Ministry of Higher Education
And Scientific Research.
University of Diyala ;
College of Medicine.

A systematic Review in:

Clinical and Histologic Mimickers of "Celiac Disease"

Partial Submitted to the Council of the College of Medicine, Diyala University, In Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.

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2023 **1444**

Abstract

Celiac disease is an autoimmune disorder of the small bowel, classically associated with diarrhea, abdominal pain, and malabsorption. The diagnosis of celiac disease is made when there are compatible clinical features, supportive serologic markers, representative histology from the small bowel, and response to a gluten-free diet. Histologic findings associated with celiac disease include intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy, and a chronic inflammatory cell infiltrate in the lamina propria. It is important to recognize and diagnose celiac disease, as strict adherence to a gluten-free diet can lead to resolution of clinical and histologic manifestations of the disease. However, many other entities can present with clinical and/or histologic features of celiac disease. The evaluation of a patient with serologically negative enteropathy necessitates a carefully elicited history and detailed review by a pathologist. Co-morbidities, ongoing medications, and consumption of oats and wheat-starch were recorded. Small-bowel morphology and intraepithelial lymphocyte count as well as laboratory parameters of malabsorption were evaluated. Gastrointestinal symptoms and psychological well-being were measured by structured questionnaires.

Method: we collected the data from online databases and we found 40 articles but we excluded 32 of them and we reviewed only 8 articles with period from 2013 until now.

Results: we found clear dominance for intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy, and a chronic inflammatory cell infiltrate in the lamina propri

Conclusion: Medications can mimic celiac disease and should be considered in all patients with a serologically negative enteropathy. Many mimickers of celiac disease have clues to the underlying diagnosis, and many have a targeted therapy. It is necessary to provide patients with a correct diagnosis rather than subject them to a lifetime of an unnecessary gluten free diet

Keywords: celiac disease, sprue , villous atrophy, Gluten sensitivity.

Introduction:

Celiac disease is a chronic immune-mediated disorder induced by dietary exposure to gluten in genetically predisposed individuals. It may affect as much as 1% of the population, with many cases remaining undiagnosed.The proximal small intestine is the major site of disease. Increased intraepithelial lymphocytosis, with or without concomitant villous atrophy, is the characteristic histologic finding. While histologic examination remains the “gold standard” for diagnosis of celiac disease, changes can be subtle when duodenal villous architecture is intact,and villous atrophy may also be encountered in various other conditions, Similarly, serologic testing using an enzyme-linked immunosorbent assay for antitissue transglutaminase (tTG) antibodies, which recognizes an important enzyme in celiac disease pathogenesis, is not fully sensitive or specific for the disease.In practice, a combination of clinical suspicion, morphologic abnormality, and positive serologic findings is used for the initial diagnosis of most patients with celiac disease. Subsequent clinical, serologic, and/or biopsy demonstration of improvement with a gluten-free diet is necessary for a definitive diagnosis of celiac disease.[1]

Interest in the morphologic features of celiac disease has renewed as we endeavor to identify cases with atypical biopsy findings that may lead to misdiagnosis. The recognition of disease patchiness, variability in villous architectural change, and cases with no architectural disturbance are among these atypical patterns. Likewise, while much attention has focused on intraepithelial lymphocytosis in celiac disease,

there is less quantified information on the presence and significance of the lamina propria inflammatory infiltrate that is a common part of the disease.[2]

This study was undertaken to document a large range of histologic features noted on initial gastrointestinal tract biopsy in a series of consecutive patients. These patients were diagnosed as having celiac disease on the basis of clinical suspicion, raised tTG level, and intraepithelial lymphocytosis in the proximal small intestine. The study focused on the presence and significance of morphologic changes in proximal small intestinal biopsy specimens and their correlation to the presence of extraduodenal lymphocytic inflammation.

The variety of clinical manifestations which coeliac disease may present complicates its recognition. A correct diagnosis can not rely on a single test, but requires a precise reconstruction of a puzzle, whose pieces are represented by the clinical, serological, genetic and histological aspects. The evaluation of all these factors, apart from genetics, must take place while the patient is still on a diet containing gluten, since a gluten-free diet changes the clinical, serological and histological pattern, making it impossible to recognize the characteristic aspects of disease.

The significant improvement in our knowledge of intolerance to gluten has made it possible to identify the socalled risk groups in which, on the basis of intestinal and extrain- testinal symptoms, and of the presence of any associated diseases and familiarity, the possibility of coeliac disease must be investigated [3]

These risk groups are made up of:1. Subjects in whom coeliac disease is strongly suspected

(cases with severe malabsorption and with highly predictive associated diseases):

• malabsorption syndrome with repeated diarrhea-like bowel movements, abdominal pain and marked weight loss;

• dermatitis herpetiformis, also called coeliac disease of the skin, since in practically all cases there is more or less severe gluten-dependent intestinal damage.

2. Subjects in whom coeliac disease is moderately suspected (cases with atypical or extraintestinal symptoms and associated diseases):

• atypical gastro-intestinal symptoms (dyspepsia, constipation, vomiting and intestinal subocclusion);

• extraintestinal symptoms (anemia – most often due to a lack of iron but also to a lack of folic acid and vitamin B12), hyposomia, oral ulcers, hypertransaminasemia, osteopenia or osteoporosis, tooth enamel abnormalities, hemorrhagic syndrome due to vitamin K malabsorption, changes in the female reproductive system (late menar- che, early menopause, recurrent miscarriage, premature labour);

• associated diseases (diabetes mellitus type 1, Hashimoto thyroiditis, Graves’ disease, selective IgA deficiency, alopecia areata, piebald skin, psoriasis, Addison’s disease, Systemic Lupus Erythematosus, polymyositis, rheumatoid arthritis, cerebellar ataxia, epilepsy with or without cerebral calcifications, peripheral neuropathy, autoimmune hepatitis, primary biliary cirrhosis, idiopathic dilated cardiomyopathy, Berger’s disease, Down’s syndrome, Turner’s syndrome, Williams’ syndrome).

3. 1st degree relatives of coeliac patients (high familiarity of coeliac disease that is present in 4–17% of 1st degree relatives of coeliac patients, but may also be found in high proportions in 2nd degree relatives).

A major role in the diagnostic process of coeliac disease is played by serology, which allows identification within the at-risk groups of the subjects who should undergo intestinal biopsy. While making it clear that no positive antibody test allows a diagnosis of coeliac disease without the necessary confirmation provided by an intestinal biopsy, some of the antibody markers show such a high diagnostic accuracy (with levels of sensitivity and specificity >95%) that they are highly predictive of coeliac disease.[4]

The histological diagnosis of CD consists of an integrated assessment of the following elementary lesions:

- **Increased intraepithelial T-lymphocytes:** a value of 25 T-lymphocytes/100 enterocytes is considered a pathological condition also called “lymphocytosis”.
- **Crypt hyperplasia**: extension of the regenerative epithelial crypts associated with presence of more than 1 mitosis per crypt.
- **Villous atrophy:** decrease in villous height, alteration of normal crypt/villous ratio (3:1) until total disappearance of villi. This assessment requires proper orientation of the biopsies.

None of these elementary lesions is specific for CD; the diagnosis of CD is based on the identification of histological alterations accompanied by clinical and serological consistent data. On the basis of the presence of one or more of these elementary lesions the histopathology of CD is subdivided into different diagnostic categories according to the Marsh classification [2,3]

Marsh classification

Type 1 or infiltrative lesion

1. Villi architecturally within normal morphological limits (normal villa/crypt ratio 3:1);

2. Increased number of intraepithelial lymphocytes (greater than 25–30 per 100 epithelial cells) (Fig. 1A–D).

Type 2 or hyperplastic lesion

1. Villi architecturally within normal morphological limits (like type 1);

2. Increased number of intraepithelial lymphocytes (greater than 25–30 per 100 epithelial cells) (like type 1)

3. Hyperplasia of the glandular elements (regenerative aspect of the glandular elements highlighted by the reduced muciferous activity and increased number of mitoses).

Type 3 or destructive lesion

1. Varying degrees of villous atrophy associated with hyper- plasia of glandular crypts;

2. Reduced surface enterocyte height, with irregular brush- border and sometimes cytoplasmic vacuoles

3. Increased number of intraepithelial lymphocytes (like type 1 and 2 lesions)

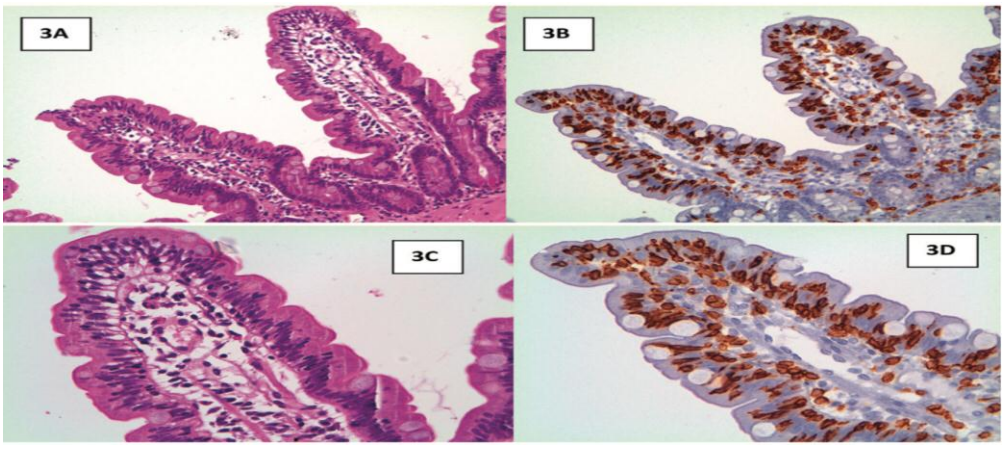


Figure1: type ½ infiltrative lesions according to Marsh-oberhuber.

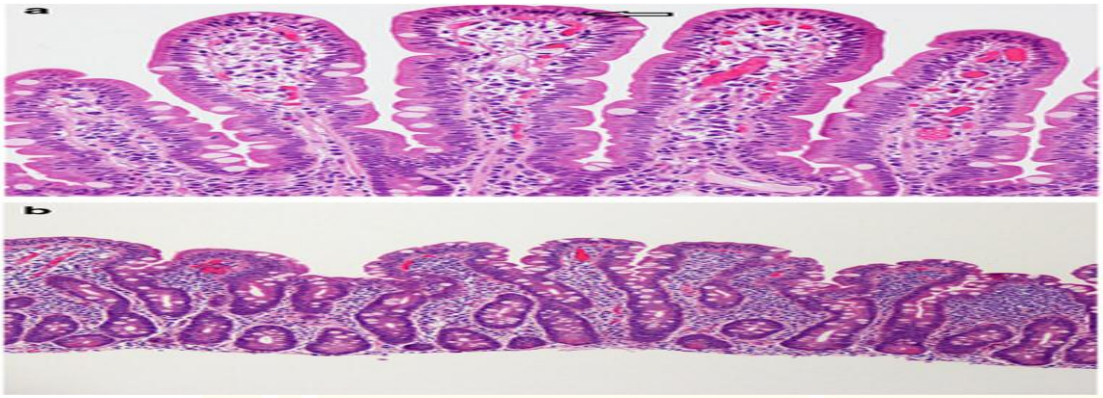
Method and materials: we searched the online scientific databases such as Google scholar, PubMed, and NCBI on the keywords (celiac disease, mimicker, histology, sprue , villous atrophy, Gluten sensitivity.) and we found 40 articles and we included 8 articles with period from 2013 until now.

Results:Corazza, Roberts [1] according to Marsh criteria found that duodenal biopsies classically demonstrate intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy, and a chronic inflammatory cell infiltrate in the lamina propria . Patients with CD should exhibit resolution of symptoms when started on a gluten-free diet. As outlined above, the absence of HLA-DQ2 and HLA-DQ8 alleles effectively rules out the disease. They also found that a gluten-free diet forms the cornerstone of management in patients with CD, with elimination of wheat, barley, and rye. Oats are generally safe in patients with CD, although there may be a small risk of oat cross-contamination or contact with gluten-containing food products; most patients with CD are allowed to ingest oat products unless they present with severe clinical features, in which case oats may be held initially. After a new diagnosis of CD is made, all patients should be referred to a skilled dietician for counseling, and testing should be performed to assess for vitamin and mineral deficiencies. Bone densitometry should also be considered in adult patients. Clinical improvement should occur soon after implementation of a gluten-free diet, while histologic response may take months to years. In patients that fail to improve on a gluten-free diet, the diagnosis of CD should be verified, dietary compliance should assessed, and histologic mimickers considered, particularly in patients with negative celiac serologies at the time of the diagnosis.

See the figure below on Histologic features associated with celiac disease which shows

(A) An early phase of celiac disease (characterized by a tip-predominant intraepithelial lymphocytosis alone (see arrow)

(B) characterized by intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy (partial in this case with a villous:crypt ratio of 1:2), and a chronic inflammatory cell infiltrate in the lamina propria.



(Figure 2 : **a** and **b**)(**a**) an early phase of celiac disease,; and (**b**) a later phase of celiac disease, (**a** at 200 ×, **b** 100 × ; Haemotoxylin and Eosin stain)

Another study done by Drossman DA [4]who found that Small intestinal bacterial overgrowth (SIBO) is known to cause diarrhea, bloating, and weight loss, which may mirror symptoms of classic CD; SIBO may also be a cause of recurrent or refractory symptoms in a patient with known CD. Patients may have carbohydrate, protein, or fat malabsorption, and deficiencies in iron, vitamin B12, and fat-soluble vitamins, which may occur, in part, due to intraluminal damage from proliferating bacteria. In healthy individuals, several physiological mechanisms exist that serve to limit bacterial growth and SIBO occurs when these protective mechanisms fail. While no universal definition of SIBO exists, the gold standard remains a small bowel aspirate demonstrating 10 or more colony forming units per milliliter of bacteria grown. The treatment of SIBO consists of managing any underlying diseases, correcting nutritional deficiencies, and use of antibiotics.

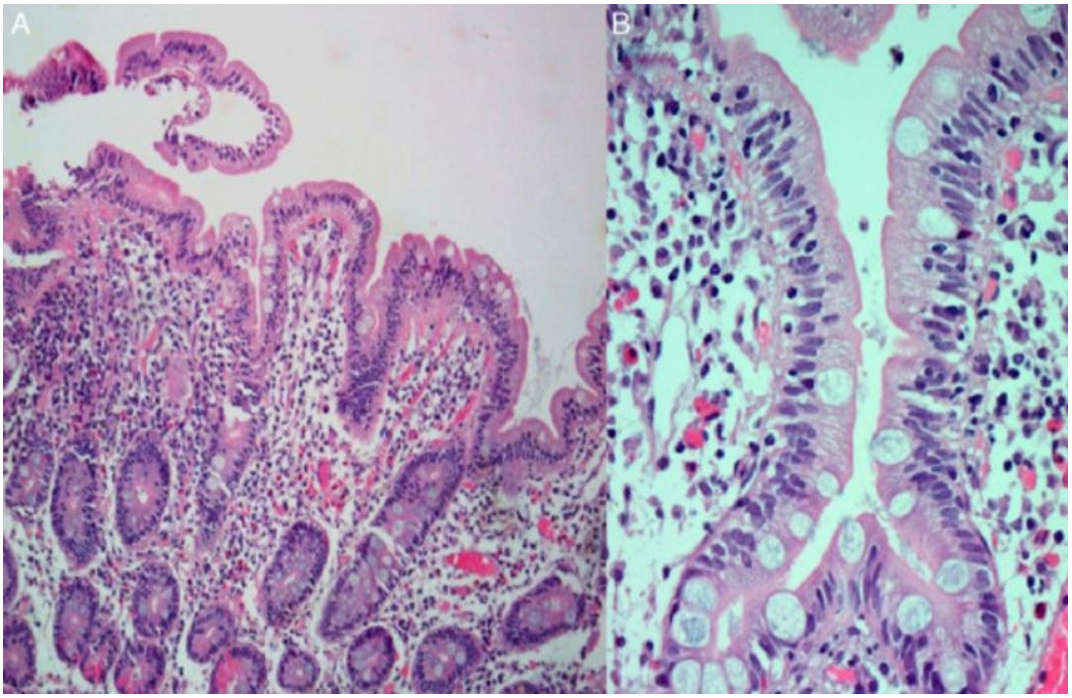


Figure 3: shows effect of small intestine bacterial overgrowth on villi.

Non-steroidal anti-inflammatory drugs

In a large retrospective study done by James Freeman H [5] , nearly 14% of patients with isolated IELs in the duodenum reported NSAID use, a percentage that may be inaccurately low due to underreporting by patients. Other studies reported NSAID use in over 20% of those with duodenal IELs. In addition, a number of those with documented CD, SIBO, *H. pylori*, IBD, and microscopic colitis were concurrently using NSAIDs, making it challenging to know the etiology of the histologic finding given the overlap in risk factors or exposures.

NSAID use has been shown to cause duodenal histopathology nearly identical to what is found in early CD. The histopathology will typically resolve with drug discontinuation, but can recur with re-introduction of the drug. Possible etiologies for these findings are may be due to the direct toxic effects of NSAIDs or their metabolites, which are excreted in bile, or due to a hypersensitivity reaction. The most susceptible region to the effects of NSAIDs is the duodenal bulb and the presence of a neutrophilic infiltration in the lamina propria may be a potential clue to NSAID use. However, these histologic findings are non-specific, and may also be seen in those with *H. pylori* infection, which may also lead to chronic active gastritis on gastric biopsies.

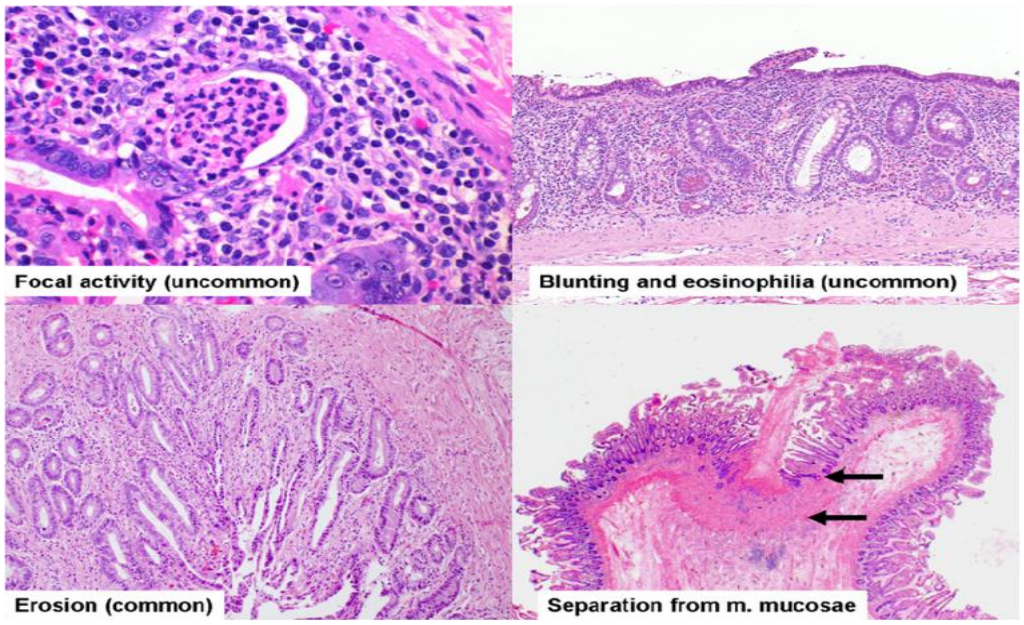


Figure4 :Histology of NSAID effect on villous atrophy (a)Focal effect ,(b)blunting and eosinophilia,(c)Erosion ,(D)Separation from mucosa.

Patterson ER [6] did a study on Crohn’s disease and inflammatory bowel disease (IBD), ulcerative colitis, may all cause clinical features that mimic CD, or be concurrently present in patient known to have CD. IBD occurs when the intestinal microbiome triggers an inappropriate inflammatory response, and while there is a genetic susceptibility to IBD, the pathogenesis is multifaceted. While individuals can be affected at any point in life, the disease typically occurs in those 15 to 30 years of age. Although Crohn’s disease can affect any part of the gastrointestinal tract, it most commonly involves the terminal ileum. Given the small bowel involvement with Crohn’s disease, clinical features may mimic CD with abdominal pain, diarrhea, weight loss, features of malabsorption. The treatment for Crohn’s disease is complex and individualized, and involves lifestyle modifications (smoking discontinuation, if applicable, and NSAID avoidance), medical management with varying degrees of immunomodulatory or immunosuppression therapy, and occasionally surgical intervention.

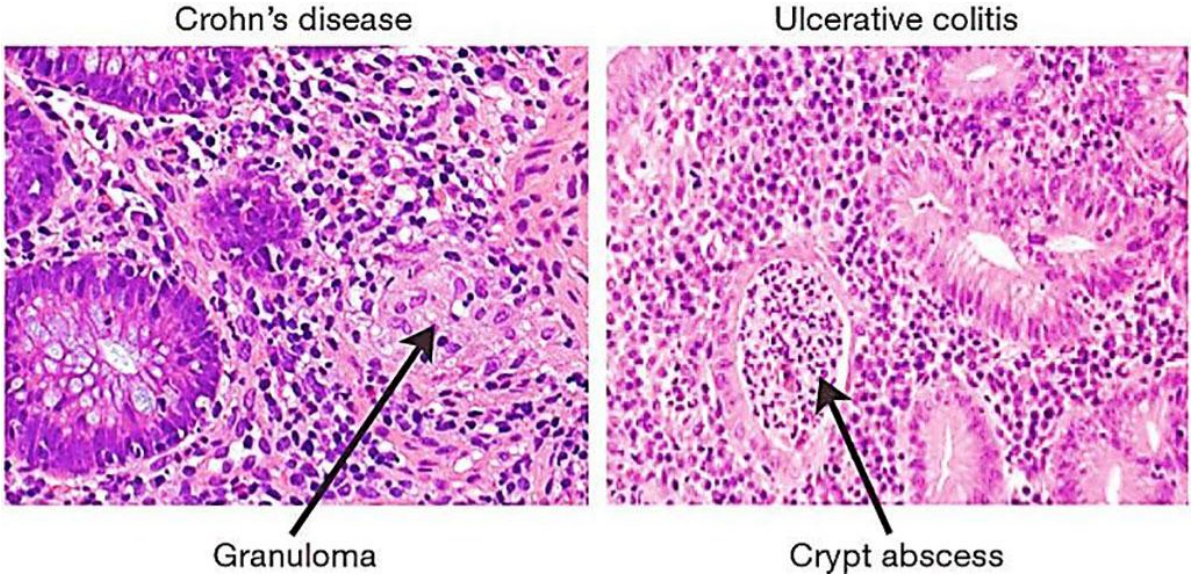


Figure5 : Histology on IBD.

Early mimickers of celiac disease:

Early histologic mimickers of CD can be defined as those conditions causing increased IELs with no villous atrophy, and crypts that are normal or have minimal hyperplasia . Prior to 2005, the “normal” number of IELs in the small bowel was defined as 6–40 lymphocytes per 100 epithelial cells. However, recent studies highlight that the upper limit of normal for lymphocyte count from duodenal biopsies is 25 per 100 epithelial cells, and from 2005 onward, many pathologists define greater than 25–30 lymphocytes per 100 epithelial cells as abnormal. The difference in the upper limit of normal IELs over time may be secondary to the use of jejunal biopsies in older studies, and the fact that some studies have based counts on anti-CD-3 staining, which is not used routinely in clinical practice.

The figure below is on early histologic mimickers which demonstrates increased intraepithelial lymphocytes, often in a non-tip-predominant pattern (see arrow), no villous atrophy, and crypts that are either normal or have minimal hyperplasia.

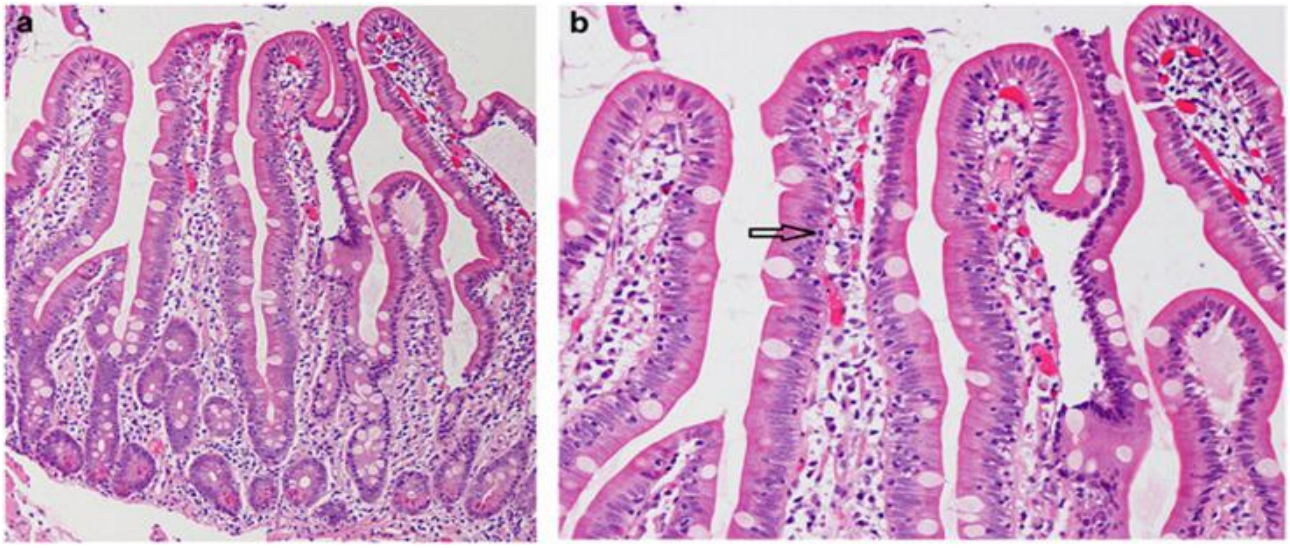


Figure 6: **a** and **b**)early mimickers of celiac disease (in this case, NSAID use) (**a** at 100 ×, **b** at 200 × ; Haemotoxylin and Eosin stain).

Inflammatory bowel disease

In a study done by Patterson ER[6] and Bernstein CN [7]that reviewed all duodenal biopsies over a 10-year period, IBD was present in 74 patients who had increased IELs and normal architecture, making up 7.2% of patients with this histologic finding. Among these patients, 13 had ulcerative colitis (UC), 54 had Crohn’s disease, and 3 had indeterminate-type IBD. The mean age of adult patients with UC and Crohn’s disease at the time of this histologic finding was 40 and 39 years, respectively, while mean duodenal IEL count for in UC and Crohn’s disease was 45 and 44 IELs per 100 epithelial cells, respectively. The IELs were evenly distributed along edges of the villi in the majority with IBD (n=62), and only three patients had a tip-predominant pattern of IELs.All three of the latter patients were negative for CD. Of the 54 patients with Crohn’s disease, gastric biopsies were obtained in 34 patients, and nearly half (n=16) had focal lymphocytic gastritis.

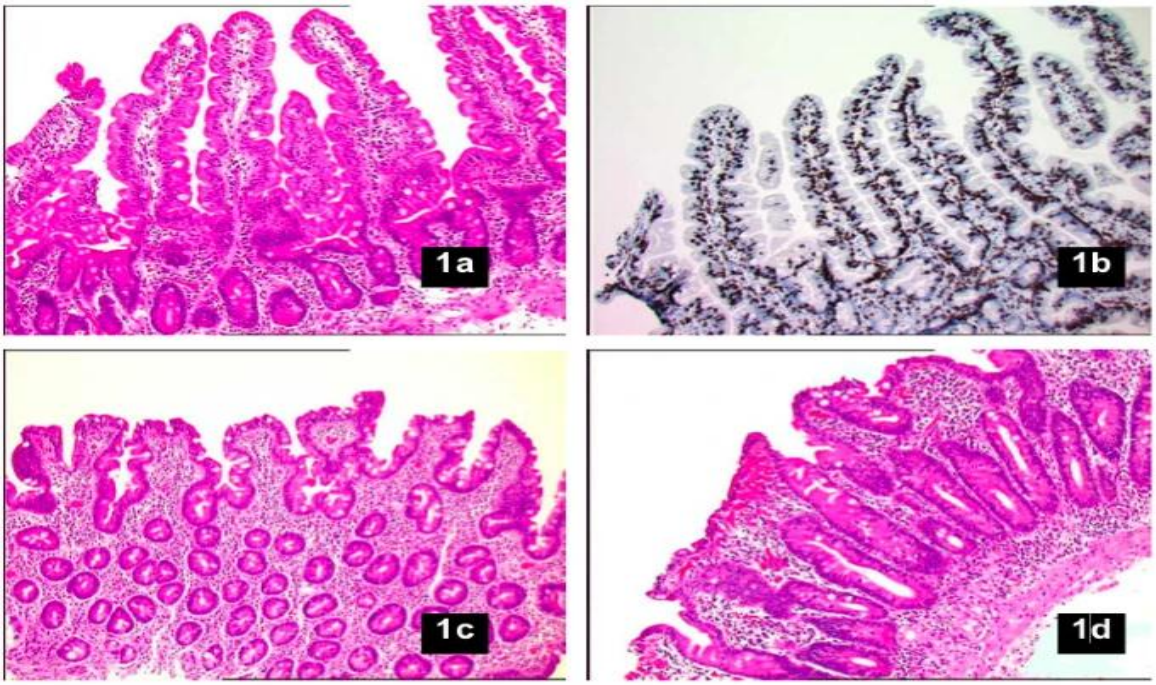


Figure7 : a. Normal mucosa. b. Inflammation (intraepithelial lymphocytosis). c. Partial VA (CD). d. Total VA (CD)

Chey WD, Kurlander J, Eswaran S.[8]and fond [9]found that Irritable bowel syndrome (IBS) has features that mimic celiac disease . Symptoms include abdominal pain along with altered bowel form and/or frequency. IBS is often associated with other disorders including somatic comorbidities. The ROME IV criteria is often used to diagnose IBS and requires recurrent abdominal pain on average at least one day per week for the last 3 months associated with two or more of the following: related to defecation, change in frequency of stool, and change in form or consistency of stool. Symptoms need to be present for at least 6 months. Before a diagnosis of IBS is made, alarm features need to be assessed, and consideration should be given to test for CD in those with a diarrhea-predominant or mixed-type pattern. Functional diarrhea is similar to IBS, yet without abdominal pain, and may also clinically mimic CD.

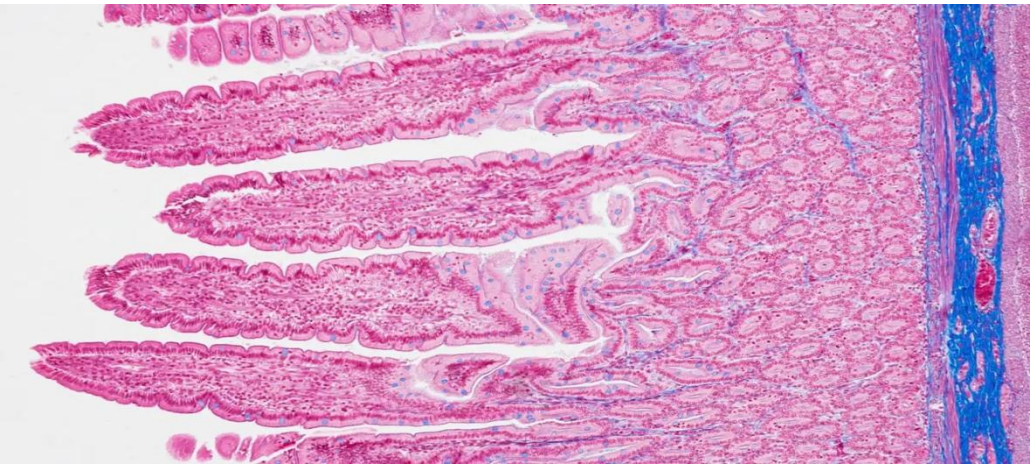


Figure8 : show IBS effect on villi.

Late Histological mimickers :

Late histologic mimickers of CD are characterized by having duodenal biopsies that demonstrate increased IELs, partial or total villous atrophy, and crypt hyperplasia . Given the more advanced enteropathy compared to early histologic mimickers, clinical features are more likely to be present. While the differential diagnosis becomes narrower with progressive degrees of enteropathy, the etiology remains elusive in a large number of patients with this finding. Late histologic mimickers are characterized by increased intraepithelial lymphocytosis, partial or total villous atrophy, crypt hyperplasia, and chronic inflammation in the lamina propria see the(figure below). This figure also demonstrates a prominent collagen band that can be seen in cases of drug-induced enteropathy.

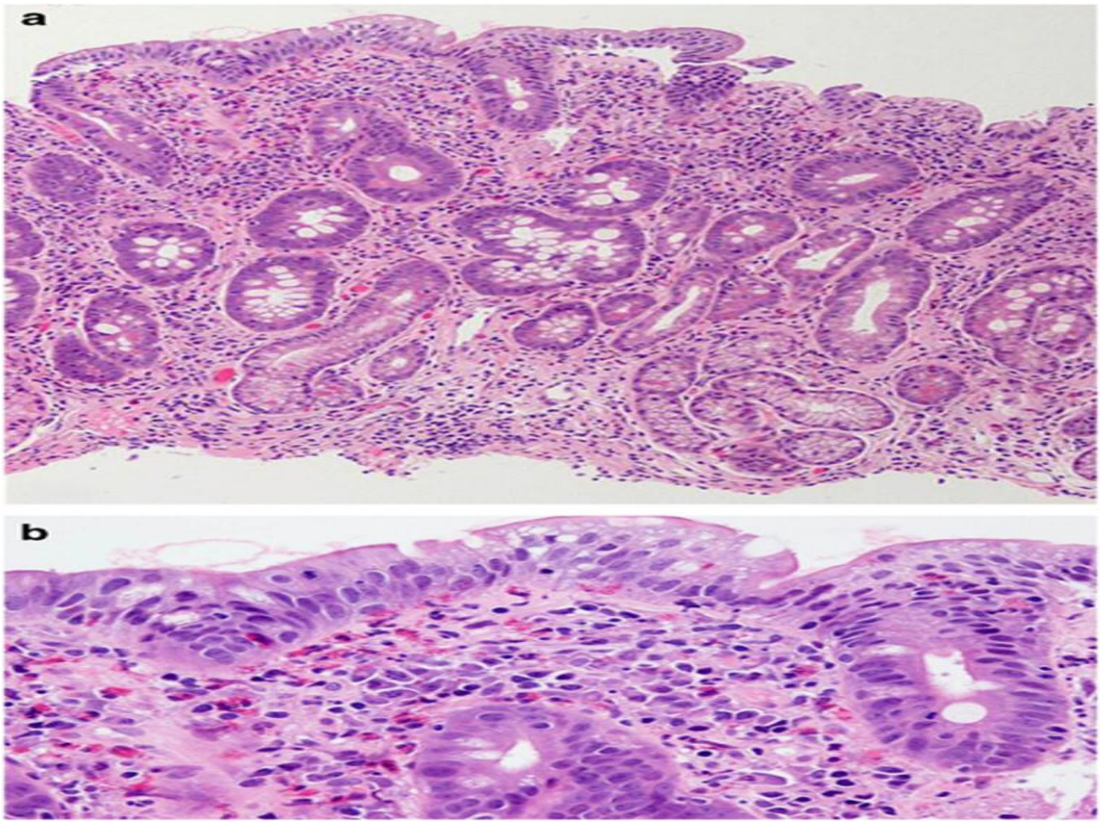
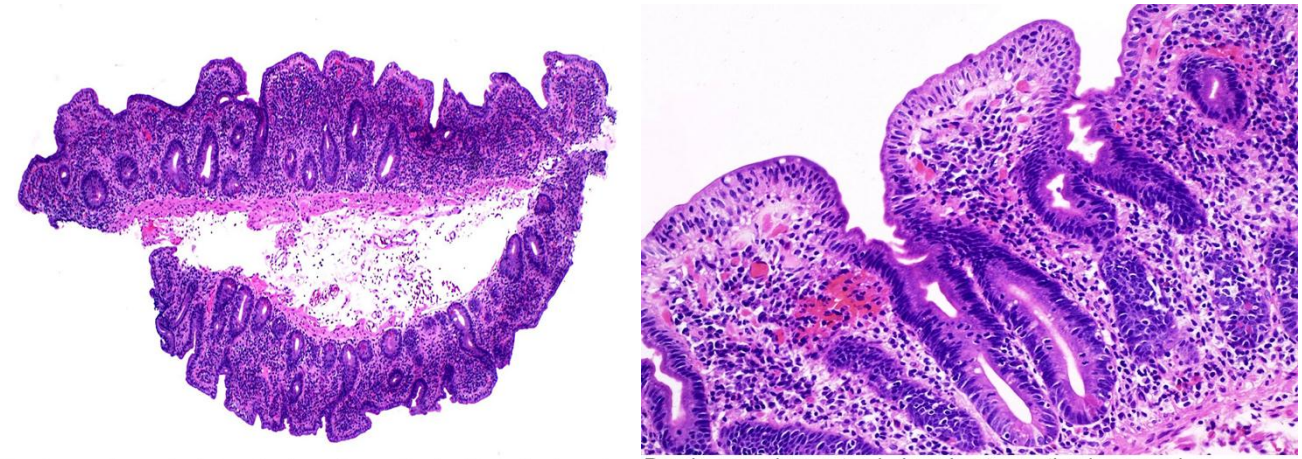


Figure 9 : (**a** and **b**) Histologic features associated with late mimickers of celiac disease (in this case, drug-induced from olmesartan). (**a** at 100 ×, **b** at 200 × ; Haemotoxylin and Eosin stain).

Olmesartan

Marthey L, Cadiot G[10]and Marco-Marqués A [11] are two separate studies, one in French and one in Spanish populations, demonstrated olmesartan-associated enteropathy in 36 and 11 patients, respectively. Among these three studies, some interesting observations were noted. The mean age for patients with olmesartan-induced enteropathy ranged from 70–72 years. The patients were on a mean dose of 40 mg daily and had been taking the drug for a mean of 2.3–3.1 years before the diagnosis was made. Diarrhea was universal in all patients while abdominal pain was present in 45–75%, and profound weight loss was noted in many. Positivity for HLA-DQ2 or DQ8 was noted in 61–100% of those tested, a percentage much higher than found in the general population. In the previously described study with 16 cases of olmesartan-induced enteropathy, 11 had prominent collagen deposition. Therefore, older age at onset, prominent collagen deposition, and neutrophilic infiltration in a patient with a serologically negative enteropathy should always prompt a careful medication review, even if the drug was started years previously; the presence of permissive HLA haplotyping may confer increased risk in those patients taking olmesartan.



Duodenum, olmesartan induced enteropathy; moderate villous atrophy and crypt hyperplasia

Duodenum, olmesartan induced enteropathy; increased intraepithelial lymphocytes

Figure 10: Olmesartan effect on villous atrophy, a and b.

Collagenous sprue

Collagenous sprue (CS), first described in 1970, results in malabsorption and diarrhea. While CS shares most of the histologic features found with CD, it also characteristically demonstrates an irregularly thickened layer of type I collagen adjacent to the surface epithelium. Normal collagen band thickness in the duodenum should be five microns or less; in CS, the collagen band is thick, irregular, often wraps around capillaries, and may result in surface epithelial detachment. The link between CS and gluten is not well-defined; management often begins with a gluten-free diet, although most patients do not fully respond. Patients with refractory CS may require treatment with corticosteroids or immunosuppresants, and histologic changes may persist following treatment. As noted previously, the finding of CS should prompt a careful medication review.

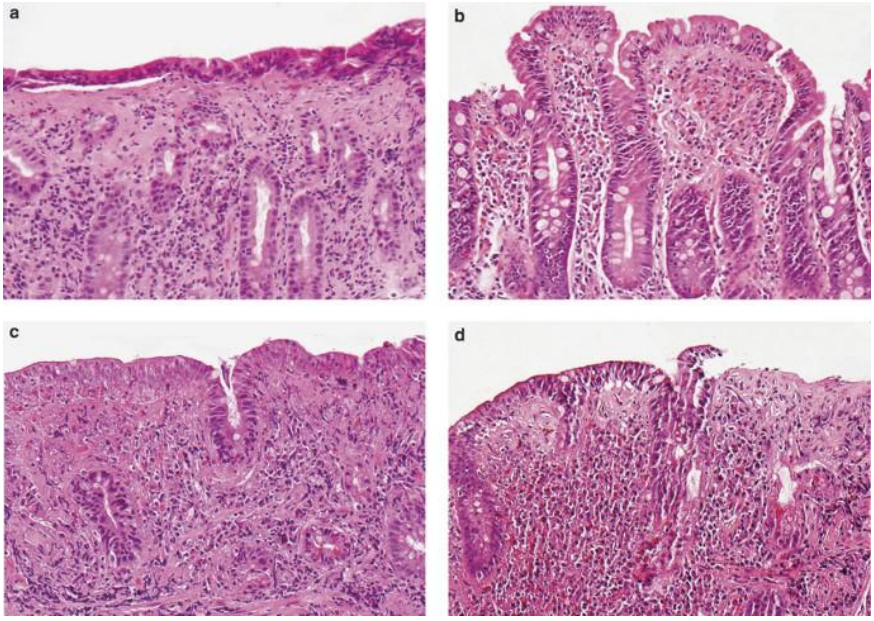


Figure11 : subsequent villous atrophy of collagenous sprue

initial total villous atrophy and marked subepithelial fibrosis (**a**, × 200), subsequently showing subtotal villous atrophy and mild fibrosis (**b**, × 200); total villous atrophy and marked fibrosis (**c**, × 200) without improvement 3 years later (**d**, × 200).

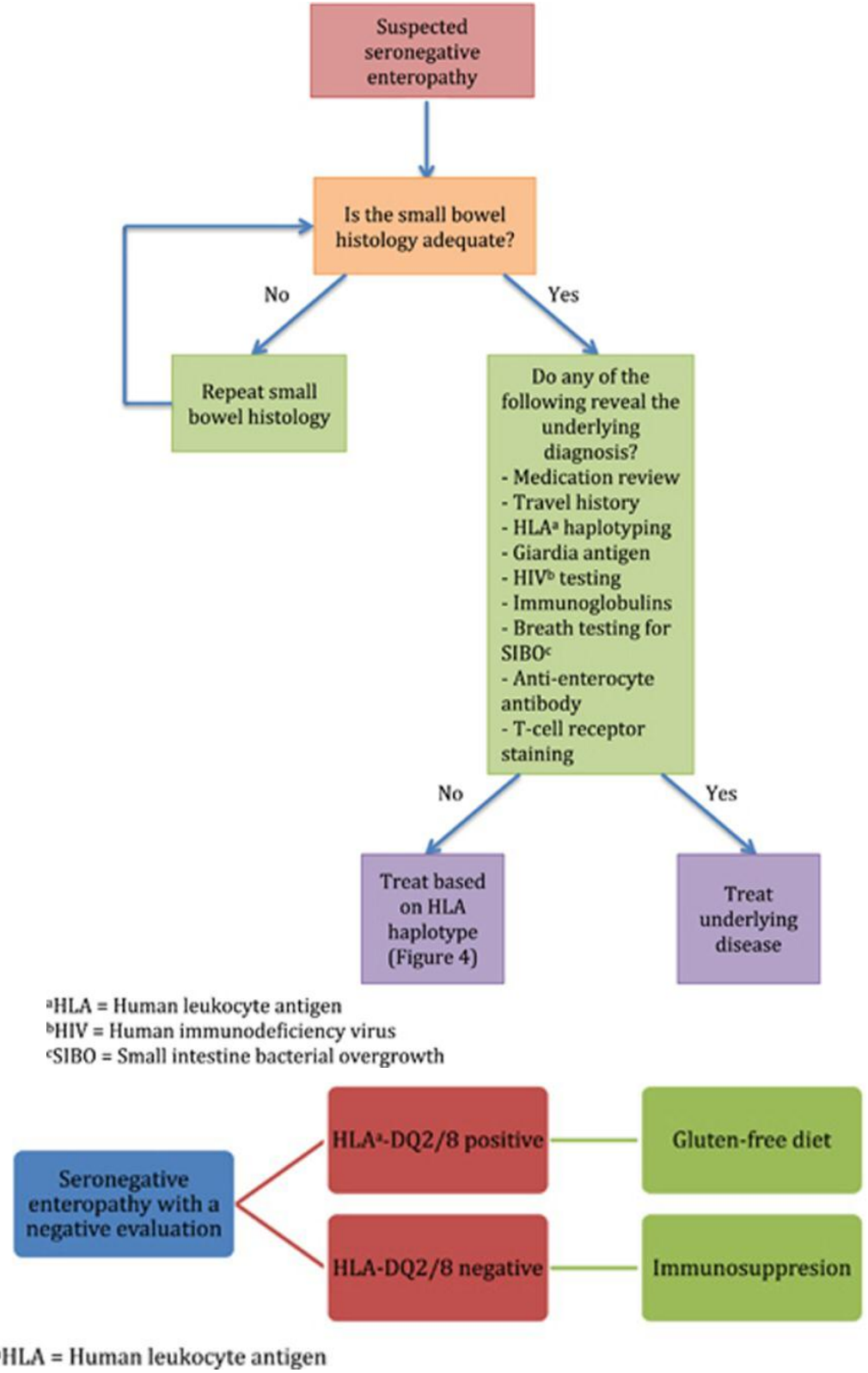


Figure12:proposed algorithm for work up and management of seronegative enteropaties.

Conclusion

According to the algorithm above (Figure 12) which shows the work-up and management of patients with a serologically negative enteropathy can be used to guide clinicians. The evaluation of a patient with a serologically negative enteropathy necessitates a detailed evaluation by an expert gastrointestinal pathologist to ensure that adequate tissue has been obtained, and to be sure histologic clues favoring another diagnosis have not been overlooked. The histologic finding of duodenal IELs with normal villous architecture is being seen with increased frequency; while up to one-third of such cases have no known cause identified, NSAID use is a strong contributing factor. Several prescription medications can mimic CD and should be considered in all patients with a serologically negative enteropathy. Many mimickers of CD have clues to the underlying diagnosis and many have a targeted therapy. It is necessary to provide patients with a correct diagnosis and appropriate therapy rather than subject them to a lifetime of an unnecessary gluten-free diet.

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