal dilatation

Esophageal strictures in EE are responsive to dilatation (53). However, because of potential risks of esophageal tearing and perforation, dilatation should be performed only in patients who fail medical therapy and have severe dysphagia. Langdon et al. (54, 55) suggests that dilatation proceed with great caution and recommends inspection of the esophagus after the passage of each dilator.

Future directions in EE therapy

As mentioned above, basic evidence supports the role of IL-5 in the eosinophilic infiltration of the esophagus. The effects of anti-IL-5 treatment using mepolizumab, a humanized blocking antibody against IL-5, have been reported in patients with various hyperesoinophilic syndromes, including an 18-year-old man with severe EE, who had been unresponsive to an elimination diet, topical fluticasone, and systemic prednisone (56). After 3 administrations of i.v. mepolizumab (10 mg/kg at 4-week intervals) he presented a marked symptomatic and endoscopic improvement, as well as a >10-fold decrease in esophageal eosinophilic infiltration. However, larger multicenter studies will be needed to address both efficacy and safety concerns before general acceptance of this treatment regimen. Theoretically, anti-IL-13 and anti-eotaxin-3 monoclonal antibody may be the target for future research strategy in the treatment of EE, but at present there is no experimental evidence of their use.

References
