Case Report

Colonic Neuroendocrine Carcinoma with Adenocarcinoma and Squamous Cell Carcinoma: Report of a Case

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ABSTRACT

Neuroendocrine carcinoma (NEC) of the colon is a rare entity; however, this type of tumor is known for its aggressive progression and poor prognosis(1). We describe a case of a 63-year-old Japanese female with a NEC of the cecum who received laparoscopic assisted right-hemicolectomy in this report. Histopathological findings of the resected specimen revealed a low-grade atypical gland (adenoma or well-differentiated adenocarcinoma) in the mucosa, but most of the tumor was composed of small cells with a high nuclear/cytoplasmic ratio mainly under the submucosa and had small foci of squamous cell carcinoma. On immunohistochemical staining, these atypical cells showed positive reactions for CD56, and the lesion was diagnosed as NEC of the colon. Chemotherapy with 5-fluorouracil / leucovorin was performed, but multiple liver metastases were detected 5 months after the operation. Hepatic arterial infusion chemotherapy with irinotecan plus 5-fluorouracil was given as second-line treatment, the patient survived for 18 months after the operation. We reported a case of colonic NEC with adenocarcinoma and squamous cell carcinoma, because of it is interest when considering the differentiation of neoplastic colonic NE cells.

Abbreviations: neuroendocrine (NE), neuroendocrine carcinoma (NEC), endoscopic mucosal resection (EMR)
INTRODUCTION

Neuroendocrine (NE) cells are distributed throughout the body and are found in the gastrointestinal tract, pancreas, lung, thyroid, adrenal gland, and many organs(2). The gastrointestinal tract has the largest population of NE cells. Despite this, neuroendocrine carcinoma (NEC) of the colon and rectum are rare(3), and its pathogenesis is still not clearly understood. At present, thanks to immunohistochemical methods, the endocrine component is frequently recognized in the epithelial colorectal tumors(4). Gastrointestinal neoplasms which contain both mucinous and endocrine cells have been reported(5,6). Rare neoplasm exhibiting tripartite differentiation, containing cells showing mucinous, squamous and endocrine features have been documented(10). We reported herein a rare case of NEC of the colon containing the components of adenocarcinoma and squamous cell carcinoma.

REPORT OF CASE

A 63-year-old Japanese woman was admitted to the hospital on May 2005, with complaint of positive occult blood test of feces. She received endoscopic mucosal resection (EMR) for a polypoid lesion, semi-pedunculated in shape and 20 mm in size, in the cecum (Fig. 1a). Histological examination revealed well-differentiated adenocarcinoma with a positive cut margin. She was transferred to the Osaka Medical College Hospital for the operation on the remnant tumor. The patient had a history of lung tuberculosis and gastric ulcer. On physical examination the patient appeared well. No lymphadenopathy was found. The head, neck and chest were normal. The abdomen was not distended, the bowel sounds were normal, and no organs or masses were palpated. The laboratory data on admission showed that the hematologic values, blood chemical and enzyme values were normal. The serum levels of carcinoembryonic antigen (0.6 ng/ml) and carbohydrate antigen 19-9 (11.8 U/ml) were in the normal range. Endoscopic examination disclosed a sessile tumor with ulcerative lesion after EMR, 14×18 mm in size, in the bottom of cecum (Fig. 2a). A computed tomography showed no detectable metastatic lesion in the lymph node or liver. We conducted laparoscopic assisted right-hemicolectomy on the end of May 2005. The surgical specimen showed a sessile tumor in the bottom of cecum measuring 14×18
mm, in association with focal ulceration (Fig. 2b). Cut surfaces demonstrated transmural involvement by an invasive solid tumor component (Fig. 2c). Histologically, three different components were seen. The elevated lesion consisted of a low-grade atypical gland (adenoma or low-grade well-differentiated adenocarcinoma) confined to the mucosa (Fig. 3a), while the invasive lesion was composed solely of highly atypical small cells with hyperchromatic nuclei, and the two tumor

![Image of colonoscopy image of the tumor after EMR.](a)
![Image of macroscopic findings of the resected specimen. The arrow indicated the tumor after EMR.](b)
![Image of the magnifying lens image of cross section of the resected specimen (H.E. staining, Loupe image).](c)

**Fig. 2**

a: Colonoscopy image of the tumor after EMR.
b: Macroscopic findings of the resected specimen. The arrow indicated the tumor after EMR.
c: The magnifying lens image of cross section of the resected specimen (H.E. staining, Loupe image).

![Histopathological findings of the resected specimen.](a)
![Histopathological findings of the resected specimen.](b)
![Histopathological findings of the resected specimen.](c)
![Histopathological findings of the resected specimen.](d)

**Fig. 3**

Histopathological findings of the resected specimen.
a: Low-grade atypical gland (adenoma or low-grade well-differentiated adenocarcinoma, H.E. staining, ×100).
b: The transitional zone of poorly-differentiated carcinoma (right side) and low-grade atypical gland (adenoma or low-grade well-differentiated adenocarcinoma) (left side) (H.E. staining, ×100).
c: The small foci of squamous cell carcinoma (arrow) (H.E. staining, ×200).
d: Lymphnode metastasis was detected in the paracolic lymphnode (H.E. staining, ×40).
components collided (Fig. 3b). Focally, keratinizing squamous cell carcinomas were detected in this tumor (Fig. 3c). Lymphatic invasions, as well as paracolic lymph node metastasis (Fig. 3d), were caused entirely by the atypical small cells. The tumor consisted of round to polygonal cells with a high nuclear/cytoplasmic ratio, and the cells were arranged in an irregular sheet-like pattern (Fig. 4a). On immunohistochemical staining, these atypical cells showed positive reactions for CD56 (Fig. 4b), and the lesion was diagnosed as NEC. Chemotherapy with 5-fluorouracil (5-FU) / leucovorin was performed, but multiple liver metastases were detected five months after the operation. Hepatic arterial infusion chemotherapy with irinotecan (CPT-11) plus 5-FU was given as second-line treatment, the patient survived for 18 months after the operation.

Fig. 4 a: Histology showed the tumor was composed small cells with a high nuclear/cytoplasmic ratio (H.E. staining, ×200).

b: Immunohistochemical study showed CD56 positive (×200).

DISCUSSION

The occurrence of neuroendocrine carcinoma (NEC) of the colon or rectum is rare. The reported incidence of this tumor represents 0.1 % and 3.9 % of all colorectal malignancies[4]. Tumors of gastrointestinal origin, in which neoplastic endocrine cells are characteristically arranged in solid, cord-like, rosette-like, or acinar structures, and grow in masses in a capillary-rich stroma, are collectively referred to as gastrointestinal endocrine tumors.

The gastrointestinal NEC are considered to include those arising from endocrine cells scattered among the epithelial cells (diffuse endocrine system) of the gastrointestinal tract, and those derived from endocrine cells that appear with the differentiation of adenoma and adenocarcinoma cells[11]. Traditionally, it was speculated that gastrointestinal endocrine tumors arose from (a) prior general adenocarcinomas, (b) prior carcinoid tumors, (c) non-neoplastic pluripotent stem cells, and (d) non-neoplastic, immature, endocrine cells[11]. However, the structures of lesions and the results of genetic analysis have led to the current belief that mainly the lump-like growth of a highly proliferative, neoplastic endocrine cell clone appearing in the deep portion of the gland tubule of prior well- and moderately differentiated, intramucosal, tubular adenocarcinomas results in the formation of gastrointestinal endocrine tumors via adeno-endocrine carcinomas[4].

The tumor in this patient consisted of three morphologically different elements (Fig. 3a-c): (a) solidly nests consisting of poorly-differentiated carcinoma with a fibrous stroma, invading to the submucosa of the colon, (b) a intra-mucosal low-grade atypical gland (adenoma or low-grade well-differentiated adenocarcinoma), growing in the mucosa around an ulcer, and (c) small foci of keratinizing squamous cell carcinoma. The first element had relatively uniform-sized, chromatin-rich, round nuclei, and grew invasively in small solid nests (Fig. 4a). Many of these carcinoma cells were positive by immunostaining for the endocrine cell marker CD56 (Fig. 4b), indicating that the cancer is a neuroendocrine cell carcinoma (NEC). A few carcinoma lesions showed differentiation into a keratinizing squamous cell carcinoma (Fig. 3c). The first element (NEC) was transited to the second element (adenoma or low-grade well-differentiated adenocarcinoma) in the deep layer of the mucosa, with partial transition.
into the latter (Fig. 3b). The area of transition and the neighboring well-differentiated adenocarcinoma were positively immunostained for CD56. These findings led to the speculation that the tumor raised from a low-grade atypical gland with polypoid growth, in some areas of which a neuroendocrine cell carcinoma, in some areas of which a adenocarcinoma, and some areas of which a squamous cell carcinoma developed, and invaded the submucosa, making this case interesting from the viewpoint of carcinogenesis.

It has been reported that colonic endocrine cells rapidly grow and invade vessels, and make the prognosis very poor\(^1\)\(^{11}\). Also in this case, multiple liver metastases were detected five months after the curative operation. Among tumors diagnosed as low-grade atypical, adenoma or well-differentiated adenocarcinoma by preoperative biopsy and treated by endoscopic mucosal resection, biologically highly malignant ones, as described here, occur rarely. We report this case to demonstrate that it should be carefully managed.

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REFERENCES


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