

Gastrointestinal manifestations of Behcet's disease

Behçet hastalığının gastrointestinal belirtileri

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ÖZET: Yukarıda Behçet hastalığının gastrointestinal komplikasyonları özetlenmiştir. Ayrıca entero Behçet ile karışabilecek hastalıklar tartışılmış ve özellikle de Crohn hastalığı üzerinde durulmuştur.

Anahtar Kelimeler: Behçet hastalığı, Crohn hastalığı, ülseratif kolit, amibik kolit

SUMMARY: The above is a summary of the gastrointestinal findings in Behçet's disease coupled with a discussion of those disease that can be mistaken for enteric Behçet's in individual cases. The important differential points between Crohn's disease and Behçet's disease are presented

Key Words: Behçet's disease, Crohn's disease, ulcerative colitis, amebic colitis

FOLLOWING the initial description of Behçet's disease as a disease characterized by recurrent oral and genital ulcerations and ocular involvement (1), many additional clinical features have been recognized as components of the disease (2-4). It is now accepted as a multisystem disorder of unknown etiology in which the vascular, neural and gastrointestinal systems are involved such that specific manifestations of vascular-Behçet's, neuro-Behçet's, and entero-Behçet's can each be identified.

The etiology of Behçet's disease remains obscure. It is considered to be an autoimmune disorder principally because vasculitis is recognized as a basic component of the pathologic lesions present within affected tissues. In addition to a cryptogenic vasculitis occurring as a consequence of a viral disease (5), an abnormality in neutrophil chemotaxis, altered cell mediated immunity (6), streptococcal infection (7) and endothelial cell dysfunction (8) have each been postulated as playing a potential pathophysiological role in the disease process. Circulating autoantibodies to human oral mucosa have been in half the cases and a familial predilection for the disease has been reported (9).

Although the disease is relatively rare in western countries, Behçet's disease is relatively common in individuals of Mediterranean and middle eastern decent and in Japan. The HLA-B5 (W51) alloantigen has been found to be present in as many as 69% of cases. Thus the relative risk for the di-

sease, in the presence of HLA B5, is 3.8 for Caucasians. The presence of HLA B5 in a Japanese individual increases the risk of having Behçet's disease 12.4 fold (10).

In addition to recurrent oral ulcerations, a diagnosis of Behçet's disease requires two of the following additional findings: 1) recurrent genital ulcerations resembling the oral ulcers; 2) eye lesions consisting of an iritis, posterior uveitis, retinal vessel occlusion, and/or optic neuritis; 3) skin lesions consisting of a folliculitis, erythema nodosum, an acne-like exanthem or a superficial migratory thrombophlebitis; 4) a positive pathergy test which is a nonspecific inflammatory skin reaction to a scratch or intradermal injection of saline (11).

The laboratory findings present in Behçet's disease are nonspecific parameters which document the presence of inflammation and consist of a leucocytosis, elevated sedimentation rate and C-reactive protein levels. The most dependable serologic test for Behçet's disease is the finding of autoantibodies to oral mucosa, which is present in nearly 50% of cases (12). Although Behçet's disease is a multisystem disease, this review will focus only on the gastrointestinal manifestations of the disease.

Gastrointestinal manifestations of Behçet's disease:

I - Oral Involvement

Oral ulcerations typical of Behçet's disease occur in almost every case. Thus, they are a sine qua

non for thi diagnosis. They can be located anywhere in the oral cavity. The ulcers are painful and often make swallowing difficult. Typically, they are 2 to 10 mm in diameter, round or oval in shape, shallow, but can be deep, and have a central yellowish necrotic base. Oral ulcers are usually the first manifestation of the disease but rarely may appear as the second sign of the disease. The oral ulcers can be either single or multiple and persist for 1 to 2 weeks. Interestingly they heal without leaving a scar. Although both the oral and genital ulcerations are characteristic in appearance, similar lesions can be seen in patients with other diseases such as inflammatory bowel disease, and systemic lupus erythematosus. Thus, they are not pathognomonic of the disease. Moreover, the oral ulcers of Behçet's are indistinguishable from conventional recurrent aphthous ulcer. In a study of 38 patients with Behçet's and 38 control with recurrent aphthous ulceration (13). The patients with Behçet's reported an increased number of multiple ulcers and involvement of the soft palate and oropharynx as compared to the control with aphthous ulcers. Thus, the number and location, site of the oral ulcers may be a diagnostic feature of Behçet's disease.

II - Esophagus

According to accumulated available data, esophageal involvement is not a common phenomenon in individuals with Behçet's disease. Its presence is reported to vary from study to study having a range extending from 2% to 11%. These figures probably underestimate the real incidence because unless the esophageal lesions are clinically manifest as odynophagia or dysphagia, patients with Behçet's disease do not undergo endoscopic examinations and the lesions remain undiscovered. In studies where endoscopy has been performed, a parallelism between the presence of oral ulcerations and esophageal lesions has been reported.

The following esophageal lesions have been reported in patients with Behçet's disease: 1) linear, oval or round ulcerations similar to those present in mouth (14,15); 2) ulcers communicating (fistula) with adjacent organs such as the trachea (16); 3) luminal strictures, 4) a pseudomembranous esophagitis (17,18,19) "downhill" or classical esophageal varices associated with either superior vena caval obstruction or portal hypertension due to portal vein thrombosis (20,21). Esophageal ulceration when it occurs in cases of Behçet's disease is

often associated with ulcers in other parts of the gastrointestinal tract such as the stomach, ileum or colon (14,22)

III - Stomach

The most common gastric lesions of Behçet's disease consist of aphthous ulcers (4,14,19). As compared to other parts of the gastrointestinal tract, the gastric mucosa appears to be the least frequently involved part of the gastrointestinal tract. In a study of 163 autopsied cases of Behçet's disease, only one individual was found to have gastric lesions.

IV - Duodenum

Aphthous ulcers can occur in the duodenum of individuals with Behçet's disease. When present, these ulcers are remarkably resistant to medical therapy (14,23). In two relatively large autopsy series (4,9), a total of 6 patients with Behçet's disease were found to have duodenal ulcers. Two cases of duodenal involvement in living patients with Behçet's disease have been reported (14,23). The first case complained of vomiting, epigastric pain and diarrhea (23). One year of medical treatment for acid peptic disease in addition to the treatment used for Behçet's disease failed to heal the ulcers. Ultimately a gastrojejunostomy was carried out. An almost similar second case has been reported by Ozenc *et al* (14). In the case reported by Özenc *et al*, the Behçet's disease was complicated by gastric outlet distention. In both of these cases of duodenal involvement, although gastric emptying abnormalities were well documented in both, no duodenal deformity was seen unlike the situation one routinely seen in cases of pyloric stenosis associated with chronic duodenal ulcer disease.

V - Intestine

The small intestine is the most frequently involved extraoral part of gastrointestinal tract involved in cases of Behçet's disease. The intestinal lesions are ulcer-like. Two types of ulcers occur in the small bowel: localized and diffuse ulcers. In a study of 136 cases subjected to surgery (4), 114 had localized ulcers. The terminal ileum was involved in 50, the ileocecal region in 39, and the cecum in 14. These three sites represented 76% of the total cases with intestinal involvement. Multiple localized ulcers were found in 81 cases (73%). The remaining cases had diffuse ulcers localized primarily in the ileum. Deep penetration or overt

perforation was noted in 56% of the cases. The more ulcers an individual had, the more likely a perforation was likely to be found.

The intestinal manifestations of Behçet's disease appear to be more common in Japan than in other countries (4,24). Although the incidence of Behçet's disease is greatest in the third decade of life, the incidence of intestinal ulcers requiring surgery in cases of Behçet's disease is greatest in the fourth decade. However, of the seven cases of intestinal Behçet's disease seen at Hacettepe University, the patients were relatively young with an age range of 21 to 35 years (25). According to Kasahara et al (4), the interval between the initial diagnosis of Behçet's disease and a laparotomy for intestinal involvement ranges from as short a period as one month to as long as 30 years, with a mean of 6.6 years. The abdominal complaints leading to surgical intervention were abdominal pain (92%), abdominal mass (21%) and/or melena (17%). Usually multiple ulcers were found in the terminal ileum and cecum. However, all parts of gastrointestinal tract from the mouth to the rectum were reported to be involved in individual cases. 22% of cases of Behçet's disease develop appendicitis-like symptoms during the course of their disease which leads to a laparotomy (26).

Intestinal ulceration in Behçet's disease is characterized by penetration to the serosa and a ring of edema around the ulcer margin which can appear as a target lesion in small bowel radiologic studies. Because the inflammation is transmural and extends to the serosa, a serositis suggesting peritonitis or an acute abdomen characterizes small intestinal involvement with Behçet's disease clinically. It is believed that there is a regional differences in intestinal involvement when compared Turkey (527) with Japan (24).

VI - Large intestine

Colonic involvement either alone or occurring in combination with other parts of the intestine, particularly the terminal ileum, is relatively common in Behçet's disease. The most frequently involved part of the colon in Behçet's disease is the cecum. A review of the Japanese literature by Baba (24) reported 49 cases of intestinal Behçet's disease, to which they added 5. Of these 54 cases, 20 involved the terminal ileum alone, 22 involved the terminal ileum plus some part of the colon, and the remaining 12 were limited to the colon. Interestingly, none involved the rectum. In a second study from

Japan (4), the most commonly involved area ultimately leading to surgical intervention was the ileocecal region.

Rectal disease in Behçet's disease is exceedingly rare. Hamza (28) reported six cases of Behçet's disease with rectal involvement with clinical and histopathological features of ulcerative colitis. However the rest of the colon in their 6 cases was normal. Boe et al. (29) have reported that when the rectosigmoid is involved in cases of Behçet's disease, the sigmoidoscopic picture can not be distinguished from that of idiopathic ulcerative colitis.

Focal colitis has been documented in colorectal biopsies obtained from the patients with Behçet's disease but without evidence of rectal involvement demonstrable by either endoscopic or radiologic examination (30). The focal nature of the colorectal involvement has been documented in a series of 7 cases, who subsequently underwent surgical resection (25). No evidence of ulceration was seen macroscopically in the resected colon or rectum but was evident histologically as a patchy focal colitis characterized by the presence of crypt abscesses, submucosal fibrosis and an accompanying inflammatory reaction but an intact mucosa.

VII - Pancreas

Abdominal symptoms consisting of epigastric pain, vomiting, flatulence, diarrhea and constipation are common in active Behçet's disease. These symptoms are usually attributed to intestinal involvement. Only one case of acute pancreatitis in a patient with Behçet's disease has been reported (31). However, Lakhanpal et al. have reported the pathologic features of pancreatitis in a large Japanese autopsy registry of subjects with Behçet's disease (19). Specifically, they reported five cases of histologic pancreatitis in a total 170 cases. Unfortunately, they did not report the preterminal clinical features of these 5 cases. Whenever a patient with Behçet's disease develops features consistent with either acute or chronic pancreatitis, other etiologic factors for pancreatitis such as gallstone, alcohol, trauma, hyperlipidemia and an infectious disease process should be ruled out before accepting the case as being related to Behçet's disease. Nonetheless as vasculitis is considered to be the unifying pathological process in Behçet's disease and since the vasculitis predominantly involves the veins and capillaries rather than arteries, a vasculitis leading to pancreatitis would not be

particularly surprising in cases of Behçet's disease. Nonetheless, incidence of pancreatitis in cases of Behçet's disease complaining of abdominal pain is currently unclear and is probably underestimated using current sonographic and CT scan techniques. Biochemical evidence of pancreatitis can occur in the absence of either sonographic or CT Findings and is relatively common in cases of Behçet's disease.

VIII-Liver

The most common hepatic complication of Behçet's disease is the Budd-Chiari syndrome (32,33) which is characterized by venous outflow obstruction of the liver usually as a result of thrombosis of the hepatic veins. Because vasculitis is a major clinicopathologic component of Behçet's disease, it is not surprising that hepatic venous involvement and the Budd Chiari syndrome occurs more often than expected in cases of Behçet's disease (21,33). It is not currently clear whether the liver parenchyma is directly affected by the vasculitic disease process of Behçet's disease as no such lesions have been reported. However, one case report (34) of an individual with small bile duct inflammation resembling small-duct primary sclerosing cholangitis has been reported and may represent such a case. The Hacettepe University experience consists of 14 patients with Behçet's disease and the Budd-Chiari syndrome. In countries such as Turkey where Behçet's disease is relatively common, Behçet's disease is frequently associated with the Budd-Chiari syndrome and is often the most frequent cause of the Budd-Chiari syndrome (32). The major determinant of survival in cases of Behçet's disease and the Budd-Chiari syndrome is the extent of the venous thrombosis extending from the hepatic veins into the adjacent inferior vena cava (21).

IX - Peritoneum

Because intestinal ulceration occurs in cases of Behçet's disease, it is not clear whether the peritoneal lesions seen in cases of Behçet's disease represent a consequence of Behçet's disease per se or are secondary to one or more microscopic perforations (4,25). Because the intestinal ulcers occurring in Behçet's disease are small, deep and

multiple, perforations when they occur are typically localized whereas the peritonitis secondary to other disease such as diverticulitis can be diffuse. Abdominal pain, vomiting and diarrhea when

seen in case of Behçet's disease cannot be attributed easily to peritonitis. Lakhanpal *et al* (19) noted 15 cases of peritonitis from their total of 170 cases of Behçet's disease that were autopsied.

X - Intraabdominal Vessels

a) Arterial Involvement : Saccular and fusiform arterial aneurysm of medium sized arteries as well as arterial occlusions, stenoses, and arteriovenous fistula have been reported in cases of Behçet's disease (32,35,36). Although rare, hepatic artery arteritis (35) and aneurysmal thrombosis with occlusion of the superior mesenteric artery leading to either intestinal infarction or intestinal perforation (37) have been reported in cases of Behçet's disease.

b) Venous Involvement : The most frequently diseased intraabdominal vein in cases of Behçet's disease is the inferior vena cava. Thrombosis is the major finding. A underlying vasculitis is the principal reason for the venous thrombosis (32). Hepatic vein thrombosis leading to a Budd-Chiari syndrome is also relatively common in Behçet's disease (32). Although rare, portal vein thrombosis with cavernous transformation have been reported in 6 cases with Behçet's disease by Bayraktar *et al* (21).

Differential Diagnosis of the Gastrointestinal Manifestation of Behçet's Disease

a) Crohn's disease : The intestinal ulcers of Behçet's disease are characterized by an absence of granuloma, a pathologic hallmark of Crohn's disease. The most characteristic pathologic feature of Behçet's disease is the finding of deep intestinal ulcers associated with a vasculitis, usually a venulitis. In cases of intestinal Behçet's disease, fistula formation and intestinal perforation tend to occur early in the course of the disease as compared with Crohn's disease. Moreover free perforation is rare in cases of Crohn's disease but can occur in Behçet's disease.

b) Ulcerative colitis : The colonic disease of Behçet's disease consists of deeper ulcers than those of ulcerative colitis. In colonic Behçet's disease, the ileocecal region is the most frequently involved colonic site. In contrast, in ulcerative colitis, the disease usually starts at the rectum and moves toward the right colon.

c) Steroid ulcers : The intestinal ulcers of Behçet's disease differ from steroid induced ulcers

Table 1. Comparison of the ulcers of three diseases

<i>Means</i>	<i>Intestinal BD</i>	<i>Crohn's disease</i>	<i>Ulcerative colitis</i>
Endoscopic			
Aphthoid ulcer	+++	-/+	+
Deep round or oval ulcers	+++	0	+
Long swallow ulcers	+	+	+
Skip area	++	-/+	0
Radiologic			
Well-defined deep ulcer	+++	0	0
Skip area	+++	++	0
Fistula formation	++	++	0
Diffuse involvement	0	+	+++
Histologic			
Granuloma	0	+++	0
Vasculitis, venulitis	+++	+	0
Localization			
Ileocecal valv	+++	+++	+/-
Rectum	+/-	+/-	+++
Recurrence after surgery	+++	+++	0
Free perforation	+	+/-	+
Malignancy	0	+/-	+++

Note: 0 = never; +/- = rare; + = occasional; ++ = frequent; +++ = characteristic

According to their data, the principal lesion is an ovoid or geographic ulcer having a mean diameter of 2.7 cm. The ulcers existed as an isolated lesion in 15 cases and were multiple in 5. Of the six resected specimens, the ulcers were found to extend to the submucosa in three, the muscle layer in one, and the serosa in two. The ulcers were localized to the ileocecal area in most cases and extended to the ascending colon in 7. Cecal deformity with incompetence of the ileocecal valve was seen in 19 on barium enema examination. Thickening of ileal folds was present in 12. Six cases with an apparent ileocecal area and are deep. They can be single or multiple and vary markedly in appearance (Table 1).

The characteristic radiologic findings of upper gastrointestinal Behçet's disease is a deep ulcer mimicking either a gastric or duodenal ulcer (24). Pylori stenosis without duodenal deformity is also common. In addition, multiple aphthoid ulcers and occasional longitudinal ulcers have been demonstrated with double-contrast examinations of the proximal gastrointestinal tract.

Crohn disease, ulcerative colitis, cecal tuberculosis, cecal amebiasis and malignant as well as benign tumors of the cecal area need to be differentiated from intestinal Behçet's disease radiologically. The ulcers of intestinal Behçet's disease tend to be larger and deeper than those of Crohn disease. Furthermore, the presence of longitudinal ulcers, a cobblestone appearance, stricture formation, and fistule are frequently identified in patients with Crohn disease and occur less often in cases of intestinal Behçet's disease. In colonic Behçet's disease, the haustra are preserved and the ulcers are more focal than that occur in ulcerative colitis. moreover, the disease in Behçet's is proximal rather than distal. The converse is true for ulcerative colitis. Finally the endoscopic appearance of colonic Behçet patients is one of multiple aphthoid or small ulcers with preservation of the haustra which is rare in ulcerative colitis (43,44).

The clinical features, distribution and radiologic findings of amebiasis are similar to these of intestinal Behçet's disease. Furthermore, amebiasis is frequently localized to the terminal ileum and cecum and is complicated by the presence of a

chronic intramural lesion (amebomas). In chronic cases of amebiasis, the cecum is involved in 90% of cases. On barium enema amebiasis is characterized by a fine granular, irregularity of the bowel margins as well as "collar-button" or undermining ulcers.

Intestinal tuberculosis is associated with abdominal pain, fever, weight loss, and the radiologic demonstration of ileocecal disease. The radiologic findings of intestinal tuberculosis are

intramural masses and strictures. The presence of longitudinal swallow ulcers in the ileocecal area with intestinal tuberculosis can mimic intestinal Behçet's disease. Skip lesions are rare in tuberculosis but are common radiologic and endoscopic features of intestinal Behçet's disease as well as Crohn's disease.

Radiologic and clinical aspects of the disease have been nicely reviewed in a book (45) which is most detailed in domestic literature.

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