



Correspondence

Very early onset inflammatory bowel diseases: Is it the time to share and define a histopathological reporting scheme?


Dear Editor,

We read with interest the paper from Ye et al. [1] concerning endoscopic and clinicopathologic features of children with a clinical diagnosis of Very Early Onset Inflammatory Bowel Diseases (VEO-IBD). This study is one of the largest on the topic, with 225 patients included, 198 of whom with intestinal biopsies [1]. Interestingly, a comparison of morphological features retrospectively acquired from histological reports (chronic architectural damage, apoptoses, eosinophilic infiltration, small bowel villous blunting, active inflammation, intraepithelial lymphocytosis, and granulomas) showed intraepithelial lymphocytosis, apoptosis and eosinophils infiltration were significantly more common among non-monogenic IBD patients. In addition, the Authors found that the frequency of some histologic features was different based on the specific type of Monogenic Disease (MD). Recently, we described histological features from esophago-gastro-duodenal-intestinal biopsies in a cohort of 93 patients with clinical suspicion of VEO-IBD, 64 children with a conclusive diagnosis of 'true' IBD in 41 cases, MD in 13 cases, and other non-MD non-IBD colites in 10 cases [2]. Differently from Ye et al., we re-evaluated all histological samples from the gastrointestinal tract, blinded to clinical information, and assigned a histological pattern as previously described [3,4]. In detail, in the MD cases, we observed a UC-like pattern in 4 cases; a Crohn's disease-like pattern in 2 cases; an Enterocolitis-like pattern in 3 cases; an apoptotic pattern in 1 case; an IBD-Unclassified (IBD-U) pattern in 3 cases. Only the IBD-U-like pattern was significantly correlated with MD ($P = 0.02$).

Although our series is smaller compared to Ye et al.'s, if we consider both case series together, some important aspects that are fundamental in VEO-IBD management become clear and we would like to take this opportunity to share our thoughts on this difficult to approach topic.

Firstly, it is impossible to differentiate a 'true' IBD from an MD on histological features alone. The therapeutic approaches are widely different between MD (personalized targeted therapy, hematopoietic stem cell transplantation, and/or biologic agents) and true-IBD (corticosteroids and immunomodulators agents which are dangerous in MD related to Primary Immunodeficiencies). Indeed, a *histological* diagnosis of 'VEO-IBD' without adequate clinical context should be avoided, so as not to exclude possible MD causes which must be clinically/genetically ruled out.

According to ECCO Guidelines 'a combination of clinical, biochemical, stool, endoscopic, and histological investigations' are necessary for a diagnosis of IBD [5], and this is even more important in children in which an MD could be hidden by IBD-like clinical and histological features, and extra-intestinal symptoms could remain unidentified for long periods.

Secondly, we found differences in histologic patterns compared to Ye et al.'s series. Apart from a UC-like and Crohn's-like pattern, we also observed an enterocolitis-like pattern (i.e. inflammation in the absence of chronic mucosal damage), an apoptotic pattern, and an IBD-U pattern in MD. This underlines the multiple histologic manifestations in MD and underlines the necessity of exploring MD in non-IBD-like patterns as well. Moreover, in 9 patients with MD, we also re-evaluated histologic slides from upper endoscopy. Interestingly, we observed focally enhanced gastritis in 3 cases; non-atrophic gastritis not associated with *Helicobacter pylori* in 1 case; a duodenal celiac-like pattern (with villous blunting and >25 CD3+ lymphocytes/100 enterocytes) in 1 case; apoptotic duodenitis in 1 case; CMV infection with isolate apoptoses in 1 case. Due to the low number of patients, we could not identify statistically significant morphological differences between MD and non-MD in esophago-gastro-duodenal histology, however, this finding emphasizes the need to perform both upper and lower endoscopy and to acquire samples from all sites at the time of first investigation.

Thirdly, routine clinical practice teaches us that the Pathologist is often asked to make a histological diagnosis *before* in-depth clinical investigation and/or all serological/biochemical/genetic tests are performed. This makes following guidelines (which require complete findings) next to impossible; however, the Pathologists cannot delay the pathology report until all tests have been performed and they are required to formulate a diagnostic hypothesis in an adequate time. In this context, we suggest describing all histologic features of mucosal damage (glandular atrophy and distortion, type and grade of lymphoplasmacytic and/or neutrophilic infiltrate, mucin depletion and/or Paneth cell metaplasia, ulcers and erosions, granulomas, eosinophilic infiltrate, apoptotic bodies in the intestinal mucosa; villous blunting and CD3-positive lymphocytes in the small bowel mucosa and duodenum; as well as ulcers and erosion, type and grade of lymphoplasmacytic and/or neutrophilic infiltrate, granulomas, glandular atrophy, apoptotic bodies in the esophago-gastro-duodenal mucosa) from all mucosal samples. This should be reported in the histologic description while the final comment should report the histologic pattern (UC-like, Crohn-like, Enterocolitis-like, Apoptotic, IBD-U-like pattern, eosinophil-rich pattern and mixed pattern). A comment on the necessity of integration with clinical/laboratory/genetic findings (which should always be made available to the Pathologist when possible in the clinical information section of the pathology request form) should be made before a definitive diagnosis is postulated.

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Finally, this multidisciplinary approach [6] relies heavily on complete interaction between the pathologist and the clinician/geneticist and it is strongly advocated to reach timely and precise diagnoses in this specific setting of VEO-IBD.

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Conflict of interest

The Authors declare no conflicts of interest in this paper.

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