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Review Article

Ulcerative Colitis: Prevalence, Etiology, Manifestations, and Management

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Abstract

Background: Ulcerative colitis is defined as an inflammatory disease characterized mainly by inflammation of the colonic mucosa that spreads from the rectum. It is also known as a chronic condition that usually includes bloody diarrhea and stomach cramps in the second or third decade of life. The condition may be confined to, or may include, the rectum (proctitis), the rectum and the sigmoid colon (proctosigmoiditis), or the left colon (left colitis), Colon (pancolitis), most or all of it. All the previously mentioned factors contribute to the choice of treatment.

Aim: In this review, we will look into the prevalence, symptoms, etiology and management of ulcerative colitis.

Conclusion: The manifestations of UC range from the typical form with bloody diarrhea to the most uncommon symptoms affecting PNS, CNS and other organs other than the intestine. The best management of UC depends mainly on full understanding of the condition, mainly severity of the condition. The management could be by using medications or surgery based on the condition itself. Final conclusion that UC could be managed if the case was diagnosed correctly and the best regimen of treatment could be chosen.

Keywords: *Ulcerative Colitis; Etiology of Ulcerative Colitis; Management of Ulcerative Colitis*

Introduction

Samuel Wilks first described ulcerative colitis (UC) in the 1800s when he described it after the death of 42 years old women who suffered from fever and diarrhea for months [1]. It is considered one of the idiopathic inflammatory bowel diseases (IBD), together with Crohn's disease. Ulcerative colitis is defined as an inflammatory disease characterized mainly by inflammation of the colonic mucosa that spreads from the rectum [2]. It is also known as a chronic condition that usually includes bloody diarrhea and stomach cramps in the second or third decade of life.

Despite our knowledge of the existence of ulcerative colitis is very obvious, total understanding of the factors predisposing to it is still unclear. Ulcerative colitis and Crohn's disease are both diseases of the large intestine, although they had different pathological characteristics at the beginning, nowadays an overlap between the two diseases is marked both pathologically and anatomically which led that our diagnosis is not definite in about 10% of patients [3].

Ulcerative colitis natural history is known to be alternative periods of alleviation and flares [4]. Chronic ulcerative colitis is characterized by frequent bloody diarrhea associated with urgency [5]. To differentiate disease activity, different indexes such as molecular and bio-

chemical markers, and the appearance of the colon using endoscope could be used [6]. Truelove and Witts [7,8] designed criteria which considered the easiest one to guide the medical and surgical therapy, also the determination of the extent of the disease is very important in the management of the condition as the disease begins in the rectum and spreads to the colon, The condition may be confined to, or may include, the rectum (proctitis), the rectum and the sigmoid colon (proctosigmoiditis), or the left colon (left colitis), Colon (pancolitis), most or all of it. All the previously mentioned factors contribute to the choice of treatment [6].

Medications used in ulcerative colitis are not for curative purposes as medicines could control the symptoms and relieve the inflammation only but they cannot cure intestinal or the extra-intestinal symptoms of the disease, however, the surgical removal of the rectum and colon could not just cure the disease but also decrease the risk of its turning to cancer, both the surgical and medical intervention is important in the management of the condition and the communication between both the gastroenterologist and gastrointestinal surgeons who follow the patient is very important in following up with the case, understanding it and subsequently the choice of the best medical regimen for the patient [6]. In this review, we will look into the prevalence, symptoms, etiology and management of ulcerative colitis.

Prevalence

An exponential increase in the prevalence of ulcerative colitis is noticed worldwide within the last decades, the statistics had shown that there is a strong relationship between the incidence of ulcerative colitis and the industrial progress this is confirmed by the spread of UC particularly in North America and Western Europe [2], the united kingdom and North America are shown to have the highest rates and prevalence of ulcerative colitis. The prevalence of ulcerative colitis in these countries is 8 - 14/100,000 individuals/Year and range in prevalence from 40 to 240/100,000,000 [9].

Considering the impact of the disease in the US, ulcerative colitis has shown great effects on the US medical resources, as statistics show that it causes more than 20,000 hospitalization, 250,000physician office visits, and a cost of about 500$ million per year for hospitalization and treatment [10]. taken into consideration that these studies do not consider the social effect of the disease as a loss of workdays and its impact, but to conclude; ulcerative colitis has a significant societal and medical impact [10].

In adult males, ulcerative colitis is more common than in females (M: F = 1.5:1).

In infants, ulcerative colitis is prevalent among females. The peak age for the incidence of ulcerative colitis is 30 - 40 years [11] and the mortality rate is comparable to the total population [12]. Also, many studies have shown that smoking protects against UC [13], this effect is dose-dependent as studies also revealed that the risk of developing UC increases by 50% when smokers stop smoking than comparing to non-smokers [14].

Every part of the colon could be affected by ulcerative colitis, but mostly restricted to the left side, but in all cases, the rectum is always involved. In about 30% of patients, UC extends to splenic flexure; in this case, it is called distal colitis or left-sided colitis, while only 15% of patients have extensive colitis, that is, inflammation that reached beyond splenic flexure.

In about 35 percent of patients with initial proctitis or left-sided colitis, proximal extension ultimately occurs [15].

Etiology

Many factors of different categories contribute to the incidence of UC, factors could be environmental, genetic, or immunological [16].

Genetic factors

Studying identical twins that have the same genetic content showed that they have a low percentage of concordance for ulcerative colitis (less than 10%) [17]. But recent meta-analysis of six genomes confirms the relation between genes and ulcerative colitis, this analysis

showed the presence of single nucleotide polymorphisms in 47 susceptibility loci for ulcerative colitis, 28 of the signals are shared with Crohn's disease [18], an examination of the gene content of the loci was necessary to understand the relationship of the pathogenesis of the disease and the loci, this examination revealed specific risk loci for ulcerative colitis that contained genes (CDH1, CDH1 and LAMB1), which confirmed how the defect in the barriers' function contribute to the disease [19,20].

Another meta-analysis showed that gene GNA12 in chromosome 7 is the main cause of ulcerative colitis as it is responsible for the assembly of the tight junctions in the epithelium cells [21]. Other genes on chromosome 7 that showed a relation to UC are the genes that encodes interferon (IFN) regulatory factor 5, which is responsible for release of cytokines such as tumor necrosis factors (TNF)-a, this gene is also common in systemic lupus Erythematosus and rheumatoid arthritis and interleukin (IL)-7 receptor gene[18].

It has been estimated that 47 susceptibility loci may explain 16 percent of ulcerative colitis heritability, and more studies on the expression of genes are currently made to find out about more genes that could have a role in the susceptibility of UC [18].

Environmental factors

Cigarette smoking is proved to decrease the susceptibility for developing ulcerative colitis, this fact is shown by many studies. a meta-analysis also showed that the susceptibility of smokers to develop ulcerative colitis is 40% comparing to non-smokers [12]. Other conditions such as primary sclerosing cholangitis and pouchitis also showed similar results in comparing the susceptibility of smokers to non- smokers for developing the disease, this all suggest that the effect of smoking is not limited just to the colon but it is systemic [12].

However the risk of developing ulcerative colitis is higher in former smoker than non-smokers, cigarette smoking not only affect the probability of incidence if ulcerative colitis but also the natural history, as undergoing colectomy is two times higher in former smokers than non-smokers or current smokers [22]. Also, studies showed that the risk for developing ulcerative colitis is decreased in those who had Appendectomy, as it has a protective effect, with subsequent reduction in ulcerative colitis susceptibility by 69% [23]. Even those who could develop UC after appendectomy, it is more likely to occur in older age, with mild symptoms and less necessity to colectomy [24].

Non-steroidal anti-inflammatory drugs have shown to favor relapse of both crohn's disease and ulcerative colitis, although aspirin itself doesn't increase the risk for ulcerative colitis [25], this all should be taken into consideration in treatment of patients with ulcerative colitis as in this case non-steroidal anti-inflammatory drugs could worsen the case [26]. While the risk of inflammatory bowel disease is increased with oral contraceptives mainly crohn's disease, but for ulcerative colitis the percentage is only 29 % which is not significant [27].

Other environmental factors tend to be associated with the development of inflammatory bowel disease, such as dietary sugar consumption, breastfeeding and perinatal paramyxoviral infections, but no clear consensus has emerged between the various studies [12].

Immunological factors

Similar to crohn's disease, UC is known to develop in genetically susceptible individuals, as irregular mucosal immune response to commensal gut flora [28] high number of neutrophils circulating in the blood is one of the manifestations in UC, which is responsible for the higher response to activating stimuli [28]. Patients with ulcerative colitis have inflamed mucosa with high IL-8, which is a neutrophil-activating substance, which cause the activation of most of the neutrophils present at this site, finding this out had been made through a specific marker; neutrophil lipocalin, that marks the activation of neutrophils, this marker was shown to be increased in the colorectal perfusion fluids of patients with UC when comparing it to normal people [29]. Antibodies are also one of the main things that exist in ulcerative colitis, although their role is still unclear, such as perinuclear anti-neutrophil cytoplasmic (pANCA) serum autoantibodies, anti-goblet cells, and anti-tropomyosin. Activated neutrophils act by producing proteolytic enzymes in the mucosa such as neutrophil collagenase and neutrophil elastase, responsible for the ulcer by degradation of extracellular matrix [30].

Chronic inflammation of the intestine is also a manifestation of UC, caused mainly by T-cells, till now efforts are to understand the different t-cells responses in both crohn's and UC, but the main conclusion they had that ulcerative colitis is mainly caused by atypical Th2, mainly IL-13 that produces natural killers that caused colitis in oxazolone mediated experiments [31], moreover the effect of IL-13 extends to the epithelial cells and causes its apoptosis [32]. The recent researches revealed 2 main subsets of CD4+T cells, which are Th17 and Th1/Th17 cells, responsible for the mucosal inflammation in both crohn's disease and ulcerative colitis [33,34].

Signs and symptoms

The traditional form of UC, manifested generally with urgency, bloody diarrhea and abdominal pain, in rare cases some patients may come with weight loss or other systemic manifestations such as low fever, ulcerative colitis generally with low symptoms that aggravate with time [35,36]. Other symptoms may also be presented in ulcerative colitis patients such as anorexia, nausea and vomiting, also proctitis may cause bleeding that looks exactly similar to the hemorrhoidal bleeding, 50% of patients come mainly with relapse or remission of the symptoms [12].

Manifestations other than the intestinal ones for ulcerative colitis, generally resembles those of crohn's disease [37]. It mainly affects skin, joints, liver and eyes [38,39]. The two most known manifestations that occur within the skin are Erythema nodosum and pyoderma gangrenosum. Arthritis is one of the most predominant symptoms of ulcerative colitis, it could be axial or peripheral, the peripheral type is subdivided into two types; type 1 and type 2, type 1 is mostly self-limited and aggravate with colitis while type 2 is mostly chronic, the kind of arthritis associated with colitis is not the same as this associated with rheumatoid arthritis or osteoarthritis, the patient in the arthritis associated with colitis usually feels pain in the morning that diminishes within the day, this pain is usually accompanied with stiffness; exercise could easily relieve it [40-42].

Peripheral and central nervous systems are also affected with the disease, the etiology by which it causes its effect could be summarized mainly into six mechanism; vitamin deficiency, infections mainly due to immunosuppression, toxic metabolites, side effects of the therapy, immunological abnormalities and thromboembolism [43,44]. Peripheral neuropathy is the main effect of UC in the peripheral nervous system, a study had been made on 9 patients with ulcerative colitis, 6 of them had peripheral nerve disorder [45], the incidence of UC is estimated to be 1.9%. The central nervous system manifestations could be shown mainly as Thromboembolism and cerebrovascular disease.

Diagnosis

The activity of the disease and the degree of response towards the medications could be assessed using The disease activity index (DAI), an endoscope is needed for this test, results are interpreted based on the following; score less than 4 is considered as being in relapse, between 4 and 10 are considered moderately active and more than 10 is considered active severe disease [46].

To test how bad the inflammation is we can use C-reactive protein as a marker and erythrocyte sedimentation rate, as presence of anemia could suggest loss of the blood due to intestinal ulceration [47]. Pancolonoscopy is also another way to test presence of any inflammation signs such as mucosal erythema and hyperemia and multiple deep ulceration. Although some of the features histologically are markers for ulcerative colitis, the condition could be not so clear in about 10 - 15% of cases where physician can find it challenging to differentiate between ulcerative colitis and crohn's disease [48].

Management

The severity, location and extent of the disease are the main factors that determine how the condition shall be managed. The main goals of the treatment are to maintain remission without corticosteroids, prevent any complications and finally improve the quality of

life. Generally, treatment is subdivided into 3 main classes' aminosalicylates, corticosteroids, and immunosuppressants. Surgery is also another action that could be made in certain conditions, now we will move to discuss each one [49].

Aminosalicylates

This group is considered the first line of treatment. Misiewicz and colleagues were the first to test the effect of sulfasalazine, as when they compared in their study the incidence of remission of UC in those who are taking sulfasalazine compared to the control, results showed that in one year, 73% of patients taking placebo had a relapse of their CUC in comparison with 21% taking sulfasalazine, this is considered the first trial for using and testing sulfasalazine, what encouraged the use of it is because it gained the antibacterial characters due to presence of sulfapyridine part that is connected to a 5-ASA portion responsible to the anti-inflammatory action of sulfasalazine [50].

Researches proved that the useful action of this group is mainly because of 5-ASA portion, while the side effects are mainly due to sulfapyridine part [51], so new preparations are made that contains only 5-ASA portion, to get the benefit of this group and terminate any undesirable side effects. The exact mechanism is still not clear, but the obvious is that it doesn't act completely as NSAIDs, not the simple that it disturbed prostaglandin synthesis only, in addition of this mechanism it also prevent the production of an important inflammatory mediators such as interleukin (IL) 1, tumor necrosis factor (TNF), and interferon, the last suggested mechanism is that it also act as antioxidant [52,53].

Glucocorticoids

Corticosteroids and Glucocorticoids gad been used in treatment of UC and CUC since a long time ago, although they are very effective in relieving symptoms of ulcerative colitis, their side effects on the long term use limit their use to short courses only. They act mainly by interaction with the intracellular glucocorticoid receptor [54], which lead to inhibition of transcription of the gene responsible for the production of tumor necrosis factors, proinflammatory cytokines and many enzymes that have a role in production of prostaglandin.

Prednisone is the main medication, it is used orally, beside their effectiveness, the suppression of adrenal function is still the main side effect so new preparations are made that intended to increase the local intestinal effect and decrease the systemic one such as budesonide [55].

Immunosuppressants

Mercaptopurine and azathioprine are the 2 main medications used in this group. Both are purine metabolites where azathioprine is a pro-drug that is converted to mercaptopurine. Their exact mode of action is still unknown but some suggestion are that its metabolites, which is thioguanine, is thought to inhibit cell proliferation by preventing DNA synthesis. Another suggestion that is thought to be the main mode of action is that it induce T-lymphocyte apoptosis [56,57].

The main disadvantage of this group is that their delayed action as it takes weeks to get the required level of active metabolites so they cannot be used in acute conditions. Another drug that is produced by soil fungus is cyclosporine, this medication should be used with caution due to its severe side effects such as hypertension, renal insufficiency, and seizures [58,59].

Surgery

Surgery could treat all the intestinal symptoms, but surgery also has many risks and can affect the life style of the patient, surgery many could be elective or in emergency cases. In emergency situations the goal is mainly to restore the patient good quality of life, surgery could also be made in case of failure of treatment (70%), perforation (< 10%), toxic colonic dilatation (20%),and severe bleeding (< 5%) [60].

Conclusion

The manifestations of UC range from the typical form with bloody diarrhea to the most uncommon symptoms affecting PNS, CNS and other organs other than the intestine. The best management of UC depends mainly on full understanding of the condition, mainly severity of the condition. The management could be by using medications or surgery based on the condition itself. Final conclusion that UC could be managed if the case was diagnosed correctly and the best regimen of treatment could be chosen.

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