Histopathology of Celiac Disease

Fei Bao, MD[a,*], Govind Bhagat, MBBS[b,*]

KEYWORDS

• Small bowel biopsy • Histopathology • Villous atrophy • Intraepithelial lymphocytes • Classification • Standardized pathology report

KEY POINTS

- Histopathologic evaluation of celiac disease.
- Site and number of small bowel biopsies.
- Histopathologic features of celiac disease and differential diagnostic considerations.
- Comparison of the old and new classifications of celiac disease.
- Benefit of standardized pathology reports.

DIAGNOSTIC CRITERIA

Histopathologic abnormalities of the small bowel mucosa were first described by Paulley in surgical resection specimens of intestines in 1954.[1] Villous atrophy was a characteristic feature observed in patients with celiac disease (CD), which is now a recognized component of the histologic triad for diagnosing CD. In earlier times, the histopathologic diagnosis of CD was based exclusively on detecting villous atrophy in small bowel biopsies.[2] The recognition of milder degrees of injury in the small bowel mucosa of patients with CD was an important step forward in expanding the histopathologic manifestations of CD. In the 1990s, Marsh[3] described and classified the histologic patterns of small intestinal mucosal injury, the spectrum ranging from normal villous architecture with increased intraepithelial lymphocytes (IELs) as the sole abnormality to total villous atrophy with crypt hyperplasia and increased lamina propria inflammation. The Marsh classification was composed of 4 categories (types 1–4) representing progressive states of mucosal injury, which was modified by Oberhuber in 1999.[4] The Oberhuber classification subdivided the type 3 lesion (flat mucosa) into 3 groups based on the severity of villous atrophy; mild to moderate (partial) villous atrophy (type 3A), marked (subtotal) villous atrophy (type 3B) and completely flat mucosa (total) villous atrophy (type 3C). The modified Marsh-Oberhuber classification is currently used by many pathologists.

The authors have no relevant financial interest.
[a] Department of Pathology and Cell Biology, Columbia University Medical Center and New York Presbyterian Hospital, VC14-238 C, 630 West 168th Street, New York, NY 10032, USA;
[b] Department of Pathology and Cell Biology, Columbia University Medical Center and New York Presbyterian Hospital, VC-14-228, 630 West 168th Street, New York, NY 10032, USA
* Corresponding authors.
E-mail addresses: fb2266@columbia.edu; gb96@columbia.edu

Gastrointest Endoscopy Clin N Am 22 (2012) 679–694
http://dx.doi.org/10.1016/j.giec.2012.07.001 giendo.theclinics.com
1052-5157/12/$ – see front matter Published by Elsevier Inc.

In recent years, the diagnostic approach to CD has changed, because of a better understanding of the clinical manifestations of CD and the availability of more sensitive and specific serologic tests, as well as high-resolution HLA typing for disease susceptibility alleles.[5–8] Most importantly, the presence of total villous atrophy is no longer necessary for diagnosing CD, provided the established spectrum of histopathologic features of CD is present.[9] Nevertheless, small bowel mucosal biopsy remains the gold standard for diagnosing CD. All serologic tests and small bowel biopsies need to be performed while the patient is on a gluten-containing diet. According to the US National Institutes of Health consensus statement,[5] serologic testing is recommended as the first step in pursuing a diagnosis of CD. Duodenal biopsy is recommended in individuals with a positive celiac antibody test, when serologic results are nondiagnostic and in individuals at risk for CD who have suggestive clinical symptoms, such as first-degree relatives of CD and patients with iron-deficient anemia, cryptogenic hypertransaminitis, and CD-associated autoimmune disorders. With positive serology and a biopsy showing characteristic findings of intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy, a presumptive diagnosis of CD can be made. Definitive diagnosis requires symptom resolution on commencing a gluten-free diet (GFD). A repeat biopsy to show normalized histology after a GFD is no longer required for diagnosing CD, although it is often used to document healing.

SITE AND NUMBER OF SMALL BOWEL BIOPSIES

Although small bowel biopsy remains the gold standard for diagnosing CD, there is a wide spectrum of histologic abnormalities, which can make interpretation problematic for pathologists. Endoscopic and pathologic findings have revealed that the mucosal damage is most severe in the proximal small intestine, including the duodenum and upper jejunum, and diminishes distally.[10] However, CD is a patchy disease, and the patchy and irregular mucosal lesions are just as prevalent as continuous and diffuse lesions.[11–13] Many studies have advocated obtaining multiple biopsies from different regions of the proximal small intestine, but there are no uniform, agreed-on recommendations or guidelines for the number (or site) of biopsies required for diagnosis. A recent large-scale retrospective study conducted in the United States showed that the probability of a new diagnosis of CD was doubled when 4 or more specimens were submitted for histopathologic assessment.[12] Another retrospective study from Canada showed that the diagnosis of untreated CD was confirmed in 90% when 2 duodenal biopsies were obtained, the detection of CD was increased to 95% when increasing the number of biopsies to 3, and 100% detection was achieved when 4 biopsies were obtained.[13] Inadequate sampling may lead to a false-negative diagnosis, and poorly oriented biopsy specimens can cause both underinterpretation and overinterpretation of the histologic abnormalities. Superficial biopsy samples lacking the muscularis mucosa can cause separation of the villous bases, resulting in shorter and thicker villi that can be misinterpreted as villous atrophy and favor a diagnosis of CD.[14] Likewise, an erroneous diagnosis of increased IELs can be rendered when only detached villi are present for review. Historically, biopsies were taken from the jejunum to diagnose CD.[15,16] Studies since the mid-1990s have shown that biopsies from the second part of the duodenum are sufficient for diagnosis without loss of sensitivity or specificity.[17,18] Biopsies from the duodenal bulb should be interpreted with caution because this area is exposed to gastric acid and is prone to peptic injury and Brunner glands can also be prominent in the bulb. The villi in this location are typically shorter in length,[19] and they may also have a bifid appearance. However, the duodenal bulb is also the most sensitive site to detect mucosal injury