

Bowel Lesions of Behçet's Disease Are Frequently Detected in Non-ileocecal Regions as Well as in the Ileocecum: Clinical Features of 51 Japanese Patients with Behçet's Disease

Tsuyoshi KOBASHIGAWA¹, Yuki NANKE¹, Hideaki ODA²,
Hisashi YAMANAKA¹ and Shigeru KOTAKE¹

¹Institute of Rheumatology, Tokyo Women's Medical University

²Department of Pathology, Tokyo Women's Medical University, School of Medicine

(Accepted March 29, 2010)

Objective: To describe the clinical features of Japanese patients with Behçet's disease (BD). We hypothesized that bowel lesions of intestinal BD (i-BD) patients are detectable throughout the bowel. **Methods:** We analyzed the clinical features of 51 Japanese BD patients (Male 16; mean age \pm SD, 39.5 \pm 12.2) hospitalized in our institute during the past 11 years. All of the BD patients fulfilled the Japanese criteria and those of the international study group. We histologically analyzed biopsy specimens of intestinal mucous membrane obtained from 33 i-BD patients. **Results:** Thirty-three of 51 BD patients demonstrated bowel symptoms; 21 (61.8%) of 33 BD patients with bowel symptoms were diagnosed as having i-BD; only one did not show bowel symptoms. Ileocecal regions were detected in 18 (85.7%) of 21 i-BD patients: Ten demonstrated only ileocecal lesions and 8 demonstrated lesions in both the ileocecal and non-ileocecal regions. Interestingly, bowel lesions were also detected in non-ileocecal regions in 11 (52.4%) of 21 i-BD patients: Three demonstrated only non-ileocecal lesions. **Conclusion:** Bowel lesions of i-BD patients were detected not only in ileocecal regions but also in non-ileocecal regions.

Key words: Behçet's disease, ileocecal lesions, inflammatory bowel diseases, ulcer, human leukocyte antigen

Introduction

Behçet's disease (BD) is a systemic inflammatory disorder characterized mainly by recurrent attacks of oral aphthous ulcers, genital ulcers, uveitis, skin lesions and arthritis. Subsequently, a number of other clinical features, including gastrointestinal lesions, vascular lesions and neurologic disease, have been noted^{1,2}. However, gastrointestinal involvement in BD is common among Japanese patients, and leads to a poor prognosis^{1,3}.

The ileocecum is a typical region of involvement for BD ulcer, but gastrointestinal lesions have been reported to occur in all areas of the gastrointestinal tract^{2,4-7}. When patients consult the hospital with colitis in the absence of ileocecal lesions on colonoscopy, these patients tend to be treated as having inflammation of the bowel due to Crohn's dis-

ease⁸⁻¹¹ or ulcerative colitis³ because the diagnosis of BD with intestinal lesions may be difficult to differentiate from other inflammatory bowel diseases such as Crohn's disease and ulcerative colitis^{3,8-11}.

Here, we describe the clinical features of patients with BD treated in our institute between November 1993 and November 2004. We hypothesized that the bowel lesions of intestinal BD patients would be detected not only in the ileocecum but also in other bowel regions.

Patients and Methods

Patients

All BD patients in this series were admitted to our hospital between November 1993 and November 2004, and all were monitored. We analyzed the clinical features in 51 patients with BD (16 males and 35 females; mean \pm SD age, 39.5 \pm 12.2 years).

Table Clinical features of BD patients in the present study

Clinical characteristics	Patients (n = 51)	%
1 Recurrent aphthous ulcers on oral mucosa	51	100
2 Skin lesions	48	94.1
3 Ocular lesions	25	49
4 Genital ulcers	38	74.5
5 Arthritis	33	64.7
6 Epididymitis ¶	1 (n = 17)	5.9
7 Gastrointestinal lesions	29	56.9
8 Central nervous system (CNS) lesions	13	25.5
9 Vascular lesions	6	11.8
10 Pathergy test *	8 (n = 19)	42.1
11 Inflammatory activities	42	82.4
12 HLA-B51 (B5) **	26 (2n = 88)	31.8

¶: Epididymitis was found in 1 (5.9%) of 17 male patients.

*: Pathergy test which was performed in 19 patients using 18-22 gage needles was 42.1% positive.

** : Examination of human leucocyte antigen (HLA) -B51 (B5) shown in 25 (56.8%) of 44 patients examined (2 Homo, 24 Hetero).

All of the patients with BD fulfilled both the diagnostic criteria proposed by the Behçet's Disease Research Committee of Japan¹²⁾⁻¹⁴⁾ and the criteria of the International Study Group for Behçet's Disease¹⁵⁾. All patients were Japanese. Approval from the ethical committee of the institute and informed consent from each patient were obtained (Table).

Tissue samples and staining of histology

For histological studies, specimens of intestinal mucous membrane were obtained by biopsy from both the ulcer lesions and from adjacent non-ulcerated tissue as surveillance biopsy for intestinal BD in 33 of 51 BD patients at the time of colonoscopy. Four-micrometer thick sections of formalin-fixed, paraffin-embedded tissues were processed routinely for hematoxylin-eosin (H-E stain).

Statistical analysis

Findings were analyzed using Fisher's exact probability test or chi-square test. P-values less than 0.01 or 0.05 were considered significant. All values are represented as mean \pm SD.

Results

Characteristics of BD patients and criteria for diagnosis of BD

The table summarized the clinical features of our BD patients. BD patients in the present series showed a significantly lower prevalence of eye lesions than the general Japanese BD patients ($p =$

0.0022). In the present study, however, gastrointestinal (GI) lesions and CNS lesions were significantly more prevalent than those in the general Japanese BD patients, ($p = 0.76 \times 10^{-6}$, $p = 0.001$, respectively). According to the Japanese criteria (13-15), the distributions of types showed that there were 13 (25.5%) patients with the complete type [5 (9.8%) males, 8 (15.7%) females] and 38 (74.5%) with the incomplete type [12 (23.5%) males, 26 (51.0%) females]. The frequencies of entero-BD, neuro-BD and vasculo-BD in the present series were 56.9% (8 males, 21 females), 25.5% (3 males, 10 females), and 9.8% (1 male, 4 females), respectively. Six females developed both intestinal and neural lesions; one male patient developed both intestinal and vascular lesions; and one female patient showed all three types of lesions.

Treatments to the patients in the present study

Sixteen (31.4%) of 51 BD patients were treated with an intermediate dose of prednisolone (PSL 20-40 mg/day); 2 patients (each one male and female) with intestinal BD and 2 females with neural BD were treated with steroid pulse therapy (methylprednisolone 500 mg/day for 3 days); 14 patients (3 males and 11 females) with intestinal BD were treated with salazosulfapyridine (1,000 mg/day); and 2 female patients with neural BD were treated with cyclosporin A (100 mg/day).

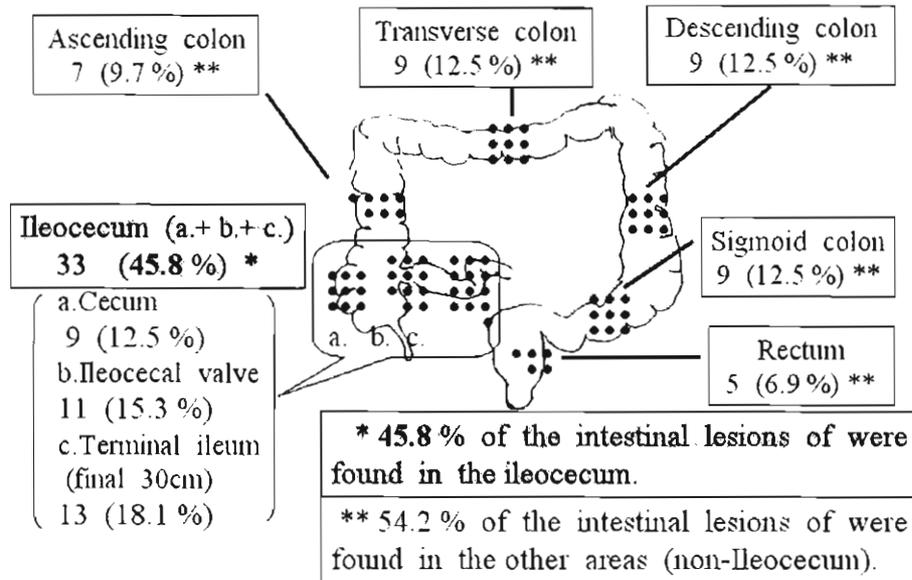


Fig. 1 The distribution of 72 intestinal lesions in 21 patients

Digestive symptoms and intestinal lesions

Thirty-three BD patients (64.7%) showed digestive symptoms and the other 18 BD patients (35.3%) did not. Twenty-one BD patients (41.2%) demonstrated intestinal lesions on endoscopy. Finally, the 51 BD patients were categorized into 4 groups: with or without digestive symptoms and with or without intestinal lesions on endoscopic examination. Intestinal lesions were found in one BD patient without digestive symptoms (2.0%). However, there were no detectable intestinal lesions in 13 BD patients with digestive symptoms (25.5%).

Age at onset of digestive symptoms in intestinal BD patients

There was no gender predominance nor predominance of patients with the complete or incomplete type ($p = 0.38$) among intestinal BD patients. Only one male patient showed the complete type of BD; 7 males showed the incomplete type (37.2 ± 11.5); 7 females showed the complete type (31.3 ± 9.9); and 14 females showed the incomplete type (32.0 ± 5.0).

The distribution of intestinal BD lesions and endoscopic findings in comparison with pathological findings

We divided 21 intestinal BD patients in to three categories. The first group had ileocecal lesions only, the second had non-ileocecal lesions only, and

the third had lesions in both regions. Ten intestinal BD patients (47.6%) demonstrated ileocecal lesions only, 3 (14.3%) of 21 intestinal BD patients had non-ileocecal lesions only, and 8 intestinal BD patients (38.1%) had lesions in both regions. Moreover, we divided the intestine into eight areas, within endoscopic observation from the anus to the area 50 cm toward the oral side across the ileocecal valve. Figure 1 shows the distribution of 72 intestinal lesions in 21 patients. The eight areas were the terminal ileum (13 lesions: 18.1%), ileocecal valve (11 lesions: 15.3%), cecum (9 lesions: 12.5%), ascending colon (7 lesions: 9.7%), transverse colon (9 lesions: 12.5%), descending colon (9 lesions: 12.5%), sigmoid colon (9 lesions: 12.5%) and rectum (5 lesions: 6.9%). The ileocecum was defined as an area including the terminal ileum, ileocecal valve and cecum (33 lesions: 45.8%). Thus, 45.8% of intestinal lesions were found in the ileocecum, while, the other 54.2% of the lesions were found in other areas. Figure 2 shows endoscopic images of each area of intestinal BD. Each area demonstrated punched-out ulcer lesions. All over pathological findings only demonstrated 'non-specific colitis or ileitis' or 'not specific inflammatory findings for Crohn's disease or ulcerative colitis'. Shapes of intestinal lesions were variable. All 21 intestinal BD patients showed deep and large ulcer, round or oval ulcers, and circular ulcers were

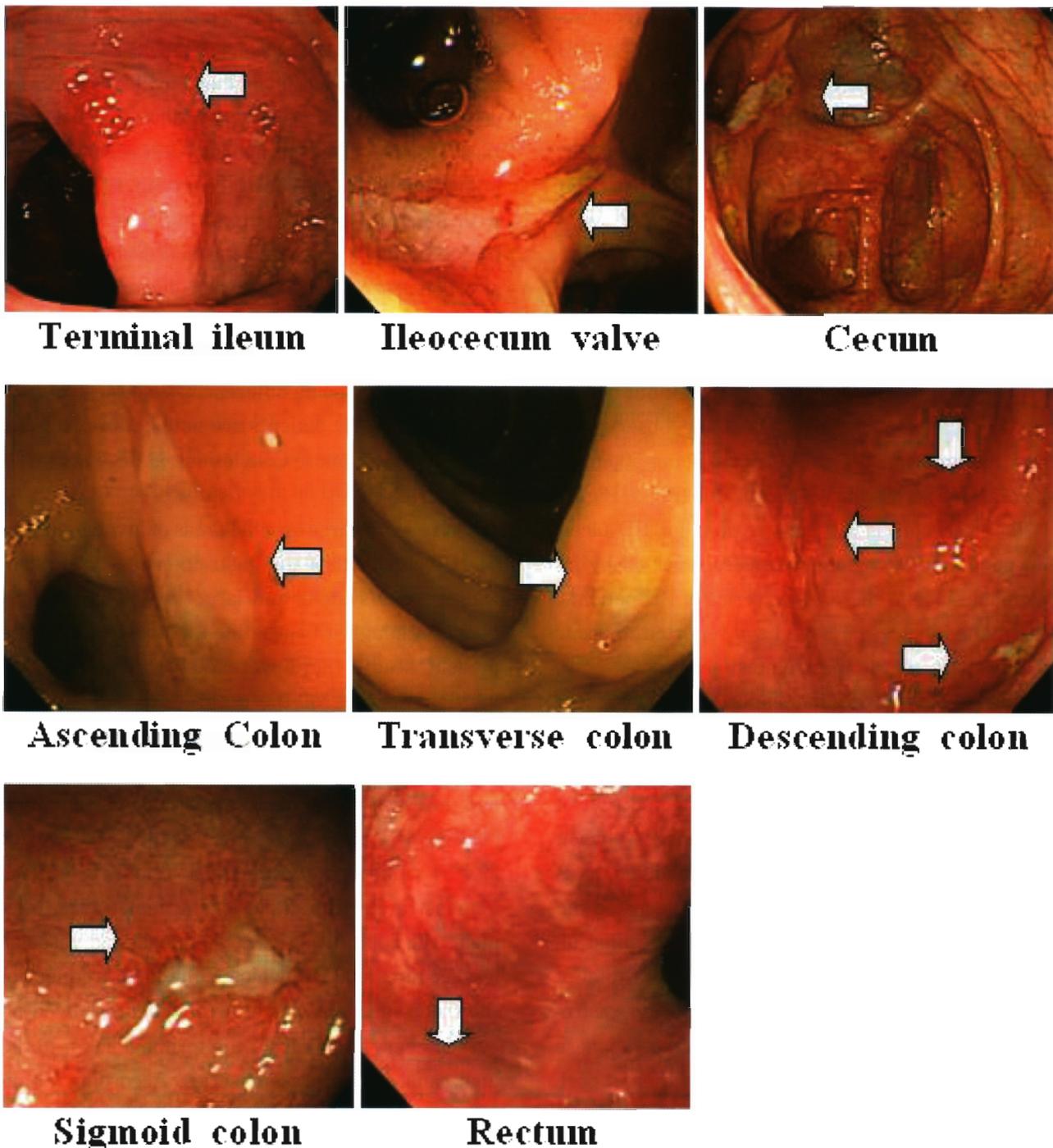


Fig. 2 Endoscopic images in each intestinal region showing punched-out ulcer lesions due to intestinal BD (Arrow: ulcer)

shown in 18 intestinal BD patient with ileocecal lesions, and neither liner nor longitudinal ulcer was detected in the present study.

Genetic factor for human leukocyte antigen (HLA) -B51 (5) and 8 lesions of BD

HLA-B51 (5) examined 26 (2 patients were homo-geneous and others were heterogeneous) of 44 BD

patients (2n = 88). There were 28 HLA-B51 (5) alleles in our study (2n = 88). In the present study, there was no relationship between HLA-B51 (5) and 8 BD lesions (eye lesion, oral, skin, genital, intestinal, vascular, neural, and arthritis), respectively.

Eye lesions and intestinal lesions

Twenty-five (49.0%) of 51 BD patients showed

eye lesions, and 7 (13.7%) of these 25 BD patients showed intestinal lesions. However, 26 (51.0%) BD patients did not show eye lesions, and 15 (29.4%) of these 26 showed intestinal lesions. There was a negative relationship between eye lesions of BD and intestinal lesions of BD ($p = 0.048$) in the present study.

Discussion

In the present study, we clearly demonstrated the epidemiology of patients with BD treated in our hospital (Table). We detected bowel lesions in 21 of 51 BD patients not only in the ileocecum but also in non-ileocecical regions on colonoscopic observation from the anal canal to the terminal ileum 50 cm to the oral side across the ileocecal valve (Fig. 1, Fig. 2).

The ileocecum is a typical regions for BD ulcer, but non-ileocecical regions were also involved by intestinal lesions in the present series of BD patients. Gastrointestinal lesion have been reported to occur in any part of the gastrointestinal tract^{214)~7)15)16)}. Shimizu et al reported that single or multiple ulcers of the esophagus, stomach, or intestine may be seen in BD patients¹⁷⁾. Sakane et al reported that the ileocecal region is the most commonly affected part of the gastrointestinal tract, but the transverse colon and ascending colon are sometimes involved, as is the esophagus²⁾. Indeed, Kasahara et al reported the surgical findings in cases of BD with intestinal ulceration in Japan; their series comprised a total of 136 surgically treated BD patients showing gastrointestinal ulcer formation reported in the Japanese literature between 1960 and 1980¹⁾. In their report, the frequency of lesions in the ileocecal region was 119 (52.2%) was roughly the same as that of those in non-ileocecical region at 109 (47.8%) of all reported cases¹⁾. Hirohata et al reported 26 cases of intestinal BDs their study classified the bowel to 7 regions, terminal ileum, ileocecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum, accessible by endoscopy and described 51 intestinal lesions among these 26 intestinal BD patients⁷⁾. There were 28 ileocecal lesion reported (54.9%), which was similar to 23 lesions in non-ileocecical regions (45.1%) among the 51 intestinal lesions in their series⁷⁾. In our study (Fig. 1), the total

number of non-ileocecical lesion was 39 (54.2%) and there were 33 (45.8%) lesions in the ileocecal region. Moreover, pathological findings by biopsy during colonoscopy did not show any differences among these lesions. Thus, the non-ileocecical region was as important as the ileocecal region in BD patients with intestinal lesions, suggesting that we should pay attention not only to the ileocecal region but also non-ileocecical regions when diagnosing intestinal BD.

The characteristics of our BD patients are shown in the table, and some differences from those of general Japanese BD patients are noted: More females, more GI lesions, more CNS lesions, and fewer eye lesions²⁾¹⁶⁾.

There were three specific areas of involvement in BD. Involvement of the gastrointestinal tract, central nervous system, and large vessels is less frequent, although it can be life-threatening¹⁾²⁾. In the present study, there were 30 BD patients with varying degrees of these three specific involvements of BD among 51 BD patients hospitalized in our institute during the past 11 years. One female had intestinal and vascular lesions. Twenty-one (41.2%) BD patients (6 male: 11.8%, 15 female: 29.4%) demonstrated intestinal lesions. 8 (15.7%) demonstrated neuronal lesions (2 male: 3.9%, 6 female: 11.8%) and only 1 (2.0%) female had vascular lesions. Intestinal BD, which is the most frequent of the three specific types of involvement, showed ulcers in every region from the terminal ileum to the anal canal in the present series. According to another study, intestinal BD lesions, which were also found anywhere from the mouth to the anal canal, sometimes caused perforations or penetrations at multiple sites along the intestine as well as malabsorption¹⁾. Thus, we need to examine all, when we encounter BD patients with or without one of the three visceral involvements: intestinal, neuronal, and vascular lesions, because any of those three has the potential to become life-threatening. In addition, clinically, it has been known that the BD patients with uveitis infrequently have gastro-intestinal lesions, which our results supports.

In the present study, we investigated the rela-

tionships between digestive symptoms and intestinal lesions detected by endoscopy. Thirty-three (64.7%) patients complained of digestive symptoms such as dysphagia, vomiting, abdominal pain, flatulence, nausea and diarrhea. However, intestinal lesions were not detected by endoscopy in 13 (25.5%) BD patients with digestive symptoms. Interestingly, in one (2.0%) intestinal BD patient, intestinal lesions involving the ileocecal valves were definitely detected by endoscopy, but the patient did not complain of any digestive symptoms. Moreover, there was no gender predominance nor predominance of patients with the complete or incomplete type among intestinal BD patients. Thus, it may be useful to examine the intestine in all BD patients.

Conclusion

The present study demonstrated that bowel lesions in BD patients are frequently detected in non-ileocecal regions as well as in the ileocecum. Thus, we should pay attention not only to the ileocecal region but also non-ileocecal regions when diagnosing intestinal BD.

Acknowledgements and Affiliations

We thank Hironari SHINDO MD PhD and Norio TAMAI (Aoyama Hospital, Tokyo Women's Medical University) for excellent technical support for colonoscopic biopsy to collect tissue samples from BD patients, Taichi EZAKI MD PhD Professor of medicine (Department of Anatomy and Developmental Biology, Tokyo Women's Medical University), Sanshiro NOGUCHI MD and Mr. Takayuki SAKAI (Department of Pathology, Tokyo Women's Medical University) for their excellent technical assistance in staining procedures, and all of the MDs involved in the care of these patients. We thank Toru YAGO MD PhD and Naomi ICHIKAWA MD PhD (Institute of Rheumatology, Tokyo Women's Medical University), and Bun-ei IIZUKA MD PhD (Department of Endoscopy, Institute of Gastroenterology, Tokyo Women's Medical University) for excellent scientific advice.

References

- 1) **Kastner DL**: Intermittent and periodic arthritic syndromes. *In* Arthritis and Allied Conditions: A

- Textbook of Rheumatology, (14th ed) . (Koopman WJ ed), pp1420–1429. Williams & Wilkins, Baltimore (2001)
- 2) **Sakane T, Takeno M, Suzuki N et al**: Behçet's disease. *N Engl J Med* **341**: 1284–1291, 1999
- 3) **Kobashigawa T, Okamoto H, Kato J et al**: Ulcerative colitis followed by the development of Behçet's disease. *Internal Med* **43**: 243–247, 2004
- 4) **Kasahara Y, Tanaka S, Nishino M et al**: Intestinal involvement in Behçet's disease: review of 136 surgical cases in the Japanese literature. *Dis Colon Rectum* **24**: 103–106, 1981
- 5) **Baba S, Morioka S**: Treatment of Intestinal Behçet's Disease (Inaba G ed), pp559–570, University of Tokyo Press, Tokyo (1982)
- 6) **Hoshino E, Tokumoto K, Motegi H et al**: Gastrointestinal Manifestations of Behçet's Disease. *Clinical Gastroenterology* **14**: 1769–1776, 1999 (in Japanese)
- 7) **Hirohata T, Kikuchi H**: Chokan-Behçet-byo: Nanchi-sei byoutai no chiryo-senryaku (Strategy of treatment for sever lesion of intestinal Behçet's Disease.). *Intern Med* **93**: 309–311, 2004 (in Japanese)
- 8) **Tolia V, Abdullah A, Thirumoorthi MC et al**: A case of Behçet's disease with intestinal involvement due to Crohn's disease. *Am J Gastroenterol* **84**: 322–325, 1989
- 9) **Masugi J, Matsui T, Fujimori T et al**: A case of Behçet's disease with multiple longitudinal ulcers all over the colon. *Am J Gastroenterol* **89**: 778–780, 1994
- 10) **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 Gastroentol* **95**: 2848–2851, 2000
- 11) **Naganuma M, Iwao Y, Kashiwagi K et al**: A case of Behçet's disease accompanied by colitis with longitudinal ulcers and granuloma. *J Gastroenterol Hepatol* **17**: 105–108, 2002
- 12) **Behçet's Disease Research Committee of Japan**: Behçet's disease: a guide to diagnosis of Behçet's disease. *Jpn J Ophthalmol* **18**: 291–294, 1974
- 13) **Mizushima Y**: Recent research into Behçet's disease in Japan. *Int J Tissue React* **10**: 59–65, 1988
- 14) **Suzuki Kurokawa M, Suzuki N**: Behçet's disease. *Clin Exp Med* **4**: 10–20, 2004
- 15) **International Study Group for Behçet's Disease**: Criteria for diagnosis of Behçet's disease. *Lancet* **335**: 1078–1080, 1999
- 16) **Nakane K, Masaki F, Hashimoto T et al**: Recent epidemiological features of Behçet's disease in Japan. *In* Behçet's disease (Wechsler B, Godeau P eds), pp145–151, Excerpta Medica, Amsterdam (1993)
- 17) **Shimizu T, Ehrlich GE, Inaba G et al**: Behçet Disease (Behçet syndrome). *Semin Arthritis Rheum* **8**: 223–260, 1979

腸管 Behçet 病患者の消化器病変は非回盲部においても認められる
—当科に入院した腸管 Behçet 病患者の臨床的特徴—

¹東京女子医科大学膠原病リウマチ痛風センター

²東京女子医科大学医学部病理学（第二）

コバシガワ ツヨシ ナンケ ユキ オダ ヒデアキ ヤマナカ ヒサシ コタケ シゲル
小橋川 剛¹・南家 由紀¹・小田 秀明²・山中 寿¹・小竹 茂¹

〔目的〕 Behçet 病 (BD) は原因不明の全身性の多臓器病変である。この度、我々は当科に入院した BD 患者について臨床症状、検査項目などを解析し、その臨床的特徴を明らかにすることを目的とした。〔対象・方法〕 最近 11 年間に当科入院の BD 患者 51 例 (男性 16 例, 女性 35 例, 平均年齢 ± 標準偏差 39.5 ± 12.2 歳) の臨床症状、検査項目を解析し、その臨床的特徴を明らかにすることを目的とした。これら全症例は日本人で、BD の厚生労働省診断基準および国際診断基準の両方を満たした。さらに、大腸内視鏡検査が施行された 33 例について、生検で得られた病理標本の組織学的検討も行った。〔結果〕 BD 患者 51 例中 33 例 (64.7%) で腸管症状を訴え、その腸管症状を訴えた 33 例中 20 例 (60.6%) が腸管 BD と診断された。残りの腸管症状を訴えなかった 18 例中 1 例 (5.56%) が大腸内視鏡検査で腸管 BD と診断された。腸管 BD 患者 21 例中 18 例 (85.7%) に回盲部病変を認めた。この 18 例中 10 例は回盲部病変のみだったが、他の 8 例では非回盲部にも病変を認めた。残りの 3 例が非回盲部病変のみだった。つまり、非回盲部病変は 21 例中 11 例 (52.4%) に認められた。内視鏡所見では腸管 BD 患者 21 例に円状や類円状の小潰瘍を認めた。回盲部病変を認めた 18 例は、深掘れの大円形、輪状または不整形潰瘍を認めた。炎症性腸疾患でいわれる線状潰瘍、数石状粘膜・炎症性ポリープ型、浮腫・充血・びらん型、腫瘍様多発隆起病変型は認めなかった。〔結語〕 腸管 Behçet 病患者の消化器病変は回盲部のみではなく非回盲部においても認められる。