Ulcerative colitis and Crohn’s disease: similarities and distinctions

ABSTRACT—Evidence is presented that ulcerative colitis and Crohn’s disease, the two major chronic inflammatory bowel diseases, are distinct diseases which differ in their clinical features, natural history, pathology, pathogenesis, genetic inheritance and therapeutic response.

Ulcerative colitis (UC) and Crohn’s disease (CD) are the two major chronic idiopathic inflammatory bowel diseases (IBD). More precisely, they are clinicopathological syndromes. The diagnostic criteria for each have been delineated most clearly by Riis [1], and are listed in Tables 1 and 2. The universal use of these diagnostic criteria is strongly recommended. It would ensure uniformity of diagnostic designation in epidemiological surveys, research analyses and therapeutic trials.

Before idiopathic IBD is diagnosed, specific causes of intestinal inflammation including infection (especially bacterial, mycobacterial and amoebic), ischaemia and iatrogenic injury (irradiation and drugs) must be excluded. In clinical practice, it is rarely possible to exclude these other diagnoses and to make a diagnosis of UC or CD according to the recommended criteria at the first consultation or immediately on admission to hospital, but it is valuable to record the presumptive diagnosis and the degree of diagnostic confidence at the initial occasion. These can subsequently be reviewed. Ultimately it is usually possible to differentiate between UC and colonic CD.

Are these syndromes distinct entities or are they different manifestations of a single disease? To be confident that they are distinct diseases we would want evidence that they differ in their clinical features, natural history, pathology, cause, pathogenesis, genetic inheritance or therapeutic response. Some evidence is available.

Disease features

Urgency of defaecation due to loss of rectal distensibility and rectal bleeding secondary to mucosal ulceration are required criteria for the diagnosis of UC. Most patients also have diarrhoea, and a variety of mechanisms are involved. Similar symptoms affect patients with CD if the rectum and colon are involved. In most patients with colonic CD other intestinal sites are also affected, and a few have granulomatous disease outside the intestine (eg skin, liver). In addition, unlike UC, the inflammation in CD may be transmural, giving rise to the development of strictures or perforation with abscess or fistula formation. The symptoms of CD are thus more heterogeneous than those of UC because of the more variable location and greater depth of intestinal injury.

Anal fissures, fleshy tags and perianal fistulae are typical of CD. Similarly, although aphthous ulceration of the mouth occurs in a number of intestinal diseases, chronic swelling and fissuring of the lips and buccal mucosa associated with IBD should lead to the diagnosis of CD.

Endoscopic appearances may aid differentiation: aphthoid and serpiginous ulceration with normal intervening mucosa favour CD but diagnosis often has to be based on examination of multiple mucosal biopsies. Separation of UC from CD is often possible but may be difficult since none of the pathological features are entirely specific for UC, and the transmural extent of CD cannot be appreciated in biopsies which include only superficial mucosa. Epithelioid granulomas, found in CD but not UC, are present in the majority of intestinal resection specimens but rarely in mucosal biopsies.

Prognosis

UC and CD are not often fatal, but surgery, particularly in malnourished or toxic patients, increases the risk of death. Cumulative colectomy rates for UC, stratified according to disease extent at presentation, were approximately 10% for proctitis alone, 20% for extensive colitis and 40% for pan-colitis at five years. Thereafter, irrespective of disease extent, the rate was approximately 1% per year [2]. In colonic CD resection rates are higher. Cumulative rates were 92% and 58% for ileocolonic and colonic CD respectively after mean follow-up of 13 years in one series [3]. These figures underestimate surgical exposure in CD, since they do not include operations to drain abscesses, de-roof fistulae or resect recurrent disease. The prognosis is particularly poor when CD involves both ileum and colon.

In a cohort of patients with juvenile onset IBD major operation rates at five and 10 years, uncorrected for site or extent of disease, were 15% at five years and 26% respectively in UC and 50% and 70% in CD [4,5]. On average, juvenile patients with CD required reoperation after four years, and 24% were left with a permanent stoma at 10 years. For UC, ileo-anal pouch anastomosis after colectomy has become more widely available and has reduced the prevalence of perma-

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nent ileostomy, but is contraindicated in CD. Although the mortality was low, the rate in CD was 2.5 times greater than in UC.

**Therapy**

Medical treatment for IBD remains non-specific since the causes are unknown. Approximately equal proportions of patients with UC and CD respond to corticosteroids. The symptoms and inflammation of CD, but not UC, frequently respond to treatment with elemental diet [6].

**Epidemiology and genetics**

In the UK over the last 50 years the incidence of CD has increased whilst that of UC is static [7–9]. These distinct epidemiological trends cannot be explained entirely by greater awareness of CD.

UC and CD have opposite associations with tobacco smoking. Patients with CD tend to smoke more than controls and smokers with CD have more active disease than non-smokers with CD. UC tends to affect non-smokers and ex-smokers. These observations have been confirmed by recent meta-analysis and suggest that the pathogenetic mechanisms of UC and CD are different [10].

The incidence of IBD in the relatives of patients is greater than the population incidence. In Japanese patients the extended haplotype A24,Bw52,DR2,DPw9 is associated with UC [11]. In North American white patients with UC, the prevalence of DR2 is greater than normal, whereas CD in this population was significantly associated with DR1 and DQw6 [12]. If the findings of separate HLA or other gene associations with UC and CD are confirmed, this will be persuasive evidence of the independence of the two syndromes.

**Table 1. Diagnostic criteria for ulcerative colitis.** Positive features from two of the four categories indicate possible UC, and from three of the four categories substantiate a diagnosis of UC.

| Symptoms                  | Abdominal pain, weight loss and diarrhoea |
|---------------------------|------------------------------------------|
| Proctoscopy               | Perineal, enterocutaneous, entero-enteric or entero-visceral fistulae |
| Fistulae, visible features| * Perianal features, buccal features |
| Radiology/ endoscopy      | X-ray: aphthous, rose-thorn or deep ulcers, cobblestone mucosa, strictures, fistulae, segmental distribution, anywhere in gut. |
| Histology                 | Transmural inflammation (requires full thick- ness sample) focal lymphocytic infiltration, epitheloid granulomas, oedema, fibrosis. |

* We have added the naked eye appearances of the mouth and anus, when involved, to the criteria of Riis [1].

**The nature of the inflammation**

Cellular and molecular studies reveal some similarities and some differences in the patterns of inflammation. In both diseases plasma proteins leak into the intestinal lumen [13] and isolated mucosal mononuclear cells produce similar amounts of interleukin-1 (IL-1) [14].

The proportion of IL-2 secreting cells is said to be increased in the mucosal lesions of CD but not UC [15,16]. This view is not universally held [17]. Possible differences in the production of such a key cytokine are of interest because of the hypothesis, founded on studies in mice, that T helper (Th) lymphocytes can be divided functionally into IL-2 and interferon-gamma (Th1) secreting cells which stimulate cell mediated immunity, and those which secrete IL-3, IL-5, IL-6 and IL-10 (Th2) which augment antibody production. In UC, IL-2 receptor is expressed on mucosal macrophages, whereas in CD it is expressed on T helper cells [18]. Taken together, these observations suggest that activation of T lymphocytes is central to the immunopathogenesis of CD but not of UC. Serum levels of IL-6 are higher in CD than in UC [19], and this may explain why levels of acute phase reactants, such as C-reactive protein, are higher in CD than UC. The cellular source of IL-6 in CD has not been localised.

The number of mucosal IgG-producing cells is increased in both UC and CD, but their sub-class distribution differs. In UC, 80% of the IgG-producing cells contain IgG1; in CD, 66% contain IgG3, and there is also significant increase in IgG2-containing cells (25%) which is not found in UC [20,21].
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IgG and complement components co-localise in the epithelial lesions in UC but, in CD, activated complement is deposited on the luminal surface of the epithelium without IgG [22]. This suggests that complement is activated by the classical (antibody) pathway in UC but possibly by the alternative pathway in CD.

Immunoglobulin extracted from colon affected by UC has been reported to include antibodies to a 40kD colonic protein. This putative autoantigen has amino-acid sequence homology with the cytoskeletal protein tropomyosin [23]. IgG, complement and this 40kD protein co-localise in the epithelium in UC, raising the possibility that complement-dependent epithelial injury in UC is mediated by IgG, anti-tropomyosin autoantibodies [24]. It has been reported that the serum of patients with UC, but not CD, contains IgG which binds to tropomyosin [23]. This autoimmune hypothesis warrants further testing. Another putative autoantibody, anti-neutrophil cytoplasmic antibody (ANCA), has been found to segregate with UC and not CD [25]. ANCA in UC have different specificity to those found in systemic vasculitis.

Conclusion

Although the causes of UC and CD remain unknown, recent studies indicate different epidemiological trends, genetic associations and inflammatory and immunological features. Some of these differences are relative and some require confirmation, but taken together they seem sufficient to distinguish the two diseases. It is possible that further work will allow recognition of subsets of disease within these two groups, particularly in UC.

Usually UC or CD can be assigned according to the criteria tabulated above, though some cases of chronic colitis will remain indeterminate. Occasionally the diagnosis will change (usually from UC to colonic CD) during follow-up. Such cases emphasise the need for review of clinical and laboratory findings in patients with chronic illness. Currently, differentiating between UC and CD enables the physician to discuss prognosis with the patient. With further study, and the development of more specific treatments, the distinction will assume broader therapeutic importance.

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