Journal of Crohn's and Colitis (2013) 7, 827–851

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CONSENSUS/GUIDELINES

European consensus on the histopathology of inflammatory bowel disease☆

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Received 31 May 2013; accepted 5 June 2013

☆ ECCO has diligently maintained a disclosure policy of potential conflicts of interests (CoI). The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors (ICMJE). The CoI statement is not only stored at the ECCO Office and the editorial office of JCC but also open to public scrutiny on the ECCO website ((https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html) providing a comprehensive overview of potential conflicts of interest of the consensus participants and guideline authors.

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[2] A further paper from this consensus working group will be published with more specialized techniques and histopathology IBD concepts.

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http://dx.doi.org/10.1016/j.crohns.2013.06.001

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KEYWORDS
Inflammatory bowel disease;
Ulcerative colitis;
Crohn's disease;
Histopathology;
Consensus

Abstract

The histologic examination of endoscopic biopsies or resection specimens remains a key step in the work-up of affected inflammatory bowel disease (IBD) patients and can be used for diagnosis and differential diagnosis, particularly in the differentiation of UC from CD and other non-IBD related colitides. The introduction of new treatment strategies in inflammatory bowel disease (IBD) interfering with the patients' immune system may result in mucosal healing, making the pathologists aware of the impact of treatment upon diagnostic features. The European Crohn's and Colitis Organisation (ECCO) and the European Society of Pathology (ESP) jointly elaborated a consensus to establish standards for histopathology diagnosis in IBD. The consensus endeavors to address: (i) procedures required for a proper diagnosis, (ii) features which can be used for the analysis of endoscopic biopsies, (iii) features which can be used for the analysis of surgical samples, (iv) criteria for diagnosis and differential diagnosis, and (v) special situations including those inherent to therapy. Questions that were addressed include: how many features should be present for a firm diagnosis? What is the role of histology in patient management, including search for dysplasia? Which features if any, can be used for assessment of disease activity? The statements and general recommendations of this consensus are based on the highest level of evidence available, but significant gaps remain in certain areas.
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1. Introduction

Inflammatory bowel diseases (IBD) are lifelong disorders that are predominantly observed in developed countries and arise from an interaction between genetic and environmental factors. The term IBD was coined to cover two specific diseases: ulcerative colitis (UC) and Crohn's disease (CD). During the last 25 years, several elements have influenced the accuracy of histologic IBD diagnosis. The widespread introduction of endoscopy allowed the analysis of multiple mucosal biopsies from different segments of the colon, ileum and other parts of the gastrointestinal tract. The precise etiology of IBD is unknown and therefore a causal therapy to cure the disease is not yet available. However, the introduction of new treatment strategies interfering with the patients' immune system may result in mucosal healing, making the pathologists aware of the impact of treatment upon diagnostic features.

The Consensus initiated by the European Crohn's and Colitis Organization (ECCO) and the European Society of Pathology (ESP) endeavors to address the different aspects of histologic diagnosis in IBD: (i) procedures required for a proper diagnosis, (ii) features which can be used for the analysis of endoscopic biopsies, (iii) features which can be used for the analysis of surgical samples, (iv) criteria for diagnosis and differential diagnosis and (v) special situations including those inherent to therapy questions that are addressed include: how many features should be present for a firm diagnosis? What is the role of histology in patient management, including search for dysplasia? Which features if any, can be used for assessment of disease activity?

The aim of the Consensus is to propose European Guidelines for the histopathological diagnosis of chronic colitides. The document is based, in parts, upon previous evidence-based ECCO consensus publications on the diagnosis and management of UC and CD.[1,2] On September 11th 2012, in Prague, these guidelines were revised at a meeting of ECCO GuiCom and ESP representatives, at the annual European Congress of Pathology (ECP).

The strategy to reach the Consensus involved six steps: four working groups (WGs) were formed each comprising three ESP delegates and one ECCO delegate: WG 1 was on UC (chaired by Ann Driessen and Gerassimos Mantzaris), WG 2 on CD (chaired by Cord Langner and Fernando Magro), WG3 on lymphocytic and collagenous colitis (chaired by Arzu Ensari and Vicenzo Villanacci) and WG 4 was on indeterminate, unclassified and infectious colitis related to IBD (chaired by Karel Geboes and Rami Eliakim). The existing ECCO guideline statements referring to the histologic diagnosis of IBD were analyzed systematically by the chairs of each WG. Guideline statements selected for change and questions unresolved in the 2008 and 2010 guidelines were distributed to the WG members. Participants were asked to answer the questions based on their experience as well as evidence from the literature (Delphi procedure).[3] In parallel, the WG members performed a systematic literature search of their topic with the appropriate key words using Medline/Pubmed/ISI/Scopus and the Cochrane database, as well as their own files. As a further selection criterion, only those features which achieved moderate reproducibility judged by kappa value, or findings that were confirmed by subsequent studies, were considered. The evidence level (EL) was graded according to the Oxford Centre for Evidence-Based Medicine.[4] Provisional guideline statements (with supporting text) were then written by the WG chairs based on answers to the questionnaire and were circulated among the WG members, prompting discussions and exchange of literature evidence. On May 31st 2012 the working party chairs submitted the proposed statements and the supporting text online on a weblog for discussion among all other Consensus participants (who have not been part of that specific WG). All participants then met in Prague on September 11th 2012 to vote and agree on the final version of the statements. Consensus was defined as such when agreement was reached by more than 80% of participants, termed a Consensus Statement and numbered for convenience in the document. Each recommendation was graded according to the Oxford Centre for Evidence Based Medicine based on the level of evidence.[4] All statements achieved 100% agreement,

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with the exception of statements 16, 23, 24 and 32, which achieved 83–92% agreement.

The final document was written by the WG chairs in conjunction with the WG members. The Consensus participants agreed to produce two separate publications. One (which will be published in the Journal of Crohn's and Colitis) summarizes the statements followed by comments is on the evidence Special attention is given to the clinico-pathologic interface, e.g. to technical procedures necessary for accurate diagnosis of IBD on endoscopic biopsies (number and way of handling of biopsies etc.). Images are not provided in this paper. The second publication (in Virchows Archiv) focuses on the histologic criteria for diagnosis and differential diagnosis (without the Consensus statements), accompanied by illustrative images. The final text of both publications was approved by all Consensus participants.

2. Procedures needed for the diagnosis of IBD

The diagnosis of IBD requires a multidisciplinary approach involving a team of specialists (e.g. gastroenterologists, pathologists and radiologists). The diagnosis should be established by a combination of medical history, clinical evaluation, laboratory data (including negative stool examinations for infectious agents) and typical endoscopic, histologic and radiologic findings.[2,5] Thus, the histologic examination of endoscopic biopsies or resection specimens remains a key step in the work-up of affected patients and can be used for diagnosis and differential diagnosis, particularly in the differentiation of UC from CD and other non-IBD related colitides.

ECCO-ESP statement 1

For a reliable diagnosis of inflammatory bowel disease, ileocolonoscopy rather than rectoscopy should be performed. A minimum of two biopsies from at least five sites along the colon, including the rectum, and the terminal ileum should be obtained [EL 1]. In patients with fulminant colitis, two samples from at least one site should be obtained [EL5]. The biopsies should be collected in separate vials, as localization of the biopsies gives important diagnostic information

In patients with suspected IBD, it is crucial to perform a histologic examination before initiation of treatment, due to changes in morphology induced by certain drugs and to establish a proper diagnosis. Notably, recent progress in endoscopic techniques, such as magnifying endoscopy, chromoendoscopy and/or confocal endomicroscopy has resulted in more punctuate sampling of biopsies, with considerable impact on diagnostic accuracy in the presence of subtle histologic changes.

The histologic diagnosis of IBD is based on the analysis of a full series of colonoscopic biopsies. A study by Dejaco et al.[6] showed that the accuracy of diagnosing colitis increases from 66% to 92% when segmental biopsies are taken rather than two biopsies throughout the colon.[7] Rectal biopsies are necessary to either confirm or reject rectal involvement and may additionally be helpful in differentiating IBD from other inflammatory lesions. Although the diagnostic accuracy of total colonoscopy (74%) compared to rectoscopy (64%) is only slightly higher in UC, cases with atypical distribution of lesions such as peri-appendiceal inflammation associated with a left-sided colitis are only detected by this approach.[8] Ileoscopy with biopsies is recommended as an additional step. In approximately 10–20% of patients with UC the inflammation may extend into the terminal ileum (backwash-ileitis). The diagnostic value of terminal ileum biopsies is, however, highest in patients with known or suspected CD.[9,10]

During follow-up examinations, a smaller number of biopsy samples may confirm the diagnosis. In post-surgical follow-up, biopsies of the neo-terminal ileum are indicated when disease recurrence is suspected. When patients have undergone ileal pouch-anal anastomosis, biopsies of the afferent limb are suggested when CD is suspected. Multiple biopsies are indicated when the patient is screened for dysplasia (=intraepithelial neoplasia).

ECCO-ESP statement 2

All tissue samples should be fixed immediately by immersion in buffered formalin or an equivalent solution prior to transport [EL5]. Since lesions may be focal, it is recommended that multiple sections from each sample are examined [EL2]

Serial sectioning of biopsy specimens is superior to step sectioning in order to detect mild or focal lesions and to increase the diagnostic accuracy.[11–13] The diagnostic yield increases with the number of sections examined. However, the ideal number of sections to be examined in routine practice has not been established, with numbers varying between 2 and 6 in different studies.[12,14] In routine practice, step-sections may be the simplest procedure. Obtaining two or three tissue levels has been proposed, each consisting of five or more sections.[15] This proposal is in agreement with guidelines proposed by the Austrian, British and German IBD study groups.[16–18] The use of multiple biopsies from different sites is supported by the expert opinion of clinicians, except for patients presenting with fulminant colitis. Though the majority of clinicians will agree to take one or two biopsy samples from fulminant colitis (from one or two regions), some clinicians do not perform endoscopy in this setting.

Endoscopic biopsies should be immediately fixed in a formaldehyde-based fixative or another solution to ascertain the quality of the material. Biopsies should be stored and transported in separate vials as this is essential to map and grade the histologic distribution and degree of inflammation in different colonic segments and in the terminal ileum. This can be done by using different containers, multi-well cassettes or an acetate strip. Orientation of the samples using filter paper (submucosal side down) before fixation may yield better results, because it allows a better assessment of architectural abnormalities. Routine staining with hematoxylin and eosin is appropriate for diagnosis. Special stains, such as

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immunohistochemistry or other techniques for diagnostic purposes are not needed routinely.

ECCO-ESP statement 3

The biopsy samples should be accompanied by clinical information including endoscopic findings as well as the age of the patient, duration of disease, duration and type of treatment, comorbidities and travel history [EI 5]

IBD diagnosis in patients with diarrhea or rectal bleeding not only is based on the morphological features observed in biopsies, but also takes into account background clinical information, endoscopic findings as well as data from laboratory and imaging procedures. Thus, for a reliable diagnosis of biopsy specimens from patients with suspected IBD detailed clinical information is inevitable. This information should include basic demographic data, disease characteristics including information on duration of symptoms, co-morbidities, recent travels, endoscopic findings, or any information regarding foregone treatment.

ECCO-ESP statement 4

A surgical sample needs complete gross examination, carried out in an orderly and systematic manner, including photographic documentation, preferably at the time when the specimen is removed [EL5]

Surgical samples are opened along the longitudinal axis (i.e., along the antimesenteric or antimesocolic border, except at the site of any carcinoma, where it may be advisable to leave a small segment unopened during fixation). Specimens for microscopy are collected, including lymph nodes, terminal ileum and appendix.[19] The optimum number of samples from a colectomy specimen that should be obtained has not been established. However, multiple samples obtained both from visible lesions and from mucosa which is normal on gross inspection improve the diagnostic yield. In addition, the macroscopic aspects and the transmural character of the disease as well as fistulas can be identified and used for diagnostic purposes.[20,21] Special attention should be paid to lesions suspicious for neoplasia.

ECCO-ESP statement 5

The pathology report in all chronic colitides should give an indication of the activity of the disease. Particularly in Crohn's disease, inactivity in the biopsy may not reflect inactivity of the disease [EL5]

The healing of mucosal inflammation has already been noted as a feature of resolution in UC. Biopsies can be used to discriminate between quiescent disease, inactive disease and different grades of disease activity. This has led to the introduction of scoring systems for the assessment of disease activity in UC and use of these systems in clinical drug trials.[22]

Adequate number of biopsies should be obtained from not only grossly inflamed but also normal looking mucosa as mild or even severe inflammation can be detected in endoscopically quiescent colitis.[23–25] In the study by Kleer et al.[24] 65% of the endoscopic and histologic findings were comparable, whereas in 25% a chronic colitis was diagnosed in biopsies from an endoscopically normal looking mucosa. In 10% the opposite was seen.[24]

In contrast to UC, disease activity is not generally assessed by pathologists for CD. This is mainly due to the discontinuous character of the disease, inducing sampling error and the fact that the ileum may be the only area involved. Sampling error is very important, especially when only rectal biopsies are available. Microscopic analysis of multiple samples from different segments of the colon and ileum may provide useful information and allow an assessment of disease activity.

Nevertheless, data available on histology and activity for CD are limited. Several clinical drug trials have shown that treatment can alter the histology, promoting healing and normalization of the mucosa.[26–31] There is, however, no general agreement among expert clinicians about the use of microscopy to assess disease activity. If biopsies are used, then multiple samples have to be obtained and analyzed. The presence of epithelial damage in association with neutrophils is a marker of disease activity.[32] A multivariate logistic regression model showed that severe lymphocytic (and eosinophilic) infiltration of the lamina propria, presence of crypt atrophy and absence of lymphocytic infiltration of the epithelium are the best variables for predicting uncomplicated disease.[33]

ECCO-ESP statement 6

Ileocolonoscopy with biopsies should be performed in all children or adolescents with suspected IBD [EL2].

Esophagogastroduodenoscopy may improve the diagnostic accuracy in the initial diagnostic assessment of children with possible IBD [EL2]

ECCO-ESP statement 7

The terminology to be used for labeling patients without a definitive diagnosis is unclear [EL1]

Labels such as "indeterminate colitis", "uncertain colitis", "inflammatory bowel disease unclassified (IBDU)", chronic inflammatory bowel disease unclassified "CIBD-unclassified" and "chronic idiopathic inflammatory bowel disease NOS (not otherwise specified)" are used in the literature for patients presenting with chronic colitis without a definitive diagnosis.

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Table 1 Macroscopic features used for the diagnosis of IBD.

	Ulcerative colitis	Crohn's disease
Localization GI tract	Especially colon and rectum	Whole GI tract
Ileum	Not except in backwash-ileitis	Often involved
Colon	Left > right	Right > left
Rectum	Commonly involved	Typically spared
Distribution GI tract	Diffuse (continuous)	Segmental (discontinuous)
Ulcers	Superficial ulcers	Aphtoid ulcers, confluent deep linear ulcers
Pseudopolyps	Common	Uncommon
Skip-lesions	Absent	Present
Cobblestone-pattern	Absent	Present
Deep fissures	Absent except in fulminant colitis	Present
Fistulae	Absent except in fulminant colitis	Present
Mucosal atrophy	Marked	Minimal
Thickness of the wall	Normal	Increased
Fat wrapping	Absent	Present
Strictures	Uncommon	Present

The term indeterminate colitis (IC) should be restricted to cases where complete histologic analysis on the basis of surgical specimens is possible.

3. Ulcerative colitis

3.1. Macroscopic diagnostic features

ECCO-ESP statement 8

Classically, macroscopic examination of a resection specimen may show a continuous inflammatory process, beginning from the rectum and extending proximally. Awareness of unusual macroscopic distribution patterns, such as the cecal patch, rectal sparing and backwash ileitis is important to avoid wrong subtyping of the inflammatory bowel disease [EL3]

Gross examination of a resection specimen in UC classically shows a diffuse and continuous chronic inflammation without skip-areas which involves the rectum and spreads proximally with gradually decreasing severity of inflammation. The transition between the involved and the normal mucosa is sharp in UC (Table 1). The mucosa has a friable granular appearance and shows superficial ulcers. In severe disease these ulcers may undermine the adjacent mucosa, finally resulting in denudation of the mucosal surface or penetration deep through the muscularis mucosae (well-like ulcers).[34,35] Extensive ulceration with sparing of remaining mucosal islands may give rise to inflammatory pseudopolyps which are common in the sigmoid and descending colon, but rare in the rectum. In fulminant colitis, the macroscopic appearance of the mucosa is not sufficiently distinct to differentiate UC from CD[7,36] and serositis may be observed.[37]

Unusual inflammation patterns are rectal sparing, cecal patch and backwash-ileitis. Rectal sparing may occur in untreated children (30%), adults with fulminant colitis (13%) or patients receiving topical or systemic treatment (44%).[36,38–41] Another therapy-related finding is patchiness, i.e. a change from continuous to discontinuous inflammation.[40,41] The association of left-sided colitis with inflammation surrounding the appendiceal orifice is called 'cecal patch'. Discontinuous periappendiceal inflammation has been diagnosed in up to 75% of patients with distal disease.[27,42,43] "Backwash ileitis" occurs in approximately 20% of patients with extensive colitis or as a primary ileal mucosal inflammation without cecal involvement.[44] Distinction from Crohn's terminal ileitis can be difficult.[45,46] In longstanding UC, tissue repair is associated with fibrosis, which, in contrast to CD, is commonly restricted to mucosa or submucosa. This fibrosis may cause strictures in 3.2% to 11.2% of cases.[47] In the quiescent phase of the disease mucosal haustration will disappear resulting in an atrophic, smooth mucosa.

3.2. Microscopic diagnostic features

ECCO-ESP statement 9

Microscopic diagnosis of ulcerative colitis is based on widespread crypt architectural distortion, a diffuse transmucosal inflammatory infiltrate with basal plasmacytosis, eventually associated with an active component, causing cryptitis and crypt abscesses. Mucin depletion is less specific, but a helpful diagnostic feature [EL 1]

UC is a chronic process with distorted architecture and an inflammatory infiltrate which is limited to the mucosa. Distorted crypt architecture (57–100%) with crypt branching and atrophy and an irregular villous architecture (17–30%) are more frequent than in CD (27–71% vs. 12%).[15,48–50] The disease is characterized by a lack of fissures.[20] In fulminant colitis ulcers may penetrate into the muscularis propria

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Table 2 Microscopic features used for the diagnosis of IBD.

	Ulcerative colitis	Crohn's disease
Crypt architectural irregularity	Diffuse (continuous)	Focal (discontinuous)
Chronic inflammation	Diffuse(continuous)	Focal (discontinuous)
	Decrease proximally	Variable
Patchiness	Uncommon	Common
Localization	Superficial	Transmural
	Transmucosal	
	Sometimes in submucosa	
Serositis	Absent except in fulminant colitis	Present
Lymphoid aggregates	Frequent in mucosa, submucosa	Common, transmural
Granulomas	Absent, except with ruptured crypts	Present
Acute inflammation	Diffuse (continuous)	Focal (discontinuous)
Crypt epithelial polymorphs	Diffuse (continuous)	Focal (discontinuous)
Crypt abscesses	Common	Uncommon
Mucin depletion	Present, pronounced	Uncommon, mild
Neuronal hyperplasia	Rare	Common
Muscular hypertrophy	Absent	Present
Paneth cell metaplasia	Present	Uncommon
Pyloric gland metaplasia	Rare	Present

(20%).[51] The inflammatory infiltrate is diffuse or continuous without any variations in intensity or skip-lesions and its severity increases characteristically towards the rectum. The mucosal inflammation is proportionate, i.e. the cellularity is higher in the mucosa than in the submucosa.[24,52] Occasionally, the inflammation may spread into the superficial part of the submucosa. The inflammatory infiltrate is composed of lymphocytes, plasma cells and neutrophils, causing cryptitis, defined as the presence of neutrophils within crypt epithelium, and crypt abscesses, defined as the presence of neutrophils within crypt lumina (Table 2). Crypt abscesses are more common in UC (41%) than in CD (19%).[48]

Plasma cells are predominantly observed between the base of the crypts and the muscularis mucosae (basal plasmacytosis). This feature is helpful in the differentiation between a first attack of UC (63%) and infectious colitis (6%), but not CD (62%).[15,49] The number of eosinophils is variable. Based on three features, namely an increase of lymphocytes and plasma cells in the lamina propria (including basal plasmacytosis), the presence of crypt branching and cryptitis, chronic inflammatory bowel disease (CIBD) can be distinguished from non-CIBD.[15] The inflammation may cause mucin depletion of the epithelium, a less diagnostic feature as it can also be found in infectious colitis and CD.[13,49,53] Depending on the degree of inflammatory activity the surface may become eroded. Features of chronicity also include Paneth cell metaplasia (especially in left-sided colitis), presence of inflammatory pseudopolyps, hypertrophy of the muscularis mucosae and the rarely identified submucosal fibrosis.[54] Granulomas are not found in biopsies of patients with UC, except those that are related to foreign bodies, ruptured crypts and mucin extravasates.[55] Le Berre et al. have shown that a villous or irregular architecture, distorted crypt architecture with crypt atrophy, mucin depletion and cryptitis are features highly predictive of UC.[56] Nevertheless, the morphologic features may change attributable to disease duration, patient age and treatment.

ECCO-ESP statement 10

Basal plasmacytosis is the earliest diagnostic feature with the highest predictive value for the diagnosis of ulcerative colitis [EL3]. Preserved crypt architecture and the absence of a transmucosal inflammatory cell infiltrate do not rule out ulcerative colitis at an early stage. Therefore, repeat biopsies are recommended not sooner than 6 weeks after the initial assessment for the diagnosis of ulcerative colitis [EL3]

Improvement of endoscopic techniques has changed the diagnostic approach to IBD with sampling of biopsies earlier in the disease course before any treatment is initiated. In early stage disease reliable diagnostic features may be absent, hampering diagnosis and distinction from CD and infectious colitis, the latter being characterized by preserved crypt architecture and acute inflammation.[57] These histologic features are however not diagnostic, as approximately 30% of patients with a similar histologic pattern will progress towards chronic CIBD.[58] Surawicz et al. have shown that infectious colitis lacks specific histologic features and is diagnosed by exclusion of histologic features favoring IBD.[12] The strongest predictor of IBD is basal plasmacytosis.[59] Microscopic features more common in UC are crypt atrophy, villous mucosal surface, superficial erosions and infiltration of the surface epithelium with neutrophils, whereas epithelioid granulomas are diagnostic for CD.[12] Not all these microscopic features are present in early stage disease, as only about 20%

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of the patients show crypt distortion within two weeks after the first symptoms of colitis. Of note, basal plasmacytosis is the earliest feature favoring IBD and can be observed in 38% of the patients within two weeks after initial presentation. During this period the distribution pattern of basal plasmacytosis is focal but may eventually change into a diffuse pattern during the disease course.[59] This finding is in contrast to the study by Nostrant et al., in which all UC patients show basal plasmacytosis in the biopsies obtained during the first attack of disease.[57]

ECCO-ESP statement 11

The diagnosis of long-standing disease is based on the widespread crypt architectural distortion and the presence of a diffuse increased transmucosal inflammatory cell infiltrate [EL 1]. In this situation the mucosal histology can be associated with some atypical features such as normal mucosa, discontinuous inflammation and rectal sparing. Awareness of these morphologic features is important to avoid misdiagnosis, in particular change of diagnosis to Crohn's disease [EL3]

In long-standing disease the extent of gut involvement decreases with time, ultimately leading to complete restoration of the rectal mucosa (rectal sparing) in 34%–44% of patients. In parallel, the distribution pattern changes mainly from diffuse to non-diffuse or discontinuous (93%). [24,41] A disturbed crypt architecture (78%) is more common than an irregular mucosal villous architecture (33%), a decrease in crypt number (44%) with mucosal atrophy (44%), or a preserved architecture (22%).[59] Restoration of the architecture may result in a normal mucosa.[24] The presence of normal crypt architecture may cause a diagnostic dilemma during follow-up. Although basal plasmacytosis is still the most important feature with the highest prevalence, it is not a distinctive feature, as it is as common in UC (63%) as in CD (62%).[15,59] Other diagnostic features favoring UC are an increase in transmucosal cellularity, cryptitis, crypt abscesses, mucin depletion and Paneth-cell metaplasia.[52,60] Long-standing UC can be associated with (endoscopic and histologic) patchiness (38%).[41]

ECCO-ESP statement 12

In quiescent disease, the mucosa in ulcerative colitis may show some features related to architectural damage and recovery, such as architectural crypt distortion (atrophy and branching) as well as epithelial regeneration, disappearance of basal plasmacytosis and increased transmucosal cellularity. Active inflammation is usually not observed [EL3]

ECCO-ESP statement 13

Histologic findings predictive of ensuing clinical relapse in patients with quiescent ulcerative colitis are basal plasmacytosis, increased transmucosal cellularity, high number of neutrophils and eosinophils, crypt abscesses, mucin depletion and damage of the surface epithelium [EL4]

Remission is defined as complete resolution of symptoms and endoscopic mucosal healing.[1] Histologically, mucosal healing is characterized by resolution of the crypt architectural distortion and the inflammatory infiltrate.[59] However, the mucosa will still show some features of sustained damage, such as a decreased crypt density with branching and shortening of the crypts.[61,62] In addition, reduced epithelial regeneration will usually reduce mucin depletion, i.e. restore the mucin content of epithelial cells.[63] The cellularity and the composition of the inflammatory cell infiltrate are variable and either a hypercellular lamina propria with presence of chronic inflammatory cells or a hypocellular lamina propria with reduced number of mononuclear cells and resolution of neutrophils can be observed. Ultimately, basal plasmacytosis decreases, resulting in normal cellularity. In contrast to neutrophils, the number of eosinophils does not change in this phase.[64] Persistence of the lamina propria cellularity with basal plasmacytosis or a high number of eosinophils is associated with a substantial risk of relapse.[59,65,66] Histological features predictive of ensuing relapse also include acute inflammatory cell infiltrate, crypt abscesses, mucin depletion and surface epithelium damage.[67] Remission may result as a complete normalization of the mucosa in approximately 24% of cases which, without clinical information, may hamper the diagnosis of UC.[68,69]

ECCO-ESP statement 14

Treatment may change the classical distribution pattern of the inflammation. Patchiness, rectal sparing up to normalization of the mucosa can be observed. Awareness of these treatment-related effects is important in the evaluation of biopsies from treated patients to avoid misdiagnosis [EL3]. The pathology report should give an indication of the activity of the disease [EL5]

ECCO-ESP statement 15

Testing for CMV reactivation on colonic biopsy should be performed in all patients with severe colitis refractory to immunosuppressive therapy. In addition, testing should be performed in biopsies with prominent granulation tissue derived from large ulcers [EL2]. Semiquantitative immunohistochemistry, reporting the number of infected cells and/or the number of CMV positive biopsy fragments, may have a predictive value. Testing in other groups should be on a case by case basis [EL5]

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Treatment may induce complete restoration of the architectural distortion with decrease of the intensity of inflammation.[70] The classical distribution pattern of the inflammation may change from diffuse or continuous to patchy or discontinuous. Discontinuity and patchiness are both features characteristic for CD. Lacking information on foregone treatment the accuracy of the initial diagnosis of UC may be questioned in these cases.[71] In clinical trials therapeutic outcomes are measured by various indices that evaluate disease activity based on clinical, hematological and endoscopic parameters.[72] Histologically, the level of activity and the stage of the disease (e.g. flaring vs. quiescent UC) can be assessed by different scoring systems.[34,73,74] Although these are not applied routinely, the pathology report should include some information on the level of activity in the biopsies in order to assess both the effect of therapy and the risk of relapse.

In patients with UC the risk for reactivation of a latent cytomegalovirus (CMV) infection is increased and is significantly higher than in CD (10%–56.7% vs. 0%–29.6%).[75] Reactivated CMV infection increases the severity of disease and is associated with higher rates of morbidity and hospitalization.[76,77] The risk of CMV reactivation depends on the type of immunosuppressive drugs used and is higher in steroid-refractory than in steroid-responding patients (25–30% vs. 0–9.5%).[75,78] CMV reactivation should be routinely sought for in case of flares or unresponsiveness to treatment. Although CMV viral inclusions may be detected on H&E-stained slides, immunohistochemistry or molecular techniques such as quantitative PCR, are more sensitive techniques with a high diagnostic accuracy.[75]

3.3. Children and adolescents

ECCO-ESP statement 16

In comparison with adults, a higher proportion of children with UC presents initially with subtotal or with extensive colitis [EL2]. As in adults, the presence of "backwash ileitis" does not exclude a diagnosis of UC. The prevalence of backwash ileitis seems to be similar in children and adults [EL3]. Periappendiceal inflammation, without more extensive and significant cecal inflammation, is frequently seen in UC. Such inflammation should not be regarded as supportive evidence for the diagnosis of CD [EL 3]. In young children with aberrant presentation of disease, ulcerative colitis should always be considered in the differential diagnosis even if histology is not typical [EL1]

IBD is an important cause of gastrointestinal pathology in children and adolescents. About 10–15% of patients are diagnosed before the age of 18 years.[79] Given the serious consequences of IBD on growth and development, early and accurate diagnosis of pediatric patients is essential. Pediatric-onset IBD is characterized by distinct phenotypic differences compared to adult-onset IBD. This finding may hamper the diagnosis, resulting in delayed or inadequate therapy. The gold standard for diagnosing pediatric IBD remains endoscopic evaluation of the upper and lower gastrointestinal tracts, with mucosal biopsies for histopathologic confirmation.[80–82] In a series of 62 children 21 (34%) had colitis limited to the rectum or rectosigmoid, 24% left-sided colitis, and in 42% extensive colitis was diagnosed. In another study, left-sided colitis was seen at diagnosis in 10% of 60 children with UC, whereas extensive colitis occurred in 90%.[79]

Untreated children most commonly present with an extensive colitis with less severe and less diffuse architectural abnormalities.[38,39,79,80,83] Backwash ileitis in children is as common as in adults. In a series of 18 children newly presenting with UC, 39% showed erythema with no erosions or ulcers and associated histologic nonspecific inflammation.[84] Regarding appendiceal involvement, only one pediatric study examined appendices from resected intestinal specimens in 17 UC and 24 CD patients who failed to medical therapy. All children had appendiceal involvement.[85] The clinical significance of such inflammation remains unclear. In children under 10 years of age, the colonic mucosa may show less architectural distortion and inflammation than adolescents or adults. Although basal plasmocytosis is less common in children (58%) than in adults (38–100%), it is an early feature in young children.[39,83] Untreated children with UC may present with a normal mucosa or mild patchy inflammation at disease onset or with an unusual inflammation pattern, such as patchiness (21%) and rectal sparing (30%).[38,39,86] Relative rectal sparing is most commonly diagnosed in children less than 10 years of age.[83] When children approach adulthood, the histologic features are similar to that found in adults.[87] Upper gastro-intestinal inflammation is not diagnostic for CD, as esophagitis, minimal to mild non-specific gastritis or focally enhanced gastritis may be present in up to 75% of children with UC.[88–90] Although *Helicobacter pylori*-negative focally enhanced gastritis is more common in children with CD (43–76%) this is also seen in UC patients (8–21%).[90–92] Granulomas, however, are only found in CD.[93] Duodenitis is also not uncommon in children with UC (22–27%).[88,93]

3.4. Colorectal cancer

The incidence of colorectal cancer (CRC) in UC is approximately 4/1000 per person year of disease, with an average prevalence of 3.5%.[94] Colorectal cancer risk is associated with disease duration and disease extent[95–98] and raises at a rate of approximately 0.5 to 1% per year after a total duration of colitis of 8 to 10 years.[99–101] The highest cancer risk is observed in extensive colitis, whereas no or only moderate risk is found in ulcerative proctitis or left-sided disease.[95,97,98] Additional risk factors include primary sclerosing cholangitis (PSC), early age of onset of colitis, severity of microscopic inflammation, the presence of pseudopolyps and a family history of CRC.[96,99,102–106]

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ECCO-ESP statement 17

Dysplasia (intrepithelial neoplasia) represents the best and most reliable marker of malignancy risk in patients with ulcerative colitis. Colitis-associated dysplasia develops only in areas with chronic inflammation and can be divided into 4 morphologic categories: negative (regenerating epithelium), indefinite and positive for low-grade dysplasia and high-grade dysplasia [EL 2]. Inter-observer agreement is poor for low-grade and indefinite dysplasia. Confirmation of dysplasia by an independent expert GI pathologist is recommended [EL 2]

Dysplasia is defined as histologically unequivocal neoplastic epithelium without evidence of tissue invasion.[107] Dysplasia is the best and most reliable marker of an increased risk of malignancy in patients with UC.[98,108,109] For diagnostic reasons, dysplasia is separated into three distinct categories: negative for dysplasia, indefinite for dysplasia ("questionable" dysplasia) and positive for dysplasia[108] (low or high grade). In 2000, the "Vienna classification" was introduced as an alternative system to grade dysplasia, and the following four categories were proposed: category 1, non-dysplastic mucosa; category 2, lesions which are indefinite for dysplasia; category 3, genuine dysplasia corresponding to non-invasive low-grade neoplasia and category 4, genuine dysplasia corresponding to non-invasive high-grade neoplasia.[110] Thus, this classification proposed the term "non-invasive neoplasia" instead of dysplasia.[110]

Dysplasia may occur in any part of the colon and is most often multifocal, presenting as isolated foci. Dysplasia related to IBD develops only in areas with chronic inflammation.[98,109] The microscopic features that are used for diagnosis of dysplasia are analogous to those characterizing neoplastic growth in general, including both architectural and cytological abnormalities. Architectural abnormalities are crowding of glands, thickening of the mucosa and lengthening and distortion of the crypts with excessive budding and increased size. Surface and crypts are lined by tall, high columnar cells in which there is some mucus differentiation. Mucin tends to be in columnar cells rather than in the usual goblet cells. Nuclear changes are morphologically similar to those seen in tubular adenomas in non-IBD patients: hyperchromatic and enlarged nuclei, with nuclear crowding and frequent overlapping. The nuclei are also typically stratified. Mitotic figures may be present in the upper part of the crypts and even in the surface (which is abnormal).[108]

A fair inter-observer agreement is noted for high-grade non-invasive neoplasia (dysplasia) and samples negative for dysplasia; however, even experienced gastrointestinal pathologists show a poor inter-observer agreement for low-grade and indefinite dysplasia. Therefore current practice emphasizes the need for a second opinion from another expert pathologist.[98,111–117]

Recent studies have focused on adjunctive methods to improve inter-observer variability in detecting dysplasia. P53 tumor suppressor gene appears as a key factor in the initial steps of IBD-associated colorectal carcinogenesis being the most frequent single founding mutation in UC-associated CRC.[118] P53 is overexpressed in 33–67% of patients with dysplasia and in 83–95% of patients with UC-associated CRC[119,120]; however, a small proportion of regenerating, non-dysplastic cases may also be positive. Therefore, p53 immunostaining is fraught with a considerable false-positive rate which makes p53 less useful for differentiating regeneration from true dysplasia. Alpha methyl-CoA racemase has been shown to be sensitive and highly specific for dysplasia in IBD with an increase in positivity in low grade dysplasia and adenocarcinoma.[121,122] Clinical follow-up data obtained from indefinite and low-grade dysplasia with p53/AMACR co-expression show an early progression to high-grade dysplasia and cancer.[123] Recently it was shown that 86% of patients with co-expression of p53 and AMACR developed advanced neoplasia compared to 27% without co-expression.[121]

ECCO-ESP statement 18

Colitis-associated dysplasia consists of flat and elevated lesions. Elevated lesions request sampling of the surrounding and remote mucosa for diagnosis and treatment decision [EL 2]

ECCO-ESP statement 19

For surveillance 4 biopsy specimens should be taken from every 10 cm of the entire colon in addition to biopsies from macroscopically visible atypical lesions [EL 2]

There are two gross patterns of dysplasia in UC: flat and elevated lesions. Flat dysplasia is defined as a lesion the thickness of which is less than two times that of normal mucosa.[124] It is a common lesion, not endoscopically visible, which carries a high risk for CRC.[94] Flat lesions are detected microscopically in random biopsies from unremarkable mucosa. To diminish the risk of sampling error current practice guidelines recommend that 4-quadrant biopsy specimens should be taken from every 10 cm of the entire colon in addition to biopsies from macroscopically visible atypical lesions.[96,125,126] Emerging endoscopic techniques, namely chromoendoscopy, high-resolution magnification endoscopy, confocal laser endomicroscopy and endocytoscopy promise to increase the yield of surveillance colonoscopy by identifying subtle lesions that would be missed by white-light endoscopy and decrease the work load of the pathologists.[127–129] Compared to conventional endoscopy with random biopsies, targeted biopsies guided by magnifying chromoendoscopy are of superior sensitivity in detecting flat dysplasia in longstanding UC.[130–134] Chromoendoscopy is increasingly being incorporated in practice guidelines of several Societies but the key point is to prove an increase in detection rates of dysplasia. Limitations are the time-length of the procedure, unequal staining, cost and potential genotoxicity of absorbed dyes.

Raised or elevated dysplastic lesions are a heterogeneous group including adenoma-like lesions and non-adenoma-like

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lesions.[135–137] Non-adenoma-like lesions can either appear as large velvety patches, irregular plaques, irregular bumps and nodules, wart-like lesions, large sessile polypoid lesions with a broad base or even as localized strictures.[135,137,138] Adenoma-like lesions are usually well-circumscribed small lesions, with sometimes a sessile configuration similar to those of sporadic adenomas unrelated to UC. Several clinical and microscopic features have been identified which may help to differentiate colitis-associated dysplasia from adenoma-like lesions[32,137,139,140] These may also be referred to in patients with CD disease and they are summarized in Table 3. On microscopic examination, non-adenoma-like elevated lesions are more heterogeneous and have a tubulo-villous appearance, with sometimes a mixture of neoplastic glands and normal crypts with intense inflammation. In this situation the flat mucosa surrounding the raised lesion may show dysplasia.[137] Thus, it is crucial to obtain samples of the surrounding non-elevated mucosa.

ECCO-ESP statement 20

Adenoma-like lesions (sporadic adenomas) may be difficult to distinguish from colitis-associated dysplasia. The distinction is however important, because the management of sporadic adenomas differs from that of colitis-associated dysplasia. The patient's age, the site and morphology (endoscopic appearance, microscopy) of the lesion, along with biopsies of flat surrounding mucosa, may be helpful in this distinction [EL2]

Flat high-grade dysplasia is frequently associated with CRC.[98] At the time flat high-grade dysplasia is diagnosed CRC may already be present in 42 to 67% of cases.[96,101] The risk of flat low-grade dysplasia is controversial in the literature with a poor consensus regarding the optimal management strategy.[141–144] A recent meta-analysis concluded that the positive predictive value for CRC in patients with flat low-grade dysplasia is 22%. Patients with low-grade dysplasia carry a 9-fold higher risk for CRC than patients without dysplasia. If patients with low-grade dysplasia are treated without surgery, the subsequent 5-year rate of progression to either high-grade dysplasia or CRC ranges from 23% to 54% but a report from Karolinska showed that none of the patients progressed to HGD or CRC during a mean follow-up of 10 (range 1–22) years.[101,116,138,141,144] Current evidence is insufficient to assess the balance of risks and benefits of colectomy for flat low-grade dysplasia. Thus, the decision to undergo colectomy versus continued surveillance in patients with flat low-grade dysplasia should be individualized and discussed at length with the patient.[96,145] The progression of colorectal neoplastic lesions in patients with long-standing UC varies in function of the colonic location. A pooled analysis by Choi demonstrated a distal predominance for UC-associated CRCs.[117,146] In addition, distal low-grade dysplasia progresses more rapidly to cancer than proximal low-grade dysplasia.[145] Consequently, it is recommended that more biopsies should be taken from the rectosigmoid area during follow-up colonoscopy.[96]

Recent data suggest that polypectomy may be an adequate treatment for patients with an adenoma-like dysplastic lesion.[109,135,140,147–149] If a polypectomy is performed, a complete excision of the lesion is necessary. Vieth et al. have shown a high rate of progression to cancer in patients with incompletely removed raised adenoma-like dysplasia.[140] By contrast, colitis-associated polypoid dysplasia has a high risk of concurrent malignancy and should thus be considered as an indication for colectomy or proctocolectomy.[138,150]

Table 3 Microscopic and clinical features used for the differential diagnosis of neoplastic lesions in inflammatory bowel disease.

Colitis-associated dysplasia
Age < 50 years
Extent of disease: usually total
Usually active disease
Longer disease duration (>10 years)
Associated flat dysplasia common (no sharp delineation)
Irregular neoplastic glands (varying configuration, size and diameter) with varying amounts of stroma
Increased (mononuclear) lamina propria inflammation common
Mixture of benign/dysplastic crypts at surface common
Adenoma-like lesion (sporadic adenoma)
Age > 60 years
Extent of disease: usually subtotal
Usually inactive disease
Shorter disease duration (<10 years)
No associated flat dysplasia (sharp delineation)
Regular neoplastic glands (similar configuration, size and diameter) with low amounts of stroma
Increased (mononuclear) lamina propria inflammation uncommon
Mixture of benign/dysplastic crypts at surface rare

3.5. Special situation

ECCO-ESP statement 21

For a proper histologic evaluation of pouchitis multiple biopsies are recommended. The exact location has not been determined but according to some data it is useful to take biopsies from the anterior and posterior wall avoiding suture lines. Samples from the posterior wall are more likely to show the inflammatory changes [EL 2]

Proctocolectomy with ileal pouch anal anastomosis (IPAA) has replaced the Kock's pouch as the procedure of choice for most patients with UC requiring colectomy. "Pouchitis" refers now to active inflammation of IPAA mucosa and is considered as a primary "non-specific, idiopathic inflammation of the neorectal ileal mucosa".[151,152] The incidence of pouchitis ranges between 10 and 59% depending on the diagnostic criteria used, the accuracy of evaluation and possibly the time interval since the IPAA operation. Risk factors include extensive colitis, primary sclerosing cholangitis, non-smoking, detection of p-ANCA and the use of

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non-steroidal anti- inflammatory drugs (NSAIDs). Interestingly, only a small minority of IPAA patients operated for adenomatous polyposis coli develop pouchitis.

Three to 20% of patients develop persistent or recurrent episodes of pouchitis.[153] Some patients may develop CD-like complications including perianal fistulas and inflammation, stenoses or fistulas in the pre-pouch ileum and/or the pouch. The diagnosis of pouchitis is based on a combination of clinical symptoms, endoscopic and histologic findings. Diagnosis based on symptoms alone is accurate in only 55% of the patients. There is a good correlation between more severe grades of histological inflammation, frequency of defecation and endoscopic appearance. Histologic changes may be patchily distributed but are more prominent in the lower and posterior regions of the pouch. Consequently, multiple biopsies from these sites are essential for the diagnosis.[154] Various scoring systems have been developed to standardize the diagnosis and assess the severity of pouchitis. The Pouchitis Disease Activity Index (PDAI) calculates symptoms, endoscopy and histology on three separate 6-point scores; a total score higher than 7 is indicative of pouchitis.[155,156] Pouchitis should be distinguished from "cuffitis" or "short-strip pouchitis", which is inflammation in the columnar cuff mucosa distal to the pouch. The top end of the anal canal is lined by columnar mucosa like that of the rectum. In a hand sewn IPAA, this mucosa is stripped, albeit often incompletely since the junction between columnar epithelium and squamous or transitional epithelium is difficult to distinguish. Islands of columnar mucosa may be left behind. This is also true in a double stapled pouch anastomosis although the amount of columnar mucosa varies widely. In these patients symptoms may be due to an exacerbation of UC.

Chronic inflammatory changes, present in up to 87% of biopsies from 'healthy' pouches, consist of architectural distortion, villous atrophy, crypt hyperplasia and infiltration of the lamina propria by mononuclear cells, eosinophils and histiocytes. Neutrophils are rarely present. Villous atrophy and crypt hyperplasia are considered to be adaptive changes ("colonic metaplasia"). The concept of "colonic phenotype" is supported by experimental data showing that human tropomyosin isoform 5 (hTM5) is expressed diffusely in the goblet cells and non-goblet cells lining the crypts and the lumen in the ileal pouch of UC patients 6 months post IPAA surgery, but is not expressed or is focally expressed only in goblet cells in genuine ileal samples. These changes were associated with shortening and reduced number of the villi.[157] Adaptive changes have been classified into three patterns: a healthy villous mucosa, a mucosa which remains flat and chronically inflamed and a mucosa with intermittent inflammation and architectural recovery. Mild ischemic changes can be observed in a few patients, while others may show features of mucosal prolapse, such as fibromuscular obliteration of the lamina propria and a disrupted muscularis mucosae. Features of prolapse are most commonly seen in samples from the anterior wall. In contrast, in pouchitis patchy intraepithelial neutrophils become more numerous and induce cryptitis, crypt abscesses and ulcerations. As "colonic metaplasia" occurs more frequently in cases with pouchitis, it has been suggested that it may be a "reparative" rather than an "adaptive" response.[158]

The histology of chronic refractory pouchitis is mostly identical to that of "usual" pouchitis. In this situation other possible causes such as infections (particularly CMV) should be considered. The development of CD-like complications in chronic pouchitis may cast doubt on the initial diagnosis. Biopsy specimens usually show features of severe inflammation with neutrophils within the lamina propria and epithelium, erosions, ulcerations and mucosal architecture distortion. Histology of excised pouches for these complications may show deep submucosal lymphoid aggregates and granulation tissue-lined fistulous tracts. Similar changes, and even granulomas, have been observed in defunctioning rectal stumps left in situ after urgent total colectomy for UC.[159] The occurrence of CD-like complications and the presence of deeply situated lymphoid aggregates should not refute the diagnosis of UC. A diagnosis of CD after IPAA surgery should only be made when re-examination of the original proctocolectomy specimens shows typical pathologic features of CD.[160] Pyloric gland metaplasia reflects chronicity of the process. Trauma, prolapse, NSAID-induced injury and CD must be considered.[161]

Diffuse mucosal active and chronic inflammation with villous and crypt distortion and ulceration can be observed in samples from the ileum above the pouch. This may occur in patients with pouchitis or without inflammation in the pouch. The lesions can be related to pouch outlet obstruction or to obstruction at the ileal-pouch anastomosis. They are not self-evident for a possible diagnosis of CD. The occurrence of ulcers in the afferent limb may predict CD. They can also rarely be observed in patients with IPAA taking NSAIDs.[162]

4. Crohn's disease

4.1. Macroscopic diagnostic features

CD may affect any part of the gastrointestinal tract form the mouth to the anus. Most commonly, the disease affects the terminal ileum, often in association with the right colon. Large bowel involvement by CD may be found in isolation (in approximately 20% of cases, with preferential right-sided localization) or may co-exist with CD at other sites.[163] Crohn's colitis and its distinction from UC was first characterized by Lockhart–Mummery and Morson.[164] Warren refers to three basic pattern of large bowel involvement: CD isolated to the rectum, stricturing large bowel CD and diffuse Crohn's colitis which typically occurs with (relative) rectal sparing.[163] Approximately 75% of patients with large bowel CD develop perianal pathology, including skin tags, deep ulcers, fissures, fistulae, abscesses, blind sinus tracts and strictures at some point during the disease course.[163] Of note, perianal CD may predate intestinal involvement by years.

Classically, the gross examination of a resection specimen in CD shows a discontinuous pattern of inflammation. Diseased segments are frequently separated by areas of uninvolved, i.e. normal bowel ("skip lesions"). Transition from involved to uninvolved areas is usually abrupt. The surface of the involved bowel segment may appear hyperemic. An inflammatory serosal exudate and/or serosal adhesions may be observed. Mainly in small bowel CD, but infrequently also in large bowel CD "fat wrapping" is seen which is characterized by adipose tissue expanding towards the antimesenteric surface. Fat wrapping has a high predictive value for the diagnosis of CD,[165]

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but it has also been observed, together with other Crohn's colitis-like changes (fissuring ulcers, granulomas, transmural lymphoid aggregates) in individuals with segmental colitis associated with diverticulosis (SCAD).[166,167] SCAD is defined as a chronic inflammatory process confined to a diverticular segment and does therefore almost exclusively affect the sigmoid colon. By definition, both the rectum and the proximal colon are endoscopically and histologically normal.[168,169] The pathogenesis of the disease is unclear. An idiosyncratic inflammatory response to diverticular disease has been discussed.[167]

The earliest grossly visible mucosal lesions of CD are small aphthous ulcers that typically develop over lymphoid follicles. Of note, the adjacent mucosa is quite normal on gross inspection. As the aphthous ulcers enlarge, they coalesce to large deep serpinginous or linear ulcers with overhanging oedematous mucosal edges. Islands of oedematous, non-ulcerated mucosa, separated by deep discrete ulcers may give rise to the classic cobblestone appearance. Inflammatory polyps and pseudopolyps may occur, the latter reflecting residual mucosa islands interspersed between area of ulceration. Healed ulcers leave scars that are typically depressed.

Fistulae are a common finding in small bowel CD. Though being relatively rare, they may be observed also in colonic CD, mainly in patients with ileal involvement and/or ileocolitis. Free perforation, however, is exceptional in colonic CD. Strictures may develop at sites of transmural inflammation with fibrosis and fibromuscular proliferation. As in the small bowel, the bowel wall may become thickened and increasingly rigid. Finally, it has to be acknowledged that in surgical specimens the macroscopic aspects and the transmural character of the disease as well as fistulae can be identified and, in general, many more features can be used for diagnostic purposes, particularly in the differentiation of CD from UC (Table 1).[20,21]

4.2. Microscopic diagnostic features

ECCO-ESP statement 22

Focal (discontinuous) chronic inflammation, focal crypt irregularity (discontinuous crypt distortion) and granulomas (not related to crypt injury) are the generally accepted microscopic features which allow a diagnosis of CD in the colon (on endoscopic biopsies) [EL2]. The same features and, in addition, an irregular villous architecture, can be used for analysis of endoscopic biopsy samples from the ileum. If the ileitis is in continuity with colitis, the diagnostic value of this feature should be used with caution [EL2]

A large variety of microscopic features have been identified which help to establish a diagnosis of CD (Table 2). The reproducibility of these features as well as their sensitivity and specificity has been studied repeatedly.

Focal (discontinuous) chronic inflammation means a variable increase in lamina propria cellularity (lymphocytes and plasma cells) across the biopsy specimen and not confined to the superficial zone. Specifically, focal inflammation implies a localized increase in round cells with or without granulocytic infiltration, confined to one or more foci. These foci of inflammation may occur against a normal round cell background or in biopsies with variable degrees of inflammation. Normal lymphoid aggregates do not denote focal inflammation. Differences in cellularity between multiple biopsy specimens can be assessed with greater reproducibility than variation within a single specimen. There may be extension of inflammation into the submucosa in a biopsy.

Crypt irregularity implies abnormalities in >10% of the crypts. Crypt irregularity may be seen in biopsies with or without inflammation. Crypt irregularity is characterized either by crypt distortion (non-parallel crypts, variable diameter or cystically dilated crypts), crypt branching and crypt shortening.[48] The presence of more than two branched crypts in a well-orientated biopsy specimen should be regarded as abnormal.[14,48]

The granuloma in CD is defined as a collection of epithelioid histiocytes (monocyte/macrophage cells), the outlines of which are often vaguely defined. Multinucleated giant cells are not characteristic and necrosis is usually not apparent. Only granulomas in the lamina propria not related to crypt injury may be regarded as a corroborating feature of CD. Granulomas associated with crypt injury are less reliable features.[55] Noncaseating granulomas, small collections of epithelioid histiocytes and giant cells, or isolated giant cells can be observed in infectious colitis (granulomas suggest *Mycobacterium* sp., *Chlamydia* sp., *Yersinia pseudotuberculosis* and *Treponema* sp.; microgranulomas suggest *Salmonella* sp. *Campylobacter* sp. and *Yersinia enterocolitica*; and giant cells suggest *Chlamydia* sp.) and must not be regarded as evidence for CD. In patients living in or originating from areas with a high prevalence of tuberculosis, intestinal tuberculosis should be actively excluded in patients with suspected CD. This is of particular relevance before starting anti-TNF therapy.[170]

In resection specimens, transmural lymphoid aggregates (transmural lymphoid hyperplasia), particularly away from areas of ulceration, and granulomas not related to crypt injury are typical discriminating features for a diagnosis of CD as opposed to other conditions, particularly UC. In a study on colectomy specimens operated upon for fulminant colitis, granulomas and lymphoid aggregates proved to be the two most specific indicators.[36]

Pyloric gland metaplasia, also referred to as pseudopyloric gland metaplasia or glandular mucoid metaplasia, is a feature indicative of chronic mucosal inflammation, commonly related to mucosal ulceration and repair (ulcer associated cell lineage – UACL).[171] The lesion can be observed in 2–27% of ileal biopsies from patients with CD and is common in ileal resections. However, the lesion is exceedingly rare in resection specimens from patients with backwash-ileitis in UC, having been described only in cases with active ileal inflammation and/or ulceration.[44]

To the best of the authors' knowledge, pyloric gland metaplasia has so far not been identified in ileal biopsies from patients with ulcerative colitis, with or without backwash-ileitis.[9,45,46] Pyloric gland metaplasia has, however, been observed in up to 40% of pouch biopsies of patients with UC and restorative proctocolectomy with ileal pouch-anal anastomosis. In this setting, pyloric gland metaplasia appears to be a

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specific marker for chronic antibiotic-refractory pouchitis or CD of the pouch.[161]

The selection of the number of features needed for diagnosis is based on a systematic literature review. They achieve a diagnostic sensitivity and specificity of at least 50% and a moderate to good reproducibility (kappa of 0.4 or percentage agreement of at least 80%).[15,50,172] They were presented to a panel of experts and scored according to the quality of the study and expert opinion. Focal crypt irregularity scored highest on the evidence of more than one valid study of adequate size and from expert opinion; focal or patchy chronic inflammation was validated by evidence from single paper and expert opinion. The features were also tested in a workshop, involving non-expert and expert pathologists and selected by 50% or more of the pathologists correctly identifying each case.[8] The patchy nature of the inflammation is only diagnostic in untreated adult patients. Inflammation can become patchy in resolution of active UC, and young children (age < 10 years) with UC may present with discontinuous inflammation.[24,38,71,83,86,173]

The presence of one single feature is not regarded as sufficient for a reliable diagnosis of CD. For single or multiple endoscopic samples there are no data available as to how many features must be present for a firm diagnosis of CD. For surgical material, it has been suggested that a diagnosis of CD disease should be made when three features are present in the absence of granulomas, or when an epithelioid granuloma is present with one other feature provided that specific infections are excluded. The same definition could be applied to endoscopic biopsies. The following features can be identified in the mucosa and thus in biopsy samples: granulomas and focal (segmental or discontinuous) crypt architectural abnormalities, in conjunction with focal chronic inflammation, or mucin preservation at active sites. These are, therefore, potentially reliable markers for the diagnosis of CD.

The majority of expert clinicians and all pathologists agree that the presence of a granuloma and at least one other feature establishes a diagnosis of CD. The second feature can be either (focal) inflammation or, preferably, architectural abnormalities. While focal architectural abnormalities favor CD, pseudovillous appearance of the colorectal surface is more consistent with a diagnosis of UC. The presence of a granuloma is not a prerequisite for the diagnosis of CD. Additional features which have been found to be useful are focal chronic inflammation without crypt atrophy, focal cryptitis (although reproducibility is poor),[8,172,174] aphthoid ulcers, disproportionate submucosal inflammation, neural hypertrophy (nerve fiber hyperplasia),[20,175] increased intraepithelial lymphocytes,[8] and proximal location of ulceration and architectural distortion. When multiple biopsies are available, ileal involvement and a distribution of the inflammation showing a proximal to distal gradient can also be useful. The absence of features that are highly suggestive or diagnostic of UC, such as diffuse crypt irregularity, reduced crypt numbers and general crypt epithelial polymorphs, can also orient towards a diagnosis of CD.

In difficult cases, esophageal, gastric and duodenal biopsies might help to establish the diagnosis of CD by the presence of granulomas or focally enhanced or focal active inflammation. In gastric biopsies, the absence of (*i.e. Helicobacter pylori*) and the presence of a perifoveolar or periglandular cellular infiltrate composed of mononuclear cells (CD3+ T cells and CD68+ histiocytes) and granulocytes are important features. On the other hand, focal gastritis is not exclusive to CD.[92,176–179]

> ECCO-ESP statement 23
>
> Despite detailed histologic criteria used to differentiate Crohn's colitis from ulcerative colitis in colonoscopic biopsies, accurate discrimination between the two diseases is not yet optimal among expert gastrointestinal pathologists [EL 2]

Colonoscopic biopsies are an essential step in the diagnostic work-up of patients with IBD. Comprehensive guidelines for reporting the diagnostic features have been published.[16,17,180–182] In contrast, few studies have analyzed in detail the reliability and/or reproducibility of the histological changes that distinguish IBD from other forms of colitis, and CD disease from ulcerative colitis.[52]

Because no single pathognomonic lesion has been identified to date for the most common forms of colitis, the diagnosis usually derives from a complex evaluation of multiple microscopic changes and their topographical distribution. The results of an International Workshop on the initial histopathologic diagnosis of colitis indicated that expert gastrointestinal pathologists correctly identified 64% of cases with CD and 74% of cases with UC.[8] These figures may be considered discouraging, at least with regard to the individual patient. Fiocca and Ceppa[183] summarized the conclusions drawn by this International Workshop of expert gastrointestinal pathologists as follows: (i) Multiple colonoscopic biopsies are necessary to provide an accurate diagnosis of CD, (ii) rectal biopsies alone are not diagnostic, (iii) overall diagnostic accuracy of endoscopic biopsies is lower in CD than in UC, (iv) discussion of diagnostic criteria and guidelines among pathologists may improve the diagnostic accuracy, especially in CD, (v) several helpful diagnostic features that contribute to the diagnosis of CD in surgical specimens, such as transmural inflammation, fibrosis and fistulas are present only in the deep layers of the bowel wall alone and therefore not accessible to endoscopic biopsy sampling, (vi) in contrast, most lesions in UC are limited to the mucosa and submucosa and consequently can be properly assessed by endoscopic biopsies.

4.3. Children and adolescents

> ECCO-ESP statement 24
>
> At onset, CD in children is associated with more colitis and less ileitis. The frequency of granulomas is higher in children than in adults. Focal inflammation in the upper gastrointestinal tract is of assistance in differentiating CD from UC [EL 2]

A subgroup of pediatric patients may have a specific disease phenotype that differs from adults. The primary

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difference is the topographical distribution and/or extent of disease. Compared to adults, first-decade pediatric onset is associated with more colitis and less ileitis.[184] In children with severe CD, all biopsies obtained during the same colonoscopic investigation may show chronic inflammation (with or without acute inflammation), including the rectal mucosa, thus introducing diagnostic difficulties in differentiating between CD and UC. In these cases, it is essential to identify, in each one of the multiple colonic biopsies, areas with inflammation alternating with areas with much less (or without) inflammation, since focal distribution of on-going inflammation is highly suggestive of CD.

A puzzling difference between CD in pediatric and adults patients is that epithelioid-cell granulomas are more frequent in children, particularly in the disease course. Thus, granulomas at initial colonoscopy were recorded in 67% of children and 66% of adults, but at subsequent colonoscopies in 54% of children and only 18% of adults, suggesting that granulomas in Crohn's colitis might evolve or regress at different time intervals during the course of the disease.[185] In another study on children with CD undergoing esophagogastroduodenoscopy and colonoscopy, granulomas were identified in 61% of untreated and 25% of treated patients.[186] Upper tract and terminal ileum biopsies were essential to the identification of 42% of patients with granulomas. In the lack of appropriate tissue sampling, there is a risk of failing to identify granulomatous inflammation. Colonic biopsies from endoscopically bland, apparently non-affected areas should always be included in patient evaluation.[187]

CD may be affected by an age gradient. There is an inverse linear relationship between age and Crohn's colitis. Hence, the younger the patient the more likely is the patient to have colonic involvement. This inverse relationship is true through age 10. In addition, pediatric patients are more likely to have upper gastrointestinal involvement than their adult counterparts.[188] They may display focal inflammation in the esophagus, the stomach and the duodenum. Notably, lymphocytic esophagitis, a rather recently described entity, has been found to affect children with distal CD.[189–191] Thus, biopsies from the upper gastrointestinal tract should routinely be investigated in pediatric patients at initial presentation of IBD.

4.4. Colorectal and small bowel cancer

Patients with CD carry an increased risk of both colorectal and small bowel adenocarcinoma.[192–196] The most important risk factors for the development of colorectal cancer are young age at onset, long disease duration and extensive large bowel involvement (pancolitis), indicating a cumulative effect of colonic inflammation (dysplasia–carcinoma sequence), as known from patients with UC.[95,197] Endoscopy with biopsy is used for secondary prevention and the detection of dysplasia in UC and may similarly be used in patients with CD depending on the extent of colon involvement. With respect to small bowel cancer, the relative risk is particularly high. Owing to the overall rarity of the disease, however, the cumulative risk is still low and surveillance is not recommended. Within the small bowel, lesions most commonly affect the distal jejunum and ileum.[198,199]

In IBD, dysplasia may arise within mucosa that it is indistinguishable from surrounding non-dysplastic mucosa (Table 3). Hence, dysplasia has traditionally been regarded as endoscopically "invisible", being detectable only on random biopsies.[200] Using a random biopsy approach, sampling error represents a well recognized limitation in the surveillance of affected patients. In CD, the optimal number of biopsies required for a reliable diagnosis of dysplasia has not been established. It has been proposed, however, that 6 to 10 samples from different sites in the colon should be obtained, as suggested for ulcerative colitis. The current recommendation is to biopsy the colon at 10 cm intervals. Biopsies are labeled separately so that the segment of colon from which the tissue is obtained can be subsequently identified. Rubin and colleagues estimated that 56 non-targeted (jumbo-forceps) biopsies need to be obtained (at each endoscopic surveillance examination) to give 95% confidence in the detection and/or exclusion of dysplasia. In that study 90% confidence was achieved with 33 non-targeted biopsies. [201]These studies on UC have not been replicated in Crohn's colitis. The focal nature of inflammation in Crohn's colitis, the possibility of strictures and the prevalence of segmental resection means that surveillance practice in UC cannot be transferred directly to Crohn's colitis.[202]

5. Indeterminate, unclassified and infectious colitis related to inflammatory bowel disease

> ECCO-ESP statement 25
>
> While "indeterminate colitis" (IC) is probably the most commonly used terminology, no uniform definition for this label is available in the literature and morphological or pathological features for this diagnosis have been confined to surgical specimens [EL1]

Labels such as "indeterminate" colitis", "uncertain colitis", "inflammatory bowel disease unclassified (IBDU)", "CIBD-unclassified" and "chronic idiopathic inflammatory bowel disease NOS (not otherwise specified)" are used in the literature for patients presenting with chronic colitis without a definitive diagnosis.

The term indeterminate colitis was first introduced in 1970 in a retrospective study of clinical and pathological (colectomy) material from 222 patients with fulminant (n = 12) and chronic inflammation of the colon. The aim was to see whether the classical morphological criteria could reliably separate ulcerative colitis and Crohn's colitis. Fourteen cases were categorized as "indeterminate" because of "overlapping features" and "data, insufficient to make a decision".[203] In 1978, Price et al. confirmed the occurrence of "indeterminate cases" in surgical specimens. In 27 of the 30 cases urgent surgery had been performed. Histologic features included areas without architectural distortion to suggest longstanding disease, deep fissuring ulcers that often went into, and sometimes through, the muscularis propria, accompanied by transmural inflammation, although usually not with the typical lymphoid hyperplasia associated with CD, and without overt granulomata.[204] By 1980 it was clear that there is a subgroup of resection specimens that are difficult to classify,[205] mainly from patients presenting with clinically severe disease. Subsequently, the necessity for a correct diagnosis of CD in patients operated for severe colitis

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became very important facing the development of restorative "pouch" operations using terminal ileal mucosa.

The introduction of endoscopy with the possibility of obtaining endoscopic biopsies led to an evolution of the terminology towards an integrated diagnosis based on clinical features and endoscopy with biopsies. The term "IC" was hence also used for patients presenting with clinical features of chronic CIBD, with inflammation restricted to the colon and no small bowel involvement. The term was used when endoscopy was non-conclusive and diagnostic features for either CD or UC were absent on biopsies while infectious colitis and other causes of colitis had been excluded. The tendency to use the term IC for patients who seem to have IBD but cannot be readily called UC or CD, became common in the pediatric gastroenterology literature because 4 to 23% of new onset cases in children present with an equivocal diagnosis. This is even more prevalent in younger age (<12 years). Sixty percent of such cases are ultimately reclassified as UC or CD.[206] Diagnosis is based on a full work-up including colonoscopy with intubation of the ileum, upper gastrointestinal endoscopy and small bowel follow through.[207,208] Whether upper gastrointestinal endoscopy can sort the diagnostic problem is unclear. The presence of focally enhanced gastritis may not be an appropriate marker, as it can occur in both CD and UC, even in children, although it is more frequent in CD.[209] Video capsule endoscopy revealing small bowel pathology may be helpful.[210] Epidemiologists also use the term IC for patients with clear evidence of IBD but insufficient data to make a definite diagnosis of UC or CD, based on the clinical, endoscopic and histologic data available.[211]

There are no histologic features reported in the literature to make a positive diagnosis of IC on endoscopic biopsies. A blinded histologic study of endoscopic biopsies from 9 segments of the colon, involving 3 experienced GI pathologists failed to identify definite features.[212] The same results were obtained in a subsequent study of 60 cases with established colitis involving 25 pathologists.[8] Furthermore, microscopy of endoscopic samples does not allow evaluation of features present in the deeper layers of the bowel wall which is in contrast with the original description of indeterminate colitis. This is however important as CD is characterized by transmural inflammation.

ECCO-ESP statement 26

The pathological diagnosis of indeterminate colitis on resected specimens relies on the presence of "overlapping features" or the absence of a "clear diagnostic pattern"; it is not a real "positive" diagnosis [EL1]

The general definition of IC is thus based on diagnostic uncertainty as to whether a patient has UC or CD but the histologic work-up can be different. To solve problems related to the ambiguous meaning of the term IC, the working party of the 2005 Montreal World congress of Gastroenterology suggested to clarify the definitions.[213] The proposal was supported by the Pathology task force of the International Organization for Inflammatory Bowel disease (IOIBD).[214] The ECCO/ESP working group for the European consensus in pathological findings in IBD equally favors an agreement on terminology in order to allow comparisons between different types of studies.

Macroscopically, IC is characterized by extensive ulcerations, involvement of transverse and right colon, with usually diffuse disease (less severe in the distal colon). Microscopy confirms extensive ulceration with a sharp transition to normal adjacent mucosa and multiple V-shaped ulcers lacking surrounding inflammation. Overlapping features are "severe mucosal and wall involvement",[203] non-aggregated transmural inflammation,[204] fissures reaching the muscularis propria and a discontinuous pattern.[204,205] Diffuse mucosal disease with normal ileum, deep mural lymphoid aggregation and nerve hypertrophy, non-necrotizing granulomata in lymph nodes, and anal fistula are reported in cases with non-severe chronic disease.[215]

ECCO-ESP statement 27

Pathologists should avoid the diagnosis of indeterminate colitis based on the evaluation of endoscopic preoperative biopsies because of the high potential for diagnostic error [EL5].
Instead the term inflammatory bowel disease unclassified could be used for patients with chronic colitis who clearly have inflammatory bowel disease based on the clinical history but macroscopy and/or endoscopic biopsies show no definitive features of ulcerative colitis or Crohn's disease [EL5]

The reasons for this proposal are: 1) the term IC was originally proposed for colectomy specimens; 2) not all diagnostic microscopic features can be assessed on endoscopic biopsy samples; 3) there are no generally accepted positive microscopic features for a diagnosis of IC on endoscopic samples; 4) post-operative examination of resections of such cases usually provides definitive evidence of UC or CD.[216,217]

Both IC and IBDU are "temporary diagnoses". Diagnostic uncertainty occurs more often in children. However, a histologic pattern of non-diffuse acute and chronic inflammation with architectural changes confined to the colon without a definite classification being possible can also be observed in adults as part of the natural history of ulcerative colitis or secondary to treatment.[24,41] Scheduled follow-up procedures at 1 and 5 years for reconfirmation of diagnosis and disease activity and revision of previous biopsies should be performed in these patients. Epidemiological studies have shown that most cases with uncertain diagnosis behave like UC.[212]

ECCO-ESP statement 28

Infections may be involved in triggering the onset of inflammatory bowel disease. Intestinal super infections may trigger flares of disease and complicate the clinical picture [EL1]

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The relationship between infections and IBD is complex. Infectious colitis must be considered in the differential diagnosis. Microbes have been proposed as possible causative agents of IBD. They can be responsible for complications such as abscesses and they have been linked with onset of the disease and relapse of symptoms.[218] Therefore it is essential to apply the appropriate diagnostic procedures for the identification of microorganisms in patients with IBD, at onset and during follow-up.

ECCO-ESP statement 29

Histology is not a good tool to identify bacterial infection of the small or large intestine (EL5). This holds true especially for *Clostridium difficile* infection [EL1]

C. difficile associated colitis can present with a variety of microscopic patterns ranging from oedema, overt active colitis without architectural abnormalities to pseudomembranous colitis. In IBD absence of pseudomembranes in *C. difficile*-associated diarrhea is noted in patients using immunosuppressive agents. Overall, the endoscopic finding of pseudomembranes is reported in 50% of *C. difficile* infected patients, and is less common (13%) in IBD patients with *C. difficile*. Similarly, the typical histologic findings of pseudomembranous colitis are usually not present.[219–221]

ECCO-ESP statement 30

In active IBD CMV can be detected using hematoxylin and eosin (H&E) staining, immunohistochemistry (IHC) and quantitative tissue PCR [EL1]

In CMV infection H&E typically reveals enlarged (cytomegalic) cells with large eosinophilic nuclear inclusions, usually surrounded by a clear halo, and smaller cytoplasmatic inclusions. However, stromal cells often show a less characteristic picture and ganglion and degenerated cells may imitate CMV inclusions. Specificity of H&E ranges from 92% to 100%, with low sensitivity of 10 to 87% reported. IHC improves histologic sensitivity and specificity. It involves identification of the CMV early antigen using monoclonal antibodies, thus identifying more infected cells in the colon. Sensitivity ranges from 78 to 93%. Qualitative PCR of colonic tissue can also be used to detect viral DNA in the colon, although the significance of a positive result in the absence of other histologic signs of infections remains unclear. Quantitative PCR may be more accurate, differing between infection and disease, however, no cut off has been defined.[222] CMV disease infers detection in the organ involved.[223] Semi quantitative immunohistochemistry, reporting the number of infected cells and/or the number of CMV positive biopsy fragments, may have a predictive value.[223–225]

6. Collagenous, lymphocytic colitis and variants

ECCO ESP statement 31

The term microscopic colitis describes a clinical pathological entity characterized by three elements: A) a clinical history of chronic watery (non-bloody) diarrhea; B) a normal or almost normal endoscopic appearance of the colon; C) a distinct histologic pattern. The latter can be either that of collagenous colitis or that of lymphocytic colitis [EL1]

Approximately 1% of the patients presenting with chronic diarrhea need specialized investigations including colonoscopy. For these patients a broad spectrum of diagnoses must be considered. Chronic non-bloody diarrhea can be due to infections (post-infectious irritable bowel syndrome, Spirochaetosis, miscellaneous infections such as *C. difficile* and *Campylobacter* sp.), drugs, allergy-associated (eosinophilic) colitis and so-called "microscopic colitis" (MC). The term MC was introduced in 1980 for a condition characterized by chronic diarrhea and a mild increase in inflammatory cells in the colonic mucosa which was macroscopically normal.[226] The disease was subsequently renamed as "lymphocytic colitis" (LC) because of its histologic characteristics.[227] A few years before, a related entity with similar features but with the additional finding of a thickened subepithelial collagenous band had been described and named "collagenous colitis" (CC).[228] In the 1980s several studies confirmed these observations.[229–233] In 1993, a French and an American research group suggested the use of MC as an umbrella term to cover any form of colitis in which there were histologic but no endoscopic or radiologic abnormalities. Later it became the umbrella term for the two major entities known as LC and CC.[234,235] These are both clinically characterized by chronic watery diarrhea while other conditions with normal endoscopy and abnormal histology may have other clinical characteristics. MC is thus a distinct clinicopathologic entity in which for the pathologists it is preferable to use the specific term related to the condition: LC or CC. The pathogenesis is still not completely understood and probably multifactorial. It is suggested to represent a specific mucosal response, in susceptible individuals to various noxious luminal agents. These can be drugs, enteric infections or other.[236]

ECCO-ESP statement 32

The diagnosis of collagenous colitis on routinely hematoxylin and eosin stained sections is based on the presence of a thick amorphous hyaline eosinophilic band immediately beneath the surface epithelium of the mucosa. This layer has an irregular, jagged aspect of the lower edge. The thickness is >10 μm. Its presence is associated with inflammation [EL2]

Two elements are important for the assessment of the collagen band: the thickness and the irregularity. There is no

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real consensus how thick the collagenous band should be. The various values proposed include 7 μm or more; 10 μm or more; 10 to 15 μm; 12 μm or more, and more than 15 μm.[237] Values as thick as 70 μm have been reported.[238] The average thickness of the normal subepithelial collagen table is approximately 3 μm.[230,239] There is also no agreement among pathologists about the "ideal method" for the assessment of the thickness of the collagen band: histologic evaluation, conventional measurement using a calibrated micrometer scale or semiautomatic micrometer measurements.[238] Although the collagen band is usually amorphous, capillaries and fusiform cells can be found within the material. The fusiform cells have ultrastructural features consistent with activated pericryptal myofibroblasts. The collagen deposition can be patchy in distribution and the thickness can be variable along the length of the colon.[240–242] Only 66% of biopsies from the rectosigmoid colon were diagnostic in one study.[242]

A common pitfall for the diagnosis is the misinterpretation of the basement membrane as collagen deposition in poorly oriented, tangentially sectioned biopsies. A trichrome stain is a useful ancillary technique because it allows the identification of collagen. Immunohistochemistry with antibodies directed against Tenascin is an alternative. The latter molecule is not present in the normal adult colon. Several studies have shown that the collagen band consists predominantly of Type VI collagen and Tenascin, with lesser amounts of collagen Type I and III unlike normal basement membrane which consists of Type IV collagen.[243–245] Thickening of the collagen band can be seen in other conditions such as ischemia, diverticular disease, mucosal prolapse, diabetes and hyperplastic polyps. In these conditions, however, the inflammatory changes necessary for the diagnosis of CC are not present. Amyloid colitis can also show thickened eosinophilic material underneath the surface epithelium. This can be identified with specific stains such as Congo red. The density of the infiltrate within the lamina propria and its composition can be extremely variable. Of note, the histologic features of CC (and LC) can regress after therapy.

ECCO-ESP statement 33

The density of the inflammatory cells in the epithelium and lamina propria is increased in collagenous colitis. The composition of the infiltrate is also changed. Eosinophils may be markedly increased and are sometimes seen infiltrating crypt and surface epithelium together with lymphocytes. The number of mast cells and lymphocytes may also be increased. Neutrophils are often present and may induce occasional crypt abscesses [EL1]

The exact number of intraepithelial lymphocytes (IELs) needed for a diagnosis of LC has not been determined. The required number varies between 10 and 20 per 100 surface epithelial cells (normal number = 4 to 10). In the study by Lazenby et al.,[227] there was an average of 24 lymphocytes per 100 surface epithelial cells. The number can vary among biopsy samples between 10 and 65 (median 30). There is no tendency for a prominent increase in a particular segment of the colon although inflammation may be less prominent in the left colon. Immunohistochemical analysis shows that the increased IELs retain the normal CD3/CD8 positive T cell phenotype. While plasma cells are numerous, T lymphocytes are the predominant cell type in the lamina propria.[246]

ECCO-ESP statement 34

The diagnosis of lymphocytic colitis is based on a diffuse increase of intraepithelial lymphocytes (IELs) (>20 IELs per 100 epithelial cells) in the surface epithelium without associated thickening of the subepithelial collagen accompanied by an increase of lamina propria inflammatory cells [EL2]

The diagnosis of LC should be made in conjunction with clinical, endoscopic and histologic findings. Resolving infections and drug reactions can lead to similar changes. While typical infections of the colon reveal a marked infiltrate of neutrophils in the lamina propria with crypt abscesses, resolving infections may have a more subtle pattern of inflammation that may resemble LC because of a mild increase of IELs. However, infectious diarrhea is usually self-limited. In addition, it can be accompanied by bloody diarrhea, endoscopic abnormalities and positive stool cultures.[12,247] Distinction of CC and LC from UC or CD, even with minimal changes, is based on a different clinical and endoscopic setting.[248] However, small series have identified patients with both a histologic diagnosis of MC and classic IBD at different time points.[249]

ECCO-ESP statement 35

In both, collagenous and lymphocytic colitis degeneration and/or detachment of the epithelium can be seen [EL1]

A close association between celiac disease and LC or CC has been observed. The association is stronger for LC. Approximately one third of all patients with celiac disease may show histologic features of LC on biopsy while as many as one fourth or patients with LC could have celiac disease.[250–253]

ECCO-ESP statement 36

The terminal ileum may be involved in microscopic colitis [EL3]

Several studies suggest that the terminal ileum can be involved in MC. An increased terminal ileal IELs count was found in 7 out of 14 patients with CC and 14 out of 18 patients with LC. In addition, subepithelial collagen

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deposition was found in the terminal ileum biopsies in some patients with CC and primary ileal villous atrophy was noted in 3 out of 14 of patients with CC and 1 out of 18 patients with LC.[254,255] CC is also occasionally associated with collagenous gastritis and duodenitis.[256]

ECCO-ESP statement 37

Given the importance of the early detection of gluten sensitivity, celiac disease should be excluded, particularly in patients with lymphocytic colitis [EL1]

Overlapping features have been reported in up to 30% of patients in some series.[257–260] In addition, several variant or atypical forms of MC have been described. The clinical presentation is usually similar to the classic form of MC but the histology is different. Rubio and Lindholm reported six patients with symptoms similar to those of LC and increased IEL count limited to the cryptal epithelium. The mean number of IELs was 46/100 crypt epithelial cells while the mean number for the surface was 7 IELs/100 epithelial cells. Immunohistochemistry with CD3 and CD8 antibodies revealed a classic phenotype. Special stains showed a normal basement membrane underneath the surface epithelium. At endoscopy the colon was essentially normal. There was no evidence that these patients suffered from celiac disease, IBD, or infectious colitis. The authors proposed the name "cryptal lymphocytic colitis".[261] The distinctive histologic features that separate "paucicellular lymphocytic colitis" from classic lymphocytic colitis are patchiness and a lower density of surface IELs.[262] Colonic biopsies show a mild increase of lamina propria cellularity with focal distribution associated with an increase of IELs. Involved areas are separated by normal mucosa. The mean surface IEL score is 11.1 per 100 epithelial cells. Some authors call this condition "colonic epithelial lymphocytosis" or "microscopic colitis, not otherwise specified (NOS)". One study raises the idea that paucicellular LC may be a separate entity with loss of expression of CD25 and FOXP3.[263] MC with giant cells is a rare atypical form characterized by the presence of multinucleated giant cells in an otherwise classic LC or CC.[264] Pseudomembrane formation has been reported in association with CC. The clinical outcome of the patients is similar to that of patients with classic CC.[265] The clinical significance of these variants has to be established.

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