

## A Case of Human Leukocyte Antigen (HLA) B27-Positive Intestinal Behçet's Disease with Crohn's Disease-Like Anal Fistulas

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**ABSTRACT:** A 49-year-old male was admitted to our hospital with complaints of perianal pain, bloody stool, and high-grade fever due to perianal abscess. Drainage was carried out; however, the patient's complaints worsened, and biopsy findings of colonoscopy showed ulcerative colitis-like lesions. The patient was diagnosed as having Behçet's disease with intestinal involvement, did not have HLA-B51, but did have HLA-B27. We describe a case of Behçet's disease with colitis, making a differential diagnosis of inflammatory bowel disease difficult.

**KEYWORDS:** anal fistula, Behçet's disease, HLA-B locus, inflammatory bowel diseases, spondyloarthropathy

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### Introduction

Behçet's disease is a systemic inflammatory disorder of unknown etiology, and it can be life-threatening.<sup>1</sup> Behçet's disease cases are distributed worldwide but are especially prevalent in Japan, the Middle East, and some Mediterranean countries.<sup>1</sup> Susceptibility to Behçet's disease is associated with the human leukocyte antigen (HLA)-B51 allele in many ethnic groups.<sup>1</sup> Intestinal Behçet's disease is a specific subtype of Behçet's disease,<sup>2</sup> and the lesions can be distributed along the full length of the gastrointestinal tract from the mouth to the anus.<sup>1,3–5</sup> However, gastrointestinal involvement seldom emerges during the course of Behçet's disease.<sup>6</sup> Extraintestinal manifestations of inflammatory bowel disease are variably reported as important and equivocal in distinguishing inflammatory bowel disease from Behçet's disease.<sup>1,3,5–7</sup> Enteropathic arthritis, one of the extraintestinal manifestations of inflammatory bowel disease, is a type of spondyloarthropathy (SpA) that is famous for its genetic association with the HLA-B27 allele in many

ethnic groups.<sup>8–10</sup> Here, we describe a HLA-B51-negative, HLA-B27-positive, male patient with intestinal Behçet's disease without ocular lesions who underwent resection of the large intestine despite immunosuppressive therapy. We followed this patient over a decade. The present case is rare, being on the borderline between Behçet's disease and inflammatory bowel disease with regard to intestinal lesions.

### Case Report

A 49-year-old male was admitted to our hospital for the purpose of emergency drainage on March 29, 2000 (day 1). He was suspected of having Crohn's disease (CD), because he had a 2-month history of perianal pain, bloody stool, and high-grade fever of around 40 degrees Celsius. He was treated with oral antibiotics and oral nonsteroidal anti-inflammatory drugs (NSAIDs); however, almost of all those drugs were ineffective. Drainage was made for his grade 4 anal fistula, and



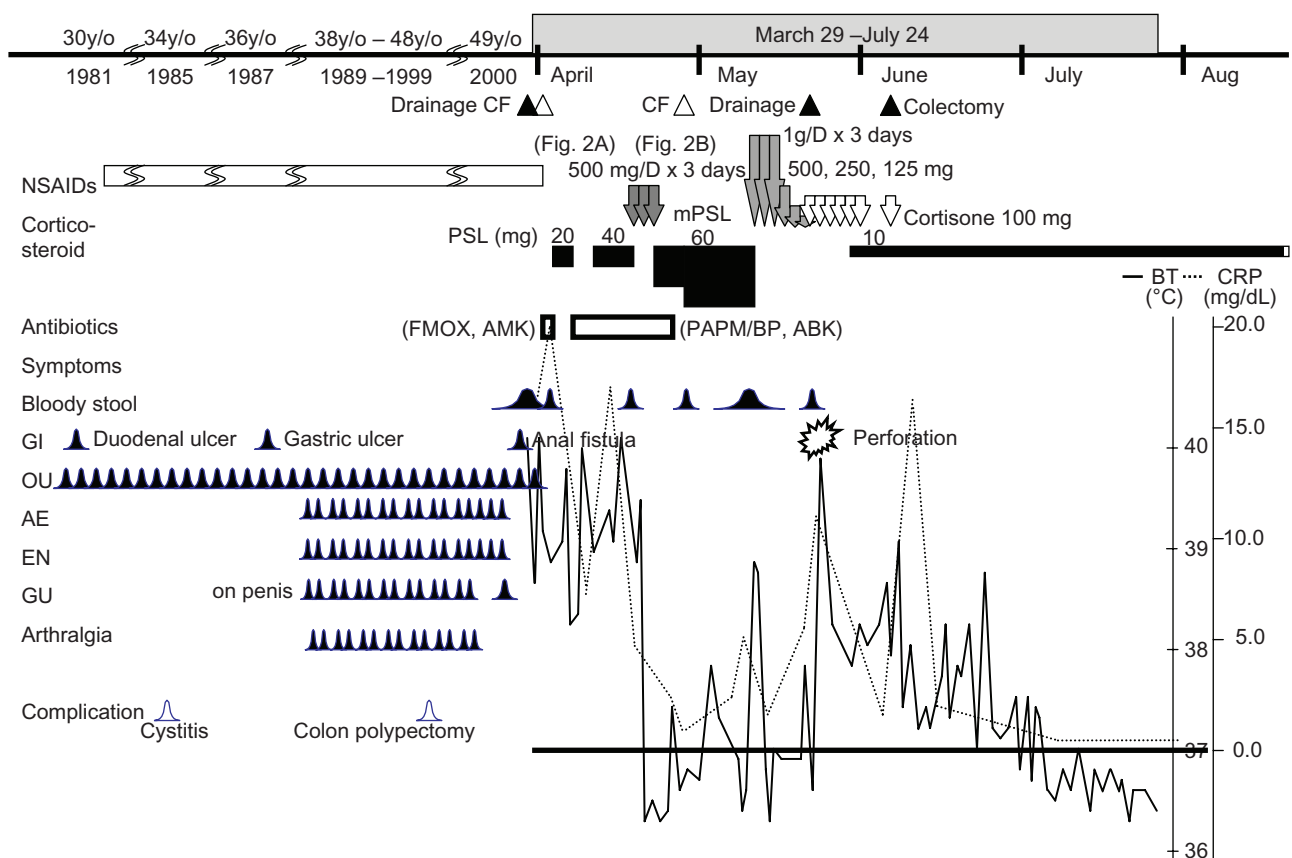
partial necrosis of the external anal sphincter was revealed; however, no additional abnormal mucosal lesions were found on his rectum by proctoscopy, confirmed after the drainage, and his complaints decreased. However, on day 6, the bloody stool recurred suddenly, with multiple punched-out ulcers and bleeding from the rectum to the sigmoid colon revealed by proctoscopy (Figs. 2A, 4).

The patient's father had ankylosing spondylitis (AS), and his mother died of peritonitis due to appendicitis. He was a hard worker with a stressful job and had been a heavy smoker (30 cigarettes a day) since he was 29 years of age; however, he did not drink alcohol. He had cystitis when he was 34 years of age and a colon polyp that was resected as soon as it was discovered when he was 48 years of age (February 1999).

The patient had a history of recurrent oral aphthous ulcers since before age 30; recurrent ulcers in the stomach and duodenum in his 30s; high-grade fever and polyarthritides since age 39; recurrent genital ulcers on his penis, recurrent skin lesions, erythema nodosum on his legs, and acuneiform eruption on his cervicofacial or truncal areas since age 40. Furthermore, bloody stool was noticed with a high-grade fever around

February 2000; however, oral and genital ulcers were absent at the time of his first visit on referral to our hospital.

Upon admission in March 2000, the patient was 170 cm tall and weighed 55 kg. An acuneiform eruption was present on his cervicofacial area. However, other symptoms of Behçet's disease, such as oral aphthous ulcers, genital ulcers, ocular lesions, polyarthritides, and the pathergy test were negative. Neurological findings were unremarkable. The patient's complete blood count showed anemia: red blood cell count at  $276 \times 10^4/\mu\text{L}$  (normal range of our laboratory are shown in parentheses following all laboratory values reported for this patient) ( $410\text{--}530 \times 10^4/\mu\text{L}$ ), hemoglobin at 8.1 g/dL ( $14\text{--}18 \text{ g/dL}$ ), and he matocrit at 25.2% ( $40\%\text{--}55\%$ ), mild leukocytosis at  $10,000/\mu\text{L}$  ( $4000\text{--}9000/\mu\text{L}$ ), and mild thrombocytosis at  $38.1 \times 10^4/\mu\text{L}$  ( $12\text{--}36 \times 10^4/\mu\text{L}$ ). Blood chemistry data were as follows: hypoproteinemia and hypoalbuminemia at 5.7 g/dL ( $6.5\text{--}8.0 \text{ g/dL}$ ) and 2.1 g/dL ( $4.1\text{--}5.1 \text{ g/dL}$ ), respectively; indicating mild liver disorder: aspartate and alanine aminotransferase levels both at 71 IU/L ( $10\text{--}33$  and  $4\text{--}30 \text{ IU/L}$ , respectively); lactic dehydrogenase level of 304 IU/L ( $210\text{--}500 \text{ IU/L}$ ); alkaline phosphatase level of 695 IU/L



**Figure 1.** Clinical course of the present case.

**Notes:** white arrowhead, colon fiber scope examination (CF); black arrowhead, operations of drainage or colectomy; white square, nonsteroidal anti-inflammatory drugs (NSAIDs); black square, prednisolone (PSL); gray arrow, methylprednisolone (mPSL); white arrow, cortisone; black mountain, each recurrent symptoms of Behçet's disease; white mountain, complications of the present case; polygonal line, transition of body temperature in the hospital; jagged balloon, perforation.

**Abbreviations:** OU, oral aphthous ulcer; AE, acuneiform eruption; EN, erythema nodosum; GU, genital ulceration; GI, gastro-intestinal lesions; BT and solid polyline, body temperature and its transition; CRP and broken polyline, C-reactive protein and its transition.

(167–345 IU/L); hyperbilirubinemia: total and direct bilirubin values at 1.4 mg/dL (0.2–1.2 mg/dL) and 0.9 mg/dL (0.0–0.4 mg/dL), respectively; total cholesterol value of 85 mg/dL (130–219 mg/dL), and normal renal function. Elevations in erythrocyte sedimentation rate at 102 mm/hour (10 mm/hour and lower) and C-reactive protein (CRP) level at 17.5 mg/dL (0.0–0.4 mg/dL) were observed. The patient had no detectable antinuclear antibodies or rheumatoid factor. Elevations of immunoglobulin (Ig) G and IgA at 2018 mg/dL (950–2050 mg/dL) and 446 mg/dL (90–400 mg/dL), respectively, and of complement titer: 50% hemolytic unit of 57.2 U/mg (29.0–48.0 U/mg) were observed. The HLA tests were positive for B27 and B60. Radiologic examinations such as X-ray and computed tomography (CT) of his joints showed no abnormalities, especially for the spine, iliosacral joints, and enthesopathy (Fig. 3).

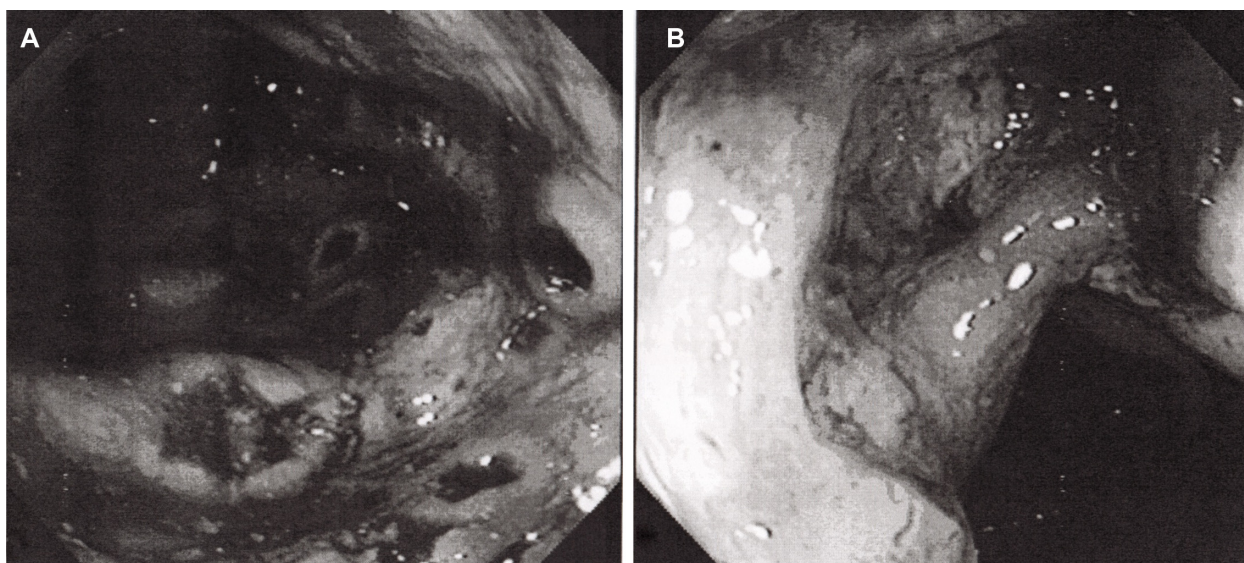
Biopsies of the sigmoid colon (Fig. 4) and rectum showed erosions and marked inflammatory cell infiltration in the lamina superficial epithelium with regeneration and crypts. Neither amebic granuloma nor other findings were observed in the lamina propria mucosae. Crypt abscesses and paneth cell metaplasia were absent. However, some glandular erosions of small lymphoid follicles and cryptitis were present. These findings of chronic and nonspecific colitis could not exclude a diagnosis of ulcerative colitis in a mildly active phase. Other microbiological cultures of sputum, urine, or stool were negative, and serological examinations were negative (eg, methicillin-resistant *Staphylococcus aureus*, *Mycobacterium tuberculosis*, and cytomegalovirus). Moreover, malignancy examinations were all negative.

From day 10, treatment with daily 20 mg prednisolone (PSL) was started to relieve the bowel inflammation. However, on day 20 massive bleeding occurred. An emergency colonoscopy

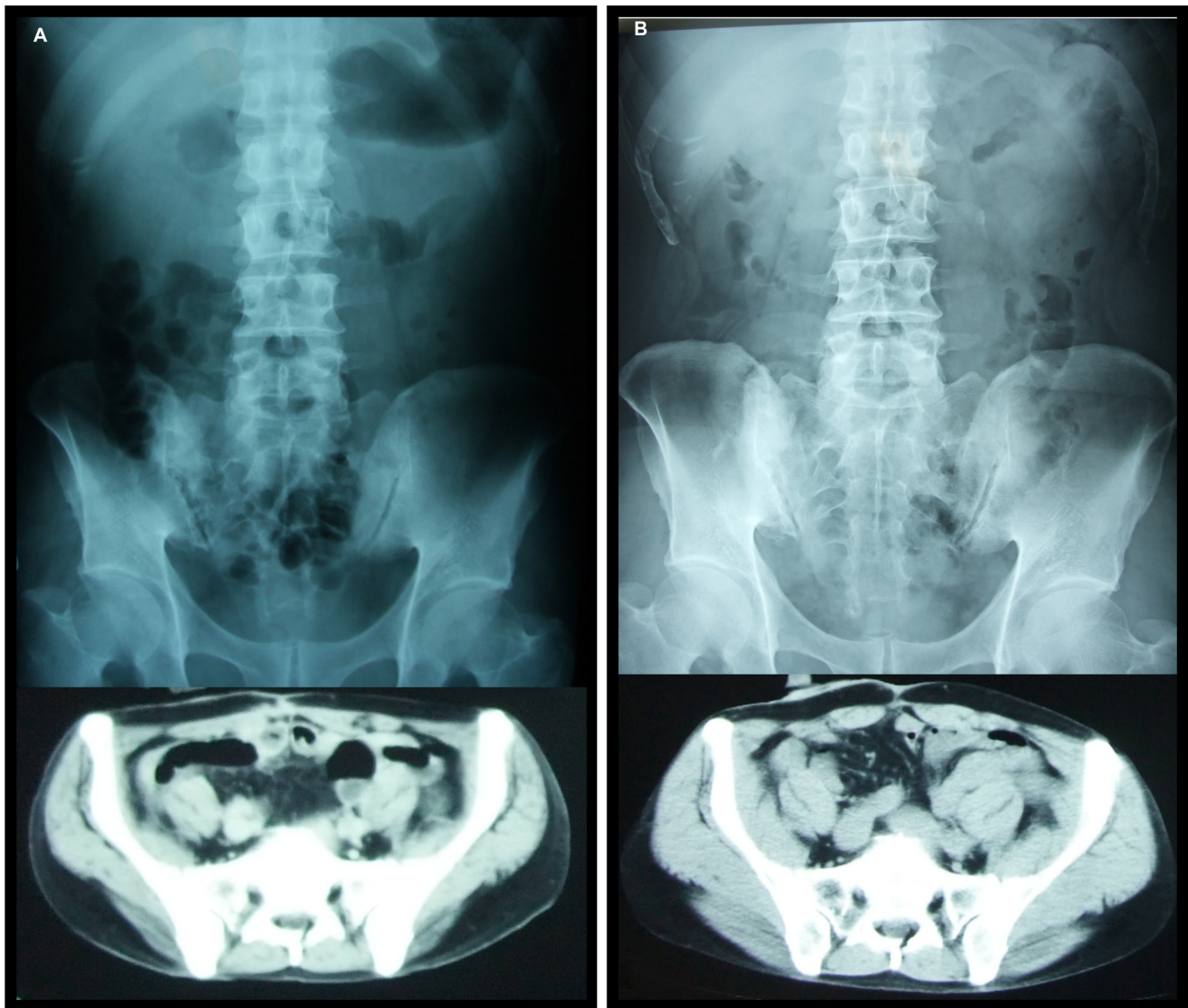
examination (Fig. 2B) revealed colorectal inflammation from the terminal ileum to the rectum, particularly in the ascending colon area, showing multiple punched-out ulcers and bleeding in their bases. Biopsy findings of the ileum and ascending colon on day 20 were similar to those of the sigmoid colon and rectum on day 6 (Fig. 4).

The patient's course of fever with oral aphthous ulcer, genital ulceration on the penis, acuneiform eruption, and polyarthritis without bone destruction on the elbows, wrists, knees, and ankles, all recurred and fulfilled both the international and Japanese diagnosis criteria for Behçet's disease.<sup>2,4</sup> Moreover, his present colitis indicated intestinal Behçet's disease, even though the pathergy test was negative, his neurological findings were unremarkable, and his eye examination revealed no evidence of uveitis. Steroidal pulse therapy with soluble methylprednisolone (s-mPSL) 500 mg daily from day 21 to 23 and oral PSL 40 mg daily as post-steroidal pulse therapy were started. The dose of PSL was increased to 60 mg because of increased fever on day 30. The fever had risen by 39 degrees by day 34. His diarrhea became more dark-reddish, and on day 43, colonoscopy was performed and revealed multiple simple ulcers throughout the colon and terminal ileum. Biopsy of the ascending and sigmoid colon showed findings similar to those on day 20. Unfortunately, his bloody diarrhea appeared recurrently, and his CRP level increased from 2.1 to 7.1 mg/dL. Despite a second course of steroid pulse therapy with s-mPSL 1 g daily from day 44 to 46, followed by s-mPSL 300 mg daily from day 47, gastrointestinal perforation occurred that night. Emergency abdominal drainage and ileostomy were performed on day 48 (May 15), and perforated sites were observed in the rectum and transverse colon.

Postoperative therapy for intestinal Behçet's disease was daily hydrocortisone with a tapering dose of 200 mg, 100 mg,



**Figure 2.** Results of colonoscopy. Multiple punched-out ulcers and multiple aphthous ulcers on the sigmoid colon on April 4, 2000 (A), and on the ascending colon on April 18, 2000 (B).



**Figure 3.** X-ray and CT of the sacroiliac joint and the lumbar spine. There was no lesion of sacroiliitis or of spondylitis on July, 2000 (A), or June 1, 2007 (B).

and 50 mg for 2 days each, followed by soluble PSL 15 mg daily thereafter. His Behçet's disease symptoms seemed to improve, but the fever persisted and did not decrease, being over 40 degrees Celsius on day 56. Thus, total colectomy (Fig. 5A), including terminal ileum and ileostomy, were conducted on day 70 (June 6). The findings of his resected colon (Fig. 5) were as follows: in the whole 130 cm length from the terminal ileum to rectum (Fig. 5A), subcutaneous abscesses with necrotic tissue adhesions were found throughout, although microbiological and serological examinations of samples from those abscesses revealed no findings, and inflammation was absent from the serous coat of the large intestine. On microscopic examination, punched-out ulcers at stage U1-3 with sharp edges were found throughout the colon (Fig. 5B); irregular oval ulcers were seen from the ascending colon to the sigmoid colon, with one in the descending colon being 5 cm in longitudinal length with perforation. Ulcer scars were seen diffusely in the sigmoid colon

and the rectum, suggesting similar ulcers from the ascending colon to the sigmoid colon; fibrosis was seen in the periulcer submucosa (Fig. 5C). Neither extension nor reduction in the muscularis propria, atrophic granuloma suspicious of Crohn's disease, vasculitis, ischemic changes, infection, or dysplasia suggesting malignancy were seen; diffuse inflammatory cell infiltrates were found in the nonperforated regions with fissures through the fascia (Fig. 5D).

Abnormal findings of endoscopic and radiologic examinations have been absent from small intestine series examined since the patient's discharge, except in February 2001, 10 months after the total colectomy, when a transient ulcerative lesion was revealed in the ileum. Corticosteroids were withdrawn 3 years after the total colectomy. In 2010, a decade after total colectomy, mild manifestations of Behçet's disease—oral aphthous ulcer, acuneiform eruption, and erythema nodosum—were present recurrently, and thus 5-aminosalicylate

1.5 g daily was continued. X-ray images of the sacroiliac joints and whole spine showed no abnormalities, and the patient did not meet the European Spondyloarthropathy Study Group (ESSG) criteria for SpA<sup>11</sup> or the Modified New York criteria for AS.<sup>12</sup>

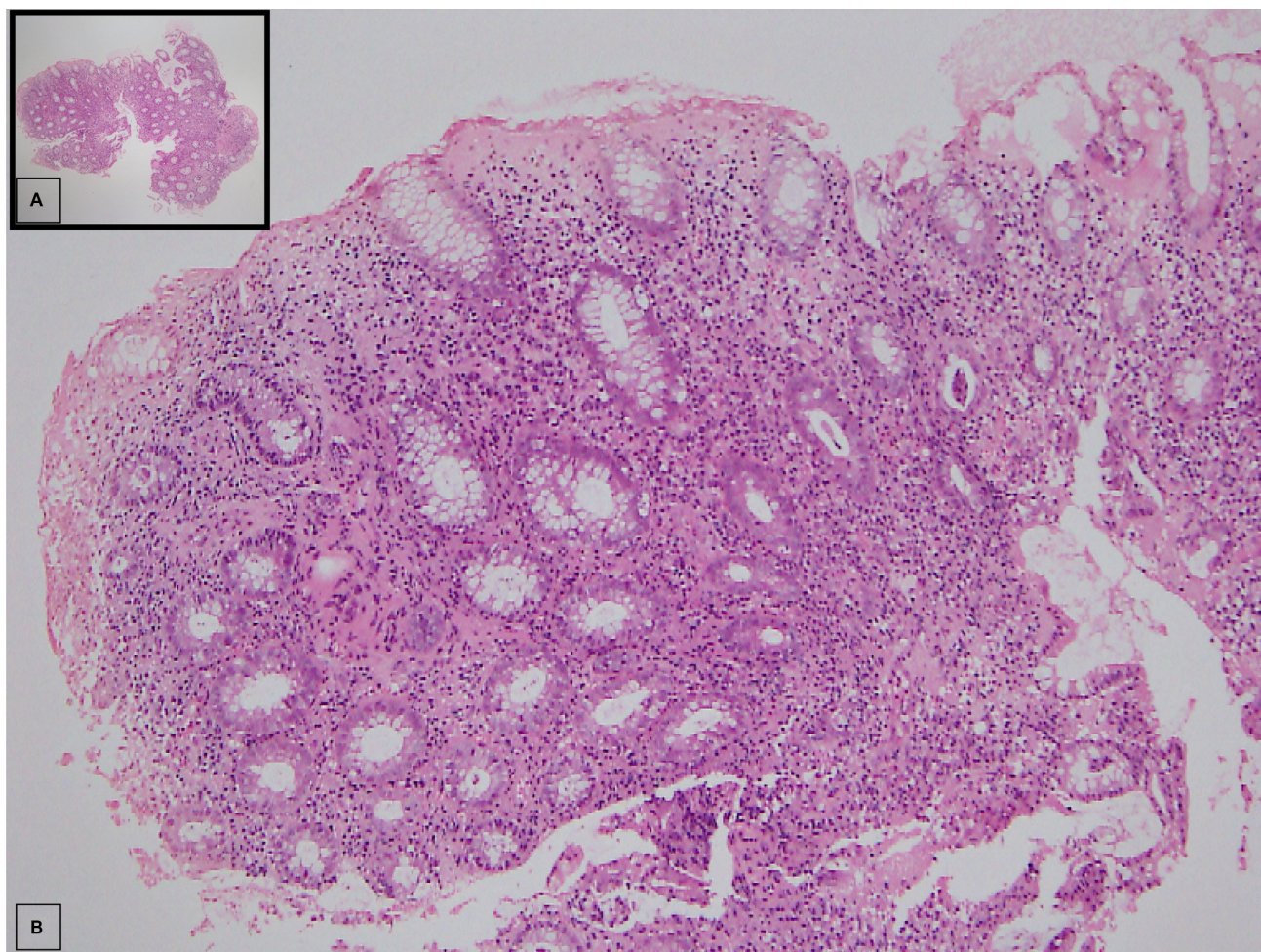
## Discussion

Intestinal lesions in Crohn's disease are characterized by the presence of longitudinal ulcers with a cobblestone appearance and noncaseating epithelioid granuloma; moreover, genital lesions with some perianal abscess or fistula are seen in patients with Crohn's disease.<sup>6,7,13</sup> Intestinal Behçet's disease is characterized by round and oval punched-out ulcers that are seldom accompanied by granulomas,<sup>6,7,13</sup> and we did not find much in the literature regarding perianal abscess in patients with Behçet's disease in PubMed. Inflammation in Crohn's disease is due to chronic colitis.<sup>13</sup> Thus, the present case can be distinguished from Crohn's disease. In contrast to the ulcers characteristic of ulcerative colitis, the ulcers in Behçet's disease are most commonly found in the terminal ileum and cecum, although they are also sometimes found in the rectum.<sup>5</sup> The

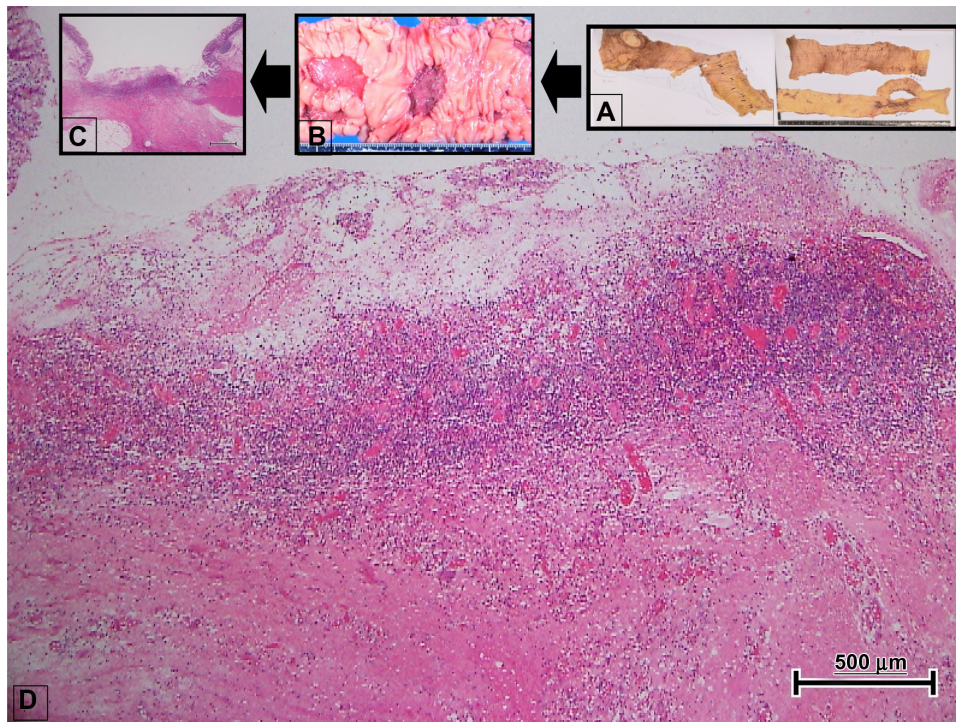
present case presented first with an anal fistula and could not be pathologically distinguished from ulcerative colitis.

Inflammatory bowel disease cases are collectively viewed as extraintestinal manifestations; arthritis, uveitis, oral aphthous ulcers, erythema nodosum, and venous thromboembolism<sup>8-10,14-18</sup> are typical clinical features in Behçet's disease,<sup>2,4</sup> and their courses frequently run independently of the course of the intestinal diseases.<sup>8-10,14-19</sup> In the present case, the digestive symptoms of bloody stool, anal fistula, and bowel lesions on colonoscopy were remarkable. Although both the international and Japanese Behçet's disease criteria<sup>2,4</sup> list recurrent oral aphthous ulcers as the most axial symptom, these were inconspicuous when the patient first arrived at our hospital. Thus, Behçet's disease was enumerated among the differential diagnoses while taking the considerably detailed history of the patient.

HLA-B51 is a closely related genetic factor in patients with Behçet's disease,<sup>1</sup> while HLA-B27 is a closely related genetic factor in patients with SpA.<sup>8-10,14-18</sup> Moreover, HLA-B27 is significantly more common among patients with inflammatory bowel disease with sacroiliitis, spondylitis,



**Figure 4.** Microscopic findings of sigmoid colon biopsy: in a low-power field (A) and in a high-power field (B).



**Figure 5.** Findings of the resected colon: macroscopic findings of the whole area (A) and the region of colon ulcers (B) and microscopic findings of the colon ulcer in a low-power field (C) and in a high-power field (D).

enthesitis, peripheral arthritis, erythema nodosum, uveitis, and oral ulcers.<sup>8–10,14–18</sup> We found some reports of patients with ulcerative colitis or Crohn's disease having HLA-B51,<sup>15,20</sup> but they were written in Japanese. Enteropathic arthritis, one of the extraintestinal manifestations of inflammatory bowel disease, is a type of spondyloarthritis (SpA) that is famous for its genetic association with the HLA-B27 allele in many ethnic groups.<sup>8–10</sup>

HLA-B27 and HLA-B51 are related to arthritis and the ocular lesions of Behçet's disease, respectively.<sup>21</sup> HLA-B27 may constitute a significant prognostic marker for disease severity.<sup>22,23</sup> A relationship between HLA-B51 and SpA was reported,<sup>24,25</sup> and some SpA cases without HLA-B27 but with HLA-B51<sup>24</sup> could not fulfill either the international or Japanese criteria for Behçet's disease.<sup>2,4</sup> The present case was HLA-B51 negative but HLA-B27 positive; moreover, the patient's father was a patient with AS. We followed the patient's disease course for 10 years, from 2000 to 2010, but no SpA symptoms developed. In addition, he developed cystitis without symptoms of reactive arthritis.

In summary, we describe a case of HLA-B27-positive but B51-negative intestinal Behçet's disease in a male presenting not only with Crohn's disease-like anal fistulas but also whose father was a patient with AS. After a 10-year course following total colectomy, his diagnosis of intestinal Behçet's disease remained unchanged. In other words, our initial diagnosis that the patient presented with Behçet's disease was supported by his 10-year-course of follow-up. In the present case,

HLA-B27 may play a role in the pathogenesis of intestinal lesions; however, many additional studies are needed to determine the role of HLA-B27 in the pathogenesis of Behçet's disease.

### Author Contributions

Analyzed the data: TK, YN, MT, KI, HY, SK. Wrote the first draft of the manuscript: TK. Contributed to the writing of the manuscript: TK, YN, MT, KI, HY, SK. Agree with manuscript results and conclusions: TK, YN, MT, KI, HY, SK. Jointly developed the structure and arguments for the paper: TK, YN, MT, KI, HY, SK. Made critical revisions and approved final version: TK, YN, MT, KI, HY, SK. All authors reviewed and approved of the final manuscript.

### DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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