Computers in Biology and Medicine 104 (2019) 335–338

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/compbiomed

Coeliac disease under a microscope: Histological diagnostic features and confounding factors

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ARTICLE INFO

Keywords:
Gluten
Intraepithelial lymphocyte (IEL)
Microscopic enteritis
Non-coeliac gluten-sensitivity
Gut microbiota

ABSTRACT

Coeliac disease (CD) and gluten-related disorders represent an important cornerstone of the daily practice of gastroenterologists, endoscopists and dedicated histopathologists. Despite the knowledge of clinical, serological and histological typical lesions, there are some conditions to consider for differential diagnosis. From the first description of histology of CD, several studies were conducted to define similar findings suggestive for microscopic enteritis. Considering the establishment of early precursor lesions, the imbalance of gut microbiota is another point still requiring a detailed definition. This review assesses the importance of a right overview in case of suspected gluten-related disorders and the several conditions mimicking a similar histology.

1. Introduction

Coeliac disease is a chronic small intestinal immune-mediated disorder, triggered by gluten exposition in genetically susceptible subjects. The term “gluten” is used to define the variety of proteins of the grain, rye and barley that can induce the damage usually observed in coeliac subjects.

An early diagnosis, preferably in childhood, and a lifelong gluten-free diet are the most important contributions to prevent subsequent complications. The first step in the diagnosis of coeliac disease, across all ages, is a reliable screening of selected populations with symptoms or risk factors. Yet, the diagnosis of coeliac disease is often considerably delayed, exposing patients to needless suffering and morbidity. The diagnosis of coeliac disease is currently based on symptoms, clinical evaluation, serologic tests in combination with histopathological assessment of small intestinal biopsy specimens. In some cases, there are no clear diagnostic criteria and a critical and challenging evaluation of laboratory and histopathology results is required.

The Oslo Consensus provided a benchmark for the definition of classical, non-classical, asymptomatic, refractory and other categories included in the wide variety of coeliac disease [1,2].

Despite the popular knowledge of this disease, there are still many controversial aspects in the management of these patients [3]. Sometimes, people begin gluten-free diet before of a definite diagnosis or before initiating a correct gastroenterological assessment. Another confusing point regards the need of histology in paediatric population, since European guidelines recommend only serological tests in opposition to American recommendations [4,5]. Coeliac disease is a typical example of expression of a continuous dialogue between gastroenterologist, endoscopist and pathologist since it is a complex alteration requiring a specific evaluation from the clinical presentation to the histopathological architecture, involving dedicated experts.

We performed a review to assess the role of histopathology in the correct diagnosis and follow-up of the adult population affected by coeliac disease.

2. Histological diagnostic features: from Marsh-Oberhuber classification to the advanced molecular biology

Histologic evaluation of the small intestinal mucosa using endoscopic biopsy samples is the mainstay of the diagnosis of coeliac disease. The unique serological diagnosis in adults should be reserved only for those patients at elevated risk for an endoscopic procedure [3]. In this setting it is usually observed a specific damage to the superficial mucosa while submucosal, muscolaris propria and serosal layers are only rarely implicated. Histological specimens should be multiple and

Abbreviations: (CD), Coeliac Disease; (GFD), Gluten-free Diet; (IEL), Intraepithelial Lymphocyte; (Vh), Villus height; (Cd), Crypt depth; (SIBO), Small intestinal bacterial overgrowth

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https://doi.org/10.1016/j.compbiomed.2018.10.020
Received 15 July 2018; Received in revised form 16 October 2018; Accepted 17 October 2018
0010-4825/

taken when patients are on a gluten-containing diet [5,6]. Since histologic alterations in CD are patchy, multiple biopsies, one to two biopsies from the duodenal bulb and no less than four from the distal duodenum should be performed. Proper tissue orientation of the biopsy sections, perpendicular to the luminal surface, is required for accurate quantitative and also qualitative classifications [7].

Macroscopic features can include the typical flat mucosa corresponding to a completely modified structure of deformed villi [8]. Advanced studies in the epithelial turnover showed that there is also an effective increase in the enteropoiesis. Marsh [9] first hypothesized that the intestinal response to gluten can express as five interrelated lesions (preinfiltrative, infiltrative, hyperplastic, destructive, and hypoplastic) that can be considered as cell-mediated immunologic responses [10]. These responses originate in the lamina propria, where a series of antigen-specific inflammatory processes has now been identified. In this perspective, the sequential progression of the intestinal damage in coeliac disease should be: normal, pre-infiltrative mucosal (stage 0) can show an increase of Intraepithelial Lymphocyte (IEL) followed by the infiltration of IEL to the *lamina propria* (stage 1), reported as the number of IELs per unit area of absorptive epithelium or as number of IELs per 100 enterocytes. Perhaps, the most contentious issue in interpretation of the histology of coeliac disease is the significance of Marsh 1 findings. Marsh did not define the number of IELs necessary to constitute an infiltrative lesion; this was first specified in the modified criteria in which > 40 EILs/100 enterocyte nuclei were considered for diagnosis [11], although this definition is fluid, recently revised to > 25 IELs/100 [12]. The presence of > 25 IELs per 100 enterocytes characterizes this stage but has also a prevalence of 5.4% in the general population [13] and therefore should always be considered in the right setting of serological and clinical expressions. Crypts' hyperplasia (stage 2) and villous atrophy (stage 3), as reported by the historical definition, are the consequent signs of disease progression. Finally, the advanced stage consists of the complete mucosal atrophy (stage 4), composed by villous atrophy, increase of the apoptosis and crypts hyperplasia. Few years later, Oberhuber and colleagues [11] proposed a revision of the Marsh III stage, which should be considered into three subcategories (a, b, c) to be used by clinical pathologists to assist in diagnosing coeliac disease through assessing and categorizing the degrees of mucosal abnormality in small intestinal biopsies.

The Marsh- Oberhuber classification relies on the subjective judgment of the pathologist and because of this, shows low interobserver agreement and therefore, reduced reproducibility. Moreover, it is considered unreliable to make an accurate assessment of changes over time.

Another classification, the Corazza-Villanacci score, divides the coeliac disease into three grades: the non-atrophic grade A with normal crypts and villus architecture but increased IELs; the grade B, consisting of B1, atrophic with Vh:Cd ratio of < 3:1 but where villi are still clearly detectable and IELs are increased, and B2 with flat and not detectable villi.

Beyond the different classifications reported in literature, three key elements are the most commonly noted as a part of routinely clinical pathology reporting: villous height (Vh), which is most often referred to in terms of a reduction (i.e., villus "blunting", "flattening", or "atrophy"), crypt enlargement (often using terms such as "elongation" or "hyperplasia"), and an increase in IEL density, especially at the tip of the villus.

The quantitative histology allows a specific measure of Vh, Cd and IEL density per 100 epithelial cells. This can rapidly give a quantification of changes over time. This method is the preferred for assessing outcomes in clinical research and therapeutics development while it has a limited application in daily clinical practice due to the lack of awareness and time consuming [14]. Quantitative histology is required to adequately measure change in histopathology over time. This is relevant to two main clinical circumstances. First, although not universal, many physicians recommend repeat biopsy after 6–24 months of treatment with a GFD both to confirm the diagnosis of a gluten-sensitive enteropathy and to evaluate the degree of response to therapy [5,6] Second, the examination of biopsy histopathology and its comparison to prior biopsies is a pivotal point in the differential diagnosis and management of non-responsive coeliac disease. Current guidelines use this assessment of histopathologic response to determine the course of further investigation and treatment [5,6]. This important evaluation is best achieved by quantitative measurement of the relevant biopsy specimens in order to provide clinicians with the best possible information as to the degree of mucosal improvement or deterioration. Moreover, quantitative histopathology is helpful in case of detection of non-coeliac villous atrophy. A reduction in villous height to Cd ratio that is not associated with a substantial increase in IELs can point to an alternative diagnosis such as peptic duodenitis or auto-immune enteropathy [15].

Quantitative histology highlights this important distinction. In clinical practice these histologic features are most commonly qualitatively assessed; however, in the context of clinical research and therapeutics development, specific, reproducible, and quantitative measures need to be utilized to monitor responses over time and allow for clear measurement to assess efficacy end points. To date, it is also difficult to confirm histologically if dietary gluten has been restricted prior to obtaining a diagnostic biopsy, a significant problem given the current growing popularity of gluten-free diets [16].

Most advanced molecular technologies supported even the possibility of a correspondence between gene expression patterns and Marsh score categories, giving the chance to future new diagnostic tools beyond the traditional histological assessment [17].

3. Challenging duodenitis and confounding factors

Despite the availability of both biopsy and serological specific features, the diagnosis of coeliac disease sometimes is not so easy as it seems [18,19].

On the one hand the broad spectrum of gluten-related disorders is today really wider than the simple entity of coeliac disease, including gluten sensitivity, gluten allergy and the wheat gluten intolerance syndrome. In the case of negative testing for CD and wheat allergy (WA), non-coeliac gluten sensitivity (NCGS) should be considered and this condition may also reveal mildly inflamed mucosa, although IELs count is not as high as in patients with CD. Infiltration of IELs may occur in the context of wheat allergy, but other microscopic characteristics are an increase in mucosal basophil and eosinophil granulocytes [20]. Studies investigating the duodenal histology of wheat allergy are rare and it is therefore impossible to establish a clear association between typical histological alterations and wheat allergy. Non-coeliac gluten-sensitivity shows the absence of a specific marker or a characteristic clinical picture, therefore the diagnosis of this entity is based solely on the exclusion of other possible diseases and the gluten-free diet represents the only effective treatment. Recently, some studies have suggested that the triggering factor might not be gliadin, but other components of wheat, such as amylase-trypsin inhibitors or fermentable oligosaccharides, disaccharides, and polyols; for this reason, the alternative nomenclature of non-coeliac wheat sensitivity has been proposed [21,22]. The histological analysis of duodenal biopsy samples in these cases usually finds a Marsh 0 or I grade enteropathy. Increased IEL infiltration is observed in up to 25% of patients [23,24] and it is still controversial a clear border line from the condition of coeliac disease. The presence of a linear T-lymphocyte infiltration in the lamina propria, occurring in about 78.5% of patients, has been proposed as a distinct feature by a single-center study, but now it represents only a single report [25]. Finally, an increase in eosinophils has also been described [26]. However, such histological pictures represent only case series reports, and the specific microscopic characteristics of non-coeliac gluten sensitivity have not been yet established.

To add confusion in the definition of these conditions, a self-

prescribed free-gluten dietary trend is rapidly growing across the developed countries and it is now the greatest challenge that clinicians face with in the diagnosis of coeliac disease [16].

On the other hand, some histopathological changes mimicking coeliac disease can be observed in several different conditions that should be evaluated for differential diagnosis. For example, an isolated finding of diagnostic histological changes in the bulb must be interpreted cautiously in order to avoid false positive diagnosis. Coeliac disease is the most common cause of villous modified architecture, but there are several different conditions leading to a similar histopathology. Kowalski et al. recently provided a complete list of the possible conditions in differential diagnosis [27].

The term “microscopic enteritis” (ME) was first described in 2009 [28] and recently defined during the Bucharest Consensus in 2015 [29]. ME indicates an histological condition implicating that the villous structure is largely preserved, but the epithelium is variably infiltrated by small lymphocytes, and there may be increases in crypt depth (crypt hyperplasia). IELs are T-lymphocytes responsible for the immune surveillance and therefore can be activated by gliadin but also bacteria, drugs ‘components and food [30,31]. The gluten related disorders associated with ME are CD with minimal macroscopic changes, gluten/wheat allergy and non-coeliac gluten sensitivity (NCGS).

In absence of positive serology and HLA DQ2/DQ8, clinicians should consider performing additional testing for parasites, bacterial or viral infections, anti-enterocyte antibodies or serum immunoglobulin level and at the same time an experienced gastrointestinal pathologist should review the biopsy specimens [32]. Medication related villous atrophy was described after some immunosuppressive agents (azathioprine, methotrexate or mycophenolate) or even with NSAIDs or sartans. Peptic duodenitis sometimes can present with VA of the duodenal mucosa, rapidly responding to acid suppressive therapy. Food allergies can lead to increased IELs and partial VA, as well as eosinophilic gastroenteritis. Crohn's disease is another critical point sometimes mimicking coeliac disease, since can bring to variable distortion of the duodenal architecture.

Infections interesting the small bowel should be suspected during a detailed medical history and include *Helicobacter pylori* and *Giardia lamblia* infection, post-viral enteropathy or small intestinal bacterial overgrowth (SIBO), AIDS enteropathy, Whipple's disease or finally tropical sprue.

Blood malignancies can involve the duodenum with an uncertain morphologic damage.

Autoimmune enteropathy is possible as well as an involvement in extraintestinal autoimmune disorders. Finally, Common variable immunodeficiency or some types of neoplasia of the white blood cells (Enteropathy-type intestinal T cell lymphoma (EITCL)/enteropathy associated T-cell lymphoma (EATL) or Immunoproliferative small intestinal disease (IPSID)) have been described as clinical cases first suspected for coeliac disease [33].

According to most recent evidence, the activation of IELs in the intestinal mucosa could be linked to the imbalance in the gut microbiota and its metabolome. Dysbiosis [34] is able to activate innate immunity leading to pro-inflammatory changes, which induces intraepithelial lymphocyte infiltration and epithelial barrier damage, ultimately resulting in increased transfer of gluten peptides and inflammatory activation leading to CD development [35,36]. *Bifidobacterium* and *Bacteroides fragilis*, indeed, are able to digest immunogenic gliadin peptides, which are rich in proline residues but resistant to human enzymes [37,38]. Interesting data arised from faecal analyses in patients affected by CD, showing a bacterial imbalance with an increased numer of *Bacteroides, Escherichia coli* and *Staphylococcus* and a less diversity in *Bacteroides* species was described as well, regardless the adoption of GFD [39].

4. Conclusion

Coeliac disease is a unique and complex disorder, affecting first the small bowel and can express with several clinical, serological and also histopathological features. The importance for gastroenterologists to face with several conditions mimicking coeliac disease and to understand the histopathology assessed is the key point of the next generations, considering the widespread use of self-imposed gluten free-diet and the gluten-related disorders not defined as coeliac disease. Gluten is considered necessary for causing coealiac disease, but probably several mechanisms concerning the gut microbiota and intestinal epithelium can precede the specific gluten-dependent immune response. Understanding these specific pathways and the promoting role of the gut microbiota could prepare the future to new therapeutic approaches [40].

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