

Well-differentiated Endocrine Cell Carcinoma of Ileum Treated by Laparoscopy-assisted Surgery – A Case Report

Shinsuke SASADA^{1,*}, Yasutomo OJIMA¹, Masahiko NISHIZAKI¹,
 Masao HARANO¹, Hiroyoshi MATSUKAWA¹, Hideki AOKI¹,
 Shigehiro SHIOZAKI¹, Satoshi OHNO¹, Motoki NINOMIYA¹,
 Hiroo MATSUURA² and Norihisa TAKAKURA¹

1) Department of Surgery, Hiroshima City Hospital, 7-33 Moto-machi, Naka-ku, Hiroshima 730-8518, Japan

2) Department of Pathology, Hiroshima City Hospital, Hiroshima 730-8518, Japan

ABSTRACT

A 72-year-old woman presented at our hospital with a 1-year history of intermittent right lower abdominal pain. Colonoscopic examination revealed a submucosal tumor with a pitted surface in the terminal ileum. Histopathological diagnosis of the carcinoid tumor was made following biopsy. Blood serotonin and urine 5-hydroxy-indoleacetic acid levels were normal, and carcinoid syndrome was not detected. Enhanced abdominal computed tomography scan and ¹⁸F-fluorodeoxyglucose positron emission tomography failed to detect multiple lesions, lymph node swelling or distant metastasis. Laparoscopy-assisted ileocecal resection with lymph node dissection was performed. The resected specimen showed a submucosal tumor with a pitted surface 11 × 11 mm in size, located at the terminal ileum. Histopathological examination revealed a well-differentiated endocrine cell carcinoma with an invasion depth to the muscularis propria. Immunohistochemical analysis showed the tumor cells to be chromogranin A and CD56-positive. The patient had no sign of recurrence for 16 months.

Key words: *Small intestinal tumor, Endocrine cell carcinoma, Laparoscopy-assisted surgery*

Endocrine tumors include so-called carcinoid tumors and, according to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute²³, the incidence and prevalence of endocrine tumors has increased substantially. Endocrine tumors of the small intestine increased from about 0.4 to 0.9 cases per 100,000 population between 1975 and 2005²³. Endocrine tumors of the small intestine are the second most common type, after endocrine tumors of the lung and bronchus²³.

Endocrine tumors of the small intestine exhibit site-related differences, depending on their location in the duodenum and proximal jejunum, or the distal jejunum and ileum². Endocrine tumors of the distal jejunum and ileum have an incidence of 0.28–0.89 per 100,000 population per year. Jejunoileal lesions account for 23–28% of all gastrointestinal endocrine tumors, making this site the second commonest location for endocrine tumors, after the appendix^{4,24}. However, in a Japanese report¹³, endocrine tumors of the small

intestine were relatively rare, and only accounted for 4.7% of all gastrointestinal endocrine tumors, after the rectum, stomach and duodenum.

Endocrine tumors secrete peptides and neuroamines, which cause a distinct clinical syndrome called carcinoid syndrome. However, many endocrine tumors remain clinically silent until late presentation with multiple symptoms⁸. We detected an early-stage endocrine cell carcinoma and the patient underwent laparoscopy-assisted resection.

CASE REPORT

A 72-year-old Japanese woman, whose medical history included a previous brain infarction, chronic hepatitis C and an appendectomy, presented with intermittent right lower abdominal pain of 1-year duration. Her height was 145.7 cm, weight was 43.6 kg, blood pressure was 116/73 mmHg and pulse rate was regular at 72/min. She had no flushing, diarrhea or carcinoid heart disease.

*Correspondence to: Shinsuke Sasada M.D., Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
 Tel: +81-82-257-5869, Fax: +81-82-256-7109 e-mail: sasachy@yahoo.co.jp

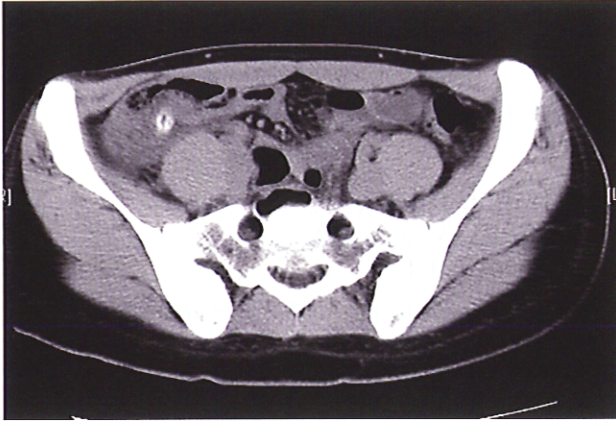


Fig. 1. Abdominal computed tomography showing a calcified region inside the cecum and slight thickening of the wall of the appendix

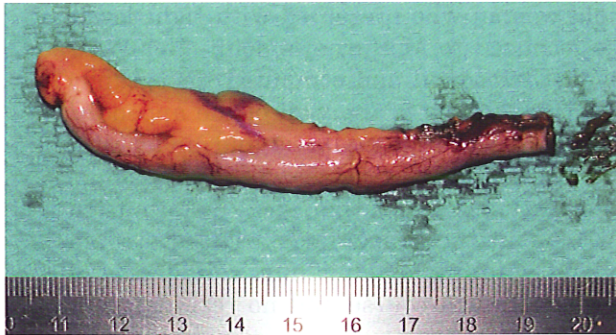


Fig. 2. The resected appendix was mildly congested (10 × 0.8 cm)

for suspected appendicitis.

Upon laparotomy, the peritoneal cavity was noted to be clean with minimal fluid. Since the appendix appeared mildly congested, we performed an appendectomy. The appendix was not adherent to other organs or the pelvic wall. It measured 10 × 0.8 cm at the widest diameter (Fig. 2). Macroscopically, the mucosa of the appendix appeared nearly normal without inflammation.

Histopathological examination of the appendix showed chronic inflammation, without evidence of acute inflammation. There were ectopic endometrial glands and stroma in the muscularis (Fig. 3A, 3B). Immunohistochemical staining showed that these stroma cells were positive for CD10 (Fig. 3C), consistent with endometrium. The final histopathological diagnosis was endometriosis of the appendix.

The patient had a good clinical course and was discharged from the hospital on postoperative day four. Her postoperative serum carbohydrate antigen 125 (CA125) level was within criteria, at 18.5 IU/ml. Postoperatively, she had no fevers during her menses and residual pain.

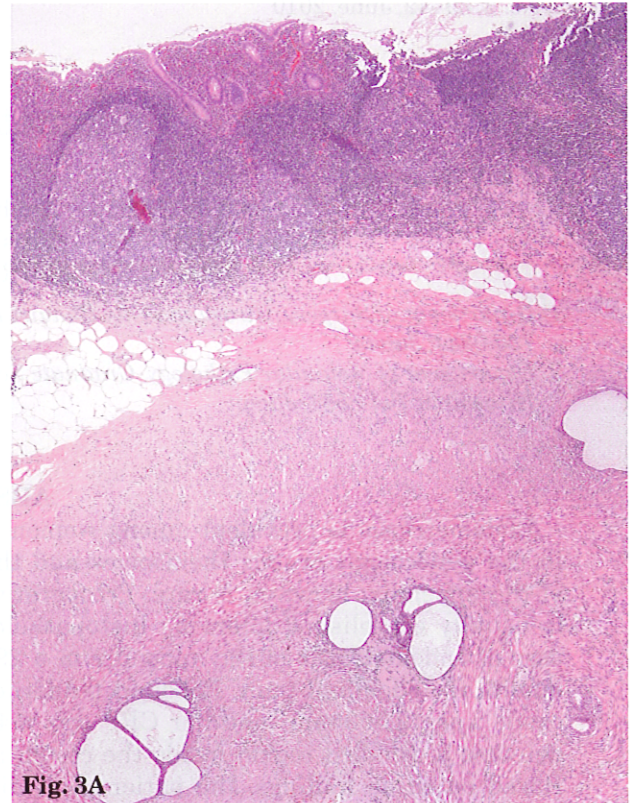


Fig. 3A

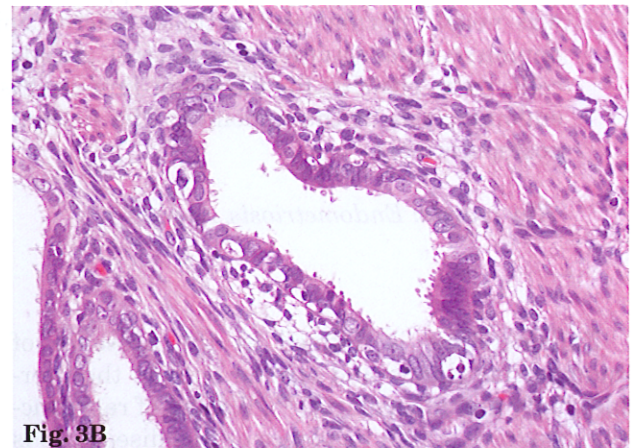


Fig. 3B

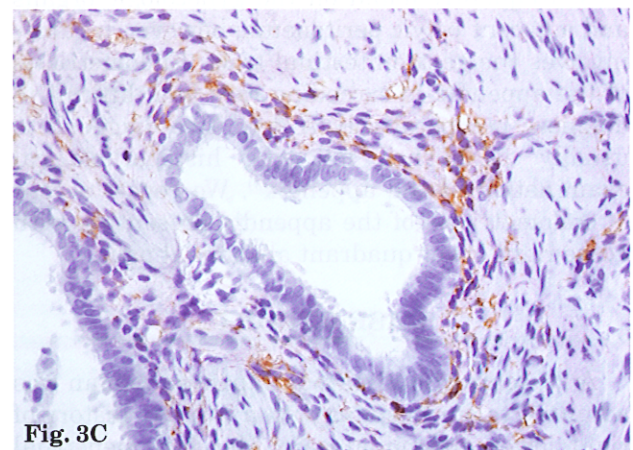


Fig. 3C

Fig. 3. Histopathology of the appendix. There are ectopic endometrial glands and stroma in the muscularis. No significant acute inflammation is present (A: H&E, ×40, B: H&E, ×400). Immunohistochemical staining showing that these stroma cells are positive for CD10 (C: ×400).

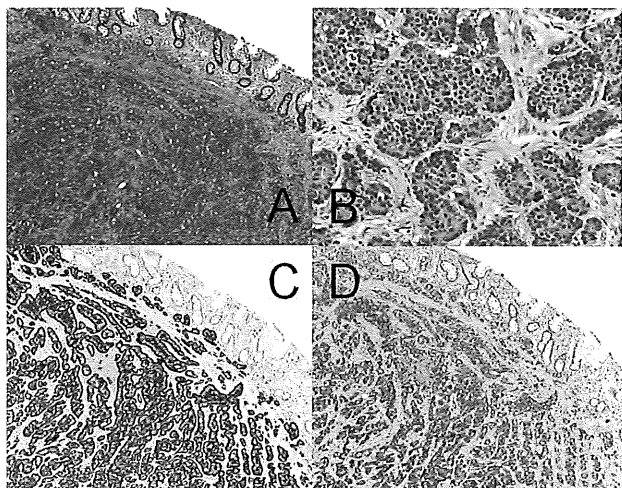


Fig. 4. A: H&E staining of the tumor. The tumor was proliferated mainly in the submucosal layer (40 \times). B: H&E staining of the tumor. The growth pattern was insular and trabecular (200 \times). C: Immunohistochemical staining revealed positive reaction to chromogranin A (40 \times). D: Immunohistochemical staining revealed positive reaction to CD56 (40 \times).

Jejunioileal endocrine tumors are multiple tumors in about 25–30% of cases^{1,9,17}. In this case, we used pre-operative FDG-PET to reveal whether solitary or multiple tumors were present. Although FDG can be a powerful functional modality for oncological imaging, it does not accumulate in endocrine tumors, except in dedifferentiated tumors and in tumors with high proliferative activity^{10,18}. We therefore examined the small intestine manually during surgery. The ¹⁸F- and ¹¹C-labelled amine precursors, L-dihydroxyphenylalanine (L-DOPA) and 5-hydroxy-L-tryptophan (5-HTP), might be useful agents for use in preoperative PET imaging¹⁸.

The present case was diagnosed histopathologically as a “well-differentiated endocrine carcinoma” by WHO classification¹⁶. TNM staging was T2N0M0 Stage IIA and grading was Grade 2¹². The overall 5-year survival rate for patients with jejunioileal endocrine tumors is approximately 60%, and the 10-year survival rate is 43%^{1,17}. Meta-analytical studies^{14,19} have reported post-operative 5-year survival rates to be 70–90.3% in patients without metastases, while in patients with nodal metastases they were 60–75% and in those with liver metastases, 30–50%. The present case had a good prognosis, and the patient remained symptom-free with no signs of recurrence or metastasis after 16 months without adjuvant therapy.

The occurrence of carcinoid syndrome is often associated with tumors of the small intestine (28.6%; overall 8.4%)¹⁵, but most endocrine tumors are non-functioning and the symptoms are often non-specific^{8,19}. Preoperative diagnosis is

difficult because the standard imaging techniques rarely identify the primary tumor, especially for smaller than 2 cm^{7,11}. In this case, the tumor was detected in the terminal ileum by colonoscopy. Colonoscopy of the terminal ileum is important because most endocrine tumors of the small intestine are located in the distal ileum, near to the ileocecal valve². Recently, advances in examination techniques of the small intestine, including enteroscopy with the double-balloon method²⁵ and capsule endoscopy³ are expected to facilitate detection of small tumors of the small intestine.

Removal of the primary tumor and regional lymph nodes by wedge resection of the mesentery is the recommended surgical technique⁶. However, there is no consensus about the surgical margin of the primary tumor and the extent of the lymph node dissection. A randomized trial showed that laparoscopic surgery was equal in morbidity, mortality and 3-year disease-free survival and required fewer analgesics and a shorter hospital stay compared with open surgery for colon cancer^{20,21}. Though there is no report of laparoscopic surgery for endocrine carcinomas of the small intestine, we performed laparoscopy-assisted resection with lymph node dissection for the purposes of radicality and a less invasive surgical procedure. Though complications arose in the present case, we consider that laparoscopy-assisted surgery can be useful in patients with small tumors of the small intestine, as in the case presented here.

(Received February 25, 2010)

(Accepted April 16, 2010)

REFERENCES

1. **Burke, A.P., Thomas, R.M., Elsayed, A.M. and Sobin, L.H.** 1997. Carcinoids of the jejunum and ileum: an immunohistochemical and clinicopathologic study of 167 cases. *Cancer* **79**: 1086-1093.
2. **Capella, C., Solcia, E., Sobin, L.H. and Arnold, A.** 2000. Endocrine tumours of the small intestine, p. 77-82. *In* SR, Hamilton and LA, Aaltonen (eds.), Pathology and Genetics. Tumours of the Digestive System. WHO Classification of Tumours. IARC Press, Lyon.
3. **de Mascarenhas-Saraiva, M.N. and da Silva, Araujo, Lopes, L.M.** 2003. Small-bowel tumors diagnosed by wireless capsule endoscopy: report of five cases. *Endoscopy* **35**: 865-868.
4. **Godwin, J.D.** 1975. Carcinoid tumors. An analysis of 2,837 cases. *Cancer* **36**: 560-569.
5. **Hamada, T., Tanaka, M., Hashimoto, Y., Yamauchi, M., Shigeoka, N., Shima, H., Nakai, K., Suenaga, K. and Nakayama, H.** 2006. A case of endocrine cell carcinoma of the ileum: sonographic findings and clinical outcome (in Japanese with English abstract). *Nippon Shokakibyo Gakkai Zasshi* **103**: 1139-1145.
6. **Kerström, G., Hellman, P. and Hessman, O.**

2005. Midgut carcinoid tumours: surgical treatment and prognosis. *Best Pract. Clin. Gastroenterol.* **19**: 717-728.
7. **Maglinte, D.D., O'Connor, K., Bessette, J., Chernish, S.M. and Kelvin, F.M.** 1991. The role of the physician in the late diagnosis of primary malignant tumors the small intestine. *Am. J. Gastroenterol.* **21**: 247-257.
 8. **Modlin, I.M., Oberg, K., Chung, D.C., Jensen, R.T., de Herder, W.W., Thakker, R.V., Caplin, M., Delle, Fave, G., Kaltsas, G.A., Krenning, E.P., Moss, S.F., Nilsson, O., Rindi, G., Salazar, R., Ruzsniowski, P. and Sundin, A.** 2008. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol.* **9**: 61-72.
 9. **Moertel, C.G., Sauer, W., Dockerty, M. and Baggenstoss, A.** 1961. Life history of carcinoid tumor of the small intestine. *Cancer* **14**: 901-912.
 10. **Pasquali, C., Rubello, D., Sperti, C., Gasparoni, P., Liessi, G., Chierichetti, F., Ferlin, G. and Pedrazzoli, S.** 1998. Neuroendocrine tumor imaging can 18F-fluorodeoxyglucose positron emission tomography detect tumors with poor prognosis and aggressive behavior? *World Journal of Surgery* **22**: 588-592.
 11. **Picus, D., Glazer, H.S., Levitt, R.G. and Husband, J.E.** 1984. Computed tomography of abdominal carcinoid tumors. *A.J.R.* **143**: 581-584.
 12. **Rindi, G., Klöppel, G., Couvelard, A., Komminoth, P., Körner, M., Lopes, J.M., McNicol, A.M., Nilsson, O., Perren, A., Scarpa, A., Scoazee, J.Y. and Wiedenmann, B.** 2007. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* **451**: 757-762.
 13. **Soga, J.** 1985. Carcinoid tumors: an analysis of Japanese series. *J. Exp. Clin. Cancer Res.* **4**: 233-244.
 14. **Soga, J.** 1997. Carcinoids of the small intestine: A statistical evaluation of 1102 cases collected from the literature. *J. Exp. Clin. Cancer Res.* **16**: 353-363.
 15. **Soga, J., Yakuwa, Y. and Osaka, M.** 1999. Carcinoid syndrome: A statistical evaluation of 748 reported cases. *J. Exp. Clin. Cancer Res.* **18**: 133-141.
 16. **Solcia, E., Klöppel, G. and Sobin, L.H.** 2000. World Health Organization, international histological classification of tumours. Histological typing of endocrine tumours, 2nd ed. Springer.
 17. **Strodel, W.E., Talpos, G., Eckhauser, F. and Thompson, N.** 1983. Surgical therapy for small-bowel carcinoid tumors. *Arch. Surg.* **118**: 391-397.
 18. **Sundin, A., Garske, U. and Örfors, H.** 2007. Nuclear imaging of neuroendocrine tumours. *Best Pract. Res. Clin. Endocrinol. Metab.* **21**: 69-85.
 19. **Sutton, R., Doran, H.E., Williams, E.M.I., Vora, J., Vinjamuri, S., Evans, J., Campbell, F., Raraty, M.G.T., Ghaneh, P., Hartley, M., Poston, G.J. and Neoptolemos, J.P.** 2003. Surgery for midgut carcinoid. *Endocrine-Related Cancer* **10**: 469-481.
 20. **The Colon Cancer Laparoscopic or Open Resection Study Group, Buunen, M., Veldkamp, R., Hop, W.C., Kuhry, E., Jeekel, J., Haglund, E., Pählman, L., Cuesta, M.A., Msika, S., Morino, M., Lacy, A. and Bonjer, H.J.** 2009. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol.* **10**: 44-52.
 21. **The Colon Cancer Laparoscopic or Open Resection Study Group, Veldkamp, R., Kuhry, E., Hop, W.C., Jeekel, J., Kazemier, G., Bonjer, H.J., Haglund, E., Pählman, L., Cuesta, M.A., Msika, S., Morino, M. and Lacy, A.M.** 2005. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol.* **6**: 477-484.
 22. **Uesato, M., Kaneko, K., Takaishi, S., Kawamura, I., Akaike, Y. and Ochiai, T.** 2000. A case of neuroendocrine carcinoma of the ileum with multiple liver metastasis presented with intestinal obstruction (in Japanese with English abstract). *Nippon Rinsho Geka Igakkai Zasshi (J. Jpn. Soc. Clin. Surg.)* **61**: 156-160.
 23. **US National Cancer Institute. SEER Database.** <http://seer.cancer.gov/> (accessed Apr 26, 2008).
 24. **Vinik, A.I., McLeod, M.K., Fig, L.M., Shapiro, B., Lloyd, R.V. and Cho, K.** 1989. Clinical features, diagnosis, and localization of carcinoid tumors and their management. *Gastroenterol. Clin. North. Am.* **18**: 865-896.
 25. **Yamamoto, H. and Sugano, K.** 2003. A new method of enteroscopy -the double-balloon method. *Can. J. Gastroenterol.* **17**: 273-274.