Chapter 10

Small Intestine Biopsy and its Interpretation: Preliminary Results in Costa Rica

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Celiac disease is an autoimmune disease with diverse histopathological changes of the small intestine which are fundamental for the diagnosis of the disease. The main changes are intraepithelial lymphocytic infiltration of the intestinal mucosa, with or without villous atrophy. The number of biopsies has to be adequate, at least six, because the histopathological abnormalities often have a patchy distribution. The disease may exhibit only minimal alterations along with the intraepithelial lymphocytic infiltrate, which can be shared with other non-celiac entities. We recommend the use of the Corazza-Villanacci classification because it has demonstrated a better correlation among pathologists.

We present the results of 258 patients (108 male and 150 female) with celiac disease in Costa Rica with lymphocytic duodenitis and villous atrophy. Mean age was 48.3 years, ranging between 16 and 90 years. Furthermore, in 35 patients, HLA-DQ2 and HLA-DQ8 genotyping was performed; 11 cases were positive for HLA-DQ2, 7 for HLA-DQ8, and 3 for both HLA-DQ2 and HLA-DQ8. 15 cases were negative, but had only lymphocytic duodenitis, which should be studied further and are currently being followed-up.
1. Introduction

The interpretation of celiac disease biopsies for CD diagnosis has evolved due to the knowledge of reliable genetic and serological markers. Correct and timely diagnosis of celiac disease is necessary to start a gluten-free diet and reduce the risk of chronic complications.

Serological tests are useful for detecting gluten intolerance, and include IgA anti tissue transglutaminase antibodies, IgA anti endomysial antibodies and IgA and IgG anti-gliadin, plus IgA anti retculin. Of these, the first two have optimal sensitivity and specificity, with a high positive predictive value. However, it has been observed that up to 5-15% of all patients with celiac disease may have normal values and up to 30% in cases with minor mucosal changes. This is associated with the fact that between 20 to 50% of the patients have no obvious malabsorption symptoms. Duodenal and jejunal biopsies remain for the time being the “gold standard” necessary to confirm the celiac disease diagnosis.

The classic histopathological small intestine mucosal alterations, such as flattening of the villi, were described originally by Paulley in 1954 in surgically obtained samples. This villous atrophy was considered for many years as the main criterion needed for the celiac disease diagnosis. Subsequently, the recognition of subtler changes, specially the intraepithelial inflammatory infiltrate and in the lamina propria, acquired importance to help understand the histological features of the disease. For these reasons, Marsh classified histological patterns of mucosal damage in the small intestine. These changes, which represent progressive stages, include increased intraepithelial lymphocyte infiltration, even in an intestinal mucosa with no atrophy, followed by the varying degrees of atrophy in four categories (1 to 4), together with the increase in the lamina propria inflammation and a progressive alteration of the mucosa. These criteria were modified by Oberhüber in 1999, who, in turn, divided the type 3 lesion into three subgroups based on the severity of atrophy and eliminated type 4. Villous atrophy belonging to type 3A is of a mild degree, type 3B is defined by moderate or subtotal atrophy and type 3C by a totally flat mucosa. This classification is now being used routinely by many pathologists.

2. Location and Amount of Biopsies

Small bowel biopsies have increased significantly in recent years, mainly because clinicians are aware of the existence of less severe forms of celiac disease; likewise, the number of endoscopic procedures of the upper gastrointestinal tract has increased. The new endoscopes allow a more detailed view of the villi, but in most patients, if there is no marked atrophy, changes are not visible. The features of "patchy" villous atrophy have been discussed in the literature in relation to the number of samples to be taken and the optimal place for taking biopsies. The American Gastroenterological Association (AGA) recommends taking at least 6 biopsies in the second duodenal, or more distal, portion in order to search for celiac disease. In daily practice, it is suggested that a total of 6 biopsies be taken: 4 biopsies from the distal duodenum, 2 from the duodenal bulb, to reduce the possibility of error attributable to the existence of an irregular or non-homogeneous distribution of the disease.
3. Normal Small Bowel Mucosa

The small intestinal mucosa should be assessed based on normal morphology, which must be known by the pathologist who will diagnose this organ biopsies. The villi biopsies under analysis must be properly oriented, the entire villi should be observable with an adequate view of the muscularis mucosae. The presence of the muscularis mucosae in the biopsy itself is critical, because it allows a comprehensive assessment and without it, the biopsy cannot be regarded as adequate for evaluation. In daily practice, the villi are not always arranged vertically and upwards but tend to bend in different directions. Furthermore, when there is lymphoid hyperplasia, villi tend to flatten, due to the effect to the lamina propria injury. To avoid interpretation problems, it has been proposed that biopsies of the small intestine should be considered representative when at least four tall villi are observed and aligned in any serial biopsy cut.¹⁴

The upper region of normal ends in an arrow shape, which occurs gradually in the villi’s upper third. Groups of 3 to 5 well-oriented villi ought to be evaluated in order to define their ratio in relation to the crypts. The villi height should be of at least 3 to 1, even 5 to 1, in relation to the crypts, depending on the biopsy site (Figure 1). Shorter villi are proximally found in the duodenum, while their height increases distally from the jejunum towards the ileum, where they shorten again.

The orientation of biopsy specimens is essential to proper interpretation and analysis. Some authors have suggested that biopsies be placed on a support surface, such as filter paper, in order to achieve an appropriate vertical orientation.¹⁵ Pathologists must help histotechnicians become aware of these facts and educate them about the importance of biopsy orientation in order to obtain a proper evaluation. Magnifying glasses must be routinely used for gastrointestinal biopsy inclusions since this helps identify the sample’s base due to the presence of dark spots, which correspond to the blood vessels cut transversally during sampling. This helps the technician guide biopsy vertically into the paraffin inclusion.¹⁶

The crypts’ volume also defines the existence of a lesion since they normally will not exceed two gland’s thickness, so that any increase should be considered as abnormal and therefore should be carefully evaluated in all aspects. Its increase implies a lengthening of the crypts of Lieberkühn within a progressive process that usually precedes the onset of villous atrophy.
Figure 1. Well-oriented normal duodenal mucosa with proper 3:1-4:1 villi/crypts ratio, with intraepithelial lymphocytes showing the pattern of progressive decrease towards the apical part.

The enterocytes lining the villi show a slightly eosinophilic cytoplasm, homogeneous in appearance. Special attention must be paid to the enterocytes found in the upper third since, should there be immune injury, the cytoplasm tends to have vacuoles.

At the lamina propria level, the normal inflammatory infiltrate is mild, including lymphocytes, plasma cells and some eosinophils against a background where light areas are still observed, without inflammation; this covers about a third of the bottom of the lamina propria. If there is an increased inflammatory infiltrate, these clear zones tend to disappear and the lamina propria fills with inflammatory mononuclear cells. Occasionally, neutrophils can be observed; this has been described in relation to the existence of activity in the disease’s inflammatory process.

4. Histological Changes of Celiac Disease

Celiac disease symptoms are thought to be more related to the extent of affected bowel than to the intensity of the lesion. The severity of the injury is also greater in the proximal small intestine than in the distal; however, in many cases, patients who are being studied due to diarrhea first undergo a colonoscopy, so terminal ileum biopsies are frequently taken to rule out the possibility of celiac disease. The pathologist must be aware for mucosal alterations in the terminal ileum, since in the literature they are described as mild, but changes such as increased
intraepithelial lymphocytes may be an important sign that leads to suspect the presence of an associated celiac disease.20-21

The morphological alterations to be evaluated are architecture abnormalities (such as shortening of the villi), crypt hyperplasia, increased presence of intraepithelial lymphocytes and expansion of the lamina propria's inflammatory mononuclear infiltrate. However, these characteristics, both individually as well as combined, may be nonspecific.

5. Intraepithelial Lymphocytic Infiltrate

Celiac disease is an immune process, therefore intraepithelial lymphocytes are responsible for the epithelial injury. This is the first change and the most sensitive indicator of the effects of gluten on the small intestine mucosa: type T lymphocytes, mainly cytotoxic.22 Furthermore, the lamina propria also will respond immunologically and a significant increase of lymphocytes, plasma cells and macrophages is observed.

Counts greater than 40 intraepithelial lymphocytes per 100 enterocytes were formerly considered abnormal. Over the years, this value been tweaked with the lowering of this threshold down to the point where today 20 intraepithelial lymphocytes per 100 enterocytes is considered to be normal, that is to say, a ratio of one lymphocyte per 5 enterocytes.23 One of the reasons for this lies in the fact that the place where biopsies are taken has gradually changed, which has led to the observation that normal jejunal mucosa has a greater count of intraepithelial lymphocytes than the duodenal mucosa. When a specific anti-CD3 lymphocyte immunohistochemistry is performed, due to a higher sensitivity than that observed with hematoxylin-eosin, a limit of 25 intraepithelial lymphocytes per 100 enterocytes ought to be considered.23 Immunohistochemistry should not be used routinely in the evaluation of biopsies to screen for celiac disease, but it must be insisted that the pathologist must analyze the largest possible number of duodenal biopsies to become familiar with the normal number of intraepithelial lymphocytes. The cost of this biopsy evaluation should not be increased, nor should the pathologist’s time be wasted or else delay diagnosis with this technique; it would be wiser rather to seek a second opinion or recommend a serological test.

In daily practice, the intraepithelial lymphocyte count can be a little impractical since it involves counting from 300 to 500 enterocytes. It should be performed in a well-oriented villi, excluding the base crypts. According to experience, a duodenal villus of mean height contains 90 to 110 enterocytes, so, while analyzing 3-5 villi, the total enterocyte count may be disregarded and only count the intraepithelial lymphocytes. The distribution pattern of normal lymphocyte density in the villi is higher towards the base and decreases as it reaches the luminal end (Figure 1).19

In recent literature, a more practical way to perform celiac disease screening in small bowel biopsies has been proposed, in which the intraepithelial lymphocytes in tips of five well-oriented villi are counted; each tips has about 20 enterocytes each (Figure 2). The normal intraepithelial lymphocyte average count using the tip counting method is equal to or less than 5 per each 20 enterocytes, while a larger number is considered suggestive of or compatible with the existence
of gluten intolerance. It must always be borne in mind that there are a variety of entities which can also lead to an increased intraepithelial lymphocyte count, so that this change cannot be considered as an exclusive diagnostic criteria for celiac disease, but should be included within a range of differential diagnoses.

Figure 2. A. The villi exhibit sharp or pointed ends, with the presence of less than 5 intraepithelial lymphocytes (hematoxylin-eosin, x400). B. The villus has a significant increase in intraepithelial lymphocytes, greater than 5 (hematoxylin-eosin, x400).

Besides celiac disease, there is a group of disorders that have a morphology similar to early celiac disease, including normal villous architecture with increased intraepithelial lymphocytes (greater than 5 per 20 enterocytes) morphology. These conditions are described below (Table 1).

<table>
<thead>
<tr>
<th>Causes of intraepithelial lymphocytosis in a small intestine with normal villous architecture (Brown, 2006).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluten sensitivity</td>
</tr>
<tr>
<td>Hypersensitivity to gluten-free foods: Cow milk protein, rice, chicken, fish, other cereals, etc.</td>
</tr>
<tr>
<td>Infections: Helicobacter pylori, giardiasis and cryptosporidiosis</td>
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<tr>
<td>Bacterial overgrowth</td>
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<tr>
<td>Non-steroidal anti-inflammatory drugs (NSAIDs)</td>
</tr>
<tr>
<td>Immunological deficiencies: common variable immunodeficiency, IgA deficiency</td>
</tr>
<tr>
<td>Immunological alterations: Hashimoto’s Thyroiditis, rheumatoid arthritis and systemic lupus erythematosus</td>
</tr>
<tr>
<td>Intestinal inflammatory disease</td>
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</tbody>
</table>
Among these, hypersensitivity to various foods may be included, among which milk proteins, rice, chicken, fish and other cereals stand out, besides the presence of infections such as *Helicobacter pylori*, *giardiasis* and *cryptosporidiosis*. *Giardiasis* also produces a significant increase in mononuclear inflammation of the lamina propria, including the presence of lymphoid follicles, which are relatively rare in celiac disease. Also, bowel bacterial overgrowth syndrome is secondary to various viral and bacterial enteritis.

An important issue is enteric damage related to the toxicity of various drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), which has been confirmed, since upon withdrawal of the drug, symptoms and histological features become normalized. Immune deficiencies such as common variable immunodeficiency (CVID), which is marked by minimal presence or complete absence of plasma cells level of the lamina propria cells, which can be corroborated through immunohistochemistry. Other immune disorders may include such as Hashimoto’s thyroiditis, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Chronic inflammatory bowel disease (IBD), can also cause lymphocytic duodenitis, particularly in cases with Crohn’s disease.

### 6. Villous Atrophy

The assessment of villous atrophy should be done only in well-oriented histological sections. These changes may be focalized, so if enough fragments were not analyzed, the result may be a false negative. If the received fragments are few (less than 4), new cuts can be made, which could show areas with alterations. It must be pointed out that diagnostic reliability is crucial because low reliability can mean a significant number of misclassified cases.

Villous atrophy has been considered as one of the most characteristic alterations in the diagnosis of celiac disease.\(^8\) However, pathologists should be aware that there are other diseases to include in the differential diagnosis, which may include various degrees of atrophy, which are listed below (Table 2).

<table>
<thead>
<tr>
<th>Causes of atrophy and flattening of the villi (Ensari, 2010)</th>
<th>Table 2. Causes of atrophy and flattening of the villi (Ensari, 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Autoimmune enteropathy</td>
<td></td>
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<tr>
<td>- Microvillus inclusions disease</td>
<td></td>
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<tr>
<td>- Tropical sprue</td>
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<tr>
<td>- Collagenous sprue</td>
<td></td>
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<tr>
<td>- Radiochemotherapy</td>
<td></td>
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<tr>
<td>- Graft vs host disease</td>
<td></td>
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<tr>
<td>- Nutritional deficiencies</td>
<td></td>
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<tr>
<td>- Chronic pancreatitis</td>
<td></td>
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<tr>
<td>- T-cell lymphoma induced enteropathy</td>
<td></td>
</tr>
</tbody>
</table>

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\(^{33}\)
7. Crypt Hyperplasia

Crypt hyperplasia produces elongation, a process that initially precedes villous atrophy. This is a change secondary to enterocyte loss on the villi surface, as an expression of immunological injury caused by celiac disease. The crypts contain cells capable of renewing enterocytes and it is common to observe the presence of significant mitotic activity at this level, which under normal conditions is rare, but not a reliable indicator of crypt hyperplasia.7

8. Histological Classification of Celiac Disease

In 1992 Marsh designed a system to classify morphological changes secondary to gluten sensitivity enteropathy, which was later amended by Oberhüer in 19998 This system integrated celiac disease pathophysiology with its histological alterations morphological changes, grading the presence of immunological disorders in conjunction with architectural changes of the mucosa (Table 3).

<table>
<thead>
<tr>
<th>Marsh-Oberhuber Classification</th>
<th>Corazza-Villanacci Classification</th>
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</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Tall and normal crypt architecture with ≥30 IELs/100 enterocytes</td>
</tr>
<tr>
<td>Type 2</td>
<td>Normal villous architecture, crypt hyperplasia and ≥30 IELs/100 enterocytes</td>
</tr>
<tr>
<td>Type 3a</td>
<td>Partial villous atrophy with crypt/villi ratio of &lt;3:1 or 2:1, crypt hyperplasia and ≥30 IELs/100 enterocytes</td>
</tr>
<tr>
<td>Type 3b</td>
<td>Subtotal villous atrophy with villi/crypt of &lt;1:1, crypt hyperplasia and ≥30 IELs/100 enterocytes</td>
</tr>
<tr>
<td>Type 3c</td>
<td>Total villous atrophy (flat mucosa) with marked crypt hyperplasia and ≥30 IELs/100 enterocytes</td>
</tr>
<tr>
<td>Type 4</td>
<td>Hypoplastic atrophic lesion (flat mucosa) with only a few crypts and near-normal IEL count</td>
</tr>
</tbody>
</table>

Table 3. Comparison of histopathological classifications of mucosal changes associated with celiac disease (Bao, 2012).34
However, this classification have had the problem that type 1 and 2 mucosal alterations are often not recognized and, in subtype 3, there is a great variability between observers, even among expert gastrointestinal pathologists. Therefore, in 2005, Corazza and Villanacci proposed a simplified classification scheme in order to reduce the possibility of disagreement in assessing celiac disease biopsies. Their proposal was to reduce the original five Marsh-Oberhübe classification categories to three (Table 3). This includes two simple categories: First, Grade A, comprising lesion without atrophy and, second, Grade B comprising atrophic lesion (Figure 3). B grade lesions are subsequently subdivided into types B1 and B2, which depend on atrophy with the presence or absence of villi. This classification is based on the recognition of type 2 Marsh-Oberhübe injury; types 3a and 3b are not essential for the diagnosis and monitoring of celiac disease.

Figure 3. Different degrees of duodenal injury. A: Normal villous height and ratio, with increased intraepithelial lymphocytic infiltrate corresponding to Corazza Villanacci Grade-A (Marsh type 2) (hematoxylin-eosin, x100). B: Moderate villous atrophy and diffuse intraepithelial lymphocyte infiltration, corresponding to Corazza-Villanacci Grade B1 (Marsh type 3b) (hematoxylin-eosin, x100). C: Marked villus atrophy with diffuse intraepithelial lymphocyte infiltration, Corazza-Villanacci Grade B2 (Marsh 3c) (hematoxylin-eosin, x100).

The simplification of histopathological classifications has been shown to increase concordance among pathologists, as it has happened with low grade and high grade dysplasia classification.

When the degree of diagnostic agreement or concordance on celiac disease between pathologists was compared, it rose from 0.35 according to the Marsh-Oberhübe classification to 0.55 with the new Corazza-Villanacci classification. Therefore, its use is recommended since it facilitates the correct interpretation of the histological lesions and it reduces the possibility of disagreement on gluten enteropathy, thus benefiting the diagnosis and management of patients.
9. Celiac Disease in Costa Rica

The preliminary results of celiac disease studies in Costa Rica are presented, from 2006 to 2012, from an open endoscopy service at CIMA Hospital and from private Endoscopy Clinics sent to the Pathology Laboratory. Biopsies were submitted with an application with the patients’ data, including age and gender as well as clinical data including studies on chronic diarrhea, abdominal pain or celiac disease. Cases with a lymphocytic duodenitis diagnosis were searched for in the laboratories’ databases, up to a total of 643 patients with their respective biopsies. These biopsies were taken from the duodenum and were analyzed by one of the authors (F.B.), classifying them using the Corazza-Villanacci system of atrophy degree definition. However, serological results in Costa Rica using ant-transglutaminase have, in daily practice, often been negative, which was demonstrated in a previous work that used an IgA and IgG anti-transglutaminase detection system. Since the expected results were not reliable and, since we only found 15% positivity in biopsies with some degree of atrophy, these were excluded from analysis in this preliminary work.

Only those patients with some degree of villous atrophy were included, including Corazza-Villanacci B1 and B2 and which responded to the gluten-free diet; a total of 258 patients (Table 4).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age ± SD (range)</td>
<td>48.3 ± 16.5 (16-90)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>108 (41.9)</td>
</tr>
<tr>
<td>Female</td>
<td>150 (58.4)</td>
</tr>
<tr>
<td>Corazza classification</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>246 (95.3)</td>
</tr>
<tr>
<td>B2</td>
<td>12 (4.7)</td>
</tr>
<tr>
<td>Number of Biopsies ± SD (range)</td>
<td>4.6 ± 1.7 (2-14)</td>
</tr>
</tbody>
</table>

*Table 4. Characteristics of 258 patients with celiac disease in Costa Rica.*

The average age was 48.3 years, with slight female predominance (58.4%) over males (41.9%). Most patients corresponded to grade B1 Corazza-Villanacci classification (mild to moderate atrophy) (95.3%). Severe atrophy (B2 level), was only observed in a small group of 12 patients (4.7%).

Since duodenal endoscopic studies were initiated in Costa Rica, special emphasis was placed on the importance of the number of biopsies taken, which is reflected in the average number of fragments, which was of 4.6 per case.

Regarding the number of cases diagnosed during the observed period, it is noteworthy that, during the first two years, the number was relatively lower than in later years probably because of the generalized idea that celiac disease was rare in our environment (Figure 4). Approximately
50% of the cases classified as grade B1 were under 50 years of age, while B2 cases, 67%, were over 50 years of age; this is compatible with a longer disease evolution. However, these data will be complete when they are analyzed and all studies are finished (Figure 5).

Regarding another issue related to these patients, peripheral blood samples were taken from a group of 36, from which DNA was extracted, and the HLA-DQ2 and DQ8 genotypes were detected with HLA-DQA1, HLA-DQB1 and HLA-DRB1 exon 2 amplification using the CeliacStrip® system from Operon (Zaragoza, Spain) as per the manufacturer's instructions. The results were displayed in a hybridization nylon membrane. The cases described responded to the GFD. This group took into account all biopsies of the total original group independently the presence or absence of an atrophy. They accounted for 29 female patients (78.4%) and 8 males (21.6%) with a mean age of 46.2 (range 18-79 years, SD 14.7 years). Most of the cases, 23 were under 50 years of age 50, 64%. The Corazza-Villanacci classification found 27 grade A cases and 9 B1 cases, with no cases of severe atrophy.

![Figure 4. Annual distribution of celiac disease cases in Costa Rica.](image-url)
Celiac Disease and Non-Celiac Gluten Sensitivity

Figure 5. Age distribution of celiac disease cases in Costa Rica classified as Corazza-Villanacci B1 and B2.

Out of 36 cases, 20 were carriers of risk haplotypes, distributed in 11 cases HLA-DQ2 (+), 7 HLA-DQ8 (*) cases and 3 cases with simultaneous HLA-DQ2 and HLA-DQ8 (+). In addition, 15 cases were negative for these haplotypes, however, further studies are required to complete these data.

Most of the cases were of biopsies without villous atrophy. These included the 11 cases which were negative for risk haplotypes, which subsequently make it imperative to corroborate whether they were celiac patients or not (Table 5).

<table>
<thead>
<tr>
<th>HLA</th>
<th>Grade A</th>
<th>Grade B1</th>
</tr>
</thead>
<tbody>
<tr>
<td>DQ2 +</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>DQ8 +</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>DQ2 + y DQ8 +</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>DQ2 – y DQ8 –</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 5. HLA-DQ2 and HLA-DQ8 duodenal biopsies from 36 Costa Rican patients classified according to Corazza-Villanacci.
10. Conclusions

Celiac disease is an immune process, which causes highly variable morphological alterations in the small intestine in genetically susceptible individuals. The small intestinal biopsy still remains the gold standard for the diagnosis of celiac disease. Small intestinal biopsies can confirm the diagnosis when clinical and serological assays suggest this disease, or else suggest it when patients have subclinical or atypical presentations or else when serology fails to support the diagnosis. Once the diagnosis is established, histological evaluation is an important appraisal of adherence to the gluten-free diet when response to it is unsatisfactory, as well as to detect possible gastrointestinal involvement. The pathologist who examines the biopsy should be aware of possible differential diagnoses of morphological changes, especially in the early stages of celiac disease.

The experience of celiac disease diagnosis in Costa Rica demonstrates that patients ought to be comprehensively analyzed by a team of professionals including gastroenterologists with adequate training for duodenal biopsies, in conjunction with pathologists able to interpret tissue-level changes, since biopsies could be the first wake-up call for further studies of the patient’s case. Serology for anti-endomysium and anti-transglutaminase antibodies are essential in addressing the patient and must have adequate quality control so that results are reliable. Finally, HLA-DQ2 studies should be a basic part of the celiac disease tests, however, the characteristics of the Latin American population have not been fully studied yet and it is necessary to seek other haplotypes that may also be related to the appearance of disease.
References


