Histopathology of perforated gastrointestinal tracts in Behçet's disease: evidence for the critical role of thrombophilia

Sirs,

Gastrointestinal involvement in Behçet's disease (BD) is relatively common in East Asia, and is called intestinal BD (1, 2). Rapid perforation is one of the characteristic features in intestinal BD (1, 3, 4). However, its precise mechanism remains unclear. We carried out histopathological examination in a patient with intestinal BD, who received surgical operation due to perforation of the ileocecal ulcer.

A 55-year-old female, who had presented recurrent oral aphthous stomatitis, folliculitis, and genital ulcer without treatment, was admitted to the hospital near her home due to the right lower abdominal pain and bloody bowel discharge. On admission, physical examination revealed fever, oral and genital ulcers, folliculitis and tenderness at lower right abdomen without rebound tenderness. Endoscopic examination disclosed penetrating large deep ulcer in the ileocecal region. No free air was found on abdominal x-ray. Therefore, ileocecal resection was performed 7 days after the endoscopy. After the surgery, the patient presented low grade fever and tongue ulcer, which was successfully treated by sulfasalazine. She was discharged and referred to our hospital for follow-up. After the referral to our hospital, she has been treated with sulfasalazine and colchicine without recurrence of intestinal ulcer or exacerbation of BD for 15 years until now.

The resected materials contained 20 cm ileum and 21 cm colon (ascending colon and cecum). Macroscopic examination revealed the giant simple ulcer of cecum 6.6 cm x 9.0 cm x 0.5 cm, penetrating into the mesocolon (Fig. 1A). The perforation was shown to be caused by infarction of the intestinal wall, due to circulation disturbances. Thus, the most prominent microscopic feature of the perforated lesion was the presence of thrombophlebitis in mesenteric veins, but not in mesenteric arteries in subserosa, as well as the formation of arteriovenous anastomosis with increased proliferation of small vessels in the ulcer scar (Fig. 1B, upper). In the thrombophlebitis, infiltration of polymorph nuclear neutrophils along with mononuclear cells was observed (Fig. 1B, lower). Of note, in the most proximal perforated area there were many lymphoid follicles (Fig. 1C). The lymphoid follicles consisted of CD20+ B cells surrounded by CD3+ T cells (data not shown). The data indicate that venous occlusion due to thrombophlebitis is involved in the perforation of intestinal BD. Notably, in both ileal and colonic ends of the resected specimen, where there was no ulceration, marked transmural thrombosis from submucosa to subserosa was found (data not shown).

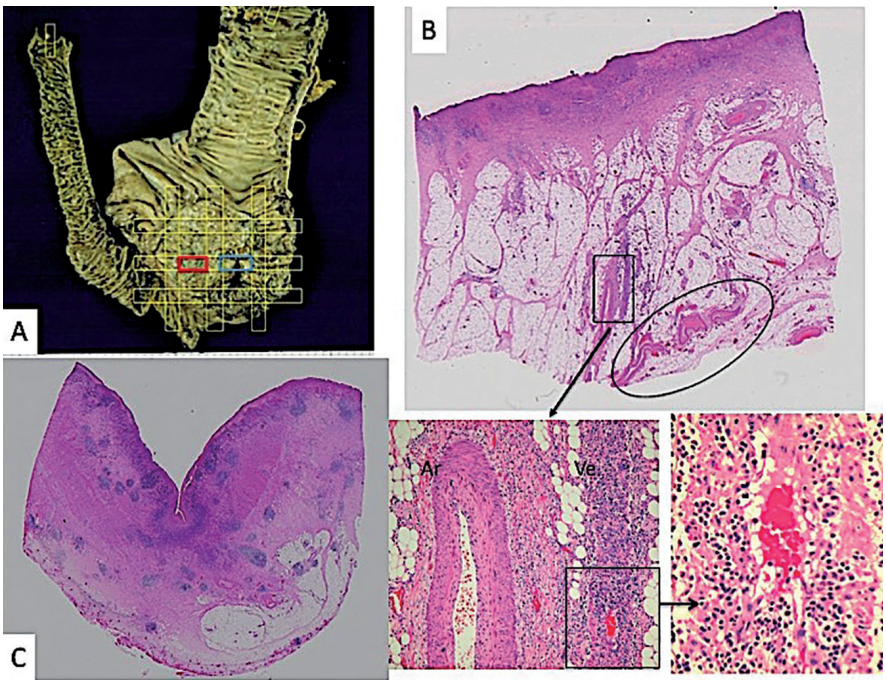

Fig. 1. Macroscopic and microscopic findings of the resected intestines.
A: Macroscopy of the resected intestines is shown with the giant simple ulcer of 6.6 cm x 9.0 cm x 0.5 cm in the cecum, penetrating into the mesocolon. Sections were set in a yellow grid form so that all the ulcerative lesions might be covered. Among the 22 sections, microscopic findings of representative 2 sections (red and blue rectangles) are examined histologically.
B: Loupe image of the section of the red rectangle in panel A shows formation of arteriovenous anastomosis with proliferation of small vessels (oval circle). In the lower left panel, magnified image of area indicated by rectangle in the loupe image is shown (Ar: artery; Ve: vein) along with the further magnified image of inflamed vein in the lower right.
C: Loupe image of the blue rectangle in panel A is shown, presenting multiple lymphoid follicles. Haematoxylin and eosin staining.

Neutrophilic phlebitis was remarkably seen in submucosal inflammatory lesions, but not in the adjacent arteries in intestinal BD (5). We further demonstrated that such thrombophlebitis was observed in mesenteric veins, but not in mesenteric arteries, in subserosa across the ulceration. Notably, neutrophil-dependent pathogenetic mechanism has been implicated in thrombosis in BD (6). Accordingly, infiltration of polymorph nuclear neutrophils along with mononuclear cells was observed in the thrombophlebitis in our patient, confirming the importance of neutrophils. The importance of vascular changes in the pathogenesis of intestinal BD might be supported by the fact that intestinal BD is frequently associated with vascular BD (7, 8).

The abundant lymphoid follicles in the perforated region suggest the involvement of humoral immunity in intestinal lesions. Consistently, anti-*Saccharomyces cerevisiae* antibody positivity was found in up to 44% of patients with intestinal BD and is associated with an increased surgical risk (9).

In conclusion, we have demonstrated that thrombophlebitis in the mesenteric veins, but not arteries, plays a pivotal role in the perforation in intestinal BD, suggesting that there might be distinct mechanisms of pathogenesis for intestinal BD, including mucosal inflammation and infarction due to venous obstruction. The degree of both components might determine various clusters of the disease.

S. Hirohata[1,2], *MD*
H. Kikuchi[1], *MD, PhD*
M. Ueda[3], *MD*
M. Kyogoku[4], *MD, PhD*

[1]Department of Internal Medicine, Teikyo University School of Medicine, Tokyo;
[2]Department of Rheumatology, Nobuhara Hospital, Hyogo;
[3]Department of Surgery, Shiraoka Central General Hospital, Saitama;
[4]Department of Pathology, Tohoku University School of Medicine, Sendai, Japan.

Please address correspondence to:
Shunsei Hirohata,
Department of Internal Medicine,
Teikyo University School of Medicine,
2-11-1 Kaga, Itabashiku,
Tokyo 173-8605, Japan.
E-mail: shunsei_tenpoint@yahoo.co.jp

ORCID iD: 0000-0003-1911-7383

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