



A Case of Diffuse Neuronal Hypertrophy in Acute Appendicitis

Hayato Yamauchi¹, Shinji Sakurai², Ritsuko Tsukagoshi¹, Masaki Suzuki¹, Yuichi Tabe¹, Takaharu Fukasawa¹, Shinsuke Kiriya¹, Minoru Fukuchi¹, Hiroshi Naitoh¹, Katsuhiko Horiuchi³, Kazuhisa Yuasa³, Hiroyuki Kuwano⁴

¹Department of Surgery, Social Insurance Gunma Chuo General Hospital, Gunma, Japan

²Department of Diagnostic Pathology, Social Insurance Gunma Chuo General Hospital, Gunma, Japan

³Department of Digestive System, Social Insurance Gunma Chuo General Hospital, Gunma, Japan

⁴Department of General Surgical Science (Surgery I), Gunma University, Graduate School of Medicine, Gunma, Japan

We report a case of neuronal hypertrophy associated with acute appendicitis in which significant neuronal fibers and the number of ganglion cells increased in the absence of inflammatory cells. Differential diagnosis from diffuse ganglioneuromatosis by the pathologic findings of resected specimen was difficult. A 33-year-old Japanese female visited our hospital complaining of acute abdominal pain. The patient underwent appendectomy upon the diagnosis of acute appendicitis on the day of admission. Postoperative examinations found no neoplastic lesions in other organs or inherited disorders such as multiple endocrine neoplasia (MEN) type 2b and von Recklinghausen's disease (VRD). The pathologic diagnosis was neuronal hypertrophy of the appendix. Because the clinical outcomes of diffuse ganglioneuromatosis and neuronal hypertrophy of the gastrointestinal tract are quite different, clinical and pathologic examination should be carefully carried out for lesions in which significant proliferation of neuronal components is seen.

Key words: Diffuse ganglioneuromatosis – Gastrointestinal tract – Acute appendicitis

Reprint requests: Hayato Yamauchi, Department of Surgery, Social Insurance Gunma Chuo General Hospital, 1-7-13 Kouun-cho, Maebashi, Gunma 371-0025, Japan.

Tel.: +81 27 221 8165; Fax: +81 27 224 1415; E-mail: m07702048@gunma-u.ac.jp

Acute appendicitis in younger people is a very common disease globally, but the diagnosis of the underlying disease can be difficult in an emergency¹ because acute appendicitis may be caused by various conditions such as infection² or malignant tumor,³ and sometimes iatrogenically.⁴ Thus, it is important to clarify the cause of acute appendicitis in order to decide on the clinical treatment after surgery.

In cases of acute appendicitis, it has been reported that neuronal components containing Schwann cells and ganglion cells proliferate accompanied by mast cell infiltration, which is thought to be a reactive process against acute inflammation.⁵ On the other hand, histologic findings of increased Schwann cells and ganglion cells are also pathologic features of ganglioneuromatosis in the gastrointestinal tract, which often develops in association with inherited disorders such as multiple endocrine neoplasia (MEN) type 2b and von Recklinghausen's disease (VRD).^{6,7}

The pathologic findings such as the lesions of neuronal cells proliferating and the existence of acute inflammatory cell infiltration may help differential diagnosis of these conditions.

We report here a case of neuronal hypertrophy of the appendix that was difficult to distinguish from diffuse ganglioneuromatosis and discuss the possible different pathogenesis of diffuse ganglioneuromatosis.

Case Report

A 33-year-old Japanese female visited our hospital in April 2011 complaining of acute abdominal pain. The patient described pain throughout the abdomen and appetite loss for the last 10 days. Physical examination revealed oppressive pain of the lower abdomen. Laboratory data on admission showed an increase of white blood cell (WBC) count (13,400 cells/mm³) and C-reactive protein (CRP) of 7.8 mg/L. She had no specific individual or family medical history.

No abnormality was found on chest or abdominal X-ray. Computed tomography (CT) demonstrated a swollen appendix with strong enhancement that indicated abscess formation around the appendix (Fig. 1). The cecal wall was thickened, but a tumorigenic mass was not found anywhere in the abdomen. The patient was clinically diagnosed with acute appendicitis with abscess formation and underwent appendectomy on the day of admission. Part of the appendix had a gangrenous wall, and there was perforation at the root. A grayish-white



Fig. 1 Contrast-enhanced CT. CT showed a swollen appendix with strong enhancement accompanied by some fluid. The cecal wall was thickened, but no mass indicating tumor was found in the abdomen.

abscess with a little white viscous liquid was found around the appendix.

Macroscopically, there was ulceration in the mucosal layer, but no hemorrhagic or necrotic lesions were observed in the body and base of the appendix. There were no polypoid or obstructive lesions in the lumen. By histologic examination after surgery, acute inflammatory cell infiltration was found at the serosa of the root of the appendix. However, there was no acute inflammatory cell infiltration in the body and base of the resected appendix. In the submucosal layer, winding neural-appearing bundles containing nests of mature ganglion-like cells significantly proliferated around the ulcerative lesion and had infiltrated into part of the adjacent mucosal layer (Fig. 2). Immunohistochemically, neural-appearing bundles were strongly positive for S100 protein, which implies that the bundles consisted of Schwann cells and ganglion-like cells that were positive for neurofilament heavy and medium subunits (Fig. 3a and 3b). Numerous mast cells that were positive for KIT had infiltrated around neural bundles (Fig. 4).

The postoperative course of the patient was uneventful, and she was discharged 9 days after the surgery.

The patient underwent upper and lower endoscopic examination 1 month after the operation, which did not indicate other digestive disease. The patient also underwent ultrasonographic examination of the thyroid gland and tests of thyroid

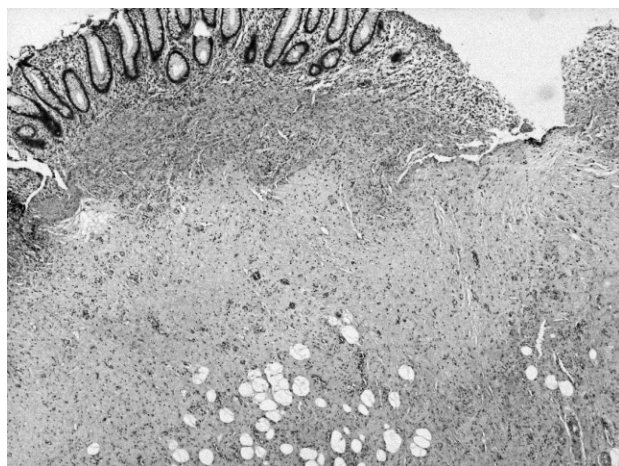


Fig. 2 Hematoxylin and eosin staining of resected specimen. Winding neural-appearing bundles containing nests of mature ganglion-like cells significantly proliferated in submucosal layer and mucosal layer.

hormone and parathyroid hormone, with negative results. She had no family history of inherited disorders.

Discussion

Initially, differential diagnosis of this case between diffuse ganglioneuromatosis of the appendix and some reactive conditions was difficult because there was no acute inflammatory cell infiltration around the proliferating neuronal component.

To our knowledge, only 5 studies of neuronal hypertrophy of appendices have been reported. Of those, immunohistochemical studies by Xiong *et al*⁵ and Amber *et al*⁸ found a significant increase in neural components and mast cell infiltration, even in cases of histologically normal appendices resected with a diagnosis of appendicitis. Nemeth *et al* also reported increased neuronal components of the myenteric plexus and neuronal hypertrophy in histologically normal appendix specimens, and they hypothesized that neuronal hypertrophy is likely to develop with or without chronic luminal obstruction or repeated inflammatory episodes.⁹

However, all these studies were examined by immunohistochemical technique using antibodies against neuronal markers such as S100 protein and Neuron Specific Enolase (NSE) and an increase of neuronal components in those cases was not evident by usual histologic examination.

Nevertheless, histologic examination revealed marked increase of Schwann-like cells and ganglion

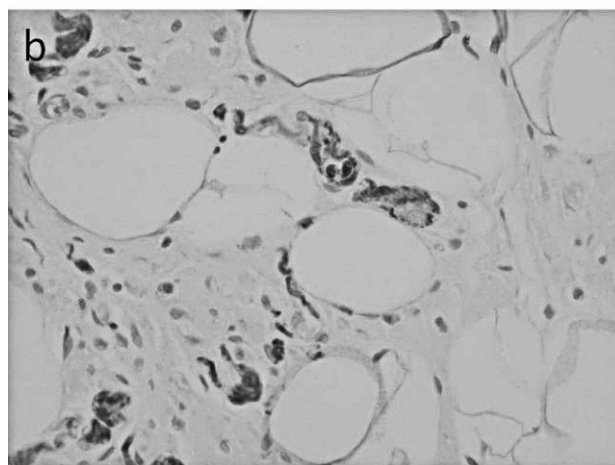
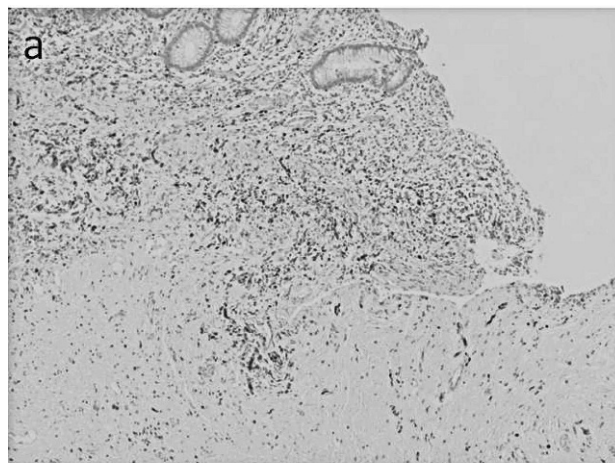


Fig. 3 S100 (a) and neurofilament (b) immunohistochemical staining of bundle-like structure resembling nerve fibers. These proliferated bundles were strongly positive for S100 protein and neurofilament.

cells in the mucosal and submucosal layers without inflammatory cell infiltration, and no changes of the myenteric plexus were evident. Since these histologic findings seemed to be different from those in previous reports, differential diagnosis from neurogenic neoplastic lesion was needed.

Diffuse ganglioneuromatosis, which is a type of ganglioneuroma, has been reported to occur in association with neurofibromatosis type 1 (NF1), MEN 2b,⁷ juvenile polyposis,¹⁰ adenomatous polyps,¹¹ Cowden disease,¹² malignant peripheral nerve sheath tumors,⁷ carcinomas,¹³ and carcinoids.^{14–16} Ganglioneuroma in the gastrointestinal tract is a characteristic feature of MEN 2b,¹⁷ although the appendix is rarely affected, and only 4 cases of appendiceal ganglioneuroma have been reported. Shekitka and Sobin reviewed 43 patients

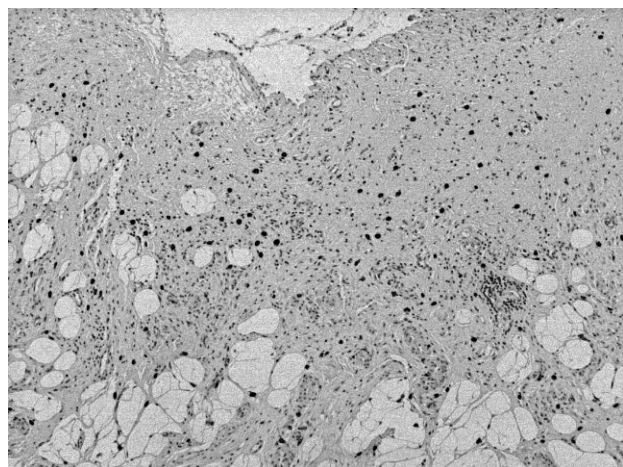


Fig. 4 KIT immunohistochemical staining of mast cells. An increased number of mast cells infiltrating around neural bundles were positive for KIT.

with ganglioneuromas of the gastrointestinal tract, of which 8 cases were classified as diffuse ganglioneuromatosis, and 7 of these were associated with other tumors such as neurogenic sarcoma, multiple neurofibroma, and plexiform neurofibroma.⁷ One patient had MEN type 2b, and one patient was clinically diagnosed with VRD. Thway and Fisher also reported an association of diffuse ganglioneuromatosis in the small intestine and NF1.¹⁸ Hirata *et al* reported a rare case of diffuse ganglioneuromatosis with plexiform neurofibromas limited to the gastrointestinal tract.¹⁹

However, there have been a few reports of patients with diffuse ganglioneuromatosis that developed around colonic adenocarcinoma¹³ or multiple rectal carcinoid tumors,¹⁴ and the patients in these cases had no other neurogenic tumors. Zarabi and LaBach reported cases of acute appendicitis caused by appendiceal ganglioneuromatosis without other tumors or systemic disease.²⁰ In these reports, familial history of inherited disease or abnormality of *NF2* or *RET* gene was not found.

Usually, the epicenter of diffuse ganglioneuromatosis lies within the muscularis propria, especially around the myenteric plexus and may extend to the mucosal, submucosal, and subserosal layers; meanwhile, in reported cases of diffuse ganglioneuromatosis associated with colon adenocarcinoma or multiple rectal carcinoids, proliferating Schwann cells and ganglion cells were located in the mucosal and submucosal layers and did not extend to the muscular layer including the myenteric plexus. Histology of these cases seems to be similar to our

case. The epicenter of proliferating neural components in our case also was located in the mucosal and submucosal layers; however, the myenteric plexuses were not affected. Moreover, there was no family history of inherited disease, and no other tumors have been found to date. Although we did not analyze germ line mutations of *NF1* and *RET* genes, the patient did not show signs of MEN 2b or VRD. These findings were similar to diffuse ganglioneuromatosis cases associated with adenocarcinoma and carcinoid tumor. Thus, differential diagnosis between neuronal hypertrophy and diffuse ganglioneuromatosis was difficult in our case.

Although inflammatory cell infiltration was not seen around the neural proliferating lesion, it was seen at the serosa of the appendiceal neck. These findings may indicate the existence of acute inflammation at the proximal site of the resected appendix. Moreover, infiltration of numerous KIT-positive mast cells was found around proliferating neuronal components. Mast cell infiltration was thought to play an important role in the development of neuronal hypertrophy in previous reports^{8,21,22} and was not described as a characteristic finding in the case of diffuse ganglioneuromatosis. Thus, we finally diagnosed our case as a neuronal hypertrophy of the appendix.

From the viewpoint of the difference of family history or accompanying malignancies, some diffuse ganglioneuromatosis cases, in which hyperplasia of Schwann cells and ganglion cells is found, similar to neuronal hypertrophy, seem to be different from the other typical cases. Although the pathophysiologic basis remain to be elucidated, carcinoma cells and carcinoid tumor cells might produce certain kinds of chemical mediators that cause neural hyperplasia. In an experimental study, the volume and density of enteric nerve fibers were changed in rats with chemically induced colon carcinomas.²³ The diffuse ganglioneuromatosis cases associated with adenocarcinoma or carcinoid tumor would be better classified as neural hyperplasia as in our case.

In conclusion, diagnostic differentiation of diffuse ganglioneuromatosis from neuronal hypertrophy of the appendix was difficult without acute inflammatory change being among the pathologic findings. The detailed mechanisms of diffuse ganglioneuromatosis and neuronal hypertrophy have not been clarified, but it is important to differentiate diffuse ganglioneuromatosis from neuronal hypertrophy clinically because physicians need to analyze systemic, neurogenic, and endocrine diseases in the former. Further studies are needed to understand

the proliferation of the neural component in the gastrointestinal tract.

References

- Covarelli P, Pimpinelli GA, Cirocchi R, Severini D, Rossi P, Mosci F. Acute appendicitis. How many uncorrect diagnosis? A clinical and histological evaluation of 124 cases treated with emergency procedure. *G Chir* 1996;**17**(5):276–278
- Lamps LW. Infectious causes of appendicitis. *Infect Dis Clin North Am* 2010;**24**(4):995–1018, ix–x
- Kim SW, Shin HC, Kim IY, Kim YT, Kim CJ. CT findings of colonic complications associated with colon cancer. *Korean J Radiol* 2010;**11**(2):211–221
- Holzer T, Pellegrinelli G, Morel P, Toso C. Appendectomy during the third trimester of pregnancy in a 27-year old patient: case report of a “near miss” complication. *Patient Saf Surg* 2011; **5**(1):11
- Xiong S, Puri P, Nemeth L, O’Brian DS, Reen DJ. Neuronal hypertrophy in acute appendicitis. *Arch Pathol Lab Med* 2000;**124**(10):1429–1433
- Lie KA, Lindboe CF, Kolmannskog SK, Haugen SE, Gram-meltvedt AT. Giant appendix with diffuse ganglioneuromatosis: an unusual presentation of von Recklinghausen’s disease. *Eur J Surg* 1992;**158**(2):127–128
- 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**(3):250–257
- Amber S, Mathai AM, Naik R, Pai MR, Kumar S, Prasad K. Neuronal hypertrophy and mast cells in histologically negative, clinically diagnosed acute appendicitis: a quantitative immunophenotypical analysis. *Indian J Gastroenterol* 2010;**29**(2):69–73
- Nemeth L, Rolle U, Reen DJ, Puri P. Nitrergic hyperinnervation in appendicitis and in appendices histologically classified as normal. *Arch Pathol Lab Med* 2003;**127**(5):573–578
- Mendelsohn G, Diamond MP. Familial ganglioneuromatous polyposis of the large bowel: report of a family with associated juvenile polyposis. *Am J Surg Pathol* 1984;**8**(7):515–520
- Weidner N, Flanders DJ, Mitros FA. Mucosal ganglioneuromatosis associated with multiple colonic polyps. *Am J Surg Pathol* 1984;**8**(10):779–786
- Haggitt RC, Reid BJ. Hereditary gastrointestinal polyposis syndromes. *Am J Surg Pathol* 1986;**10**(12):871–887
- Snover DC, Weigert CE, Sumner HW. Diffuse mucosal ganglioneuromatosis of the colon associated with adenocarcinoma. *Am J Clin Pathol* 1981;**75**(2):225–229
- Haraguchi M, Kinoshita H, Koori M, Tsuneoka N, Kosaka T, Ito Y. Multiple rectal carcinoids with diffuse ganglioneuromatosis. *World J Surg Oncol* 2007;**16**(5):19
- Katdare MV, Fichera A, Heimann TM. Familial rectal carcinoid: report of two first-degree relatives with rectal carcinoid and review of the literature. *Tech Coloproctol* 2006;**10**(2):143–146
- Hansen OP, Hansen M, Hansen HH, Rose B. Multiple endocrine adenomatosis of mixed type. *Acta Med Scand* 1976;**200**(4):327–331
- Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;**86**(12):5658–5671
- Thway K, Fisher C. Diffuse ganglioneuromatosis in small intestine associated with neurofibromatosis type 1. *Ann Diagn Pathol* 2009;**13**(1):50–54
- Hirata K, Kitahara K, Momosaka Y, Kouho H, Nagata N, Hashimoto H. Diffuse ganglioneuromatosis with plexiform neurofibromas limited to the gastrointestinal tract involving a large segment of small intestine. *J Gastroenterol* 1996;**31**(2):263–267
- Zarabi M, LaBach JP. Ganglioneuroma causing acute appendicitis. *Hum Pathol* 1982;**13**(12):1143–1146
- Coskun N, Indel SM, Elpek GO. Mast cell density and neuronal hypertrophy in patients with acute appendicitis. *Turk J Gastroenterol* 2003;**14**(1):54–58
- Keles N, Yavuz Arican R, Coskun M, Elpek GO. Histamine induces the neuronal hypertrophy and increases the mast cell density in gastrointestinal tract [published online ahead of print Month day, 2011]. *Exp Toxicol Pathol*. 2011 Feb 10. doi:10.1016/j.etp.2011.01.005
- Sitohy B, El-Salhy M. Changes in the colonic enteric nervous system in rats with chemically induced colon dysplasia and carcinoma. *Acta Oncol* 2002;**41**(6):543–549