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Primary Poorly Differentiated Rectal Neuroendocrine Carcinomas: Four Case Reports and Literature Review

KEYWORDS

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ABSTRACT *In this article, we present four cases with primary poor differentiated rectal neuroendocrine carcinomas. The first case was a 34-year-old man with liver metastases at the time of diagnosis. Following six cycles of cisplatin-etoposide therapy, gastrointestinal obstruction developed and he underwent palliative surgery. Brain metastases occurred after surgery. The patient died due to the neurological complications. The second case was a 72-year-old man with intraabdominal lymph nodes at the time of diagnosis. Following three cycles of cisplatin-etoposide therapy, the patient had metastases in the lungs. The third case was a 58-year-old male patient with a bladder and prostate invasion of mass at the time of the diagnosis. Because of the haematuria, carboplatin-etoposide was initiated after a palliative RT. The fourth case, a patient already diagnosed with prostate cancer, was diagnosed with metacron rectal neuroendocrine carcinoma. Radiotherapy and carboplatin-etoposide therapy were given. The patient died after one cycle of therapy due to neutropenic fever and sepsis. All four of our cases had locally advanced or metastatic stage at the time of diagnosis and they were given platinum and etoposide therapy. Treatment protocols of poorly differentiated rectal neuroendocrine carcinomas have yet to be clearly defined. In order to establish treatment protocols for these rarely diagnosed cases, more case studies are needed.*

Introduction

Rectal neuroendocrine carcinomas (RNCs) account for 18% of all neuroendocrine tumours and 27% of gastrointestinal neuroendocrine tumours (1). According to the SEER (The Surveillance, Epidemiology and End Results) data, the incidence of colorectal neuroendocrine tumours has been increasing (2). Rectal neuroendocrine tumours are generally seen in the younger population and the median age of the diagnosis is 56 years (3). Rectal tumours are usually small, polyploidy lesions located at the anterior or posterior rectum wall, from 4 to 20 cm to the dentate line and are incidentally detected during sigmoidoscopy.

Rectal neuroendocrine tumours are typically non-functional and rarely lead to carcinoid syndrome. In case reports, it has been shown that only three patients had carcinoid syndrome among 38 patients (4). However, serotonin secretion is found in one out of 36 patients (5). Immunohistochemically, 45% of the patients have positivity with serotonin dyed even though the blood levels of these patients are normal (6).

Small rectal neuroendocrine tumours rarely metastasize and the endoscopic and trans anal approach is curative. Nevertheless, large tumours have a high potential for metastasis to the bone, the lymph nodes and the liver (7). Based on the SEER database, rectal neuroendocrine neoplasms have been shown to metastasize at a rate of 2-3% (8).

Rectal neuroendocrine neoplasms are classified with WHO 2010 guidelines. They are categorised into three groups, namely as neuroendocrine tumours (NETs), neuroendocrine carcinomas (NECs) and mixed adenoneuroendocrine carcinomas (MANECs). Similarly, tumours cells are graded at three levels, based on their proliferation index: G1 tumour: mitosis <2 Ki-67: ≤ 2%; G2 tumour: mitosis 2-20 Ki-67: 3-20%; G3 tumour: mitosis >20 Ki-67: >20%.

Neuroendocrine tumours are well differentiated neuroendocrine neoplasms. Cell atypia and proliferative activity are very low. This category was previously defined as carcinoid tumour.

On the other hand, neuroendocrine carcinomas are highly proliferative, consisting of poorly differentiated, high-grade malignant cells and demonstrating atypia and necrosis. This group was previously referred to as small-cell carcinoma, large-cell neuroendocrine carcinoma or as poorly differentiated endocrine carcinoma. Neuroendocrine carcinomas are categorised into two groups, i.e., the small-cell and the large-cell. Small-cell neuroendocrine carcinomas are predominantly located at the distal colon and the rectum, whereas large-cell carcinomas are more often found at the right colon.

Case Reports

Case 1: A 34-year-old male presented to the clinic with abdominal pain and rectal bleeding. At colonoscopy, an intraluminal lesion was detected inside the rectum. The biopsy result was reported as infiltrative neuroendocrine carcinoma. The abdominal Computerized Tomography (CT) scan revealed a lesion with a diameter of 5x5x9 cm at the rectum, with liver metastasis and paraaortic and perirectal multiple lymph nodes. Since the scintigraphy of the octreotide was positive at the rectum, liver and intraabdominal lymph nodes, Sandostatin 30mg was given with cisplatin–etoposide chemotherapy. After three cycles of chemotherapy, a partial response was achieved. Gastrointestinal obstruction was seen after the mass at the rectum progressed. He underwent a palliative operation of the rectum. Post-operatively, irinotecan based chemotherapy was given as a second line therapy. During irinotecan treatment, multiple brain metastases were detected. The patient received palliative radiotherapy (RT). He died thirteen months after diagnosis due to the neurological complications.

Case 2: A 72-year-old male presented to the clinic with abdominal pain and constipation complaints. At colonoscopy, a mass was detected at the rectum. The biopsy result was reported as poorly differentiated neuroendocrine carcino-

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ma. A mass at the rectum and metastasis at the paraaortic lymph nodes were seen at the abdominal CT scan. Cisplatin-etoposide treatment was initiated. The patient developed lung metastases after three cycles of treatment and eventually died thirteen months later due to respiratory failure.

Case 3: A 58-year-old male presented to the clinic with abdominal pain and rectal bleeding. At colonoscopy, an ulcero-vegetan mass was detected at the rectum. The biopsy result revealed poorly differentiated neuroendocrine carcinoma. During the abdominal CT scan, a mass at the rectum invading the bladder and the prostate, and paraaortic lymph nodes were observed. Because of haematuria, the patient initially received a palliative RT, and carboplatin-etoposide treatment followed. He died four months after treatment initiation due to **renal failure**.

Case 4: A 50-year-old patient, already diagnosed with prostate carcinoma, underwent a colonoscopy for rectal bleeding and a mass was detected at the rectum. In order to clinically distinguish a prostate carcinoma invasion from a primary rectal carcinoma, a biopsy was performed. Pathology results revealed poorly differentiated neuroendocrine carcinoma. Radiotherapy and subsequently carboplatin-etoposide therapy were administered. The patient died after one cycle of therapy due to neutropenic fever and sepsis caused by pseudomonas.

Discussion

Rectal tumours can be detected incidentally during sigmoidoscopy and colonoscopy. Symptoms may include changes in bowel movements, weight loss, bleeding, tenesmus and abdominal pain. At the metastatic stage, pain in the upper right side of the abdomen, hepatomegaly and weight loss may be observed. Bowel obstruction is rare, but can be seen with rectosigmoid area tumours and intraabdominal advanced disease. At the time of diagnosis, 75-85% of the patients have localized disease. Based on SEER data, 2-4% of the patients have metastasis at the time of diagnosis. According to the SEER database, the five-year survival rate in well and moderately differentiated neuroendocrine tumours is 90%, 62% and 24% for local, locally advanced and metastatic disease, respectively (9).

The risk categorisation of the rectal neuroendocrine neoplasm is made using four parameters involving the size, depth of the invasion, vascular invasion and the mitosis rate. The invasion of the muscularis propria displays an aggressive course. Both size and the invasion of the muscularis propria are the best prognostic predictors. It is important for the disease to be atypical and to have a high mitotic index. Mucosal depression and ulceration at the centre of the tumour, indicates a high metastatic potential. Using CT colonography, it can be determined if the colon tumour is multifocal and/or there is an invasion to the perirectal fat tissue and the fascia. Using rectal ultrasonography, the size and the invasion of the tumour and/or a perirectal lymph node involvement can be evaluated preoperatively.

Surgery is the only curative treatment method for colorectal neuroendocrine tumours. It can be classified into two groups: 1. Conventional surgery: colectomy, anterior resection and abdominoperineal resection. 2. Local resection: endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and transanal endoscopic microsurgery (TEM).

Lesions smaller than 1 cm have low metastatic potential. If the tumour has G1 or G2, without invasion to the muscularis mucosa, resection is recommended. Especially if there are G2 or G3 tumours with muscularis invasion, transanal excision is recommended. Tumour invasion is determined by endoscopic ultrasonography and Magnetic Resonance Imaging. The risk of metastasis for rectal neuroendocrine tumour lesions with a size of less than 1 cm is < 3%. If endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and transanal endoscopic microsurgery (TEM) are compared with each other as the choice of local treatment, complete resections are performed with ESD compared to EMR. The most effective treatment is achieved using TEM, with no recurrence after surgery.

Lesions between the sizes of 11 and 19 mm may mimic large lesions. The rate of metastasis for these lesions is approximately 10-15% (10). However, in cases of G1 or G2 node negative tumours with no invasion to the muscularis, transanal excision can be performed, but for G2-G3 and node positive tumours with muscularis invasion, anterior resection should be chosen.

Lesions greater than 2 cm have a high metastatic potential of 60-80%. In this group, an invasion to the muscularis propria can be seen. Major surgical interventions such as mesorectal excisions can be performed. Local resection does not contribute to survival in metastatic disease, but can provide symptomatic improvement (11). Palliative surgery at the metastatic stage is recommended in cases of an intestinal obstruction or complications.

There is no evidence relating to the use of adjuvant therapy following surgery. In the G3, poorly differentiated group, use of chemotherapy is controversial in cases if R0 resection is not possible.

During the Indium-111-Octreotide scan, after the octreotide is marked by indium-111, the cell expressing the somatostatin receptor is visualized and used for metastasis scanning. High-grade rectal neuroendocrine tumour cases do not express somatostatin receptors (12). For high-grade tumours not expressing somatostatin receptors, PET CT may be used for staging the disease (13). Gallium 68-DOTA octreotide PET is a more sensitive method, compared to indium-111.

Somatostatin analogues can provide symptom control in patients with carcinoid syndrome. There is no evidence for the use of somatostatin analogues as antitumours in non-functional colorectal neuroendocrine tumours (14). However, the PROMID study showed that compared to placebo, an improvement in progression-free survival is achieved with octreotide LAR (15). Somatostatin analogues are recommended if R0 resection is not possible and if these analogues are shown to be functional.

With the binding of interferon to the receptor of the neuroendocrine cells, the tumour suppressive genes are activated. Moreover, interferon has an antiangiogenic characteristic (10).

Chemotherapy is the most effective treatment in G3 neuroendocrine carcinomas. After first-line cisplatin-etoposide therapy, temozolomide + bevacizumab ± capecitabine or irinotecan ± 5-FU can be recommended as a second-line treatment (16). The combination of Flourouracil + streptozotosin + doxorubicin is also frequently used. Studies using antiangiogenesis or mTOR inhibitors are still ongoing.

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In the Radiant-2 study, an improvement in progression-free survival in locally advanced G1-G2 colorectal neuroendocrine neoplasms was determined in patients receiving everolimus plus octreotide LAR, compared to those receiving placebo plus octreotide LAR. Protocols including temozolomide may be used as well.

Peptide receptor radio-targeting therapy might be used in metastatic neuroendocrine tumours, after somatostatin receptor positivity has been shown during an octreotide scan or a galium-68 octreotide scan (17).

Treatment protocols of poorly differentiated rectal neuroendocrine carcinomas with a poor prognosis have yet to be clearly defined. In order to establish treatment protocols for these rarely diagnosed cases, more case studies are needed.