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Column: Prospective Study

Title: Proposed criteria to differentiate heterogeneous eosinophilic gastrointestinal disorders of the esophagus, including eosinophilic esophageal myositis

Authors: Nao Nakajima, Kazuya Takahashi, Go Hasegawa, Ken-ichi Mizuno, Satoru Hashimoto, Satoshi Ikarashi, Kazunao Hayashi, Yutaka Honda, Junji Yokoyama, Yuichi Sato and Shuji Terai

Reviewer code: 03548292 and 03009698

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Dear Drs. Damian Garcia-Olmo, Stephen Strom, and Andrzej Tarnawski:

Thank you for your insightful comments and assessment of our manuscript (NO: 31461). We have considered all comments and suggestions in our revised manuscript, and have provided our responses.

We sincerely hope that we have fully responded to the reviewer's comments and editorial suggestions and that the revised manuscript is now acceptable for publication.

Sincerely yours,

Hiroki Sato, MD, PhD, Division of Gastroenterology and Hepatology, Niigata University
Medical and Dental Hospital 757-1, Asahimachidori, Chuo-ku, Niigata City, Niigata 951-8510,
Japan pyloki@yahoo.co.jp

Reviewer 1:

- (1) Are you aware that out of 10 patients that were studied, 5 of them (50%) have the same disease (EoE) - the distribution far from ideal.

Our study group was formed of 10 consecutive patients with esophageal eosinophilia from our clinical practice. We do acknowledge that 5 of these 10 cases were EoE. Although this high relative proportion of EoE compared to sEOE and EoEM constitutes an internal bias of our study cohort, the higher proportion of EoE does indicate that EoE is a main EoGD in the esophagus, compared to sEOE or EoEM. As this is an important issue, we did address it in our discussion as follows:

This was a small-size pilot study and further studies, including larger sample sizes, are needed to confirm our findings. In fact, we are continuing to collect data using our procedure outlined in Figure 6 with the aim of supplementing our case series in future reports. Future research should also specifically aim to include a larger number of patients with sEOE patients.

- (2) Why was s-IgE so high in one patient with sEOE? Why is that relevant hence this patient cannot be differentiated from the patients with EoEM?

As we have presented in our discussion, an elevation of s-IgE is indicative of a current allergy as well as of a past history of allergy or sensitization to an allergen. Therefore, an elevation in s-IgE needs to be carefully interpreted, and the association between an elevated s-IgE and disease pathogenesis does require further evaluation. What we do propose in our study is that an impairment in esophageal motility, in combination with an elevated s-IgE, may be related with esophageal eosinophilia other than EoE, even if no eosinophilia are identified on mucosal biopsy.

- (3) The group with achalasia was used as the control group in this study - why?

We agree that this is an important point and have improved our justification for using patients with achalasia as a control group in our section on limitations, as follows:

mRNA analyses for cases of symptomatic achalasia were used as a control for two reasons. First, tissue samples are obtained using the same POEM-b method. Second, tissue samples in achalasia do not show eosinophilia in the esophageal muscle layer^[37]. Non-symptomatic individuals without any known esophageal disorders would provide a more appropriate control.

although this would pose a difficult ethical problem.

- (4) The sex ratio is not properly chosen (1F:9M). The incidence of disease is the highest before the fifth decade of life. Nevertheless, 5 cases refer to patients that were over 53 years of age at least. 50-80% of cases show coexisting atopy, while in this particular study, 3 out of 10 cases show allergies.

As you have correctly indicated, EoE is principally identified in middle-aged males and is an allergy disorder. This is reflected in our study cohort, with four out of five cases of EoE being middle-aged males, with two having a past history of allergies. In this way, our study cohort corresponds to previously reported prevalence data for EoE. The fact that our patients were over the age of 50 years could reflect the general aging of the population in Japan. In our study cohort, cases of sEoE and EoEM were also middle-aged males. However, further research is needed to determine whether sEoE and EoEM are sufficiently different from EoE.

Why wasn't the POEM/POEM-b done on sEoE patient as well?

We appreciate that for consistency, POEM/POEM-b should have been performed in all patients. However, the similarity in the clinical course of sEoE and EoE has already been reported by Yamabe et al. Clin J Gastroenterol. 2014. We have described this in our Introduction as follows:

However, a subtype of EoE, with esophageal symptoms and subepithelial eosinophilia (SE) observed in the lamina propria and muscularis mucosa in esophageal samples obtained by conventional biopsy, has also been reported recently^[4], and termed “subepithelial eosinophilic esophagitis (sEoE)”. Using peroral esophageal muscle biopsy (POEM-b), we have also previously reported an eosinophilic infiltration in the esophageal muscle layer^[5-7]. However, as this eosinophilic infiltration of the esophageal muscle layer was not identifiable using conventional biopsy, it cannot be defined as EoE.

Reviewer 2:

- (1) The number of patients with sEoE is only one. Could you increase the number of cases?

As we have previously mentioned, we recognize the internal bias of our study cohort. However, it is important to note that we had a pre-defined study period and during that time, only one case of sEoE presented to our clinic. As the criteria for diagnosis of sEoE have been previously reported, as presented in our Introduction, we are confident that this was a case of sEoE.

Why do you choose patients with achalasia as the control group?

This is important issue was also raised by Reviewer 1 and we have improved our justification for using patients with achalasia as a control group in our section on limitations, as follows:

mRNA analyses for cases of symptomatic achalasia were used as a control for two reasons. First, tissue samples are obtained using the same POEM-b method. Second, tissue samples in achalasia do not show eosinophilia in the esophageal muscle layer^[37]. Non-symptomatic individuals without any known esophageal disorders would provide a more appropriate control, although this would pose a difficult ethical problem.