Eosinophilic Esophagitis: A Novel Chronic-Inflammatory Disease of the GI Tract
Falk Symposium 194 (Part I)
XXIII International Bile Acid Meeting
Bile Acids as Signal Integrators and Metabolic Modulators
October 8 – 9, 2014

Falk Symposium 195 (Part II)
Challenges and Management of Liver Cirrhosis
October 10 – 11, 2014

Falk Workshop
Pathophysiology and Treatment of Cholangiocarcinoma
Tübingen, Germany
January 23 – 24, 2014

Falk Symposium 192
IBD 2014: Thinking Out of the Box
Paris, France
May 30 – 31, 2014

Falk Symposium 193
Celiac Disease and Other Small Bowel Disorders
Amsterdam, The Netherlands
September 5 – 6, 2014

VII Falk Gastro-Conference
Freiburg, Germany
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Falk Workshop
The Challenge of Drug-Induced Liver Injury (DILI)
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Falk Symposium 195 (Part II)
Challenges and Management of Liver Cirrhosis
October 10 – 11, 2014
Eosinophilic Esophagitis (EoE), a new syndrome that in all probability did not exist 30 years ago, has so far attracted little attention while its incidence continues to rise. What is known today about the disorder, how to best diagnose it and what treatment options are available were the issues discussed at the International Falk Symposium 189 in Graz.

Difficulties swallowing, especially involving solid foods, up to and including complete obstruction of the esophagus are the cardinal symptoms of eosinophilic esophagitis (EoE). Patients often report considerable difficulty swallowing food, and they often experience the feeling that a morsel of food is lodged in the esophagus. We are dealing with a very real concern because bolus obstruction is one of the central complications of EoE, according to Prof. A. Straumann, Olten. This complication, which is unpredictable in clinical practice, is not only unpleasant, but also dangerous because it can lead to choking or interventionally induced perforations of the esophagus.

The complaints are often not taken seriously, since "solid food dysphagia" is – wrongly – not perceived as a warning sign. The disease is therefore often not diagnosed until after years of suffering. This is not only a nuisance but also involves an inherent risk of stricture formation.
There are now multiple documented instances demonstrating that eosinophilic inflammation of the esophagus, if left untreated, leads to organ change involving stiffening and thickening of the wall and to stricture. Unfortunately, as was made apparent in Graz, in spite of increased incidence and prevalence of EoE, it is not receiving the attention it is due within Europe.

Eosinophilic Esophagitis – the "little sister" of Crohn's disease and ulcerative colitis

The symptoms are caused by a chronic, immune-mediated inflammation of the esophagus. "That makes EoE practically the little sister of Crohn’s disease and ulcerative colitis," commented Prof. Straumann, who along with Prof. S. Attwood, North Shields, first described the syndrome in the early 90s. EoE is characterized by massive infiltration of eosinophilic granulocytes into the epithelium of the esophagus. This is followed by a chronic inflammatory reaction, thickening of the smooth muscle tissue, a remodeling with fibrotic changes to the tissues, and the formation of furrows, rings and strictures, which narrow the lumen of the esophagus. The changes induce an esophageal dysmotility, which in turn explains the characteristic symptom of dysphagia. Additionally, EoE can manifest itself as chest pain, nausea, and reflux.

Males dominate, and even children can be affected

EoE is most prevalent among Caucasians, and is far more often found in males than females, according to Prof. Straumann: “Nearly 75% of patients are males.” The disease most commonly manifests itself in middle age, but can appear at any age and even affect children. There seems to be a genetic predisposition to EoE.

Similar to inflammatory bowel diseases, the disease can clearly be triggered by the interplay of environmental factors and genetic predisposition. Diagnosis is made by the clinical picture, endoscopy, and histology.

Several biopsies, however, are required in order to record the inflammatory lesions, commonly seen in the mucosa as patches.
Closely associated with allergies

There is also a strikingly close association with allergic diseases. About 70% of patients with EoE have atopic symptoms, most exhibit allergic rhinitis, bronchial asthma, or atopic dermatitis. Food allergies dominate in children. Dysphagia often arises after eating certain foods, so diet restriction is often an important means of treatment.

Some have had good experiences with the Six Food Elimination Diet (SFED), on which the patient avoids the 6 most common food allergens that appear to trigger EoE. These include:

- Milk and dairy products (62%)
- Wheat products (29%)
- Eggs (26%)
- Fish and seafood (19%)
- Nuts (17%)
- Soy (14%)

Topical steroids are the treatment of choice

In addition to diet restrictions, drugs can be used to treat EoE. Topical corticosteroids such as budesonide or fluticasone are the drugs of first choice, although they are currently used off-label in this respect. However, the active substance requires long-term administration. Symptoms recur within a few weeks of discontinuation. In severe cases with pronounced stenosis, a further treatment option is endoscopic dilation of strictures.

All the treatments mentioned are empirical and are not evidence-based. “There are still many unanswered questions concerning eosinophilic esophagitis syndrome,” concludes Prof. Straumann.

Poster prizes awarded

3 poster prizes were awarded at the 189th Symposium of the Falk Foundation. The winners are:

1st prize: Javier Molina-Infante, Madrid, for his study "Proton-pump inhibitor-responsive esophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression".

2nd prize: Katie Amsden, Chicago, for her study “Effect of four food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis”.

3rd prize: J. Rodríguez-Sánchez, Valdepeñas, for the study “Remission of eosinophilic esophagitis with an exclusion diet of less than 4 foods: Is this possible?”
Eosinophilic Esophagitis – from principles to treatment

Pronounced remodeling

According to Prof. Dr. Dr. H.-U. Simon, Bern, eosinophilic esophagitis is a chronic immune system disease mediated by T helper cells (Th2 cells). PD Dr. M. Vieth, Bayreuth, suggests it causes typical mucosal lesions. According to Dr. S.S. Aceves, San Diego, the persistent inflammation induces a pronounced remodeling that induces fibrosis, angiogenesis, and strictures. It results in wall stiffness and uncoordinated muscle contractions, causing dysmotility of the esophagus, expressed clinically as dysphagia and carrying the risk of food bolus obstruction. If the disorder is not treated early, according to Prof. Dr. P. Valent, Vienna, there is a risk of considerable organ damage.

Successful treatment with budesonide

Dr. Aceves cites the positive outcomes from administration of budesonide as evidence that inflammatory processes form the basis of the pathogenesis. Studies demonstrate that this topical steroid does not only improve clinical symptoms, but also reduces the eosinophilia. There are also clear indications of regression of fibrosis under the treatment. “This underscores the importance of early diagnosis and treatment,” Dr. Aceves emphasized. This provides the best chance of a regression of structural changes that have already occurred. This was confirmed by Dr. U. von Arnim, Magdeburg, who stated that topical corticosteroids had proved a highly effective treatment for EoE, with symptomatic relief generally correlating with an improvement in the histologic picture.

Despite reports of successful treatment using budesonide, Prof. Straumann cautions that the drug has not received official authorization for treatment of EoE.

Solid foods are often avoided

Since the diagnosis is often delayed, many of those affected have adjusted to their condition. They have gotten used to mostly eating very slowly and chewing food thoroughly. They often avoid solid foods, especially meat, because eating them causes problems. In severe cases, people suffering with EoE subsist on a liquid diet, meaning eating out is a burden or impossible. According to Prof. Dr. S. Attwood, North Shields, they often withdraw socially and their quality of life is severely impaired.

Children and adults present different symptoms

According to Prof. Dr. S. Miehlke, Hamburg and Prof. Dr. N. Gonsalves, Chicago, children generally present a different clinical picture to adults. EoE often manifests itself in infants as a refusal to eat, nausea, abdominal pain, and growth retardation. Besides non-specific stomach aches and nausea, older children often exhibit reflux, loss of appetite, and sleep disorders, while fibrotic lesions such as furrows and strictures and concomitant dysphagia dominate the picture in adults.

Close association with allergies

According to Prof. Dr. D. Simon, Bern, about 70% of patients with EoE also suffer from one or more allergies that frequently precede the onset of EoE. About 60% of adults suffer from allergic rhinitis, nearly 40% from bronchial asthma, and nearly 30% from atopic dermatitis.

This high prevalence of respiratory allergies explains the seasonal peaks in EoE diagnosis, according to Prof. Simon. “Most cases are diagnosed in the months of April and May.” In general, there is a significant increase in cases in the spring and early summer compared to autumn and winter. “There is evidently a relationship to pollen count,” explained Prof. Simon. There is also a direct correlation with food allergies.

Six Food Elimination Diet as treatment

We can derive an alternative to drug treatment from the close association between EoE and allergies. Prof. Dr. N. Gonsalves, Chicago, mentions good experience with an SFED (Six Food Elimination Diet). Patients avoid the consumption of milk and dairy products, foods containing wheat, eggs, fish and seafood, ground nuts and tree nuts as well as soy products.

Providing that they stick closely to the diet, nearly 70% of patients not only enjoy clear relief from symptoms but also an improvement in both histologic and endoscopic findings. “We are seeing recovery in both adults and children,” emphasized Prof. Gonsalves.

That applies to children, according to Dr. A.F. Kagalwalla, Chicago, and to adults with EoE, according to Dr. A.J. Lucendo, Tomelloso.

Do proton pump inhibitors have a therapeutic use?

According to Prof. Dr. D.A. Katzka, Rochester, gastroesophageal reflux disease (GERD) has been shown again and again to be linked to EoE. There are clearly patients who show an improvement in EoE symptoms when treated
with a proton pump inhibitor (PPI). “It’s quite possible that there is a subgroup of EoE patients with a PPI-sensitive phenotype,” emphasized Prof. Katzka. We should assume that nearly 10% of patients classified as having GERD actually have EoE.

According to Dr. Y. Romero, Rochester, the “Mayo Dysphagia Questionnaire” can be a useful means of differentiating the two. It is a structured questionnaire covering a period of 30 days.

PD Dr. A. Schoepfer, Lausanne explained that an activity index that included EoE-specific symptoms differentiated by children and adults would also be useful.

**Clear genetic predisposition**

As with inflammatory bowel diseases, the exact cause of EoE is unknown. However, there are many indications that a pronounced genetic predisposition is involved. This explains why those affected are almost exclusively Caucasians, nearly 70% of patients are male and also the family clustering shown by Dr. C. Blanchard, Lausanne. However, it does not follow a simple Mendelian inheritance pattern. “The genetic component of the disease appears to be very complex,” reported Dr. Blanchard.

**Confirmation of diagnosis by histology**

A suspected diagnosis of EoE can be confirmed by biopsies that demonstrate a relevant eosinophilic inflammation, according to Dr. M.H. Collins, Cincinnati, and Dr. C. Bussmann, Basel. Since the inflammatory response does not generally affect the entire length of the esophagus, multiple biopsies are required, according to Dr. E.S. Dellen, Chapel Hill. Further investigative procedures that can yield supplementary information to exclude other diseases are advisable, according to Prof. Dr. I. Hirano, Chicago. Differential diagnosis can exclude in particular GERD, PPI-sensitive EoE, eosinophilic gastroenteritis, and also Crohn’s disease. In view of the pronounced parallels in pathogenesis, the often seasonal variations in symptoms, and EoE’s close association with respiratory allergies, the presence or lack of bronchial asthma must also be clarified, according to Prof. Dr. J.C. Virchow, Rostock. And an allergy test for EoE patients to further clarify the presence of atopia is absolutely necessary, according to Prof. Dr. B. Ballmer-Weber, Zürich.

**String test as a new diagnostic tool**

Although initial diagnosis is by biopsy and histology, Prof. Dr. G.T. Furuta, Aurora, strongly suggests less invasive or non-invasive techniques during follow-up examinations. Repeated endoscopic examinations with tissue biopsies are a severe strain, especially for children. The string test is one approach to less distressing diagnostic procedures. It was first developed to prove parasitic infection. Simply stated, the procedure involves the patient swallowing a capsule attached to a long thread which then remains in the esophagus overnight. The thread fills with liquid and is removed the next morning. The absorbed liquid can be analyzed and conclusions formed about the inflammatory activity based on the isolated substances.

**EoE – the third chronic-inflammatory disease of the gastrointestinal tract**

According to PD Dr. P. Hruz, Basel, the prevalence of EoE varies by region. Detailed investigations in the USA show a prevalence of 55/100,000 in 2004. The prevalence in Switzerland was 43/100,000 in the same period. Both the USA and Switzerland show a steady increase in the disease since the 90s, according to Dr. Hruz.

In general, it must be assumed that at present in Europe, North America, and Australia there is 1 patient per 2000 – 2500 residents diagnosed with EoE. Prof. Dr. A. Straumann, Olten: “This shows EoE is not as common as asthma or hypertension, for example, but it is by no means a rare disease.” The prevalence corresponds roughly to that for Crohn’s disease. EoE fulfills the classic criteria of chronic-inflammatory bowel disease and we are justified in classifying it as a chronic-inflammatory disease of the gastrointestinal tract along with Crohn’s disease, ulcerative colitis, and microscopic colitis, according to Prof. Straumann.
EoE has since been established as a distinct syndrome

Interview with Prof. Dr. Alex Straumann, Olten

Editor: Professor Straumann, what is the significance of eosinophilic esophagitis as a syndrome?

Professor Straumann: Until 10 years ago, gastroenterologists were still arguing about whether eosinophilic esophagitis even existed. Since then, EoE has been recognized and there is no longer any doubt that it is a distinct syndrome. There are clear diagnostic criteria, and we have several ways to treat it, although they remain largely non-evidence-based. Therefore, there are still uncertainties with respect to EoE, and many unanswered questions remain about the disease.

Editor: Is the significance of EoE sufficiently appreciated?

Professor Straumann: No, in my opinion the disease has been theoretically established, but its importance is still largely underestimated. Swallowing difficulties are not interpreted as warning signals by the general population and unfortunately, not by many physicians either, although an organic disease of the esophagus is almost always behind solid food dysphagia. Patients often adapt to the disability by avoiding foods they have difficulty swallowing.

More than a third of patients are only diagnosed after food bolus obstruction begins, and the patient requires emergency inpatient treatment. In Europe, it still takes about six years for the correct diagnosis following the onset of symptoms. We absolutely must take patient reports of dysphagia more seriously and understand them as a warning signal as well as a potential sign of carcinoma, and arrange the appropriate diagnostic procedures.

Editor: How is it connected to allergic diseases?

Professor Straumann: We see that more than 70% of patients with EoE suffer from allergies. These are mainly food allergies in children, while in adults they are more often respiratory allergies. The cause of the connection is so far unclear; we don’t know whether there is an underlying classical allergy in EoE or whether the connection is due to a barrier disorder caused by the inflammation. In my opinion, there is reason to believe that a barrier disorder is involved, which allows increased penetration of allergens. The observed correlation with allergies has a definite therapeutic importance because we see that prevention of exposure using a targeted diet generally improves the eosinophilic inflammation or even leads to remission.

Editor: With that in mind, do you think EoE ought to be treated by gastroenterologists rather than allergy specialists?

Professor Straumann: That’s an unqualified “yes”. It’s a gastroenterological syndrome and so diagnos-
tic procedures and treatments both naturally belong in that discipline. However, EoE patients should naturally also undergo allergy testing to try to uncover any classical food allergies.

**Editor:**
How do you treat it?

**Professor Straumann:**
Theoretically, we can treat it using an elimination diet, administering topical steroids such as budesonide, and by widening strictures and stenoses using an endoscopic procedure. Personally, I favor drug-based treatments, because many patients cannot stick to the elimination diet which involves avoiding milk, wheat, eggs and other foods.

Naturally, we have to discuss the options with the patient and offer the elimination diet as one treatment possibility if they prefer it to the others.

**Editor:**
How do you treat it with drugs?

**Professor Straumann:**
We know that topical steroids such as budesonide or alternatively fluticasone and ciclesonide are at least as effective as systemic steroids but have significantly fewer side effects. We can treat about 80% of patients satisfactorily using topical steroids. A wide variety of other drugs have been tested, from various categories of anti-allergics to biological agents. Unfortunately, none of the other tested drugs even approached the efficacy of steroids. Complicating this is the fact that so far no drug, not even reliably effective topical corticosteroids, has been officially authorized for treatment of EoE.

Additionally, there is still no special pharmaceutical formulation for topical use in the esophagus. The active substances are therefore dissolved and swallowed after breakfast and before bedtime so they linger in the esophagus as long as possible. Clinical trials of budesonide are currently underway and there is work being done on a special pharmaceutical formulation that can be used topically in the area of the esophagus. That gives us some grounds to hope that there will be advances in treatment in the foreseeable future.

Professor Straumann, thank you very much for the interview.
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