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【 CASE REPORT 】

Primary Neuroendocrine Carcinoma of the Anal Canal with Cancer Genome Profiling

Ryuichi Morita[1], Seiya Sugeta[1], Juichiro Yoshida[2], Tomohiro Ueda[1], Tasuku Hara[1], Yasutaka Morimoto[1], Akiko Shibuya[1], Tomoyuki Ohno[1], Tomoki Nakajima[1], Nobuaki Fuji[3], Eiichi Konishi[4] and Norimasa Yoshida[1]

Abstract:
Primary neuroendocrine carcinoma (NEC) of the anal canal is a rare, highly malignant tumor with a poor prognosis. Despite the standard first-line treatment with etoposide or irinotecan combined with cisplatin, effective second-line therapies are lacking. In 2019, Japan approved cancer genome profiling (CGP) tests for solid tumors to enhance genomic understanding. We present the case of a 79-year-old woman with NEC of the anal canal, treated with etoposide, carboplatin, and amrubicin. As Post-standard therapy, CGP suggested pemigatinib, a tyrosine kinase inhibitor; however, the patient died before receiving it. This case highlights the potential of personalized medicine to improve outcomes in such cases.

Key words: neuroendocrine carcinoma, anal canal, cancer genome profiling

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Introduction

Neuroendocrine tumors (NENs) of the gastrointestinal tract are classified according to the 2019 World Health Organization classification (1) as follows: neuroendocrine tumors (NETs), which grow slowly and exhibit well-differentiated histology, and neuroendocrine carcinomas (NECs), which progress aggressively and are poorly differentiated irrespective of their origin (2). NECs are exceedingly rare, constituting <1% of all neuroendocrine tumors. In the gastrointestinal tract, NECs also represent <1% of all malignancies (3, 4). Although approximately 60% of NENs are believed to originate from the rectum (5), the prevalence of NECs in this area remains largely unknown owing to their scarcity. NECs of the anal canal are even more uncommon, with only 1 study from Japan reviewing 10 cases of primary NECs of the anal canal (6).

Since the introduction of cancer genome profiling (CGP) tests covered by health insurance in Japan in 2019, the genomic profiling of various malignant solid tumors has been progressively elucidated. However, the genomic profiles of primary NECs in the anal canal have not been documented.

In this report, we describe a remarkably rare case of primary NEC of the anal canal that was managed to delineate the genomic profile linked to its carcinogenesis. We report the genomic profiling characteristics of this patient, compare them with those of NECs in other organs, and discuss the potential of personalized medicine in treating this disease.

Case Report

A 79-year-old woman with no significant medical history presented to our hospital complaining of anal pain and a persistent sensation of incomplete stool evacuation for 3 months. Blood tests were largely normal except for elevated levels of serum carcinoembryonic antigen (CEA; 38.2 ng/mL) and CA19-9 (39.3 ng/mL). There were no signs of anemia or hepatorenal dysfunction.

[1]Department of Gastroenterology and Hepatology, Kyoto Saiseikai Hospital, Japan, [2]Department of Gastroenterology and Hepatology, Japanese Red Cross Society Kyoto Daiichi Hospital, Japan, [3]Department of Digestive Surgery, Kyoto Saiseikai Hospital, Japan and [4]Department of Surgical Pathology, Kyoto Prefectural University of Medicine, Japan
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Correspondence to Dr. Ryuichi Morita, mryuich@koto.kpu-m.ac.jp

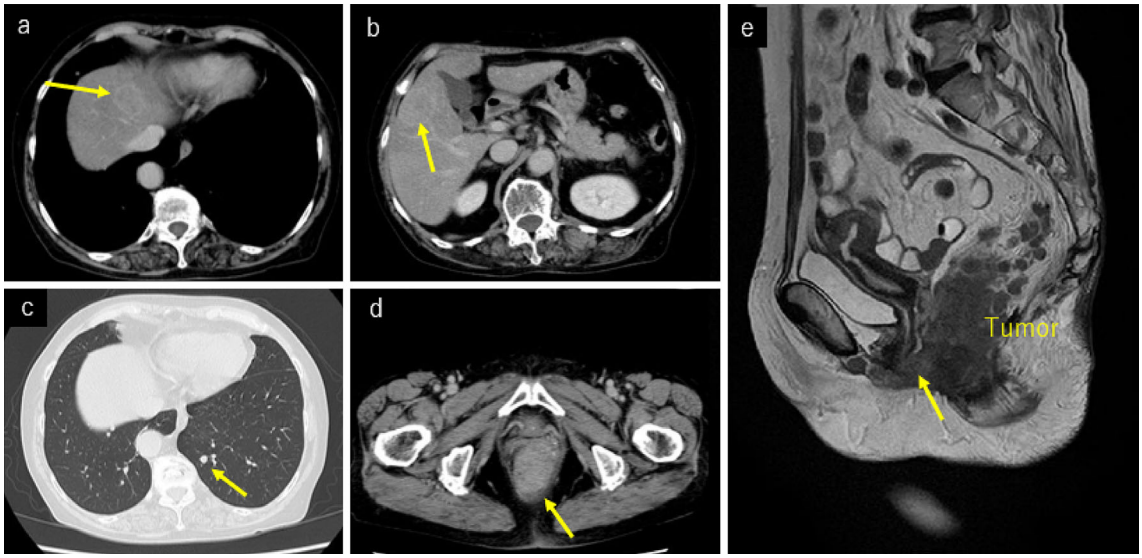

Figure 1. **Contrast-enhanced CT showed hepatic (a, b) and pulmonary metastatic lesions (c), and the primary lesion appeared as a mass with contrast enhancement (d). MRI showed invasion of the primary lesion into the vaginal wall (e).**

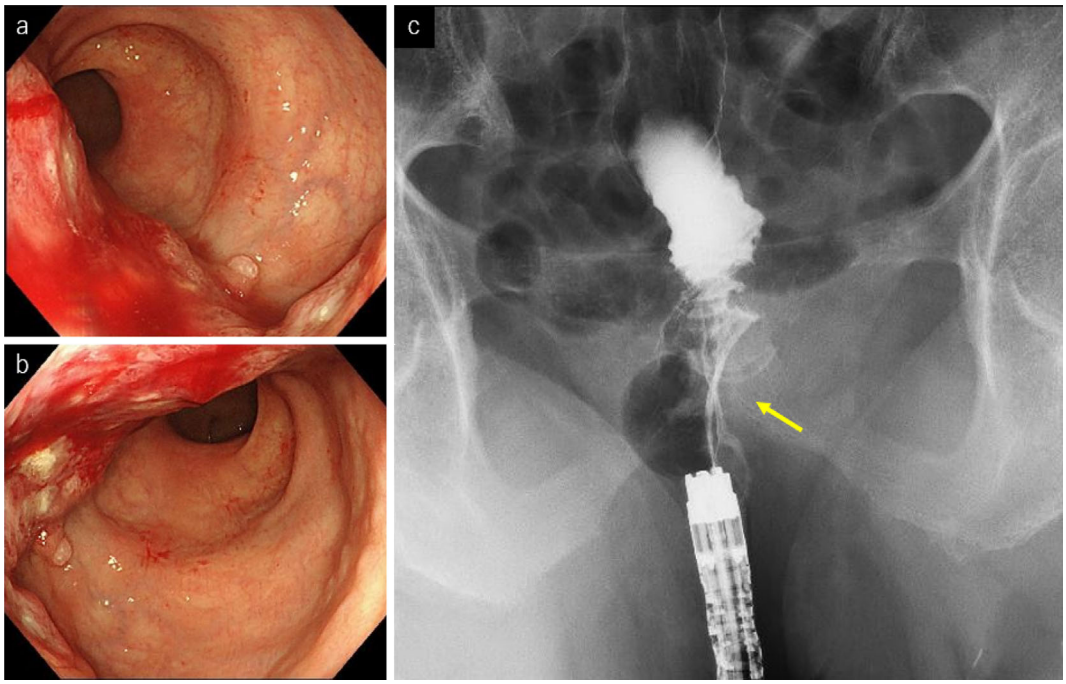

Figure 2. **Colonoscopy showing semi-peripheral tumor growth from the dentate line to the anterior wall of the rectum (a, b). A contrast-enhanced examination showing stenosis (c).**

Abdominal computed tomography (CT) revealed a contrast-enhancing mass at the junction of the rectum and anus with multiple liver metastases and a single metastasis in the left lung (Fig. 1). Colonoscopy revealed that the tumor occupied nearly half of the lumen of the anal canal and extended into the anterior rectal wall (Fig. 2). A histopathological examination of the surgical specimen revealed a Hematoxylin and Eosin-stained image of diffuse proliferation of large round cells with a high nuclear-to-cytoplasmic ratio. Immunohistochemical staining was predominantly positive for synaptophysin and CD56, and weakly positive for chromogranin A. High proliferative activity, indicated by 70% Ki-67 positivity, supported the diagnosis of primary neuroendocrine carcinoma (Fig. 3). Despite the presence of distant metastases, severe symptoms of anorectal stenosis led to perineal rectal amputation and colostomy, which successfully alleviated her symptoms. Postoperatively, she received 4 courses of systemic chemotherapy consisting of carboplatin at an area under the blood concentration time curve of 4 and 80 mg/m^2 etoposide, maintaining a stable disease response according to RECIST version 1.1.

Given her advanced age and poor tolerance to high-dose

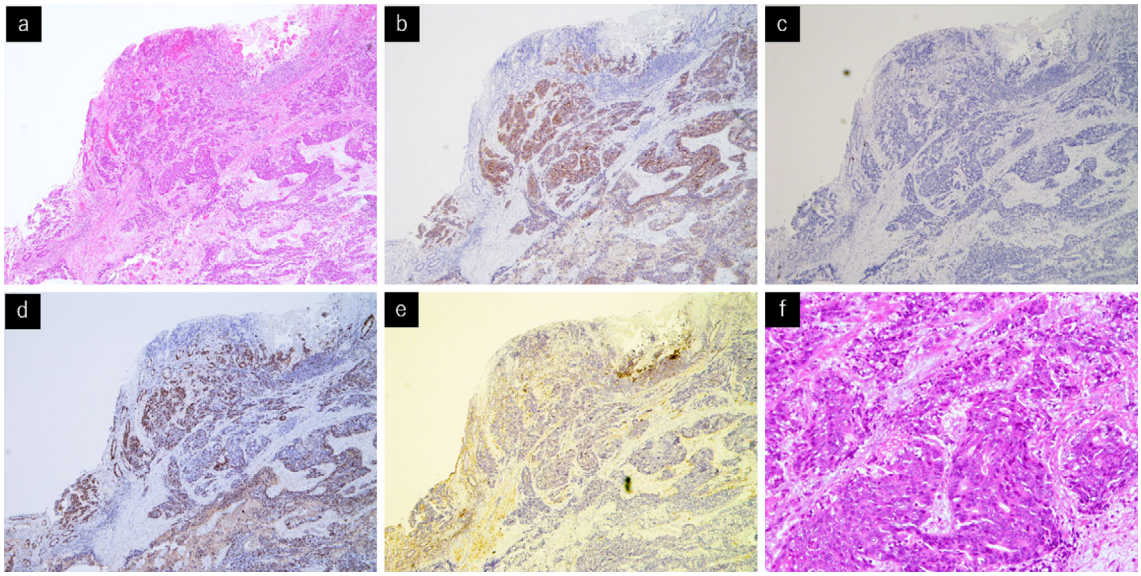

Figure 3. **Histopathological images. (a) Hematoxylin and Eosin (H&E) staining, (b) synaptophysin, (c) chromogranin A, (d) Ki-67, (e) CD56, (f) H&E staining with higher magnification (a-e: ×40, f: ×160).**

Table. **Variants Detected in This Case.**

Biomaker/Gene	Alteration	Clinical significance
Microsatellite status	Stable	
Tumor mutational burden	8 muts/Mb	
CCND1	Amplification	Pathogenic
FGF19	Amplification	Pathogenic
FGF3	Amplification	Pathogenic
FGF4	Amplification	Pathogenic
KRAS	Q61R	Pathogenic
TP53	P152fs*14	Pathogenic
APC	P1934L	VUS
BCL6	V277L	VUS
CARD11	S725fs*73	VUS
GNAS	A40V	VUS
PRDM1	R296W	VUS
RAD51D	D256E	VUS
REL	Splice site 30303_307delTAGTTTCC	VUS
SMAD4	Amplification	VUS

VUS: variant of uncertain significance

hydration, carboplatin was chosen over cisplatin. Subsequently, she received 35 mg/m^2 amrubicin, similar to the treatment for non-small-cell lung cancers. Concurrently, the resected tumor sample was sent for FoundationOne® CDx CGP testing. After one cycle of amrubicin monotherapy, her general condition deteriorated rapidly, leading to treatment discontinuation.

The CGP test identified amplification of *CCND1, FGF3, FGF4*, and copy number alterations in *FGF19* along with substitution variants in *TP53* and *KRAS* (Table). Germline variants were not detected. An expert panel recommended a phase I clinical trial of futibatinib (JapicCTI-195063), an FGF inhibitor that targets the amplification of *FGF3* and *FGF4*. However, her condition quickly worsened, and she died on day 163 without participating in the trial.

Discussion

Colorectal NECs account for only 0.2% of all colorectal malignancies (7), and NECs of the anal canal are even rarer. The prognosis for this disease is dismal, with a 1-year mortality rate of 63% and 3-year survival rate of only 7% (8). In the present case, the diagnosis was confirmed by immunohistochemical staining; however, as previously reported (9), the endoscopic findings were indistinguishable from those of advanced colorectal cancer. The Japanese

Neuroendocrine Tumor Society clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms state that resection is indicated in cases of NECs if possible, and adjuvant chemotherapy can be used to prevent recurrence after surgery (9). There is evidence that surgery alone is insufficient for treatment (10). Furthermore, there are some reports of successful drug therapy (11), the lack of standard treatments remains a challenge for this rare malignancy. In Japan, cancer genome profiling testing was approved in 2019 for patients who had completed (or were expected to complete) standard therapies. This test is particularly valuable for cancers with few standard treatment options, as was the case here. Although there have been a few case reports of primary NEC of the anal canal (12, 13), our report is the first to detail both the clinical course and genomic profiles globally.

As observed in many case reports (6), symptoms such as anal pain and sensation of residual stool were key in diagnosing NEC in our patient. At the time of the diagnosis, the patient had multiple metastases in the liver and lungs, making a radical cure unlikely. After perineal rectal amputation and colostomy, systemic chemotherapy was initiated for the remaining lesions. In 2022, a randomized phase III clinical trial demonstrated that etoposide or irinotecan combined with cisplatin significantly improved the overall survival and is recognized as the primary treatment regimen for gastrointestinal NEC (14). Since these results had not yet been obtained, and combination therapy including platinum was recommended for small-cell lung cancer (15), we initiated combination chemotherapy using carboplatin and etoposide in our case. The patient maintained stable disease after four courses of the regimen. However, due to the lack of established second-line therapies, we opted for amrubicin monotherapy, following treatment protocols for small- and non-small cell lung cancer. Simultaneously, the sample from the resected tumor was subjected to FoundationOne® CDx, a CGP test, to search for new treatment regimens.

The drug suggestion rate for CGP tests has been reported to be 8.1% (16), indicating that rare malignant solid tumors, such as the one in this case with few or no standard treatments, are prime candidates for CGP testing. As of May 2024, there have been no cases of NEC among the 79 cases listed under "Primary Site" as "anus and anal canal" in The Cancer Genome Atlas (https://www.cancer.gov/ccg/research/genome-sequencing/tcga), an open database in the United States. This underscores the uniqueness of our case and its contribution to the data supporting personalized medicine.

In our case, pathological genetic variants involved in carcinogenesis included amplification of *CCND1*, *FGF3*, *FGF4*, and *FGF19*, along with substitution variants of *TP53* and *KRAS* (Table). According to previous studies (17), NECs of non-pancreatic gastrointestinal origin often feature *TP53* variants combined with *RB1, CCNE1*, or *MYC* (the latter being mutually exclusive with *CCNE1*). However, our patient's genetic profile did not show pathological variants in *CCNE1* but in *CCND1*, which also plays a role in cell cycle progression. Cyclin E1, encoded by *CCNE1*, forms a complex with CDK2, whereas cyclin D1, encoded by *CCND1*, forms a complex with CDK4/6. Both complexes phosphorylate RB1, promoting cell cycle turnover and the transcription of genes related to S-phase initiation. *CCNE1* and *CCND1* have similar functions in this regard (18). Amplification and overexpression of these genes have been linked to carcinogenesis, as seen in gastric cancer (19), and previous reports (17) predominantly discuss colorectal carcinoma, and it remains unclear whether they include cases of primary anal canal carcinoma. Furthermore, the genomic profile influenced by viral infections showed no variants in *TP53* or *RB1*, suggesting that the genetic landscape of neuroendocrine carcinoma of the anal canal might differ from that of colorectal neuroendocrine carcinoma or that our case may have been triggered by a viral infection. For treating patients with these variants, CDK4/6 inhibitors such as palbociclib and abemaciclib are in clinical use but have recently shown resistance in breast cancer patients with *RB1* variants (20). In addition, a CDK2 inhibitor is currently undergoing a phase I clinical trial (jRCT2031220091). Thus, further research is necessary to develop effective therapeutics for the genetic variants involved in cell cycle progression.

In the present case, the use of pemigatinib, not covered by insurance, for amplification of *FGF3, FGF4,* and *FGF19*, and a phase I clinical trial (JapicCTI-195063) that combined futibatinib with pembrolizumab for *FGF3* and *FGF4* amplification, was proposed as the next treatment option. The U.S. Clinical Trials. gov database (https://clinicaltrials.gov/) lists 158 trials recruiting as of May 2024 for pathological variants of the *FGF* family, including those detected in this study, indicating robust activity in the development of new therapies for these variants. For instance, futibatinib (21) and pemigatinib (22) have been approved for the treatment of biliary tract cancer with FGFR2 variants in Japan. As of January 2024, Japan has Patient-Proposed Healthcare Services for infigratinib (jRCTs041180017) and pemigatinib (jRCTs041230105). Given the variants identified in this case, personalized medicine has the potential to improve the prognosis.

The genetic profiles from this case should not be generalized to all cases of NEC of the anal canal, as this is a single report from one institution on a rare malignancy.

In conclusion, we documented a case of primary neuroendocrine carcinoma of the anal canal, revealing its genomic profile for the first time. We anticipate that further research on the pathological variants of this disease will aid in the development of new therapies and enhance the prognosis.

Informed consent was obtained from all patients for inclusion in this study.

The authors state that they have no Conflict of Interest (COI).

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