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ORIGINAL ARTICLE

Odynophagia and Retrosternal Pain Are Common in Eosinophilic Esophagitis and Associated with an Increased Overall Symptom Severity

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Abstract

Background and Aims Dysphagia is the hallmark symptom in eosinophilic esophagitis (EoE). However, data are limited regarding the overall prevalence and potential implications of atypical symptoms like odynophagia and retrosternal pain.

Methods Patients enrolled into the Swiss EoE cohort study (SEECS) were analyzed regarding the presence of odynophagia and retrosternal pain. Demographics, other EoE-related symptoms, histologic and endoscopic activity were compared between EoE-patients with vs. without odynophagia and/or retrosternal pain.

Results 474 patients (75.2% male) were analyzed. In their individual course of disease 110 (23.2%) patients stated to have ever experienced odynophagia and 64 (13.5%) retrosternal pain independent of food intake, 24 (5%) patients complained about both symptoms. Patients with odynophagia consistently scored higher in symptom severity ($p < 0.001$), EREFS score (median 3.0 vs. 2.0, $p = 0.006$), histologic activity and a lower quality of life ($p = 0.001$) compared to patients without odynophagia. Sex, age at diagnosis, EoE-specific treatment, complications such as candida or viral esophagitis and disease duration were similar in patients with vs. without odynophagia. Also patients with retrosternal pain scored higher in symptom severity (2.0 vs. 1.0, $p = 0.001$ and 2.0 vs. 1.0, $p < 0.001$ in physician and patient questionnaire assessment, respectively). However, there was neither a difference in endoscopic/histologic disease activity nor in quality of life according to presence or absence of retrosternal pain. Due to logistic reasons, a stratification regarding the presence of concomitant dysphagia was not possible.

Conclusion Odynophagia and swallowing-independent retrosternal pain are common symptoms in patients with EoE, associate with an overall higher EoE-related symptom severity and for the case of odynophagia lower quality of life. However, the influence of concomitant dysphagia and its severity remains unclear and needs to be included in future analyses.

Keywords Eosinophilic esophagitis · Symptoms · Odynophagia · Retrosternal pain

Fritz R. Murray and Philipp Schreiner have shared authorship.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic progressive immune-mediated inflammatory disease with a rising incidence and prevalence [1–3]. Untreated, EoE leads to fibrostenotic remodeling of the esophagus, which is directly associated with the length of the diagnostic delay (DD) [4, 5]. Each additional year of undiagnosed EoE increases the risk for esophageal strictures by 9% [6]. However, despite increasing educational and research efforts, diagnostic delay remains high [7] with one-third of patients having a delay of ≥ 10 years. One potential reason for this finding may be atypical symptoms leading to deferring actions by patients (e.g., denial and/or various coping strategies) or treating physicians (refraining from endoscopy and esophageal biopsies) [8].

Therefore, it is of utmost importance to recognize symptoms of potential EoE early in order to initiate further diagnostic steps. Clinical manifestation is dependent of patients' age with great differences between clinical patterns in early child- and in adulthood [9]. Children often present with unspecific symptoms like food refusal, failure to thrive, abdominal pain or regurgitation [10, 11]. In contrast, adults usually complain about more EoE-typical symptoms, with dysphagia resembling the leading symptom in more than 70% of EoE cases or present with esophageal food impaction [12–14].

One way to presumably improve early recognition of potential EoE-patients might be to bring attention to less known clinical manifestations than the most common presentation being dysphagia. Symptoms as retrosternal pain and odynophagia have been linked to EoE, however, no systematic studies exist as of yet to determine their prevalence.

After EFI or dilation of the esophagus, EoE-patients may experience retrosternal pain [15], a symptom which, however, has also been described in a small number of EoE-patients without preceding interventions [13]. Odynophagia is known in immunocompetent EoE-patients with herpes simplex esophagitis [16]. Also, there exists evidence that odynophagia accompanies dysphagia in lymphocytic esophagitis [17, 18], a now established variant of EoE [19] and mast cell esophagitis [20].

To the best of our knowledge there are no systematic studies investigating atypical symptoms like odynophagia or retrosternal pain in EoE. This study therefore aimed to shift attention to less known symptoms in EoE.

Materials and Methods

Patients and Study Design

Since 2016, EoE-patients are prospectively being recruited into the Swiss Eosinophilic Esophagitis Cohort Study (SEECS) [21]. The inclusion criteria for the SEECS have been described elsewhere [21]. In short, adult (age > 18 years) patients diagnosed with EoE according to the published diagnostic criteria (history of EoE-typical symptoms and ≥ 15 esophageal eosinophils per high/power field, HPF) are principally eligible [1]. Prior to inclusion, all patients gave their written informed consent. The SEECS was approved by ethics committees of all participating centers throughout Switzerland (leading approval CER/VD 148/15).

At the time of the analysis, 474 patients were enrolled in the SEECS. Patients could already have had a previous EoE diagnosis, hence clinically and histologically active but also inactive patients were included. All of these were retrospectively analyzed regarding the presence of odynophagia and/or retrosternal pain. Odynophagia was defined by either painful swallowing in the prior 7 days reported in the physician questionnaire or pain associated to swallowing reported in the patient questionnaire. Retrosternal pain was defined by pain independent of food ingestion in the last 7 days reported in the physician questionnaire. Analog to previous analysis of our group [22], global symptom assessment was analyzed according to information provided by physicians and patients during initial or follow-up consultations based on a Likert-Scale from 0 (no symptoms) to 10 (most severe symptoms) for recall periods of 24 h, 7 days, and 30 days (physician only). Endoscopic activity was scored according to the EoE endoscopic reference score (EREFS, 0–16 points, higher scores indicating a more severe endoscopic disease) [23]. In the SEECS, histologic activity is routinely assessed by documenting the peak eosinophil count in proximal and distal esophageal biopsies. In addition, thickening of the basal layer, fibrosis of the lamina propria and the presence of eosinophilic abscesses are documented. Quality of life (QoL) was scored according to an EoE-specific QoL-score for adults (EoE-QoL-A), ranging from 0 to 96 (7 days recall period) with higher values indicating worse QoL [24]. Demographics, EoE-related symptoms, histologic and endoscopic activity were compared between EoE-patients with vs. without odynophagia or retrosternal pain. In addition, patients were screened for concomitant candida esophagitis and/or viral esophagitis, as well as previous esophageal dilations. Due to logistic reasons, an analysis regarding the concomitant presence of "dysphagia" and, hence, a stratification of odynophagia and/or retrosternal pain according to dysphagia severity was not possible.

Outcomes

The primary objective of this study was to determine the prevalence of odynophagia and retrosternal pain in EoE-patients. Secondary objectives were the evaluation of the influence of concomitant candida esophagitis, viral

esophagitis, and prior esophageal dilations. In addition, baseline characteristics as well as clinical, endoscopic and histological activity as well as quality of life in patients with odynophagia or retrosternal pain were compared to EoE-patients without these symptoms.

Statistics

Categorical data is presented as raw numbers and percentages. Differences in categorical variables distribution between two or more groups were assessed using the Chi-square test, or the Fisher's exact test in case of small sample size (*n* smaller than 20). Continuous data distribution normality was assessed using normal QQ-plots. Normally distributed variables are summarized as mean, standard deviation, and range, while non-normally distributed variables are presented as median, interquartile range, and range.

Results

Baseline Characteristics

Of the 474 analyzed patients (75.2% male patients, 67% with atopic disease), 110 (23.2%) experienced odynophagia and 64 (13.5%) retrosternal pain (Table 1 and Fig. 1).

Table 1 Number of patients with odynophagia and/or retrosternal pain

	No retrosternal pain	Retrosternal pain	Total
No odynophagia	324	40	364 (76.8%)
Odynophagia	86	24	110 (23.2%)
Total	410 (86.5%)	64 (13.5%)	474

Only a minority of 24 patients (5%) complained about both symptoms.

Concomitant *Candida* or Viral Esophagitis

Information regarding concomitant candida or viral esophagitis was available in 268/474 patients (56.5%). Among these, 27 patients were diagnosed with esophageal candidiasis (10.1%). However, within these 27 patients, only 3 patients (11%) also complained about odynophagia and 2 (7%) of retrosternal pain. Three of 268 patients were diagnosed with viral esophagitis (1.1%), with none of these patients reporting odynophagia or retrosternal pain.

Previous Esophageal Dilation

Sixty-five patients (14%) underwent esophageal dilation within 16 months prior to our analysis. Twelve (18.5%) of these patients complained about odynophagia, 4 (6%) about retrosternal pain, and 1 (1.5%) about both. In addition, dilations in general (irrespectively of the timeframe prior to the underlying study; Tables 2 and 3) were not significantly associated with odynophagia or retrosternal pain.

Endpoints in Respect to Odynophagia and Retrosternal Pain

Tables 2 and 3 summarize the outcomes of patients divided according to symptoms: no odynophagia vs. odynophagia (Table 2) and no retrosternal pain vs. retrosternal pain (Table 3).

In both groups, gender and age at diagnosis or at last visit, as well as disease duration since the first occurrence of EoE-typical symptoms, the smoking status or concomitant atopic disease were not associated with higher rates of either of the two symptoms. Also, the presence of erosive esophagitis

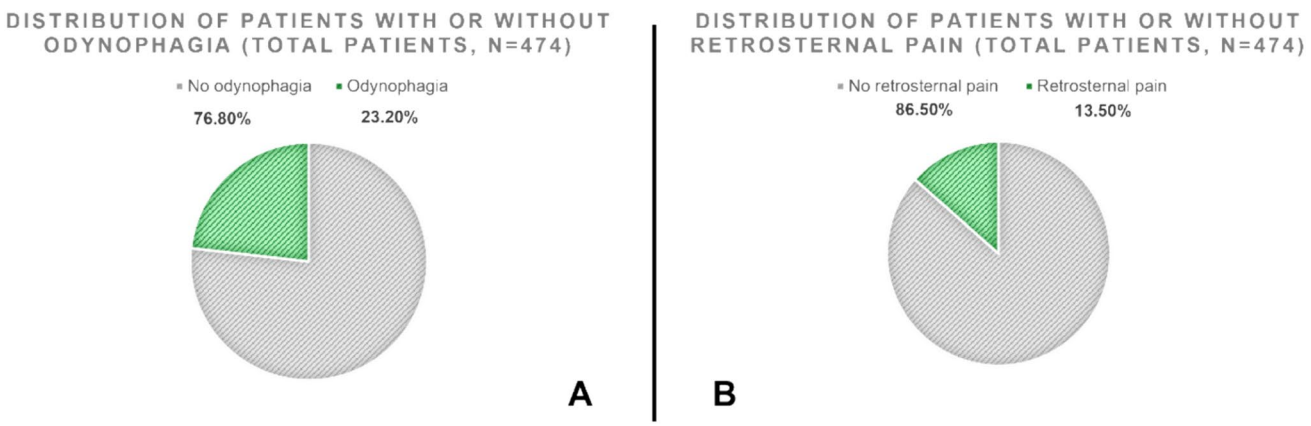

Fig. 1 Number of patients with odynophagia and/or retrosternal pain. A: Distribution of patients with odynophagia; B: Distribution of patients with retrosternal pain

Table 2 Results stratified by odynophagia

	No odynophagia	Odynophagia	*p*-value (chi2 or Wilcoxon)
Number of patients	364 (76.8%)	110 (23.2%)	
Gender			
Male	280 (76.9%)	76 (69.1%)	0.096
Female	84 (23.1%)	34 (30.9%)	
Age at…			
…diagnosis (median, IQR, range)	37.1, 28.4–46.8, 8.3–79.0	36.0, 26.2–43.3, 8.7–70.4	0.065
…last visit (median, IQR, range)	43.2, 34.5–53.0, 17.9–83.1	40.2, 31.2–49.8, 18.8–75.8	0.049
Used to be a smoker			
At least once	28 (8.0%, $n=352$)	13 (12.0%, $n=108$)	0.193
At last visit	18 (5.2%, $n=343$)	8 (7.6%, $n=105$)	0.363
Symptom severity (judged by physician) in the last…			
…24 h (median, IQR, range)	0.0, 0.0–2.0, 0.0–10.0	1.0, 0.0–3.0, 0.0–7.0	**< 0.001**
…7 days (median, IQR, range)	1.0, 0.0–3.0, 0.0–9.0	2.0, 0.0–4.0, 0.0–10.0	**< 0.001**
…30 days (median, IQR, range)	1.0, 0.0–3.0, 0.0–9.0	3.0, 1.0–4.0, 0.0–10.0	**< 0.001**
Symptom severity (judged by patient) in the last…			
…24 h (median, IQR, range)	0.0, 0.0–1.0, 0.0–10.0	1.0, 0.0–3.0, 0.0–10.0	**< 0.001**
…7 days (median, IQR, range)	1.0, 0.0–2.0, 0.0–10.0	2.0, 1.0–4.0, 0.0–10.0	**< 0.001**
EREFS score			
Maximal (median, IQR, range)	1.5, 0.0–3.0, 0.0–8.0	2.0, 1.0–4.0, 0.0–7.0	**0.008**
Proximal + Distal (median, IQR, range)	2.0, 0.0–5.0, 0.0–15.0	3.0, 1.0–6.0, 0.0–14.0	**0.006**
Erosive Esophagitis			
Presence erosive esophagitis (y/n)	117 (32.1%)	33 (30.0%)	0.672
Endoscopic reflux activity (median, IQR, range)	1.0, 1.0–2.0, 1.0–5.0	2.0, 1.0–2.5, 1.0–5.0	0.297
Histologic activity			
High number of eos. per HPF (proximal, y/n)	125 (36.9%, $n=339$)	59 (55.1%, $n=107$)	**0.001**
High number of eos. per HPF (distal, y/n)	177 (51.8%, $n=342$)	73 (68.9%, $n=106$)	**0.002**
Eosinophilic abscess (y/n)	72 (21.7%, $n=332$)	42 (39.3%, $n=107$)	**< 0.001**
Fibrosis of lamina propria (y/n)	198 (90.0%, $n=220$)	76 (96.2%, $n=79$)	0.088
Ever had a dilation			
No	233 (64.0%)	65 (59.1%)	0.349
Yes	131 (36.0%)	45 (40.9%)	
Concomitant atopic disease			
No	95 (28.0%)	28 (26.7%)	0.786
Yes	244 (72.0%)	77 (73.3%)	
Complications			
Oral candidiasis	24 (11.7%, $n=206$)	3 (4.8%, $n=62$)	0.118
Viral esophagitis	3 (1.5%, $n=206$)	0 (0.0%, $n=62$)	0.339
Disease duration since first symptoms			

Table 2 (continued)

	No odynophagia	Odynophagia	*p*-value (chi2 or Wilcoxon)
Median, IQR, range	10.1, 5.2–18.0, 0.2–48.1	11.2, 6.5–18.7, 1.5–48.9	0.319
Quality of life at last visit			
Median, IQR, range	14.0, 6.0–26.0, 0.0–76.0	18.0, 10.0–32.0, 0.0–77.0	**0.001**

(defined as any Los Angeles (LA) grade) or the endoscopic reflux activity (according to the prevalence of LA grades A-D), were not associated with neither odynophagia nor retrosternal pain.

Patients with odynophagia had higher symptom severity in the last 7 days (assessed by physician and patient questionnaire 2.0 vs. 1.0, $p < 0.001$ and 2.0 vs. 1.0, $p < 0.001$, respectively), as well as higher endoscopic and histologic disease activity represented by a higher EREFS score (median 3.0 vs. 2.0, $p = 0.006$), higher eosinophilic counts per HPF (proximal 55.1% vs. 36.9%, $p = 0.001$; distal 68.9% vs. 51.8%, $p = 0.002$) and a higher number of eosinophilic abscesses (39.3% vs. 21.7%, $p < 0.001$, Fig. 2). In addition, the quality of life, measured with the EoE-QoL-A, was lower compared to patients without odynophagia (median 18 vs. 14, $p = 0.001$).

In patients with retrosternal pain, a higher symptom severity in the last 7 days (assessed by physician and patient questionnaire 2.0 vs. 1.0, $p = 0.001$ and 2.0 vs. 1.0, $p < 0.001$, respectively). However, patients with retrosternal pain showed no difference in endoscopic or histologic disease activity (Fig. 2) nor in the QoL compared to patients without retrosternal pain.

Discussion

Our analysis demonstrates that odynophagia and swallowing-independent retrosternal pain are, in addition to the well-known symptom of solid-food dysphagia, frequently occurring symptoms in EoE.

In 2008, Kapel et al. conducted a retrospective analysis of a national pathology database in the US, in which they identified 363 EoE-patients (321 adults and 42 children) from a cohort of upper endoscopies for any clinical reason [25]. All of these cases were further analyzed regarding the indication for upper endoscopy. In the adult population, the majority of patients were endoscopically assessed as a consequence to dysphagia (70.1%), followed by gastroesophageal reflux disease (GERD)/heartburn (27.1%). However, in 5.3% of the population the indication was odynophagia and in 3.4% chest pain. In children, on the other hand, the leading indication was GERD/heartburn (38.1%), followed by abdominal pain/dyspepsia (31%). Compared to the adult population, dysphagia was present in a considerably lower number of cases (26.2%). Analog to the adult population, odynophagia (2.4%) and chest pain (4.8%) were rare indications for upper endoscopy in children. In our cohort, consisting of only adult patients, odynophagia was present in almost one quarter (23.2%) of all patients. This rate is considerably higher than the one observed by Kapel et al. and almost as high as the rate they demonstrated for GERD/heartburn. Therefore, odynophagia as a key symptom in the diagnostic of EoE seems to be underestimated. In addition, the rate of retrosternal pain in our cohort (13.5%) was substantially higher than in the above-mentioned study (3.4%), as long as the terms of "chest pain" (used by Kapel et al.) and "retrosternal pain" (used in our study) are comparable. However, our results provide evidence that swallowing-independent retrosternal pain is a considerably frequent symptom in EoE-patients, comparable to the rates of abdominal pain/dyspepsia (13.1%) in adults and nausea/vomiting (14.3%) in children [25].

In accordance to the above mentioned, in their review Furuta et al. nicely pointed out, that adult patients most often describe dysphagia as their leading symptom, while children often complain of GERD-like symptoms, failure to thrive, emesis, and abdominal pain without dysphagia [26]. "Chest pain," the symptom most similar to retrosternal pain, was mentioned to be present in a range of 1–58% in adults and 17–20% in children, however, was not included in their recommendation of symptoms "suggestive of eosinophilic esophagitis" (Table 3 in their publication). Odynophagia, probably due to not existing data, was not mentioned at all.

The identification of symptoms potentially caused by an underlying EoE is especially important, as the diagnostic delay remains high (median = 4 years; in one-third ≥ 10 years [7]), resulting in the presence of pharmacologically not treatable esophageal strictures in > 30% of patients at diagnosis [4]. Part of the reason is the differing diagnostic approach to upper gastrointestinal symptoms between age groups, as endoscopic evaluation is performed less frequently in younger patients [7]. As EoE is a disease of the young, with more than half of the patients being younger than 31 years

Table 3 Results stratified by retrosternal pain

	No retrosternal pain	Retrosternal pain	*p*-value (chi^2 or Wilcoxon)
Number of patients	410 (86.5%)	64 (13.5%)	
Gender			
Male	306 (74.6%)	50 (78.1%)	0.548
Female	104 (25.4%)	14 (21.9%)	
Age at…			
…diagnosis (median, IQR, range)	36.8, 27.2–46.2, 8.3–79.0	36.7, 30.1–48.4, 16.7–75.5	0.595
…last visit (median, IQR, range)	42.7, 32.8–52.1, 17.9–83.1	42.2, 35.5–52.3, 22.0–76.7	0.395
Used to be a smoker			
At least once	32 (8.1%, $n=396$)	9 (14.1%, $n=64$)	0.119
At last visit	21 (5.4%, $n=386$)	5 (8.1%, $n=62$)	0.412
Symptom severity (judged by physician) in the last…			
…24 h (median, IQR, range)	0.0, 0.0–2.0, 0.0–10.0	1.0, 0.0–3.0, 0.0–7.0	**0.001**
…7 days (median, IQR, range)	1.0, 0.0–3.0, 0.0–10.0	2.0, 1.0–4.0, 0.0–7.0	**0.001**
…30 days (median, IQR, range)	2.0, 0.0–3.0, 0.0–10.0	2.0, 1.0–4.0, 0.0–7.0	**0.001**
Symptom severity (judged by patient) in the last…			
…24 h (median, IQR, range)	0.0, 0.0–1.0, 0.0–10.0	2.0, 0.0–3.0, 0.0–7.0	**< 0.001**
…7 days (median, IQR, range)	1.0, 0.0–2.0, 0.0–10.0	2.0, 1.0–4.0, 0.0–7.0	**< 0.001**
EREFS score			
Maximal (median, IQR, range)	2.0, 0.0–3.0, 0.0–8.0	2.0, 0.0–3.0, 0.0–7.0	0.505
Proximal + Distal (median, IQR, range)	2.0, 0.0–5.0, 0.0–15.0	2.0, 0.0–4.5, 0.0–12.0	0.372
Erosive Esophagitis			
Presence of erosive Esophagitis (y/n)	128 (31.2%)	22 (34.4%)	0.614
Endoscopic reflux activity (median, IQR, range)	1.0, 1.0–2.0, 1.0–5.0	1.5, 1.0–5.0, 1.0–5.0	0.464
Histologic activity			
High number of eos. per HPF (proximal, y/n)	157 (40.9%, $n=384$)	27 (43.5%, $n=62$)	0.693
High number of eos. per HPF (distal, y/n)	211 (54.7%, $n=386$)	39 (62.9%, $n=62$)	0.225
Eosinophilic abscess (y/n)	95 (25.2%, $n=377$)	19 (30.6%, $n=62$)	0.365
Fibrosis of lamina propria (y/n)	232 (91.7%, $n=253$)	42 (91.3%, $n=46$)	0.929
Ever had a dilation			
No	259 (63.2%)	39 (60.9%)	0.731
Yes	151 (36.8%)	25 (39.1%)	
Concomitant atopic disease			
No	107 (28.1%)	16 (25.4%)	0.659
Yes	274 (71.9%)	47 (74.6%)	
Complications			
Oral candidiasis	25 (10.3%, $n=242$)	2 (7.7%, $n=26$)	0.671
Viral esophagitis	3 (1.2%, $n=242$)	0 (0.0%, $n=26$)	0.568
Disease duration since first symptoms			

Table 3 (continued)

	No retrosternal pain	Retrosternal pain	*p*-value (chi^2 or Wilcoxon)
Median, IQR, range	10.3, 6.1–18.3, 0.2–48.9	9.8, 4.7–19.1, 0.6–48.1	0.642
Quality of life at last visit			
Median, IQR, range	14.0, 6.0–28.6, 0.0–77.0	17.4, 10.5–26.5, 0.0–55.0	0.065

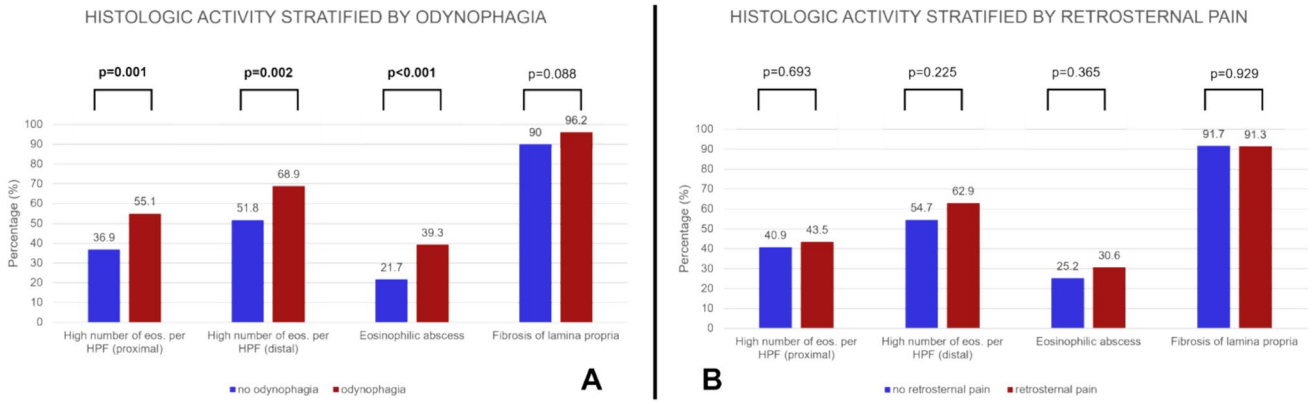

Fig. 2 Histologic activity. A: Histologic activity stratified by odynophagia; B: Histologic activity stratified by retrosternal pain

and 30% even younger than 21 years [7], the identification or EoE-typical symptoms is even more important.

In order to objectify disease activity several different scoring systems exist. In a comprehensive review, Warners et al. identified these and discussed their value and outcome measures [27]. In accordance to the above mentioned, the authors pointed out, that the existing scores mainly focus on dysphagia in the adult population, while in the pediatric population multiple other symptoms are included [27]. For example, the Dysphagia Symptom Questionnaire and the Straumann Dysphagia Index both focus on dysphagia, but are limited by neglecting other EoE-related Symptoms [28, 29]. In adults, Warners et al. conclude, that the Eosinophilic Esophagitis Activity Index for patient-reported outcome (EEsAI PRO) appropriately measures EoE symptoms in adults [8, 27]. In fact, the EEsAI PRO additionally includes questions regarding "pain when swallowing." In the underlying study, we were able to retract information regarding odynophagia ("pain when swallowing") from the physician questionnaire that is systemically used in the SEECS, which enabled the underlying analysis. In children, the Pediatric Eosinophilic Esophagitis Symptom Score (PEES v2.0) and a multiple-item symptom index developed by Aceves et al. include questions regarding "chest pain" and "painful swallowing" [30, 31]. However, as of now, neither odynophagia, nor retrosternal pain are included in diagnostic guidelines or follow-up scores as EoE-typical symptoms. As long as odynophagia and retrosternal pain are not officially recognized as potential EoE related, the diagnostic and clinical follow-up process is hampered in a potentially large group of patients.

In the present analysis, patients with odynophagia had a significantly higher symptom burden (judged by the physician and the patient), than patients without odynophagia. In addition, odynophagia occurred significantly more often in patients with higher endoscopic (EREFS score) and histologic activity (high number of eos per HPF and eosinophilic abscesses). The latter must be considered with reservations. We could show that overall histologic activity at one point was higher in patients with odynophagia. However, based on the available data we were not able to specifically link the symptom of odynophagia to active EoE as symptom assessment could have been taken place in then already treated disease.

Increased symptom severity seems logic. An association to higher endoscopic and histologic activity is questionable. Analog to our results, in the study of Kapel et al. patients with dysphagia had a significantly higher peak eosinophilic count [25]. However, the majority of existing literature could only show a moderate correlation between symptoms and endoscopic or histologic activity [32]. In addition, even with significant reduction of eosinophilic infiltration, clinical

remission was not achieved in several studies in the past [33–35]. One reason might be, that the present study did not analyzes all features of the EoE histology scoring system (EoE-HSS), known to correlate better with EoE activity than the simple EoE count per HPF [36]. However, lamina propria fibrosis, one feature of the EoE-HSS, was evaluated and did not show a difference in patients with or without odynophagia. In addition, no association of current disease activity was shown in our study. One other histologic feature, that was not analyzed in the present study, was the degree of mast cell infiltration, which has been shown to be increased in EoE-patients [37, 38]. In regard to odynophagia, mast cells might play an important role, as results of a few recent studies suggest that they remain activated in disease remission with potential influence on persisting symptoms, particularly pain, without correlation with eosinophilic counts in otherwise controlled patients [39–41].

Matching the increased symptom severity, patients with odynophagia reported a significantly worse QoL, which again seems logic.

In accordance to patients with odynophagia, patients with retrosternal pain also had a significantly higher symptom severity (judged by physicians and patients). All other analyzed features, including QoL, showed no differences between patient with and without retrosternal pain, which is in line with the above discussed literature.

Of note, 5% of patients in the present study experienced both symptoms, odynophagia and swallowing-independent retrosternal pain, with a significant association ($p = 0.004$) to each other, indicating that pain in general is a feature of EoE. Of crucial importance regarding this observation, neither odynophagia, nor retrosternal pain was associated to concomitant erosive esophagitis, despite the fact that the most prevalent clinical symptom of erosive esophagitis is pain–with and without swallowing. Furthermore, only a few of the patients analyzed in our cohort underwent previous esophageal dilation. And even though the number of cases in our cohort were very low, only very few patients complaining about odynophagia or retrosternal pain were diagnosed with concomitant esophageal candidiasis or viral esophagitis. All of the above mentioned indicates that retrosternal pain (with or without swallowing) is a general feature of EoE and not a consequence to complications or treatment.

Data in the SEECS are being prospectively collected since 2016 according to a straight protocol. In addition, the sample size is rather large and data are gathered at multiple sites all over Switzerland. However, two major limitations hamper the results of the underlying study. First, as already discussed above, we do not have information regarding mast cell infiltration, which might play an important role in pain. Second, we are not able to discriminate patients with odynophagia and/or retrosternal pain with or without concomitant dysphagia. In other words, we cannot determine how many patients would have been additionally diagnosed, if odynophagia or retrosternal pain would have been the only upper GI symptom. For the same reason, it can only be speculated that the knowledge regarding odynophagia and retrosternal pain as potential EoE associated symptoms might influence the diagnostic delay. Also, as no stratification according to dysphagia severity and active disease was possible, the potential influence of concomitant dysphagia and active disease on symptom severity and quality of life is unclear. Lastly, as no data regarding outpatient reflux monitoring are available, it cannot be ruled out that some of the analyzed patients may have had concomitant non-erosive reflux disease causing or adding to odynophagia and/or retrosternal pain.

In conclusion, especially odynophagia, but also swallowing-independent retrosternal pain, are frequent features of eosinophilic esophagitis. Further studies are needed to confirm our findings, with special focus on concomitant dysphagia and mast cell infiltration in order to potentially implement both symptoms into clinical practice. Until then, EoE should be ruled out in any patient (in general and specifically the one with concomitant atopic disease) with an otherwise unexplained presence of the mentioned symptoms, independently of concomitant dysphagia.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval The study adhered to and was conducted according to the principles of the Declaration of Helsinki and current good clinical practice guidelines. The SEECS was approved by various ethics committees of all participating centers throughout Switzerland (leading approval CER/VD 148/15). All patients gave their written informed consent prior to inclusion.

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