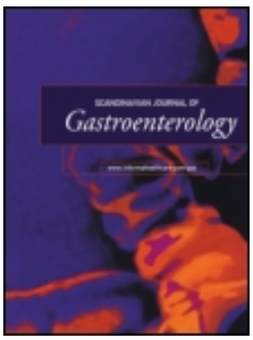

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CASE REPORT

Single or multiple perforations with varying locations as a complication of intestinal Behçet's disease: Report of three cases

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Abstract
Intestinal ulcers in Behçet's disease (BD) tend to cause perforation with significant morbidity. The optimal surgical procedure in such cases is controversial and the postoperative period can be eventful with an unpredictable course. We report three cases of perforations with varying locations in three patients with long-standing Behçet's disease. Two patients required two and one patient required four operations. It is emphasized that the clinician must be alert in a patient with BD when abdominal symptoms accompany the clinical picture. As soon as the diagnosis is reached, surgical intervention with limited resection must be performed. Endoscopic examination and careful medication play major roles in the follow-up.

Key Words: *Behçet's disease, intestinal Behçet's disease, perforation*

Introduction

Behçet's disease (BD) is an inflammatory multisystemic disorder characterized by symptoms including recurrent oral and genital ulcerations and skin lesions in association with relapsing inflammatory ocular lesions [1]. Duration and frequency of the exacerbations and remissions during the course of the disease are unpredictable. This vasculitic disorder may involve both arteries and veins of all sizes, the joints, the central nervous system and the gastrointestinal tract [2]. No clinicopathologic finding is pathognomonic and the diagnosis is still based primarily on the clinical criteria [3]. Non-specific gastrointestinal complaints such as pain, diarrhea, constipation, nausea, anorexia and abdominal distension are common during the indolent and chronic course of the disease (15–65%) [4–6]. On the other hand, gastrointestinal ulcers are rare and were found in only 1–2% of all cases [4,5]. When these ulcers are confirmed by radiography, endoscopy or surgery, the disease is termed as intestinal BD. Substantial gastrointestinal involvement varies in different geographical locations and the rate is 0–5% in Mediterranean countries, including Turkey [2,7,8].

This report documents three cases of perforation with varying locations due to intestinal BD. The BD diagnoses of our patients were made in accordance with the criteria set by the International Study Group for Behçet's Disease [3].

Case 1

A 45-year-old man presented to the emergency department with an 8-h history of severe and diffuse abdominal pain, nausea, vomiting and diarrhea. He had a past history of BD which had been diagnosed 20 years earlier and treated with 1 mg/day colchicine during exacerbation periods. On physical examination, the patient had a temperature of 37.1°C, blood pressure of 110/70 mmHg and heart rate of 100/min. There was rebound tenderness and muscular rigidity especially in the right lower quadrant of the abdomen. The patient had multiple oral ulcers and and an active ulcer on the scrotum and there were multiple pustular lesions on the trunk. Laboratory

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data revealed a hemoglobin rate of 11 g/dl, a white blood cell count of 18,000/mm^3 and ESR of 74 mm/h. Subphrenic free air on abdominal X-ray film was recognized. A diagnosis of peritonitis was made due to a perforation of the hollow viscus, and an emergency laparotomy was performed. Approximately 500 cc purulent fluid was aspirated from the pelvis. There was a single perforation arising from a discrete 1.0×1.0 cm oval punched-out ulcer in the terminal ileum 5 cm proximal to the ileocecal valve and the ascending colon seemed edematous. A right hemicolectomy with a terminal ileostomy was performed. The postoperative period was uneventful apart from a wound infection, which cleared up on day 14. Treatment with colchicine (1 mg/day) and sulfasalasine (4 g/day) was commenced. Histopathologic examination showed acute ulceration with nonspecific inflammatory cells infiltrating surrounding capilleries and venules.

Three months after the initial operation, colonoscopy and endoscopy from the ileostomy were performed and all the findings were within normal limits. The patient was hospitalized for reversal of the ileostomy and the operation was performed without any complications. Sulfasalazine was discontinued at the end of the first year. The patient has been followed-up for 9 years since the initial operation and has remained free from any flare-up of intestinal ulcers.

Case 2

A 29-year-old woman had presented to the emergency department of another hospital with severe diffuse abdominal pain, nausea and vomiting of 3 days' duration. For 6 weeks she had been suffering from abdominal pain, diarrhea and fever, which responded to antibiotics for one week. She had a past history of BD which had been diagnosed 9 years earlier and treated with 1 mg/day colchicine during exacerbation periods. The frequency of exacerbations of oral, genital and skin lesions had increased during the past year. At the same hospital, she underwent an emergency laparotomy with a diagnosis of acute abdomen. Laparotomy had revealed a perforation arising from a discrete 0.5×1.0 cm geographical shaped punched-out ulcer in the transverse colon. There were additional multiple nonperforated ulcers of the same nature in the terminal ileum, cecum, ascending and transverse colon. The surgeon had primarily sutured the perforation after debriding the edges.

On the third postoperative day the patient was referred to our center with a presumptive diagnosis of sepsis. She had a temperature of 37.7°C, blood pressure of 110/50 mmHg and heart rate of 112/min. There was a 1-cm atrophic ulcer scar on the right labia majoris. On admission, laboratory data included a hemoglobin rate of 8.6 g/dl, white blood cell count of 26,700 mm^3, CRP of >200 mg/l and ESR of 61 mm/h. The next day her vital signs worsened and she underwent an emergency laparotomy with the presumptive diagnosis of intra-abdominal sepsis. All the ulcers observed in the initial laparotomy were perforated. There was leakage from the sutured transverse colon lesion. A right hemicolectomy with a terminal ileostomy was performed. The postoperative period was uneventful except for a wound infection, which cleared up on day 16. Treatment with colchicine (1 mg/day), mesalazine (750 mg/day) and prednisolone (20 mg/day) was commenced. Histopathologic examination showed multiple perforated punched-out ulcerations and focal lymphocytic venulitis (Figures 1 and 2). There was a slight increase in intraepithelial lymphocytes. Distant from the ulcers, the colon appeared normal.

Prednisolone was gradually discontinued. Three months after the initial operation, colonoscopy and endoscopy from the ileostomy were performed and all the findings were within normal limits. The patient was hospitalized for reversal of the ileostomy and the operation was performed without any complications.

The patient has been in follow-up for 18 months since the initial operation with colchicine and mesalazine treatment. She has remained free from any flare-up of intestinal ulcers since then.

Case 3

A 28-year-old man had presented to the emergency department of another hospital with severe diffuse abdominal pain, nausea and vomiting and diarrhea of 2 days' duration. He had a past history of BD

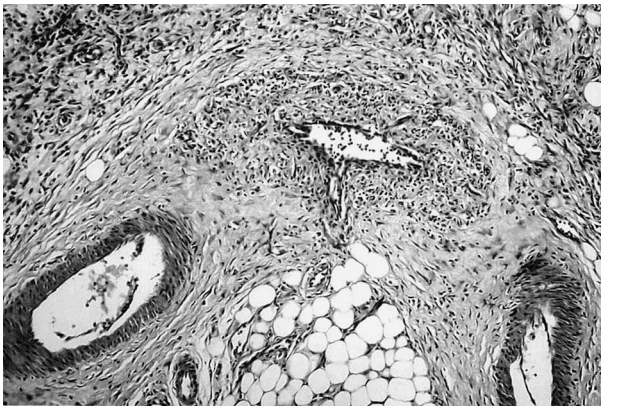

Figure 1. Mesenteric vessels far from the mucosal lesion; only the vein shows inflammatory cells in the muscular wall (X100, hematoxylin and eosin stain).

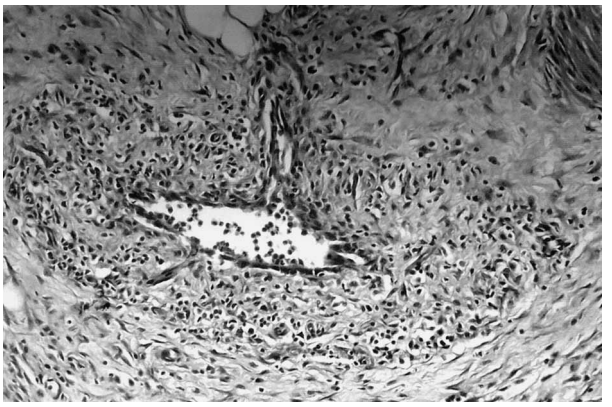

Figure 2. Inflammatory cells are mainly lymphocytes, supporting the diagnosis of lymphocytic venulitis ($\times 200$, hematoxylin and eosin stain).

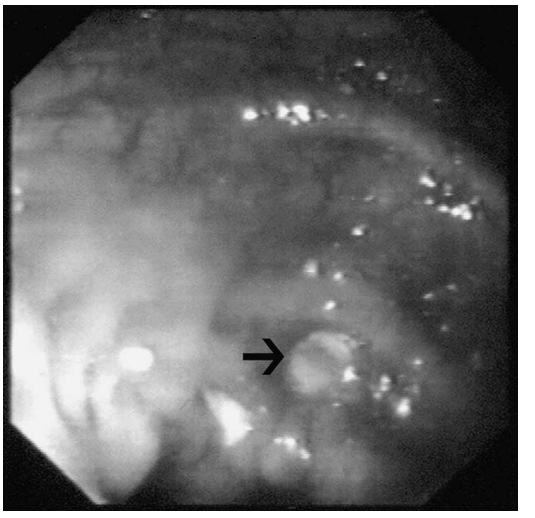

Figure 3. Endoscopic view of the largest ulcer in the ileocecal region.

which had been diagnosed 6 years earlier and was treated with 1 mg/day colchicine during the first year. Later, he stopped this therapy and follow-up but he intermittently suffered from abdominal pain and diarrhea. There, he underwent an emergency laparotomy with a diagnosis of perforated appendicitis. Two perforations were revealed by laparotomy; one in the second half of the transverse colon and the other in the sigmoid colon just distal to the splenic flexure. The surgeon had primarily sutured the perforations and after obtaining a biopsy specimen, he performed a transverse end colostomy. On the same day the patient was referred to our center. He had a temperature of 36.1°C, blood pressure of 110/70 mmHg and heart rate of 96/min. The patient had four oral aphthous ulcers and one ulcer on the scrotum with acneiform nodules on the trunk. Laboratory data included a hemoglobin rate of 12.1 g/dl, a white blood cell count of 11,500/mm^3, CRP of >200 mg/l and ESR of 64 mm/h. Treatment with colchicine (1 mg/day), mesalazine (750 mg/day) and prednisolone (20 mg/day) with appropriate antibiotics was commenced. Histopathologic examination showed acute ulceration and venous vasculitis.

Colonoscopy and endoscopy from the ileostomy revealed 5 ulcers in the ileocecal region, the largest having a diameter of 10 mm (Figure 3). Mesalazine in enema form was also initiated from the stoma. Prednisolone was gradually discontinued at the end of the first month.

On the second month of the initial operation there was still some purulent discharge from the wound, suggesting a colonic fistula. A colonoscopy was performed and slight hyperemia was seen in the closed end of the transverse colon. Endoscopy was also performed from the stoma and showed that the ulcers in the ileocecal region had healed. A new operation was planned for both the fistula and closure of the colostomy.

At laparotomy, dense, fibrous adhesions were seen, especially in the splenic flexure of the colon and around the transverse colon. After adhesiolysis, the fistula tract was resected and a colo-colostomy was performed. On day 9, a re-laparotomy was performed because of leakage from the anastomosis. A right hemicolectomy with terminal ileostomy was performed. On the fourth day of this operation, a laparatomy was performed again because of jejunal perforation and resection (nearly 20 cm) and terminal jejunosotomy was performed. After this operation, treatment with prednisolone was commenced again, in addition to mesalazine and colchicine. Histopathologic examination of the hemicolectomy material showed active colitis and examination of the small intestine showed severe foci of inflammation destructing the muscular layer. The patient was discharged at the end of the second month postoperatively and prescribed prednisolone (8 mg/day), colchicine (1 mg/day) and mesalazine (750 mg/day) medication. Prednisolone was gradually discontinued. The patient was followed-up in two-week periods. In the sixth month of his discharge, he suffered from exacerbation of oral, genital and skin lesions. Laboratory data included a hemoglobin rate of 13.6 g/dl, white blood cell count of 11,700/mm^3, CRP of >200 mg/l and ESR of 75 mm/h and slightly increased liver function tests. Upper abdominal ultrasonography showed cholelithiasis, which was not found in the initial examinations, and thickening of the walls of the small intestine in multiple segments. Later, endoscopies from the anorectum, ileostomy and jejunostomy were performed. The small intestine seemed normal up to the extent that the endoscope could be inserted. There were

superficial erosions and slight edema in the mucosa of the remaining colon. Prednisolone was commenced again and, in addition, azathioprine at a dose of 2.5 mg/kg/day was initiated. After two weeks, white blood cell count, CRP and ESR gradually returned to within the normal range while liver function tests still remained slightly increased. Oral, genital and skin lesions disappeared. The patient is still being closely followed-up in the seventh month of his discharge and we do not plan to reverse the stomas before a complete remission of one year has been achieved.

Discussion

Behçet's disease was originally described in 1937 as a triad of symptoms involving oral and genital ulceration and ocular inflammation [1]. In 1940 Bechgaard first described the intestinal involvement of BD [9]. This form of the disease accounts for approximately 1–2% of BD which sometimes leads to severe complications [4,5]. Hemorrhage, fistulization, penetration and perforation occur in up to 50% of intestinal BD [4,10,11]. Hemorrhage can be life-threatening and perforation can lead to pan-peritonitis, with a poor prognosis [4,5,11–13]. In most reports these complications are the indications for surgery. In a review by Kasahara et al., intestinal perforation or penetration was reported in 56% of all surgical cases [4].

The most frequent area of involvement is the ileocecal region (75%) (8). Discrete ulcers typically have a round or oval "punched-out" appearance and with a tendency to bleed or perforate. It has also been reported that in 14% of patients, the ulcers were longitudinal and these types of ulcers usually occurred in almost the entire colon (77%) [14]. Intestinal involvement is typically discontinuous [15]. Pathological examination reveals lymphocytic vasculitis involving small- and medium-sized vessels with aseptic neutrophil infiltration into the lesions.

Barium study and enteroclysis findings may be helpful in determining the presence, form and severity of intestinal involvement [7]. CT scans and MR imagining seem to be helpful in detecting the extent and identification of complications [16,17]. On the other hand, colonoscopy is the most useful tool in identifying ulcers, taking into consideration that the most frequent location is the ileocecal region. Furthermore, milder forms of the disease that can respond to medical treatment can be disclosed at an earlier stage.

The optimal surgical procedures for intestinal BD are controversial. Toynton reported successful simple closure of 7 ileal ulcer perforations in one case, but the patient required reoperations for severe adhesions because of inflamed segments [18]. In our one case, because of such an attempt, the patient required a reoperation because of suture failure in the inflamed tissue. In the other case, although a diverting end colostomy had been performed, fistulization occurred from the closed distal end just proximal to the primary sutured perforation site. Some researchers advocate a wide resection with normal intestine to decrease the chance of recurrence [4,5,12] while others recommend a limited resection involving only the affected segment [10,19]. No significant relationship has been shown between the recurrence, reoperation rates and the extent of the normal intestinal segment that should be included in the resection specimen [19,20]. Therefore, as in our cases, minimal surgical intervention should be taken into consideration, i.e. the resection of only the involved segments, but maximum attention must be paid in order not to overlook other small, shallow ulcers in different locations. One of our patients had his fourth laparotomy because of an overlooked jejunal ulcer. If such ulcers are seen, these must also be resected.

The postoperative recurrence rate is 40–87.5%, mostly demonstrated near the anastomotic site at 2-year follow-ups [4,19–23]. Patients with a history of perforation or fistulization have a recurrence rate of 88% in the fifth postoperative year [19]. Furthermore, the rate of patients requiring reoperations is 37.5–47% [16,23]. Applying intra-operative endoscopy seems to lower these recurrences [20].

Achieving a complete remission with medical treatment in the early postoperative period is also essential to preclude recurrences. Sulfasalazine and corticosteroids have been the preferred drugs as in other inflammatory bowel diseases. However, because of the unknown pathogenesis of the disease, no definite therapies are available. Many systemic or local medications are described alone or in different combinations with colchicine and corticosteroids [14,22–32]. We were able to achieve remissions with colchicine, corticosteroid and mesalazine. One patient needed additional therapy with azathioprine.

Conclusion

Immediately a patient with BD reports abdominal symptoms, intestinal involvement should be borne in mind and all efforts must be focused on revealing the possible underlying gastrointestinal pathology. Colonoscopies must be performed not only for diagnosis but also periodically in the follow-up to evaluate the effectiveness of the therapy and to demonstrate the recurrences that can respond to additional medical treatment.

Simple closure of the perforated ulcers must not even cross one's mind. During the operation, maximum attention must be paid in order not to overlook other small, shallow ulcers in different locations. If such ulcers are seen, these must also be resected.

If a proximal stoma has been performed after resection because of intra-abdominal contamination, patience must be exercised regarding the timing of the closure. A complete remission must be achieved with medical therapy and this must be demonstrated with endoscopy and radiography also performed from the stoma.

We experienced single or multiple perforations in various locations in three cases. Two patients required two and one patient required four operations. The postoperative course of the disease is difficult to predict. Careful medication plays a major role in this period and a multidisciplinary approach must be exhibited during the diagnosis, treatment and follow-up of intestinal BD. There may be significant morbidity and even mortality [4,5,12,15].

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