CASE REPORT

Multifocal diffuse large cell neuroendocrine carcinoma of the colon

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Abstract

Background: Large cell neuroendocrine carcinomas (LCNEC) of the colon are an extremely rare and aggressive type of colorectal cancer. While multifocality is more frequently seen in small intestine NECs, no cases of multifocal NEC of the colon have been reported before.

Aim: A 69-year-old male patient presented with abdominal pain. Colonoscopy revealed a necrotic-polypoid mass in the sigmoid colon and the biopsy result was reported as malignant epithelial tumor. Laparoscopic anterior resection was performed with the preliminary diagnosis of colon adenocarcinoma. Histopathological examination revealed three polypoid tumors, the largest of which was 4 cm, in the sigmoid colon. Immunohistochemical examination showed positivity for synaptophysin, chromogranin, and CDX2. High Ki67 proliferation index, high mitosis, and widespread p53 expression were observed in all tumors. With these findings, a diagnosis of multifocal large cell NEC was made. To the best of our knowledge, this is the first report describing a case of multifocal large cell NEC of the colon.

Relevance for Patients: LCNECs of the colon are very aggressive. Here, we report for the first time a case of multifocal LCNEC. In a short period of 1 month after the surgery, new widespread metastases were detected in the liver. Therefore, these tumors should be followed more closely than usual for early treatment.

1. Introduction

Neuroendocrine carcinomas (NECs) are a highly malignant subgroup of neuroendocrine neoplasms. Although they originate from the peripheral neuroendocrine cell system distributed in all organs, they are usually seen in the lung and gastroenteropancreatic (GEP) systems [1,2]. NECs of the colon and rectum are very rare, accounting for <1% of colorectal cancers, while large cell NECs are even rarer, accounting for only about 0.25% of colorectal cancers [3,4]. Despite its rarity, the prognosis of GEPNECs is extremely poor and the median survival is limited to 4-16 months [1,3]. Although multifocality is known in gastric and small intestine NECs, it has not been reported in colonic NECs so far. Here, we present for the first time a case of multifocal large cell NEC located in the sigmoid colon.

2. Case Report

A 69-year-old Turkish male patient was admitted to the general surgery outpatient clinic with complaints of abdominal pain and constipation for about a month. In his history, it was learned that he had received medical treatment for hypertension. He had no history of smoking and alcohol use. He had a history of surgery and radiotherapy for prostate cancer a year ago. There was no history of cancer in the patient’s first-degree relatives. The patient’s body mass index was 39 kg/m², and on his physical examination, there was a midline...
incision under the umbilicus due to prostate surgery. Colonoscopy revealed a necrotic-polypoid vegetative mass surrounding one-third of the colon lumen, approximately 40 cm from the anal border, and the biopsy result was reported as a malignant epithelial tumor. Abdominal and thoracic computed tomography (CT) performed for pre-operative clinical staging showed diffuse fatty degeneration of the liver and irregular wall thickness in the sigmoid colon. Distant organ metastases or pathological lymph nodes were not detected (Figure 1). Pre-operative tumor markers were in the normal range (carcinoembryonic antigen 1.3 ng/ml and cancer antigen 19-9 [CA 19-9] 7.2 U/mL). Based on these findings, it was decided to perform laparoscopic anterior resection. Laparoscopic exploration revealed a tumoral mass in the sigmoid colon that did not extend to the serosa, while distant organ metastases, liver metastases, or peritoneal implants were not detected. The surgery was performed without complications, following the oncological surgical principles (complete mesocolic excision and high ligation of the vessels), and the patient was discharged on the 4th post-operative day without any problems.

In the pathological examination of the surgical specimen, metastases were not detected in any of the 20 harvested lymph nodes, and the surgical margins were tumor-free. The gross evaluation revealed three polypoid tumors with the dimension of $4 \times 3.5 \times 1.2$ cm, $1.3 \times 1 \times 0.8$ cm, and $0.3 \times 0.2 \times 0.2$ cm, respectively. The histopathological examination of the tumors showed organoid proliferation of large cells with abundant eosinophilic cytoplasm, finely granular chromatin, and prominent nucleoli. There were large areas of tumor necrosis and extremely frequent mitotic figures (Figure 2a). High mitotic rate was detected as $>20/2 \text{mm}^2$ (57/2 mm$^2$ in the greatest one) (Figure 2b). Immunohistochemical analysis demonstrated positivity for synaptophysin, chromogranin, and CDX2 (Figure 2c). The Ki67 proliferation index was around 60–70% in the most mitotically active part of the tumors (Figure 2d). Diffuse and strong “mutant type” p53 expression was also observed for all tumors (Figure 2e). Based on the histopathological characteristics and results of the immunohistochemical staining, the tumors were diagnosed as “multifocal large cell neuroendocrine carcinoma.” The pathological stage was classified as T2 (m)N0 with muscularis propria invasion according to AJCC eighth edition.

Positron emission CT (PET/CT) performed at the 1st post-operative month revealed multiple hypermetabolic lesions (SUVmax: 33.79) in both lobes of the liver up to 30 mm in diameter (Figure 1). The patient was started on etoposide ($100 \text{mg/m}^2$) and cisplatin ($75 \text{mg/m}^2$) as systemic chemotherapy.

Figure 1. (a) Pre-operative computed tomography showed diffuse fatty degeneration of the liver and irregular wall thickness in the sigmoid colon (blue arrow) (b) Positron emission computed tomography performed at the 1st post-operative month revealed multiple hypermetabolic lesions in both lobes of the liver.
on pre-operative CT was irregular wall thickness increase in the...multifocality was not reported in large cell NECs of the colon in two large series [4,10]. In a study of appendiceal NETs, a 5 mm distance was used for multifocality [11]. In our case, according to the histopathology results, three different polypoid masses were detected 2 cm apart, which were not continuous with each other.

Large cell NECs of the colon have a very aggressive course, and in approximately one-third of the cases, there are liver and lymph node metastases at the time of diagnosis [4]. In our case, there was no pre-operative liver or other distant organ metastasis. No metastasis was detected in the post-operative pathological evaluation of the 20 lymph nodes harvested. We encountered diffuse metastasis in the liver in the PET/CT taken at the 1st post-operative month. It is not known whether this aggressive course is due to multifocality, strong p53 expression, or high Ki-67 index (60–70%) and mitotic index (>20/2 mm²), but each of them probably has a separate contribution.

The role of surgical resection in NECs of the colon and rectum has been controversial in studies conducted so far. Smith et al. found that resection of the primary tumor did not provide a survival advantage in neither localized nor metastatic disease [3]. On the other hand, another recent study by Fields et al. reported that the combination of surgical resection and chemotherapy is associated with the best survival, with or without metastatic disease. In the same study, in the presence of metastatic disease, longer survival rates were found in patients who received both surgery and chemotherapy compared to chemotherapy alone or surgery alone (5-year survival rates 6.1%, 1.6%, and 3.7% respectively, P < 0.001) [10]. Neoadjuvant treatments have been tried in NETs of other organs, such as the stomach, cervix, rectum, anal canal, and breast [12-15]. The almost routine use of neoadjuvant therapy in locally advanced adenocarcinomas of the mentioned organs may be one reason for this. However, we could not find any information in the literature regarding neoadjuvant therapy in NECs of the colon.

Chemotherapy includes platinum-based agents just as in small cell lung cancer. As a matter of fact, in our case, a cisplatin/etoposide-based systemic chemotherapy was started every 21 days after laparoscopic anterior resection. PET/CT performed for evaluation of response to treatment after three cycles of chemotherapy was reported as minimal regression of lesions in the liver compared to the first PET/CT. The patient’s oncological treatment continues in the 6th month after surgery.

4. Conclusion

In this case, we report for the first time a case of multifocal large cell NEC of the colon. In a short period of 1 month after the surgery, new widespread metastases were detected in the liver. Although it is not known whether multifocality has an effect on...
such an aggressive course, these tumors should be followed more closely than usual for early treatment.

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Conflict of Interest

The authors declare no conflict of interest.

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