Virchows Archiv (2019) 474:641–642
https://doi.org/10.1007/s00428-019-02522-y

LETTER TO THE EDITOR

Morphologic spectrum of gluten-related disorders: how far to go?

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Received: 30 December 2018 / Accepted: 4 January 2019 / Published online: 19 January 2019

Dear Editor,

We read the letter written by Barbara Zanini, Anna Bozzola, and Vincenzo Villanacci regarding our paper titled "Discriminant value of IEL counts and distribution pattern through the spectrum of gluten sensitivity: a simple diagnostic approach" [1], with great interest. We are glad to see that our paper has incited a pleasant discussion among experts in which we would like to participate and clarify certain points raised by Zanini et al. in their letter.

Ours was a retrospective study, so we do not know whether the non-celiac IELosis group corresponds to NCGS, as the diagnosis depends on the exclusion of the other causes of IELosis together with response to GFD followed by a single or double-blind placebo-controlled gluten challenge [2]. It seems likely, however, that some of our cases may indeed be NCGS, based on their symptoms, negative serology, and normal or mildly increased IEL counts in the duodenal biopsy [1]. Nevertheless, we did not compare the histology of non-celiac IELosis with the histological features proposed by Zanini et al. [3] for NCGS, but rather based our discussion on the assumption that at least some of our non-celiac IELosis cases, if evaluated by Salerno Experts' criteria [2], could be true NCGS, especially, those with an IEL count < 25/100 enterocytes.

Regarding their histological assessment, Zanini et al. have elegantly proposed that NCGS mucosa showed increased eosinophils in the lamina propria (> 5 per high-power field), a linear disposition of T lymphocytes in the deeper mucosa, and small clusters of T lymphocytes ¾ in the superficial epithelium which contained < 25 IEL on both H&E and CD3 stains [3]. Working on the assumption that some members of the non-celiac IELosis group may represent NCGS, we searched for the presence of the above features in our study. To our surprise, our controls, non-celiac IELosis, and type 1 celiac groups, all showed "linear disposition of T lymphocytes in the deeper mucosa" (Fig. 1a–c) on CD3 stain while some of the controls and non-celiac IELosis cases showed "small clusters of T lymphocytes in the superficial epithelium" (Fig. 1a, b depicted in circles) which was interpreted as "focal/uneven distribution" in our paper [1]. In the duodenum, although still controversial, mucosal eosinophilia has been defined as > 22 eosinophils per 5 high-power fields at the base of crypts [4] which corresponds to Zanini's definition of > 5 eosinophils per high-power field [3]. We find it difficult, however, to relate the eosinophilia specifically to NCGS, as it may result from various other conditions affecting the duodenal mucosa including celiac disease.

We, therefore, believe that the defined histologic features of NCGS seem rather non-specific (some may even be considered as "normal") and that, before confirmed by others, should not be attributed to a controversial and yet poorly defined entity. To support this view, we plan to extend our studies further to include NCGS cases and compare the histopathological features with those of controls, non-celiac IELosis, and type 1 celiac cases. No doubt, with further high-quality research like Zanini et al's [3], it will be possible to improve our understanding of the morphologic spectrum of gluten-related disorders [5].

Ethical responsibilities of authors section All the authors are qualified for the following criteria:

- Substantial contributions to the conception or design of the study or the acquisition, analysis or interpretation of data for the study
- Drafting the study or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved

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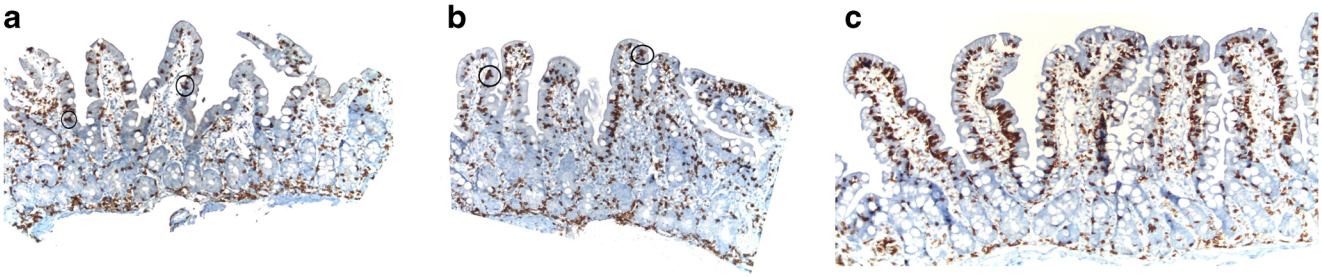

Fig. 1 Duodenal mucosa of (**a**) control, (**b**) non-celiac IELosis, (**c**) type 1 celiac showing linear T lymphocytic infiltration in the basal lamina propria (CD3 IHC; × 100) and small clusters of T lymphocytes in the villous epithelium of (**a**) control and (**b**) non-celiac IELosis depicted in black circles

Contributions Ayca Kirmizi and Arzu Ensari wrote together the manuscript and gave final approval for publication.

Compliance with ethical standards

The authors declare that the study has been done according to ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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