Mapping histologic patchiness of celiac disease by push enteroscopy

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Background: Despite great improvements in serologic testing, duodenal biopsies are still required to diagnose the majority of celiac disease (CD) cases. Nevertheless, the histologic pattern of CD is often patchy, leading to the risk of missing the diagnosis.

Objective: To evaluate the patchiness of the CD histologic lesions along the small bowel (SB), push enteroscopy has been performed instead of conventional upper GI endoscopy.

Design: Prospective, single-center study.

Setting: Tertiary-care referral center.

Patients: A total of 41 pediatric patients with suspected CD.

Intervention: Prospective evaluation of bulb, duodenal, and jejunal biopsy specimens in the diagnosis of CD.

Main Outcome Measurements: Pattern of lesion distribution along the SB (from bulb up to 60 cm beyond the ligament of Treitz) and yield as well accuracy of pediatric CD diagnosis by using push enteroscopy.

Results: There was a homogeneous pattern of histologic damage in 17 patients (41.5%), whereas 24 patients (58.5%) had a lesion pattern of patchiness. The second and fourth duodenal regions were involved in 38 children (92.7%) and 37 children (90.2%), respectively; the bulb was involved in 37 patients (90.2%); both distal and proximal jejunal samples showed histologic lesions in 38 children (92.7%). In 1 patient, without lesions in the bulb and duodenum, CD was diagnosed according to proximal and distal jejunal biopsies only (3B and C, respectively). A significant correlation was found between the degree of villous atrophy and the serum anti-transglutaminase titer.

Limitations: Small sample size; academic tertiary-care setting.

Conclusion: CD histologic lesions often have a discontinuous distribution along the SB, occasionally with an exclusive jejunal involvement. A high degree of villous atrophy correlates with a high anti-transglutaminase titer. When the new ESPGHAN "biopsy-sparing" criteria are not applicable, in case of potential CD, push enteroscopy might be a valuable second-step tool to re-evaluate and identify false "potential" CD hiding exclusive jejunal lesions. (Gastrointest Endosc 2014;79:95-100.)

Abbreviations: CD, celiac disease; ESPGHAN, The European Society for Paediatric Gastroenterology Hepatology and Nutrition; MO, Marsh-Oberhuber.

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Celiac disease (CD) is a permanent immune-mediated systemic disorder triggered by gluten, a storage protein of wheat and related cereals, in genetically susceptible individuals. It is characterized by different clinical manifestations, CD-specific antibodies (anti-transglutaminase and anti-endomysial antibodies), human leukocyte antigen (HLA-DQ2 and/or DQ8 haplotypes), and different degrees of enteropathy.[1] In CD, the ingestion of gluten activates an aberrant immune response leading to progressive damage of the small-intestine mucosa and impaired small-bowel absorptive functions and to medium-term and long-term adverse events.[2]

Except for selected symptomatic cases in the pediatric patient with high titers of CD-related antibodies and compatible human leukocyte antigen typing, the diagnosis of CD still relies on multiple duodenal biopsy specimens obtained by upper GI endoscopy.[1] Because it has been widely described that the histologic pattern of CD is often patchy, multiple biopsies are mandatory to reduce the risk of missing the diagnoses.[3,4] Histologic lesions of CD may vary notably from site to site; moreover, some authors highlighted that different degrees of severity may be found even within the same biopsy specimen.[5]

The current European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) statement advises taking at least 4 biopsy specimens from the second and/or third portion of the duodenum and at least 1 from the duodenal bulb.[1] However, the debate on where to perform biopsies still animates the medical community. Because it has been reported that histologic damage may be confined to the duodenal bulb,[6-8] it has been recommended to obtain 4 biopsy specimens from the bulb and 4 from the duodenum in order to increase the diagnostic yield,[9] but this finding has not been confirmed by others[10]; moreover, a survey has emphasized a wide gap between recommendations and clinical practice, showing that even experienced endoscopists were reluctant to take more than 4 duodenal biopsy specimens for the diagnosis of CD.[11] It was also reported that villous atrophy may be merely present in the jejunum.[12-14]

Therefore, we aimed to further evaluate the pattern of distribution of the histologic lesions along the small bowel in a pediatric cohort of CD patients at diagnosis by using push enteroscopy instead of conventional upper GI endoscopy.

Take-home Message

- This study has investigated the possible implication of push enteroscopy in the diagnosis of pediatric celiac disease.
- This study stimulates the debate on which small-bowel sites the endoscopic biopsies should be performed in order to identify histologic lesions and, thus, to confirm the diagnosis. Moreover, it might introduce a novel and second-step diagnostic approach to so-called potential celiac disease.

MATERIALS AND METHODS

Fifty-seven pediatric patients with suspected CD were referred to the Pediatric Gastroenterology and Liver Unit of the Sapienza University in Rome from May 2011 to July 2012. During the whole recruiting period (14 months), 41 CD patients were recruited for the experimental protocol, whereas 16 patients were not included in the study (9 patients underwent conventional upper GI endoscopy because of parental denial of the research protocol, and 7 were not confirmed by intestinal biopsy for clinical reasons or parental denial).

All 41 of the recruited patients (15 boys, aged from 1.6-15.1 years) were gluten-free naïve, on a long-lasting, gluten-containing diet; none of them had been previously diagnosed with CD. All patients had positive test results for anti-transglutaminase antibodies and strong positivity for anti-endomysial antibodies.

The study protocol for the experimental use of push enteroscopy in the diagnosis of CD had been previously approved by the Ethics Committee of University Hospital. Before recruitment, both the study and the procedure written consent were obtained from all parents and patients when applicable, after thorough explanations of the research protocol and the differences with standard clinical practice. Conventional upper GI endoscopy was offered at the same time as a standard and comprehensive procedure for diagnosis.

Push enteroscopy was performed with patients under general anesthesia and by using Olympus Enteroscope SIF 180 Q without overtube and Olympus Endojaws disposable forceps Model FB 230V (Olympus, Hamburg, Germany). A single endoscopist performed all 41 procedures. The enteroscope was introduced to 60 cm distally from the ligament of Treitz, with a mean procedure duration comparable to conventional upper GI endoscopy under general anesthesia. Standard biopsy specimens were taken from 5 different sites (1 biopsy per site): bulb, second, and fourth duodenal regions, proximal and distal jejunum (30 cm and 60 cm beyond the ligament of Treitz, respectively). In each region, biopsy specimens were obtained where endoscopic findings ("cobblestone" mucosa, scalloping) were present; when no endoscopic feature was altered, small-bowel specimens were randomly collected in each site. All samples were carefully oriented on acetate cellulose filters and sent to the same expert GI tract pathologist, who was aware of the clinical indication to the small-bowel biopsy but blinded both to endoscopic features and sampling sites. Specimens were graded according to the Marsh-Oberhuber (MO) criteria (in brief: MO 0 = normal mucosa; MO 1 = increased number of intraepithelial lymphocytes; MO 2 = crypt hyperplasia; MO 3a = partial villous atrophy; MO 3b = subtotal villous atrophy; MO 3c = total villous atrophy).

Relative patchiness was defined as the presence, in the same patient, of a certain degree of lesion in 1 site and a