

## Case Report

# Rare finding of a large cell poorly differentiated neuroendocrine tumor in the colon

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## ABSTRACT

A 43 year old female presented to the emergency department for nausea, vomiting and abdominal pain secondary to a bowel obstruction subsequently revealed to be a poorly differentiated large cell neuroendocrine tumor of the colon. After a CT scan showed a mass in the ascending colon with possible metastasis to the right lobe of the liver, an exploratory laparotomy was performed. A hemicolectomy was performed with biopsy of the liver mass. Pathology was consistent with large cell neuroendocrine tumor in all specimens including the liver biopsy, ascending colon, and transverse colon. Although large cell neuroendocrine tumors of the colon are a rare malignancy, they are an important consideration in the workup of multiple colonic masses with metastases, especially in patients presenting with bowel obstruction. The literature on poorly differentiated large cell neuroendocrine cancer and treatment is reviewed. Poorly differentiated large cell neuroendocrine tumor is a rare pathology but should be included in the differential diagnosis in patients presenting with a colon mass and bowel obstruction.

**Keywords:** Large cell neuroendocrine tumor, Neuroendocrine tumor, Poorly differentiated neuroendocrine tumor, Large bowel mass

## INTRODUCTION

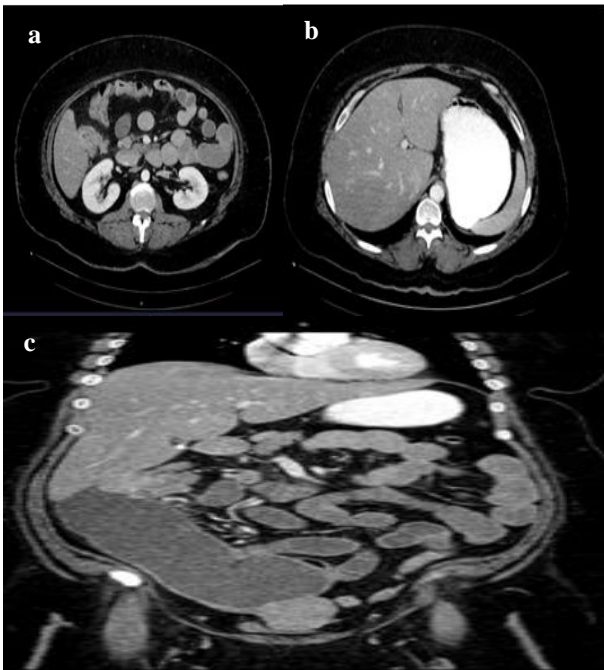
Neuroendocrine (NEC) tumors arise from amine precursor uptake and decarboxylation APUD cells.<sup>1</sup> These cells have certain characteristics based on what secretory granules they possess. These cells transmit information in between synapses depending on the neurosecretory granules released. NEC tumors are rare in the gastrointestinal system.<sup>1,2</sup> They most commonly occur as carcinoid tumors in the appendix which are less aggressive than their rarer counterpart; neuroendocrine carcinomas. Neuroendocrine carcinomas in the colon only occur 0.1-3.9% of all cases and of those cases, only 0.2% have the large cell NEC subtype.<sup>3,4</sup> Large cell NEC is an aggressive subtype with metastases often present at the

time of diagnosis.<sup>4</sup> This cancer is usually diagnosed around 65 years of age, with most patients being male.<sup>5</sup>

## CASE REPORT

A forty-three years old female with a history of hypertension, diabetes, and obesity and past surgical history of hysterectomy and cholecystectomy presented to the emergency department for nausea, vomiting and abdominal pain. In the emergency room, a CT scan was performed showing a colonic mass of the hepatic flexure measuring 5.7x4.3 cm with associated dilatation of the ascending colon, cecum, and small bowel. Additionally, there was associated mesenteric lymphadenopathy measuring 1.4 cm. There was also direct invasion of the

mass into the adjacent caudal aspect of the right lobe of the liver.



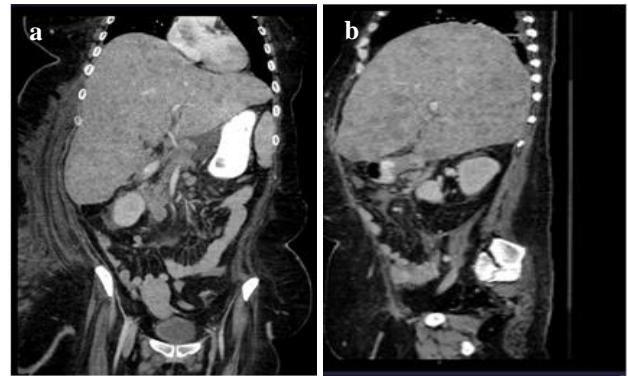
**Figure 1: (a) The bowel demonstrates luminal narrowing, mural heterogeneous enhancement and soft tissue nodularity in the ascending colon, (b) there appears to be direct invasion of this mass into the adjacent caudal aspect of the right lobe of the liver, and (c) the mass is noted under the liver.**

The patient was admitted, optimized, and subsequently scheduled for an exploratory laparotomy in which a right hemicolectomy was performed with primary anastomosis of the terminal ileum and transverse colon. A 5mm nodule over the superior surface of the right lobe of the liver was identified in which a wedge resection of that area was performed. Intraoperatively, multiple mesenteric lymph nodes noted. Specimens from the liver, colon mass, and lymph nodes were sent to pathology for evaluation. Patient was in stable condition and transferred to the ICU.

Pathology revealed poorly differentiated large cell neuroendocrine carcinoma with positive synaptophysin, CD56, and keratin markers. Histopathological report showed the colon mass was pT4bN1bM1. The proximal and distal margins of the right colon specimen were uninvolved by invasive carcinoma. The circumferential margin was unable to be adequately assessed. Of the 15 lymph nodes assessed, 2 were positive for tumor invasion. There was also minimal perineural invasion but the omentum and appendix were free of tumor.

Post-operatively, the hospital course was complicated by an anastomotic leak on POD 12 and abdominal wall abscess for which she underwent an anastomotic reversal with creation of an end ileostomy and abdominal wall

abscess drainage. Patient ultimately tolerated diet with ostomy functioning and was discharged on post op day 33. Subsequently, 2 months later, the patient was admitted to the hospital for weakness and fatigue. A CT scan was performed at that time showing multiple masses in the liver. The patient had a sepsis workup and was admitted to the inpatient medicine floors for further treatment. Oncology was consulted at this time and the patient was deemed unfit for chemotherapy treatment due to severity of sepsis. Patient passed away 6 days later from renal and respiratory failure.



**Figure 2: (a) Innumerable multiple hepatic metastases and (b) the liver is enlarged.**

## DISCUSSION

Neuroendocrine tumors have been categorized into three subtypes; well differentiated NEC, well differentiated endocrine carcinoma, and poorly differentiated endocrine carcinoma.<sup>1,3,6</sup> These classifications are based on tumor characteristics such as size, angioinvasion, proliferative activity, histological differentiation and presence of metastases.<sup>1,3</sup> For highly malignant NEC tumors that were not well described by atypical carcinoid, or small cell NEC, a third category of large cell carcinoma was created.<sup>1,2</sup> According to Travis et al, in their description of NEC of the lung, the major differentiating features of large cell neuroendocrine carcinoma are the polygonal shape under light microscopy, low nuclear-cytoplasmic ratio, positive synaptophysin staining, coarse nuclear chromatin, high mitotic rate (greater than 20 per 10 HPF) or ki 67 index of greater than 20%.<sup>1,3,4</sup>

NEC most commonly metastasizes to the liver.<sup>7-10</sup> In a large study of 2,155 reported cases of colon cancer, only 5 were of neuroendocrine origin.<sup>8</sup> Of these 5 cases, two patients presented with metastases to the liver.<sup>8</sup> The five patients had very poor prognoses with the median survival rate being 7 months. One of the patients expired due to liver failure and one patient was treated ongoingly with 5-fluorouracil and streptomycin.<sup>8</sup>

The primary treatment for large cell neuroendocrine tumor is surgical excision.<sup>4,11</sup> The median survival rate of large cell NEC is approximately 10 months with one-year survival rate being 46%.<sup>4</sup> There has been no published

benefit of treating this cancer with chemotherapy or radiation.<sup>8</sup> However, per Nojima et al, a Japanese female with moderately differentiated rectal neuroendocrine carcinoma showed a favorable prognosis with post-operative adjuvant chemotherapy.<sup>9</sup> This patient had a 40mm diameter tumor on the rectal wall with associated regional wall lymphadenopathy, and subsequently underwent abdominoperineal resection. Post-operatively she was treated with radiotherapy and 800mg doxifluridine for 5 years. 5 years post op the patient remained stable with no metastases or tumor recurrence.

Further, there is new, but limited, research on platinum-based chemotherapy in treating poorly differentiated neuroendocrine tumors.<sup>12-14</sup> A study by Mitry et al implemented a regimen of etoposide and cisplatin in a group of patients with poorly differentiated NEC. Of the 41 patients, the objective response rate was 41.5% and the median survival was 15 months. 63% of the patients expired after 54 months follow up. The two years survival rate still remains under 20%.<sup>12</sup> This chemotherapy is recommended in patients with metastases which are often present in poorly differentiated NECs.<sup>12-14</sup>

In another study performed by Yamaguchi et al where they analyzed 259 patients with poorly differentiated NEC of the GIT tract, the median survival in patients with cancer of the colon was 7.9 months.<sup>15</sup> These patients either had unresectable disease or disease that was primary excised but had recurrence. They were treated with cisplatin and etoposide or cisplatin and irinotecan. There was no significant difference in median survival rate between the two regimens in patients with colorectal NEC at 13.4 months versus 14 months respectively. This data provides some evidence to the use of platinum therapy on treating poorly differentiated NEC. However, Yoshida et al used a regimen of irinotecan and cisplatin on a patient with colorectal NEC.<sup>16</sup> Unlike the other cases, this tumor did not show a significant response. The patient died 4 months after implementation of this regimen. There is a wide variability in response to chemotherapy treatment in patients with poorly differentiated LEC.

## CONCLUSION

Large cell poorly differentiated NEC of the colon carries a poor prognosis. Surgical excision remains the standard of care as investigations into the benefit of adjuvant chemoradiotherapy remains in question. Although rare, NEC of the colon should remain in the differential diagnosis of a patient presenting with bowel obstruction.

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