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Case Report

Management of colorectal large cell neuroendocrine carcinoma: case report and literature review

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ABSTRACT

Large cell neuroendocrine carcinoma (LCNEC) of the colorectum is a rare, aggressive subtype of neuroendocrine cancer with a dismal prognosis. Accounting for a mere 0.25% of colorectal cancers, LCNEC is associated with a median overall survival of 4 to 16 months, and nearly all patients succumb within a year. Pure colorectal LCNEC reports are scarce, and this review and case study presents a 40-year-old male, the youngest reported patient, diagnosed with rectal LCNEC. A comprehensive PubMed search for "large cell neuroendocrine carcinoma" and "colorectal" was conducted. Titles were meticulously screened for relevance to the nuanced management of colorectal LCNEC. Despite aggressive therapeutic interventions, including chemotherapy with carboplatin and etoposide, the patient experienced rapid disease progression, emphasizing the challenging nature of LCNEC. The paper discusses the evolving classification of NEC, morphological features, and immunophenotypic characteristics that differentiate LCNEC from other neuroendocrine tumours. Survival rates underscore the aggressive nature of colorectal NEC, and treatment options, primarily relying on retrospective studies, reveal limited efficacy. While surgery remains the preferred approach for localized disease, the optimal chemotherapy regimen for LCNEC is yet to be established. Current evidence suggests platinum-based therapy as a common first-line treatment, but the demand for more effective options persists. The paper highlights the need for additional research, including prospective trials, to elucidate the genuine benefits of adjuvant chemotherapy and to explore emerging therapies, such as immunotherapy, in the context of LCNEC.

Keywords: Large cell neuroendocrine carcinoma, Colorectal, Neuroendocrine tumor of the colon

INTRODUCTION

Large cell neuroendocrine carcinoma (LCNEC) is a rare, aggressive and fast-growing subtype of high-grade neuroendocrine cancer that can occur throughout the body.[1] Neuroendocrine carcinomas (NEC) account for approximately 1-2% of all colorectal cancers, with LCNEC being an extremely rare subgroup, likely accounting for 0.25%. The prognosis is poor, with a median overall survival usually between 4 and 16 months, with an estimated 1-year survival rate of 46%.[2-7]

Over the last 20 years, the definition and classification of NEC have evolved, based on histology and subgrouping them according to their grade and level of differentiation. According to the 2019 World Health Organization (WHO) classification, NEC is defined as a Ki-67 index >20% or mitotic count >20 cells per 2 mm^2 and categorized into the small and large cell types. They express neuroendocrine markers such as chromogranin A (CgA) and synaptophysin, as well as INSM1. Also according to the WHO classification, NEC can be pure or have a non-neuroendocrine component amounting to at least 30% of tumour mass (i.e. adenocarcinoma, squamous cell carcinoma, and others), and are defined as mixed neuroendocrine–non-neuroendocrine neoplasms (MiNEN).[8,9]

Reports of pure colorectal LCNEC (not MiNEN) are scarce in the English literature accounting for 18 patients reported to date, with only 5 of them being in the rectum, and to our knowledge, our patient is the youngest ever reported.[10-19]

CASE REPORT

A 40-year-old male presented to our hospital emergency department with a 3-month history of per rectum bleeding, constipation, tenesmus, lethargy, reduced stool calibre and a 12 kg weight loss. He had previously presented to his general practitioner with the same symptoms and was managed as constipation. His past medical history included eradicated hepatitis C, opioids and benzodiazepines dependence and post-traumatic stress disorder. The patient had no significant family history for bowel cancer. On examination he showed signs of weight loss and cachexia, and his digital rectal exam showed a mass in the anterior aspect of the rectum 6 cm from the anal verge. A computed tomography (CT) showed an ill-defined soft tissue mass centered within the rectum, measuring approximately 8 cm in length, as well as multiple liver metastasis and a 32 mm right adrenal gland lesion, likely representing metastasis (Figure 1a). Magnetic resonance imaging (MRI) showed a 7 cm tumour of the upper third of the rectum with extension into the presacral and mesorectal spaces (T3d), with large lymph nodes with irregular margins consistent with extra capsular extension (N2) and extensive extramural vascular invasion (Figure 1b and c).

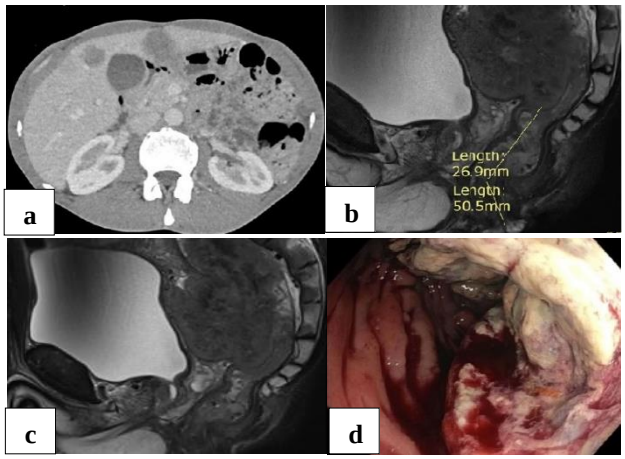

Figure 1: (a) CT abdomen at the time of presentation, (b) and (c) MRI rectum, and (d) flexible sigmoidoscopy showing fungating mass in mid-rectum.

He proceeded to have a flexible sigmoidoscopy that showed a near obstructing mass 5 cm from the anal verge, unable to be traversed (Figure 1d). Histopathological examination of the biopsy revealed a poorly differentiated epithelioid malignancy invading large intestinal mucosa. The malignant cells exhibited sheet-like growth and had abundant eosinophilic cytoplasm, large oval nuclei, vesicular chromatin, and prominent nucleoli (Figure 2 a-d). Up to 11 mitotic figures per single high power field were identified within the tumour. Additional immunohistochemical stains performed demonstrated the tumour cells were positive for broad spectrum cytokeratins AE1/AE3 and CK8/18, as well as CK20 (Figure 3a and b). The tumour cells exhibited strong, diffuse staining for SATB2, as well as neuroendocrine markers, synaptophysin and chromogranin (Figure 3c-e). Overall, the morphological and immunophenotypical features were in keeping with a large cell neuroendocrine carcinoma of colorectal origin. Ancillary investigations revealed mismatch repair protein expression was intact and a BRAF p.V600E variant was detected on next generation sequencing. His Ki67 was 80% (Figure 3f).

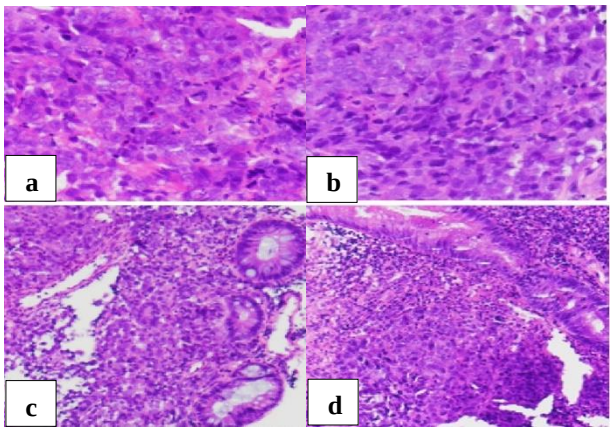

Figure 2: (a)-(d) H&E demonstrating poorly differentiated malignant cells infiltrating large intestinal mucosa with features of large cell neuroendocrine carcinoma: cells >3x lymphocyte, large nuclei, prominent nucleoli.

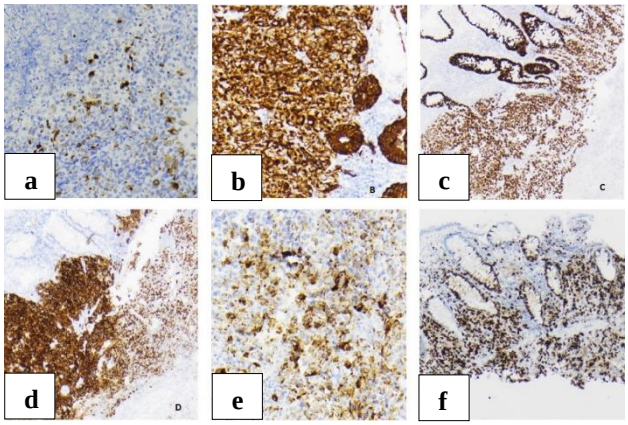

Figure 3: (a) CK20, (b) CK8/18, (c) SATB2, (d) synaptophysin, (e) chromogranin, and (f) Ki-67.

During his admission, he underwent a laparoscopic assisted colostomy formation. Subsequently, a positron emission tomography (PET) scan was performed and showed intense F-fluorodeoxyglucose (FDG) hypermetabolism of the the primary rectal malignancy and numerous metastatic lesions located in the lymph nodes,

liver, and adrenal glands (right and suspected left).

The patient had 2 cycles of chemotherapy with carboplatin and etoposide, but unfortunately presented with significant radiological disease progression, and was switched to leucovorin, fluorouracil and irinotecan (FOLFIRI). After 4 cycles, chemotherapy was ceased due to further interval progression in size of the liver metastasis. Pelvic and rectal pain was difficult to manage with oral medications, and he underwent a ganglion impar block with good resolution.

The patient passed away 4 months after his diagnosis.

DISCUSSION

Colorectal LCNEC is an uncommon and poorly differentiated tumour, falling within the least favourable prognostic category among primary colorectal neoplasms. A study by Bernick et al involving 6,495 colorectal cancer patients revealed that only 0.6% had neuroendocrine carcinomas, and a mere 0.2% had LCNECs.[2] Despite their rarity, it is crucial to distinguish neuroendocrine carcinomas from adenocarcinomas of the colon and rectum pathologically, as alternative cytotoxic chemotherapeutic regimens may benefit patients. The case presented underscores the typically aggressive nature of this disease, often marked by metastasis at the initial presentation.

Over time, the definition and classification of NEC has undergone revision. According to the latest WHO classification in 2019, NEC is now characterized by a Ki-67 labelling index exceeding 20% or a mitotic rate surpassing 20 cells per $2mm^2$. It is further classified into small and large cell types. In contrast to the 2010 criteria, where G3 was defined by tumours with a mitotic rate exceeding 20 mitoses per 2 mm^2 and Ki-67 exceeding 20%, this definition previously encompassed both well-differentiated neuroendocrine tumours with high proliferation and poorly differentiated high grade NEC, such as LCNEC and small cell NEC (SCNEC). The 2019 WHO GI NET criteria introduced a novel category for well-differentiated (G3) neuroendocrine tumours. This update acknowledges that well-differentiated tumours can be high grade while remaining distinct from SCNEC and LCNEC. The WHO 2019 grading system also altered the terminology for mixed tumours, now referred to as mixed neuroendocrine-nonneuroendocrine neoplasms (MiNEN).[20,21]

LCNEC of the colorectum shares general morphological and immunophenotypic features with those found in other anatomic locations, principally the lung.[22] Well-differentiated NETs display so-called organoid growth patterns; groupings of cells into nests, trabeculae, rosettes, and glandular structures. LCNEC can also display an organoid growth pattern, although typically shows more abundant tumour necrosis than a G3 NET. LCNEC is also distinguished from G3 NET based on cytological features. As its name suggests, LCNEC is characterised by large cells: cells greater in size than three resting lymphocytes. Additionally, the cells of LCNEC typically have coarse chromatin and prominent nuclei, in contrast to the finely dispersed, granular chromatin pattern seen in NETs. SCNEC on the other hand, while also a poorly differentiated neuroendocrine neoplasm, is characterised by cells less than three times the size of a resting lymphocyte, usually with scant cytoplasm, and homogenously dispersed, dusty chromatin. While the morphology of SCNEC is sufficient to render a diagnosis, LCNEC must be shown to express neuroendocrine markers with immunohistochemistry for synaptophysin, chromogranin A, or INSM1 for example.[23]

The survival rates for colorectal NEC, as reported by various authors, highlight the aggressive nature of these tumours and their association with a dismal prognosis. This case, consistent with others, demonstrates that most patients are diagnosed at an advanced stage with metastatic disease. Much like colorectal adenocarcinoma, the liver emerges as the primary site for metastasis. According to multiple studies, the prognosis remains bleak, typically indicating a median overall survival ranging from 4 to 16 months, with an estimated 1-year survival rate of 46%.[2-7,24]

Information regarding the treatment of colorectal LCNEC is limited and primarily relies on retrospective studies. In a study involving 126 patients diagnosed with colorectal high-grade NEC, of which 47 had an anorectal primary, the application of surgical resection and adjuvant chemotherapy in cases of metastatic disease did not yield improvements in overall survival. The available evidence underscores the need for additional research to elucidate the genuine benefits of adjuvant chemotherapy and radiotherapy in the context of high-grade colorectal NEC.[25]

Numerous retrospective studies have investigated the effectiveness of first-line chemotherapy in metastatic gastrointestinal high-grade neuroendocrine carcinoma. In a study evaluating platinum-based chemotherapy, 20 patients were retrospectively analysed. Of these, 75% received cisplatin and etoposide as their first-line treatment, while 25% received carboplatin and etoposide. The overall response rate (ORR) observed was 68%, and the median overall survival (OS) reached 13.5 months.[26] Additionally, a comprehensive review of the national cancer database focused on patients with high-grade NEC of the colon and rectum. Among the 1208 identified cases, 127 had rectal LCNEC and 46.7% of all the patients presented with metastatic disease. Through multivariable analysis, factors such as resection, chemotherapy, and a rectal primary site were found to be associated with improved OS. The median OS was 9 months.[27]

In the context of advanced high-grade LCNEC, two prospective studies have investigated treatment specifically for gastrointestinal NEC. Li et al conducted a prospective, single-arm phase II study that explored the efficacy of irinotecan and cisplatin followed by

maintenance with octreotide long-acting release (LAR). This study enrolled 8 patients with LCNEC. The ORR across the cohort was 45%, and the median OS reached 12.8 months.[28]

Limited retrospective literature exists for second-line treatment in advanced GI HGNEC.[1] The potential role of immunotherapy in this population is anticipated to gain significance in the future, but additional studies are necessary to establish its efficacy. Another crucial area of investigation pertains to identifying biomarkers that can predict responses to immunotherapy in LCNEC.

CONCLUSION

In conclusion, LCNEC, characterized as rare and aggressive tumours, currently demonstrates optimal response to surgery for local disease, coupled with adjuvant chemotherapy involving platinum and etoposide or platinum and irinotecan. In cases of advanced disease, the historical use of platinum-based therapy, either in combination with etoposide or irinotecan, remains a widely employed first-line treatment. However, as in our case report, alternative regimens like 5-fluorouracil and oxaliplatin (FOLFOX), folinic acid, 5-fluorouracil and irinotecan (FOLFIRI) or capecitabine plus temozolomide (CAPTEM) can also be considered. The demand for more effective and safe treatment options in this challenging scenario is pressing and further research is needed.

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