13
How to diagnose Behçet's and intestinal Behçet's disease?

A. F. ÇELIK, Ö. N. PAMUK, M. MELIKOĞLU and H. YAZICI

WHAT IS BEHÇET'S DISEASE?

Behçet's disease (BD) was first described by Hulusi Behçet, as a triad consisting of aphthous stomatitis, genital ulcers and uveitis[1]. It was later shown that many organs, including joints and other systems, e.g. pulmonary and neurological systems, can be affected[2].

Although generally considered as a vasculitis there can be lesions, e.g. in the central nervous system, in which a clear-cut vascular disease cannot be discerned. There is no distinctive histological characteristic.

The underlying cause is unknown, but it seems to be a multifactorial disease in which genetic components and external factors jointly influence the course and clinical expression of disease[3,4]. Histologically, $CD4^+$ T lymphocytes seem to be major cell type in inflammatory infiltrates[5] and peripheral T cells have a predominant Th1-type cytokine pattern[6,7], suggesting a role of T cell-mediated immune response in the pathogenesis.

PREVALENCE OF BD

The prevalence of BD is relatively higher in Asia, especially around the ancient trade line known as the 'Silk Route'. Turkey, as a bridge between Asia and Europe, has the highest prevalence (420/100 000)[8]. BD is also common in the Middle East, Korea and Japan[9,10], but rare in Europe, the UK[11], and the USA[12]. In addition to the most common presentation with mucocutaneous lesions, in which oral and genital ulcers are present along with folliculitis and sometimes arthritis, the major morbidities are ocular and nervous system involvement[13] in addition to vascular disease. Pulmonary artery aneurysms, with thrombotic events, especially cause mortality[14].

DEDICATED CENTRE EXPERIENCE ON BD AND GASTROINTESTINAL BD (GIBD)

In the past 30-year period more than 7000 BD cases were registered in our dedicated multidisciplinary Behçet centre. In this centre the patients are under the care of rheumatologists, ophthalmologists, dermatologists, neurologists, vascular surgeons and gastroenterologists.

For more than 7 years now our GI department has also been running a regular inflammatory bowel disease (IBD) clinic under a senior gastroenterologist. Currently we have 23 registered GIBD patients; of these 17 were diagnosed at this centre. The remaining six patients with BD had been referred to our unit from peripheral hospitals located either in or outside Istanbul with their GIBD diagnosis already made. Therefore, as a dedicated centre our yearly GIBD hospital incidence is 23/7 = 3.3 patients per year. According to this hospital incidence the prevalence of GIBD in our centre is less than 1%, which is in accordance with the prevalence of our recent file search of a group of BD patients younger than 18 years old[15] and a previous controlled study[16].

HOW TO DIAGNOSE BD

In diagnosis of BD the presence or a history of oral aphthae (OA) is almost a must. The International Behçet's Disease Study Group classification criteria for BD are shown in Table 1[17]. Although classification criteria of BD are sufficient to accurately classify most of the cases, some rare cases, especially those without OA, or cases without genital ulcers or lack of genital scars, may create problems in diagnosis. A positive pathergy test, which is an assessment of inflammatory skin reaction to needle-prick, may help to complete the diagnostic criteria. Since OA are also commonly seen in the normal population, to ascribe to BD one should not forget that, according to the criteria, the frequency of OA should be more than three times a year with a tendency to persist longer than usual.

OA do not seem to have any relation to GI involvement. First, in contrast to the almost ubiquitous presence of OA, GIBD is rare. While OA appear and disappear, ulcerations in GIBD persist and often show Crohn's disease (CD)-like chronicity. In our retrospective analysis of 35 Behçet's patients the upper endoscopic examinations along the GI canal distal to the oral cavity, down to the upper jejunum, we could not find any case in whom there was an ulcer, which could not be explained by other factors (unpublished observations).

It has been shown that cessation of smoking may cause flares in OA[18] and a nicotine patch[19] reduces its frequency and severity. However, smoking is one of the well-known causes which increase CD activity[20]. This effect, however, is reversed for ulcerative colitis (UC)[21]. As stressed above, OA and GIBD activities do not seem to act together; therefore, although there is no study on the effect of smoking on GIBD, the similar GI location[16] and morphology compared with CD, lead us to believe that smoking may play a role in GIBD activity.

Table 1 International Study Group criteria for the classification of BD[17]

Recurrent oral ulceration	Minor aphthous, or herpetiform ulceration, observed by physician or patient, which recurred at least three times in one 12-month period.
Plus two of:	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient.
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreus on slit-lamp examination, or retinal vasculitis observed by ophthalmologist.
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesion or acneiform nodules in post-adolescent patients not on corticosteroid treatment.
Positive pathergy test	Read by a physician at 24–48 h.

Genital ulcers (GU) or scar formation are strong indicators for the presence of BD; however, like other manifestations of BD, GU have a tendency to be more frequent in the early phase of the disease. This frequency diminishes with time and GU may disappear without leaving scar formation. Therefore, in the relatively late phase of the disease, only the presence of scar formation in the genital area is helpful for diagnosis. Nevertheless, genital scars may be easily missed by the inexperienced eye.

HOW COMMON IS GIBD IN BD-PREVALENT AND NON-PREVALENT COUNTRIES?

Although non-specific gastrointestinal symptoms are common in BD[16], clinically important and BD-related GI involvement is a rare event[22]. The frequency of GIBD varies widely in different countries (Table 2). While some early studies from Japan[23] reported high frequencies (50%), surprisingly, a figure of less than 1% was reported from a country where BD is endemic, i.e. Turkey[15]. Although there are reported high frequency rates, the majority indicates less than 10% frequency [11,15,16,24–33].

Why is GIBD a rare event in a country endemic for BD, such as Turkey? Why it is very common in another endemic region, e.g. Asia? Is this connected to the prevalence of IBD in these regions? There are no published reports on the prevalence of IBD in Turkey. However, according to a single large survey involving 17 000 people[34], involvement and the recent assessment of the IBD registry of the Turkish Society of Inflammatory Bowel Diseases (Epidemiology of Inflammatory Bowel Disease in Turkey, Ülku Dağli, see related chapter in this book), it is no less than 36/100.000. This moderate prevalence rate suggests that IBD is not very uncommon in Turkey; therefore, we consider that this discordance may partly arise from misdiagnosis related to an overestimation of GIBD in Asia.

Table 2 Frequency of BD gastrointestinal involvement in various countries

Reference	*Country*	*Year*	*n*	*GI involvement (%)*
Yamamoto et al.[24]	Japan	1972	2031	25
Eun et al.[25]	Korea	1984	114	5.3
Dilsen et al.[26]	Turkey	1996	496	5
Yurdakul et al.[16]	Turkey	1997	1000	0.7
Kaklamani et al.[27]	Greece	1998	64	3
Bang et al.[28]	Korea	2001	1155	4
Bang et al.[29]	Korea	2001	3497	7.3
Chang et al.[30]	Korea	2002	73	15
Tursen et al.[31]	Turkey	2003	2313	1.4
Seyahi et al.[15]	Turkey	2003	121	0.8
Chamberlain et al.[11]	UK	1977	32	10
O'Duffy et al.[32]	USA	1971	10	30
Jankowski et al.[33]	UK	1992	15	40

None of the studies listed in Table 2 has been specifically designed to discern the prevalence of GIBD. The reports quoted are from different disciplines and thus are biased towards the referred discipline. This is one of the reasons why the prevalence of GIBD can vary even in the studies that arise from the same region. Since some recent reports indicate a relatively low number of GIBD cases in Asia[24,25] it is unclear whether GIBD is as common as has been claimed in earlier reports[23].

In the countries where BD prevalence is low there is a potential for a type of referral bias. Intestinal involvement may not receive so much attention, unless sporadic cases present with severe inflammation, intestinal ulcers and bleeding. As a GI specialist if you see BD sporadically in a country with low prevalence, and come across with GIBD as a rare event, and/or when you diagnose GIBD mostly in severe cases and cases with complications, you may miss a much more mucocutaneous form of BD, which is the most common and mild form of the disease. Obviously missing these patients in a cumulative assessment would relatively increase GIBD prevalence among the BD group, and this would make GIBD prevalence much higher than expected in low prevalent countries such as the USA[32] and the UK[11].

Different prevalence rates may also reflect differences in design and methodology of the quoted papers. In this regard surveys conducted in multidisciplinary clinics, such as ours[16], we maintain, would give less biased results. In this particular study the frequency and history of diarrhoea were generally similar in patients with BD and controls. In addition, in none of the BD patients were diarrhoea and histological examination inflammatory in origin.

GIBD: DIAGNOSTIC TOOLS

Although a supportive role of radiology cannot be ignored, endoscopic examination is the gold standard for diagnosis of GIBD. However, macroscopic and microscopic details of gastrointestinal involvement are not disease-specific, and easily confused with other IBD such as CD and UC.

In a population of BD patients in which arthritis and arthralgia-related non-steroidal anti-inflammatory drugs (NSAID) use is common, even colonoscopic diagnosis of GIBD would not be good enough without controlling other factors, such as NSAID use[35,36] comorbid pathologies, and repeating the colonoscopy under these controlled circumstances.

In our Behçet's centre within a 7-year period the number of patients who suffered from abdominal complaints and having proved intestinal ulcerations with colonoscopy, was 30. However, detailed history-taking and repeating of colonoscopies within a 3-month period, indicated that nearly one-third of BD patients with colonoscopic lesions did not have real intestinal involvement of BD. They suffered rather from NSAID-related enterocolitis, or intestinal tuberculosis, antibiotic-associated haemorrhagic colitis (unpublished data). We therefore recommend repeating colonoscopy within 3–6 months after stopping NSAID and other related drugs.

In addition, most of the above-mentioned prevalence figures (Table 2) do not have endoscopic confirmation, and the methodology in many others is retrospective and not uniform. In a radiology-based study enteroclysis findings in Turkish patients with GIBD showed that the intestinal ulcers were usually shallow, multiple, and generally localized to the terminal ileum[37]. This contrasted with the findings in another recent colonoscopic study from Korea in which usually single, large, and deep ulcers with distinct borders were described[38]. Therefore, the straightforward comment is the possibility of regional differences between Turkey and Far East Asia, for the type of bowel disease as well as for the frequency. However, according to our cohort of BD patients with intestinal involvement (unpublished data) 15 out of 23 GIBD patients (70%) had been found to have single, large ulcers at endoscopy as previously described by the Korean group. This observation leads us to consider that the method of assessing the signs of inflammation in the bowel (radiological versus endoscopic or both) is quite important.

As emphasized above, in some studies, even GI symptoms have been taken as indicators of GIBD where prevalences reach up to 50–60%[23]. At the beginning of the 1970s when use of flexible endoscopic procedures spread worldwide, the prevalence of GIBD in Asia, especially in the pioneer countries of endoscopic procedures, was found to be considerably lower than before[24,25]. However, even this prevalence rate was not free from the risk of referral bias and the risk of diagnosing any irrelevant mucosal lesion as GIBD by endoscopic assessment. So, through endoscopy more accurate morphological diagnosis appeared with the risk of misclassification of a non-relevant mucosal lesion as GIBD.

On the other hand, one may consider that endoscopy might also make us aware of some cases of asymptomatic GIBD. However, as we know from IBD clinics, endoscopically documented asymptomatic involvement is rather mild and may heal without any sign of GI disease. So, as practising physicians, we

may decide not to be very interested in discerning asymptomatic BD patients who have only endoscopic mucosal evidence of GI involvement.

In IBD diagnosis histology is a non-specific diagnostic tool. Except for rare cases of caseous granuloma formation, which may indicate intestinal tuberculosis, mucosal punch biopsies may only be helpful in demonstrating acute or chronic inflammation, mainly in the mucosa and rarely in the submucosa. Although granuloma formation mostly but not necessarily indicates CD, sensitivity of mucosal punch biopsies for granuloma is low. Among CD patients granuloma formation is seen in around 25–30% in full-thickness intestinal biopsies[39,40], and its much less than this in mucosal punch biopsies. Unless it is caseous, specificity of granuloma formation is arguable, since some non-CD cases with granuloma, including GIBD, have been reported[41].

OTHER GI INVOLVEMENT

Except for relatively common hepatic venous vascular occlusion by thrombosis, Budd–Chiari syndrome, other intestinal and extraintestinal involvement such as pancreatitis is rare, and it is difficult to say that they are causally related to BD[42].

DIFFERENTIAL DIAGNOSIS

Similar to CD and intestinal tuberculosis (IT), GIBD is most commonly seen in the ileocaecal area[16,42]. Diagnosis of GIBD needs macroscopically documented inflammation in a patient with BD.

Furthermore, as with macroscopic study, microscopic details of inflammation are also not specific for GIBD and can easily be confused with other IBD, such as CD, UC, IT and some potential inflammatory causes such as NSAID use.

Similarities and dissimilarities between CD and GIBD (Table 3) may create diagnostic difficulty. Extraintestinal involvement such as arthropathy (5–20%), and ophthalmological manifestations (1.6–4.6%) are relatively rare in IBD[43],

Table 3 Comparison of GIBD and CD (similarities and dissimilarities)

Features	*GIBD*	*CD*
Non-specific histology	Yes	Yes
Major vascular involvement	Yes	No
Serious eye event	Yes	No
Central nervous system involvement	Yes	Yes
Inflammatory morphology	Yes	Yes
Ileocaecal involvement	Yes	Yes
CARD15/NOD susceptibility	No	Yes
Positive ASCA	No?	Yes

Table 4 Frequencies of Behçet's clinical features in UC and CD patients

	Crohn's Disease (n = 93)	*Ulcerative colitis (n = 130)*	*p-Value*
Oral ulcer >3/year	20/93 (20%)	32/130 (25%)	n.s.
Positive pathergy	10/93 (10%)	11/130 (9%)	n.s.
Uveitis	2/93 (2%)	2/130 (2%)	n.s.
Arthritis	3/93 (3%)	2/130 (2%)	n.s.
Nodular lesion	2/93 (2%)	3/130 (2%)	n.s.
Pustule	22/93 (24%)	23/130 (18%)	n.s.
Genital ulcer	4/93 without scar	0/130	–
No. of patients fulfilling the Behçet's criteria	0/93	1/130 (1%)	n.s.

n.s., not significant.

while it is much more common in BD (50%)[44]. Although there are as yet no controlled studies, it is generally regarded that, with more perforation and bleeding, GIBD has a more guarded prognosis when compared to CD or UC[45].

In a recent work (Table 4), we applied BD diagnostic criteria to our group of CD and UC patients. Although around 20–25% oral aphthae and 10% pathergy positivity were present in CD and UC groups, except for two patients in the UC group none of the patients fulfilled the diagnostic criteria for BD[46]. When compared with IBD the discriminatory value of BD diagnostic criteria is fairly high. A drawback of this study was the rather limited number of patients with CD or UC.

CARD15/NOD2

At least two separate papers failed to indicate an association with CARD15/NOD2 variants in Behçet's patients from Turkey and the UK[47,48]. Nevertheless, whether this is also true for GIBD has not yet been assessed. Studies similarly reporting no such association with CARD15/NOD2 mutation among Turkish CD patients[49] may simply indicate that CARD15/NOD2 is not the major genetic mutation which may be held responsible from CD-like IBD.

ANTI-*SACCHAROMYCES CEREVISIAE* ANTIBODY (ASCA)

There is conflicting evidence regarding the presence of ASCA in GIBD. Table 5 shows comparisons of the ASCA values in CD, BD, and GIBD in the available literature[50–52]. In a recent report from India, where tuberculosis is endemic, it has been shown that ASCA is 40% positive also in intestinal tuberculosis[53]. The results suggest that ASCA might be a non-specific intestinal inflammatory indicator; therefore its clinical value in differential diagnosis of bowel inflammations is not yet clear.

Table 5 Comparison of available ASCA literature in CD, BD and GIBD

		Any ASCA positivity (IgG or IgA)				*For CD*	
	Method	*Controls*	*BD*	*GIBD*	*CD*	*Sensitivity*	*Specificity*
Krause et al.[50]	ELISA	1/10 (10%)	13/27 (48%)	–	–	n.a.	n.a.
Fresko et al.[51]	ELISA	3/21 (14%)	18/85 (21%)	2/7 (28%)	15/24 (62%)	60%	62%
Choi et al.[52]	IFA	4/45 (8.8%)	1/30 (3%)	47/106 (44%)	–	53%	67%

DISEASE FOLLOW-UP

'Disease burden' of BD is usually confined to the early years of its course, and in many patients the disease 'burns out'[13]. Although during the follow-up a small number of CD patients may turn into the fibrostenotic type without any inflammatory activity, in general CD is a chronic, persistent and progressive disease. However, whether GIBD behaviour is similar to CD in this regard remains to be formally studied.

TREATMENT

Treatment modalities in GIBD are no different from those of IBD. Because of the relatively low prevalence of GIBD, placebo-controlled studies are lacking, and we mostly have to rely on case-based or small-numbered open-label limited observations.

Even open-label studies in GIBD are not available; however, it is known that there are morphological, histological and clinical similarities between IBD and GIBD. Therefore in the treatment of GIBD we have to rely on information obtained from IBD. Commonly the outcome of the treatment is mainly judged on an arbitrarily chosen subjective clinical symptomatology. As in IBD treatment protocols, 5-aminosalicylic acid (5-ASA), immunosuppressives, and biological agents, either used singly or in combination, are the three main steps of treatment in GIBD[42,54]. Except for patients with mild clinical activity and/or low colonoscopic score, we do not use 5-ASA in our IBD clinic; the same applies to our GIBD cases. As in CD and UC, mainly azathioprine (AZA), and in cases who cannot tolerate AZA, or also having arthritis, methotrexate are two drugs as immunosuppressive in GIBD treatment. As a third step, in addition to immunosuppressive treatment, we can use the anti-tumour necrosis factor infliximab[55–57] or thalidomide[58] for some patients who do not respond to immunosuppressives.

References

1. Behçet H. Über rezidivierende aphthöse, durch ein Virus Verursachte Geschwüre am Mund, am Auge und an den Genitalien. Dermatol Wochenschr. 1937;105:1152–7.
2. Shimizu T, Ehrlich GE, Inaba G et al. Behçet's disease (Behçet's syndrome). Semin Arthritis Rheum. 1979;8:223–60.
3. Yazici H, Fresko I, Yurdakul S. Behçet's syndrome: disease manifestations, management, and advances in treatment. Nat Clin Pract Rheumatol. 2007;3:148–55.
4. Direskeneli H. Autoimmunity vs autoinflammation in Behçet's disease: do we oversimplify a complex disorder? Rheumatology (Oxford). 2006;45:1461–5.
5. Ben Ahmed M, Houman H, Miled M, Dellagi K, Louzir H. Involvement of chemokines and Th1 cytokines in the pathogenesis of mucocutaneous lesions of Behçet's disease. Arthritis Rheum. 2004;50:2291–5.
6. Frassanito MA, Damacco R, Cafforio P, Dammacco F. Th1 polarization of the immune response in Behçet's disease: a putative pathogenetic role of interleukin-12. Arthritis Rheum. 1999;42:1967–74.
7. Melikoglu M, Uysal S, Krueger JG et al. Characterization of the divergent wound-healing responses occurring in the pathergy reaction and normal healthy volunteers. J Immunol. 2006;177:6415–21.

8. Azizlerli G, Köse AA, Saryca R et al. Prevalance of Behçet's disease in İstanbul, Turkey. Int J Dermatol. 2003;42:803–6.
9. Saylan T, Mat C, Fresko İ, Melikoğlu M. Behçet's disease in the Middle East. Clin Dermatol. 1999;17:209–23.
10. Marshall SE. Behçet's disease. Best Prac Res Clin Rheumatol. 2004;18:291–311.
11. Chamberlain MA. Behçet's syndrome in 32 patients in Yorkshire. Ann Rheum Dis. 1977;36:491–9.
12. O'Duffy JD. Summary of international symposium on Behçet's disease. J Rheumatol. 1978;5:229–33.
13. Kural-Seyahi E, Fresko I, Seyahi N et al. The long-term mortality and morbidity of Behçet syndrome. A 2-decade outcome durvey of 387 patients followed at a dedicated center. Medicine (Baltimore). 2003;82:60–76.
14. Hamuryudan V, Yurdakul S, Moral F et al. Pulmonary arterial aneurysms in Behçet's syndrome: a report of 24 cases. Br J Rheumatol. 1994;33:48–51.
15. Seyahi E, Ozdogan H, Yurdakul S et al. The outcome of children with Behçet's syndrome. Clin Exp Rheumatol. 2004;22(Suppl. 34):116a.
16. Yurdakul S, Tüzüner N, Yurdakul I, Hamuryudan V, Yazici H. Gastrointestinal involvement in Behçet's syndrome: a controlled study. Ann Rheum Dis. 1996;55:208–10.
17. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet. 1990;335:1078–80.
18. Soy M, Erken E, Konca K, Ozbek S. Smoking and Behçet's disease. Clin Rheumatol. 2000;19:508–9.
19. Kaklamani VG, Markkomichelakis N, Kaklamanis PG. Could nicotine be benefical for Behçet's disease. Clin Rheumatol. 2002;21:341–2.
20. Cottone M, Rossellini M, Orlanda A et al. Smoking habits and reccurence in Crohn's disease. Gastroenterology. 1994;106:643–8.
21. Jick H, Walker AM. Cigarette smoking and ulcerative colitis. N Engl J Med. 1983;308:261–3.
22. Chajec T, Fainaru M. Behçet's disease: report of 41 cases and review of the literature. Medicine. 1975;54:179–96.
23. Oshima Y, Shimizu T, Yokohari R et al. Clinical studies on Behçet's syndrome. Ann Rheum Dis. 1963;22:36–45.
24. Yamamoto S, Toyokawa H, Matsubara J et al. A nation-wide survey of Behçet's disease in Japan. 1. Epidemiological survey. Jpn J Ophthalmol. 1974;18:282–90.
25. Eun HC, Chung H, Choi SJ. Clinical analysis of 114 patients with Behçet's disease. J Korean Med Assoc. 1984;27:933–9.
26. Dilsen N, Konice M, Aral O et al. Risk factors of vital organ involvement in Behçet's disease. In: Weschler B, Godeau F, editors. Behçet's Disease. Proceedings of the Sixth International Conference on Behçet's Disease. Amsterdam: Excerpta Medica, 1993:165–9.
27. Kaklamani VG, Vaiopoulos G, Kaklamanis PG. Behçet's disease. Semin Arthritis Rheum. 1998;27:197–217.
28. Bang D, Yoon KH, Chung HG, Choi EH, Lee ES, Lee S. Epidemiological and clinical features of Behçet's disease in Korea. Yonsei Med J. 1997;38:428–36.
29. Bang D, Lee JH, Lee ES et al. Epidemiologic and clinical survey of Behçet's disease in Korea: the first multicenter study. J Korean Med Sci. 2001;16:615–18.
30. Chang HK, Kim JW. The clinical features of Behçet's disease in Yongdong districts: analysis of a cohort followed from 1997 to 2001. J Korean Med Sci. 2002;17:784–9.
31. Tursen U, Gurler A, Boyvat A. Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease. Int J Dermatol. 2003;42:346–51.
32. O'Duffy JD, Carney A, Deodhar S. Behçet's disease: report of 10 cases, 3 with new manifestation. Ann Intern Med. 1971;75:561–70.
33. Jankowski J, Crombie I, Jankowski R. Behçet's syndrome in Scotland. Postgrad Med J. 1992;68:566–70.
34. Cakir N, Pamuk ON, Dervis E et al. The prevalance of rheumatologic diseases in Havsa: the initial evaluation. Annual European Congress of Rheumatology, Vienna, Austria. Ann Rheum Dis. 2005;64(Suppl. III):551.
35. Puspok A, Kiener HP, Oberhuber G. Clinical, endoscopic, and histologic spectrum of nonsteroidal anti-inflammatory drug-induced lesions in the colon. Dis Colon Rectum. 2000;43:685–91.

36. Laine L, Connors LG, Reicin A et al. Serious lower gastrointestinal clinical events with nonselective NSAID or Coxib use. Gastroenterology. 2003;124:288–92.
37. Korman U, Cantasdemir M, Kurugoglu S et al. Enteroclysis findings of intestinal Behçet disease: a comparative study with Crohn disease. Abdom Imaging. 2003;28:308–12.
38. Kim JS, Lim SH, Choi IJ et al. Prediction of the clinical course of Behçet's colitis according to macroscopic classification by colonoscopy. Endoscopy. 2000;32:635–40.
39. Ramzan NN, Leighton JA, Heigh RI, Shapiro MS. Clinical significance of granuloma in Crohn's disease. Inflamm Bowel Dis. 2002;8:168–73.
40. Pulimood AB, Ramakrishna BS, Kurian G et al. Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. Gut. 1999;45:537–41.
41. Fukuda Y, Watanabe I. Pathological studies on intestinal Behçet's (entero-Behçet's) disease. In: Dilşen N, Koniçe M, Övül C, editors. Behçet's Disease. Proceedings of an international symposium on Behçet's disease. London: Royal Society of Medicine Services, 1986:289.
42. Celik AF, Hatemi I. Gastrointestinal involvement of Behçet's syndrome. Turkiye Klinikleri J Int Med Sci. 2005;1:48–54.
43. Su CG, Judge TA, Leichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Clin N Am. 2002;31:307–21.
44. Yurdakul S, Yazici H, Tuzun Y et al. The arthritis of Behçet's disease: a prospective study. Ann Rheum Dis. 1983;42:505–15.
45. Chou SJ, Chen TK, Jan HC, Lou MA, Liu YM. Intestinal perforations in Behçet's disease. J Gastrointest Surg. 2007;11:508–14.
46. Hatemi I, Hatemi G, Celik A et al. İnflamatuvar barsak hastalığında Behçet sendromu sıklı ğı. Romatoloji Kongre Kitabı. 2006, İzmir, 115:127.
47. Uyar FA, Saruhan-Direskeneli G, Gül A. Common Crohn's disease-predisposing variants of the CARD15/NOD2 gene are not associated with Behçet's disease in Turkey. Clin Exp Rheumatol. 2004;22(Suppl. 34):S50–2.
48. Ahmad T, Zhang L, Gogus F et al. CARD15 polymorphisms in Behçet's disease. Scand J Rheumatol. 2005;34:233–7.
49. Ozen SC, Dagli U, Kilic MY et al. NOD2/CARD15, NOD1/CARD4, and ICAM-1 gene polymorphisms in Turkish patients with inflammatory bowel disease. J Gastroenterol. 2006;41:304–10.
50. Krause I, Monselise Y, Milo G, Weinberger A. Anti-*Saccharomyces cerevisiae* antibodies – a novel serologic marker for Behçet's disease. Clin Exp Rheumatol. 2002;20(Suppl. 26):S21–4.
51. Fresko I, Ugurlu S, Ozbakir F et al. Anti-*Saccharomyces cerevisiae* antibodies (ASCA) in Behçet's syndrome. Clin Exp Rheumatol. 2005;23(Suppl. 38):S67–70.
52. Choi CH, Kim TI, Kim BC et al. Anti-*Saccharomyces cerevisiae* antibody in intestinal Behç et's disease patients: relation to clinical course. Dis Colon Rectum. 2006;49:1849–59.
53. Govid KM, Sachdev V, Gupta R, Lal S, Pandey RM. Anti-*Saccharomyces cerevisiae* antibody does not differentiate between Crohn's disease and intestinal tuberculosis. Dig Dis Sci. 2007;52:33–9.
54. Naganuma M, Iwao Y, Inoue N et al. Analysis of clinical course and long-term prognosis of surgical and nonsurgical patients with intestinal Behçet's disease. Am J Gastroenterol. 2000;95:2848–51.
55. Hassard PV, Binder SW, Nelson V, Vasiliauskas EA et al. Anti-tumor necrosis factor monoclonal antibody therapy for gastrointestinal Behçet's disease. Gastroenterology. 2001;120:995–9.
56. Travis SP, Czajkowski M, McGovern DP et al. Treatment of intestinal Behçet's syndrome with chimeric tumor necrosis factor alpha antibody. Gut. 2001;49:725–8.
57. Lee JH, Kim TN, Choi ST et al. Remission of intestinal Behçet's disease treated with anti-tumor necrosis factor alpha monoclonal antibody (infliximab). Korean J Intern Med. 2007;22:24–7.
58. Celik AF, Seyahi EK, Coskun S et al. Thalidomide in azathioprine resistant gastrointestinal (GI) Behçet's syndrome: 3 cases. Clin Exp Rheumatol. 2004;22(Suppl. 34).