Role of the pathologist in the differential diagnosis of malabsorption

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Abstract

Histological examination of small intestinal biopsies is an essential step in the assessment of malabsorption syndromes. Multiples biopsies should be taken in the proximal jejunum or distal duodenum and correctly oriented. Histological evaluation has to be systematic considering villous architecture, inflammation and specific diagnostic elements. In celiac disease, even with the development of serology tests, the biopsy remains useful to follow the patient and to detect potential complications. (Acta gastroenterol. belg., **2006**, 69, **49-51**).

Key-words : intestinal biopsies, malabsorption, small intestine histology, celiac disease.

Diseases that can lead to malabsorption are numerous and variably classified. They may or may not be associated to morphological anomalies of the small intestine, which is the reason why microscopic examination of small intestinal biopsies is an essential step in their assessment.

A few practical recommendations (1,2)

A biopsy taken for the assessment of a malabsorption syndrome must imperatively be sampled either in the distal duodenum or proximal jejunum. Specific lesions are indeed mostly little developed or atypical in the proximal duodenum, and evaluation of the degree of normality of the villous architecture may be rendered difficult by the presence of Brunner's glands or lymphoid aggregates. Furthermore, lesions that are peptic in origin could also be the cause of architectural and inflammatory changes in the mucosa and lead to diagnostic errors. The biopsies should consist in the full-thickness of the mucosa, including the muscularis mucosae that maintain the general architecture and therefore the right orientation of the fragments.

Biopsies should be multiple, as the pathologies concerned are not all diffuse in nature. They should be orientated correctly, ideally prior to fixation, and then embedded and serial sections should be performed. Formalin fixation is preferable as it enables complementary molecular analyses. In some cases, it may also be useful to freeze certain sampled specimens.

Beside these technical considerations, certain factors optimise diagnostic efficiency of the histological interpretation, such as precise clinical information, a systematic histological examination, and a good knowledge of both intestinal diseases that can cause malabsorption and of the normal intestinal histological spectrum.

Normal intestinal histology (1, 2)

In the normal small intestinal mucosa, the villosity-to-crypt ratio can be anywhere between 2/1 and 5/1. When three to four consecutive well-oriented axes of villi and crypts have a normal ratio, villous architecture can be considered to be preserved (Fig. 1). Surface epithelium is unistratified and consists of enterocytes and caliciform cells. A brush border is clearly visible at the apical pole of enterocytes, while the nuclei are regularly positioned in a line along the basal pole. There are intra-epithelial lymphocytes (IEL) in the proportions of approximately 1 lymphocyte for 5 enterocytes (range : 6-30%). The majority of these IEL (70-90%) are type CD3+/CD8+, the others are CD4+. A minority of IEL (< 5%) is CD8-/CD4-. Most of IEL have surface receptors of the $\alpha\beta$ type ; the others (1-10%) possess receptors of the $\gamma\delta$ type. Other cells commonly found in the lamina propria include inflammatory cells, plasmocytes, macrophages, polynuclear eosinophils, and lymphocytes of the CD3+/CD4+ type.

Intestinal histology in malabsorption syndromes (1, 2)

The biopsies can appear strictly normal or present two main categories of histological anomalies : specific lesions without significant alteration of the villous architecture or architectural anomalies of the villi with or without specific diagnostic elements.

Normal mucosa

This will be observed in disaccharidase deficiency and in malabsorption linked to extra-intestinal pathology, such as pancreatitis, alcoholism, cirrhosis or hepatitis.

Specific anomalies without anomalies of the villous architecture

The main pathology is Crohn's disease, where the pathologist will identify focal inflammation with non-necrosing granulomas. A-betalipoproteinemia, in which

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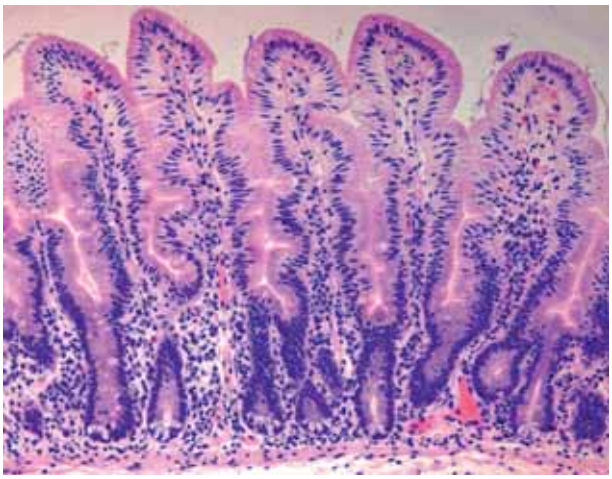

Fig. 1A. — Normal histology of the small intestine mucosa. (Hematoxylin-eosin, original magnification ×20).

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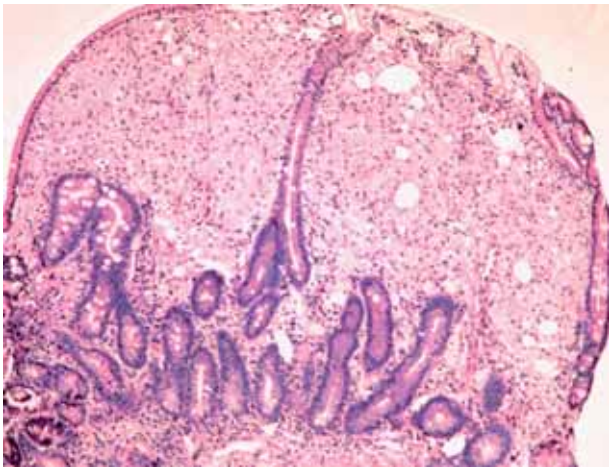

Fig. 1B. — Typical features of Whipple disease. (Hematoxylin-eosin, original magnification ×10).

enterocytes at the surface of the mucosa appear lipid-laden, has also to be kept in mind, as well as hemochromatosis, amyloidosis, and other rarer diseases such as lipid overload disease with vacuolized macrophages, or systemic mastocytosis.

Anomalies of the villous architecture

– *variable villous atrophy with specific histological elements*

This is essentially seen in infections due to Giardia or parasites (Cryptosporidium, Isospora belli, Strongyloides), Whipple's disease (Fig. 2), infection due to *Mycobacterium avium intracellulare*, mycoses (Candida, Histoplasma), viral infections such as CMV or Herpes and more rarely, eosinophilic gastroenteritis, lymphangiectasis or common variable hypogammaglobulinemia (characterized by lymphoid hyperplasia and absence of plasmocytes in the lamina propria).

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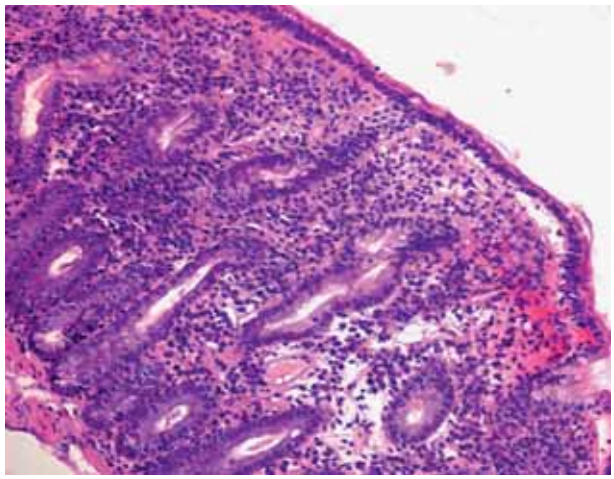

Fig. 1C. — Complete villous atrophy with crypts hyperplasia, intra-epithelial lymphocytosis and inflammation, suggestive of celiac disease. (Hematoxylin-eosin, original magnification ×20).

– *variable villous atrophy without specific histological elements*

This is mainly seen in subclinical celiac disease, dermatitis herpetiformis, infectious gastro-enteritis, stasis syndrome with microbial proliferation, drug-related enteritis, certain types of tropical sprue, and Zollinger-Ellison syndrome. Also to be found in this category are graft-versus-host disease (GVH) and HIV-associated enteropathy, both characterized by an important apoptosis at the base of the crypts.

– *complete villous atrophy with compensatory hyperplasia of the crypts*

The first diagnosis in our countries is celiac disease. Other causes then have to come to mind, such as other types of protein allergies, lymphocytic enterocolitis, certain forms of tropical sprue, refractory sprue and familial enteropathy. In collagen sprue, total atrophy is usually accompanied by thickening of the sub-epithelial collagen lamina.

– *complete villous atrophy with crypt hypoplasia*

This occurs mainly as a consequence of radio- and/or chemotherapy treatment, and in cases of Vitamin B12 and folate deficiencies, malnutrition and kwashiorkor.

Intestinal biopsy in celiac disease

In celiac disease, intestinal biopsy may be performed either because serological analysis yielded results suggesting the presence of the disease, or because clinical examination is suggestive but associated to negative serological results. The biopsy might also be taken during an endoscopy performed for another reason, as the clinician visualizes villous atrophy or simply performs a routine biopsy. Histological appearance can be highly

variable, ranging from total villous atrophy with intra-epithelial lymphocytosis (40-150%) to a mucosa showing only an isolated intra-epithelial lymphocytosis (3). The pathologist never makes a formal diagnosis of celiac disease but indicates in his report that the observed lesions are totally in agreement with this clinical diagnosis (Fig. 3). Only a near-total reversal of the lesions seen at microscopy following a strict gluten-free diet will confirm the diagnosis. The performance of a gluten-challenge test is no longer required (4).

However, performing an intestinal biopsy has become slightly controversial since the appearance of the serology tests (5). Hence the recommendation by some to only perform microscopic examination in those cases where the diagnosis of celiac disease is raised clinically but where serology is negative. Nevertheless, only a biopsy will indicate the degree of severity of the disease and enable its follow-up, it will encourage adherence to the diet and be an important element in case of poor response to the gluten-free diet and re-appraisal of the diagnosis. Moreover, immunohistochemistry and/or molecular biology techniques that can be applied to these biopsies will help the differential diagnosis in cases where villous architecture is preserved (particular IEL distribution and different phenotypic proportions in celiac disease) (6-9) and in cases with a suspicion of a main complication of the disease, i.e. refractory sprue (particular immunohistochemical profile of the IEL, which are a majority of CD3+/CD8- and possess an oligoclonal rearrangement of the TCRγ gene) or T-cell lymphoma resulting from a monoclonal expansion of the IEL, which have a CD3+/CD8-/CD4- or rarely CD3+/CD8+/CD56+ phenotype (10-11).

In conclusion, intestinal biopsy performed in the investigation of a malabsorption syndrome will not only offer an elegant evaluation of intestinal mucosal modifications and/or the identification of specific elements but it can also be useful for specific biochemical, histochemical and immunohistochemical analyses which are indispensable for a diagnosis. It will furthermore enable control of the follow-up of the patient and the detection of eventual complications.

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