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Case Report

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Neuroendocrine carcinoma of the rectum

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ABSTRACT

Neuroendocrine carcinoma (NEC) of the rectum is rare. Most patients have metastatic disease at the time of diagnosis. These malignancies have a worse prognosis compared with conventional adenocarcinoma, and there is no standard treatment protocol. We report herein a case of NEC of the rectum with a short survival. A 60-year-old female was admitted to the emergency service with jaundice, abdominal pain, back pain and confusion, without a history of rectal bleeding. The imaging studies showed a rectal tumor, abdominal lymphadenopathies, and multiple liver and vertebral metastases. Rectal biopsy was performed. The histopathologic findings were consistent with those of NEC. Palliative radiotherapy was planned for the spinal metastases, but the patient died before completing radiotherapy, within 1 month from diagnosis. In conclusion, these neoplasms show a dramatic course, particularly in metastatic patients, and there is a clear need for studies involving larger numbers of colon and rectum NEC patients.

1. Introduction

Neuroendocrine cells are located diffusely throughout the human body, with most located in the intestinal tract (Vilallonga et al., 2008; Minocha et al., 2014). According to the 2010 World Health Organization (WHO) classification, neuroendocrine neoplasms are classified into three categories as follows: low-grade (Grade 1 = mitotic rate of less than 2 per 10 high-power fields (HPF) and a Ki-67 proliferative index (PI) of less than 2%) neuroendocrine tumor (NET), intermediate-grade (Grade 2 = mitotic rate of 2-20 per 10 HPF and a Ki-67 PI of 3-20%) NET, and high-grade (Grade 3 = mitotic rate of more than 20 per 10 HPF and a Ki-67 PI of more than 20%) NET or neuroendocrine carcinoma (NEC) (Öberg et al., 2012). Large cell and small cell NECs falls within the NET grade 3 category (Minocha et al., 2014).

NEC is extremely rare and constitutes less than 1% of all colon and rectal cancers. However, the incidence of these neoplasms is increasing (Shafqat et al., 2015). The symptoms of these neoplasms are similar but are extremely aggressive and are associated with a high

mortality rate compared with adenocarcinomas (Nojima et al., 2010; Aytac et al., 2013). Most of the patients are metastatic on presentation (Smith et al., 2014; Shafqat et al., 2015). The overall survival at 5 years in patients with metastatic disease is 3-5.5% (Kang et al., 2007; Shafqat et al., 2015).

There have been no prospective studies on or standard treatments developed for patients with NEC of the colon and rectum because of its rarity. Treatments are based on case reports, small retrospective studies, adenocarcinoma of the rectum and small cell carcinoma of the lung (Aytac et al., 2013; Smith et al., 2014; Shafqat et al., 2015). We herein report a rare case of NEC of the rectum that showed a dramatic course.

2. Case report

A 60-year-old woman was admitted to the Ondokuz Mayis University Hospital emergency department with jaundice, inability to remove gas or stool, and abdominal and back pain. Her consciousness was blurred and not cooperative. She was icteric. Her Karnofsky performance status was 40%. There was no history of rectal bleeding. Physical examination revealed hepatomegaly. There was no blood or mass on digital rectal examination. The complete blood count, serum biochemistry and serum tumor marker results were as follows: hemoglobin, 13.3 g/dL (reference range (RR) = 12.00-15.00 g/dL); total bilirubin, 18.21 mg/dL (RR = 0.1-1.5 mg/dL); direct bilirubin, 15.8 mg/dL (RR = 0.00-0.40 mg/dL); aspartate aminotransferase (AST), 117.7 U/L (RR = 8-46 U/L); alanine transaminase (ALT), 80.5 U/L (RR = 7-46 U/L); gamma-glutamyl transferase (GGT), 562 U/L (RR = 5-36 U/L); carcinoembryonic antigen (CEA), 1.02 ng/mL (RR = less than 4.3 ng/mL) and carbohydrate antigen (CA) 19-9, 19.4 U/mL (RR = 0-37 U/mL). The postero-anterior chest X-ray results were normal. Abdominal ultrasonography detected multiple liver masses. Abdomino-pelvic computed tomography (CT) detected hepatomegaly, multiple liver masses, a mass in the 3.5-cm proximal segment of the rectum and pathological enlargement of the perirectal, presacral, paraaortic, portocaval and celiac lymph nodes (Fig. 1).

Sigmoidoscopy showed a mass that completely filled the proximal lumen of the rectum. Biopsy of the rectal mass was performed. Immunohistochemical (IHC) staining of the tumor was positive for synaptophysin and CD56 but negative for chromogranin A (Cg-A). The Ki-67 PI was greater than 20%. The mitotic rate was more than 20 per 10 HPF. These histopathologic findings were consistent with NEC (Fig. 2).

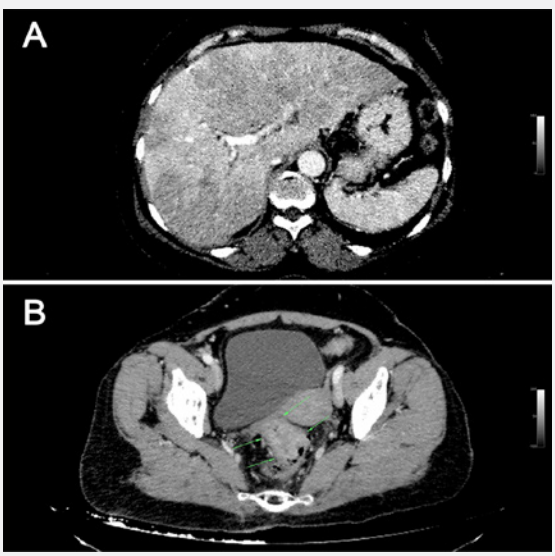

Fig. 1. (A) Computed tomography showing numerous hypodense masses throughout the liver consistent with liver metastasis. (B) Contrast-enhanced computed tomography of the pelvis reveals a rectal mass involving the proximal segment of the rectum (shown with arrows).

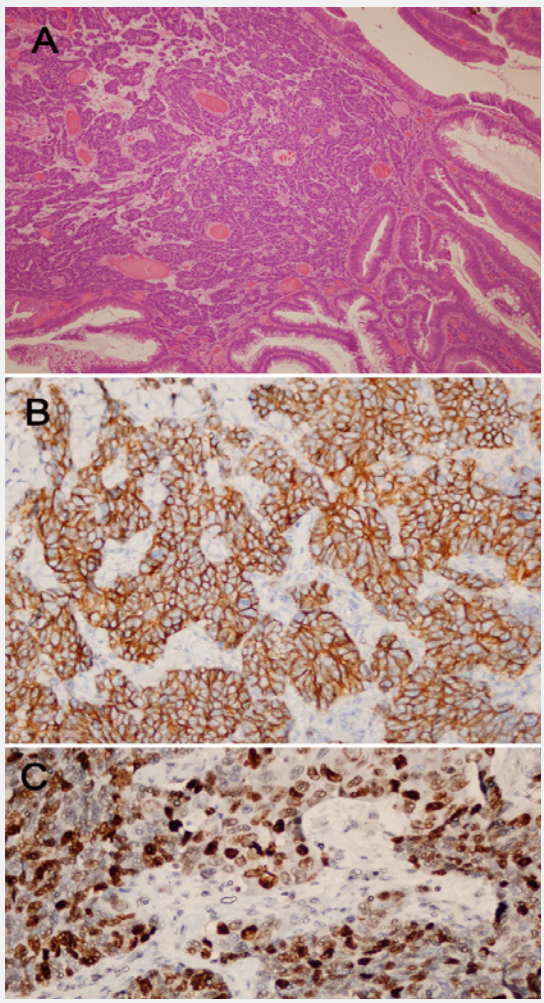

Fig. 2. Pathological findings: hematoxylin and eosin (HE) and immunohistochemistry staining images. (A) HE staining (×100). (B) CD56 immunostaining (×400). (C) Ki-67 immunostaining (×400).

Chest CT was normal after a definite diagnosis. Spinal magnetic resonance imaging was planned due to back pain, and multiple vertebral metastases were detected. Palliative radiotherapy (RT) was planned for the vertebral metastases. The patient died of hepatic failure during RT.

3. Discussion

NEC of the large bowel was first described by Gould and Chejfec in 1978 (Gould and Chejfec, 1978). The most frequent localization of NEC in the large bowel is the rectum, and the reported rates vary between 26.5% and 42% (Smith et al., 2014; Shafqat et al., 2015). Most of the rectal tumors are located in the mid and upper rectum (Aytac et al., 2013). The clinical presentation of rectal NEC is similar to that of adenocarcinoma. The most frequently seen symptoms are abdominal pain, hematochezia, constipation, tenesmus and fecal occult blood. The symptoms of paraneoplastic or carcinoid syndromes and metabolic abnormalities are rarely seen (Vilallonga et al., 2008; Aytac et al., 2013; Minocha et al., 2014). As in our case, most (57.9 - 67%) patients present with metastatic disease, and the liver is the most frequently (51 - 68%) seen site of metastasis at presentation (Okuyama et al., 1999; Miyamoto et al., 2006; Sorbye et al., 2013; Smith et al., 2014).

NEC is diagnosed according to the aforementioned WHO classification, with a high proliferation rate reflected by the number of mitoses and a Ki-67 PI greater than 20% (Öberg et al., 2012). The Ki-67 PI is the best available marker of tumor cell proliferation. It predicts the invasive potential of these neoplasms. Highly proliferating tumors with a Ki-67 greater than 10% have extensive angioinvasion and show high potential for developing into metastatic disease. Additionally, these tumors usually stain positively for one or more neuroendocrine IHC markers such as Cg-A, synaptophysin, neuron-specific enolase (NSE) and CD56 (Minocha et al., 2014). The reported positivity rates of Cg-A, synaptophysin and NSE staining in patients with neuroendocrine neoplasms are 72.62-94%, 76.19-96% and 32.74%, respectively (Sorbye et al., 2013; Zhang et al., 2014). Our case was synaptophysin positive, CD56 positive, and CgA negative and met both criteria of the WHO classification.

The treatment for patients with NEC of the colon and rectum has not been clearly defined. NEC of the colon and rectum is morphologically and phenotypically related to NEC (large and small cell types) of the lung. Therefore, particularly in metastatic patients, cytoreductive chemotherapy (ChT) with platinum-based regimens is generally recommended (Miyamoto et al., 2006; Minocha et al., 2014). However, platinum-based ChT does not provide sufficient benefit in patients with a Ki-67 value less than 55% (Sorbye et al., 2013). There is no established second-line ChT agent for these neoplasms, but the efficacy of temozolomide alone or in combination with capecitabine ± bevacizumab was reported in some retrospective studies (Öberg et al., 2012). Some NECs contain non-neuroendocrine components, such as adenocarcinomas. In such situations, the chemotherapeutic regimen should be chosen according to the predominant cell type in the tumor (Aytac et al., 2014). Surgery is the mainstay of treatment for localized disease but does not provide a survival benefit for metastatic patients (Smith et al., 2014). On the other hand, localized non-small cell NEC patients obtain a survival benefit with surgery, but this is not valid for small cell NEC patients (Shafqat et al., 2015). Postoperative concurrent chemoradiotherapy (CRT) and/or ChT are recommended in patients with a high risk of local recurrence, such as those with positive lymph nodes and a positive resection margin (Miyamoto et al., 2006; Nojima et al., 2010; Aytaç et al., 2014). Prophylactic whole-brain irradiation, as in patients with small cell lung carcinoma, is not recommended due to the rarity of brain metastases (Smith et al., 2014).

The reported 5-year survival rates of patients with these neoplasms at stage I, II, III and IV are 57.4%, 56.4%, 26.3% and 3%, respectively (Shafqat et al., 2015). Poor prognostic factors are small cell histology, increasing age, male gender, stage III-IV tumors, poor performance status, a high platelet count and a high lactate dehydrogenase level (Sorbye et al., 2013; Shafqat et al., 2015). Our patient was admitted with widespread metastatic disease and died within a month before the completion of palliative RT.

In conclusion, NEC of the colon and rectum is extremely rare. Most patients have metastatic disease at the time of diagnosis. These tumors have a worse prognosis than that of conventional adenocarcinoma, and there is no standard treatment protocol. There is a clear need for studies involving a greater number of colon and rectum NEC patients.

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