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ORIGINAL ARTICLE

The phenotype of adults with complicated eosinophilic esophagitis is dominated by a 5-year longer diagnostic delay: A population-based study of the DanEoE cohort

Stine D Henriksen,[*,†,‡] Stine K Hansen,[§] Mia Heinesen,[¶] Jacob H Terkelsen,[†,¶] Martin Hollænder,[†,¶] Kasper Bredal,[†,¶] Dorte Melgaard[†,‖,**] and Anne L Krarup[†,§,¶]

[*]Department of Gastrointestinal Surgery, [‡]Clinical Cancer Research Center, [§]Department of Gastroenterology and Hepatology, [¶]Department of Emergency Medicine and Trauma Center, [**]Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, [†]Department of Clinical Medicine, Aalborg University, Aalborg and [‖]North Denmark Regional Hospital, Hjørring, Denmark

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Correspondence
Anne L Krarup, Department of Emergency Medicine and Trauma Center, Hobrovej 18-20, DK-9000 Aalborg, Denmark.
Email: apslk@rn.dk

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Abstract

Background and Aim: The DanEoE is a previously described population- and register-based cohort of 236 adult patients with eosinophilic esophagitis (EoE) in a well-defined Danish region with a population of 580 000 and free medical treatment. The aim of the study was to compare the phenotype and treatment response between EoE patients with complications to patients without complications at diagnosis.

Methods: A retrospective cross-sectional study of the DanEoE cohort's 236 adult EoE patients diagnosed between 2007 and 2017 in the North Denmark Region. Patients were divided into a group who had had complications (dilated or food bolus obstruction [FBO]) before or at the diagnosis, and a group without.

Results: At the diagnostic endoscopy, 61% had never had a complication, and 39% had either had FBO ($n = 77$) or been dilated ($n = 15$). The complicated group had the same mean age at symptom debut (37 [SD = 16] *vs* 37 [SD = 17] years, $P = 1.0$), but were diagnosed significantly later with a resulting longer diagnostic delay (13 [SD = 13] *vs* 7.9 [SD = 11] years, $P = 0.01$). Almost half of all patients were never treated to symptomatic remission (uncomplicated 40%, complicated 49%). The histological remission was not secured in the majority (uncomplicated 68%, complicated 70%). Despite this, <15% of patients with previous FBO experienced this after the diagnosis.

Conclusion: In the population-based DanEoE cohort, results indicated that the complicated EoE phenotype was a patient with a 5-year longer diagnostic delay. In the current study, the complication status did not predict the treatment response.

Introduction

Eosinophilic esophagitis (EoE) is a chronic immune/antigen-mediated esophageal disease, internationally defined in 2007, 2011, and 2018.[1–3] It is characterized clinically by esophageal dysfunction, and histologically by ≥15 eosinophils per high-power field (eos/hpf) in the esophageal mucosa.[1–3] Esophageal dysfunction in adults is most often dysphagia and/or occurrences of food bolus obstruction (FBO).[4] The chronic symptoms of EoE, and especially recurrent FBO, negatively impacts patients' quality of life (QoL), primarily due to disease and choking anxiety.[5] The incidence of EoE, especially among adults, has been increasing drastically in the Western world, to a level now matching that of Crohn's disease.[6–9] In Denmark, Krarup *et al.* reported a 50-fold increase in the incidence of EoE among adults in the North Denmark Region, from year 2007 to 2017, following updated regional guidelines.[10] This would suggest a lack of awareness of the disorder among some clinicians.[10] The delayed diagnosis and subsequently delayed treatment are problematic as studies have found increasing rates of complications, for example, fibrostenosis with increasing diagnostic delay.[4] Furthermore, as esophageal fibrosis increases, distensibility decreases, and the risk of FBO increases.[4] Aside from diagnostic delay having an impact on rates of complications, EoE has been described to have multiple phenotypes (inflammatory, fibrostenotic, mixed), where the fibrostenotic phenotype also increases the risk of complications.[11] The literature suggests that the specific EoE phenotype dictates appropriate treatment.[4] Both the inflammatory and fibrostenotic phenotypes should be treated with proton pump inhibitors (PPI), topical steroids or elimination diets, while the fibrostenotic phenotype may also benefit from supplementary esophageal dilation.[4] It would be beneficial to be able to predict

which EoE patients will develop complications such as FBO, and why, to initiate appropriate treatment quickly, and increase QoL.

Even though EoE is increasingly common, the phenotype of patients developing complications is still not fully elucidated. The aim of this study was to identify and compare EoE patients with complications and their phenotype with that of EoE patients without complications.

Methods

The study database was approved by the Danish Data Protection Agency via the Department of Clinical Medicine, Aalborg University, with ID number 2018-59. The Regional Ethics Committee evaluated the project as not needing ethical approval within Danish law. All hospitals involved approved the study as a quality project with ID number 2017-011259.

Study population. The study was designed as a retrospective, cohort study based on the previously described DanEoE database.[10] Briefly, the cohort is registry-based using SNOMED data of topography and pathology from the Danish pathohistology registry since 1997.[10] All Danish citizens have assigned a unique personal identification number enabling to identify all individuals in a region with esophageal eosinophilia. The personal identification number is linked to all registries in Denmark and to all medical information, which gives ideal possibilities for population-based studies.[12,13] Patients having at least one biopsy coded with both the SNOMED code for inflammation with eosinophilia defined as 15+ eosinophil in one HPF (M47150) and esophagus mucosa (T62010) were included in the DanEoE database; details were published previously.[10]

All patients with esophageal eosinophilia in the North Denmark Region diagnosed between January 1, 2007, and December 31, 2017, with follow up to December 31, 2018 were included in DanEoE. Of the 308 DanEoE patients, 76% ($n = 236$) had EoE (55% purely EoE and 21% EoE+ gastro-esophageal reflux disease [GORD]) and 18% ($n = 54$) had GORD with eosinophilia but not EoE. Via the unique personal identification number, all patient files, histology reports, radiology reports, referral documents, and medication history were reviewed in detail for the current study by two EoE experts.[12,13]

Patient groups. All EoE patients fulfilled the international diagnostic criteria for EoE according to the AGREE 2 consensus.[3] The subgroup "Uncomplicated EoE" was defined as EoE patients who had never had FBO or been dilated before. The subgroup "Complicated EoE" was defined as EoE patients who had either had FBO or been dilated at the diagnosis. Since few patients were dilated, FBO and dilated strictures were both pooled in the complicated EoE group. In addition, subgroup analysis of the complicated EoE group was presented for EoE patients who had been dilated *versus* those not dilated.

Symptoms. If the medical chart stated that the patient was symptom free, this was defined as total symptom resolution.

Table 1 Baseline data of EoE patients in the population-based DanEoE cohort with complications compared with the uncomplicated

Patient group	Uncomplicated EoE	Complicated EoE (FBO or dilated)	Only FBO	Dilated ± FBO	*P*
Descriptive statistics					
Number (% of all EoE patients)	144	92	77	15	
<2011, % of year, number	66%, 4	33%, 2	33%, 2	0%, 0	
2012–2014, % of year, number	56%, 59	44%, 47	35%, 37	9.4%, 10	
2015–2017, % of year, number	66%, 80	34%, 42	31%, 46	3.3%, 4	
Ratio men:women	3.5:1	2.5:1	2.7:1	2:1	
Age at diagnose, mean (SD) years	45 (15)	49 (15)	48 (15)	52 (15)	0.04
Age at symptom debut, mean (SD) years‡	37 (16)	37 (17)	38 (17)	34 (19)	1.0
Diagnostic delay, mean (SD) years‡	7.9 (11)	13 (13)	12 (12)	18 (15)	0.01
Phenotype at the index endoscopy, proportion of group (%), number					
Allergy	38%, 55	32%, 30	30%, 23	47%, 7	0.4
Asthma‡	32%, 36/112	24%, 21/89	23%, 16/74	33%, 5/15	0.2
Dysphagia	91%, 131	99%, 91	100%, 77	93%, $n = 14$	0.01
Comorbid GORD	28%, 41	27%, 25	26%, 20	33%, 5	0.8
Index endoscopy, proportion of group (%), number					
Sedation: none‡	56%, 79	31%, 28	26%, 20	57%, 8	<0.001
Normal macroscopical	31%, 45	32%, 29	35%, 27	13%, 2	0.9
Macroscopic EoE signs	42%, 61	46%, 42	39%, 30	80%, 12†	0.6
Rings or stenosis	28%, 40	37%, 34	29%, 22	80%, 12†	0.1
Esophagitis LA-A + B/LA C + D	17%, 25/0.7%,1	7.6%/, 7/0%, 0	9.1%, 7/0%, 0	0%, 0/0%, 0	0.03
Inflammation at debut, mean (SD) eos/hpf	46 (42)	55 (55)	57 (60)	44 (18)	0.2

†$P < 0.05$ for comparison between uncomplicated, FBO only, and dilated (three groups), but not between complicated and uncomplicated (two groups).

‡Division shows that as the group number decreases, the percentage reflects missing data decrease.

EoE, eosinophilic esophagitis; eos, eosinophilic granulocytes; FBO, food bolus obstruction; GORD, gastro-esophageal reflux disease; hpf, high-power field; *n*, number; PPI, proton pump inhibitor.

Partial symptom resolution was defined as if the chart stated that some residual symptom was present. Symptomatic follow up was defined as an interview by a doctor.

Complications. Complications were defined as FBO requiring a hospital visit or strictures of the esophagus requiring dilations.

These definitions were chosen to increase validity of complications. FBO does not have a definition with regards to duration. To minimize recall bias, FBO solved at home was not included. With regard to strictures and stenosis, there is still not a clear definition nor a clear guideline to describe them endoscopically. This has over time led to many different approaches in the literature. Furthermore, recent studies have shown that the sensitivity and specificity for endoscopy in diagnosing EoE strictures are very poor.[14] For that reason, only those who had strictures severe enough to have undergone dilation were included.

The data in the current study come from clinical practice in the region. Very few patients had a manometry or Barrium swallow performed. If a pathological manometry result or Barrium swallow had been found, and if the results explained the dysphagia, the patient was excluded (e.g. achalasia).[15]

Guidelines during the study period. During the study period, the guidelines changed for PPI treatment, which is reflected in the results. The regional guideline from 2011 to 2014 stated first-line treatment to be Pantoprazol 40 mg × 1 (the only PPI mentioned), and in ultimo 2014 this was changed to Pantoprazol 40 mg × 2. In 2015, the first national EoE guideline was published in Denmark, defining correct PPI treatment to be "standard dose PPI × 2 daily."[16] In the current study, we defined high PPI as the recommended standard dose twice daily.

Statistics. Descriptive statistics were given as median and range (25–75 percentile [IQR]) for continuous variables or mean

Table 2 Treatment of EoE patients in the population-based DanEoE cohort with complications compared with the uncomplicated

Patient group	Uncomplicated EoE $n = 144$	Complicated EoE: FBO or dilated $n = 92$	Only FBO $n = 77$	Dilation ± FBO $n = 15$	*P*
% of patients in group assessed, number					
PPI treated patients	92%, 133/144	91%, 83/91[†]	91%, 69/76[†]	93%, 14/15	0.8
PPI started before EoE diagnosis	4.2%, 6	12%, 11	7.8%, 6	33%, 5	0.03
High dose PPI	49%, 71	51%, 47	52%, 40	47%, 7	0.7
Diet	0.1%, 1	0.0%, 0	0.0%, 0	0.0%, 0	NA
Topical steroids (fluticasone)	24%, 35	30%, 30	27%, 21	60%, 9	0.4
Dose ≥750 μg × 2	46%, 16	54%, 15	52%, 11	44%, 4	0.6
No treatment	6.9%, 10	8.7%, 8	9.1%, 7	6.7%, 1	0.6
Symptomatic follow up on treatment: % of those assessed, number					
Symptomatic follow up on PPI	91%, 121/133	89%, 74/83	87%, 60/69	100%, 14/14	0.6
Completely asymptomatic on PPI	61%, 74/121	51%, 38/74	58%, 35/60	21%, 3/14	0.2
No effect of PPI	17%, 21/121	19%, 14/74	15%, 9/60	36%, 5/14	0.08
Symptomatic follow up on steroids	91%, 32/35	70%, 21/30	66%, 14/21	78%, 7/9	0.08
Completely asymptomatic steroids	59%, 19/32	62%, 13/21	64%, 9/14	57%, 4/7	0.03
No symptomatic effect of steroids	25%, 8/32	4.8%, 1/21	0.0%, 0/14	14%, 1/7	0.06
Histological efficacy of those assessed: % of those assessed, number					
Followed up on PPI, histological	63%, 84/133	65%, 54/83	61%, 42/69	86%, 12/14	0.8
Remission on PPI (<15 eos/hpf)	48%, 40/84	35%, 19/54	41%, 17/42	17%, 2/12	0.2
Followed up on steroids, hist.	43%, 15/35	46%, 13/28	38%, 8/21	56%, 5/9	0.8
Remission on steroids (<15 eos/hpf)	53%, 8/15	62%, 8/13	50%, 4/8	80%, 4/5	0.7
Not treated to proven symptomatic or histologic remission in total					
Never in symptomatic remission (incl. never treated)	40%, 57	49%, 45	49%, 38	47%, 7/15	0.2
Never in histological remission (incl. no histology or not treated)	68%, 98	70%, 64	71%, 55	60%, 9	0.8
Time to remission, median days (IQR)					
Symptomatic remission	53 (16–152), 53	65 (24–98), 32	65 (24–126), 27	64(16–74), 5	0.3
Histologic remission	171 (103–281), 28	166(90–375), 23	166 (93–321), 39	194(77–418), 7	0.6
Complications on treatment					
FBO after diagnosis	NA	13%, 12	11	1	NA
And on treatment	NA	4.4%, 4	4	0	NA
Dilation after diagnosis	NA	5.3%, 5	NA	5	NA
And on treatment	NA	5.3%, 5	NA	5	NA

[†]Lower number due to missing value.

EoE, eosinophilic esophagitis; eos, eosinophilic granulocytes; FBO, food bolus obstruction; hpf, high-power field; IQR, interquartile range; *n*, number; PPI, proton pump inhibitor.

(SD) as appropriate. For categorical variables, counts and percentages were displayed. Comparing the two groups of (i) uncomplicated and (ii) complicated, EoE *t*-test or Kruskal–Wallis tests were used as appropriate. When dividing the complicated group into two, a two-way ANOVA was used. Comparison of proportion between groups was done using the χ^2 test. The data management and statistics were done using SAS enterprise guide 71 (SAS Institute Inc., Cary, NC, USA) and figures using SigmaPlot 11.0 Build 11.1.0.102 (Systat Software Inc., CA, USA).

Results

The complicated EoE patients had a longer diagnostic delay. Table 1 shows the characteristics of the 236 patients with EoE in the North Denmark Region in 2007–2017, where 61% ($n = 144$) were placed in the uncomplicated EoE group as they had never been hospitalized with FBO or had an esophageal dilation. The remaining 39% ($n = 92$) were placed in the complicated EoE group: 77 had had at least one FBO, and the last 15 had been dilated. During the period, the percentage of complicated patients decreased (Table 1). The complicated EoE group had the same mean age at symptom debut (37 [SD = 16] *vs* 37 [SD = 17] years, $P = 1.0$), but they were diagnosed at a significantly older age with a resulting longer diagnostic delay (13 [SD = 13] *vs* 7.9 [SD = 11] years, $P = 0.01$). Per definition, the complicated EoE group had more often rings or stenosis described at the index endoscopy. Furthermore, the complicated group had less often erosive esophagitis (Table 1).

There was no difference in complication rates between EoE subgroups (Table S1, Supporting information).

Symptomatic and histologic remission were secured in less than half of both groups. In Table 2, the treatment specifics are shown for both groups. The treatments started were remarkably similar, except for the complicated EoE group having had PPI prescribed to a slightly higher degree compared with the uncomplicated group (12% *vs* 4.2%, $P = 0.03$). The symptomatic follow up on PPI was high for both groups, but for steroids it was only 60% in the complicated EoE group. Histologic follow-ups were done in 63–65% in the PPI groups, but only 43–46% on topical steroids. In total, 40–49% were never secured in symptomatic remission, and 68–70% never in histological remission (Table 2).

A subgroup analysis of the complicated patients showed that no patient had FBO while in histologic remission. Dilations

Table 3 Complicated patients in the population-based DanEoE cohort divided with regard to achieved histologic remission

Patient group Histological remission (<15 eos/hpf)	Complicated EoE Yes, $n = 28$	Complicated EoE No, $n = 64$	*P*
Follow up time: Mean years (SD)			
Since diagnose	3.2 (1.7), $n = 28$	4.7 (1.8), $n = 64$	<0.001
On PPI	3.3 (2.2), $n = 28$	4.6 (2.2), $n = 52$	0.01
On topical steroid (Fluticasone)	2.6 (1.6), $n = 12$	3.6 (2.3), $n = 18$	0.4
Rings or stenosis described on endoscopy: Proportion of group, *n*			
At diagnose	46%, 13/29	33%, 21/64	0.2
After diagnosis	29%, 7/23	11%, 7/34	0.4
Developed on PPI (none at index)	0%, 0/16	7.0%, 3/43	NA
Ring remission on PPI	39%, 5/13	57%, 12/21	0.4
Developed on topical steroids	9.1%, 1/5	0.0%, 0	NA
Remission on topical steroids	9.1%, 1/5	0.0%, 0	NA
Food bolus obstruction: Proportion of group, *n*			
In total	93%, $n = 27$	88%, $n = 61$	0.4
Before or at diagnosis in total	93%, $n = 27$	88%, $n = 61$	0.5
After diagnosis in total	3.5%, 1	4.5%, 3	0.8
In histological remission at the FBO	0%, 0	0%, 0	NA
Dilations: Proportion of group, *n*			
In total	21%, $n = 6$	17%, $n = 12$	0.7
Before or at diagnosis in total	17%, 5	12%, 8	NA
After index endoscopy	3.5%, 1	7.3%, 5	NA
On treatment	3.5%, 1	7.3%, 5	NA
PPI at the time of dilation	100%, 1	60%, 3	NA
Dose low	100%, 1	100%, 3	NA
Symptomatic efficacy	0%	0%, 3	NA
Histological efficacy	100%, 1	0%, 3	NA
Fluticasone at the time of dilation	0%	60%, 3	NA
Dose low	NA	100%	NA
Symptomatic efficacy	NA	33%, 1	NA
Histological efficacy	NA	0%	NA

EoE, eosinophilic esophagitis; eos, eosinophilic granulocytes; FBO, food bolus obstruction; hpf, high-power field; PPI, proton pump inhibitor.

were rarely done in any of the patients after the index endoscopy, but only one of them were in histologic remission (Table 3).

Discussion

Summary. This is to our knowledge the first study to examine the phenotypes of complicated and uncomplicated EoE in a population-based setting. In this cohort of 236 adult Danish EoE patients, we found that 39% had either had FBO or been dilated at the time of diagnosis. Compared with the patients without complications, the group of patients with complications had the same mean age at symptom debut, but a 5-year longer diagnostic delay. In the group of EoE with complications, 49% were never treated to symptomatic remission, and 70% were never treated to histological remission, *versus* 40% and 68% in the EoE group without complications. Despite this, <15% of patients with previous FBO experienced this after the diagnosis.

Diagnostic delay, stenosis/stricture, and dysphagia. A 5-year longer diagnostic delay was found in the complicated EoE group. This is not surprising as mathematical models suggest that strictures and fibrosis develop over time, and it has been speculated that this may be prevented by early diagnosis and effective treatment.[14] The importance of early diagnosis and treatment is emphasized when looking at the factors influencing QoL among EoE patients. Recurrent food impaction and the symptom duration are two of the most important factors for QoL among EoE patients according to the literature and can both be prevented or limited with shorter diagnostic delay.[5] The assessment of QoL is beyond the scope of this study, but it would be interesting to investigate how the complicated EoE group is affected compared with the uncomplicated group. It is difficult to know how to avoid the diagnostic delay of EoE in the future. However, a diagnostic delay of 10 years in the DanEoE cohort calls for focus on education.[15]

Aside from a longer diagnostic delay, the complicated EoE group also had a higher prevalence of stenosis/stricture and dysphagia at the time of diagnosis compared with the uncomplicated EoE group. This is explained by our definition of complications, as esophageal dilation was used as a proxy for stenosis/stricture, and FBO is an excessive form of dysphagia. There is not yet an international accepted definition of stenosis or stricture. This is partly due to the poor sensitivity and specificity for the clinically available tools, for example, sensitivity of endoscopy of 15%.[14] We therefore chose to use the need for dilation as proxy for fibrostenosis. This will underestimate the true number of fibrostenosis but is the most reliable definition for clinical data as of now. In addition, it is unknown whether the stenosis in these patients solely is due to the EoE or partly is caused by a peptic stricture. The international definition of FBO is also still lacking, but the EoE consensus has previously suggested to use hospitalization as separation from dysphagia, which we used here as well.[2]

Treatment response. The proportion of patients treated with PPI, corticosteroids, and dietary treatment was the same in both the uncomplicated and complicated EoE groups. In the PPI subgroup, however, more patients from the complicated EoE group, compared with the uncomplicated EoE group, were already treated with PPI prior to the diagnosis of EoE. This discrepancy could be due to the longer diagnostic delay found in the complicated EoE group. We speculate that the symptoms of patients in the complicated EoE group were attributed to other diseases, including GORD, for longer than patients in the uncomplicated EoE group. As GORD is treated with PPI, this would lead to more patients being treated with PPI prior to the diagnosis of EoE.

With regard to symptomatic and histological follow up and complete remission rates, only one difference was found between the two groups. Fewer patients from the dilated subgroup of the complicated EoE group achieved complete symptomatic remission on PPI than those from the uncomplicated EoE group. This was not surprising, as symptoms from esophageal stenosis/stricture are well treated with dilations, but the effect is only short-termed and does not lower the amount of esophageal inflammation.[14,17] Apart from this, the aforementioned remission rates were the same in the two groups, and in concordance with published literature.[18] It is worth noting, that in the subgroup treated with corticosteroids, more patients in the complicated EoE group achieved some symptomatic relief than in the uncomplicated EoE group. It is therefore tempting to speculate that EoE patients with complications benefit greater from corticosteroids than those without. However, the strength of this observation is limited by the population size of the corticosteroid subgroup.

When pooling symptomatic and histological remission rates across all treatments, both groups had unsatisfying rates, indicating that both EoE patients with and without complications are treated insufficiently. One caveat to this is that these rates are from the first effective treatment and not after trying multiple treatments, as treatment guidelines recommend when remission is not achieved.

Food bolus obstruction. The study found that only a minority of patients in the complicated EoE group experienced FBO after diagnosis, and even fewer while on medication. This is consistent with data from a Swiss EoE Cohort Study database, where a study demonstrated that an increasing frequency of swallowed topical corticosteroids was associated with a lower risk of FBO during follow up.[19]

It is however still noteworthy, that <15% of the patients with previous FBO did experience additional FBO after diagnosis, when symptomatic and histological remission was only achieved in 51% and 30%, respectively. This could be because patients, after experiencing FBO once or twice before diagnosis, have learned a coping mechanism for future instances. Clinicians in the emergency department use sparkling water and steroids as first-line aid for FBO. Steroids are not available for patients without a prescription, but sparkling water certainly is. Many patients report having sparkling water for emergencies at home. Handstand has also been reported by patients as their go-to maneuver when experiencing FBO. If patients have learned to prevent or terminate an ongoing FBO episode, it is possible that future instances will be dealt with at home by themselves.

Over 90% of all included patients did in fact receive PPI treatment, and almost 30% also advanced to further steroid treatment. It is likely that the treatment has helped, and although not led to a complete remission, a number of patients may have seen some positive histological changes and fewer symptoms, which have lowered the risk of reoccurrences of FBO in the patients.

Macroscopic findings. Almost a third of patients in the study population had normal macroscopic findings. This is

inconsistent with data presented in the literature, where 7–17% of patients had a normal endoscopy with no macroscopic findings.[20] The inconsistency in the results could be due to a difference in sample size, guidelines, and the skill level of the clinician performing the endoscopy, with high-volume centers having more focus and experience in reporting the macroscopic findings of EoE, compared with low-volume centers. In Denmark, patients presenting with dysphagia for more than 2 weeks are offered a gastroscopy, with the primary focus to rule out cancer.[21,22] In these cases, other less obvious macroscopic abnormalities, for example, edema might not be noted and reported.

Another difference between groups of macroscopic findings was that significantly fewer patients had erosive esophagitis at diagnosis in the complicated EoE group, compared with the uncomplicated EoE group. This may be explained by the fact that more patients in the complicated EoE group was treated with PPI prior to diagnosis than in the uncomplicated EoE group. Another explanation could be that the main objective of an endoscopist facing an FBO is to remove the food. In addition, the mucosa of the esophagus can be extreme affected by the pressure of the FBO, which may lead to partial necrosis. In such cases, it may be extremely difficult for the endoscopist to describe, for example, esophagitis, based on the macroscopic findings.

Conclusion

This is to our knowledge the first study to examine the phenotypes of complicated and uncomplicated EoE in a population-based setting. Results from the 236 EoE patients in the DanEoE cohort indicated that the complicated EoE phenotype was a patient with a 5-year longer diagnostic delay; furthermore, the results indicated that the rings or stenosis were already present at the first endoscopy. In the current study, the complication status did not predict the treatment response, but less than half of patients were treated to remission according to guidelines.

References

1 Furuta GT, Liacouras CA, Collins MH *et al*. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007; **133**: 1342–63.

2 Liacouras CA, Furuta GT, Hirano I *et al*. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. *J. Allergy Clin. Immunol.* 2011; **128**: 3–20.

3 Dellon ES, Liacouras CA, Molina-Infante J *et al*. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. *Gastroenterology*. 2018; **155**: 1022–1033.e10.

4 Lucendo AJ, Molina-Infante J, Arias Á *et al*. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United Eur. Gastroenterol. J.* 2017; **5**: 335–58.

5 Lucendo AJ, Arias-González L, Molina-Infante J, Arias Á. Determinant factors of quality of life in adult patients with eosinophilic esophagitis. *United Eur. Gastroenterol. J.* 2018; **6**: 38–45.

6 Shaheen NJ, Mukkada V, Eichinger CS, Schofield H, Todorova L, Falk GW. Natural history of eosinophilic esophagitis: a systematic review of epidemiology and disease course. *Dis. Esophagus*. 2018; **31**: doy015.

7 Molina-Infante J, Gonzalez-Cordero PL, Ferreira-Nossa HC, Mata-Romero P, Lucendo AJ, Arias A. Rising incidence and prevalence of adult eosinophilic esophagitis in midwestern Spain (2007–2016). *United Eur. Gastroenterol. J.* 2018; **6**: 29–37.

8 Ng SC, Shi HY, Hamidi N *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017; **390**: 2769–78.

9 Navarro P, Arias Á, Arias-González L, Laserna-Mendieta EJ, Ruiz-Ponce M, Lucendo AJ. Systematic review with meta-analysis: the growing incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. *Aliment. Pharmacol. Ther.* 2019; **49**: 1116–25.

10 Krarup AL, Drewes AM, Ejstrud P, Laurberg PT, Vyberg M. Implementation of a biopsy protocol to improve detection of esophageal eosinophilia: a Danish registry-based study. *Endoscopy*. 2021; **53**: 15–24.

11 Lipka S, Kumar A, Richter JE. Impact of diagnostic delay and other risk factors on eosinophilic esophagitis phenotype and esophageal diameter. *J. Clin. Gastroenterol.* 2016 Feb; **50**: 134–40.

12 Frank L. Epidemiology. The epidemiologist's dream: Denmark. *Science*. 2003; **301**: 163.

13 Frank L. Epidemiology. When an entire country is a cohort. *Science*. 2000; **287**: 2398–9.

14 Dhar A, Haboubi HN, Attwood SE *et al*. British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults. *Gut*. 2022; **71**: 1459–87.

15 Melgaard D, Westmark S, Laurberg PT, Krarup AL. A diagnostic delay of 10 years in the DanEoE cohort calls for focus on education – a population-based cross-sectional study of incidence, diagnostic process and complications of eosinophilic oesophagitis in the North Denmark Region. *United Eur. Gastroenterol. J.* 2021; **9**: 688–98.

16 Danish National Guidelines [Internet]. Available from URL: https://dsgh.dk/wp-content/uploads/2022/06/EoE.pdf

17 Moawad FJ, Cheatham JG, Dezee KJ. Meta-analysis: the safety and efficacy of dilation in eosinophilic oesophagitis. *Aliment. Pharmacol. Ther.* 2013; **38**: 713–20.

18 Laserna-Mendieta EJ, Casabona S, Guagnozzi D *et al*. Efficacy of proton pump inhibitor therapy for eosinophilic oesophagitis in 630 patients: results from the EoE connect registry. *Aliment. Pharmacol. Ther.* 2020; **52**: 798–807.

19 Kuchen T, Straumann A, Safroneeva E *et al*. Swallowed topical corticosteroids reduce the risk for long-lasting bolus impactions in eosinophilic esophagitis. *Allergy*. 2014; **69**: 1248–54.

20 Kim HP, Vance RB, Shaheen NJ, Dellon ES. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012; **10**: 988–96.e5.

21 Dansk selskab for Almen Medicin. *Dyspepsi Udredning og behandling af voksne med symptomer fra øvre mave-tarm-kanal*, 2009.

22 Sundhedsstyrelsen. *Pakkeforløb for kræft i spiserør, mavesæk og mavemund*, 2016.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. EOE subgroup analysis of complications.