Chapter 1

Introductory Chapter: Inflammatory Bowel Disease

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1. Introduction

Inflammatory bowel disease (IBD) is a collection of inflammatory forms of the colon and small intestine (**Figure 1**).

Under this umbrella is Crohn's disease (CD) and ulcerative colitis (UC) which they are the main types of it. Crohn's disease affects the gastrointestinal tract from the mouth to the anus, whereas ulcerative colitis principally affects the colon and the rectum [1]. A third type of bowel inflammation had emerged known as indeterminate colitis (IC) or inflammatory bowel

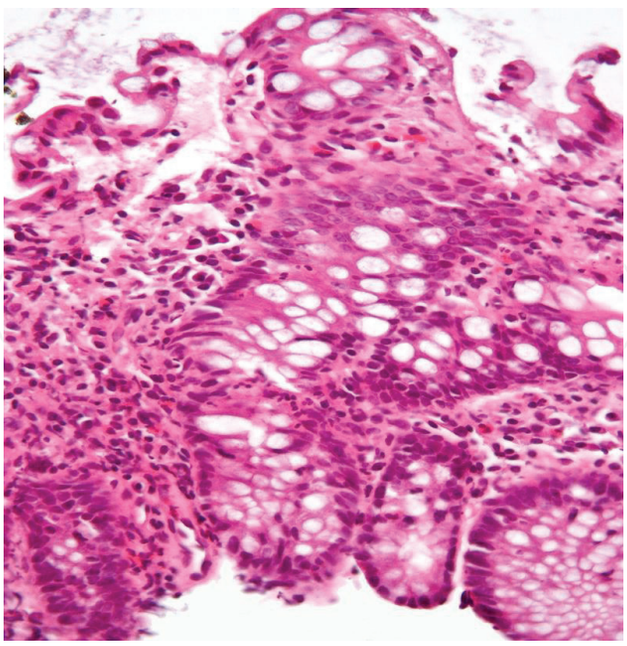

Figure 1. Colonic biopsy of the mucosa shows numerous neutrophils within the crypt and several eosinophils.

disease unclassified (IBDU) when the differentiation between UC and CD is difficult due to the absence of standard golden test that differentiates between these two diseases [2]. IBD can affect any age of the population, but it is more common between 15 and 40 years of age (both young adults and elderly). About 7–20% of IBD patients are children and 60–85% are adults below 40 years of age [3]. There is a bimodal distribution of CD in American cohort population and European and Canadian population; the peak incidence of CD is 15–29 years of age, while the incidence of UC is 20–29 years of age [4]. In smokers, the onset of UC is at later years of age compared to non-smoker patients [5]. Hospital admissions of the patients who were over the age of 65 years of age represent 25% of all hospital admissions for IBD patients [6].

2. Signs and symptoms

Inflammation anywhere along the gastrointestinal tract disrupts the normal mucosal integrity. Thus, IBD can be very painful and disruptive, and it may be life-threatening in some cases. The symptoms are vary from abdominal pain, cramps, swelling in the stomach, recurring or bloody diarrhea, weight loss, tiredness, fever, vomiting, anemia. Other rare symptoms are joint pain, painful red eyes, painful red skin nodules, and jaundice. The characters of these symptoms are remission and relapse [7].

3. Causes

The precise cause is unknown, and it may be due to interaction between environmental and genetic factors leading to immunological responses and inflammation in the intestine.

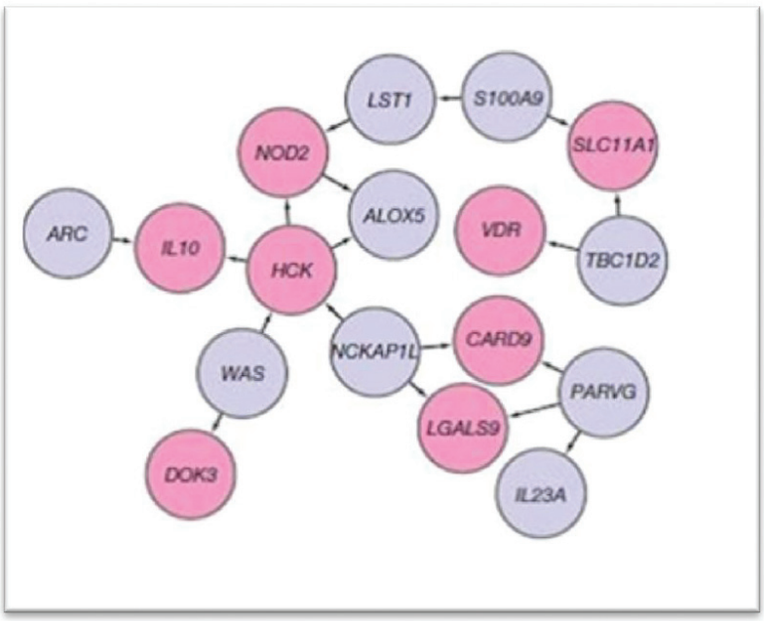

Figure 2. Loci associated with IBD. Pink genes are in IBD-associated loci, blue are not [8].

3.1. Genetic factor

It is more likely to develop IBD if it has a sibling or parent with the IBD. There are about 163 loci that are related to 300 known genes related to cytokine production, lymphocyte activation, and the response to bacterial infection. The most important genes are NOD2, Il10, and CARD9 that had a relation with bacterial interaction and gene HCK which had an important role in anti-inflammation (**Figure 2**) [8].

4. Environmental factors

4.1. Microbiota

The gastrointestinal tract contains many microbiota that maintain normal symbiosis. When there is an alteration in this enteral bacteria may leads to gut inflammation [9]. About 30–50% reduction in *Lachnospiraceae* and *Bacteroides* in the gut of IBD patients and have been prescribed antibiotics for them in the last 2–5 years ago [10]. These drugs in association with other types of food like concentrated milk fat can alter the commensalism bacteria in the gut [11].

4.2. Intestinal barrier

Intestinal epithelial mucosa is an important innate immune mechanism that acts as a barrier preventing microbial gut from invading the epithelial tissue [12]. Changes in intestinal microorganisms lead to uncontrolled immune response that leads to damage this barrier through dysfunctioning of TLR signaling and invading of bacteria initiating an inflammatory immune response [13]. The immune system protects the gut from pathogen like bacteria and virus that leads to inflammation in the digestive tract.

4.3. Diet

The type of diet is an important factor in initiation of IBD [14]. It had been found that animal protein in meat and fish is associated with UC, while plant protein had no effect due to the presence of sulfur-containing amino acid like methionine [15]. Diet containing either intact proteins or free amino acids like elemental, semielemental, and polymeric diets during intestinal inflammation may lead to immunological changes like decrease of serum IgG; increase in the production of IL-6, IL-17A, TGF-β, and IL-10 in the small and large intestines; increase in intestinal permeability; increased number of total and activated CD4+ T helper cells in the small intestine; and proliferating cells in the colon. So, the design of nutritional therapeutic intervention for inflammatory bowel diseases may contribute in the treatment [16]. Eating habit is an important factor in initiation IBD especially in western countries like imbalance in the ratio of n-6/n-3 polyunsaturated fatty acids (PUFAs) in favor of n-6 PUFAs, and a higher ratio of n-6 PUF versus n-3 PUF was associated with an increased UC incidence [17].

5. Risk factors of IBD

5.1. Smoking

Smoking is one of the most important risk factors for developing Crohn's disease but in ulcerative colitis affects non-smokers and ex-smokers. Smoker patients will be affected later on than non-smoker ones [5].

5.2. Ethnicity

Certain ethnic groups like Caucasians and Ashkenazi Jews have a higher risk for developing IBD. Non-Caucasians had more severe disease performance than Caucasians. Non-Central European descent patients who were born in Europe were diagnosed at lower years of age with this disease than those born outside Europe and migrated to The Netherlands [18].

5.3. Age

IBD can occur at any age group, but mainly it starts before the age of 35 [19].

5.4. Family history

Individuals whose parents, sibling, or child have IBD are at a much higher risk of developing IBD. So genetic with epidemiological factors could be used as predictors of the disease course. For example, ileal localization of CD patients was more common in NOD2-variant carriers and IL-6 GC + CC genotypes, identifying C allele as a probable marker of increased risk for ileal CD and earlier onset of the disease in CD patients with a positive family history for IBD. Patients with CD who are TLR4 299Gly carriers are at higher risk for surgery compared with TLR4 299Asp-variant-carrier patients [20].

5.5. Geographical region

Population who live in urban areas and industrialized countries are more liable to develop IBD because they tend to eat more fat and processed food. In addition to that, IBD is more common among people living in northern cold climates. The incidence and prevalence of inflammatory bowel disease show different variations in different geographical regions. IBD is more common in North America and Northern and Western Europe; later on, the incidence was increased in Eastern European and Asian countries [21].

5.6. Gender

IBD affects both sexes equally. Ulcerative colitis is more common among males, while Crohn's disease is more common among females.

6. Complications of IBD

- Malnutrition with resulting weight loss. The frequency of malnutrition in patients with inflammatory bowel disease was high. One of the predictive factors of malnutrition is avoidance

of some foods during flares which were associated with higher risk of malnutrition, and many patients had self-imposed food restrictions depending on their beliefs and thoughts [22].

- Colon cancer and other types of tumors. IBD diagnosis at an advanced age had an association with colitis-associated colorectal cancer. Using chemotherapy like thiopurine in older IBD patients leads to an increased risk of non-Hodgkin's lymphoma, nonmelanoma skin cancer, and urinary tract cancers. Furthermore, older age group is accompanied by multimorbidity factors like malnutrition and decreased life expectancy. This needs good cancer screening and medical treatment [23].
- Fistulas or ulcers that go through the bowel wall creating a hole between different parts of the digestive tract that need surgical intervention [24]. The rate of abdominal surgery has decreased and reserved for severe and complicated IBD disease complications due to advances in medical therapy, surveillance, and management methods. The emergency surgery stills in the same rates and increases in surgical recurrence in spite of the reduction in surgical rate morbidity [25].
- Intestinal rupture or spontaneous perforation of the small intestine is rare but can occur in the clinical course of Crohn's disease [26].
- Bowel obstruction. Whether intestinal or colonic obstruction is troublesome for neoplasm as the first clinical manifestation of IBD. This is a clinical thing for surgeons, pathologist, and gastroenterologist to be alert of this. The management of these lesions is surgery like hemicolectomy, segmental colonic resection of the portion involved according to the condition [27].
- Blood loss. One of the complications of IBD is bleeding per rectum or bloody diarrhea that leads to shock [28].

7. Diagnosis

This can be achieved starting from history about chief complain ending with family history. This followed by physical examination and laboratory tests:

1. **Stool sample**: To diagnose the causative microbial agent that causes the disease using fecal samples and assess disease severity. IBD is associated with alteration in the gut microbiota (gut dysbiosis). Bacteria that produce urease leads to transfer of nitrogen to the gut microbiota that is used for amino acid synthesis resulting in a predominance of *Proteobacteria* species and dysbiosis. A possible role for altered urease expression and nitrogen flux in the development of gut dysbiosis suggests that bacterial urease may be a likely therapeutic target for inflammatory bowel diseases [29]. Other fecal tests are S100A12, neopterin, elastase, fecal hemoglobin, alpha-1 antitrypsin, gelatinase-associated lipocalin, chitinase-3-like-1 protein, matrix metalloproteinase-9, lysozyme, M2 pyruvate kinase, myeloperoxidase, fecal eosinophil proteins, beta-defensin-2, and beta-glucuronidase. Some of them had high sensitivity and specificity and correlated with disease activity and response to therapy, and another test is mucosal healing. Fecal calprotectin or fecal lactoferrin is the typical test for assessing IBD activity, even though its specificity and sensitivity are not optimal and it does not have a validated cutoff [30].

2. **Blood test**: There is a panel of blood tests in diagnosis and screening for ulcerative colitis and Crohn's disease like hemoglobin, platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin are widely used [31]. Other laboratory tests have been included like interleukin-1 receptor antagonist, eotaxin, anti-neutrophil cytoplasmic and anti-*Saccharomyces cerevisiae* antibodies, tumor necrosis factor alpha, and thrombopoietin [32–36].
3. **Plain film and barium X-ray (follow-through and enema)**: Plain X-ray can be used when perforation is suspected. Barium X-ray demonstrates the site and the severity of the lesion in the large and small intestine. It also tracks the movement of a thick, chalky liquid barium through the intestines [37].
4. **Flexible sigmoidoscopy and colonoscopy**: This is a direct visualization to sigmoid colon for any ulcers, fistula, and other lesions with biopsy taken. Colonoscopy surveillance is used for early dysplasia detection and treatment, thus preventing progression to colorectal cancer. Techniques and technologies are available to enhance optical diagnosis of dysplasia in inflammatory bowel disease [38].
5. **Capsule endoscopy**: Colon capsule endoscopy is a wireless and simply invasive method for direct visualization of the whole colon and small intestine, screening and monitoring disease activity in inflammatory bowel diseases [39]. The diagnosis of IBD using a panenteric video capsule endoscope that visualizes both the small and large bowels is more higher than ileocolonoscopy in patients with active disease [40].
6. **Computer tomography (CT) and magnetic resonance imaging (MRI)**: Used to examine the small intestine and detect any complications of IBD like abscesses, fistulas, and intestinal obstruction. It also excludes other conditions that cause symptoms similar to those associated with IBD like appendicitis. The patient usually drinks an oral contrast, and intravenous contrast may also be injected into a vein prior to the test. Magnetic resonance (MR) enterography has the advantage over other methods of being detection active inflammation noninvasive, lacking ionizing radiation, and demonstrating excellent soft tissue contrast to evaluate patients with inflammatory bowel disease [41].

8. Treatment

1. **Anti-inflammatory drugs** that decrease inflammation of gut mucosa in spite of its side effect like sulfasalazine and corticosteroids. Sulfasalazine is a sulfa antimicrobial that is used not only to treat IBD that affects gut microbes in the fecal samples by the increasing amount of SCFA-producing bacteria and lactic acid-producing bacteria as well as the decreasing amount of *Proteobacteria* but also to modulate the dysregulated function of the TNBS-induced colitis, increased capacity for carbohydrate metabolism and citrate cycle, and a decrease in the oxidative stress of riboflavin, sulfur, cysteine as well as bacterial pathogenesis like cell motility and secretion, bacterial motility proteins, and flagellar assembly. Furthermore, a higher proportion of *Mycoplasma* concentration [42].
2. **Immunosuppressant drugs** (immunomodulators): It acts on immune response preventing it from attacking the bowel and causing inflammation like anti-TNF antibodies (infliximab)

(IFX). Some patients will respond to this treatment, while others will not. The transmembrane TNF-α might be linked to response to IFX by promoting reverse signaling-induced apoptosis in inflammatory cells. The percentage of tmTNF-α bearing lymphocytes and monocytes and the intensity of tmTNF-α in the circulating leukocyte were directly related to primary response to IFX. Immunosuppressants have many side effects including rashes and infections [43].

3. **Antibiotics**: The pathogenesis of inflammatory bowel disease is complex and involves the interaction between genetic and environmental factors. One modality is prescription of antibiotic like oral vancomycin with or without gentamicin that targets and kill Gram-negative and anaerobic bacteria that may trigger or aggravate IBD symptoms [44].
4. **Antidiarrheal drugs and laxatives**: Diarrhea is a common clinical symptom of inflammatory bowel diseases with abdominal pain, urgency, and fecal incontinence. The pathophysiology of it is due to a defect in absorption of salt and water by the inflamed bowel with inflammation. So, one mode of treatment is antidiarrheal drugs to treat IBD symptoms [45].
5. **Lifestyle choices**: IBD is increased in both developed and developing countries due to lifestyle which is important in patients with IBD like obesity which is increased in parallel with IBD. The possible cause is due to adipose tissue that produces pro-inflammatory adipokines and provides a possible mechanism for the links between obesity and IBD. Other possible methods of lifestyle are drinking plenty of fluids, which helps to compensate for those lost in stool, and vitamin and mineral supplements, which can help in patients with nutritional deficiencies. Avoiding dairy products and stressful situations also improves symptoms. Exercising and quitting smoking can improve the IBD [46].
6. **Surgery** can sometimes be necessary for people with IBD, like strictureplasty, to widen a narrowed bowel, closure or removal of fistulas, removal of affected portions of the intestines, and removal of the entire colon and rectum, for severe cases of ulcerative colitis [47].

8.1. Prevention

The hereditary causes of IBD cannot be prevented. However, you may be able to reduce your risk of developing IBD or prevent a relapse [48]. This can be achieved by eating healthy foods like regular consumption of extra virgin olive oil, which is the main source of fat in the Mediterranean diet [49]. Other methods are exercising regularly and quit smoking. In addition to that, using infliximab helps to prevent recurrence [50].

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