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Review Article

Challenges in Celiac Disease Diagnosis

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Abstract: Celiac disease (CD) is the most common immune-related gastroenterology which is evoked by the ingestion of gluten peptides found in several types of grains, a condition that rises up both intestinal and extra-intestinal manifestations. Multiple disease may simulate the CD both in the clinical or pathological diagnosis. This issue should be remembered in dealing with suspicious patients having CD. This article focuses on the main pathologies that may pose similarities with CD.

Keywords: Celiac Disease (CD), Gluten, Immunological, Histopathological.

INTRODUCTION

Celiac disease (CD) is an autoimmune gluten-triggered gastroenterology disease with both intestinal and extraintestinal manifestations. The incidence of CD has been progressively increased since the firstly focusing on the disease in 1970s.The etiology for this increasing is unknown but the change in the feeding habits, agricultural manipulation for the seeds and the development of the high sensitivity and specificity diagnostic tools [1].

Although the progression in the invention of highly specific and sensitive serological antibody titer but the histological interpretation still the cornerstone in diagnosing CD [2, 3].

The most prevalent manifestations of CD include malabsorption, mineral deficiency and anemia. Several conditions have similar clinical presentations to CD that may induce a diagnosing challenge, especially the condition Known as non-celiac gluten-sensitivity (NCGS). A defiance in diagnosing CD exists in both the clinical and histological levels [4]. Nevertheless, many cases of CD are still underdiagnosed due to the heterogeneous manifestations and the ignorance about the disease [5, 6].

DIAGNOSIS OF CELIAC DISEASE

A chameleon is the pattern that CD is compared to, since there is wide variability in the symptoms from patient to another. Combination of clinical, serological ,genetic and histopathological assessment is required for the exact diagnosis of celiac disease [7, 8].

Serological Markers: The primary diagnosis of CD is made by the serological measurements (as non-invasive tools) for the titers of the CD-specific antibodies. In the last decades, there was a progression in both the specifity and sensitivity of these antibodies which may allow the diagnosis without requiring for a duodenal biopsy. Anti tissue transglutaminase and anti-deamidated gliadin are the most usable tests nowadays [9, 10].

Fecal Gluten immunogenic Peptide (GIP): is considered as advanced quantitative technique to and diagnose and measure the activity of CD.

Genetic study: All patients with CD are positive for HLA-DQ2 andDQ8. This genetic assessment is used mainly in highly suspected cases when there is high discrepancy between the erological and histological findings. Also it is applied discover the predisposition of first degree relative in a families having patients with CD [11, 12]. About 30-40% of western Caucasian population may have this haplotype without developing CD [13].

Histopathological Assessment: In spite of the progress of the serological and genetic investigations but still the histopathological evaluation is the cornerstone in the diagnosis of CD [14]. Duodenum is the standard site for biopsy interpretation. Recently most of biopsies are taken by the endoscopic maneuver [(15].

Several Points Regarding the Handling of the Biopsy Include:

Site of the duodenal Biopsy: at least 4 pieces(2 from the bulb and 2 from the 2nd portion) should be taken during the endoscopy since the intestinal changes can be patchy and not uniform [16].

Sample Handling: is considered as an important issue to clarify the histological changes associated with the CD. A proper orientation , fixation and embedding of the biopsy is a crucial event in order to avoid artifacts in diagnosis and this is best achieved with the use of cellulose acetate filters [17, 18].

Histological Analysis: villi height, villi to crypt ratio (normally 3:1), intraepithelial lymphocytosis (IEL) are the most important points to deal with a biopsy for cases suspected of CD. The existence of lymphocytes in between the enterocytes is considered as usual observation but should not exceed 25:100 enterocytes [19]. The application of CD3 (anti-T lymphocytes) immunostaining started to be a routinely used technique in some centers. Anti CD3 immunostaining detect the distribution and the count of IEL which facilitates the diagnosis of CD [20]. Since the duodenum interacts with variable antigenic challenges associated the food, existence of different types of inflammatory cells in the lamina propria is accepted. This includes plasma cells, eosinophils, mast cells lymphocytes and histiocytes. Neutrophils are usually absent except in active duodenitis [21]. High count of eosinophils is associated with eosinophilic gastroenteritis [22].

Histopathological changes: Essential points to consider in the diagnosis of CD are:

Increased intra-epithelial lymphocytes (IEL): More than (30 lymphocytes in duodenum or 40 in jejunem) per 100 enterocytes.

Crypt Hyperplasia: Increased extention of the regenerative crypt with at least more than one mitosis.

Villi disfiguration(atrophy): With progressive loss of it' height and a reverse percent to the crypt extention.

All the above changes are not specific to CD and can be observed in other disorders. Combination of clinical , serological, histopathological and genetic study is essential to reach the final diagnosis of celiac sprue [23]. The modified Marsh-Oberhuber classification of the histological classification is most accepted and used system as shown in the following table [24].

Marsh grade	IEL:>40/100 Enterocytes jejunum	IEL:>40/100 Enterocytes duodenum	Crypt hyperplasia	villi
0	< 40	< 30	Normal	Normal
1	>40	>30	Normal	Normal
2	>40	>30	Increased	Normal
3a	>40	>30	Increased	Mild atrophy
3b	>40	>30	Increased	Moderate Atrophy
3c	>40	>30	Increased	Sever atrophy
4	>40	>30	atrophic	flat

Differential diagnosis of Celiac disease

Wide list of pathogenic entities may simulate CD both in the clinical and histopathological features. This issue may induce a challenge in the diagnosis. These disorders may present as malabsorption, diarrhea, weight loss and even anemia. Some of them may run as an acute episode like tropical sprue or bacterial overgrowth.

Non celiac gluten sensitivity (NCGS)

Non celiac gluten sensitivity (NSGS) is a clinical condition with both intestinal and/or extra-intestinal symptoms that evoked by ingestion of gluten and can be improved once the gluten is removed from the diet. The term NCGS is included within a group of disorders called Gluten-related disorders(GRD) with other two disorders ,CD and wheat allergy(WA),two entities that should be rule out before diagnosing NCGS [25, 26].

The histological changes of the NCGS is variable and non specific, occasionally with normal to mild villous shortening, mild increase of IEL in the superficial epithelium and linear deposition of T-lymphocytes in the deep mucosa and mild eosinophilia in the lamina propria [7, 27].

Infectious diseases

Wide range of parasitic (especially the giardia [28] and cryptosporidiosis [29]),viral, bacterial &tropical sprue [30]. Helicobacteria duodenitis may cause similar clinical /or histopathological manifestations [31].Whipple disease is another infectious entity that may evoke a diagnosis ambiguity [32]. There are multiple diagnostic tools including the PCR, to discriminate between the infectious gastroenteritis from celiac disease [33].

Drugs

Different drugs may induce histopathological changes in duodenum. These include non-steroidal anti-inflammatory drugs, anti-neoplastic, immune modulatory and angiotensin receptor blockers. The endoscopy may reveal erosions, mucosal edema and ulcerations. The associated histological changes are variable and can be seen as neutrophilic infiltration, erosions, villous atrophy, crypt distortion and apoptosis [34].

Other Inflammatory Conditions

Other inflammatory conditions may mimic CD in both presentations and histological features.

Autoimmune enteritis, collagenous sprue may evoke a challenge in the diagnosis of CD [35].

Common variable immune deficiency (CVID), the most common form of the primary immune deficiency is commonly associated with intestinal histopathological changes. Variable degree of mucosal atrophy is associated with the CVID and this may rise a diagnostic similarity with the CD. Other microscopical changes include disappearance of mucosal plasma cells and the infiltration of polymorphonuclear inflammatory cells. Of course, Gluten free diet can differentiate between the two entities. Noticeably both CD and CVID can present in the same patient [36].

Duodenal Crohn's disease has characteristic histology with granuloma formation and transmural lymphoid aggregate. Sometimes, the changes are patchy and non specific with mucosal erosion and villous destruction [37].

Helicobacter pylori (HP) duodenal involvement is associated with mucosal lymphocytogenesis with minimal villous atrophy and evident neutrophilic infiltration. All these changes may aid in separating CD from HP duodenitis [38].

CONCLUSION

Celiac disease is beholden as one of the most common gastrointestinal disorders with variable intestinal and extra-intestinal manifestations. In spite of that, the diagnosis of CD is not an easily task since multiple pathological conditions can mimic CD both clinically and histologically. Even the genetic investigations of CD may be found as a haplotypes in 30% of general population, a dilemma that may complicate the diagnosing issue. Several factors may influence the detection of CD like the handling and proper orientation of the duodenal biopsy by the endoscopist and technician which is an essential step in the discovery of CD. Final diagnosis of CD depends on combinations of the following factors; clinical examination, proper endoscopic maneuver, accurate histological detection, using high sensitivity-serological test and the assistance of HLA-genetic testing.

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