

Gastrointestinal manifestations of Behçet's disease: advances in evaluation and management

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ABSTRACT

Behçet's disease is a chronic, recurrent, inflammatory disorder characterised by orogenital ulcers and skin lesions; serious manifestations also include ocular, large vessel, gastrointestinal and neurological involvement. Genetic and unknown environmental factors customise the wide clinical expression of the disease. Gastrointestinal involvement is not unusual, albeit with a highly variable frequency among different ethnic populations. However, given the fact that gastrointestinal symptoms such as reflux, bleeding, diarrhoea are common in the general population, their clinical significance needs to be carefully interpreted. Apart from mouth the ileocecal area is typically involved, but inflammatory and/or vasculitic lesions may affect any part of the gastrointestinal tract. Complications such as perforation carry high morbidity rates and even mortality. Herein, we review all available information pertinent to gastrointestinal involvement of Behçet's disease and discuss the published advances in evaluation and its empirical management, including anti-TNF biologic therapies.

Introduction

Behçet's disease or syndrome (also referred as Adamantiades-Behçet's disease, ABD) is a chronic, recurrent, multisystemic, inflammatory vasculitic disorder of unknown etiology (1). The wide clinical spectrum of ABD include oral aphthous ulcers, ocular inflammation, skin lesions, genital ulcerations as well as neurological, gastrointestinal, cardiovascular and joint manifestations (2). Any age can be affected, with the highest prevalence at the third decade of life. Both genders may suffer from ABD, although the clinical spectrum and severity of the disease present differences between men and women (2).

ABD is a worldwide disease but has a strong predilection for certain ethnic populations and for certain areas, particularly the Far East, Middle East and the Mediterranean basin countries, where the prevalence of HLA-B5(51) is higher (2, 3). This is explained by the effect of genetic and environmental factors, as it has been shown by the low prevalence of ABD in Germans, the higher prevalence in Turkish immigrants in Germany and the even higher prevalence in Asian Turkey (3), as well as by the absence of ABD among Japanese immigrants in Hawaii and the presence of ABD in Japanese living in their own country (4). Turkey has one of the highest prevalence with 20-420 cases per 100,000, whereas prevalence in Korea, China, Japan, Iran, and Saudi Arabia ranges from 13.5 to 20 cases per 100,000 inhabitants. Western countries present lower frequencies such as 0.64 cases per 100,000 in the United Kingdom and 0.12-0.33 per 100,000 in the United States (5).

ABD has not been categorised yet etiopathogenetically as it "wanders" in the continuum between autoimmune and autoinflammatory disorders (6). Immune-mediated interactions are regarded as key players in the etiopathogenesis of the disease, under the influence of genetic and environmental factors. Polymorphonuclear cell hyper-reactivity, T-cell aberrations, cross-reactivity and molecular mimicry, endothelial injury, autoantibodies and genetic predisposition HLA-B5(51) have been reported (1). Interestingly, HSV-DNA has been detected in intestinal but not oral ulcers in ABD patients (1). Regarding ABD-associated intestinal lesions, a Th1 cell response has been documented recently (7). Moreover, IL-17A, IL-23R, and STAT4 polymorphisms may be involved in the pathogenesis of intestinal ABD (8). Additionally the copy

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number variations of the α -defensin-1 gene may predispose to intestinal involvement (9).

The diagnosis is based on clinical grounds alone, since pathognomonic laboratory findings are lacking. The criteria applied for the diagnosis and classification of the disease have been created by an International Study Group (10). Clinical manifestations can be clustered, *e.g.* acne/arthritis or vascular cluster, highlighting the complex nature of the disease (6). While ethnic and/or geographical differences seem to be responsible for clusters, we could not identify clusters among Greek patients, probably due to the relatively high genetic homogeneity of the population. In a series of 142 consecutive Greek patients, oral ulceration was the most common symptom (89%), while 12.7% experienced intestinal symptoms (11). Herein, we focus on the gastrointestinal involvement in ABD and after describing the relevant clinical manifestations we discuss recent advances in diagnosis and management.

Epidemiology

The most common site affected in gastrointestinal tract, apart from mouth (>90% of cases), is the ileocecal region. Oesophagus, stomach, duodenum, jejunum, and colon may be also affected, while rectal, hepatobiliary and pancreatic manifestations are rather infrequent (Table I) (2, 12, 13). The prevalence of gastrointestinal manifestations varies between different ethnic groups and geographical regions from 30-50% in Far East to <1% in Middle East (3, 6, 14). Such differences confirm the different clinical expression of the disease among countries. Other studies report a prevalence (%) of gastrointestinal symptoms in various countries as follows: Iran, 7.6; China, 8.8; Korea, 7.3; Germany, 12; Turkey, 2.8; Jordan, 20; Lebanon, 10; USA, 8; Spain, 5; and Japan, 16. (2). It is noteworthy that study design, number of patients and inclusion criteria applied, affect the outcome. Moreover, significant differences in the prevalence of gastrointestinal symptoms are reported between patients with and without eye involvement. In a Japanese study 266

of 412 ABD patients presented with eye involvement; interestingly, gastrointestinal symptoms were more frequent by 3-fold in the absence of ocular involvement (19% vs. 6% in patients without or with ocular involvement, respectively) (5). A recent larger study from Korea including 842 patients, reported that 15.3% of them suffered from upper gastrointestinal symptoms (14).

Oral ulcers

The frequency of recurrent oral aphthae during the course of the disease ranges from 90 to 100% of patients (2, 5). Oral aphthous ulcers are also the most frequent initial manifestation of the disease (~70%) that preceded the diagnosis by ~7 years (12, 13, 15). Oral ulcers resemble those seen in other clinical conditions such as recurrent clinical aphthosis (RAS) and Crohn's disease, and the ulcers seen in 25% of otherwise healthy individuals. RAS affects almost 10% of the US population, although prevalence varies among different ethnic groups (16). Single, multiple, large, medium and herpetiform lesions can be seen. Oral ulcers are painful, last for few days, rarely more than one week and only exceptionally leave a scar after healing (Table I) (17). Recurrences are frequent but the number of ulcers can diminish or ulcers can disappear during long follow-up. It has been documented that smoking can decrease the frequency and severity of oral ulcers (18). Oral health has a pivotal role in the development of oral ulcers as well as in the clinical course and severity of ABD (19). As a result, maintenance of oral health has a great impact on the preservation of high quality of life among ABD patients (20). Histologically, vasculitis with infiltration of lymphocytes and monocytes is prominent in new ulcers, whereas neutrophils are prominent in older ulcers. These infiltrates are localised around the blood vessels and are rarely accompanied by fibrinoid necrosis (12).

Oesophageal involvement

Oesophageal manifestations in ABD are quite uncommon (12, 21) (Table I). In the recent Korean study which included 842 patients, oesophageal involvement

was documented in 6 out of 129 patients with gastrointestinal symptoms (4.7%) (14). Another study has revealed oesophageal involvement in 11% (1 out of 9 patients) (22), whereas other investigators have reported a frequency of 66.6% (14 out of 21) with endoscopy, biopsy or manometry, although endoscopy was abnormal in only one patient (4.8%) (23). Oesophageal involvement has also been detected in 1 out of 93 Korean patients with gastrointestinal manifestations (24). In general, oesophageal disease causes ulceration, although the ulcers are diverse and non-specific (14). However, the prevalence of oesophageal lesions is probably underestimated because endoscopic examination is not performed routinely (23). Ulcers, erosions, diffuse esophagitis, perforation and stenosis, although non-specific for ABD, have been reported (21, 23), most often at the middle of the oesophagus (14, 21). Common clinical manifestations of oesophageal involvement include substernal/abdominal pain, dysphagia and occasionally haematemesis (12, 14, 23). These symptoms may also appear in common conditions such as gastroesophageal reflux disease (around 15% prevalence in Western countries and lower prevalence in Asia) (25, 26). Moreover, herpetic esophagitis associated with immunosuppressive therapy may cause the generation of similar discrete ulcers, and therefore should be included in the differential diagnosis (27). However, the majority of patients may be asymptomatic.

Several endoscopic, manometric and histological studies of the oesophagus have been published (14, 22, 23, 28). Endoscopy may reveal esophagitis or ulceration in some patients and manometric studies may show oesophageal motor abnormalities, such as lower oesophageal pressure (14, 23, 28, 29). Most researchers suggest that endoscopy or manometry should not be performed routinely and are only indicated in cases with marked oesophageal symptoms. Although some patients may suffer from upper gastrointestinal symptoms and oesophageal involvement may occur even in asymptomatic patients, oesophageal involvement in ABD is rare (14, 22, 23). Histological examination

Table I. Clinical manifestations and management of gastrointestinal involvement in Behçet's disease.

Site	Manifestation	Symptom	Treatment	Reference
Mouth	Ulcer - aphthous - herpetiforme	Symptomless or painful	Oral hygiene Topical measures with steroids/ antiseptics, colchicine, azathioprine, cyclophosphamide, interferon- α , thalidomide anti-TNF agents	(2, 12, 15, 17, 19, 20, 80, 84)
Oesophagus	Ulcer, erosion, diffuse esophagitis <i>Complications:</i> distention, penetration, stenosis, perforation, fistula	Substernal pain, dysphagia, haematemesis	PPIs, mesalazine, sulfasalazine, steroids, azathioprine, thalidomide, anti-TNF agents, surgery	(12, 14, 21-24, 29, 80, 86, 87)
Stomach	Ulcer, gastritis <i>Complications:</i> pyloric stenosis, Dieulafoy's ulcer	Epigastric pain	? HP eradication sulfasalazine, steroids, azathioprine, thalidomide, anti-TNF agents, surgery	(2, 12, 14, 23, 31, 35-37, 39, 80)
Intestine	Ulcers, mucosal inflammation, ischaemia, infraction <i>Complications:</i> bleeding, perforation, fistula	Abdominal pain, bloating, cramping, diarrhoea, melena, haematochezia, weight loss, indigestion	sulfasalazine, steroids, azathioprine, thalidomide, colchicines, anti-TNF agents, surgery ? methotrexate, clarithromycin, interferon- α , mycophenolate sodium, tacrolimus	(12, 24, 27, 33, 40, 48, 50, 52, 55, 59, 61, 65, 79, 80, 89, 91-101, 105-108)
Hepatobiliary	Budd-Chiari, hepatitis, fatty liver, cholecystitis, primary biliary cirrhosis, abscess		Steroids, immunosuppressives, surgery	(12, 34, 39, 40, 42, 43, 46, 47, 80)
Pancreas	Pancreatitis		Steroids, immunosuppressives, surgery	(12, 39, 40)
Amyloidosis	Type AA	Diarrhoea, malabsorption	Immunosuppressives, colchicine	(12, 39, 40, 110)

reveals non-specific findings consisting of infiltration with neutrophils and lymphocytes, while vasculitis was only rarely seen (21, 23). At the ulcer's base granulation and increased fibroblasts are typically found (14). Similar lesions may be seen in the stomach (30).

Although the complications of the oesophageal involvement are unusual, they may be serious and life-threatening. The most serious complications include perforation, distention, penetration, stenosis and oesophagobronchial fistula formation (12, 14, 22, 29). In the Korean study no patient experienced serious complications such as oesophageal stricture, oesophageal bleeding or oesophageal perforation during follow-up. In the same study it has been shown that total oesophageal ulceration can be single or multiple, shallow or deep, small or large (14).

Gastric manifestations

Gastric involvement in ABD is rather infrequent (Table I). The prominent finding in the stomach is either ulcers or gastritis, with epigastric pain the most common presenting symptom (2, 12, 14, 23, 31). As in the case of the rest gastrointestinal tract, symptoms from

gastric involvement, are not specific and resemble those found in common gastrointestinal disorders such as peptic ulceration and gastric cancer and therefore should be carefully interpreted (25, 26, 32). A study from Taiwan, which included 28 ABD patients, presented a 43% prevalence rate of gastric/duodenal ulceration (31), which is very high compared to other studies. These authors suggested that ulcers are induced by vasculitis and respond well to corticosteroids and immunosuppressant drugs, rather than to conventional H₂-blockers (31). Out of 136 surgical cases from the Japanese literature, gastric/duodenal ulceration was detected in 3 cases (33), whereas Houman *et al.* reported 2 cases out of 21 ABD patients (23). Data obtained from 170 autopsies revealed 15 cases of gastric and 4 cases of duodenal ulcers (34). Similarly, out of 93 patients with gastrointestinal involvement only one was found to have gastric involvement after endoscopy (24). In the large Korean study gastric ulceration was documented in 12 out of 129 patients with gastrointestinal symptoms (9.2%), gastric erosions in 16 (12.4%) and duodenal ulceration in 6 (4.7%) (14).

Rare complications include pyloric

stenosis due to hypertrophy of pyloric ring and Dieulafoy's ulcer due to the developmental malformation of a submucosal gastric ulcer (35, 36). The co-existence of pyloric stenosis, duodenal ulcers and oesophageal ulcerations has been reported in a 43 year-old patient with ABD (30). The gastric pathogen *Helicobacter Pylori* (HP) may induce ulcers in the gastrointestinal tract (37). It has been reported that after eradication of HP, the number and size of oral and genital ulcers as well as other clinical manifestation regressed, although HP seroprevalence did not show significant difference between patients with ABD and controls (37). However, in a more recent study, the eradication rate, endoscopic findings and prevalence of HP were found identical in ABD patients and controls (38). Recent data from Turkey, report similar results and some authors suggest that routine endoscopy and screening for HP infection is not necessary in asymptomatic patients (32).

Hepatobiliary and pancreatic involvement

During the long clinical course of the disease, patients may experience hepa-

tobiliary and pancreatic manifestations (12, 39-41). Budd-Chiari syndrome (BCS), a cause of portal hypertension due to thrombosis of the hepatic veins, is the most common hepatobiliary complication. BCS presents with abdominal pain, ascites and hepatomegaly (40, 42). In a series of 493 ABD patients from Turkey, 14 suffered from BCS, suggesting that BCS is a relatively frequent complication. Additionally, it seems that the portal vein as well as the inferior vena cava are often affected (43). Similar results have also been obtained from analysing the records of 220 ABD patients, who demonstrated that 7 men were diagnosed with BCS (44). Indeed, ABD has been shown to be the third most common cause of BCS (9%) through the prospective study of 75 patients (45). Moreover, ABD clinical course may be complicated by acute and chronic non-viral hepatitis, cholangiolithiasis, cholecystitis, primary biliary cirrhosis and fatty liver (34, 46, 47).

The pancreas is also affected, although rarely. Patients may suffer from acute or chronic pancreatitis, which present with the common clinical signs and symptoms, such as epigastric pain, vomiting and diarrhoea. Therefore other common causes of pancreatic disorders should be excluded before defining ABD as a causal factor (12, 34, 39-41).

Intestinal involvement

Clinical manifestations and complications

Ulceration of the ileocecal region represents the most common gastrointestinal site affected (2). Intestinal ABD may also manifest in duodenum, jejunum, colon and rarely in rectum (13). As shown in Table I, the usual complaints of patients include floating, cramping, abdominal pain, diarrhoea and melena/haematochezia, while weight loss and indigestion are rather infrequent (14, 24, 48). Again, such manifestations should be carefully interpreted as they appear in the majority of common gastrointestinal diseases including diverticular disease, inflammatory bowel disease and colorectal cancer (25, 26). Intestinal manifestations occur generally 4-6 years after the onset of oral ulceration (13, 49). Two forms of in-

testinal involvement have been distinguished: small vessel disease with mucosal inflammation causing ulcers and large-vessel disease resulting in ischaemia and infarction (12). Histologically, ulceration, vasculitis of the small veins with lymphocytic infiltration, chronic ileitis, active ileitis, occasionally eosinophilic ileitis and focal colitis have been reported (40, 50). The histopathological findings together with the clinical symptoms, which may precede the development of gastrointestinal lesions, help in the diagnosis of ABD (51).

In a Korean study, among 94 patients with ABD intestinal involvement, the endoscopic findings were ulcers larger than 1cm (76%), round/oval shaped (77%), shallow (38%), deep (62%) and with discrete margins (80%). Ulcers can be single localised (67%), multiple localised (27%), multisegmental (2%) or diffuse (4%) (48). In another study, which retrospectively analysed the characteristics of 43 patients with intestinal ABD, the location of lesions was as follows: ileocecal (88%), terminal ileum (67%), ileocecal valve (35%) and cecum (67%) (52). Recent data show that an irregular/geographic-shaped ulcer with focal distribution suggests intestinal ABD instead of Crohn's disease (53). A polypoid lesion may show central ulceration (27, 54) Endoscopic findings from one of our patients with intestinal involvement and persistent diarrhoea are depicted in Figure 1.

Intestinal X-ray examination with Barium usually reveals the presence of solitary or multiple discrete ulcers accompanied by thickening of the surrounding mucosa folds (27, 54). In a study, which included 17 patients, enteroclysis revealed intestinal involvement in 12 cases. The most frequent finding was aphthous ulcers (10 cases, 83.3%), while linear ulcerations were reported in 4 patients (33.3%). Pseudopolyp formation was reported in 6 cases and fold thickening in 5 (55). The recently applied capsular endoscopy may also aid the diagnosis of intestinal involvement, as in the case of a 24-year old where small aphthous and pseudopolyp lesions without villi were demonstrated (56). In selected cases of intestinal ABD, complications of endo-

scopic or Barium examination should be avoided and instead CT and MRI can be performed as an alternative (27, 54). In a limited number of cases, identification of the inflammatory site of the intestine can be localised using indium 111 labeled leucocytes (57). The application of computed tomographic enterography (CTE) may be helpful in cases of patients with otherwise unexplained gastrointestinal symptoms, especially those with elevated CRP levels, which cannot be diagnosed with standard diagnostic tests (58).

The number and appearance of intestinal ulcers in ABD patients differ considerably among populations. Multiple shallow ulcers (aphthous ulcerations) located mainly at the terminal ileum were reported in 10 of 12 patients who underwent enteroclysis (55). Comparable results have been also obtained from another group of ABD patients from Turkey (50). On the contrary, the ulcers of patients from Far East are more often solitary, large, deep with distinct borders and are categorised as volcano-type, geographic and aphthous (12, 48, 59). In a study from Korea, single ulcers were reported in 72 and round ulcers in 83 out of 115 patients (53). Furthermore, in the study of Chung *et al.*, out of 93 patients, 62% presented solitary and 57% deep ulcers (24). In other studies from the same area, similar frequencies of ulcers in terms of distribution and morphology have been reported, supporting this notion (48, 59). The differences from these studies reflect the influence of environmental and genetic factors. Interestingly, intestinal permeability is increased as measured by urinary secretion of orally ingested chromium-51 ethylene diamine tetraacetic acid (EDTA) in both ABD and control patients compared to healthy individuals (60).

Severe intestinal complications include perforation, massive haemorrhage and fistula formation (24, 27, 52, 55, 59, 61). Perforation is the most common complication and usually occurs at the ileum and the ileocecal region (48, 59, 61). The depth of intestinal penetrated ulcers varies (48). The exact perforation mechanism of intestinal ulcers remains unclear. However, several risk factors

have been implicated, such as younger age at diagnosis (less than 25 years), history of prior laparotomy, long-term steroid use, volcano-shaped intestinal ulcers, bowel dilatation and the presence of large discrete and excavated ulcers (59). Several studies have shown that intestinal perforation occurs more commonly in the Far East, particularly in Korean patients (33, 48, 54, 59). Patients with massive bleeding due to rupture of arterial aneurysm have also been reported (62). Intestinal bleeding may be also caused by vasculitis of the sigmoid colon and rectum (63). Coeliac disease, toxic megacolon, proctitis with retro-vaginal fistula formation and colon cancer are rare complications (64–68). A case of a 34 year-old man with ulcerative colitis, who subsequently developed ABD, has been reported (69). According to recent data, the majority of patients with intestinal ABD goes into remission or has a mild clinical course at the first 5 years. A smaller number of patients may suffer from relapses or go into chronicity (70). A disease activity index for intestinal disease (DAIBD) which allows the assessment of the disease's severity in a simple manner without the need of endoscopic or laboratory findings has been proposed, although further studies are needed to determine this tool's clinical usefulness (71). In addition, an endoscopic severity model has been introduced in order to link endoscopy and clinical findings. The authors propose that the higher numbers of intestinal ulcers (>2) as well as the presence of volcano-shaped ulcers may predict a more severe disease course (72). Several factors including younger age, higher ESR and CRP levels, lower albumin levels, and higher DAIBD at diagnosis may predispose to a more severe clinical outcome (59, 70). Data regarding serological markers are limited. Anti-Saccharomyces cerevisiae antibodies (ASCA) and the baseline percentage of CD8+DR+ lymphocytes in peripheral blood have been proposed as markers of relapse and aggressiveness (73, 74). Recently the use of anti-alpha-enolase IgM antibodies has been discussed as a putative diagnostic and prognostic factor for intestinal ABD with promising results (75).

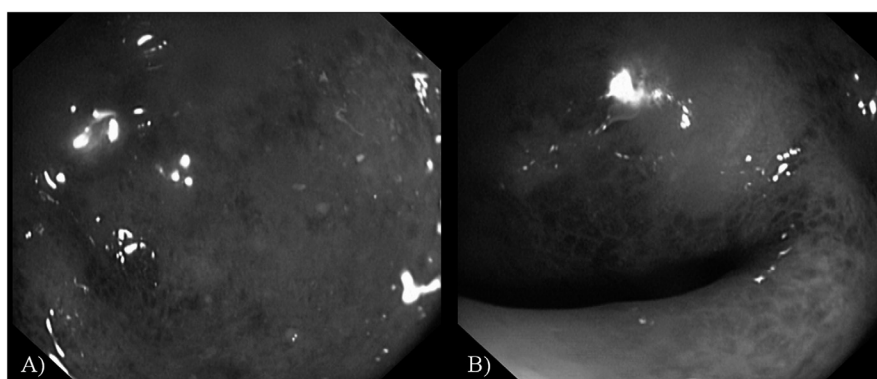


Fig. 1. Diffuse inflammation in colonic mucosa (A) and a shallow ulcer in the middle of inflamed mucosa (B) in a woman with Behçet's disease and persistent diarrhoea.

Similarities and differences between ABD and Crohn's disease

Differential diagnosis of intestinal lesions should include inflammatory bowel disease and particularly Crohn's, Reiter's syndrome, viral colitis and other intestinal diseases (12, 17). Intestinal Tuberculosis, amebiasis and corticosteroid or NSAIDs induced ulcers should be also considered (13). ABD and Crohn's share certain common characteristics such as oral and gastrointestinal ulceration, erythema nodosum, arthritis and uveitis (76, 77). Both conditions may present chronic non-specific inflammation, "skip lesions" and generally spare rectum, which highlights the importance in distinguishing the two conditions (12).

Ulcers in ABD are more likely to be five or fewer, round, focal, aphthous, with normal in thickness intestinal wall and without granulomas. These lesions are deep and are characterised as volcano type. Pseudopolyp formation may also be seen. Scalloping, abscesses, ulceronodular patterns and cobblestone appearance are usually absent. The presence of vasculitis of small veins is characteristic of ABD. On the other hand, ulcers in Crohn's tend to be linear, granular, more than five in number, with irregular/geographic shape and segmental/diffuse distribution. Cobblestoning, fold thickening, abscess formation and bowel thickening with lumen narrowing are frequent, whereas scalloping, fistulas and ulceronodular patterns can also be observed in Crohn's (12, 13, 40, 53, 55). Findings in ABD are usually milder. Enteroclysis and endoscopy are useful tools in our

diagnostic arsenal that can help in determining the diagnosis and the severity of intestinal involvement (13, 53, 55). Saccharomyces cerevisiae has been related to Crohn's for many years. ASCA aid in the differential diagnosis between Crohn's and ulcerative colitis. ABD patients with gastrointestinal symptoms had more ASCA compared to those without intestinal symptoms, although less than in Crohn's (77), but serological testing for ASCA in Greek patients did not reveal any correlations (78). Recent evidence suggests that the long term clinical course and postoperative outcome of Crohn's and ABD follow a similar path (74).

Management of gastrointestinal manifestations

In 2007 three groups of Japanese gastroenterology specialists developed consensus-based practice guidelines for diagnosis and treatment of intestinal ABD by using a modified Delphi approach (79). More recently, a task force from the European League Against Rheumatism (EULAR) has published evidence-based recommendations for the management of ABD, including the involvement of the gastrointestinal tract (80, 81). In general, all therapeutic approaches in these patients should be tailored by taking in account age, gender, severity of mucocutaneous and joint involvement, as well as the presence of large vessel and organ involvement (76). The proposed management of gastrointestinal ABD is summarised in Table I.

The result of treatment for oral ulcers is often difficult to judge, as the disease is

subject to spontaneous transient remissions (17). Symptomatic and empirical treatment is suggested, but it remains unsatisfactory due to the uncertainties about the underlying etiopathogenesis and the lack of well-controlled clinical studies. Therefore, effective treatment remains elusive (12, 82). Mouth-washes with local steroid preparations, lidocaine gel and chlorhexidine are regarded as the first line medication (17, 80). Mouth-washes with sucralfate suspensions have also been used (83). Oral hygiene should be ensured in any case as it affects both the development and severity of oral ulcers and concomitantly the quality of patients' life (19, 20, 80, 83). Additionally, dental and periodontal care seems to be beneficial in the long-term as it is related with the reduction of oral ulceration (84). The administration of colchicine or minocycline may offer some relief. In resistant cases, azathioprine, cyclophosphamide, interferon- α , thalidomide and other immunosuppressive drugs, can be tried. In cases of severe and resistant oral manifestations anti-TNF agents administration may relieve the symptoms and sustain remission (80, 81, 85).

In cases of oesophageal involvement the use of proton pump inhibitors, mesalazine, corticosteroids and colchicine may prove helpful (14, 86, 87). Gastroduodenal lesions may prove resistant to conventional ulcer approaches against ulcers, whereas corticosteroids may slow-down healing. HP eradication has been shown to reduce genital and oral ulceration (12, 37, 39). Other authors however suggest the use of corticosteroids and immunosuppressant instead of conventional H2-blockers (31). The treatment of hepatobiliary and pancreatic involvement includes steroids and immunosuppressives (12, 39, 40, 80).

Currently there are no controlled trials in ABD patients with intestinal manifestations and treatment is in general empirical. The relapsing-remitting natural history and specific therapeutic approaches, *i.e.* corticosteroids that prolong healing but provoke perforation, complicate the evaluation of efficacy (12, 39). The high resemblance of ABD with Crohn's disease is in accordance with the effectiveness of similar thera-

peutic approaches (76). Complications such as perforation require emergency surgery, which however is characterised by high recurrence and reoperation rates in the long-run (40, 80, 81). With the exception of emergencies, conservative therapy should be tried initially (80, 81). Conservative treatment may include daily sulfasalazine (up to 4 gr), prednisolone (up to 1mg/kg), azathioprine (up to 200mg), and probably colchicine (24). The dose of those drugs can be tapered according to clinical and laboratory improvement.

The administration of 5-aminosalicylate (5-ASA) or sulfasalazine may be used as a maintenance therapy of intestinal ABD. Several factors such as younger age at diagnosis, high CRP levels, and high DAIBD score could determine patients with high risk of poor response to 5-ASA/sulfasalazine and relapse (88). Alternatively, azathioprine could be used in maintaining clinical remission. Similarly younger age at diagnosis, low haemoglobin levels, and history of surgery could predict a worse clinical outcome (89). Colchicine and corticosteroids should be administered with caution in the treatment of enteric ABD because it may induce intestinal perforation and worsen the pancreatitis (33, 90). In a survey from Japan, intestinal perforation was reported in 41% of patients (28 out of 68) with a clinical history of steroid administration, whereas in 33% (5 out of 15) in those not treated with steroids (33).

Response to Anti-TNF therapy

Relevant published data exist mainly from case reports or small series of patients with refractory or life-threatening disease that responded well to TNF inhibition, especially infliximab and adalimumab (65, 91-101). The majority of patients manifested abdominal pain, bloody diarrhoea, nausea, anorexia, weight loss, whereas colonoscopy findings included deep ulcerations, mostly in the ileum. Symptoms resolved rapidly after infliximab administration and colonoscopy confirmed remission.

Data from a prospective study assessing anti-TNF agents for severe intestinal involvement report that all 10 patients who failed to benefit from corticoster-

oids responded directly to infliximab monotherapy, and presented long-term amelioration of abdominal CT and colonoscopy findings (102). In a series of Japanese patients, the combination of methotrexate with infliximab resulted in long-term alleviation of intestinal inflammation and was associated with excellent tolerability (97). Interestingly a patient with ankylosing spondylitis developed intestinal ABD despite being treated with adalimumab. The addition of steroids and azathioprine led to clinical remission (103).

Overall, results are promising; however larger studies are clearly needed. In the Japanese consensus statement for the management of intestinal ABD the anti-TNF monoclonal antibody infliximab was considered as experimental therapy (79). More recent data suggest that anti-TNF therapy is indeed highly beneficial in difficult patients (80, 81, 85, 97). Proposed criteria for selecting patients with ABD eligible for anti-TNF treatment apply in case of failure of two immunosuppressive agents and prednisolone requirement at a dosage $>7.5\text{mg/day}$. (104). In refractory isolated cases the administration of low-dose clarithromycin in combination with 5-ASA (105), interferon- α (coexistence with acute myelitis) (106), mycophenolate sodium (107) or tacrolimus (108) has proven beneficial.

Surgical approaches

Surgical intervention is an alternative therapeutic measure, mainly for the treatment of complications, such as perforation. Recent data revealed that a subset of patients with acute intestinal symptoms may benefit from a surgical approach as initial treatment (109). Two forms of intestinal perforation have been reported: localised and diffuse (33). In the Japanese literature, the interval between the initial diagnosis of ABD and laparotomy for intestinal ulcers ranged widely, from one month to 30 years with a mean of 6.6 years (33). Recurrences of intestinal ABD are not unusual and the cumulative rate has been documented as 24.9% at 2 years and increased to 43.0% at 5 years, while the cumulative rate for surgery has been reported as 6.7% and 15.1% at 2 and 5

years after diagnosis, respectively (24). Intestinal perforation is a severe complication. The indications for surgery include acute abdominal pain, intestinal obstruction, intractability to medical treatment, perforation, bleeding, fistula formation and abdominal mass (24, 52, 90). In a Japanese study, 13 patients out of 108 (12%) died and 6 of these died after the operation for recurrent ulcers (33). Immunosuppressive therapy, which is initiated earlier before surgery, may diminish complications and relapse after surgery (89). Maintenance conservative treatment in patients who underwent operation should include azathioprine at least (52).

Conclusion

ABD is a chronic, recurrent, inflammatory disorder characterised by orogenital ulcers, skin lesions, eye involvement, vasculitis, gastrointestinal, musculoskeletal and neurological manifestations. ABD is classically seen in the "ancient silk route", although its prevalence has spread worldwide. Immunological aberrations under the influence of unknown environmental factors and genetic background are involved in the pathogenesis of the disease and are responsible for the wide spectrum and ethnic differences of clinical manifestations. Recurrent oral ulcers are the hallmark of the disease. The remaining gastrointestinal tract is not frequently affected. However, intestinal involvement is a serious complication and perforation is not unusual and requires emergency surgery. It is crucial to highlight the importance of the careful interpretation gastrointestinal manifestations in these patients, as they resemble the clinical presentation of various other common gastrointestinal disorders, including gastroesophageal reflux disease, peptic ulceration and colorectal cancer. ABD should be included in the differential diagnosis of intestinal infections, intestinal tuberculosis and inflammatory bowel disease, especially Crohn's. ABD and Crohn's share common clinicohistological and endoscopic findings but ABD ulcers are more likely to be round/oval with focal distribution whereas in Crohn's are longitudinal with segmental or dif-

fuse distribution. The prognosis of gastrointestinal involvement is not grave, but complications may occasionally be lethal. Current therapeutic approaches are empirical due to the absence of controlled trials. Patients who do not respond to sulfasalazine, corticosteroids, azathioprine, and/or thalidomide may benefit from anti-TNF treatment which should be always tried before surgery.

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