

[CASE REPORT]

Diffuse Intestinal Ganglioneuromatosis Showing Multiple Large Bowel Ulcers in a Patient with Neurofibromatosis Type 1

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Abstract:

A 67-year-old Japanese man with neurofibromatosis type 1 underwent right hemicolectomy owing to abscess formation around the cecum. A pathological analysis revealed diffuse intestinal ganglioneuromatosis in the cecum and colon. Colonoscopy performed eight months after hemicolectomy revealed multiple ulcers throughout the colon and rectum. The colorectal ulcers failed to respond to conservative treatment and ultimately required surgical resection. Diffuse ganglioneuromatosis was observed again in the resected specimen. This report illustrates a rare manifestation of diffuse intestinal ganglioneuromatosis in a patient with neurofibromatosis type 1.

Key words: diffuse intestinal ganglioneuromatosis, neurofibromatosis type 1, colorectal ulcers

(Intern Med 56: 3287-3291, 2017)

(DOI: 10.2169/internalmedicine.8671-16)

Introduction

Neurofibromatosis type 1 is a genetic disorder that can involve the brain, spinal cord, nerves, and skin. Typical skin manifestations of this disease include multiple neurofibromas and café au lait spots. Plexiform neurofibromas, scoliosis, learning disabilities, and epilepsy also occur in some patients. In the gastrointestinal tract, neurofibromas, leiomyomas, and gastrointestinal stromal tumors arise in association with neurofibromatosis type 1 (1). Furthermore, although the prevalence of this condition is low, the proliferation of nerve ganglion cells, nerve fibers, and supporting cells of the enteric nervous system can be observed in the gastrointestinal tract, which is known to represent diffuse in-

testinal ganglioneuromatosis.

We recently encountered a case of neurofibromatosis type 1 diagnosed as diffuse intestinal ganglioneuromatosis, which we report here. It was noteworthy that the patient presented with a rare morphology showing multiple colorectal ulcers, in addition to concomitant anal fistula and a history of intra-abdominal abscess. We also review the literature describing cases with neurofibromatosis type 1 accompanied by diffuse intestinal ganglioneuromatosis.

Case Report

A Japanese man was diagnosed with neurofibromatosis type 1 at 23 years of age, based on the existence of café au lait spots and multiple cutaneous neurofibromas. One of the

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Received: December 7, 2016; Accepted: April 24, 2017; Advance Publication by J-STAGE: October 11, 2017

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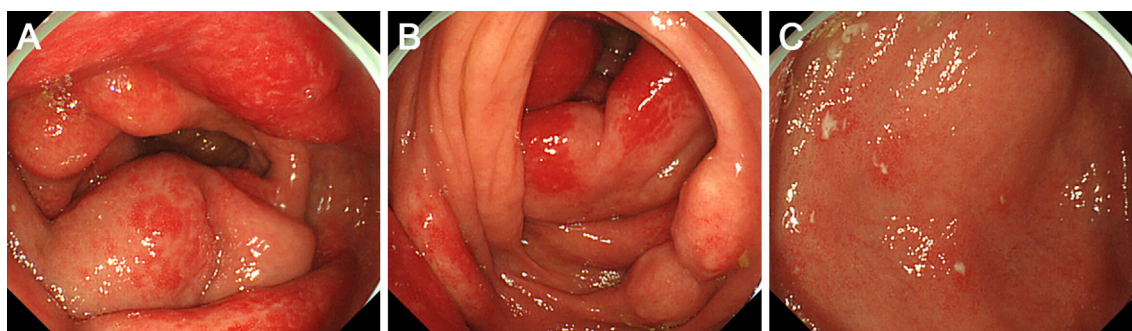


Figure 1. Colonoscopy images at 65 years of age. Colonoscopy reveals the emergence of a reddish surface on the tumors (A, B) and erosion in the transverse colon (C).

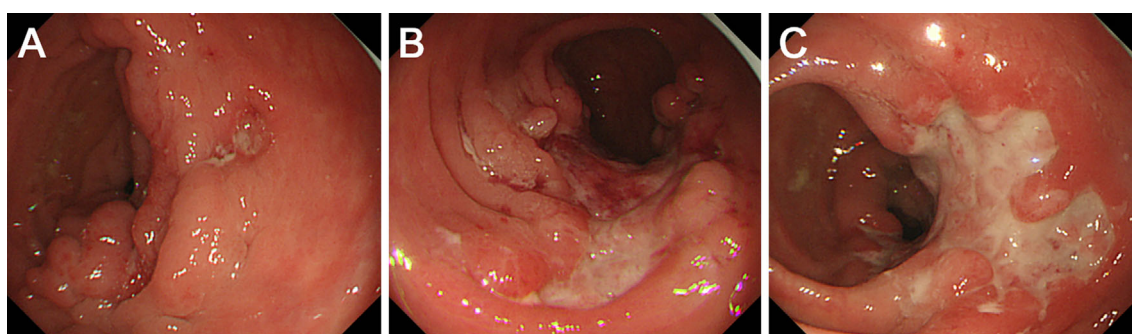


Figure 2. Colonoscopy images at 67 years of age. Multiple ulcers throughout the colon and rectum are observed.

cutaneous nodules was resected and was histologically confirmed as a neurofibroma. He had a history of 2 early esophageal cancers, both of which had been curatively treated via endoscopic submucosal dissection at 57 and 60 years of age. He had undergone injection sclerotherapy twice for anal fistula at 60 years of age. There was no family history of neurofibroma.

At 59 years of age, the patient underwent colonoscopy for screening purposes, and multiple submucosal tumors were identified in the ascending and transverse colon. He was asymptomatic, and biopsy sampling was not performed at that time. Colonoscopy performed at 65 years of age revealed the emergence of a reddish surface on the tumors and erosions in the ascending and transverse colon (Fig. 1). The cecum, descending and sigmoid colon, and the rectum were intact. Biopsy samples from the tumors contained interlacing fascicles of spindle cells and few differentiated ganglion cells, suggesting diffuse intestinal ganglioneuromatosis.

At 67 years of age, the patient presented with lower abdominal pain. Computed tomography imaging showed abscess formation around the cecum. Although the intra-abdominal abscess was partially improved after percutaneous drainage, the abscess recurred 15 days after the procedure. The patient therefore underwent right hemicolectomy to remove the abscess, which had adhered to the cecum. The pathological features of the resected cecum and ascending colon were compatible with diffuse intestinal ganglioneuromatosis. There were no ulcers in the mucosa, and a histo-

logical analysis revealed no fistula formation between the abscess and the bowel. The appendix was intact and did not contain proliferation of neural elements. The abscess disappeared, and the patient was discharged 50 days after admission.

Three months later, the patient experienced persistent abdominal pain. Treatment with tramadol failed to relieve his pain. He was referred to our hospital for further investigation and treatment of the abdominal pain. The patient had been taking irbesartan and benidipine for hypertension, in addition to tramadol. A physical examination revealed disseminated café au lait spots and cutaneous neurofibromas in the body. Conjunctival pallor was evident. There were Lisch nodules in both eyes. The patient had epigastric tenderness and a surgical scar in the abdomen from right hemicolectomy. There was no muscle guarding or rebound tenderness. His bowel sounds were weak. A laboratory examination revealed anemia (red blood cells: $3.84 \times 10^6/\mu\text{L}$, hemoglobin: 9.7 g/dL, hematocrit: 30.3%), hypoproteinemia (total protein: 5.5 g/dL, albumin: 2.3 g/dL), and inflammation [white blood cells: $7,830/\mu\text{L}$, erythrocyte sedimentation rate: 54 mm/h, C-reactive protein (CRP): 6.80 mg/dL]. Cytomegalovirus IgG antibody was positive; however, IgM antibody was negative. Both a cytomegalovirus antigenemia test and interferon-gamma release assay (T-SPOT.TB) showed negative results.

Colonoscopy performed eight months after hemicolectomy revealed multiple ulcers throughout the colon (Fig. 2)

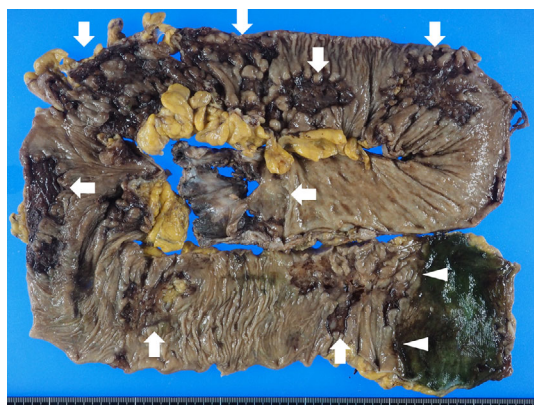


Figure 3. Surgically resected specimen after total colectomy with proctectomy. Multiple ulcers are seen in the resected gut mucosa (arrows). The arrowheads indicate anastomosis of the ileum to the transverse colon.

and rectum. The microscopic features of the biopsied specimen from the periphery of the colorectal ulcers were compatible with diffuse intestinal ganglioneuromatosis. Esophagogastroduodenoscopy showed a submucosal tumor, which was considered to be a gastrointestinal mesenchymal tumor based on the findings of endoscopic ultrasonography. Video capsule enteroscopy revealed multiple small, subpedunculated polyps in the jejunum and ileum. Ulcers were not present in the small intestine. Biopsy samples from the ileal polyp contained fascicles of spindle cells that were positive for synaptophysin, indicating the involvement of the ileum along with diffuse ganglioneuromatosis.

We proposed total colectomy to relieve the abdominal pain; however, the patient refused surgery. Two months later, his abdominal pain worsened, and he experienced anal pain with pus discharge from the anal fistula. Colonoscopy showed no change in the colorectal ulcers. Consequently, total colectomy with proctectomy was performed. Multiple ulcers were also identified in the resected specimen (Fig. 3, arrows). A pathological examination showed interlacing fascicles of spindle cells in the submucosa of the colorectum, which were positive for S100 staining and synaptophysin (Fig. 4A-C, arrowheads). Few differentiated ganglion cells were also present (Fig. 4A-C, arrows). In addition, binuclear cells were observed in the myenteric plexus (Fig. 4D, arrow), suggesting dysplastic proliferation of nerves. Thus, a final pathologic diagnosis of diffuse intestinal ganglioneuromatosis was made. There were no intranuclear or cytoplasmic inclusion bodies or cells stained positive for cytomegalovirus. Epithelioid cell granuloma was also absent. The capillary vessels in the mucosal and submucosal layers were congested and enlarged. Although some thrombus and intimal thickening were observed, infiltration of inflammatory cells was not noted in the blood vessels. The patient's abdominal pain disappeared after the surgery.

Discussion

Intestinal ganglioneuromatosis is a rare disease entity showing neural hyperplasia. This disease may affect any part of the gastrointestinal tract (2). Pathologically, it is characterized by atypical proliferation of ganglion cells, nerve fibers, and spindle-shaped neural cells probably originating from Schwann cells (3). It can affect all layers of the intestinal wall or may predominantly involve the myenteric plexus or the mucosal plexus. Shekitka and Sobin reviewed 43 patients with ganglioneuromas affecting the gastrointestinal tract, classifying the condition into 3 types: polypoid ganglioneuroma (n=28), ganglioneuromatous polyposis (n=7), and diffuse ganglioneuromatosis (n=8) (4, 5). Polypoid ganglioneuroma is a polypoid lesion presenting with sessile or pedunculated morphology. It is either a solitary exophytic lesion or found as a few polyps (6). Ganglioneuromatous polyposis typically consists of multiple discrete polyps with a sessile or pedunculated form. Diffuse ganglioneuromatosis refers to poorly demarcated intramural or transmural lesions involving the myenteric plexus. Although diffuse ganglioneuromatosis is sporadically found in individuals without underlying systemic disease, it has an established association with neurofibromatosis type I and multiple endocrine neoplasia syndrome type IIB (7). Morphologically, diffuse intestinal ganglioneuromatosis presents as submucosal tumors or diffuse bowel wall thickening with or without associated stricture formation (5, 8-11).

Table shows the clinical characteristics of the 16 previously reported cases of patients with neurofibromatosis type 1 diagnosed as diffuse intestinal ganglioneuromatosis (2, 7, 11-23). These included 11 men and 5 women with a median age of 32.5 (range, 2-67) years. Symptoms related to diffuse intestinal ganglioneuromatosis included abdominal pain (n=6), constipation (n=5), megacolon (n=3), abdominal distention (n=2), and vomiting (n=2). Among the gastrointestinal sites, the colon was the most frequently involved site (n=9, 56.3%), followed by the ileum (n=7, 43.8%), rectum (n=4, 25.0%), and jejunum (n=2, 12.5%). Macroscopically, mucosa of the affected intestine was reportedly unremarkable in six cases. Since most of these patients presented with megacolon, constipation, and/or distention of the intestine, it is likely that diffuse ganglioneuromatosis mainly affected the gut motility (10, 11), whereas it had little influence on the gut morphology. In other patients, wall thickening (n=4), polypoid lesions (n=3), and tumorous lesions (n=2) were observed. Although ulceration was focally observed along with polypoid lesions in two cases, none of the patients, except our patient, presented with multiple ulcers in the gastrointestinal tract.

In the present patient, colonoscopy performed at 65 years of age revealed the emergence of erosion in the transverse colon. The descending and sigmoid colon and the rectum were intact at that time. Subsequent colonoscopy performed at 67 years of age showed multiple ulcers through the trans-

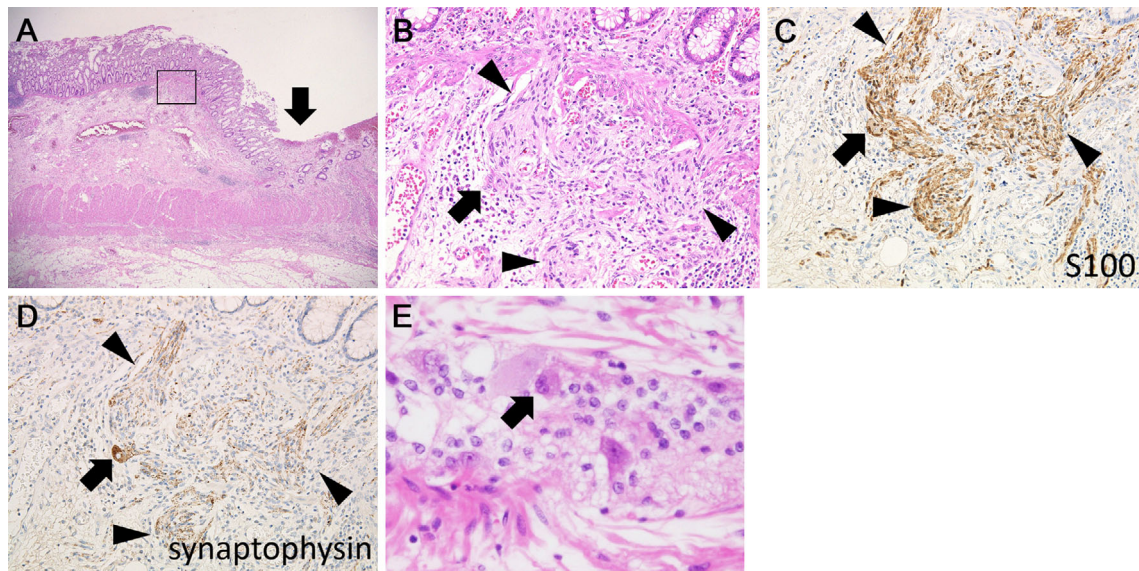


Figure 4. Pathological images. An ulcerated lesion is seen in the colonic mucosa (A). Interlacing fascicles of spindle cells are identified in the submucosa of the colorectum (A: open square, B: arrowheads). These cells are positive for S100 staining (C: arrowheads) and synaptophysin (D: arrowheads). Few differentiated ganglion cells are also present (B-D: arrows). Binuclear cells are observed in the myenteric plexus (E).

Table. Clinical Characteristics of Patients with Neurofibromatosis Type 1 with Diffuse Intestinal Ganglioneuromatosis.

No.	Reference	Age	Sex	Symptoms	Affected organs	Morphology
1	12	8	M	Constipation	Colon, rectum	Wall thickening
2	13	33	F	Constipation, megacolon	Colon	Unremarkable
3	14	26	M	Constipation, megacolon	Colon	Unremarkable
4	15	2	M	Constipation, megacolon	Esophagus, stomach, jejunum, ileum, colon, rectum	Unremarkable
5	16	16	F	Constipation, abdominal pain, sigmoid colon volvulus	Sigmoid colon, rectum	Unremarkable
6	17	49	F	Decreased frequency of stool, abdominal distention, anorexia, vomiting	Colon	Unremarkable
7	18	9	F	Vomiting, diarrhea	Small intestine	Unremarkable
8	19	42	M	Abdominal pain, abdominal distention	Ileum, colon	Wall thickening
9	20	15	M	Abdominal mass, malabsorption	Appendix	Tumor
10	21	48	M	Melena	Colon	Polyps with ulceration
11	22	40	M	Abdominal pain	Ileum	Wall thickening
12	7	32	M	None*	Ileum	Polypoid, focal ulceration
13	11	26	M	Diarrhea, hemorrhagic ulcers in the papilla of Vater	Duodenum	Wall thickening
14	23	39	M	Abdominal pain	Ileum	Tumor
15	2	51	F	Abdominal pain, bloody diarrhea, weight loss	Jejunum, ileum	Polypoid
16	Our case	67	M	Abdominal pain	Ileum, colon, rectum	Multiple ulcers

*Right hemicolectomy was performed, as thickening of the ileal wall was observed during retroperitoneal tumor resection.

verse colon to the rectum. This indicates that lesions associated with diffuse intestinal ganglioneuromatosis can alter the morphology of the intestine over the course of the disease. The leading cause of colorectal ulcers in the present case may have been ischemia, mechanical damage due to intestinal peristalsis, and/or infection caused by some microorganisms. Since congestion of the capillary vessels and thrombus

in the blood vessels were partly observed, one possible explanation is that partial destruction of vascular structures and ischemia of the colorectal mucosa occurred due to the proliferation of neural elements. Another explanation is that vasculopathy associated with neurofibromatosis type 1 triggered ulcer formation. Although the etiology of vascular diseases has not been fully explained, concentric growth of the

intima, disruption of the elastica, and nodular proliferation occur in the blood vessels in patients with neurofibromatosis type 1 (24, 25). Because intimal thickening was partly observed in the present patient, vascular occlusion due to vasculopathy might exist. Regardless of the cause, it is possible that the healing process of the damaged mucosa was hampered because of the existence of ganglioneuromatosis. The present patient also showed abscess formation around the cecum, which was surgically treated at another hospital. Although a pathological analysis revealed no fistula between the intestinal tract and the abscess, we speculate that perforation occurred in the cecum, causing abscess formation. However, the definite mechanism underlying the abscess formation is unknown.

Diffuse intestinal ganglioneuromatosis generally fails to respond to conservative treatment. Thus, surgical resection of the diseased segments is required in symptomatic cases (9, 10). In the present patient, since the pathological features of diffuse ganglioneuromatosis were also detected in the ileal small polyps, ulcers in the ileum and ileal lesions should, in general, be carefully observed and monitored.

In conclusion, we treated a patient with diffuse intestinal ganglioneuromatosis presenting as multiple colorectal ulcers. Although the prevalence of this disease is low, this case indicates that the endoscopic appearance of the diseased bowel can change from intact mucosa to multiple ulcers over the course of the disease, ultimately requiring surgical resection in some cases.

The authors state that they have no Conflict of Interest (COI).

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