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CASE REPORT

성인에서 상피하 종양으로 나타난 대장의 미만성 신경절신경종증: 2예 보고

김태준, 임 현, 강호석, 문성훈, 김종혁, 박충기, 권미정[1], 이봉화[2]
한림대학교 의과대학 한림대학교성심병원 내과학교실, 병리학교실[1], 외과학교실[2]

Diffuse Ganglioneuromatosis of the Colon Presenting as a Large Subepithelial Tumor in Adults: Report of Two Cases

Tae-Jun Kim, Hyun Lim, Ho Suk Kang, Sung Hoon Moon, Jong Hyeok Kim, Choong Kee Park, Mi Jung Kwon[1], and Bong Hwa Lee[2]
Departments of Internal Medicine, Pathology[1], and Surgery[2], Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

Colonic diffuse ganglioneuromatosis is a benign neoplastic condition characterized by disseminated, intramural, or transmural proliferation of neural elements involving the enteric plexuses, sometimes associated with von Recklinghausen's disease and other multiple tumor syndromes. Colonic diffuse ganglioneuromatosis is usually large, ranging from 1 to 17 cm, and thus can distort the surrounding tissue architecture as well as infiltrate the adjacent bowel wall. However, colonic diffuse ganglioneuromatosis is an exceptional finding in adults and only individual cases are reported in the literature. Herein, we report two unusual cases of adult patients with colonic diffuse transmural ganglioneuromatosis presenting as a large subepithelial tumor. **(Korean J Gastroenterol 2015;66:111-115)**

Key Words: Ganglioneuroma; Subepithelial tumor; Endoscopy; Colon

INTRODUCTION

Ganglioneuromas are slow-growing, well-differentiated neuroectodermal neoplasms, typically derived from the sympathetic ganglia and adrenal glands, and more common in children. Ganglioneuromas can be found in different anatomic sites, but they are rare in the colon. Colonic ganglioneuromas fall into three subgroups (polypoid ganglioneuromas, ganglioneuromatous polyposis, and diffuse ganglioneuromatosis). They possess diverse clinical and endoscopic characteristics (e.g., an isolated small polyp, numerous sessile or pedunculated mucosal and/or submucosal lesions, and diffuse involvement of the bowel wall) according to the degree of ganglioneuroma formation.[1] Of the subgroups, colonic diffuse ganglioneuromatosis is large, ranging from 1 to 17 cm, and it can distort the surrounding tissue architecture as well as infiltrate the adjacent bowel wall. However, only individual cases of colonic diffuse ganglioneuromatosis in adults have been reported.[2,3] In this report, we describe two cases of adult patients with colonic diffuse ganglioneuromatosis that endoscopically presented as large subepithelial tumors.

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교신저자: 임 현, 14068, 안양시 동안구 관평로 170번길 22, 한림대학교성심병원 소화기내과
Correspondence to: Hyun Lim, Department of Internal Medicine, Hallym University Sacred Heart Hospital, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Korea. Tel: +82-31-385-3044, Fax: +82-31-380-5912, E-mail: hlim77@hallym.or.kr

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CASE REPORTS

1. Case 1

A 70-year-old man visited the outpatient department with a four-week history of diarrhea. He was diagnosed with prostate cancer one month prior and had received antiandrogen therapy. His family history was unremarkable for intestinal neoplasms. Initial vital signs were blood pressure of 130/70 mmHg, pulse rate of 85 beats/minute, and respiration rate of 18 breaths/minute. Physical examination revealed normal bowel sounds, no tenderness, and no palpable mass in the abdomen. A colonoscopy was performed for evaluating chronic diarrhea, revealing an 8 cm sized large subepithelial tumor on the recto-sigmoid junction that occupied half of the lumen (Fig. 1A). Biopsy specimens revealed spindle-shaped cells with Schwannian features and ganglion cells in the mucosa. Computed tomography scan of the abdomen and pelvis revealed subtle enhancement at the left wall in the recto-sigmoid junction without pericolic infiltration or lymph nodes enlargement (Fig. 1B). The patient underwent low anterior resection because malignancy could not be excluded. Gross examination of the low anterior resected specimen revealed an 8.5×6.5 cm-sized, polypoid mass with a yellowish granular surface (Fig. 1C). The cut surface of the lesion and the rectal wall had a thickened, yellowish, solid appearance, apparently involving the entire rectal wall (Fig. 1D). Pathologic examination of the specimen revealed prominent proliferation of thick nerve fibers with ganglion cells in the thickened mucosa that extended into the submucosa and muscle layer (Fig. 1E). The submucosa and muscle layer showed proliferation of haphazardly arranged large nerve plexuses. Immunohistochemical staining for S-100 protein highlighted the abnormal proliferation of Schwann and ganglion cells (Fig. 1F), and the strong immunoreactivity of chromogranin revealed ganglion cells proliferation (Fig. 1G). These findings were consistent with a diagnosis of diffuse rectal ganglio-

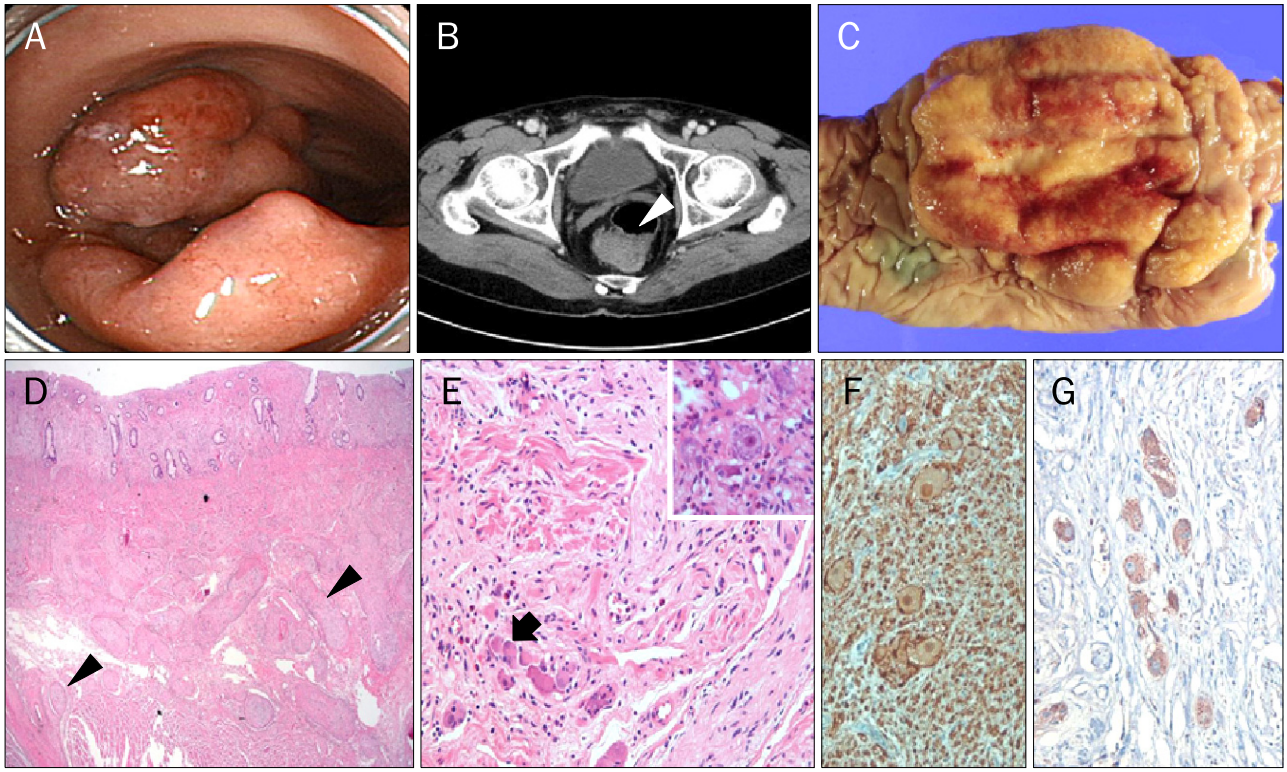

Fig. 1. Rectal diffuse ganglioneuromatosis. (A) Colonoscopy shows an 8 cm sized subepithelial tumor in the rectum that occupies half of the lumen. (B) CT scan shows subtle enhancement at the left-side wall in the recto-sigmoid junction (white arrowhead). (C) The huge polypoid mass and adjacent mucosa reveal yellowish granular surface after overnight fixation in 10% neutral formalin. (D) The thickened mucosa is noted. The submucosa and muscle layer show proliferation of haphazardly arranged, large nerve plexuses (arrowheads) (H&E, ×40). (E) The thickened mucosa shows ganglion cell clusters (arrow) with nerve fibers (H&E, ×100; inset: ×400). (F) Immunohistochemical staining for S-100 protein highlights the abnormal nerve fibers and ganglion cells in the mucosa of colon (S-100, ×400). (G) The immunoreactivity for chromogranin reveals ganglion cell proliferation in the mucosa of colon (chromagranin, ×400).

neuromatosis. There was microscopic disease at the distal resection margin. The distal margin of the rectum had mildly increased numbers of enlarged nerve fibers as well as ganglion cells in the mucosa and submucosa. To determine whether the patient had systemic disease, he underwent twenty-four hour urine vanillylmandelic acid (1.6 mg/day), metanephrine (0.2 mg/day), serum CEA (1.81 ng/mL), serum calcium (8.7 mg/dL), serum calcitonin (2.4 pg/mL), and thyroid ultrasonography; the results were all negative. The final diagnosis was colonic diffuse ganglioneuromatosis without systemic disease. The patient is being observed without recurrence thus far.

2. Case 2

A 35-year-old man with no personal medical history visited the outpatient department for screening colonoscopy. His family history was unremarkable for intestinal neoplasm. Initial vital signs were blood pressure of 120/70 mmHg, pulse rate of 75 beats/minute, and respiration rate of 18 breaths/minute. Physical examination revealed normal bowel sounds, no tenderness and no palpable mass in the abdomen. Colonoscopy showed a 5 cm sized subepithelial tumor on the ascending colon that endoscopically presented as a non-granular type of laterally spreading tumor (Fig. 2A). Biopsy specimens displayed proliferation of the Schwannian spindle cells and scattered ganglion cells in the lamina propria of the mucosa. Computed tomography scan of the abdomen revealed an approximately 5-cm sized eccentric haustral fold thickening at the distal ascending colon without pericolic infiltration or lymph nodes enlargement (Fig. 2B). The patient underwent right hemicolectomy. Gross examination of the resected specimen revealed a 5.5×4.0 cm sized polypoid mass with finger-like projections that involved part of the circumference of the bowel (Fig. 2C). The finger-like projec-

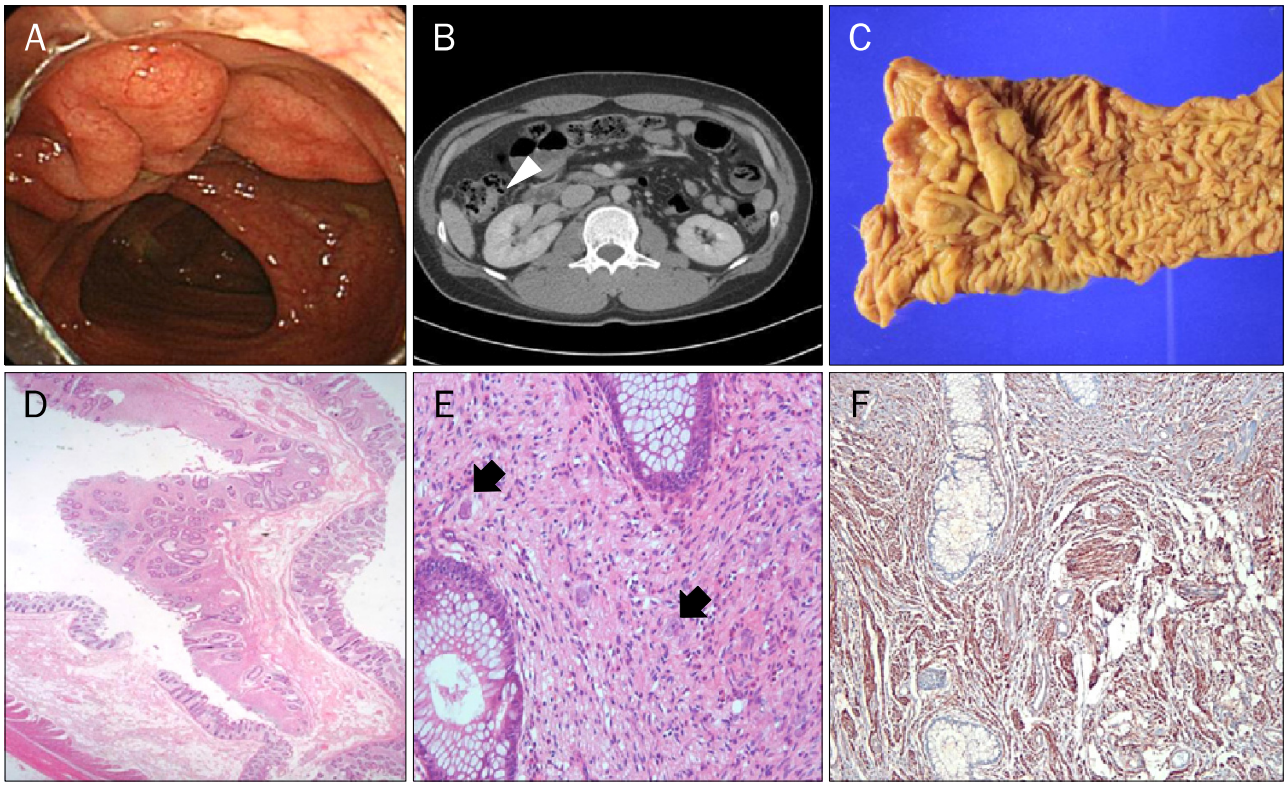

Fig. 2. Diffuse ganglioneuromatosis of ascending colon. (A) Colonoscopy shows a 5 cm sized laterally spreading tumor in the ascending colon that has intact overlying mucosa. (B) CT scan shows an approximately 5 cm sized eccentric haustral fold thickening in the distal ascending colon (white arrowhead). (C) The surgical specimen shows a polypoid mass with finger-like projections. (D) The finger-like projection of the lesion consists of mucosal thickening and submucosal proliferations of thick nerve bundles (H&E, ×40). (E) The mucosa shows a uniform appearance of scattered ganglion cells (arrows) mixed with bland, spindle-shaped cells with Schwannian features (H&E, ×100). (F) Immunohistochemical staining shows strong positivity for S-100 protein in the mucosa of colon, consistent with the proliferation of ganglion and Schwann cells (S-100, ×40).

tions of the lesion consisted of mucosal thickening and submucosal proliferations of thick nerve bundles (Fig. 2D). The lamina propria of the mucosa consisted of a relatively uniform appearance of scattered ganglion cells mixed with bland, spindle-shaped cells that had Schwannian features (Fig. 2E). Immunohistochemical staining showed strong positivity for S-100 protein (Fig. 2F) and positivity for chromogranin and CD 56, consistent with proliferation of the ganglion and Schwann cells. The muscle layers showed transmural proliferation of large abnormal nerve bundles and ganglion cells, consistent with a diagnosis of diffuse colonic ganglioneuromatosis. The neoplastic cells in specimen did not show other features of malignancy. The ileum, appendix, and cecum were negative for neoplasia. To determine whether the patient had systemic disease, he underwent twenty-four hour urine vanillylmandelic acid (0.9 mg/day), metanephrine (0.3 mg/day), serum CEA (3.13 ng/mL), serum calcium (8.5mg/dL), serum calcitonin (3.7 pg/mL), and thyroid ultrasonography; the results were all negative. The final diagnosis was colonic diffuse ganglioneuromatosis without systemic disease. The patient is being observed without recurrence thus far.

DISCUSSION

Ganglioneuromas are rare neoplasms in the colon; only four cases have been reported in Korea (Table 1).[4-7] Among the subtypes of colonic ganglioneuroma, colonic diffuse ganglioneuromatosis is an exceptional finding in adults and has never been reported in Korea. Herein, we presented two cases of adult patients with colonic diffuse ganglioneuromatosis that endoscopically presented as large subepithelial tumors. The tumors were removed surgically.

Colonic ganglioneuromas are benign, hamartomatous neoplasms consisting of ganglion cells, nerve fibers, and supporting cells of the enteric nervous system.[8] Although no exact mechanism is known, an hypothesis was proposed that a soluble nerve growth factor might contribute to ganglioneuroma development.[9] Depending on ganglioneuroma formation, three types are recognized. Polypoid ganglioneuroma, the most common type, is a single tumor arising in the mucosa and submucosa, resembling an adenoma or juvenile polyp. Ganglioneuromatous polyposis is characterized by ill-defined, loose aggregates of mature ganglion cells within the colonic mucosa, giving rise to multiple, small mucosal polyps mimicking familial adenomatous polyposis. Finally, diffuse ganglioneuromatosis is a poorly demarcated nodular and disseminated proliferation of ganglioneuromatous tissue that involves the enteric plexuses. In addition, diffuse ganglioneuromatosis has two variants: a purely mucosal form and a transmural form. Both variants can occur in children, but a mucosal form is more common in adults.[2] This is in contrast to the transmural cases reported here.

The clinical presentation of colonic ganglioneuromas depends on the size, anatomical location, and subtype. Symptoms including rectal bleeding, watery diarrhea, abdominal pain and acute occlusion in rare cases.[1,2] However, very few cases of colonic ganglioneuromas diagnosed with symptomatic and fortuitous pathologic findings after undergoing surgery or endoscopy for unrelated conditions have been reported.[10]

Endoscopic findings are diverse for the different subgroups of colonic ganglioneuromas.

Polypoid ganglioneuroma generally shows small, sessile, or pedunculated polyps. These lesions are solitary or few in number and the sizes are smaller than 2 cm in the greatest dimension. They are endoscopically indistinguishable from hyperplastic or adenomatous polyps.

Ganglioneuromatous polyposis is typically distinguished by numerous (greater than 20) sessile or pedunculated polyps. However, the size range is similar to that of polypoid ganglioneuroma.

Diffuse ganglioneuromatosis can involve any part of the

Table 1. Summary of Colonic Ganglioneuroma reported in Korea

Study	Age (yr)	Sex	Location	Size (cm)	Type	Treatment
Jung et al.[4]	50	M	Ascending colon	0.6	Isp polyp	Polypectomy
Bang et al.[5]	33	F	Descending colon	0.7	Isp polyp	Polypectomy
Kim et al.[6]	58	F	Sigmoid colon	0.6	Is polyp	Polypectomy
Park et al.[7]	56	M	Cecum	0.7	Is polyp	Polypectomy

Is, sessile; Isp, subpedunculated.

colon, but not the ileum. The size is larger than other subtypes, reaching 1 to 17 cm in diameter. They present as diffuse bowel wall thickening, submucosal nodularities, and strictures, and may distort the architecture of the surrounding tissue.

Colonic ganglioneuromas can be an isolated finding, but they more commonly arise as a component of multiple endocrine neoplasia (MEN) IIB syndrome, Von Recklinghausen's disease, Cowden's disease, or Ruvalcaba-Myhre-Smith syndrome.[1,11-13] Because of the cancer risk associated with these syndromes, patients should be carefully screened for tumors in the thyroid, breast, colon, and uterus. Urine vanillylmandelic acid, serum calcitonin, and serum calcium tests may be helpful in excluding endocrinopathies found in MEN IIB. Genetic testing is recommended to detect an underlying inherited disorder. With our patients, although we did not perform genetic testing, further clinical examination and biochemical screening showed no features of systemic disease.

Pathologic examination including immunohistochemistry staining allows a definitive diagnosis. The histologic diagnosis of ganglioneuromas is mainly based on the identification of ganglion cells mixed with the proliferation of Schwann cells. Hematoxylin and eosin staining is usually sufficient to make the diagnosis. Stains for S-100 protein, neuron-specific enolase, synaptophysin, vasoactive intestinal peptide and neurofilament are helpful in confirming the neural origin of the lesion.[1,2]

Due to poor response to medical management, the standard treatment for colonic ganglioneuromas is surgical resection of the diseased bowel as well as a work-up for any associated syndromes. However, the treatment methods can differ based on the patient's clinical history as well as ganglioneuroma size and location. Moreover, complications such as bleeding or obstruction should be considered. Endoscopic resection can be a curative method for polypoid ganglioneuroma due to having benign nature, but surgery may be necessary for ganglioneuromatosis polyposis, diffuse ganglioneuromatosis or large polypoid lesion.[14]

In summary, we presented two unusual cases of adult patients with colonic diffuse ganglioneuromatosis that endoscopically manifested as large colonic subepithelial tumors. Despite its rarity in adults, this condition should be considered in patients with large subepithelial tumors detected by colonoscopy.

REFERENCES

1. Shekitka KM, Sobin LH. Ganglioneuromas of the gastrointestinal tract. Relation to Von Recklinghausen disease and other multiple tumor syndromes. Am J Surg Pathol 1994;18: 250-257.
2. Chambonnière ML, Porcheron J, Scoazec JY, Audigier JC, Mosnier JF. Intestinal ganglioneuromatosis diagnosed in adult patients. Gastroenterol Clin Biol 2003;27:219-224.
3. Mateş I, Iosif C, Dinu D, Constantinoiu S. Solitary ganglioneuromatosis of the descending colon, presenting as giant retroperitoneal tumour. Chirurgia (Bucur) 2013;108:584-588.
4. Jung YW, Jang BI, Chang KA, Kim KO, Kim MJ. The solitary polypoid ganglioneuroma of the ascending colon. Korean J Gastrointest Endosc 2010;41:390-393.
5. Bang BW, Jeong S, Kim CH, et al. A case of polypoid ganglioneuroma of the colon. Korean J Gastrointest Endosc 2008;36:48-51.
6. Kim SH, Choi CH, Paik YH, Kim WH, Kim H. Isolated polypoid ganglioneuroma in the rectum. Korean J Pathol 2001;35: 344-346.
7. Park JY, Kang YN, Park KS, Choe M. Solitary polypoid ganglioneuroma of the cecum. J Korean Soc Coloproctol 2009;25: 264-267.
8. Miettinen M, Fletcher CDM, Kindblom LG, Tsui WMS. Mesechimal tumors of the colon and rectum. In: Bosman FT, Carneiro F, Hruman RH, Theise ND, eds. WHO classification of tumours of the digestive system. 4th ed. Lion: IARC, 2010: 140-141.
9. DeSchryver-Kecskemeti K, Clouse RE, Goldstein MN, Gersell D, O'Neal L. Intestinal ganglioneuromatosis. A manifestation of overproduction of nerve growth factor? N Engl J Med 1983; 308:635-639.
10. Srinivasan R, Mayle JE. Polypoid ganglioneuroma of colon. Dig Dis Sci 1998;43:908-909.
11. Carney JA, Go VL, Sizemore GW, Hayles AB. Alimentary-tract ganglioneuromatosis. A major component of the syndrome of multiple endocrine neoplasia, type 2b. N Engl J Med 1976; 295:1287-1291.
12. Hochberg FH, Dasilva AB, Galdabini J, Richardson EP Jr. Gastrointestinal involvement in von Recklinghausen's neurofibromatosis. Neurology 1974;24:1144-1151.
13. DiLiberti JH, Weleber RG, Budden S. Ruvalcaba-Myhre-Smith syndrome: a case with probable autosomal-dominant inheritance and additional manifestations. Am J Med Genet 1983; 15:491-495.
14. Urschel JD, Berendt RC, Anselmo JE. Surgical treatment of colonic ganglioneuromatosis in neurofibromatosis. Can J Surg 1991; 34:271-276.