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.

**Key Words:** Ganglioneuroma; Subepithelial tumor; Endoscopy; Colon
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 (chromogranin, ×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 hemicolecotomy. 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-
ions 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.7 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>
<thead>
<tr>
<th>Study</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Type</th>
<th>Treatment</th>
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<td>Jung et al.4</td>
<td>50</td>
<td>M</td>
<td>Ascending colon</td>
<td>0.6</td>
<td>Is polyp</td>
<td>Polypectomy</td>
</tr>
<tr>
<td>Bang et al.5</td>
<td>33</td>
<td>F</td>
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<td>0.7</td>
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<td>Polypectomy</td>
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<tr>
<td>Kim et al.5</td>
<td>58</td>
<td>F</td>
<td>Sigmoid colon</td>
<td>0.6</td>
<td>Is polyp</td>
<td>Polypectomy</td>
</tr>
<tr>
<td>Park et al.7</td>
<td>56</td>
<td>M</td>
<td>Cecum</td>
<td>0.7</td>
<td>Is polyp</td>
<td>Polypectomy</td>
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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 polyoid ganglioneuroma due to having benign nature, but surgery may be necessary for ganglioneuromatosis polyposis, diffuse ganglioneuromatosis or large polyoid 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