

## Case Report

### Rarely seen rectum tumor with bad prognosis: A case of large cell neuroendocrine carcinoma

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**Abstract.** Large cell neuroendocrine carcinoma forms an extremely aggressive and poor prognostic subset of neuroendocrine tumors with a tendency to early metastasis. However palliative chemotherapy in patients with metastatic disease may provide longer progression-free survival but the important issue is to detect and surgically treat the disease at an early stage. In this article, we present a case of large cell neuroendocrine carcinoma of the rectum which was admitted to our hospital with a complaint of rectal bleeding for about a month and multiple distant metastases at the time of diagnosis. The patient received palliative chemotherapy with cisplatin plus etoposide and zoledronic acid and an overall 6 month survival time was achieved. Generalizing the screening programs for colorectal cancers and facilitating access to colonoscopy are essential for early diagnosis and therapy of rectal neuroendocrine tumors.

**Keywords:** Rectal neoplasms, carcinoma, large cell, neuroendocrine

#### Introduction

Neuroendocrine tumors originate from the neuroendocrine cells which exist almost in any part of the body. Although these cells are present most commonly in gastrointestinal system, neuroendocrine tumors are rather rare in colon and rectum. Large cell neuroendocrine carcinoma constitutes an extremely aggressive subgroup with poor prognosis and it has a tendency to early metastasis [1]. We present a case of large cell neuroendocrine rectum tumor with multiple distant metastases at the time of diagnosis.

#### Case Report

A seventy-one year old male patient admitted to our hospital with a complaint of rectal bleeding that started about one month earlier. Hemogram, biochemical analysis and tumor markers were all within normal limits. A colonoscopy was performed upon palpation of a mass on the anterior rectum in rectal examination. Colonoscopy revealed a tumoral mass initiating from 3rd cm of the rectum and multiple biopsies were obtained. Pathologic examination revealed glands with normal appearance as well as infiltrating tumor as solid areas and trabecular structures. Tumor cells had large, hyperchromatic, pleomorphic nuclei with large cytoplasm. Mitotic and apoptotic activity was marked in tumor cell nuclei (Fig1). In immunohistochemical studies, a wide positivity was

observed with synaptophysin (Fig 2) and focal positivity with CD56 (Fig.3), both of which being neuroendocrine markers. These findings were considered as consistent with large cell neuroendocrine carcinoma. Metastasis screening by positron emission tomography (PET) imaging revealed widespread multiple metastases in lungs, liver and bone. With the diagnosis of metastatic large cell neuroendocrine carcinoma, palliative chemotherapy was initiated at the oncology clinic. Cisplatin with a dosage of 75mg/m<sup>2</sup> and etoposide with a dosage of 100mg/m<sup>2</sup> were administered. Due to widespread bone metastasis, zoledronic acid 4 mg IV was given. Disease progression developed in the patient following 3 courses of chemotherapy treatments. Overall a 6 month of survival could be achieved.

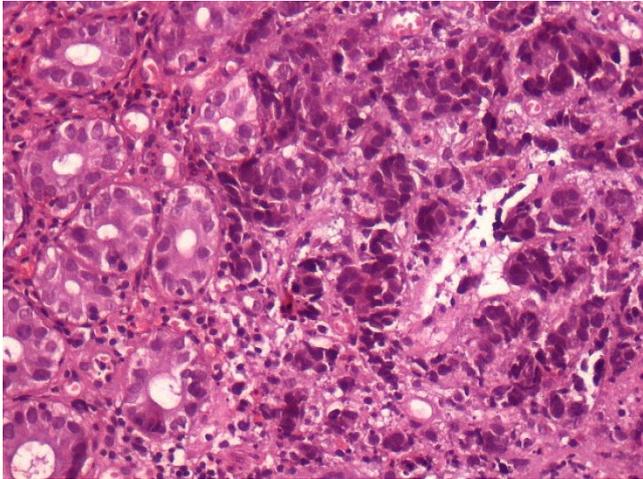
#### Discussion

Neuroendocrine tumors are rare neoplasms that have a rather wide clinical presentation. Classifications of neuroendocrine tumors have been done according to organ systems. Therefore many recent classifications and revisions caused inconsistencies and confusions on defining and reporting these rare tumors. In order to provide standardization, World Health Organization (WHO) and European Neuroendocrine Tumor Society (ENETS) carried out studies. Gastrointestinal system neuroendocrine tumors were divided into 3 main groups in a classification done by WHO in 2010; Grade 1, 2 and 3 neuroendocrine carcinomas. Neuroendocrine carcinomas

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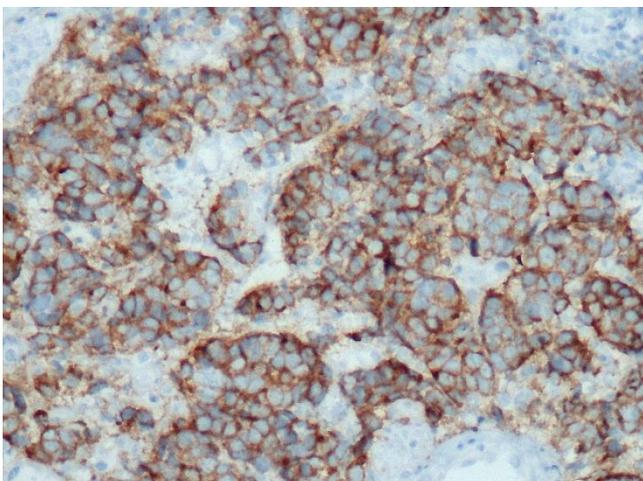
were further divided into two subgroups as large cell and small cell carcinomas [2]. Grading was done according to the number of mitosis; less than 3, between 3 and 20 and above 20, reflecting Grade 1, 2 and 3, respectively. In cases where biopsy material was small, Ki 67 index should be used because mitosis count can be problematic [3].

Neuroendocrine tumor cells are characterized by presence of neurosecretory granules and neurosecretory markers in cytoplasm that can be observed with electron microscope. These markers are specific neuron enolase (NSE), chromogranin, synaptophysin and CD56 [4].



**Figure 1** Glandular structures belonging to the normal-appeared rectum showing tumor islands with large hyperchromatic and pleomorphic nuclei and large cytoplasm on the right side (Hematoxylin and eosin stain x200).

Approximately half of the patients with diagnosis of rectal neuroendocrine tumor are asymptomatic and they were incidentally diagnosed during colonoscopies done for other indications and for colorectal cancer screening. Change in bowel habits, hematochezia and rectal pain are the major symptoms [5]. Size of the tumor, depth of inva-

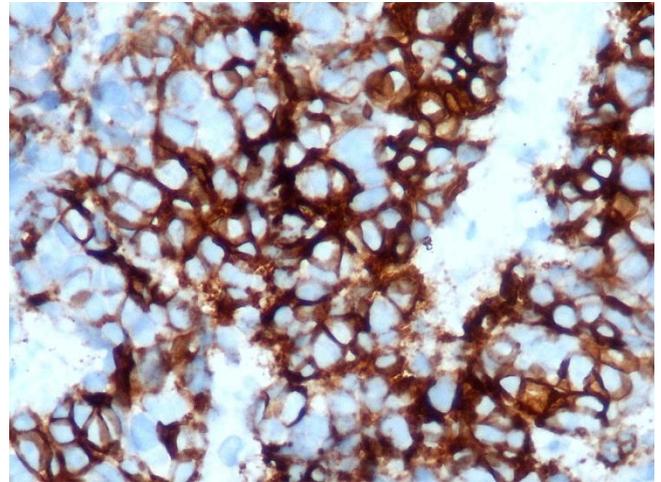


**Figure 2** Widespread positivity for synaptophysin (Immunohistochemical stain x200)

sion and lymph node positivity are the important factors indicating malignant behavior. In a study, patients with

rectal tumor less than 1 cm had 10% metastasis while those with tumors between 1 and 2 cm had 10-15% and those with tumors larger than 2 cm had 60% metastasis [6].

Similar to adenocarcinomas, liver is the most common distant organ where metastasis occurs [7]. When metastasis develops, these tumors manifest rather an aggressive course.



**Figure 3** Focal positivity for CD56 (Immunohistochemical stain x200)

The term “large cell neuroendocrine carcinoma” was first used by Bernick et al. [8]. In their studies, neuroendocrine carcinoma was detected in only 0.6% of the patients with colorectal cancer, whereas 0.2% was evaluated as large cell neuroendocrine carcinoma. Most of these patients were in advanced stage at the time of diagnosis and average survival period was reported as 10.4 months. One year survival rate was 46% and our patient had an overall survival period of 6 months [8]. Surgery and systemic chemotherapy is the main treatments for local disease. Case series include cisplatin and fluorouracil, cisplatin and etoposide based combinations along with oxaliplatin, 5-fluorouracil and leucovorin combinations (FOLFOX) in systemic chemotherapies [9-11]. We used cisplatin and etoposide treatment regimen in our patient; however we could not achieve a response because he had already widespread metastasis at admission and his performance was poor.

In conclusion large cell neuroendocrine malignancies are rather rare in rectum. They have a rather aggressive and poor prognosis because of tendency for early metastasis. Limited number of cases in literature challenge to establish recommendations about the treatment. Although palliative chemotherapy options could provide longer survivals without progression in the patients, diagnosing the illness at early stage and surgical treatment are of prime importance. Generalizing the screening programs for colorectal cancers and facilitating access to colonoscopy are crucial for diagnosing rectal neuroendocrine tumors at early stage.

#### Conflict of Interest

The authors declare no conflicts of interest.

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