



Review Article

Pathology of inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease is a group of inflammatory disorders of unknown etiology. Various genetic factors, mucosal immune response, inappropriate activation of immune system driven by the presence of various luminal flora and epithelial defects have been postulated. Crohn disease and Ulcerative colitis are the two most common inflammatory bowel diseases. Since, specific clinical laboratory features are lacking which may help in establishing a diagnosis histopathological diagnosis remains the gold standard. This review highlights the known hypothesis regarding the etiopathogenesis of these two diseases and also describes pertinent histological features.

INTRODUCTION

The term inflammatory bowel disease (IBD) is employed for a group of inflammatory disorders thought to be the result of inappropriate activation of the mucosal immune system driven by the presence of normal luminal flora. Most common inflammatory bowel disease includes Ulcerative colitis and Crohn disease. It is postulated that both of the diseases are due to exaggerated immunological response to unknown etiology. As a result, there are no specific clinical or laboratory features that may help establish a diagnosis. Diagnosis of Ulcerative colitis and Crohn disease relies upon pathologic interpretation of biopsy or resection specimens.¹⁻⁵ Both the disease sometimes may have overlapping histological features; clinical features and endoscopic or gross features may come into aid in reaching to the diagnosis.⁶

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CROHN DISEASE

Crohn disease is a relapsing inflammatory disease, mainly affecting the gastrointestinal tract from oral cavity to anus but also may involve skin, blood vessels etc. These patients frequently present with abdominal pain, fever, and clinical signs of diarrhoea with passage of blood or mucus, or both. Because its incidence and prevalence are rising in all ethnic groups and because of the systemic nature of the illness, Crohn disease concerns an increasingly diverse group of clinicians.⁷

Etiology and pathophysiology

The causes of IBD remain unknown. However, most investigators believe that IBD results from a combination of errant host interactions with intestinal microbiota, intestinal epithelial dysfunction, and aberrant mucosal immune responses. This view is supported by epidemiologic, genetic, and clinical studies as well as data from laboratory models of IBD.⁸

Genetics

Familial aggregation has been known for more than 70 years and large concordance studies in twins in northern Europe were early indicators of a genetic component in Crohn disease. A study done in German⁹ showed that 35% of monozygotic pairs, but only 3% of dizygotic pairs, were concordant for the disorder. In 70% of discordant monozygotic pairs the first-born had IBD.⁹ Substantial phenotypic (location, behaviour, and age at diagnosis) concordance exists, both at diagnosis and longitudinally, in monozygotic twins.¹⁰ Familial aggregation is confirmed.¹¹ Moreover, prevalence in Ashkenazi Jews is higher than in any other ethnic group and Jewish descent is an independent risk factor for the disorder.

In recent years, genome-wide association studies (GWAS) that assess single-nucleotide polymorphisms have been used to broaden the search for IBD-associated genes.⁸ Advances have occurred in understanding the genetics of human IBD, from studies based on single nucleotide polymorphism (SNP) and candidate gene approaches, and from studies in mouse experimental colitis that used transgenic and deletion (knockout) techniques.^{12,13} Several genes implicated in both IBD and experimental colitis are seen in Table 1. These genes regulate immunoregulation, mucosal barrier integrity and microbial clearance and/or homeostasis.¹⁴

The first gene found to be associated with Crohn disease was CARD 15 formerly known as NOD2 (nucleotide oligomerization binding domain 2) as a susceptibility gene in Crohn disease. CARD 15 encodes a protein that binds to intracellular bacterial peptidoglycans and subsequently activates NF- κ B. It has been postulated that disease-associated NOD2 variants are less effective at recognizing and combating luminal microbes, which are then able to enter the lamina propria and trigger inflammatory reactions. Other data suggest that NOD2 may regulate immune responses to prevent excessive activation by luminal microbes.⁸ There are three mutations—causing amino-acid substitutions Arg702Trp and Gly908 Arg and the frame shift 1007fs—found within the region of CARD15 that encodes a leucine-rich repeat, which is responsible for bacterial recognition. At least one of these mutations is present in 25–35% of Crohn disease patients of European ancestry, but not in Asian or African American Crohn disease patients.^{12,14}

Other genes, involved in the pathogenesis of Crohn disease, are SLC22A4 and SLC22A5 along with DLG5 gene, and PPARG genes. Mutations in the transcribed region of SLC22A4, which encodes OCTN1, and the promoter region of SLC22A5, which encodes OCTN2, affect the transcription and function of these carnitine and organic cation transporters. These variants are most actively expressed in the intestinal epithelium, macrophages and T cells, and cause decreased carnitine transport. Although

many studies have associated the region of chromosome 5 that contains SLC22A4 and SLC22A5 with Crohn disease, some investigators are hesitant to identify the mutations in these genes as causative of Crohn disease because of the tight linkage disequilibrium that exists between multiple genes in this chromosomal region.¹⁵

Similarly DLG5 gene encodes scaffolding protein for epithelium; its mutation leads to weakening in epithelial integrity in IBD.¹⁶ PPARG (peroxisome proliferative-activated receptor γ) variants have been linked with susceptibility in the SAMP1/YitFc mouse model of spontaneous chronic ileitis, and rare PPARG polymorphisms were found to be associated with human Crohn disease.¹⁷ PPAR γ is a nuclear receptor that inhibits NF κ B activity: its expression is decreased in patients with active ulcerative colitis and its expression is upregulated by 5-aminosalicylic acid.¹⁸ In addition to a potential role in protecting against intestinal inflammation, treatment with the PPAR γ ^{18,19} ligand rosiglitazone was effective in an open-label trial involving ulcerative colitis patients as well as in mouse experimental colitis.^{20,21}

ATG16L1 (autophagy-related 16-like-1) is other gene which is a part of the autophagosome pathway and is critical to host cell responses to intracellular bacteria. Similarly, IRGM (immunity-related GTPase M), is also involved in autophagy and clearance of intracellular bacteria. NOD2, ATG16L1, and IRGM are expressed in multiple cell types, and their precise roles in the pathogenesis of Crohn disease have yet to be defined. Like NOD2, however, ATG16L1 and IRGM are related to recognition and response to intracellular pathogens, supporting the hypothesis that inappropriate immune reactions to luminal bacteria are important in pathogenesis of IBD.⁸

Environmental factors

Apart from genetics, several alternative explanations, mostly related to lifestyle, are possible. The importance of environment is suggested by increasing incidence rates in previously less affected ethnic groups such as Asians and Hispanics²² and in immigrants from low incidence regions moving to areas with a traditionally high incidence.²³ Industrialisation has greatly changed people's lifestyle. However, adoption of a sedentary lifestyle, exposure to air pollution, consumption of a western diet often containing excessive amounts of sugar and polyunsaturated fats, and increased tobacco use.^{24–28} Though nicotine is not the cause, studies have shown that early tobacco use significantly increases the risk of developing the disorder.²⁹

Microbiota

Crohn disease frequently occurs after infectious gastroenteritis,³⁰ has a distinct mucosal flora (dysbiosis),³¹ and increased numbers of intramucosal bacteria³² often featuring

adhesive species³⁴ and thus efforts to identify a causative infectious agent continue. Infectious granulomatous ileitis conditions including intestinal tuberculosis and Johne's disease are zoonosis caused by *Mycobacterium avium* paratuberculosis, which induces similar immune responses to Crohn disease.³⁵ Controlled trials with antituberculous drugs have failed.⁷ Mycobacteria-related Crohn disease research frequently comes from ruminant farming areas where alternative explanations including contaminated foods and drinking water occur. However, mycobacteria still stand out from all other suspected infectious causes since genome wide association studies showed shared susceptibility loci with leprosy (ie, NOD2, LACC1) and polymorphisms in autophagy (ie, CARD9, IRGM1) required for mycobacterial clearance. Despite a growing body of data that suggest that intestinal microbiota contribute to IBD pathogenesis, their precise role remains to be defined.⁷

Immune responses

Both Crohn disease and ulcerative colitis patients have activated innate (macrophage, neutrophil) and acquired (T and B cell) immune responses and loss of tolerance to enteric commensal bacteria.^{36,37} Tolerance, in normal hosts, is mediated by regulatory T cells, B lymphocytes, natural killer T cells and dendritic cells that secrete transforming growth factor and interleukin, interferon- α/β and prostaglandin J2. Antibody-neutralization studies have implicated tumor necrosis factor (TNF) and IL-12 p40 in the pathogenesis of Crohn disease.¹⁴

Crohn disease seems to result from an impaired interaction of the intestinal commensal microbiota that is normally in a state symbiotic mutualism with the human host (immune system). Despite enormous progress in understanding the many facets of this ancient relation, distinction between primary inciting events and secondary occurrences is challenging. Although the mechanisms by which mucosal immunity contributes to the pathogenesis of ulcerative colitis and Crohn disease are still being deciphered, immunosuppressive and immunomodulatory agents remain mainstays of IBD therapy.⁸

The TH1 cytokine profile, which includes IFN- γ and IL-12 p40, is dominant in patients with Crohn disease. Traditional TH1 responses are mediated by IFN- γ , the production of which is stimulated by IL-12, produced by antigen-presenting cells. Most experimental colitis models also have a dominant TH1 response, although in several models TH1 responses can change into TH2 (type 2 T-helper lymphocyte) responses as the inflammatory process matures. IL-17 mediates TH17 responses. The production of this cytokine is stimulated by the production of IL-6, TGF β and IL-23 by innate immune cells and APCs, especially dendritic cells. Bacterial colonization stimulates IL-23 expression by ileal dendritic cells. The levels of both

IL-23 and IL-17 are increased in Crohn disease tissues and most forms of experimental colitis. Of pathogenic importance, the IL-12-IFN- γ and IL-23-IL-17 pathways seem to be mutually exclusive, since IFN- γ suppresses IL-17, and vice versa. The levels of an IL-12-related protein, IL-27, are also increased in patients with Crohn disease. In addition, production of IL-21 is induced by IL-12 and is selectively increased in Crohn disease. Like IL-12, IL-21 stimulates T-bet, an intracellular transcription factor that is key to TH1 cell differentiation and activation.¹⁴

Mucosal defects

The first line of defense of the mucosal immune system is a single layer of columnar epithelial cells covered by mucus produced by goblet cells with interspersed bacteria. Depletion in expression of MUC1 in the terminal ileum in patients with Crohn disease suggests that mucin cover becomes insufficient.⁷ Similarly defects in intestinal epithelial tight junction barrier function are present in patients with Crohn disease and a subset of their healthy first-degree relatives.

This barrier dysfunction co-segregates with specific disease associated NOD2 polymorphisms, and experimental innate and adaptive mucosal immunity and sensitize subjects to disease. Interestingly, the Paneth cell granules, which contain antimicrobial peptides that can affect composition of the luminal microbiota, are abnormal in patients with Crohn disease carrying ATG16L1 mutations, thus providing one potential mechanism where a defective feedback loop between the epithelium and microbiota could contribute to disease pathogenesis.⁸

One model that unifies the roles of intestinal microbiota, epithelial function, and mucosal immunity suggests a cycle by which transepithelial flux of luminal bacterial components activates innate and adaptive immune responses. In a genetically susceptible host, the subsequent release of TNF and other immune-mediated signals direct epithelia to increase tight junction permeability, which further increases the flux of luminal material. These events may establish a self-amplifying cycle in which a stimulus at any site may be sufficient to initiate IBD. Although this model is helpful in advancing the current understanding of IBD pathogenesis, a variety of factors are associated with disease for unknown reasons. For example, the risk of Crohn disease is increased by smoking, whereas that of ulcerative colitis is reduced.⁸

Morphological features

Grossly, segmental distribution of the lesions (skip lesions) and preference for the right side of the colon are important diagnostic features. Other gross findings include: stricture and fissure formation, a cobblestone appearance, transmural involvement and creeping fat.⁶

Classical microscopic features of active Crohn disease include abundant neutrophils that infiltrate and damage crypt epithelium. Crypt abscess and crypt destruction are another common findings. Ulceration is common in Crohn disease, and there may be an abrupt transition between ulcerated and normal mucosa. Mucosa has relatively normal appearance and retains most of the mucin producing goblet cells even adjacent to ulceration. The main features are presence of noncaseating granulomas, preservation of goblet cells, lymphoid aggregate etc. The absence of granulomas does not preclude a diagnosis of Crohn disease. Repeated cycles of crypt destruction and regeneration lead to distortion of mucosal architecture; the normally straight and parallel crypts take on bizarre branching shapes and unusual orientations to one another. Epithelial metaplasia (pseudopyloric metaplasia), Paneth cell metaplasia also may occur.^{6,8}

Unusual Patterns of Disease in Crohn Disease

Approximately 50% of Crohn Disease patients have colonic involvement and nearly 20% develop colitis without involvement of the oesophagus, stomach or small intestine. Unfortunately, many of the 'classic' features of Crohn Disease, such as transmural inflammation, strictures and fistulous tracts occur less commonly in the colon. Thus, some cases of Crohn Disease of the colon may mimic Ulcerative colitis by demonstrating only superficial mucosal involvement without inflammatory changes in the submucosa or muscularis propria, diffuse and continuous disease, or even pancolitis.³⁸ In this situation, evaluation of mucosal biopsy samples of the distal ileum and colon for evidence of other 'hardcore' features of Crohn Disease³⁹⁻⁴³, combined with correlation with the clinical and endoscopic features of the patient (such as upper GI tract involvement), may help establish an accurate diagnosis.

Dysplasia and Cancer in Crohn Disease

Patients with Crohn disease are at increased risk for intestinal carcinoma. Small-bowel carcinoma in a patient with Crohn disease occurs at younger age. The carcinomas most often occur in ileum actively involved by Crohn disease. The carcinoma tends to be poorly differentiated and is associated with poor prognosis. Colon cancer; in patient with Crohn disease; occurs on average 10 years earlier. These carcinomas tend to be better differentiated than in small intestine.⁴⁴

Ulcerative colitis

Ulcerative colitis was first described in the mid-1800s,⁴⁵ When inflammatory bowel disease is identified in a new population, ulcerative colitis invariably precedes Crohn disease and has a higher incidence. The incidence of ulcerative colitis is 1.2 to 20.3 cases per 100,000 persons

per year, and its prevalence is 7.6 to 246.0 cases per 100,000 per year, as compared with an incidence of 0.03 to 15.6 cases and a prevalence of 3.6 to 214.0 cases per 100,000 per year for Crohn disease.⁴⁶ Ulcerative colitis is closely related to Crohn disease. However, ulcerative colitis is limited to the colon and rectum. Some extraintestinal manifestations of ulcerative colitis overlap with those of Crohn disease, including migratory polyarthritis, sacroiliitis, ankylosing spondylitis, uveitis, skin lesions, pericholangitis, and primary sclerosing cholangitis.⁸ Similar to Crohn disease, etiopathology of Ulcerative colitis is largely unknown. The discovery that NOD2 variants are associated with susceptibility to Crohn disease opened a new era in the study of the genetic basis of inflammatory bowel disease.^{47,48}

Etiopathology of Ulcerative colitis

As Crohn disease, ulcerative colitis is believed to result from a combination of errant host interactions with intestinal microbiota, intestinal epithelial dysfunction, and aberrant mucosal immune responses.

Genetics

In studies of twins, and in genome wide association studies suggest larger number of susceptible loci for Crohn disease that genetic influences play a greater role in Crohn disease than in ulcerative colitis.⁴⁹ Forty seven loci are confirmed till date to be associated with ulcerative colitis, of which 19 are specific for ulcerative colitis and 28 are shared with Crohn disease.⁵⁰ Risk loci for ECM1, HNF4A, CDH1, and LAMB1 implicate dysfunction of the epithelial barrier; an association with DAP suggests a link to apoptosis and autophagy; and associations with PRDM1, IRF5, and NKX2-3 suggest defects in transcriptional regulation. In addition, multiple genes in the interleukin-23 signaling pathway overlap in ulcerative colitis and Crohn disease (e.g., IL23R, JAK2, STAT3, IL12B, and PTPN2). HLA-DR and genes involved in helper T-cell types 1 and 17 (Th1 and Th17) differentiation, such as IL10, IL7R, IL23R, and IFN- γ are risk loci linked to immune system-mediated diseases and also to ulcerative colitis.

The multidrug resistance gene MDR1 encodes P-glycoprotein 170, a transporter that governs efflux of drugs and possibly xenobiotic compounds from cells. P-glycoprotein 170 might also function as a 'flippase' that moves amphipathic substrates from the inner to the outer leaflet of the cell membrane. MDR1 variants have been associated with ulcerative colitis.¹⁴ Ulcerative colitis appears to be as genetically heterogeneous as Crohn disease, but given the large number of implicated genes and the small additive effect of each, genetic screening is not currently indicated to assess the risk of ulcerative colitis.

Microbiota

Intestine harbors a greater and more diverse number of microorganisms than any other organ.⁵¹ Thus intestinal health depends on a beneficial host–microbe interaction. The gut immune system is generally tolerant of this microbial load, and a breakdown in tolerance is postulated to be central to the pathogenesis of inflammatory bowel disease.⁵² Although loss of tolerance to the gut microbiota is demonstrable in animal models of IBD, there is no evidence in with ulcerative colitis.

It has also been postulated that alterations in the composition of the gut microbiota, defects in mucosal immunity, or the both factors combined could lead to ulcerative colitis. However, supportive evidence is sparse. There is a consensus that the density of microbiota is greater in patients with ulcerative colitis than in healthy control subjects, but whether there are reproducible, disease-specific alterations is unclear.² The fact that antibiotic therapy has no clinical effect on ulcerative colitis argues against an important role of bacteria in this disease.² Although serum antibacterial antibodies are present in patients with ulcerative colitis, they are much more common and are found in higher titers in patients with Crohn disease. Furthermore, the range of antibodies against bacterial antigens (anti-I2, anti-OmpC, and anti-CBir1 antibodies) and fungal antigens (anti-*Saccharomyces cerevisiae* antibodies [ASCA]) is broader in Crohn disease, whereas the only ulcerative colitis–associated antibody is perinuclear antineutrophil cytoplasmic antibody (pANCA), which recognizes nuclear antigens that may cross-react with bacterial antigens.²

Immune Response

Intestinal homeostasis requires a controlled innate immune response to the microbiota, which is recognized by toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)–like receptors on epithelial and immune cells.² This recognition process contributes to tolerance, but when the process is dysregulated, inflammation ensues. At present, there is no clear evidence of specific, innate immune defects in Ulcerative colitis. Overexpression of TLR2 and TLR4 by colonocytes⁵³ is probably secondary to inflammation. The production of proinflammatory cytokines, such as interleukin-1 β , interleukin-6, tumor necrosis factor α (TNF- α), and tumor necrosis factor–like ligand 1 (TL1A), is universally increased in patients with inflammatory bowel disease but does not allow one to discriminate between ulcerative colitis and Crohn disease. Abnormalities in humoral and cellular adaptive immunity occur in ulcerative colitis. Elevated IgM, IgA, and IgG levels are common in IBD, but there is a disproportionate increase in IgG1 antibodies in ulcerative colitis.^[6-(31)] Abnormalities of adaptive immunity that differentiate ulcerative colitis from Crohn disease are defined by mucosal CD4+ T

cells, which were initially divided into two lineages: Th1 and type 2 helper T cells (Th2). Crohn disease is a Th1-like condition, on the basis of evidence of increased production of interferon- γ . In contrast, ulcerative colitis represents an atypical Th2 response, as indicated by the presence of nonclassical natural killer T cells in the colon that secrete abundant interleukin-13, which mediates epithelial-cell cytotoxicity, apoptosis, and epithelial barrier dysfunction. Interleukin-5–producing Th2-polarized T cells are also present in ulcerative colitis. The balance between Th1 and Th2 has been used to differentiate between ulcerative colitis and Crohn disease. Defects in T-cell regulatory function have not been reported in ulcerative colitis.⁵⁴⁻⁵⁹

Autoimmunity may play a role in ulcerative colitis. In addition to pANCA, this disease is characterized by circulating IgG1 antibodies against a colonic epithelial antigen that is shared with the skin, eye, joints, and biliary epithelium; since these are the sites of extraintestinal manifestations in ulcerative colitis, it is possible that cross-reacting antibodies against the colon cause organ-specific damage. Tropomyosin 5, a structural protein, is the putative target autoantigen of the IgG1 antibodies, but evidence of classical antibody-mediated autoimmunity in ulcerative colitis is still lacking.^{60,61}

Mucosal Defects

Ulcerative colitis typically does not extend into the small intestine and occurs in proximity to the epithelium. Colonocytes are implicated in the pathogenesis of this disease. In ulcerative colitis there is an epithelial-barrier defect and impaired expression of peroxisome proliferator–activated receptor γ (PPAR- γ), a nuclear receptor that regulates inflammatory genes. Variants of the XPB1 gene, the product of which is a component of the stress response of the endoplasmic reticulum in epithelial cells, have been linked to IBD, reinforcing the concept that colonocytes are involved in its pathogenesis.⁴⁵

Morphological features

Ulcerative colitis is characteristically a left-sided disease, which usually begins in the rectosigmoid area. In acute phase, mucosa is markedly hyperemic and petechias are seen. Longitudinal ulcers are seen in the mucosa along with several pseudopolyps in an otherwise flat surface. In chronic phase the colon is narrowed and shortened and becomes fibrotic.²

Diffuse active colitis

Untreated ulcerative colitis in an active phase demonstrates a diffuse abnormality. The luminal border of the mucosa is irregular. In the lamina propria increased numbers of chronic inflammatory cells are present and may spill over

Table 1: Genes with functions associated with inflammatory bowel diseases and experimental colitis.

Gene	Chromosome	Function
CARD15	16	NFκB activation and/or regulation, killing of intracellular pathogens, Paneth-cell function, (α-defensin production)
SLC22A4 & SLC22A5	5	Organic cation, carnitine transporters, possibly transport xenobiotic substances
DLG5	10	Epithelial scaffolding protein
PPARG	3	Intracellular inhibitor of NFκB and cellular activation
ATG16L1	2	The protein encoded by this gene is part of a large protein complex that is necessary for autophagy
IRGM	5	The encoded protein may play a role in the innate immune response by regulating autophagy formation in response to intracellular pathogens.

Abbreviations: CARD15, caspase recruitment domain family, member 15 (formerly NOD2); DLG5, discs large homolog 5 (Drosophila); PPARG, peroxisome proliferative-activated receptor gamma; SLC22A4 and SLC22A5, solute carrier family 22 (organic cation transporter), members 4 and 5 (formerly OCTN1 and OCTN2); ATG16L1, autophagy-related 16-like-1; IRGM, immunity-related GTPase M

into the superficial portion of submucosa. Goblet cell population is depleted. Cryptitis and crypt abscess are prominent. Atrophy, branching and budding of crypts are noticeable even in early stage. The most useful criteria for the diagnosis of ulcerative colitis are crypt distortion along with basal plasmacytosis.⁴⁴

Focal active colitis

Focal active colitis refers to the patchy distribution of combined architectural change and inflammation in a mucosal biopsy. Focal active colitis pattern consists of limited areas of increased inflammatory cells associated with focal architectural distortion; characteristically, some areas of the biopsy specimen maintain an essentially normal morphology. Focal active pattern is usually not seen in ulcerative colitis and presence of it suggests Crohn disease or infectious colitis. However, the focal active pattern may be present in resolving ulcerative colitis under medical treatment.⁴⁴

In most instances, these two disorders may be readily distinguished from each other pathologically, particularly when each exhibits classic histological features (Table 2). However, some patients with IBD show overlapping pathological features of Crohn's disease and Ulcerative colitis, which make definite distinction between these two

disorders difficult. Under these circumstances, the term "indeterminate" colitis (IC) has been used. However IC is not a disease entity and has no diagnostic criteria. Rather, it represents a provisional descriptive term to be used by pathologists' only when he or she is unable to establish a definite diagnosis given the information available at the time of surgical sign out. In fact, in up to 80% of cases, the true nature of the patient's underlying IBD usually becomes apparent within a few years.¹

Indeterminate colitis

Historically, the term 'IC' was originally used to describe the pathological findings in colectomy specimens from patients with fulminant colitis, which is a severe form of colitis associated with systemic toxicity and, occasionally, colonic dilation (toxic megacolon).³⁸ Fulminant colitis often shows extensive transverse ulceration affecting right colon more severely than the distal colon.⁶² In most cases, the colitis is diffuse and continuous, but some may show complete, or relative, rectal sparing. Fissuring may also be present in some of the cases and are characterized by the presence of knife-like defects that extend into the superficial half of the muscularis propria. These ulcers are also often associated with transmural lymphoid inflammation. All these features are typically associated with Crohn disease. Some authors believe that the presence of fissuring ulcers supports a diagnosis of Crohn disease, whereas others regard them as part of the spectrum of severe Ulcerative colitis.³⁸ However in other study superficial fissuring ulcers in their colectomy specimens were observed in 20% of cases with severe chronic active colitis.³⁸ In another study of 67 patients with fulminant IBD, Swan et al. found that 87% could be accurately classified as either Ulcerative colitis or Crohn Disease based solely upon pathological evaluation of colectomy specimens. In that study, only the presence of granulomas and transmural inflammation in regions of intact mucosa predicted the development of Crohn Disease.³⁸ It is well recognized that the presence of chronic active inflammation of the ileum, transmural lymphoid aggregates in areas underlying intact mucosa, deep fissuring ulcers that extend into the outer aspects of the muscularis propria, segmental involvement of the colon in a previously untreated patient, and the presence of noncaseating epithelioid granulomas unassociated with ruptured crypts, are individual features that strongly favour a diagnosis of Crohn Disease. Unfortunately, recognition of these 'hardcore' features may be difficult, particularly when the findings are limited, or masked, by extensive ulceration. Nevertheless, failure to recognize and accept any of these features as definitive evidence of Crohn Disease may lead to a potentially erroneous diagnosis of IC.

The most common reasons for rendering a diagnosis of IC are noted in Table 3

Table 2: Common macroscopic and microscopic features of Crohn disease and Ulcerative colitis

Features	Crohn Disease (Small intestine)	Crohn Disease (Colon)	Ulcerative colitis
Macroscopic			
Bowel region	Ileum ± colon	Ileum ± colon	Colon
Distribution	Skip lesion	Skip lesion	Diffuse
Stricture	Early	Variable	Rare/Late
Wall appearance	Thickened	Variable	Thin
Dilation	No	Yes	Yes
Microscopic			
Pseudopolyps	None	None	Yes
Ulcer	Deep, linear	Deep, linear	Superficial
Lymphoid reaction	Marked	Marked	Mild
Transmural inflammation	Yes	Yes	No
Fibrosis	Marked	Moderate	Mild
Serositis	Marked	Variable	Mild
Granuloma	Yes	Yes	No

Many cases of Ulcerative colitis and Crohn Disease, particularly those that are limited to the colon, have overlapping clinical signs and symptoms. Some pathologists may be tempted to differentiate Ulcerative colitis from Crohn Disease in preoperative biopsy specimens. However, this practice should be avoided because of the high potential for diagnostic error. Mucosal biopsy specimens are typically superficial in nature and provide little information regarding the depth of disease activity, the presence or absence of transmural inflammation, or the type of ulcers present. Unfortunately, the mucosal features of Ulcerative colitis and Crohn Disease are often indistinguishable. In fact, features typically associated with Crohn Disease, such as relative or absolute rectal sparing, skip areas, and active ileal inflammation, may also occur in Ulcerative colitis. Only the presence of epithelioid granulomas unassociated with ruptured crypts and/or chronic active ileitis are features highly suggestive of Crohn Disease on mucosal biopsy analysis.³⁸

Morphologic variants of Ulcerative colitis

There are several circumstances in which the 'classic' morphological features of Ulcerative colitis may be altered or entirely absent. In some cases Ulcerative colitis may show discontinuous or patchy disease with rectal sparing involvement ileum, transmural inflammation or even granuloma formation. All these may lead to diagnostic dilemma and raise the possibility of diagnosing as IC in a colonoscopic biopsy specimen.⁶³⁻⁶⁵

Patchy involvement in Ulcerative colitis is seen children, patient after partial treatment and rarely left-sided Ulcerative colitis associated with either right-sided colonic involvement (with sparing of the transverse colon)

or appendiceal involvement.⁶⁶⁻⁶⁸

In contrast to Crohn Disease, Ulcerative colitis does not typically involve non-colonic areas of the gastrointestinal tract. However, incompetence of the ileocaecal valve that result in retrograde flow of colonic contents into the distal ileum and inflammation, which is often referred to as 'backwash' ileitis.³⁸ In most cases (88%), inflammatory changes consisted of a mild degree of neutrophilic inflammation in the lamina propria, which was often patchy in distribution and occasionally associated with focal cryptitis, crypt abscesses and a mild degree of villous atrophy and regenerative epithelial changes. Inflammation in the ileum may be considered part of the spectrum of Ulcerative colitis if the inflammatory changes are mild, superficial and confined to the distal 2–3 cm of ileum, and occur in a patient in whom all of the clinical, radiological and pathological features support a diagnosis of Ulcerative colitis.³⁸ Transmural lymphoid aggregates are present in most cases of Crohn Disease involving the ileum, and less frequent in the colon. Occasionally, transmural mononuclear cell inflammation may be present in Ulcerative colitis as well; especially when superficial fissuring ulcers extend into the deep submucosa or superficial muscularis propria. However, in contrast to Crohn Disease, mural inflammation in Ulcerative colitis typically not in the form of discrete lymphoid aggregates and usually underlies areas of severe ulceration.³⁸ Thus, lymphoid aggregates in areas under intact mucosa are not a feature of Ulcerative colitis and, in fact, favour a diagnosis of Crohn Disease.

Approximately 30–40% of Crohn Disease cases contain either mucosal, or mural, non-necrotic granulomas.³⁸ Epithelioid granulomas represent one of the few features that, when present in mucosal biopsies, may aid in

Table 3: Common conditions leading to diagnosis of Indeterminate colitis

Fulminant colitis
Failure to accept definite evidence in favour of Crohn Disease or Ulcerative colitis
Attempt to establish a diagnosis on mucosal biopsy specimen
Insufficient clinical and radiologic information
Presence of other associated disease
Failure to recognize unusual manifestation or morphological variants

Table 4: Features favouring Dysplasia

Nuclear hyperchromasia associated with pleomorphism
Irregular nuclear contour
Marked nuclear stratification with crowding
Loss of polarity

the distinction between Ulcerative colitis and Crohn Disease.⁶⁹⁻⁷¹ However, granuloma may form due to ruptured crypts, or extravasated mucin and may occur in Ulcerative colitis as well as in other non-IBD forms of colitis.⁷²⁻⁷⁴ The clues to differentiate granuloma arising due to ruptured crypts are presence of neutrophils and lymphocytes along with histocytes and multinucleated giant cells.

Dysplasia and Cancer in Ulcerative Colitis

Patients with longstanding Ulcerative colitis are at increased risk for colorectal adenocarcinoma. Colitis associated carcinomas are often flat, infiltrate, and difficult to visualize by standard radiographic techniques, most gastroenterologists recommend regular surveillance for cancer or dysplasia, using colonoscopy with biopsy.⁴⁴ The incidence of dysplasia in Ulcerative colitis is difficult to estimate; studies suggest a 5% incidence of dysplasia after ten years and a 25% incidence after 20 years.¹ The cumulative incidence of colorectal cancer after 25–35 years of Ulcerative colitis ranges from 3.1% to 43%.

Dysplasia, the presumed precancerous epithelial lesion, has been recognized adjacent to and distant from colitis-associated carcinoma. Furthermore, adenoma-carcinoma sequence has well been accepted. Thus identifying dysplasia and its subsequent adequate management remains vital for preventing it to transform into carcinoma. Dysplasia is recognized by well-defined criteria. However, epithelial repair may mimic as dysplasia, as both dysplasia and repair are associated with nuclear enlargement and hyperchromasia, increased mitoses and depletion of intracellular mucin. None the less, nucleus in repair are often round to oval with a smooth contour, they are evenly spaced and contain granular chromatin with single or multiple nucleoli. The nuclear-to cytoplasmic ratio is often decreased and the cell cytoplasm is eosinophilic. However, nearby crypt abscesses

and cryptitis help to confirm the diagnosis of repair. Features that favour dysplasia over repair are shown in table 4.

The Inflammatory Bowel Disease- Dysplasia Morphology Study group has proposed the following three-tier classification for biopsy interpretation in IBD: Positive, negative and indefinite for dysplasia. Positive biopsy specimens are further graded into high grade or low grade dysplasia.⁴⁴

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