Histopathology of intestinal villi in neonatal and paediatric age: main features with clinical correlation - Part II

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Summary

In this paper, we will continue the description of histological findings of infantile and paediatric small bowel alterations with the main clinical pictures and differential diagnosis. We emphasise once again the need to evaluate the biopsies in an adequate clinical contest and with a systematic approach, including epithelial alterations, lamina propria changes, mucosal architecture, and the distribution of inflammation, together with other morphological signs more specific of certain diseases. We describe the histological findings of coeliac and Crohn’s disease, gastrointestinal food allergic diseases, Langerhans cell histiocytosis, nutritional deficiencies and infections. Finally, we suggest the principal issues in the drafting the pathological report for appropriate interpretation and usefulness in clinical practice.

Key words: coeliac disease, Crohn’s disease, gastrointestinal food allergic diseases, langerhans cell histiocytosis, infections, paediatric enteropathies, small bowel

Coeliac disease

Coeliac disease (CD) is an immune-mediated systemic disorder elicited by gluten, a protein found in wheat, barley, rye, spelt, and kamut. It occurs in genetically predisposed individuals, mostly females (male/female ratio 1:2) 1. The age at presentation vary from early childhood to elderly, according to the age at introduction of gluten in the diet, the quantity consumed and individual sensitivity 1,2. In Western countries, the prevalence of histologically confirmed CD is around 0.6% 3. In the last decades, due to sensitive and specific screening tests, there has been a significant increase in the number of new cases of CD 4. Diagnostic workup is carried through a thorough evaluation of clinical, serological, genetic and histological aspects. In order to achieve a correct diagnosis, it is essential to examine the patients while they are still exposed to gluten. In fact, a gluten-free diet may alter the clinical, serological and histological features of CD, making it unrecognisable 5.

Clinical presentation

According to Caio et al., CD presentation can be subdivided in two main phenotypes: intestinal and extra-intestinal, which may occur individually or in combination 4. In paediatric patients, the classic presentation
consists in loss of appetite, abdominal distention, diarrhoea and failure to thrive. Growth retardation and delayed puberty may be major manifestations in adolescents. Extra-intestinal manifestation are common in both children and adults and are mainly related to malabsorption or chronic inflammation. They include iron deficiency-related microcytic anaemia (most frequent) or macrocytic anaemia due to folic acid and/or vitamin B12 deficiency. Most patients also manifests osteopenia or osteoporosis due to altered absorption of calcium and vitamin D. Neurological manifestation may include headache, paraesthesia, depression, cerebellar ataxia and gluten encephalopathy. Other symptoms include aphthous stomatitis, dental enamel hypoplasia, and hepatitis. CD can be associated with different immune disorders including dermatitis herpetiformis, type 1 diabetes, alopecia, Hashimoto’s thyroiditis and selective IgA deficiency.

**Histological diagnosis and classification**

Histological evaluation still remains of critical importance in CD diagnosis. Should undergo an intestinal biopsy:

- Individuals with positive serology, characterised by the presence of IgA class antitransglutaminase (tTGA) and antiendomysial antibodies (EMA), and children younger than 2 years with isolated IgA antigliadin (AGA) positivity.
- Individuals with deficiency of IgA, positive for tTGA IgG (and even children aged < 2 years with positivity for AGA IgG with or without tTGA IgG).
- Individuals in whom coeliac disease is strongly suspected, with a severe malabsorption syndrome, irrespective of antibody test results.

To obtain a valid diagnosis, at the time of the biopsy, the patient must be on a normal diet containing gluten. Biopsy should be performed in the duodenal bulb and in the distal duodenal portion. It is recommended to collect at least 4 biopsies, 2 for each of the areas mentioned above. Particularly in children, the evaluation of the duodenal bulb can be essential in CD diagnosis. Multiple studies have shown that CD modifications can be restricted to the duodenal bulb in 2.5% to 13% of patients, especially in children.

In a multicentre study of 102 paediatric patients performed by Bonamico et al, it has been demonstrated that involvement of the duodenal bulb was present in all subjects, in 25% of whom it was the only site of injury. Furthermore, a study published by De Leo and Villanacci shows that bulb duodenal analysis led to a 12% increase in CD diagnosis, emphasising the critical role of bulb duodenal biopsies in CD (Fig. 1). Positioning of biopsies on cellulose acetate filters is recommended. This method ensures proper orientation of the histological sample.

The distinctive histological features of CD are:

1. *Increased intraepithelial T lymphocytes*: a value > 25 T lymphocytes/100 enterocytes (lymphocytosis).
2. *Crypt hyperplasia*: extension of the regenerative epithelial crypts associated with the presence of > 1 mitosis per crypt.
3. *Villous atrophy*: decrease in villous height, alteration of normal crypt/villous ratio (3:1) until total.

![Figure 1](Image)

The same case: A-B normal villi in distal duodenum; T lymphocytes < 25/100 epithelial cells. A H&E 4x, B CD3 immunostain 4x; C-D moderate-severe villous atrophy in bulb; T lymphocytes > 25/100 epithelial cells (Type 3B + 3C/Grade A + B2) with pathological increase of T lymphocytes. C H&E 4x, D CD3 immunostain 4x. The same case: E-F normal villi in distal duodenum; T lymphocytes < 25/100 epithelial cells. E H&E 10x, F CD3 immunostain 10x; G-H severe villous atrophy in bulb; T lymphocytes > 25/100 epithelial cells (Type 3C/Grade B2) with pathological increase of T lymphocytes. G H&E 10x, H CD3 immunostain 10x.
disappearance of villi. This assessment requires proper orientation of the biopsies.

Up to now, several classifications exists to describe the histopathological alteration of CD, and they are briefly reported in Table I. Unfortunately none of the above mentioned characteristics is pathognomonic for CD; for an accurate diagnosis the histological pattern has to be integrated with clinical, serological and genetic data.

In the histological report, atrophic lesions (Type 3a, 3b or 3c/Grade B) should be indicated as “consistent with CD”, while for non-atrophic lesions with intraepithelial lymphocytosis (Type 1 or 2/Grade A) the term “suggestive for CD” is more appropriate. In the conclusive diagnosis the pathologist should only give a description of the lesion, stressing the idea that these injuries are not exclusive of CD and should therefore necessarily be placed in the right clinical setting and supported by serological and genetic confirmation.

## IMMUNOHISTOCHEMISTRY

The application of immunohistochemistry in CD diagnosis can be helpful to clearly identify the lymphocytosis condition. Albeit the increase of intraepithelial T lymphocyte can be observed also on haematoxylin-eosin stain, we suggest, especially in the easy forms, the use of CD3 monoclonal antibodies for a more accurate evaluation of the epithelial lymphocytosis. CD8 monoclonal antibodies can be useful in elderly patients, in order to exclude a refractory form of CD, not responsive to a gluten-free diet. In this condition, regarded by many as pre-lymphomatous, the expression of CD8 may be reduced.

## DIFFERENTIAL DIAGNOSIS

CD shares its duodenal histopathologic features with a large variety of intestinal disorders. Numerous conditions are associated with increased intraepithelial lymphocytes, with or without villous blunting. Therefore clinical and serological correlation is mandatory. Regarding the paediatric population, the main conditions that must be ruled out are Helicobacter pylori gastritis, parasitic infections and gastrointestinal food-protein enteropathies, common variable immunodeficiency, and autoimmune enteropathy; these conditions are discussed in part I of this review, in following sections of this work, and other papers in this same Special Issue.

In regards to collagenous sprue, small bowel biopsies may show an increase in chronic inflammatory cells in the lamina propria in association with increased intraepithelial lymphocytes and patchy epithelial degenerative changes; the detection of a subepithelial band-like collagen deposit in the proximal small bowel may lead the pathologist to a correct diagnosis.

### Table I. Coeliac disease classification systems.

| Marsh Classification | Oberhuber modifications |
|----------------------|-------------------------|
| **Type 1 – Infiltrative lesion** | 3a: mild villous atrophy and pathological increase of intraepithelial lymphocytes. |
| Villi within normal morphological limits (normal villous/crypt ratio 3:1) | 3b: moderate villous atrophy and pathological increase of intraepithelial lymphocytes. |
| Increased number of intraepithelial lymphocytes (greater than 25/100 epithelial cells) | 3c: total villous atrophy and pathological increase of intraepithelial lymphocytes. |
| **Type 2 – Hyperplastic lesion** | Corazza-Villanacci Classification |
| Villi architecturally within normal morphological limits (like type 1) | **Grade A lesions** |
| Increased number of intraepithelial lymphocytes (greater than 25/100 epithelial cells) (like type 1) | Normal villi but with a pathological increase in intraepithelial lymphocytes |
| Hyperplasia of the glandular elements (regenerative aspects highlighted by the reduced mucinous activity and increased number of mitoses). | **Grade B lesions** |
| **Type 3 – Destructive lesion** | B1: villus/crypt ratio is less than 3:1 and pathological increase of T lymphocytes |
| Varying degrees of villous atrophy associated with hyperplasia of glandular crypts | B2: villi are no longer identifiable and pathological increase of intraepithelial lymphocytes |
| Surface enterocytes with reduced height, irregular brush border and sometimes cytoplasmic vacuoles | Congenital defects of small intestine epithelial differentiation |
| Increased number of intraepithelial lymphocytes (like type 1 and 2 lesions). | **Grade A – non atrophic type** |
| No architectural changes (villous/crypt ratio preserved) and increased IELs count (> 25/100 epithelial cells) | Villous atrophy (mild-moderate-severe degree), crypt hyperplasia (mitoses > 1/crypt) and increased IELs count (> 25/100 epithelial cells). |
**Crohn’s Disease in childhood**

Crohn’s disease (CrD) is, together with ulcerative colitis, an inflammatory bowel disease (IBD), a chronic, multifactorial, immune-mediated disorder with a relapsing and remitting course, which may cause, to a variable degree, inflammation of the entire digestive tract 21,22.

Incidence and prevalence of CrD greatly varies by geographic region, having the highest prevalence in Europe and North America. Nevertheless, since 1990, CrD incidence is accelerating in the newly industrialized countries, such as Asia, South America and Africa, while being stable or even decreasing in North America and Europe 23.

Up to 30% of CrD cases develop during childhood or adolescence 24, with an annual incidence ranging from 2 to 5 per 100,000 children 25. According to patient age at IBD diagnosis, it is possible to distinguish 2 main groups in IBDs: very-early-onset IBDs (VEO-IBDs), diagnosed before 6 years of age, and early-onset IBDs, diagnosed between 6 and 16 years of age 21. For a more detailed overview of VEO-IBD, we invite the reader to refer to another paper in this Special Issue by Parente et al. 26.

IBD pathophysiology is still not completely known; nonetheless, genetic, environmental, immunological and microbiome-related factors have been proved to contribute, at various rates, to its development 22.

Paediatric CrD is demonstrated to have a more severe behaviour compared to its adult form 22,28, partly because some of VEO-IBDs are represented by a monogenic form (i.e., XIAP deficiency, interleukin 10 signalling defect, IPEX-like), which typically has an aggressive phenotype and less frequently responds to traditional treatments 22.

Common symptoms and signs of paediatric CrD include abdominal pain, diarrhoea, weight loss, growth failure, anorexia, malaise, fatigue, anaemia and fever 22. Beside clinical evaluation, imaging of the small bowel, esophagogastroduodenoscopy, ileo-colonoscopy and multiple biopsies from the gastrointestinal tract are recommended to achieve a correct diagnosis 25,29.

Upper gastrointestinal involvement appears to be very frequent in paediatric CrD, having an incidence rate of 30-70% 30,31 and resulting to be significantly more frequent in patients with an extensive ileocolonic inflammation 32. The endoscopic finding usually observed in small bowel include erythema, oedema, erosions, aphthous ulcers, mucosal granularity, pseudopolyps, “cobblestone” appearance of mucosa and stenosis 32,33. Small intestine histological abnormalities may include patchy or diffuse, chronic or mixed, inflammation in lamina propria, erosions, lymphoid aggregates, cryptitis, partial villous atrophy and non-caseating, epithelioid or giant cells, granulomata 32-34. Although no single endoscopic finding is pathognomonic, some of them (i.e., aphthous ulcers in any part of the gastrointestinal tract, mucosal skip lesions, ulcerations or strictures of the terminal ileum, significant perianal disease), particularly if coupled with biopsies showing typical IBD-associated lesions (mostly if they include granulomata), may make straightforward the diagnosis of CrD and help in the differential diagnosis with the much rarer form of ulcerative colitis involving the upper gastrointestinal tract 22,25,29,32,34.

**Gastrointestinal food allergic diseases**

Gastrointestinal food allergic diseases are classified in 3 groups, with regard to their underlying pathogenesis: i) IgE-mediated, which occur very rapidly and frequently have a systemic, severe involvement, ii) mixed IgE/non-IgE-mediated, such as the previously discussed EGIDs (chapter 10), iii) non-IgE-mediated, in which circulating food-specific IgE are typically absent and onset of gastrointestinal symptoms is generally delayed after food allergens exposure 35.

Non-IgE-mediated gastrointestinal food allergic diseases (non-IgE-GI-FA) may be further subclassified into 3 main disorders, according to how extensively the digestive tract is involved: a) food protein-induced proctocolitis, limited to colorectum and characterised by mild symptoms and by a high relative frequency among non-IgE-mediated food allergic disorders, b) food protein-induced enteropathy (FPE), affecting the small intestine and characterised by a moderate severity of symptoms, c) food protein-induced allergic enterocolitis syndrome (FPIES), the least common non-IgE-GI-FA, characterised by severe symptoms and involving whole gastrointestinal tract 35.

FPE is relatively uncommon, accounting for about a fifth of the number of the coeliac patients, and it seems to be decreasing over time 36. FPIES is a rare disease, with a cumulative incidence ranging from 0.34 to 0.7% in infancy 37,38. Co-atopy is highly represented in non-IgE-GI-FA, affecting up to 44% 39 and 55% 40 of FPE and FPIES patients, respectively.

Non-IgE-GI-FA pathophysiology is not completely clarified; a combined implication of both cellular immunity 41 and innate immune system 42, in the absence of a notable humoral immunity 43, has been suggested. 

Clinics and oral food challenge (OFC) are sufficient for FPIES diagnosis, while histologic confirmation is mandatory for FPE diagnosis 35. The commoner culprit foods involved in are cow’s milk, soy, rice, poultry, fish, wheat, eggs, fruits, corn and vegetables 35.
Common histological findings in jejunal biopsies of FPE and FPIES patients include mild to severe villous atrophy, crypt hyperplasia and, occasionally, an increased number of eosinophils and intraepithelial lymphocytes. These alterations are independent to the offending food. Ultrastructurally, epithelial cells display abnormally located nuclei and short and furry microvilli containing large aggregates of lysozymes.

**Langerhans cell histiocytosis**

Langerhans cell histiocytosis (LCH) is, albeit its rarity, one of the most common histiocytic disorder, characterised by a clonal proliferation, and consequent accumulation, of immature Langerhans cells within different organs. With regard to its localisation, LCH may be classified into three main groups: single-system single-site, single-system multi-site and multisystem disease, with or without risk organ involvement. Estimated annual incidence for LCH is 2-9 cases/1 million people, with a peak incidence between 1-4 years of age, and male to female ratio of 1.5:1. LCH with gastrointestinal involvement is quite rare, usually affects patients under 2 years of age, with a 2-fold male predominance, and is associated with a multisystemic presentation and a poor prognosis.

Gastrointestinal involvement of LCH may have various presentations, comprising vomiting, failure to thrive, haematochezia, intractable diarrhoea, malabsorption, constipation, abdominal pain, protein-losing enteropathy, intestinal perforation and strictures. In these patients, esophagogastroduodenoscopy usually shows erosions or ulceration of duodenal mucosa. Molecular studies have showed that up to 75% of LCHs harbour mutually exclusive mutations of BRAF (V600E), MAP2K1 and N/KRAS genes, all of which determine the activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) cascade. Histology remains the gold standard for LCH diagnosis. Biopsy samples display, in lamina propria, a proliferation of medium-sized mononuclear cells, characterised by ovoid nuclei with a longitudinal nuclear groove (the so-called “coffee-bean” appearance) and a moderate amount of eosinophilic cytoplasm, admixed with a variable number of eosinophils, macrophages, stromal cells, multinucleated giant cells and T cells. In fact, LCH cells have been proved to produce a large variety of proinflammatory cytokines and chemokines, inducing the migration of several inflammatory cells in the involved site. Diagnosis requires confirmation of the histiocytic tumour’s nature by immunohistochemistry. Langerhans cells express CD1a, CD207/langerin, S100 and may also result positive for CD68, vimentin and p53. Electron microscopy typically shows pathognomonic cytoplasmic tennis racquet-shaped organelles, the Birbeck granules, which have been demonstrated to strictly correlate with the immunohistochemical expression of CD207/langerin.

**Nutritional deficiencies (zinc and iron deficiencies and kwashiorkor)**

Nutritional deficiency is defined as a low or insufficient intake of micronutrients (i.e. vitamins and dietary minerals) and macronutrients (i.e. protein, carbohydrates and fat), due to dietary or inherited causes. During childhood, many nutritional deficiencies may lead to retardation in growth and development.

Nowadays, malnutrition affects predominantly children < 5 years of age living in low-income and middle-income countries. Zinc is a micronutrient essential for growth, and the immune, nervous and endocrine systems, particularly during infancy. Since preterm infants are in negative zinc balance at birth due to a lower capacity for gut absorption, they have an increased risk of zinc deficiency. Two rare, inherited disorders, caused by mutations in zinc transporters genes, may determine zinc deficiency in children: i) *acrodermatitis enteropathica*, an autosomal recessive disease, characterised by cutaneous and gastrointestinal manifestations, due to a reduction in intestinal zinc absorption, ii) *transient neonatal zinc deficiency*, causative for low concentration of zinc in mother’s breast milk.

Microscopically, duodenal biopsies of patients with *acrodermatitis enteropathica* show loss of villous architecture, with flattened villi, increased inflammatory infiltrate in lamina propria and reactive changes in epithelial cells, such as cuboidal cellular shape, enlarged nuclei and open chromatin distribution. Furthermore, ultrastructural examination of intestinal epithelial cells has revealed the presence of numerous intracellular vesicles. After treatment, cellular and villous modifications have been proved to fully recover.

Iron deficiency, also causative for anaemia, is another rare cause for the alteration of small intestine villous pattern in pediatrics. It has been estimated that, during infancy, only 1/7,000 children is affected. Reported duodenal-jejunal changes include blunting, shortening or fusion of villi, coupled with dense infiltration of inflammatory cells in lamina propria. After iron therapy, small intestine histology generally improves or returns to normal.

Kwashiorkor is a form of severe malnutrition, caused by low protein intake.
Histological studies, mostly performed on malnourished children from underdeveloped and developing countries, have depicted variable lesions in small intestine mucosa, ranging from mild shortening to flattening and thickening of villi, according to the different quality of the examined individuals' diet. Ultrastructural studies on jejunal mucosa have shown an accumulation of fat in the endoplasmic reticulum, in the Golgi apparatus and in the cytoplasm of epithelial cells, as well as in the intercellular space and in lamina propria. These findings probably result from a derangement of fat metabolism. Furthermore, a shortening of microvilli, rounded mitochondria and an increase in polyribosomes have also been observed. All these histological and ultrastructural changes may be reversed after an adequate refeeding.

Infections

A complete discussion of all the infections that can affect the small intestine in paediatric age is beyond the scope of this review; it is still of note, however, to mention some relevant infective diseases that can act as mimickers of organic disorders affecting the villous epithelium of the duodenum. *Helicobacter pylori* (HP) gastric infection is rather common in the paediatric age, and can cause a peptic duodenitis, with increased IELs and normal or minimally atrophic villous architecture. Reactive hyperplasia of Brunner glands and gastric metaplasia may be present, and the latter has been shown to harbour HP in a small percentage of cases. Nevertheless, the identification of HP on gastric epithelium is required for a diagnosis of HP-related peptic duodenitis. Other infectious disease that can cause villous atrophy with increased intraepithelial lymphocytes and must therefore be considered in the differential diagnosis in a paediatric patient are viral and parasitic infections; in the latter category, *Giardia lamblia* infection should be ruled out before diagnosing an organic disorder of the villi. Cryptosporidiosis, albeit less frequent, is another known parasitic infection mimicking villous atrophy in the duodenum. As for *G. lamblia*, identification of the offending parasite on the brush border of the affected villi in a child should prompt careful examination of the laboratory exams and history so as to avoid overdiagnosis of an organic condition.

A final note of caution must be issued when examining biopsies of the small intestine in which a prominent macrophage infiltrate is recognized; careful examination and use of special stains can help differentiate storage disorders from the more common infections by intracellular microorganisms: *Tropheryma whipplei* (PAS-D-positive, Acid-fast-negative) and *Mycobacterium avium* complex (Acid-fast-positive, PAS-D-negative) are the most common conditions that must be excluded.

Pathological report

The wide variety of conditions and indications that may lead to the performance of a small bowel biopsy in the paediatric age mandates that the pathologist maintains a certain degree of flexibility in writing the report. Table II and Table III report respectively a sum-

| Table II. Main histologic features of paediatric small bowel mucosal disorders. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Disorder                        | Villous atrophy | Intraepithelial lymphocytosis | Lamina propria inflammation | Characteristic histologic features |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Congenital enzymatic and transport deficiencies** | | | | |
| Congenital disaccharidase deficiencies | absent | absent | absent | normal small bowel histology |
| Congenital lipid trafficking deficiencies | absent | absent | absent | fat-filled, multivacuolated enterocytes; lipid droplets in the intercellular/extracellular spaces (only in Anderson disease) |
| Ion and nutrient transport deficiencies | rare and usually mild | absent | possible | dense inspissated mucus in cystic fibrosis |
| **Congenital defects of small intestine epithelial differentiation** | | | | |
| Microvillos inclusion disease | present, usually severe | absent | present | absence of brush border; PAS+ (or CD10+) inclusions on the apex of enterocytes |
| Congenital tufting enteropathy | present, usually severe | absent | mild | “tufts” of teardrop-shaped surface enterocytes; crypt dilatation and hyperplasia; reduced EpCAM expression |

continues
Table II. Main histologic features of paediatric small bowel mucosal disorders (follows).

| Enteroendocrine cell dysgenesis | possible, usually mild | absent | absent | absence of chromogranin-positive neuroendocrine cells |
| Tricho-hepato-enteric syndrome | present | absent | absent | none |

**Autoimmune disorders**

| Coeliac disease | present | present | present | crypt hyperplasia, regenerative changes |
| Autoimmune enteropathy | present, usually severe | absent | present | absence or severe reduction in goblet and Paneth cells |

**Immunodeficiencies**

| Common variable immune deficiency | present | present | present | absence of plasma cells, nodular lymphoid hyperplasia |
| Selective IgA deficiency | present | present | present | absence of plasma cells, nodular lymphoid hyperplasia |
| Chronic granulomatous disease | absent | absent | absent | granulomas with pigment-laden macrophages in the crypt, with possible extension to the villus if particularly florid |

**Graft-versus-host disease**

| present, usually mild | present, usually mild | mild (if present) | epithelial apoptotic bodies, gland destruction and loss of Paneth cells |

**Infections and bacterial overgrowth syndrome**

| rare and patchy | rare | possible | none |

**Gastrointestinal food allergic diseases**

| present, mild to moderate | possible | absent | histological alterations in biopsy from for protein-induced enteropathy (FPE) and for protein-induced allergic enterocolitis syndrome (FPIES) |

**Eosinophilic gastroenteritis**

| absent | absent | present | dense lamina propria infiltration by eosinophils; crypt abscesses or cryptitis may be present |

**Crohn's disease**

| possible, usually mild | absent | present | granulomata, erosions, lymphoid aggregates, cryptitis |

**Ulcerative colitis-associated duodenitis/backwash ileitis**

| absent | absent | present | chronic active inflammation and crypt distortion |

**Lymphangectasia**

| present | absent | absent | dilated lymphatic vessels in the superficial or deep mucosa |

**Storage diseases**

| Congenital disorders of glycosylation | present | absent | present | small bowel manifestations are usually present only with deficit of phosphomannose isomerase (MPI-CGD, former CGD type Ib) and mutations in the gene encoding alpha-1,3-glucosyltransferase (ALG6-CDG, formerly CDG type Ic) |
| Mucopolysaccharidosis | absent | absent | absent | scarce; reported enlarged lymphatic vessels in the lamina propria in Sanfilippo syndrome |
| Lysosomal acid lipase deficiency (LAL-D) | possible | absent | present | PAS+ foamy macrophages in the lamina propria in Wolman disease and CESD |
| Tangier disease | possible | absent | present | PAS-negative foamy macrophages in the lamina propria |
| Glycogen storage diseases | possible, usually mild | absent | present | mild alterations possibly found in GSD type Ib as a Crohn-like enteritis |
| Glycolipid storage disorders | absent | absent | absent | enlarged ganglion cells with foamy cytoplasm in Fabry disease |
| Nutritional deficiencies (zinc, iron, kwashiorkor) | possible, usually mild | usually absent | possible | cellular and villous alterations regress after supplementation of the lacking nutrients |
| Langherans Cell Histiocytosis | absent | absent | present | medium-sized mononuclear cells, characterised by ovoid nuclei with a longitudinal nuclear groove and a moderate amount of eosinophilic cytoplasm (CD1a+, langerin +, S100+) |
| Necrotising Enterocolitis | absent | absent | absent | ischaemic colitis with patchy or diffuse haemorrhagic necrosis of the mucosa, coagulative necrosis of the muscular layers |
mary of the most common histological modifications of the pathologic conditions reported in this review and some common non-pathological mimics of disease. An extensive and thorough description of the findings should be provided in the pathological report, including: i) a note on the orientation of the sample, especially if it is suboptimal, fragmented or there are crushing artefacts that could impair the correct evaluation of the structure of the villous, ii) degree of villous atrophy, iii) presence, distribution and composition of the inflammatory infiltrate. iv) any additional relevant histologic sign, v) changes in the submucosal or muscular layers, if present in the biopsy sample, vi) presence of microorganisms. When the diagnosis is straightforward and guidelines exist to grade and report a specific condition, the latter should be suitably applied and reported in the final pathological report; however, in many cases, the final diagnosis can only be reached by integrating the histological picture with the clinical and laboratory information.

Conclusions

Diagnosis of small bowel disorders and their specific aetiology requires an integrated clinical and pathological approach. In-depth knowledge of histopathological lesions and the main differential diagnosis are imperative in daily pathological practice for appropriate management of these patients.

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Table III. Most common histologic mimics of small bowel pathologic conditions and their differential diagnosis.

| Diagnosis                      | Histology                                                                 | Differential diagnosis                                                                 |
|--------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Melanosis and pseudomelanosis  | Dark, pigmented macrophages in the lamina propria                         | Lysosomal storage diseases, chronic granulomatous disease                              |
| Barium granuloma               | Granulomatous reaction with fine, refractile material                      | Lysosomal storage diseases, IBD, chronic granulomatous disease                         |
| Pseudolipomatosis              | Clear spaces in the submucosa, without epithelial or endothelial lining    | Lymphangectasias                                                                      |
| Foreign body injury            | Nonspecific necrosis, inflammation; may progress to ulcer or perforation   | Ischaemic enteritis                                                                  |
| Drug-related injury            | Nonspecific enteritis                                                      | IBD                                                                                   |
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