Chapter

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Newer Concepts in Inflammatory Bowel Disease

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INTRODUCTION

Idiopathic inflammatory bowel diseases (IBD) include ulcerative colitis (UC) and Crohn's disease (CD) or regional ileitis. Important differences between these two conditions are summarized in Table 1[1-5]. However, in some patients with colitis, it may be difficult to differentiate between these two diseases due to overlapping features, or they do not have enough features of either disease. The disease in these patients is called indeterminate colitis. Though about 10% patients with IBD from West have been reported as having indeterminate colitis, this has been less often reported from India. In the past, IBD was believed to be uncommon in India. However, a recent study indicated UC to be as common in India as in the West[6].

Table 1: Differences between Crohn's disease and ulcerative colitis

	Crohn's disease	*Ulcerative colitis*
Abdominal pain	Commoner	Less common
Small bowel diarrhea due to malabsorption	Commoner	Rare
Extraintestinal manifestations	Commoner	Less common
Perianal disease	Commoner	Rare
Osteopenia	More severe	Less severe
Skip lesion	Common	Rare
Small bowel involvement	Commoner	Rare
Rectal sparing	Common	Rare
Site of colon affected	Mainly right colon	Mainly left with variable extension
Fistula	Commoner	Rare
Transmural inflammation	Common	Rare
Granuloma	Commoner	Rare
Perinuclear anti-neutrophil cytoplasmic antibody	Less often +ve	More often +ve
Anti-*Saccharomyces ceruvisiae* antibody	More often +ve	Less often +ve

Major advances in IBD in last decade have been in the area of pathogenesis and treatment of the disease. Hence, in this article these areas will be reviewed.

PATHOGENESIS OF IBD

IBD results from abnormal immunological response to normal gut flora. Interest in the genetic predisposition to IBD has grown progressively since the familial occurrence of inflammatory bowel disease was brought to our attention, 37 years ago by Kirsner[7]. Table 2 summarizes epidemiological evidence suggesting genetic susceptibility of IBD. IBD is a polygenic disorder involving several gene mutation, which results in similar phenotype and penetrance is highly variable and environment plays a major role[8]. To summarize, in genetic terms IBD is complex because classical Mendelian inheritance attributable to a single gene locus is not exhibited.

NOD2 [subsequently renamed C-terminal caspase recruitment domain (CARD15)] on chromosome 16q12 (IBD1) locus has been identified to be the first CD susceptibility gene. IBD2 locus has been found to be relatively specific to UC. Genetic basis have even been implicated in extent of disease, its behavior (primary inflammatory, fistulizing or fibrostenotic) and response to treatment. Some studies from India also documented association between single gene polymorphism in some gene and IBD and association with histocompatibility leukocyte antigen (HLA)[8].

Table 2: Epidemiological evidence for genetic susceptibility to inflammatory bowel disease

1.	Ethnic differences in disease prevalence
2.	Twin studies
3.	Familial aggregation and patterns of disease
	Sibling relative risk
	Concordance for disease type, site, behavior, E1Ms Low prevalence in spouses
4.	Low prevalence in families of adopted children with IBD
5.	Association with genetic syndromes
	Turner's syndrome
	Hermansky-Pudlak syndrome
	Pachydermoperiostosis Association with other diseases with recognized genetic susceptibility
	Ankylosing spondylitis
	Psoriasis
	Eczema

Clinical Features

Ulcerative colitis: UC is characterized by remissions and exacerbations. Acute exacerbations of UC may be mild and easily controlled with corticosteroids or may be severe requiring hospitalization, intravenous hydrocortisone, cyclosporine or even surgical treatment. Exacerbation of UC is characterized by bloody diarrhea with urgency, mucus, tenesmus and even toxic megacolon. Medical treatment failed in about 20% patients with acute attack of UC[9]. In patients in whom medical treatment with immunosuppressive drugs has failed, one needs to keep in mind re-activation of cytomegalovirus infection particularly in female patients receiving more than one immunosuppressive drug[10]. Intravenous cyclosporine has been used before surgery in patients with severe attack of UC not responding to intravenous corticosteroids for more than 1 week.

Crohn's disease: Like UC, CD is also characterized by remissions and exacerbations. CD is most common in the third decade of life. A second peak is observed in the elderly who are more likely to have distal colitis and anorectal disease. Females are more commonly affected than males. Diarrhea is the predominant symptom—stools are loose and semisolid and contain mucus. Recurrent episodes of subacute intestinal obstruction due to small bowel narrowing resulting from fibrostenosing disease of distal small bowel with or without involvement of the right colon is a common mode of presentation. Patients with colonic CD commonly present with bloody diarrhea like ulcerative colitis; however, in contrast to UC, tenesmus is uncommon as rectum is spared in more than half of patients with CD. Rectal bleeding is occasional and is more common in colonic lesions. Chronic occult bleeding results in anemia. Almost half of the patients have perianal lesions—these are present in 25% of those with small intestinal disease and 75% of those with colonic lesions. Most patients have minor lesions like skin tags and fissures while some have perianal and ischio-rectal abscesses, sinuses and multiple fistulae which are a cause of major morbidity. Aphthous ulcers may be present in the oral cavity[11].

Atypical Presentation of CD

CD may present in several forms other than those described above. Small bowel CD may present with malabsorption syndrome[12]. Malabsorption in these patients may result from several mechanisms that include, small bowel bacteria overgrowth resulting from intestinal stricture and entero-colic fistula, extensive small bowel disease, lymphatic blockage, previous surgery and amyloidosis; entero-colic fistula may also result in direct passage of nutrients from proximal small bowel to colon resulting in short bowel-like pathophysiological state. In a series from our center as high as 30% patients with CD had malabsorption syndrome[12].

Obscure gastrointestinal bleeding, either occult or overt, may be another atypical presentation of CD. Such bleeding results from ulcerated lesions in the small bowel. In a series of 40 patients with obscure GI bleeding, eight were found to have CD[13].

At times, patients may present with acute onset right lower quadrant pain which may be associated with a mass suggestive of acute appendicitis with appendicular mass. Pyrexia of unknown origin is another rare and atypical presentation of CD[11].

Extraintestinal Manifestations

Arthritis: This is the commonest extraintestinal manifestation of IBD. Axial arthropathy such as spondylitis associated with IBD, like idiopathic ankylosing spondylitis, is not related to activity of intestinal inflammation of IBD. A symmetric sacroiliitis without progression to ankylosing spondylitis may occur and is also unrelated to intestinal inflammation. In contrast, peripheral arthritis, which may be oligoarticular or polyarticular correlates with intestinal inflammation and therefore remits after control of enteritis[11].

Mucocutaneous manifestations: Pyoderma gangrenosum and erythema nodosum are the two cutaneous manifestation of IBD. Though some of the previous Indian studies suggested extraintestinal manifestations

to be somewhat uncommon in patients with IBD in India, these studies were retrospective and nature and hence, prospective studies are required to prove or disprove this issue[11].

Ocular: Episcleritis, scleritis and uveitis are ocular complications of IBD including CD. Prolonged or repeated use of corticosteroids may also lead to development of cataract[11].

Genitourinary: Renal stones occur more often in CD than UC[11]. Fat malabsorption that binds with calcium leads to excessive absorption free oxalate, which is thought to result in hyperoxaluria and renal stones[11]. However, absence of oxalate metabolizing bacteria in the intestine has been reported to contribute to development of renal stones[14]. Development of fistula between genitourinary tract is devastating complication of CD. Hydronephrosis may result of ureteric obstruction. Renal amyloidosis is rare.

Hepatobiliary: Fatty liver, pericholangitis, primary sclerosing cholangitis are not related to activity of IBD. Frequency of gallstones is increased in patients with CD, more so after ileal resection[11].

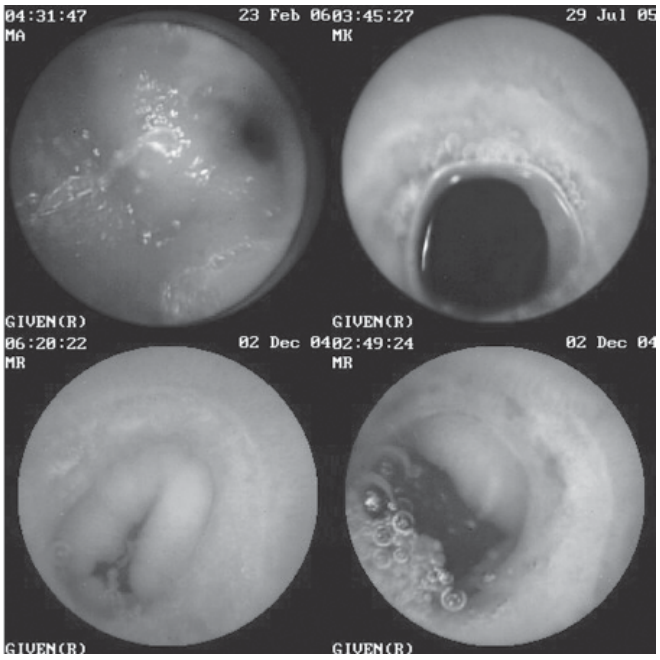

Fig. 1: Capsule endoscopy pictures of a few patients with intestinal ulceration suggestive of Crohn's disease

RECENT ADVANCES IN DIAGNOSIS OF IBD

Major advances in diagnosis have been made in recent years due to improved methods of imaging small bowel either endoscopically or radiologically. As CD affects small bowel, these advances made significant impact in diagnostic work-up in patients with CD. Capsule endoscopy is a recently described technique in which patient ingests a small capsule containing a camera, light emitting diodes, radifrequency transmitter, antenna and battery. Capsule records two images per second for eight hours. Several studies documented superiority of capsule endoscopy over conventional barium small bowel series to diagnose small intestinal lesions of Crohn's disease[15]. However, in India a small intestinal ulcer may be due to tuberculosis also. Fig. 1 shows some of the images of small intestinal ulcers. CT enteroclysis and MR enteroclysis are the other recently described modalities of imaging small bowel.

TREATMENT

Acute exacerbations of UC as well as CD are managed with either intravenous or oral or per-rectal corticosteroids depending of severity and extent of the disease. Subsequently, remission is maintained by aminosalicylate (salazopyrine or 5-ASA or balsalazide). However, maintenance of remission of CD usually requires other immunosuppressive agents such azathioprine, 6-mercaptopurine or methotrexate[11]. About a fifth of patients with UC are steroid dependent, which means that there would be relapse either during tapering corticosteroids or within two months of stopping it. These patients would also require steroid-sparing drugs such as azathioprine or 6-mercaptopurine. Patients on these drugs must be monitored for bone marrow suppression or hepatotoxicity. It is not clear how long should a patient on remission with these drugs should continue these? Though an open study reported that patients with CD in remission who have taken azathioprine for longer than 3.5-year are at low risk of relapse after stopping azathioprine, a randomized trial refuted this and suggested that discontinuation of azathioprine even after 3.5-year leads to relapse more often and hence it is better to continue the drug even beyond 3.5-year[16].

Anti-TNF Antibody in Management of IBD

In last decade, remarkable improvement has been made in management of IBD, particularly CD with new biological agents.

Development of anti-TNF-α antibody: There are two anti-TNFα antibodies currently under evaluation for Crohn's disease—Infliximab, which was the first to be evaluated clinically, and CDP571. Although both antibodies bind free and membrane bound TNF, their

construction differs. The initial use of murine monoclonal antibodies was limited by their immunogenicity in humans. The use of genetic engineering to construct a partially human antibody aimed to retain the high binding affinity of the mouse antibody, while increasing efficacy by lengthening the half-life and reducing the immunogenicity. 'Chimaeric' antibodies, such as infliximab, retain the entire variable domain from the murine antibody, attached to the human constant (C) region, and are therefore approximately 25% mouse and 75% human. In contrast, 'humanized' antibodies, such as CDP571, contain only the murine complementarity determining regions (CDR) responsible for antigen binding, attached to a human C region, and are approximately 5% mouse and 95% human[17].

Theoretically there are three levels of potential immunogenicity. Pure murine antibodies produce the strongest immune response. Chimaeric antibodies are also immunogenic, but the strength of the human antichimera antibody (HACA) response is variable, and may be related to the homology between the murine V region and an individual's V region. Humanized antibodies are substantially less immunogenic than pure murine antibodies and chimaeric antibodies. Chimaeric and humanized antibodies have a significantly longer half-life in humans than pure murine antibodies. Differences in immunogenicity may have implications for the half life and efficacy of therapeutic antibodies, although this is not yet fully understood[17].

Mechanism of action: Infliximab is a chimaeric antibody consisting of variable regions of a mouse antihuman TNF monoclonal antibody cA2 attached to human IgG1 with kappa light chains. It binds strongly to soluble and transmembrane TNF. Although this paradoxically prolongs the half-life of TNF, the TNF to which it is bound is rendered biologically inactive. *In vitro,* the transmembrane binding leads to complement activation and antibody dependent cell cytotoxicity of activated CD4+ T-cells and macrophages. Administration of infliximab results in a reduction in lamina propria CD4+ and CD 8+ T-cells, and CD68+ monocytes. There is a parallel reduction in mucosal Th1 cytokine production, and reduced levels of the proinflammatory cytokines IL-1 and IL-6, and adhesion molecules E-selectin and ICAM-l. In addition, it has been shown in rheumatoid arthritis, that infliximab causes a decrease in the serum levels of matrix metalloproteinase 1 and 3. These enzymes are also thought to be responsible for tissue destruction in inflammatory bowel disease. A recent report has suggested that infliximab is able to induce apoptosis in stimulated T-cells *in vitro.* It is unknown if this model is a true reflection of *in vivo* events. It has been postulated that the loss of activated T-cell clones accounts for the prolongation of clinical response beyond the half-life of the drug (10-14 days)[17].

CDP571 is a humanized antibody formed by the replacement of the CDR of human IgG4 with the CDR of a mouse antihuman TNF monoclonal antibody. It binds to soluble TNF with a similar affinity to infliximab, and is also thought to bind to membrane-bound TNF. It has been documented to reduce serum IL-1, IL-8, and MCP-1 in an animal model of bacterial sepsis. The choice of an IgG4 backbone means that it does not fix, complement or cause antibody dependent cell cytotoxicity *in vitro,* in contrast to infliximab[17].

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