Mixed large cell neuroendocrine carcinoma with squamous cell carcinoma of the rectum: Report of a rare case and review of the literature

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INTRODUCTION: Mixed large cell neuroendocrine neoplasms of the rectum are rare and aggressive neoplasms. Survival is poor due to the high rate of lymph node metastases and distant metastases at the time of diagnosis.

PRESENTATION OF CASE: We report a case of a 50-year-old male patient with a mixed large cell neuroendocrine carcinoma with squamous cell carcinoma of the rectum located 8 cm from the anal verge, treated with low anterior resection and total mesorectal excision with free surgical margins. There were lymph nodes metastases but no distant metastases at the time of diagnosis. The patient refused to receive adjuvant chemotherapy and died 6 months later due to liver failure as a result of multiple hepatic metastases.

DISCUSSION: There are not known predisposing factors for the development of neuroendocrine rectal carcinoma. A neuroendocrine carcinoma of the rectum is a rare tumor with an incidence of less than 0.1% of all colorectal malignancies. The median survival ranges from 5 to 10.4 months in several studies and there are not sufficient data in bibliography about ideal adjuvant therapy after resection of mixed squamous large cell neuroendocrine carcinoma of the rectum.

CONCLUSION: Low anterior resection and total mesorectal excision with free surgical margins in the presence of lymph nodes metastasis is not a sufficient treatment for rectal neuroendocrine carcinoma. More studies should be done in order to determine the ideal adjuvant treatment of these rare and aggressive tumors.

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1. Introduction

Neuroendocrine carcinoma (NEC) is a poor differentiated, high grade malignant neoplasm composed of tumor cells that express endocrine markers (synaptophysin, chromogranin A) and show marked cellular atypia, frequent necrosis and high proliferative activity. We can recognize small cell NEC, large cell NEC and mixed NEC. Mixed adenoendocrine tumors are rare and generalizations about their behavior cannot be made. Moreover, squamous differentiation has not been observed in large cell NECs until now, while the coexistence of small cell carcinomas with an associated small cell carcinoma component has been described. We report the first case in bibliography of a mixed large cell NEC with squamous cell carcinoma of the rectum, a highly aggressive and rare tumor.

2. Presentation of case

A 50-year-old male patient was admitted to our hospital with the major complaint of mild rectal bleeding for the last 5 days. He described changes in bowel habits during the last month, but no weight loss. He had free past surgical history and had never undertaken a colonoscopy examination. Basic laboratory tests of peripheral blood on admission were normal (hematocrit 43%). The serum levels of Cancer Antigen (CA) 19-9, Carcinoembryonic Antigen (CEA) and α-fetoprotein (AFP) were within normal range. Digital examination was negative.
Colonoscopy was performed, which revealed an ulcerative mass of 6 cm in length (Fig. 1), with its lower margin located 8 cm from the anal verge. Microscopic analysis of biopsy specimens showed morphological and immunohistochemical characteristics of poorly differentiated neuroendocrine carcinoma (chromogranin A+, Synaptophysin A+). The proliferation marker Ki-67 was diffusely stained and was approximately 80%. Cytokeratines C5/6 were negatives. Computed tomography (CT) scan of the abdomen revealed pathological enlarged mesocolic lymph nodes (Fig. 2) without obvious liver metastases, while chest CT scan was normal.

A low anterior resection with total mesocolic excision and lymph nodes dissection was performed, with free macroscopic surgical margins. The specimen included an ulcerative tumor 6 cm x 4 cm, with its lower edge located 2 cm from the distal surgical margin. The tumor had elastic consistency, compact form, grayish and partially brownish color, and infiltrated the entire muscular wall. There was extension of the tumor to pericolic fat in many sites. Four of 24 resected lymph nodes were positive for metastatic tumor. There were, also, neoplastic emboli in lymphatics and vessels.

After microscopic examination and immunohistochemical study, the diagnosis of poorly differentiated large cell neuroendocrine carcinoma was established. It was composed of isolated large cells with scant eosinophil cytoplasm and nucleus with large prominent nucleolus, while there were areas of organoid, nesting and trabecular pattern. Surprisingly, squamous cell carcinoma coexisted, representing 5–10% of tumor population (Fig. 3). The mitotic rate was >20 per high power fields and Ki-67 was 80%. It was classified as G3 neuroendocrine carcinoma according to WHO classification 2010 of tumors of the digestive system, and pT4N1M0 according to the AJCC/2010 staging system. The immunophenotype of neuroendocrine carcinoma was: Synaptophysin (+), Chromogranin A (+), CD56 (+), CK5/6 (−), CD-X-2 (+) in few cells, CK20 (+) in a small percentage of cells. The immunophenotype of squamous cell carcinoma component was: Synaptophysin (−), Chromogranin A (−), CD56 (−), CK5/6 (+), CDX2 (+), p63 (−), CK20 (−).

The patient had an uneventful recovery and was discharged on the 10th postoperative day. He refused to receive adjuvant chemotherapy despite oncologist recommendations, and died 6 months later due to liver failure as a result of multiple hepatic metastases.

3. Discussion

Neuroendocrine rectal tumors (NRTs) constitute 7.2–27% of all neuroendocrine tumors. Incidence in general population ranges from 0.24 to 1.65 per 100,000 persons. According to the WHO classification 2010 neoplasms of the digestive system with neuroendocrine differentiation are subdivided into neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs) and mixed neuroendocrine carcinomas (MANECs). The term NETs includes well differentiated tumors (carcinoids), and their grade is either G1 (Grade 1) or G2 (Grade 2). The term NECs includes poorly differentiated, high grade, small and large cell neuroendocrine carcinomas, and their grade is always G3 (Grade 3). We can use the term MANEC only when there are both neuroendocrine and non-neuroendocrine epithelial malignant components and each component exceeds 30%. In our case, we had a G3 large cell NEC. The diagnosis of MANEC could not be established, because the squamous cell carcinoma represented the 5–10% of tumors cells.

A NEC of the rectum is a rare tumor with an incidence of less than 0.1% of all colorectal malignancies. We have found less than 100 cases in bibliography. According to Bernick, only 22 cases (0.03% of total colorectal cancers) of small cell neuroendocrine carcinoma and 16 cases (0.02%) of large cell neuroendocrine carcinoma were
identified from their database of colorectal cancers that included approximately 6500 patients, in a period of 23 years. Only 14 cases were located in the rectum. 5 In a recent review of 10 years management of neuroendocrine rectal tumors, only 2/37 patients (5.4%) of the total NRTs had tumors that were classified as neuroendocrine carcinoma. 6 Li et al. analyzed the pathologic characteristics of mixed colorectal glandular-neuroendocrine tumors. A total of 87 cases were included in their study, after search strategy. None of these tumors was found in the rectum, with the majority of them located in the right colon (56%) and the left colon (41%). In addition to this, only 9% had an ulcerating lesion, as in our case. Squamous cell carcinoma was mixed with glandular epithelial component in 12% of total cases. 7 Mixed G3 large cell NEC with squamous carcinoma of the rectum is extremely rare. We have not noticed any other case in bibliography.

There are no known predisposing risk factors associated to the development of neuroendocrine tumors. Genetic factors may play the major role in susceptibility to NET formation. Women with diabetes and positive family history for cancer have an increased incidence of gastric NETs. This is attributed to the increased genetic susceptibility for NETs development in women as compared to men. 9 Our patient had a free family history for cancer and no diabetes. Especially for MANEC, there is the theory of a stem cell precursor. This is based on the presence of transitional tumor cells that revealed common immunoreactivity for CA 19–9, keratin 19, cluster of differentiation protein 117 and epithelial cell adhesion molecule. 9

Neuroendocrine tumors may be found incidentally at colonoscopy (40%), or patients may present with rectal bleeding, changes in bowel habits, tenesmus, discomfort and weight loss. Features of carcinoid syndrome are very rare for rectal tumors. Lesions <2 cm with a low grade and intact muscularis propria can mostly be removed by local resection. Rectal tumors >2 cm, T3 or T4 stage, G3 or rectal tumors with locoregional lymph node involvement should be treated similarly to adenocarcinoma. For rectal NETs >2 cm, anterior resection with total mesorectal excision or abdominoperineal extirpation should be performed. 1

Neuroendocrine carcinomas of the colon and rectum are extremely aggressive neoplasms. 2-6 The median survival ranges from 5 to 10.4 months in several studies. 3,10 The longest 6-month survival is 58% 11 and the longest 1-year survival is 46% in the Bernick’s study. 5 This is due to the high rate of lymph node metastases, that exceeds 60% in all studies, and the high rate of distant metastases at diagnosis that exceeds 35% 11 and reaches 73% in the Gaffey’s study. 12 In our case, the patient had lymph nodes metastases without distant metastases at the time of diagnosis. Nevertheless, the carcinoma showed a highly aggressive behavior and the patient died 6 months later.

We have to underline that the NEC in our case had Ki-67 label Index 80%, thus explaining its aggressive behavior and that the patient had a large sized NEC mixed with a squamous carcinoma component. Furthermore, the patient did not receive any adjuvant therapy. There are not sufficient data in bibliography about survival and ideal adjuvant therapy after resection of mixed squamous large cell NEC of the rectum. It seems that these neoplasms behave as other NECs. 13 According to the NANETS consensus guidelines, the combination of etoposide and cisplatin is the first line therapy for extrapolmonary NECs, without specific reference in mixed squamous NECs. 14 Various other chemotherapeutic regimens have been used in a small number of patients with NECs with good results. A case of effective use of chemoradiotherapy for the treatment of large cell NEC of the rectum has been published. 15

4. Conclusion

Low anterior resection and total mesorectal excision with free surgical margins in the presence of lymph nodes metastasis is not a sufficient treatment for rectal neuroendocrine carcinoma. More studies with larger number of patients with mixed rectal NECs should be done in order to determine the ideal treatment of these rare and aggressive tumors.

Conflicts of interest

The authors declare that there is no conflict of interest.

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None.

Ethical approval

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Konstantinos Vardas wrote the paper. Konstantinos Vardas, Georgios Papadimitriou and Papakonstantinou Alexandros performed the operation. Maria Chantziara coordinated the pathology report of the specimen. Spiros Drakopoulous is the consultant of the unit and provided overall supervision, direction and suggestions for the case report.

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