Intestinal Perforations in Behçet’s Disease

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Abstract Behçet’s disease accompanied by intestinal involvement is called intestinal Behçet’s disease. The intestinal ulcers of Behçet’s disease are usually multiple and scattered and tend to perforate easily, so that many patients require emergency operation. The aim of this study is to determine the extent of surgical resection necessary to prevent reperforation and to point out the findings of concurrent oral and genital ulcers and multiple intestinal perforations in all patients of our series. During a 25-year study period, information of 125 Behçet’s disease cases was gathered. Among the 82 patients who were diagnosed with intestinal Behçet’s disease, 22 cases had intestinal perforations needing emergency laparotomy. We investigated and analyzed these cases according to the patients’ demographic characteristics, clinical presentations, laboratory data, and surgical outcome. There were 14 men and 8 women ranging from 22 to 65 years of age. Nine cases were diagnosed preoperatively, and the diagnoses were confirmed in all 22 cases during the surgical intervention. Surgical resection was performed in every patient, with right hemicolecystomy and ileocecal resection in 11 cases, partial ileum resection in 8 cases with two reperforations, and ileocecal resection in 3 cases with one reperforation.

Keywords Behçet’s disease · Intestinal ulcers · Intestinal perforations

Introduction

Behçet’s syndrome is a systemic process affecting multiple organ systems. Surgeons need to be aware of the lethal complication of Behçet’s disease with intestinal ulcers, which tend to perforate at multiple sites. A review of the literature reveals that involvement of the gastrointestinal tract is not infrequent. Most cases reported in the literature are in the eastern Mediterranean countries and Japan. We report here a series of 22 cases of intestinal Behçet’s disease with multiple perforations, treated by emergency surgical resections.

Materials and Methods

During the 25 years from July 1979 to June 2004, 125 patients with Behçet’s disease were encountered at the Cardinal Tien Hospital and Tri-Service General Hospital, Taipei, Taiwan. Eighty-two patients were diagnosed as having intestinal Behçet’s disease, which was based on the Mason–Barnes criteria (Table 1). Among these patients,
22 had intestinal perforations (see Table 2 for the details of these 22 cases).

In 13 of these 22 cases, the diagnosis was confirmed at surgical resection for multiple perforations. Nine of the 22 cases had Behçet’s disease with intestinal involvement, which was confirmed preoperatively, six were confirmed by endoscopic examination; two by radiological examination; and one patient had gastrointestinal symptoms of intermittent abdominal pain, diarrhea, and nausea.

### Table 1 The Mason–Barnes Criteria

| Major Symptoms                  | Minor Symptoms               |
|--------------------------------|------------------------------|
| Buccal ulcerations             | Gastrointestinal lesions     |
| Genital ulcerations            | Thrombophlebitis             |
| Ocular lesions                 | Cardiovascular lesions       |
| Skin lesions                   | Arthritis                    |
|                                | Neurologic lesions           |
|                                | Family history               |

Three major or two major and two minor criteria are required to establish the diagnosis of Behçet’s disease.

### Results

#### Patient Characteristics

There were 14 men and 8 women in the 22 cases investigated. The ages of the patients with perforated intestinal Behçet’s disease ranged from 22 to 65 years, with a mean age of 35.3 years. The age at onset of symptoms of Behçet’s disease varied from 18 to 64 years on diagnosis, with a mean age of 33.1 years.

In Table 2, oral ulcers with gastrointestinal symptoms and signs were found concurrently in all 22 cases, genital ulcers in 19 cases, ocular lesions in 12 cases, and skin lesions in 11 cases. The painful oral ulcers (Fig. 1) occurred on oral mucosa, lips and in the larynx. They varied from 2 to 8 mm in size and invariably healed without scarring. The genital ulcers (Fig. 2) resembled the oral ulcers in appearance and course, except that vaginal ulcers were painless. Four patients had anterior uveitis and eight had a mild relapsing conjunctivitis as their sole ocular lesion. The nodular cutaneous lesions resembled those of erythema nodosum and were chronic and multiple. Most lesions

### Table 2 Intestinal Perforation in Behçet’s Disease Encountered at CTH and TSGH (from 1979 to 2004, n=22)

| Case No. | Age (years) | Sex | Oral Ulcer | Genital Ulcer | GI S & S | Ocular Signs | Skin Lesion | Pathergic Reaction | Arthritis or Arthalgia |
|----------|-------------|-----|------------|---------------|----------|--------------|-------------|---------------------|-------------------------|
| 1        | 38          | M   | +          | +             |          |              |              |                     |                         |
| 2        | 45          | M   | +          | +             | +        |              |              |                     |                         |
| 3        | 26          | F   | +          | −             | +        |              |              |                     |                         |
| 4        | 47          | M   | +          | +             | +        |              |              | −                   |                         |
| 5        | 28          | F   | +          | −             | +        |              |              | −                   |                         |
| 6        | 36          | F   | +          | +             | +        |              |              | −                   |                         |
| 7a       | 22          | M   | +          | +             | −        | −            |              | −                   |                         |
| 8        | 42          | M   | +          | +             | +        |          |              |                     |                         |
| 9        | 22          | M   | +          | +             | −        | +            |              | +                   |                         |
| 10       | 28          | F   | +          | −             | −        |              |              | −                   |                         |
| 11       | 65          | M   | +          | +             | −        |              |              | +                   |                         |
| 12a      | 23          | M   | +          | +             | −        | +            |              | −                   |                         |
| 13       | 32          | F   | +          | −             | +        |              |              | −                   |                         |
| 14       | 24          | M   | +          | +             | −        |              |              | +                   |                         |
| 15       | 34          | M   | +          | +             | −        |              |              | −                   |                         |
| 16       | 41          | F   | +          | +             | −        |              |              | +                   |                         |
| 17b      | 38          | M   | +          | +             | +        |              |              | +                   |                         |
| 18       | 33          | M   | +          | +             | −        |              |              | +                   | −                       |
| 19       | 25          | M   | +          | +             | −        | +            |              | −                   | +                       |
| 20       | 48          | F   | +          | +             | +        |              |              | −                   |                         |
| 21       | 29          | M   | +          | +             | −        |              |              | +                   | −                       |
| 22       | 50          | F   | +          | +             | +        |              |              | −                   | +                       |

Plus signs mean that the feature is present; minus signs mean that the feature is not present.

CTH = Cardinal Tien Hospital, TSGH = Tri-Service General Hospital, S & S = symptoms and signs

* a Reperforations at ileum after partial resection of ileum

* b Reperforation at ileum after ileocecal resection
occurred on the chest wall, back (Fig. 3), and legs. Biopsy of dermal subcutaneous lesions had been done in 10 cases. In each of them, a nonspecific vasculitis of subcutaneous capillaries and venules was present (Fig. 4). Pathergic reaction was found positive in 7 of 10 patients.

There were no specific immunologic abnormalities in any of the 16 patients tested (Table 3). The levels of immunoglobulin were variable. IgG was increased in 3 of 16 patients, IgA in 5 patients, and IgM in 3 patients. There was a significant decrease of IgG in two patients and of IgA in one patient. The total hemolytic complement was normal in all 16 serum samples. Alpha-2 globulin was increased in 9 of 16 patients, and gamma globulin was increased in seven patients.

Multiple concurrent penetrating ulcers (Fig. 5) were found in all 22 cases, with multiple perforation sites identified from terminal ileum to the ascending colon (Table 4). The size and number of perforated ulcers were variable, ranging from 0.2 to 6 cm in size, and 4 to 16 in number. The perforations were found at the ileocecal region and ascending colon in 10 cases, at the terminal ileum in 8 cases, and at the cecum and ascending colon in 4 cases.

Operative Treatment and Outcome

All 22 perforated intestinal Behçet’s disease cases were confirmed at operation, with nine of them correctly diagnosed preoperatively. Surgical resection of the perforated intestinal ulcers was done in all cases, with right hemicolectomy and ileocecal resection in 11 cases, partial ileum resection in 8 cases, and ileocecal resection in 3 cases. No reperforation occurred in the group of patients who underwent right hemicolecotmy and ileocecal resection. However, two reperforations occurred in patients who underwent partial ileum resection alone and one in the ileocecal resection group.
The pathologic study of the resected specimens showed nonspecific inflammatory reactions with the infiltration of lymphocytes and plasma cells as the predominant finding (Fig. 6). Histological sections from the ulcer walls showed changes consistent with a nonspecific ulcerative inflammatory process and infiltration containing both plasma cells and chronic inflammatory cells.

After operation on these 22 patients with Behçet’s disease and intestinal perforation, four patients died during the postoperative course due to septic shock, which was present prior to the surgical intervention; three died from complications of hypertension and diabetes mellitus; and three were lost to follow-up. Thus, only 12 patients are still under observation, without evidence of gastrointestinal complications up to this date. The remaining 60 cases of intestinal Behçet’s disease, without perforations, are still under surveillance.

Discussion

In 1937, Behçet described a chronic relapsing triple-symptom complex of oral ulceration, genital ulceration, and ocular inflammation. Over the years, it has become apparent that the process is a systemic recurrent inflammatory disease affecting a number of organs consecutively. In 1940, Bechgaard first described intestinal involvement in Behçet’s disease. Tsukada et al. proposed the term “intestinal Behçet’s disease” in 1964. Baba et al. agreed to this proposal and cited 49 cases of the disease treated from 1975. Since then, the number of operations reported has increased rapidly, but perforated intestinal Behçet’s disease is still rarely reported.

In a large review series, Oshima and colleagues reported that 40% of patients with Behçet’s disease had gastrointestinal complaints, such as nausea, vomiting, and abdominal pain. The age at onset of these symptoms ranges from 16 to 67 years, and the male-to-female ratio ranges from 1.5:1 to 2:1. Our cases were in accordance with this reported age range and sex ratio. The third decade is the most commonly reported age of onset for Behçet’s disease, and the fourth decade for intestinal Behçet’s disease. In our study, intestinal Behçet’s disease occurred at a mean age of 33.1 years. However, Behçet’s disease and intestinal involvement were diagnosed simultaneously in some of these patients, most of whom had already experienced systemic manifestations.

The exact cause of this disease still remains an enigma. Current hypotheses include allergic vasculitis of small vessels, autoimmune disease, and immunologic deficiency. The deposition of immune complexes in the walls of small blood vessels was found by the laboratory results of three of our cases, and this process has been proposed as one of the underlying pathologic mechanisms in intestinal Behçet’s disease.

Since no clinicopathologic findings are pathognomonic in this disease, the diagnosis is made on the basis of combinations of various clinical symptoms and signs. Mason and Barnes constructed an elaborate set of major and minor criteria for diagnosis. They suggested the triad of buccal ulceration, genital ulceration, and eye lesion and skin lesion as major symptoms. The minor symptoms included gastrointestinal lesions, arthritis, thrombophlebitis,

| Table 3 Laboratory Data |
|-------------------------|
| Case No. | Immunoglobulins (mg/dl) | Serum Complement (mg/dl) | Globulin (%) |
|          | IgG | IgA | IgM | C’3 | C’4 |
| 1        | 1,976 | 375 | 250 | 145 | 38 | 13.8 | 23.8 |
| 2        | 1,726 | 245 | 174 | 92  | 40 | 12.0 | 10.8 |
| 4        | 2,150 | 400 | 240 | 110 | 45 | 14.2 | 24.6 |
| 5        | 1,500 | 590 | 300 | 38  | 25 | 10.5 | 18.0 |
| 7a       | 740  | 185 | 60  | 90  | 38 | 7.8  | 14.3 |
| 8        | 1,180 | 195 | 140 | 59  | 32 | 6.6  | 12.2 |
| 9        | 2,270 | 464 | 262 | 127 | 46 | 14.0 | 16.2 |
| 11       | 1,850 | 380 | 250 | 190 | 50 | 12.5 | 23.5 |
| 12a      | 1,300 | 320 | 235 | 88  | 39 | 9.6  | 15.0 |
| 14       | 2,350 | 490 | 295 | 180 | 48 | 13.3 | 25.0 |
| 16       | 680  | 98  | 56  | 150 | 35 | 13.0 | 21.8 |
| 17b      | 1,650 | 475 | 280 | 76  | 34 | 9.4  | 12.5 |
| 18       | 1,800 | 290 | 150 | 105 | 45 | 13.8 | 23.2 |
| 19       | 2,418 | 581 | 209 | 166 | 40 | 14.4 | 28.0 |
| 21       | 1,880 | 330 | 250 | 180 | 35 | 10.5 | 20.0 |
| 22       | 1,985 | 386 | 228 | 168 | 38 | 13.8 | 24.2 |

Normal range: IgG 950–2,110, IgA 170–410, IgM 54–262, C’3 47–27, C’4 4.8–8.8

Figure 5 Surgical specimen of ileocecal region showing multiple penetrating ulcers.
cardiovascular lesions, neurologic lesions, and family history. Three major criteria or two major criteria and two minor criteria are necessary for diagnosis. These various symptoms are not usually present at the same time. If we hold the original triple-symptom complex as a prerequisite for the diagnosis, cases may be missed. In 1990, the International Study Group for Behçet’s Disease introduced a diagnostic criteria requiring the presence of oral ulcerations plus any two of the following: genital ulcerations, typical eye lesions, typical skin lesions, or positive results to a pathergy test. However, some reports have shown that almost 20% of patients with Behçet’s disease presented without oral lesions initially. Furthermore, 2–5% of patients did not show any oral lesions at all. In our series, all patients had manifestations of concurrent oral ulceration. All perforated cases present oral or genital ulcerations at the same time. Because we warned that patients of intestinal Behçet’s disease may have abdominal pain and oral or genital ulcerations concurrently, intestinal perforations should always be kept in mind.

A phenomenon of pathergy was first described by Blobner in 1937 and was further elaborated by Katzenellenbogen in 1968. It consists of an intradermal test applied to Behçet’s disease patients with a sharp needle prick causing skin hypersensitivity, which is characterized by the formation of a sterile pustule 24 to 48 h after the trauma. Biopsy at the intradermal puncture site is taken 48 h after for histopathologic evaluation. In a study conducted by Tuzum et al., this reaction was found to be positive in 84% of 58 patients with the disease, as compared to 3% of 90 healthy controls. A positive pathergic reaction should make us aware of the possibility of the disease in the presence of any of the accepted symptoms of this process. However, the recent

![Figure 6](image)

**Figure 6** Chronic inflammatory response and perivascular infiltration (hematoxylin and eosin; 10×10).
results and interpretations of pathergy tests have varied widely according to the technical aspects of the tests and ethnic differences of the patients.

The histological lesions in Behçet’s disease are rather uncharacteristic. Nonspecific perivascular infiltrations of plasma cells and lymphocytes are usually found in the cutaneous and mucosal lesions. The intestinal ulcers in Behçet’s disease are characterized not only by the absence of the granulomatous formation of Crohn’s disease, but also by deeper penetration of the ulcers to areas nearer to serosa membrane than the ulcers of ulcerative colitis. The ulcers tend to be undermined, and the submucosal connective tissues are usually destroyed. The bases of the ulcers are avascular with edema-like swelling and crater-shaped formation around the ulcer margin. These ulcers are usually found in the terminal ileum and the cecum, but they may be present at any site throughout the digestive system and tend to perforate at multiple sites. The gross pathologic characteristics of our intestinal Behçet’s disease included perforations at multiple sites concurrently in variable sizes and configurations, extending from the ileocecal region to ascending colon, in accordance with the reported literature.

The medical treatment of the intestinal Behçet’s disease remains unsettled. The beneficial effect of steroid therapy has not been convincing in most series. It may control the disease initially, but recurrences are common. Topical application of corticosteroids decreases the ocular inflammation, and is also useful in relieving the pain of oral ulcers. Haim and Sherf reported a favorable response to fresh blood and plasma in cases of Behçet’s disease, but the nature of the useful component in hemotherapy is unknown. In our two patients with perforations, steroid therapy was given for 2 weeks after surgery with favorable outcomes.

Resection of the ileocecal region or the right half of the colon is the usual operation in the treatment of gastrointestinal complications. In our series, perforations at multiple sites were found in all cases; right hemicolectomy and ileocecal resection were performed in 11 cases without reperforation; ileocecal resection in 3 cases with one reperforation; and partial resection of the ileum in 8 cases with two reperforations.

Conclusion

Because concurrent oral and genital ulcers were found in all patients in our series, the presentation of this seemingly innocuous clinical manifestation along with gastrointestinal symptoms should raise the level of suspicion that intestinal involvement and complications of perforations may have already happened. The other constant finding among our 22 patients is that all the intestinal perforations were located between the terminal ileum and the ascending colon. Therefore, to prevent reperforations, wide excision of the terminal ileum with right hemicolectomy is recommended for perforated intestinal Behçet’s disease. We found out that the specimens of the resected bowel of the 19 nonreperforated patients all had more than 60 cm of terminal ileum, but those of the three perforated cases had less than 60 cm. Furthermore, the perforation sites were all at 10 to 12 cm proximal to the anastomosis. This is the main reason we recommend the resection of up to 80 cm of ileum from the ileocecal valve at the time of right hemicolectomy.

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References

1. Haim S, Gilhar A. Clinical and laboratory criteria for the diagnosis of Behçet’s disease. Br J Dermatol 1980;102:361–362.
2. Ketch LL, Buerk CA, Liechty RD. Surgical implication of Behçet’s disease. Arch Surg 1980;115:759–760.
3. Kasahara Y, Tanaka S, Nishino M, Umemura H, Shirama S, Kuyama T. Intestinal involvement in Behçet’s disease. Review of 136 surgical cases in Japanese literature. Dis Colon Rectum 1981;24:103–106.
4. Baba S, Maruta M, Ando K, Teramoto T, Endo I. Intestinal Behçet’s disease: Report of five cases. Dis Colon Rectum 1976;19:428–440.
5. O’Duffy JD, Carney JA, Deodhar S. Behçet’s disease: Report of 10 cases, three with new manifestations. Ann Intern Med 1971;75:556–570.
6. Chajek T, Fainaru M. Behçet’s disease. Report of 41 cases and a review of the literature. Medicine 1975;54:179–196.
7. Hyman NM, Sagar HJ. Behçet’s syndrome: Unusual multisystem involvement and immune complexes. Postgrad Med J 1980;56:182–184.
8. Bayraktar Y, Ozaslan E, Van Thiel DH. Gastrointestinal manifestations of Behçet’s disease. J Clin Gastroenterol 2000;30:144–154.
9. Lehner T. Oral ulceration and Behçet’s syndrome. Gut 1977;18:491–511.
10. Yazici H, Tuzun Y, Pazarli H, et al. Influence of age on set and patient’s sex on the prevalence and severity of manifestations of Behçet’s syndrome. Ann Rheum Dis 1984;43:783–789.
11. Brodie TE, Ochsner JL. Behçet’s syndrome with ulcerative esophagitis: Report of the first case. Thorax 1973;28:637–640.
12. Gamble CN, Wiesner KB, Shapiro RF, et al. The immune complex pathogenesis of glomerulo-nephritis and pulmonary vasculitis in Behçet’s disease. Am J Med 1979;66:1031–1039.
13. Sakane T, Takeno M, Suzuki N, et al. Behçet’s disease. N Engl J Med 1999;341:1284–1291.
14. International Study Group for Behçet’s Disease. Criteria for diagnosis of Behçet’s disease. Lancet 1990;335:1078–1080.
15. Lee S. Diagnostic criteria of Behçet’s disease: Problems and suggestions. Yonsei Med J 1997;38:365–369.
16. Kim HJ, Bang D, Lee SH, et al. Behçet’s syndrome in Korea: A look at the clinical picture. Yonsei Med J 1988;29:72–78.
17. James DG. Behçet’s syndrome. N Engl J Med 1979;301:431–432.
18. Fresko I, Yazici H, Bayramicli M, et al. Effect of surgical cleaning of the skin on the pathergy phenomenon in Behçet’s syndrome. Ann Rheum Dis 1993;52:619–620.
19. Dilsen N, Konice M, Aral O, et al. Comparative study of the skin pathergy test with blunt and sharp needles in Behçet’s disease: Confirmed specificity but decreased sensitivity with sharp needles. Ann Rheum Dis 1993;52:823–825.
20. Lockhart JM, McIntyre W, Caperton EM. Esophageal ulceration in Behçet’s syndrome. Ann Intern Med 1976;84:572–573.
21. Thach BT, Commings NA. Behçet’s syndrome with “aphthous colitis”. Arch Intern Med 1976;136:705–709.
22. Boe J, Dalgaard JB, Scott D. Mucocutaneousocular syndrome with intestinal involvement: A clinical and pathological study of four fatal cases. Am J Med 1958;25:857–867.
23. Smith GE, Col LT, Kime LR, Pitcher JL. The colitis of Behçet’s disease: A separate entity? Colonoscopic findings and literature review. Dig Dis 1973;18:987–1000.
24. Empey DW. Rectal and colonic ulceration in Behçet’s disease. Br J Surg 1972;59:173–175.
25. Parkin JV, Wight DGD. Behçet’s disease and the alimentary tract. Postgrad Med J 1975;51:260–264.
26. Levack B, Hansson D. Behçet’s disease of the esophagus. J Laryngol Otol 1979;93:99–101.
27. Fujisawa K, Ueno H. Four cases of intestinal Behçet. Nippon Shokakibyo Gakkai Zasshi 1980;1805–1809.
28. O’Connell OJ, Courtney JV, Riddell RH. Colitis of Behçet’s syndrome-radiologic and pathologic features. Gastrointest Radiol 1980;5:173–179.
29. Goldstein SJ, Crooks DJM. Colitis in Behçet’s syndrome: Two new cases. Radiology 1978;128:321–323.
30. Kimura T, Tsukiyama J, Masamune O, Iwakoshi K, Ohshiba S, Watanabe S. Case of intestinal Behçet who responded to steroid and salazopyrin treatment. Gastroenterol Endosc 1981;23:1424–1430.
31. Lee KS, Kim SJ, Lee BC, et al. Surgical treatment of intestinal Behçet’s disease. Yonsei Med J 1997;38:455–460.