Chapter 8

Intestinal Biopsy in the Diagnosis of Celiac Disease: Is it Still the Gold Standard?

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Abstract

Pathology plays a crucial role in the diagnosis of celiac disease (CD). The pathologist's role is to confirm the diagnosis of CD; to exclude other diseases that share morphologic features with CD and to diagnose complications in patients with CD. Therefore, the significance of the small bowel biopsy includes confirming the diagnosis but also reassuring the clinician that other etiologies are excluded. Some of these diseases share many similarities with CD, such as villous atrophy and intraepithelial lymphocytosis, and the small bowel biopsy helps with this distinction.

The use of standarized pathology reporting including the appropriate classification system is highly recommended in order to facilitate the interpretation of the pathology report and the communication between pathologists and clinicians. Despite the need for a small bowel biopsy in the initial work up of CD, some patients and particularly children, may be spared a small bowel biopsy if certain clinical and laboratory findings are present in order to confirm the diagnosis without a biopsy. It is important to emphasize that the pathologic findings need to be correlated with the clinical, endoscopic and serologic findings in all the patients suspected of CD.

Keywords

Celiac disease, pathology, differential diagnosis, villous atrophy.

1. Introduction

Celiac disease is known to affect people of all ages with an increasing recognition in older individuals as well as children. The increased awareness has led to more individuals being suspected of having celiac disease (CD) and as such pathologists have encountered in their practice an increasing number of small bowel biopsies. The diagnosis of CD includes clinical, laboratory, endoscopic and pathologic features[1-5]. The question that has emerged in recent years is how important and what role the biopsy of the small bowel plays in the diagnosis of CD[2,6]. Should all the patients suspected of having CD be biopsied? Also, the endoscopic procedure to biopsy the small bowel is not exempt of risk, can be expensive and time consuming.

The role of the pathologist in the study of patients with celiac disease is three fold. If the biopsy is done initially to confirm the diagnosis, the pathologist will be able to identify the changes seen in CD such as villous blunting, intraepithelial lymphocytosis (IELs) and crypt hyperplasia[4,7,8]. If the biopsy is normal, the possibility of CD cannot be excluded. In order to increase the possibility of finding abnormal features multiple small bowel biopsies are recommended including from the duodenal bulb. When the patient carries the diagnosis of CD and is rebiobsied, the pathologist can evaluate the response to therapy and render a report regarding the changes seen in the small bowel compared to the initial biopsy. The third situation is when the patient has either an atypical presentation or a suspected complication of CD[4,9]. In these cases, the pathologist plays a key role in confirming the diagnosis of CD, excluding other diseases that may show similar changes to CD, or diagnosing a complication of CD such as lymphoma, adenocarcinoma or collagenous sprue.

According to recent guidelines published by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPHGAN) children and adolescents can be spared a small bowel biopsy as long as the classic symptoms of celiac disease are present and the antibody titers are high (TTG-IgA levels >10 times ULN) and positive HLA-DQ2 or DQ8 subtyping[6].

These patients are thought to have enough evidence to support the diagnosis of CD, without histologic confirmation, so that they can be treated without biopsy confirmation[6]. Additional data with follow ups and comparison with patients who have small bowel biopsies in the workup are necessary to confirm the current recommendations advanced by ESPHGAN.

In the adult population suspected of having CD, most authors agree that small bowel biopsies should be an integral part of the work up of all patients[2,5]. Even in patients with negative serology but clinical findings suspicious of CD, a biopsy is frequently recommended[2]. A problem that could potentially arise if no small bowel biopsy is done in the initial work up of CD is that follow-up biopsies performed for lack of improvement, doubts about the diagnosis or a complication may not be easy to interpret to confirm or exclude the diagnosis of CD. The lack of improvement of the pathologic features of the small bowel biopsy has been associated with progression to refractory sprue[1]. Therefore, the lack of a baseline biopsy from the small bowel can potentially hampered the interpretation after the patient has been on a diet and treatment.

In CD, an early microscopic finding may include only IELs with or without evidence of villous blunting[7,8]. Both of these changes are non-specific and other conditions may show these features, only villous blunting or IELs. This is one of the main reasons proponents of performing a small bowel biopsy in all patients suspected of CD is justified in order to confirm the diagnosis.

The classic findings in small bowel biopsies in CD include: villous blunting that can range from minimal to severe flat mucosa, IELs and crypt hyperplasia (Figure 1). The villous: crypt ratio is variable and ranges from 1:1 to 3:1. In addition to these changes, there is an increased number of intraepithelial lymphocytes of over 25 lymphocytes per 100 enterocytes. The typical distribution in celiac disease is for the lymphocytes to be seen along the entire length of the villi. The presence of increased lymphocytes at the tip is more common in CD than in other conditions but it is not a specific finding[7,8]. The use of immunohistochemistry in the evaluation of intraepithelial lymphocytes is not recommended for routine use, however, there are

pathology laboratories that used the markers in all small bowel biopsies. These markers of T lymphocytes, CD3 and CD8, can be useful when there is doubts as to whether the intraepithelial lymphocytes are increased and in cases suspected of refractory sprue (RS). When they are used, the immuhistochemical stains should be interpreted with caution in order not to diagnose IELs and then consider that the patient may have CD. The number of IEL's should be increased to 30 per 100 enterocytes.

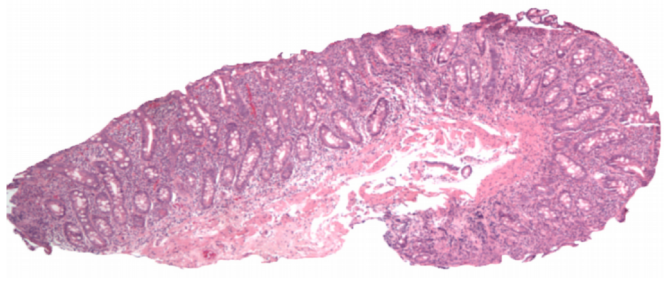

Figure 1. Small bowel mucosa showing severe villous blunting in a patient with untreated celiac disease.

In order to standardize reporting the interpretation of small bowel biopsies in patients with CD, two classification systems have been proposed[5,10]. They are the Marsh modified Oberhuber and the Corazza classifications[5,10]. The Marsh/Oberhuber system takes into consideration increased intraepithelial lymphocytes, crypt hyperplasia and the degree of villous atrophy. The Marsh classification uses a five tier system ranging from type 0 (normal) to type 3c (where the three parameters are abnormal with severe villous blunting). The Corazza/Villanacci system is a simplified version with only three categories: Grade A, that shows only increased intraepithelial lymphocytes, B1, with partial villous atrophy and B2 with total villous atrophy in addition to intraepithelial lymphocytes and crypt hyperplasia. Currently, the most widely used classification is the Marsh/Oberhuber system, however, the Corazza/Villanacci system includes only three groups and it is easier to apply and helps decreased the interobserver variability in the reporting of CD. The use of one of these systems is encouraged to facilitate the interpretation of the biopsy and the communication between gastroenterologist and pathologist.

2. The Differential Diagnosis of the Abnormal Small Bowel Biopsy

In addition to confirming the diagnosis of CD, the importance of the microscopic examination of the small bowel lies in identifying possible mimickers of CD which otherwise are difficult to recognize clinically.

The technical handling of the biopsy for a correct orientation of the tissue is crucial for the accurate interpretation. Whether there is villous atrophy or IELs or both, a biopsy that is not properly oriented will make the interpretation of the changes more difficult and may lead to the incorrect diagnosis. The right orientation will avoid artifact and misinterpretation of the biopsy as representing CD and this fact needs to be emphasize when handling small bowel biopsies.

The finding of villous blunting in small bowel biopsies is a non-specific finding and there are other conditions that show abnormal villi and do not represent CD[1,7,11,12]. Recognizing the possibility of other conditions and their microscopic features is one of the primary roles of pathologists when interpreting small bowel biopsies. No single pathologic feature of the small bowel biopsy is considered specific for the diagnosis of CD.

The conditions in the small bowel that can show villous atrophy excluding celiac disease are summarized in Table 1.

Table 1. Non-celiac causes of villous atrophy in the duodenum.

Tropical sprue
Small-bowel bacterial overgrowth
Autoimmune enteropathy
Drug-associated enteropathy
Whipple disease
Collagenous sprue
Crohn's disease
Infectious enteritis (tuberculosis; giardiasis)
Graft versus host disease
Malnutrition
Peptic duodenitis

These conditions include the following: tropical sprue, Crohn's disease, collagenous sprue, intestinal lymphoma, medications, infections, bacterial overgrowth, autoimmune enteropathy and common variable immunodeficiency (CVID). In addition to abnormal villi, these conditions can show IELs making the differential diagnosis with CD even more challenging.

The serologies in all of them are negative and before diagnosing CD the above entities should be excluded. For the pathologist, the presence of abnormal villi in patients that do not have other features of CD poses a significant challenge and is important to be aware of these mimmickers. A brief description of these conditions and their most important pathologic findings are presented below.

Medications that have been associated with villous blunting are olmesartan, mycophenolate mofetil, methotrexate and azathioprine[11,13-16]. For patients suspected of medication effect, the discontinuation of the medication leads to clinical and pathological improvements. An example of a small bowel biopsy showing villous blunting and a thickened basement membrane secondary to Olmesartan is illustrated in Figure 2.

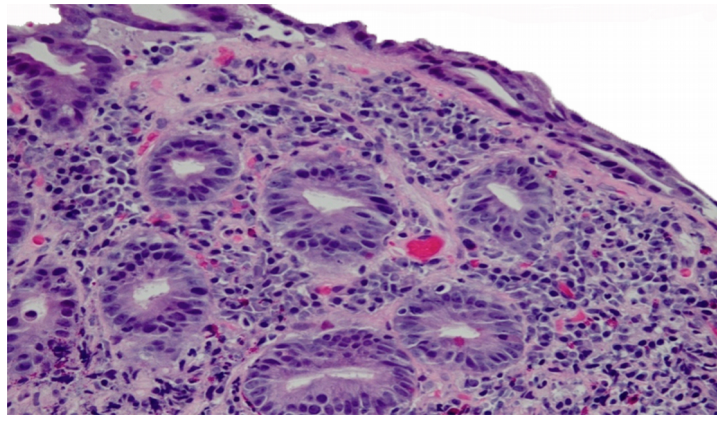

Figure 2. Small bowel mucosa of a 74 male with nausea, vomiting, abdominal pain, diarrhea and weight loss. The patient was taken Olmesartan.There is severe villous blunting and a thickened basement membrane.

CVID shows small bowel mucosa with decreased or absent plasma cells in the lamina propria and decreased serum levels of immunoglobulins.

Collagenous sprue is characterized microscopically by a diffusely thickened basement membrane and villous blunting. Collagenous sprue can be seen as an independent disease unrelated to CD or as a complication of CD[4,17]. Tropical sprue is seen in patients with a history of travel and who respond to antibiotic therapy.

Bacterial overgrowth develops in patients with motility disorders or anatomic abnormalities of the small bowel that promote colonization by gram negative flora from the colon. These patients have a positive breath test and they respond to antibiotic therapy. The small bowel biopsy can show mild to moderate villous blunting (in up to 25% of the patients) and less commonly IELs[18].

The SB biopsies may show abnormal villous architecture and acute inflammation involving the lamina propria and the crypts. CD can show mucosal acute inflammation in up to 50% of cases, and its presence should not preclude the diagnosis of CD. However, crypt abscesses and mucosal erosions are uncommon in CD[7]. When the biopsy shows acute inflammation, the possibility of other etiologies should be excluded[1,7]. Peptic duodenitis (injury) is a common diagnostic pitfall and represents the damage seen in the small bowel mucosa, frequently more prominent in the duodenal bulb, secondary to medication effect or gastric acid. Peptic injury shows acute inflammation in the lamina propria and foveolar metaplasia. Upper gastrointestinal Crohn's disease also shows acute inflammation, crypt abscesses and occasionally granulomas which are more common to see in the stomach than in the duodenum (Figure 3). Autoimmune enteropathy can affect children and adults. In the affected patients, the small bowel biopsy shows acute inflammation in the form of acute cryptitis absent goblet and parietal cells, apoptosis with villous blunting[19].

The SB biopsies that show only IELs with preserved villous architecture are a frequent pathologic finding in daily pathology practice. The minority of these patients have CD and it is estimated that between 5 to 15% of patients with IELs have celiac disease[20,21]. Other conditions that can be associated with IELs are medications (anti-inflammatory drugs), food allergies, H. pylori

gastritis, diabetes, inflammatory bowel disease, morbid obesity and autoimmune disorders[20-22].

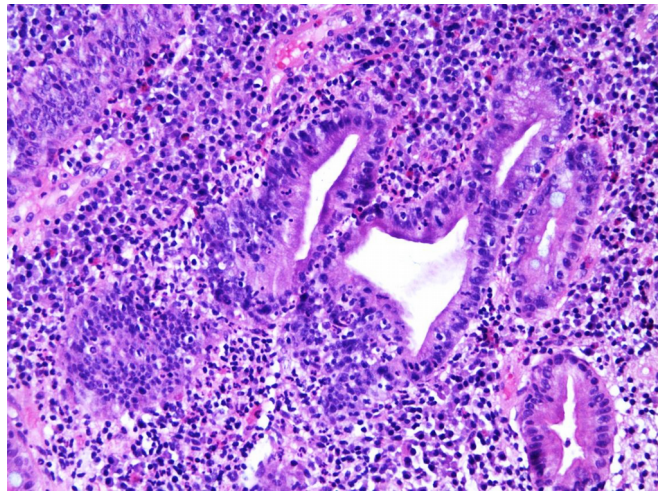

Figure 3. Small bowel biopsy from a patient with Crohn's disease showing acute inflammation involving the lamina propria and crypts.

Interestingly, some patients may have biopsies from either the stomach or large bowel that show increased IELs or a thickened basement membrane (collagenous gastritis and colitis), preceding the lymphocytosis of the small bowel[23]. If a small bowel biopsy is not available for review, the clinician needs to be alerted as to the possibility of celiac disease in these cases that show diffuse lymphocytosis throughout the gastrointestinal tract[1,23].

2.1. Refractory Sprue

The role of the pathologist is not confined to the initial diagnosis of CD and to the differential diagnosis with other conditions, but also in the workup of patients suspected of having refractory sprue (RS).

Refractory sprue is a complication of CD that develops in 1-2% of patients[5,9,24]. Patients are suspected to have RS when despite being in a gluten free diet their malabsorption symptoms persist. RS is an important diagnosis to make since the progression rates to T cell lymphoma and mortality secondary to infections are considerably higher in patients with RF type II. The lymphocytic phenotype of RS type I is similar to that seen in untreated CD[24].

The first step the pathologist should do when ask to evaluate a biopsy of a patient suspected of RS is to review the previous small bowel biopsy to confirm the diagnosis of CD. In the process of reviewing the biopsies the pathologist can exclude other diseases that present with increased intraepithelial lymphocytes or villous atrophy and that can simulate CD. If other diagnostic possibilities are excluded the use of immunohistochemical stains to characterize the presence of an aberrant clonal lymphocytic population can be done. Specifically, CD3 and CD8 are T cell markers that are analyzed in paraffin embedded material. If both of these markers are positive the differential diagnosis includes untreated CD or refractory sprue type I assuming that the patient has CD and other conditions have been excluded. If the biopsy shows an abnormal phenotype (lack of CD8 immunohistochemical staining) the possibility of refractory sprue type II should be considered. Type II refractory sprue is a more aggressive disease with a larger number of cases progressing to ulcerative jejunitis and small bowel lymphoma (Figure 4). The presence of an abnormal lymphocytic phenotype is a predictive factor but not a precondition to develop overt lymphoma[24]. In order to confirm the diagnosis of lymphoma of the small bowel, the use of molecular techniques to search for T cell receptor gamma gene rearrangement can be useful. Molecular analysis may reveal a monoclonal T-cell expansion of the lymphocytes in the small bowel mucosa.

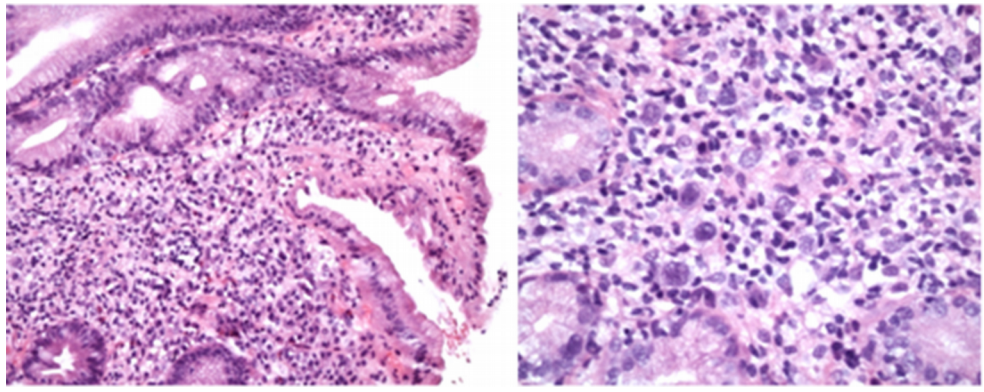

Figure 4. T-cell lymphoma of the small bowel in a patient with long standing celiac disease. Notice the atypical lymphocytes expanding the lamina propria and infiltrating crypts.

3. Conclusion

Pathology plays a crucial role in the diagnosis of celiac disease and in the interpretation of small bowel biopsies to confirm or exclude CD. The spectrum of changes in the biopsies of patients suspected of CD has broadened and the diagnosis can be subtle with minimal histopathologic changes. In order to confirm the diagnosis of CD, the pathologic features should be correlated with the clinical, endoscopic, serological findings and HLA haplotypes.

The small bowel biopsy should be considered an important diagnostic component in the workup for the diagnosis in all the patients suspected of having CD. It is crucial to be aware that other conditions share similar pathologic features with celiac disease. The clinician will decide in each individual case how important it is to biopsy the small bowel in order to confirm or exclude the possibility of celiac disease.

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