INTRODUCTION

Ganglioneuroma is a rare disorder characterized by the distribution of tumors originating from the ganglion cells, supporting cells, and nerve fibers in different organs of the body. Although ganglioneuroma can occur in any tissue in which the autonomic nervous system is present, it is very rare in the colon. Colonic ganglioneuroma is mainly diagnosed in childhood and is occasionally accompanied by hereditary disorders, such as neurofibromatosis type I or multiple endocrine neoplasia type 2B. Here, we report a case of a patient in whom colon cancer developed 12 years after the initial diagnosis of colonic diffuse ganglioneuromatosis, which suggests a possible association between colonic diffuse ganglioneuromatosis and colorectal cancer.

Keywords: Colon; Colorectal cancer; Diffuse ganglioneuromatosis

CASE REPORT

Development of colon cancer in a patient with longstanding colonic diffuse ganglioneuromatosis: a case report

Jin Sun Oh¹, Seung Wook Hong², Jin Hee Noh³, Jiyoung Yoon³, Hyo Jeong Kang³, Young Soo Park³, Dong-Hoon Yang², Jeong-Sik Byeon³

¹Department of Internal Medicine, Hoengseong Daeseong Hospital, Hoengseong; Departments of ²Gastroenterology and ³Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Colonic diffuse ganglioneuromatosis is an extremely rare disease in which multiple tumors derived from the ganglion cells, nerve fibers, and supporting cells are distributed in the colon. It is generally considered to be a benign neoplastic condition and is occasionally associated with rare hereditary conditions such as neurofibromatosis type I or multiple endocrine neoplasia type 2B. Here, we report a case of a patient in whom colon cancer was confirmed on surveillance colonoscopy after the initial diagnosis of colonic diffuse ganglioneuromatosis, a subtype of ganglioneuroma, 12 years ago.

Keywords: Colon; Colorectal cancer; Diffuse ganglioneuromatosis

INTRODUCTION

Ganglioneuroma is a rare disorder characterized by the distribution of tumors originating from the ganglion cells, supporting cells, and nerve fibers in different organs of the body. Although ganglioneuroma can occur in any tissue in which the autonomic nervous system is present, it is very rare in the colon. Colonic ganglioneuroma is mainly diagnosed in childhood and is occasionally accompanied by hereditary disorders, such as neurofibromatosis type I (NF type 1) or multiple endocrine neoplasia type 2B (MEN 2B). Colonic ganglioneuroma is considered a benign condition, and there has been little research on its natural course and malignant potential. Here, we report a case of a patient in whom colon cancer was confirmed on surveillance colonoscopy after the initial diagnosis of colonic diffuse ganglioneuromatosis, a subtype of ganglioneuroma, 12 years ago.

CASE REPORT

A 26-year-old male patient with no particular medical history visited Asan Medical Center for the evaluation of intermittent bloody stools that he had been complaining of for the past 5 years. The patient denied any abdominal pain, weight loss, or change in bowel habits. The patient had no specific family history, especially of colorectal cancer or hereditary diseases. Initial vital signs were normal. Blood pressure of 110/70 mmHg, pulse rate of 70/min, respiration rate of 18/min, and body temperature of 36.8°C were recorded. Physical examination revealed normal bowel sounds sound with no tenderness or palpable mass in the abdomen. There were no cutaneous café-au-lait spots, axillary freckling, or plexiform neurofibroma. Initial colonoscopy revealed multiple sessile polyps of varying sizes in the colon.
diameters, dispersed between the descending and sigmoid colon. The mucosal surface of the polyps was intact, with no erosion or ulcer (Fig. 1). Histopathological examination of the biopsied tissue showed scattered ganglion cells admixed with a proliferation of spindle cells in the expanded lamina propria of the mucosa. Immunohistochemical staining showed ganglion cells with positive neuronal nuclei (NeuN), spindle cells with positive S-100 protein, and neuronal components with positive

Fig. 1. Initial colonoscopic findings of colonic diffuse ganglioneuromatosis. (A) Colonoscopy revealed the presence of multiple sessile polyps of varying diameters in the descending colon. (B) Some sessile polyps showed a hyperemic surface, but the overlying mucosa was intact with no definitive erosion or ulcer.

Fig. 2. Microscopic and immunohistochemical findings. (A) Histological examination of the biopsied tissue showed proliferation of the ganglion and spindle cells in the lamina propria (hematoxylin & eosin, ×100). Immunohistochemical stainings showed diffuse positivity for (B) neuronal nuclei (×200), (C) S-100 protein (×200), and (D) synaptophysin (×400).
synaptophysin (Fig. 2). These findings were consistent with the diagnosis of colonic ganglioneuroma. Laboratory tests were performed to investigate the presence of coexisting hereditary diseases. Serum calcitonin was 1.9 pg/mL (normal range, 0–10 pg/mL) and carcinoembryonic antigen was 2.2 ng/mL (normal range 0–6). Qualitative test for vanillylmandelic acid was negative. Computed tomography scan of the abdomen and pelvis, thyroid ultrasound, and esophagogastroduodenoscopy were performed to exclude MEN 2B and Cowden syndrome, which did not show any specific findings. Magnetic resonance imaging of the brain showed no brain or optic nerve tumors. The patient was diagnosed with colonic diffuse ganglioneuromatosis without any hereditary diseases.

The patient was followed up with regular surveillance colonoscopy at an interval of 1 to 2 years. Surveillance colonoscopy, 12 years after the initial diagnosis, revealed a 2.9 cm subpedunculated polyp in the sigmoid colon. The mucosal surface was hyperemic with type IV and V Kudo pit patterns (Fig. 3). Mucosal biopsy revealed adenocarcinoma. The patient underwent total colectomy. Histologic examination revealed moderately differentiated adenocarcinoma confined to the mucosa arising from a tubular adenoma in the sigmoid colon, and diffuse ganglioneuromatosis with involvement of the entire colonic wall from the descending to the sigmoid colon (Fig. 4). Pathological tumor staging was pTis, N0, and M0 (American Joint Committee on Cancer staging system, 8th edition). The patient was healthy without recurrence on follow-up 7 months after surgery.

**DISCUSSION**

Ganglioneuroma, which originates from the neural crest, is considered a benign tumor composed of ganglion cells, supporting cells, and nerve fibers. Although ganglioneuroma can occur in any part of the body in which autonomic nervous system is present, it develops most commonly in the adrenal medulla, posterior mediastinum, and retroperitoneum, where major sympathetic ganglia are present. It is the most common tumor of the sympathetic nervous system in adults. Although ganglioneuroma can occur in any part of the body in which autonomic nervous system is present, it develops most commonly in the adrenal medulla, posterior mediastinum, and retroperitoneum, where major sympathetic ganglia are present. It is the most common tumor of the sympathetic nervous system in adults. Ganglioneuromas of the gastrointestinal tract can be divided into three groups: (1) polypoid ganglioneuroma, (2) ganglioneuromatous polyposis, and (3) diffuse ganglioneuromatosis. Polypoid ganglioneuroma is the most common form of
gastrointestinal ganglioneuroma. It comprises of a single or a small number of polyps confined to the mucosa or submucosa. It grossly resembles a hyperplastic polyp, a juvenile polyp, or an adenoma. It is not related to systemic diseases and has a good prognosis since it is a benign tumor. Ganglioneuromatous polyposis is defined as multiple, often more than 20, sessile or pedunculated ganglioneuromatous polyps. Diffuse ganglioneuromatosis is characterized by poorly demarcated nodular and disseminated lesions. It is composed of diffuse intramural or transmural proliferation of ganglioneuromatous tissues that involve the enteric plexus. These lesions can produce stricture-like thickening of the bowel wall or distort the surrounding tissue architecture. Diffuse ganglioneuromatosis can exist solitarily in the gastrointestinal tract or as a component of a systemic disease associated with MEN 2B or NF type 1.

Symptoms of gastrointestinal ganglioneuroma can vary from asymptomatic to abdominal pain, constipation, chronic diarrhea, bowel obstruction, and gastrointestinal bleeding, depending on the anatomical location and size of the tumor.

Ganglioneuroma is histologically diagnosed by identifying ganglion cells in the tissue. In general, hematoxylin and eosin staining is sufficient for histological diagnosis. However, immunohistochemical staining can be helpful in confirming the diagnosis by identification of ganglion cells using NeuN, neuron-specific enolase, synaptophysin, neurofilament protein, and vasoactive intestinal peptide. In addition, neural tissue composed of spindle cells can be identified using S-100 protein, vimentin, and glial fibrillary acidic protein. Ganglioneuromas should be differentiated from neurofibromas and schwannomas. Since there are no ganglion cells in a neurofibroma or schwannoma, these differential diagnoses can be ruled out by confirming the presence of ganglion cells in the tissue.

There is no established association between gastrointestinal ganglioneuromas and malignant tumors. Polypoid ganglioneuroma has been reported to have a good prognosis with no malignant potential. However, some studies have reported...
that ganglioneuromatous polyposis and diffuse ganglioneuro-
matosis might be accompanied by adenomatous polyps or
colorectal cancer, although the incidence is rare. The first case
of cecal adenocarcinoma surrounded by diffuse ganglioneu-
romatosis in a 54-year-old male patient was reported by Snover
et al. in 1981. Other reports described patients presenting with
coexisting hereditary diseases, colonic ganglioneuroma, and
colorectal neoplasia. Tomita et al. reported a case of a 42-year-
old male patient diagnosed with NF type 1 and diffuse gangli-
oneuromatosis with well-differentiated adenocarcinoma in the
rectum that was treated with ileocolectomy and chemotherapy.
Trufant et al. reported another case of a 42-year-old male
patient diagnosed with Cowden syndrome and gangliomatous
polyposis with colonic adenomatous polyps and signet-ring ad-
enocarcinoma in the colon with lymph node metastasis. Kanter
et al. suggested that ganglioneuromatous polyposis might be
a premalignant condition in their report of a 40-year-old male
patient with ganglioneuromatous polyposis and coexisting col-
orectal cancer in the same lesion.

In our case, the patient was initially diagnosed with colonic
diffuse ganglioneuromatosis without any hereditary diseases.
He was followed up with regular annual or biennial surveil-
ance colonoscopy for 12 years, when colorectal cancer was
diagnosed. Because genetic and epigenetic studies on the sur-
gorically resected colon cancer specimens were not performed
in our case, we could not determine whether the colon cancer
caused by diffuse ganglioneuromatosis developed through the
general carcinogenic pathway, such as the adenoma-carcinoma
sequence or the serrated pathway. Investigation of the carcino-
genic pathways may help determine the etiopathogenesis of
colon cancer caused by colonic ganglioneuroma, which should
be performed in future studies.

Our case raises several issues. First, we suggest that colonic
diffuse ganglioneuromatosis can be associated with colorectal
cancer, similar to several previous reports showing the coex-
istence of ganglioneuroma and colorectal neoplasia. In our
case, colon cancer was diagnosed as a ganglioneuromatous
mass lesion (Fig. 3), which suggests the possibility of the pre-
malignant nature of ganglioneuroma. However, the suggestion
that ganglioneuroma may itself directly develop into colorectal
cancer remains controversial because ganglioneuroma is a tu-
mor originating from the submucosal layer whereas colorectal
adenocarcinoma develops from the epithelial layer. Therefore,
we suggest that diffuse ganglioneuromatosis of the colorectum
may lead to chronic mucosal inflammation that may result in
colorectal cancer, such as colitic cancer caused by chronic in-
flammatory bowel diseases. Further studies, including histolog-
ical and genetic investigations, are needed to confirm the possi-
ble association between ganglioneuroma and colorectal cancer
and its carcinogenic mechanism. The second point raised by
our case is the importance of regular surveillance colonoscopy
for colonic diffuse ganglioneuromatosis. The stage of colorectal
cancer in our patient was pTis, N0, and M0, which is a very ear-
ly stage, contrary to the advanced stages necessitating chemo-
therapy mentioned in previous reports. We believe that the
detection of carcinoma at this early stage can be attributed to
the regular surveillance colonoscopy. Although, currently, there
is no established consensus on the necessity of surveillance
colonoscopy and its appropriate interval for early detection of
adenocarcinoma in the background of gastrointestinal gangli-
oneuromatosis, we suggest a 1 to 2-year interval in surveillance
colonoscopy based on our experience and recommendations in
the literature.

In summary, we presented a case of diffuse ganglioneuro-
matus in the background of gastrointestinal ganglioneuromatosis that was accompanied by colon cancer diagnosed at an early stage by regular surveillance colonoscopy. Colonic ganglioneuroma, especially ganglioneuromatous polyposis and diffuse ganglioneuromatosis, may be associated with colorectal cancer, and regular surveillance colonoscopy should be consid-
ered for this condition.

Conflicts of Interest
The authors have no potential conflicts of interest.

Funding
None.

Author Contributions
Conceptualization: JSO, JSB; Data curation: SWH, JHN, JY, DHY;
Formal analysis: SWH, JHN, JY, DHY; Methodology: JSO, HJK,
YSP, JSB; Project administration: JSB; Supervision: DHY, JSB;
Visualization: SWH, JHN, JY, DHY; Resources: JSB; Writing-original
draft: JSO; Writing–review & editing: JSO, SWH, JHN, JY, HJK, YSP,
DHY, JSB.

ORCID
Jin Sun Oh https://orcid.org/0000-0001-9951-9256
Seung Wook Hong https://orcid.org/0000-0003-1440-9950
Jin Hee Noh https://orcid.org/0000-0001-6720-9528
REFERENCES

1. Jass JR, Sobin LH, Watanabe H. The World Health Organization's histologic classification of gastrointestinal tumors: a commentary on the second edition. Cancer 1990;66:2162–2167.
2. Dellinger GW, Lynch CA, Mihas AA. Colonic ganglioneuroma presenting as filiform polyposis. J Clin Gastroenterol 1996;22:66–70.
3. Rafiq S, Hameer H, Sitrin MD. Ganglioneuromatous polyposis associated with juvenile polyps and a tubular adenoma. Dig Dis Sci 2005;50:506–508.
4. Shekittka 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.
5. d’Amore ES, Manivel JC, Pettinato G, et al. Intestinal ganglioneuromatosis: mucosal and transmural types: a clinicopathologic and immunohistochemical study of six cases. Hum Pathol 1991;22:276–286.
6. Ferro de Beça F, Lopes J, Maçoas F, et al. Tactoid body features in a Schwann cell hamartoma of colonic mucosa. Int J Surg Pathol 2014;22:438–441.
7. Abdelfatah M, Sangah G, Harvin G. What do we need to know about colonic polypoid ganglioneuroma? A case report and a comprehensive review. J Gastrointest Cancer 2018;49:327–332.
8. Snover DC, Weigent CE, Sumner HW. Diffuse mucosal ganglioneuromatosis of the colon associated with adenocarcinoma. Am J Clin Pathol 1981;75:225–229.
9. Tomita H, Miya K, Tanaka H, et al. Ganglioneuroma and adenocarcinoma associated with neurofibromatosis type 1 in the colorectal region. Int J Colorectal Dis 2006;21:89–91.
10. Trufant JW, Greene L, Cook DL, et al. Colonic ganglioneuromatous polyposis and metastatic adenocarcinoma in the setting of Cowden syndrome: a case report and literature review. Hum Pathol 2012;43:601–604.
11. Kanter AS, Hyman NH, Li SC. Ganglioneuromatous polyposis: a premalignant condition. Report of a case and review of the literature. Dis Colon Rectum 2001;44:591–593.