Large cell neuroendocrine carcinoma of the colon with brain metastasis: A case report

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ABSTRACT
BACKGROUND: Large cell neuroendocrine carcinoma of the colon is rare, and its prognosis is very poor especially when diagnosed at a metastatic stage. Early diagnosis can allow early curative surgery that can increase the survival for more than 5 years.

CASE REPORT: We report a 62-year-old man who presented for neurologic signs and symptoms followed by constipation. He was diagnosed with large cell neuroendocrine carcinoma of the colon with brain metastasis. Patient was treated with right hemicolectomy due to obstructive gastro-intestinal symptoms, followed by chemotherapy (cisplatin and etoposide).

DISCUSSION: Because of its rarity, effective treatment of large cell neuroendocrine carcinoma of the colon has not been established. If local large cell neuroendocrine carcinoma is completely resected, the prognosis can be largely influenced, and patients can benefit from a 5-year survival rate of 61% compared to 0% in patients without curative surgery. However, most patients are metastatic and not candidates for curative resection. The efficacy of systemic chemotherapy is highest in patients with poorly differentiated neuroendocrine tumors with a combination of cisplatin and etoposide.

CONCLUSION: Patient with metastatic large cell neuroendocrine tumor have very poor prognosis with a 1 year survival rate of 10% without curative surgery. Increasing awareness of these types of cancer and their prognosis, may allow better comprehension of the importance of screening to allow early diagnosis and better outcomes. In case of late presentation, palliative surgery is always a must in patients with obstruction, bleeding or perforation.

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1. Introduction

Neuroendocrine tumors can develop at many different sites of the body, but rarely can be found in the colon as a primary site [1,2]. The majority of neuroendocrine tumors in the colon are carcinoids with a good prognosis, whereas large cell neuroendocrine carcinoma is aggressive with a bad prognosis. Here we present a case of large cell neuroendocrine carcinoma of the colon presenting to University Hospital with neurologic manifestation and obstructive gastrointestinal symptoms.

This case was reported in line with the SCARE criteria [3].

2. Case presentation

62 y o male patient, heavy smoker (80 pack-year), allergic to penicillin, known to have hypertension, coronary artery disease s/p coronary artery bypass graft surgery (April 2011) and percutaneous transluminal coronary angioplasty (March 2015), admitted to the hospital for left sided numbness involving left side of the head, left arm and left leg. Patient reported one-month history of right arm numbness and weakness (motor function 4/5). Also a few weeks history of constipation was prominent.

Magnetic resonance imaging (MRI) brain was performed and showed: multiples diffuse well defined masses in the temporal,
Adenopathies

**Fig. 1.** MRI brain without gadolinium showing multiple brain lesions. (A) sagittal T1. (B) (C) axial T2. (D) axial T1. (E) coronal T2. (F) axial T1.

**Fig. 2.** Computed tomography CT scan of the chest abdomen and pelvis showing: (a) small adenopathies in the Barety’s space (the largest one measuring 13 mm), (b) multiple adenopathies in the retroperitoneal space (the largest one measuring 3 cm in diameter), and (c) a 6 cm mass attached to the right colon proximal to the liver flexure.

Parietal, frontal, occipital lobes and the cerebellum ranging in size between 1 cm and 3.3 cm, compatible with metastasis (Fig. 1).

Computed tomography (CT) of the chest, abdomen and pelvis with PO and IV contrast was performed and showed: small adenopathies in the Barety’s space (the largest one measuring 13 mm), multiple adenopathies in the retroperitoneal space (the largest one measuring 3 cm in diameter). A 6 cm mass attached to the right colon proximal to the liver flexure (Fig. 2).

Laparotomy was performed and revealed a large obstructing mass of the right colon proximal the liver flexure. Right hemicolectomy with anastomosis was performed, and mesenteric tumor, mesenteric lymph nodes and omentum were excised (Fig. 3).

The gross specimen inspection showed a colonic fragment measuring 38 cm in length and 6 cm in maximal diameter, tumor measuring $6 \times 5 \times 3$ cm infiltrating the submucosa with focal ulceration of the adjacent mucosa. In addition, there were 13 mesenteric lymph nodes ranging from 0.2 cm to 1.3 cm. The excised omentum fragments were containing 2 nodules (0.5 cm and 1 cm). The mesenteric tumor was measuring $5 \times 5 \times 2$ cm.

On microscopic examination, results were consistent with a poorly differentiated large cell neuroendocrine colonic carcinoma grade 3 (WHO) measuring around 10 cm infiltrating the serosa, sub-mucosa and omentum, characterized with a polygonal cells and moderately irregular nucleus arranged in strands (Fig. 4). Immunohistochemical stains revealed strong positivity for synaptophysin, Ki 67 around 80%, and negative CD56. Mitotic index is high (>20/20 hpf), with presence of vascular invasion and metastasis to eight of thirteen lymph nodes with capsular rupture. This tumor can be classified as stage 4 according to the TNM classification.

The patient started chemotherapy (cisplatine + etoposide). Unfortunately, only one cycle of chemotherapy was given, after which the patient deteriorated and passed away after two months due to progression of the malignancy and brain metastasis.

3. **Discussion**

Neuroendocrine tumors are defined as epithelial neoplasms with predominant neuroendocrine differentiation and may be detected in most organs of the body. They have a wide spectrum of clinical presentations and the current classifications rely on differentiation, grade, and stage.

Differentiation is attributed to the extent to which the neoplastic cells resemble their non-neoplastic equivalent [1,2].
Well differentiated neoplasms have characteristic organoid arrangements of the tumor cells which are usually uniform and closely resemble to their non-neoplastic equivalent. Whereas poorly differentiated neuroendocrine tumors have less resemblance to non-neoplastic neuroendocrine cells with a diffuse nonuniform architecture. Histologic grade is determined by the aggressiveness of the neoplasm with high-grade having a more aggressive and less predictive course; poorly differentiated NETs are considered high grade. Tumor stage refers to the extent of tumor spread [4].

Neuroendocrine tumors can develop at many different sites of the body, but rarely can develop in the colon as a primary focus [1,2]. At this site, carcinoids represent the majority of neuroendocrine tumors, and usually harbor a good prognosis, compared with large cell neuroendocrine carcinomas which are rare and aggressive with a bad prognosis [2,5]. Bernick et al. publish a study that showed that 0.6% of patients with malignant colorectal tumors had neuroendocrine carcinoma and only 0.2% of those were large cell neuroendocrine carcinomas [6]. There is paucity of paper reporting large cell colonic neuroendocrine carcinomas (LCNEC) in literature [7–12].

LCNEC is a neuroendocrine tumor that has features in common with neuroendocrine-differentiated tumors as well as specific cytological features: large cell size, polygonal shape, low nuclear-cytoplasm ratio, a mitotic index in excess of 10/10 per high power field, occasionally prominent nucleoli, and necrosis [2,13]. These features must be carefully examined and should not be overlooked, because differenting LCNEC from adenocarcinoma is of paramount importance, where patients can benefit from variable chemotherapy regimen [10]. The tumors are argyrophilic and stain positive for immunohistochemical panels including synaptophysin, chromogranin, Ki 67, and negative CD56 and neuron specific enolase [10]. Our case meets the criteria for the diagnosis of LCNEC. His high Ki 67 expression (around 80%) reflects its extremely high
mitotic ratio, extensive angio-invasiveness, and metastatic potentials.

Clinical presentation of LCNEC is similar to other colonic carcinomas (anemia, abdominal pain, hematocritemia, constipation, tenesmus). However, higher stage of metastasis is typically present at the presentation [10]. This makes the prognosis of most LCNEC very poor; studies show a 5–11 months median survival time, and a 1 year survival rate of 10% [5].

In addition to these presentations, clinician should always be aware of the unique features of neuroendocrine tumors, which can presents as hypersecretion syndrome such as the paraneoplastic or carcinoid syndrome [2]. Mass related complication such as obstruction, bleeding and perforation should not be overlooked. Interestingly, neurologic manifestations from brain metastasis, have preceded the colonic manifestation (constipation and obstruction) in our patient.

Treatment option depends on the staging of the tumor; Local non metastatic tumor can be treated with radical excision. Successful surgery can yield up to 61% 5-years survival rate. However, this is not the case of most of the neuroendocrine tumor of the colon. In fact, most of these patients – including our patient – presents with metastatic tumor that are not candidate for curative surgery. These patients should be treated with cytoreductive therapy or systemic chemotherapy [14]. The efficacy of systemic chemotherapy is highest in patients with poorly differentiated neuroendocrine tumors with a combination of cisplatin and etoposide [15].

Patients with metastatic disease can benefit from surgical interventions only in the case to deal with complications of the tumor such as obstruction, bleeding and perforation.

4. Conclusion

In conclusion, colonic large-cell neuroendocrine carcinomas are rare and aggressive tumors. The most primary sites cecum or the rectum, mainly present as metastatic disease, and have a poor prognosis with median overall survival reported to be 10.4 months (range of 0–263.7 months) [5]. While surgical resection is the primary treatment modality, the benefit of chemo- or radiation therapy, as used for conventional colorectal adenocarcinomas, has not been established for colonic large cell neuroendocrine carcinoma [2,6,15].

Declaration of Competing Interest

This article has no conflict of interest with any parties.

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Ethical approval

The study type is exempt from ethical approval.

Consent

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