Chapter 10
Behçet's Disease: Gastrointestinal Involvement

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Introduction

Gastrointestinal (GI) tract involvement in Behçet's disease (BD) was first described by Bechgaard in 1940 [1]. It often leads to severe complications such as perforation or massive bleeding. As such it is a major cause of morbidity and mortality.

Epidemiology

A substantial number of BD patients complain of GI symptoms [2–5], present in at least 50% of BD patients in Japan [2]. On the other hand, GI complaints are rather common in the general population and it is difficult to discern whether a GI symptom in a BD patient is actually related directly to BD. The reported frequency of gastrointestinal Behçet's disease (GIBD) shows wide variation (Table 10.1). There is a list of issues to consider:

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Table 10.1 Frequency of BD gastrointestinal involvement in different studies

References	Country	Year	Number of patients with BD	GI involvement (%)
Shimizu et al.[a] [2]	Japan	1971	?	50
O'Duffy et al.[b] [6]	USA	1971	10	30
Yamamato et al.[a] [144]	Japan	1974	2,031	25
Chamberlain et al.[b] [8]	UK	1977	32	6
Eun et al.[b] [7]	Korea	1984	114	5.3
Jankowski et al.[a] [10]	UK	1992	15	40
Dilsen et al.[a] [9]	Turkey	1993	496	5
Yurdakul et al.[b] [12]	Turkey	1996	1,000	0.7
Gürler et al.[b] [13]	Turkey	1997	2,147	2.8
Bang D et al.[b] [14]	Korea	1997	1,155	4
Bang D et al.[a] [11]	Korea	2001	3,497	7.3
Chang et al.[b] [16]	Korea	2002	73	15
Bang DS et al.[b] [37]	Korea	2003	1,901	3.2
Tursen et al.[b] [18]	Turkey	2003	2,313	1.4
Seyahi et al.[b,c] [15]	Turkey	2003	121	0.8
Yi et al.[c] [19]	Korea	2008	842	15[a]/8[b]

[a] GI involvement diagnosed according to GI symptoms

[b] GI involvement diagnosed according to GI symptoms and endoscopic/radiologic documentations

[c] Pediatric data

1. Practically all the available data about the frequency of GIBD are based on the experience of different and separate clinical disciplines, like gastroenterology, dermatology, etc. This has the potential of considerably over- or underestimating the true frequency.
2. Different reports have used differing diagnostic criteria to diagnose the primary illness. For example, the presence of GI lesions is one of the items in the Japanese criteria [20]. This makes a patient with GI involvement more likely to be diagnosed with BD by the said criteria.
3. It might be said that in order to make a firm diagnosis of intestinal BD, the intestinal lesions must be identified by an objective method. However, in some studies (Table 10.1), the mere presence of GI symptoms has been used to make the diagnosis. For example, one study from Istanbul [12] did not have the specialty bias since it came from a multidisciplinary unit. On the other hand, the authors only considered the GI symptoms in assessing the frequency of GIBD. This was not backed by endoscopy or radiology. A recent Korean study [19] reported that 125/842 (15%) patients experienced GI symptoms and 69 (8%) of these were found to have GI involvement by endoscopic examination. However, even endoscopic observation of GI lesions might not strictly indicate GIBD because of the specificity issues (see section Differential Diagnosis). Furthermore, intestinal involvement may not receive much attention, unless sporadic cases present with severe inflammation, intestinal ulcers, or bleeding. This may seemingly increase the prevalence of GIBD [6, 8, 10], especially in low prevalence countries, where the mucocutaneous cases without GI involvement are more easily missed.

4. Although intestinal BD usually presents with lesions in the small and large intestine, on rare occasions it manifests in the esophagus and the stomach and may not be recognized.
5. Gastrointestinal endoscopic lesions in patients with BD may be explained by other reasons, like non-steroidal anti-inflammatory drug (NSAID) related GI lesions, (see differential diagnosis). This point was paid nearly no attention in previous GIBD prevalence discussions.

Some distinct and reproducible real geographic trends in incidence, however, have been discerned. Despite a high prevalence of BD, intestinal involvement has been reported to be rare in Mediterranean BD patients, ranging from 0 to 5% [12, 13, 21–23]. However, in East Asia, including Korea and Japan, where BD is also highly prevalent, intestinal involvement is relatively common (5–25%) [14, 16].

Data on esophageal involvement are scarce and mostly based on patient symptoms. The quoted prevalence of 11 and 66% is likely to be unduly high [24, 25]. A recent Korean endoscopic survey found the frequency to be quite low (0.7%) [19].

According to two surveys in surgical patients, the frequency of gastroduodenal involvement was reported to be as low as esophageal involvement [26, 27]. However, an endoscopic study in BD patients with upper GI symptoms [19] showed three times more gastric and duodenal ulcers (14%) than esophageal ulcerations (4.7%). NSAID use might at least partially explain these findings. While BD is diagnosed frequently among patients aged 20–30 years [28, 29], the onset of GIBD is in the fourth or early fifth decade [4, 30–32]. On the other hand, no age group is immune [33] and GIBD has even been reported in an 11-month old baby [34]. According to one report, juvenile BD accounts for 3–7% of all cases of GIBD [35]. Interestingly, the rate of intestinal involvement has been reported higher (69%) among Japanese children with BD as compared to that found among the adults (25–50%) [36].

The male/female ratio of GIBD was found 1:1 in one Turkish study [18]. In contrast, studies throughout Korea [30–32] and Japan [26] have shown a slight preponderance for males (1.2–2.0:1). Whether males with GIBD have more severe disease, as is the case for many other manifestations of BD, needs to be further assessed. However, in another Korean study, the frequency of severe GI disease was not found to be similar between males and females [37].

Clinical Manifestations

GI Manifestations

Symptoms of GIBD can vary from mild GI discomfort to more severe symptoms with complications, such as bleeding, fistula, or perforation [2, 21]. The most common symptom is abdominal pain followed by diarrhea, bleeding, vomiting, bowel habit changes, and weight loss. This is similar to what is usually observed in inflammatory bowel disease (IBD) [2, 30–32]. The location and pattern of pain often correlates

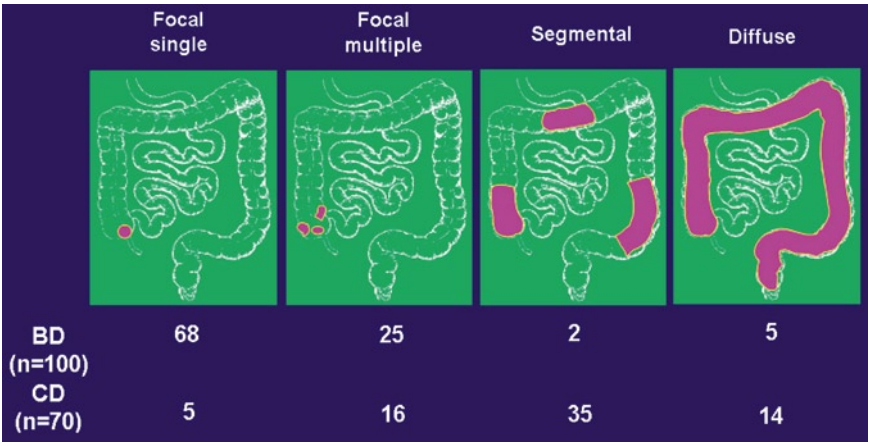

Fig. 10.1 Distribution pattern of lesions in GIBD

with the location of the pathology. As in Crohn's disease (CD), one common pain pattern of GIBD is cramps in the right lower quadrant in patients with ulcers in the ileocecal area. Deep, penetrating ulcers increase the complication rate [21, 26]. Perforating ulcers tend to occur repeatedly, and at multiple sites [17, 38, 39].

GI involvement in BD may affect all areas from the lips to the anus. The ulcers are most commonly found in the terminal ileum and the cecum and less frequently in the colon, sparing the rectum [26, 40]. Less than 15% of cases diffusely involve the colon (Fig. 10.1) [31]. Perianal ulcers, like orogenital ulcers, may rarely accompany GIBD [41]. Bleeding can be life threatening in some patients [42, 43]. The GI manifestations usually appear 4–6 years after the onset of the oral ulcers. Constipation or tenesmus is not usual. Similar to what is seen in other IBDs, the clinical features in GIBD vary considerably over time [44–46].

Esophageal involvement occurs more frequently in males [47], causing substernal pain, dysphagia, and hematemesis. Esophageal lesions are most frequently located in the middle esophagus and are nonspecific. Various other forms of esophageal lesions including erosions, aphthous, linear, or perforating ulcers, widely spreading esophagitis, dissection of the mucosa, varices, and stenosis [19, 48–50] have been reported. Usually, biopsy and cultures are required to differentiate this condition from infectious or malignant conditions. Moreover, involvement may not be correlated with systemic disease activity, disease duration, or any other disease aspect. In more than 50% of the cases, esophageal involvement is accompanied by other GI manifestations, mainly jejunal and ileocolonic ulcers [19]. In addition, rare, serious complications such as stricture, bleeding, fistula, or perforations have been described [51].

The gastroduodenal mucosa appears to be the least frequently involved segment in GI tract. Aphthous ulcers can occur in the duodenum [27]. Differentiating between gastric involvement of GIBD and gastric or duodenal ulcer may be difficult.

Finally, possible involvement of other intra-abdominal organs including liver, pancreas, or spleen, has also been reported [21]. However, it is difficult to say that they are causally related to BD [52].

Extraintestinal Manifestations

Many of these manifestations are shown in Table 10.2. Budd–Chiari syndrome is an important extraintestinal manifestation carrying a grave prognosis [61].

Laboratory Findings

In a prospective study, ESR and CRP showed poor performance as markers of disease activity in patients with complete and possible types of GIBD [62]. Moreover, CRP is not usually markedly elevated in BD in general [63]. Therefore, very high levels of

Table 10.2 Comparison of GIBD and CD characteristics

	GIBD	CD
Extraintestinal involvement [15, 53–55]		
Oral ulcer	100%[a]	20%
Genital ulcer/Genital scar	95%/~60%[a]	4%[c]/No case
Nodular lesion	50%[a]	2–10%
Arthritis	20%	5%
Venous thrombosis	15%[a]	<1%
Eye involvement	45%[a]	3–6%[d]
Neurologic involvement	5%[a]	<1%
Intestinal involvement [26, 40, 56]		
Ileocecal	50–90%	40–60%
Rectal	<1%	10%
Upper GI	1%	5%
Perianal	1%[b]	10–15%
Complications [21, 26, 56]		
Perforation/fistula/stricture	25–50%/5–10%[b]/8%	2%/(20–30%)/17%
Pyoderma gangrenosum	<1%	1–10%
Laboratory assessment [56–60, 145]		
ASCA (IgA or IgG)	28–49%	62–41%
Distribution and endoscopic morphology of intestinal ulcers	Round, focal, isolated	Longitudinal, diffuse segmental
Granuloma (in mucosal biopsy)	<1%	10–15%

[a] Prominently less in females

[b] No anal fistula formation

[c] History based; no real description of typical genital ulcer

[d] Rarely progress to blindness

CRP in a patient with GIBD indicate complications like, stricture, fistula, and abscess formation. These pathologies as well as distinctly high CRP levels, on the other hand, are more common in CD, and can help in differential diagnosis of this condition from GIBD (Table 10.2). A specific laboratory marker that accurately reflects the involvement of the GI tract in BD is yet to be found. It has been proposed that anti-*Saccharomyces cerevisiae* antibodies (ASCA), a well known hall mark of CD [64] could be also high in patients with BD and GIBD [57, 58, 65, 66]. Intestinal tuberculosis, on the other hand, can also be associated with high ASCA levels (I-TBC) [67].

Endoscopic and Radiologic Findings

Radiological and endoscopic findings of GIBD are very similar to what is seen in CD. When intestinal involvement is suspected, colonoscopy is necessary. To identify possible small intestine lesions proximal to the terminal ileum, small bowel barium follow-through or enteroclysis are required. Recently, entire direct small bowel evaluation has been feasible using wireless capsule endoscopy or double balloon endoscopy [68]. A case series showed that capsule endoscopy is also promising in patients with GIBD [69, 70].

Well-demarcated punched-out ulcers, or aphthoid ulcers are the most common lesions of GIBD [31, 40]. The smaller ulcers have been considered histologically and perhaps pathogenetically to be similar to the oral aphthous ulcers [71]. Larger ulcers usually have an oval or irregular configuration. The depth of ulcer penetration varies. Superficial ulcers have occasionally been shown to resolve, but deeper ulcers often extend through the bowel wall [59, 72, 73]. It has been reported that the typical colonoscopic findings in GIBD are single or a few deep round/oval ulcers with a discrete elevated margin in the ileocecal area or anastomotic site (Fig. 10.2) [3, 4, 31]. Although the ulcers are found most frequently in the ileocecal area, they may be present

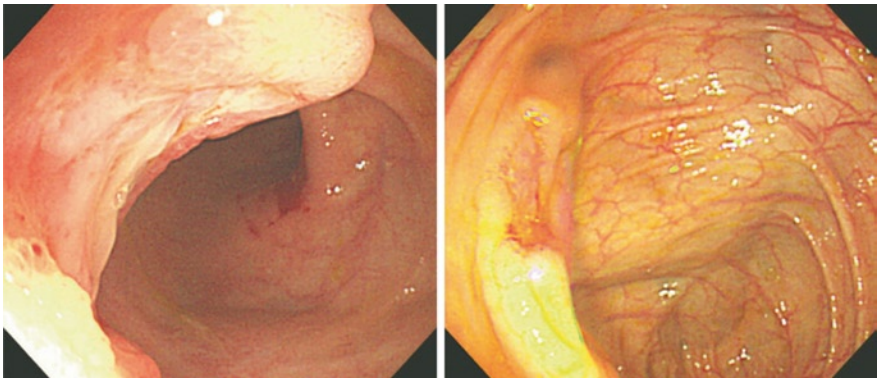

Fig. 10.2 Colonoscopic findings. Single or a few deep round/oval ulcers with a discrete elevated margin are observed in the ileocecal area

at any site throughout the digestive system. Enteroclysis findings among Turkish BD patients with GI involvement showed intestinal ulcerations that were usually shallow, multiple, and commonly localized to the terminal ileum [74]. This contrasted with the findings in the colonoscopic study from Korea, in which large isolated ulcers were more prominently seen [59]. More recently, a 10-year colonoscopy experience from Turkey (Celik, unpublished data), however, is more in line with the Korean data. It might be enteroclysis had overestimated intestinal disease.

Radiological findings of GIBD parallel endoscopic findings. Barium study is useful for demonstrating the characteristic features of BD involving the GI tract, and in determining the extent of these lesions. With barium study, the characteristic radiological findings include single or multiple discrete, collar button-shaped or ring-shaped lesions with considerable thickening of the surrounding mucosal folds (Fig. 10.3) [75, 76]. The double contrast technique is considered to be more valuable in diagnosis.

CT is useful in demonstrating bowel wall thickening and lesions in the extraluminal space. It is recommended for early detection of complications as well as for the exclusion of other abdominal pathologic conditions [77]. Sometimes, GIBD presents as an ileocecal mass, or obstructed and conglomerated bowel loops, requiring surgical resection to differentiate an inflammatory mass from a neoplasm [75].

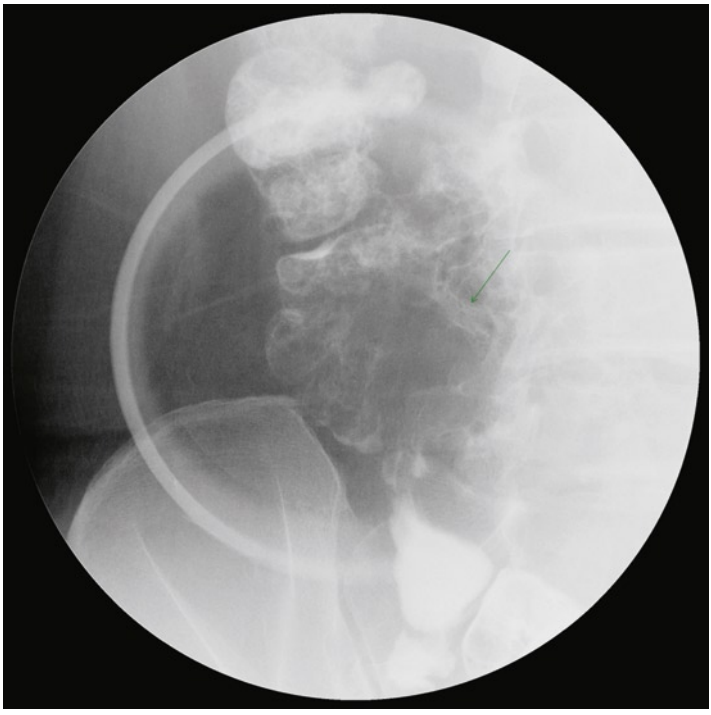

Fig. 10.3 Barium enema findings. About 2-cm sized geographic ulcer is seen at ileocecal valve (*arrow*)

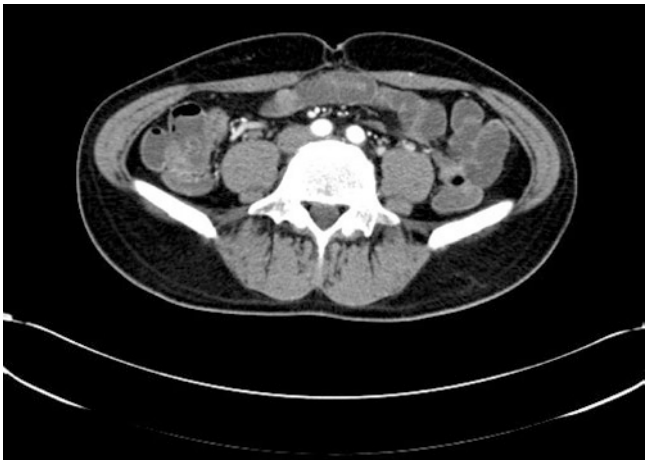

Fig. 10.4 CT enterography shows focal wall thickening involving ileocecal valve and terminal ileum

It is particularly useful in assessing lesions proximal to the ileocecal valve. CT may be necessary and enough tool to localize the lesion before doing barium follow through or enteroclysis, especially in case of obstruction and/or localized abdominal pain companion. Finally, it also helps to assess the possibility of an abscess or perforation.

Although CT and MR enterographies/enterocolysis are promising techniques (Fig. 10.4) in diagnosing of IBD and GIBD, they are not yet in routine use except in some experienced radiology clinics. The abdominal ultrasonography has limited usefulness for bowel evaluation.

Pathogenesis

Immune Abnormalities

Much remains unknown about the pathogenesis of BD and GIBD (see Chap. 14). The GI tract is one of the major ports of entry for a variety of environmental, immune-provoking agents, so one hypothesis is that GIBD represents an intestinal immune response to possible infectious agents. M cells, which are optimized for antigen adherence and transport, play a pivotal role as a portal of entry for potentially pathogenic agents in gut-associated lymphoid tissue [78] and ileal lesions in BD frequently coincide with Peyer's patches [79, 80]. A recent study indicated that TLR (toll-like receptor)-2- and TLR-4-expressing cells accumulated in the intestinal lesions of BD, suggesting that IL-12 produced by TLR-2-expressing cells may contribute to the induction of a Th1-dominant immune response in GIBD. Expression of both TLR-2 and TLR-4 mRNAs was detected in BD intestinal

lesions [81]. A yet unidentified pathogen might stimulate both TLR-2 and TLR-4 in GIBD. Changes in vascular endothelial cells and neutrophil hyperfunction, triggered by signal transduction from TLR-2 or TLR-4 and exemplified by increased chemotaxis and hydroxyl radical production, are thought to be involved in the pathological mechanisms of intestinal BD [82–84]. Adhesion molecules on leukocytes and endothelial cells may also play important roles in pathogenesis [84, 85]. Intercellular adhesion molecule (ICAM)-1 is strongly expressed in the majority of venules with inflammatory changes in GIBD. These LFA-1/ICAM-1 interactions might result in the transmission of neutrophils through the endothelial cells of postcapillary or collective venules [82]. In the active stage, inflammatory cells that are mainly infiltrating neutrophils are found principally in intestinal BD lesions in the absence of infection [26, 82, 86], and histological studies have found neutrophil-mediated vasculitis in the intestinal area [21, 40]. The association of neutrophils with GI ulcer formation or vasculitis has also been convincingly demonstrated in BD. Chronic, persistent hypoxia from the intestinal wall has been implicated as the cause of ulcer formation [21]. The exact underlying mechanisms of abnormal neutrophil hyperactivity are still under investigation and the enhanced spontaneous neutrophil function has been observed particularly in HLA B51-positive BD patients [87]. Moreover, activated $CD8^+$ T cell participation in the pathogenesis of GIBD was reported in a study of peripheral blood lymphocytes [88]. Recent reports have shown that T cell immune responses were skewed toward Th1 dominance in GIBD and Txk-expressing Th1 cells, and suggested that Th1-associated cytokines may play a critical role in the pathogenesis of this disease [89]. Cytokines such as INF-α, IL-12, TNF-α, IL-2, and IL-18 are released by Th1 cells in BD patients. Among these, TNF-α plays a pivotal role in BD, and anti-TNF-α therapy both reduces TNF-α production and modulates the functional activity of Th1 cells. This provides an immunological background for using thalidomide or anti-TNF-α therapy, such as infliximab, in treatment [22].

Genetics

The association of CARD15/NOD2 polymorphisms are well established in CD but not in ulcerative colitis (UC). Two separate studies did not find an association with CARD15/NOD2 variant in BD patients from Turkey [142] and the UK [90]. On the other hand, CARD15/NOD2 polymorphisms were also not found to be associated with CD either, in Turkey [91, 92]. The association of GIBD with the CARD15/NOD2 polymorphism among patients in regions where this association with CD is well established has thus far not been studied.

A possible association has been reported between the development of gastroduodenal ulcers and the A2/B46/Cw1 or A11/B46/Cw1 genotypes in Taiwanese BD patients [27].

Finally, there are two case reports indicating concordance of GI involvement between monozygotic twins [93, 94].

Environment

It has been shown that the cessation of smoking may cause flares in oral ulcers, [95] and nicotine patches reduce their frequency and severity in BD [96]. On the other hand, there is no formal information about the possible effects of smoking on intestinal disease in BD, as is the case in IBD [97, 98].

Intestinal Permeability

Increased intestinal permeability was described in two reports [99, 100]. The relevance of this finding to the disease mechanism remains to be seen.

Diagnosis

The diagnosis of GIBD usually requires two steps: (1) The patient should have BD; (2) Intestinal lesions for which no other explanation can be discerned must be identified. For example, GIBD can be diagnosed if there is a large, typically shaped ulcer in the small or large intestine, and clinical findings meet the BD diagnostic criteria, with the exclusion of infectious enterocolitis, intestinal tuberculosis (I-TBC), CD, and other possible causes, including NSAID colitis. Some GI ulcers in BD patients are difficult to differentiate from those seen in IBD and I-TBC (Fig. 10.5). The latter point is especially important in geographies in which BD and TBC are both common.

To aid in the differential diagnosis, formal guidelines have been proposed. One such set is a consensus-based practice guideline for the diagnosis and treatment of GIBD using a modified Delphi approach, as proposed in Japan (Table 10.3) [101].

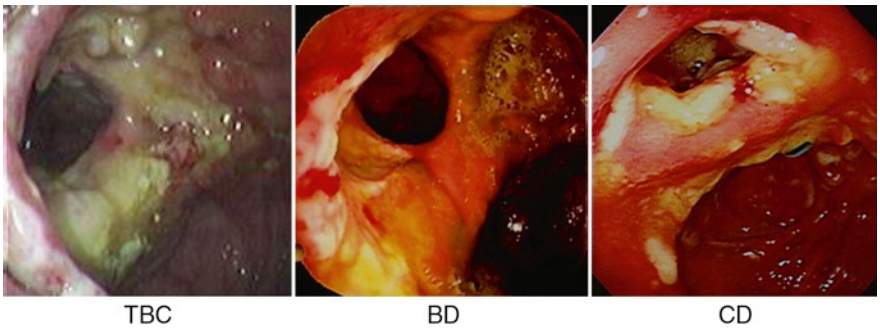

Fig. 10.5 Behçet's disease (BD), Crohn's disease (CD), and Intestinal tuberculosis (I-TBC); they are three similar inflammatory pathology with common ileocecal localization and mostly undistinguishable morphology (From Dr. Çelik's personal archive)

Table 10.3 Guideline statements for diagnosis of intestinal Behçet's disease (Japan)

Diagnosis of intestinal Behçet's disease can be made if: A. There is a typical oval-shaped large ulcer in the terminal ileum, OR B. There are ulcerations or inflammation in the small or large intestine, AND clinical findings meet the diagnostic criteria of Behçet's disease

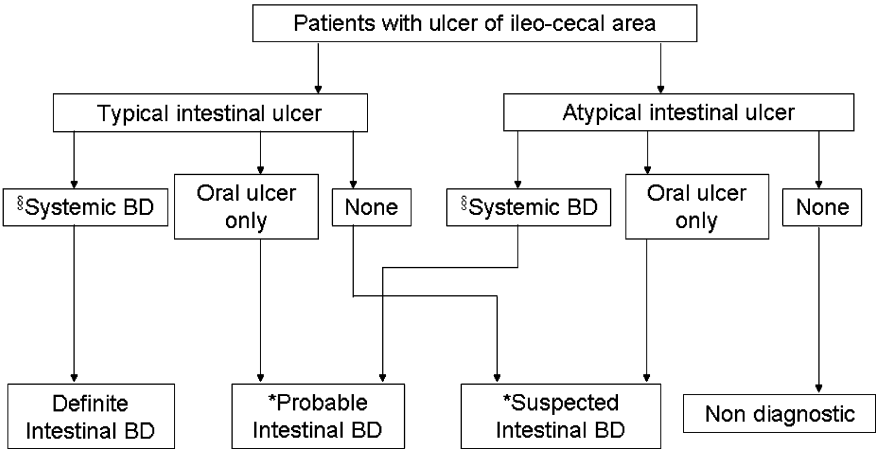

Fig. 10.6 Algorithm for the diagnosis of intestinal Behçet's disease based on the type of ileo-colonic ulcerations and clinical manifestations. *Section*: complete, incomplete, and suspected subtypes of systemic Behçet's disease were classified according to the diagnostic criteria of the Research Committee of Japan. *Asterisk*: close follow-up is necessary

On the other hand, not all patients with GIBD satisfy the systemic BD criteria at the time of colonoscopic evaluation, and systemic manifestations may sequentially develop over a period of many years [102, 103]. Based on this, new diagnostic criteria for GIBD were developed, reflecting temporal changes in systemic manifestations of BD [104]. In this scheme, the patients are categorized into four groups for the diagnosis of GIBD: definite, probable, suspected, and nondiagnostic (Fig. 10.6). The sensitivity for the combined definite, probable, and suspected groups was 99% while the specificity was 83.0%. Further prospective studies with international validation are needed.

Differential Diagnosis

Inflammatory Bowel Disease

IBD and BD may be closely related, and some authors have reported that they are part of a spectrum of diseases rather than distinct disease entities [105]. Both commonly

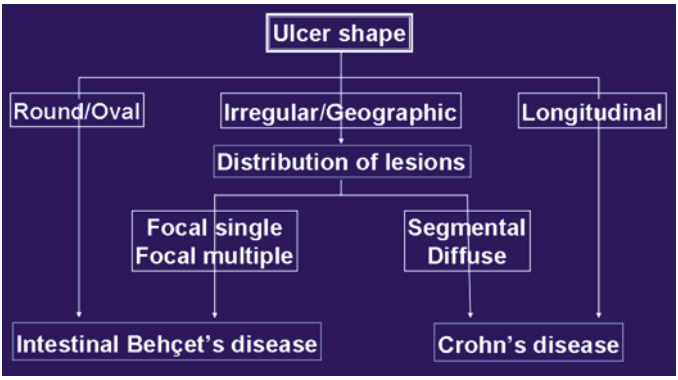

Fig. 10.7 Classification analysis regression tree for the differential diagnosis between GIBD and Crohn's disease

have a young age of onset, nonspecific GI manifestations, similar extraintestinal manifestations, and a chronic, waxing and waning course. GIBD has similar findings with CD in many aspects, including intestinal, extraintestinal involvement, complications, and laboratory parameters (Table 10.2) [53]. It is generally regarded that GIBD has a more guarded prognosis when compared to CD or UC. BD patients with longitudinal colonic ulcers with or without granuloma, more typical of CD, have also been described [106, 107]. Moreover, there are several reports on the coexistence of BD and CD [108]. It is difficult to distinguish whether these patients did in fact have BD or CD with extraintestinal complications, or both BD and CD. UC may also resemble BD with colonic lesions [109]. As mentioned above, rectal involvement is rare in GIBD [56].

In a study from a tertiary dedicated center, both for IBD and BD, the performance of ISGBD criteria [110] was tested in differentiating IBD from BD [53]. The performance of the ISGBD criteria was quite satisfactory, however, whether these results would remain robust in a nontertiary or low BD-prevalent setting needs to be further looked at.

According to a recent endoscopic report, GIBD and CD could be differentiated in more than 90% of the cases by the shape and the distribution patterns of ulcers by endoscopy [56] (Fig. 10.7). A classification tree was proposed as a simple and accurate method for differentiation (Fig. 10.7) [56]. However, lacking of the gold standard for discrimination of both disease may have some influence on the results of this study.

Intestinal Tuberculosis

I-TBC must also be differentiated from GIBD (Fig. 10.5). Patients with I-TBC lack extraintestinal features of BD, and they often have a previous history of pulmonary

tuberculosis. The presence of bowel wall thickening in short segments especially in the ileocecal region, multiple enlarged lymph nodes with central low attenuation or calcification in CT, favor the diagnosis of I-TBC [111]. In suspected cases, endoscopic punch biopsy culture and tissue PCR for *Mycobacterium tuberculosis* help diagnosis.

NSAID (Nonsteroidal Antiinflammatory Drugs) Enterocolitis

Although large series are lacking, case reports and uncontrolled endoscopic cohorts [112, 113] clearly indicate the existence of an NSAID-related enterocolitis. BD patients frequently use NSAIDs for control of arthralgia or arthritis. In a multidisciplinary Behçet's center in Turkey, one-third of BD patients with colonoscopic lesions suggestive of GIBD were decided not to have GIBD [114] in that their intestinal ulcerations healed 2–3 months after stopping NSAIDs. This observation is quite in line with the endoscopic findings in patients under NSAID treatment for other reasons [115]. In the late 1960s and early 1970s, extensive use of flexible colonoscopic procedures, for which the Japanese were the pioneers, made us to recognize NSAID-related lower GI pathologies and ulcerations. Perhaps this was why the reported GIBD frequency from Japan was rather high in these earlier years (Table 10.1).

Simple Ulcer Syndrome

A disease entity has been described with deep discrete, punched-out, ulcerations of round or oval appearance in the ileocecal region, histologically showing nonspecific inflammation [116]. These simple ulcers of the colon, also known as a nonspecific or idiopathic ulcers, is a well-recognized clinical entity showing macroscopic and microscopic similarities to GIBD as well as to CD. Whether GIBD and simple ulcer represent the same disease or separate disease entity is controversial [82, 103, 116]. Simple ulcers, especially in the ileocecal area, at the onset may be followed by the systemic manifestations of either BD or CD suggesting that they might represent incomplete forms of either disease. Because of similar pathology with NSAID's, a careful history is also important.

Malignancy

Infiltrative GI lymphoma involving the terminal ileum with bowel wall may resemble GIBD. However, by contrast enhanced CT, pathological segment of the bowel appears to be much less pronounced in lymphoma [77] than GIBD. Giant, bulky, postinflammatory polyps may occasionally form in the colon and simulate carcinoma. Endoscopy with biopsy is necessary to differentiate these from malignancy.

Other Enterocolitides

Appendicitis or diverticulitis must also be differentiated from GIBD. CT is useful in making this differentiation. In appendicitis, the perienteric or pericolonic infiltration is usually more severe than the changes observed in the bowel wall [77].

Disease Activity Index/Inflammatory Bowel Disease Questionnaire

Even though the clinical disease activity in patients with GIBD fluctuate considerably over time, similar to what is seen in GIBD, there are currently no specific disease activity indexes for GIBD. Some physicians adopt Crohn's Disease Activity Index (CDAI) [44, 45, 101].

The Inflammatory Bowel Disease Questionnaire (IBDQ) is frequently used to evaluate therapeutic efficacy of medical or surgical interventions in patients with IBD [117]. Similar to its use in UC or CD, the IBDQ has been shown to be a stable and useful instrument in assessing health-related quality of life. Similar to what is observed in CD, it strongly correlated with disease activity index, among BD patients in a Korean study [44].

Pathology (See Chap. 13)

Treatment (See Also Chap. 19)

Although usually having an undulating course, GIBD may be intractable, and due to complications, it can be the direct cause of death, as in CD [118]. The goal of management is to treat early to avoid recurrences, surgical procedures, and irreversible damage [5]. No controlled trials are available. Similar to IBD treatment protocols, 5-aminosalicylic acid (5-ASA), immunosuppressives, and biological agents, either used singly or in combination, are the three main modalities of medical treatment [28].

Medical Management

5-ASA or Sulfasalazine

Sulfasalazine or 5-ASA has been shown to be effective in treating intestinal or esophageal BD in some uncontrolled studies and case series [119–121], while it was not reported as effective in others [122]. The therapeutic effects of mesalazine on oral and esophageal ulcers [121] may be explained by the systemic antiinflammatory effect of the active form of 5-ASA in the peripheral blood, which is unacetylated

5-ASA. The usual dose of 5-ASA is 2–4 g/day. When sulfasalazine is used, the optimal dose is 3–4 g/day. Authors agree that unless clinical and endoscopic activity is mild, 5-ASA in GIBD is not warranted.

Glucocorticoids

Glucocorticoids have also been reported to be effective in treating GIBD [28, 109]. They often reduce the size of ulcerations and are used as a first-line drug during the acute phase of the disease. They are usually used in 5-ASA-refractory cases or those with severe systemic symptoms, recurrent GI bleeding, or moderate or severe disease activity. The dosage depends on severity. The initial dose is 0.5–1 mg/kg/day of prednisolone for 1–2 weeks [28]. Intravenous pulse therapy with methylprednisolone (1 g/day) is sometimes used [28]. Dose reduction often results in recurrent symptoms.

Immunomodulators

Immunosuppressive agents are indicated when patients are corticosteroid-dependent or -resistant [4]. Azathioprine, as in IBD, at 2–2.5 mg/kg/day, is the recommended first line agent. In a Korean retrospective study, maintenance therapy with azathioprine had a beneficial effect on the reoperation rate after surgery [30] and the authors recommended that azathioprine be included in the maintenance treatment regimen at least in patients undergoing operations.

Thalidomide

Thalidomide is known to be effective in mucocutaneous BD [123] and IBD [124]. Similarly, a recent Japanese case series reported that seven patients with resistant GIBD achieved complete remission with thalidomide at an initial dose of 2 mg/kg/day [125]. In another case series from Turkey, 4/5 patients with GIBD responded well to this same dose thalidomide [143].

Biological Agents

Several case reports and case series have suggested that infliximab could be useful in inducing [126–129] and maintaining remission in GIBD [130]. To prevent surgery, infliximab should be used before severe or extended intestinal lesions are observed. This strategy is consistent with the results of recent studies in CD and is called top–down therapy [131]. Esophageal ulcer perforation in BD was successfully treated with a simple drainage operation in combination with infliximab [132]. Moreover, infliximab use was reported to treat massive bleeding from an

ileal ulcer in a BD patient [133]. Treatment is usually instituted as outlined for CD, i.e., a 0-week, 2-weeks, and 6-weeks regimen.

Autologous Hematopoietic Stem Cell Transplantation

In two case reports, patients with severe refractory GIBD were successfully treated with lymphocyte-depleted autologous stem cell transplantation following high-dose immunosuppressive therapy [134, 135]. The rationale for this therapy is the assumption that a vigorous immunoablative regimen can delete autoaggressive lymphocyte clones, thus allowing a reset of the immune system.

Endoscopic Therapy

Obstruction and fibrotic strictures rarely occur and can be adequately treated using balloon dilation. GI bleeding is a serious and common complication of GIBD. The spraying of absolute ethanol has been shown to be effective in a case series from Japan [122]. The effect of ethanol is thought to be achieved through the decrease or disappearance of neutrophils or mononuclear cells from ulcer surface.

Surgical Treatment

Surgery is considered in patients who are unresponsive to medical treatment or those with bowel complications such as perforation or persistent bleeding [12]. Optimal surgical procedures and the length of normal bowel to be resected are still controversial. Some reports suggest that a more extensive surgical resection such as hemicolectomy with as much as 60–100 cm of ileal resection is preferable [26, 136]. However, others recommended a more conservative approach, resecting only grossly involved segments of bowel [30, 137], since there seems to be no difference in the rate of recurrences after either modality. Intestinal lesions, usually at the ileocecal area, tend to recur at the anastomosis site, and often require multiple operations because of perforations and fistula formation [72]. Because of mechanical trauma induced inflammation, the pathergy phenomenon might be important here [138]. To prevent this, authors do not agree on the value of short term corticosteroids use [28, 139]. The type of operation, the location of lesion, and the number of ulcers did not appear to be related to the recurrence in one surgical case series [72]. The recurrence rate of intestinal lesions was approximately 50% at 2 years postoperatively [88]. Several types of postoperative recurrence exist, with the most common type being one or two new deep ulcers, followed by multiple aphthous ulcers and enterocutaneous fistulas. Lesions were found at or near the anastomotic

site in 80% of recurrent cases. The usual practice is to examine the bowel during surgery, and bowel resection should include a generous normal resection margin as well as skip lesions. Since preoperative diagnosis is difficult and the recurrence rate is high, postoperative periodic follow-up with endoscopy is strongly recommended, with special attention to the anastomosis site.

Prognosis

The prognosis in GIBD appears to be more guarded than in CD. Medical treatment for GIBD is rather effective in initially inducing remission [140]. This was 67% within 8 weeks in a Korean retrospective survey [140]. In other studies, which included patients with previous abdominal surgery, the initial response rate to medical treatment was lower, 38–46% [30, 88].

The eventual recurrence rates, however, are high. Intestinal lesions recur frequently (25–78%) after medical treatment. In one study, GIBD patients had a poor clinical outcome, with a cumulative recurrence rate of 25% and 43% and cumulative surgery rate of 7% and 15% after 2 and 5 years of diagnosis [140]. According to another Korean study, the overall recurrence rate after successful treatment was 28%; 13% after remission with medical treatment and 50% after surgery [59]. A Japanese survey reported cumulative recurrence rates of 25% and 49%, and cumulative operation rates of 28% and 32% after 2 and 5 years of diagnosis [88]. The cumulative probabilities of reoperation were 18% at 2 years, and 38% at 5 years.

A list of poor prognostic factors have been proposed including, the absence of remission after initial medical treatment and apparent GI symptoms at the time of diagnosis [140]. Furthermore, the shape of intestinal ulcer correlates with prognosis, with typical volcano type ulcers necessitating more frequent surgery [59]. Extensive disease involving the ileum along with the presence of ocular disease and the presence of ASCA were also proposed as poor prognostic markers [65]. The recurrence rates are also relatively high in patients who undergo surgery as a result of perforation or fistula formation.

We do not have much information about the postsurgical follow-up data beyond 10 years. As in other manifestations of BD [141], the GIBD burden may be confined to the early years of the disease course.

Summary

BD commonly involves the GI tract with clinical manifestations similar to those in IBD. Although the true frequency of GIBD is still a matter of debate, it probably is not more than 10–15% in patients with BD. Despite recent advances in diagnosis and treatment, the prognosis remains unsatisfactory.

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