

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2022 November 15; 14(11): 2088-2301



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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

INDEXING/ABSTRACTING

The WJGO is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJGO as 3.404; IF without journal self cites: 3.357; 5-year IF: 3.250; Journal Citation Indicator: 0.53; Ranking: 162 among 245 journals in oncology; Quartile category: Q3; Ranking: 59 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The WJGO's CiteScore for 2021 is 3.6 and Scopus CiteScore rank 2021: Gastroenterology is 72/149; Oncology is 203/360.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

November 15, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Silent advanced large cell neuroendocrine carcinoma with synchronous adenocarcinoma of the colon: A case report

Hyeon Seok Baek, Sang Wook Kim, Soo Teik Lee, Ho Sung Park, Seung Young Seo

Specialty type: Oncology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Liu J, China; Liu Z, China; Niu JK, China; Tanabe H, Japan

Received: July 22, 2022

Peer-review started: July 22, 2022

First decision: August 19, 2022

Revised: August 31, 2022

Accepted: October 12, 2022

Article in press: October 12, 2022

Published online: November 15, 2022



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Abstract

BACKGROUND

Large cell neuroendocrine carcinoma (LCNEC) accounts for about 0.25% of colorectal cancer patients. Furthermore, synchronous LCNEC and adenocarcinoma coexistence in the colon is very rare. LCNEC are usually aggressive and have a poor prognosis. Usually, colorectal LCNEC patients complain of abdominal symptoms such as pain, diarrhea or hematochezia because it is often diagnosed as an advanced disease that accompanies metastatic lesions.

CASE SUMMARY

We describe a case of relatively asymptomatic synchronous LCNEC and colon adenocarcinoma. A 62-year-old male patient visited our hospital due to anemia detected by a local health check-up. He did not complain of melena, hematochezia or abdominal pain. Physical examination was unremarkable and his abdomen was soft, nontender and nondistended with no palpable mass. Laboratory tests revealed anemia with hemoglobin 5.1 g/dL. Colonoscopy revealed an ulcerofungating lesion in the ascending colon and about a 1.5 cm-sized large sessile polyp in the sigmoid colon. Endoscopic biopsy of the ascending colon lesion revealed the ulcerofungating mass that was LCNEC and endoscopic mucosal resection at the sigmoid colon lesion showed a large polypoid lesion that was adenocarcinoma. Multiple liver, lung, bone and lymph nodes metastasis was found on chest/abdominal computed tomography and positron emission tomography. The patient was diagnosed with advanced colorectal LCNEC with liver, lung, bone and lymph node metastasis (stage IV) and synchronous colonic adenocarcinoma metastasis. In this case, no specific symptom except anemia was

observed despite the multiple metastases. The patient refused systemic chemotherapy and was discharged after transfusion.

CONCLUSION

We report a case of silent LCNEC of the colon despite the advanced state and synchronous adenocarcinoma.

Key Words: Large cell neuroendocrine carcinoma; Colon; Synchronous; Adenocarcinoma; Case report

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Core Tip: Large cell neuroendocrine carcinoma (LCNEC) account for about 0.25% of colorectal cancer patients. Furthermore, LCNEC with synchronous or metachronous adenocarcinoma in the colon has been reported in only a few cases. We report the diagnostic experience of a 62-year-old patient with advanced LCNEC in the colon and synchronous adenocarcinoma metastasis but no definitive symptoms except anemia. We suggest the possibility of an association between the two types of primary colon cancer. Therefore, if a patients diagnosed with LCNEC in the colon, appropriate screening tests are required. Further studies are needed on the pathogenesis of the two primary cancers.

Citation: Baek HS, Kim SW, Lee ST, Park HS, Seo SY. Silent advanced large cell neuroendocrine carcinoma with synchronous adenocarcinoma of the colon: A case report. *World J Gastrointest Oncol* 2022; 14(11): 2266-2272

URL: <https://www.wjgnet.com/1948-5204/full/v14/i11/2266.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v14.i11.2266>

INTRODUCTION

Large cell neuroendocrine carcinoma (LCNEC) accounts for about 0.25% of colorectal cancer patients [1]. Patients with colorectal LCNEC are usually found to be in an advanced stage with metastasis at the time of diagnosis [2]. Furthermore, LCNEC with synchronous or metachronous adenocarcinoma in the colon has been reported in only a few cases [3,4].

The symptoms of colorectal LCNEC are not different from those of conventional colonic adenocarcinoma. Patients with colorectal LCNEC usually present with abdominal symptoms such as abdominal pain, diarrhea, hematochezia or tenesmus. Paraneoplastic and carcinoid syndromes which have resulted from excessive hormone production, may rarely be a clinical presentation [5]. Contrast enhanced computed tomography (CT) and magnetic resonance imaging are useful for initial diagnosis and staging of disease in patients with gastroenteropancreatic neuroendocrine tumors (NETs) [6]. However, there are no specific characteristic imaging findings of colorectal LCNEC.

The diagnosis of LCNEC is based on pathologic findings. Histologic features of LCNEC are trabecular growth, organoid nesting, rosettes and perilobular palisading patterns. The tumor cells are generally large and shows moderate to abundant cytoplasm. Nucleoli are often detected and their presence facilitates distinction from small cell carcinoma. Several immunohistochemical markers such as synaptophysin, chromogranin and neural cell adhesion molecule (CD56) are useful for confirmation of neuroendocrine differentiation. However, one positive marker is enough if the staining is clearcut [7].

Here, we report on a case of advanced LCNEC (stage IV) in the colon and synchronous adenocarcinoma metastasis in a patient with no specific symptoms except anemia. This case report was approved by the Institutional Review Board of Jeonbuk National University Hospital (IRB No. CUH 2022-07-002), and the patient has signed the informed consent for publication of the case (date of the consent: 2022-04-14).

CASE PRESENTATION

Chief complaints

A 62-year-old male patient visited the hospital for anemia detected by a local health check-up.

History of present illness

He denied abdominal symptoms such as pain, diarrhea and hematochezia.

History of past illness

His medical history was unremarkable.

Personal and family history

He was a non-smoker and non-alcohol drinker and had no significant family history.

Physical examination

Physical examination was unremarkable.

Laboratory examinations

Laboratory tests revealed anemia with hemoglobin 5.1 g/dL and a normal liver function test. Serum carcinoembryonic antigen (3.01 ng/mL) and carbohydrate antigen 19-9 (< 9.0 U/mL) were also within normal limits.

Imaging examinations

Esophagogastroduodenoscopy and colonoscopy were performed to find the cause of anemia. Colonoscopy revealed a circumferential ulcerofungating mass in the ascending colon and a biopsy was performed (Figure 1A). Furthermore, about a 1.5 cm-sized large sessile polyp was seen in the sigmoid colon and endoscopic mucosal resection was performed (Figure 1B). Advanced ascending colon cancer was suspected and the patient underwent a chest/abdominopelvic CT. The abdominopelvic CT showed irregular wall thickening over a length of about 10 cm in the ascending colon with regional fat stranding and multiple pericolic lymph node enlargements, thickening and nodularity in the adjacent peritoneum. Moreover, numerous low-density lesions with a maximal 8.7 cm diameter in both the liver lobe (Figure 2A). The chest CT showed left supraclavicular lymph node enlargement (Figure 2B) and a tiny nodule of about 6 mm in the right lung upper lobe.

In the pathology report, an ulcerofungating mass in the ascending colon was confirmed as LCNEC, and a large polypoid lesion in the sigmoid colon was confirmed as adenocarcinoma (Figure 3). The LCNEC showed strong immunoreactivity for synaptophysin. The mitotic index was > 30/10HPF and the Ki-67 index was 65.7%, suggesting a poor prognosis. Both the LCNEC and colonic adenocarcinoma showed positive immunohistochemical stain for CK20.

Positron emission tomography revealed abnormal fluorodeoxyglucose uptake at the ascending colon with enlarged lymph nodes at the adjacent mesentery and hematogenous metastasis in the liver, lung, bones, peritoneum and supraclavicular lymph node (Figure 4).

FINAL DIAGNOSIS

The patient was diagnosed with advanced colorectal LCNEC with liver, lung, bone and lymph nodes metastasis (stage IV) and synchronous colonic adenocarcinoma metastasis.

TREATMENT

Systemic chemotherapy was considered but the patient refused treatment and was discharged.

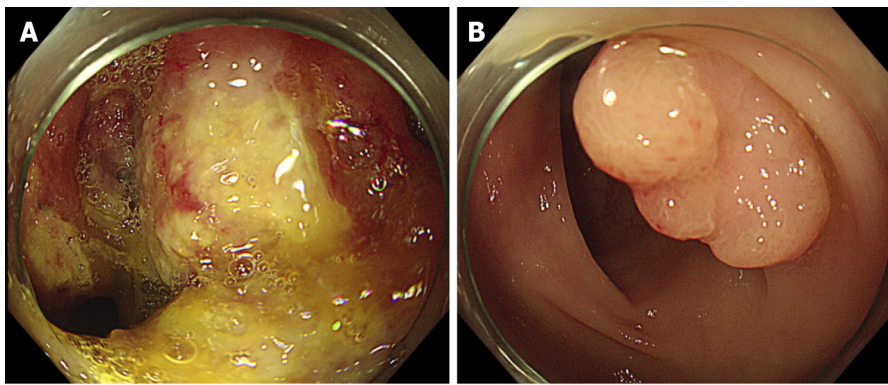
OUTCOME AND FOLLOW-UP

At 3 mo after diagnosis, the patient received the best supportive care and was still alive.

DISCUSSION

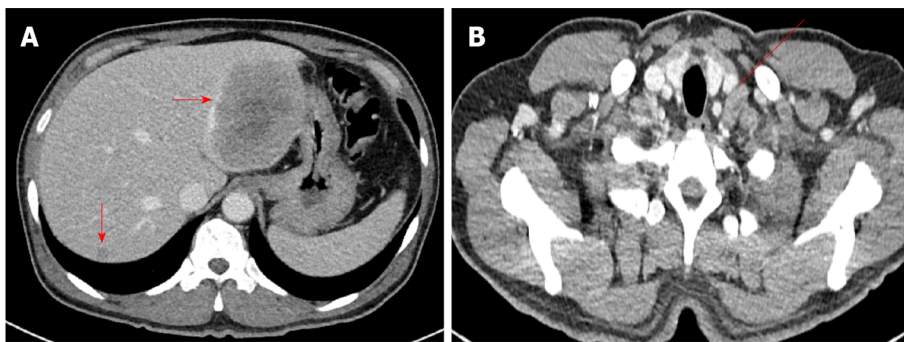
Gastroenteropancreatic neuroendocrine neoplasms (NENs) occur in the neuroendocrine cells of the gastroenteropancreatic tract and are also known as carcinoids and islet cell tumors. Well-differentiated NENs are classified as NETs G1 or G2. NET G1 can be identical with carcinoid. The term NEC refers to all poorly differentiated NENs. NEC is classified into minor and large cell variants[8]. Most NETs are carcinoids and have a better prognosis than conventional adenocarcinomas.

On the other hand, LCNEC is known to be an aggressive disease and have a poor prognosis[9]. However, in this case, the patient had no abdominal symptoms such as melena, hematochezia or pain despite the advanced LCNEC with multiple metastases. Moreover, no progressive LCNEC-associated symptoms except asymptomatic anemia were observed in this case.



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Figure 1 Colonoscopy images. A: Ulcerofungating lesion involving the luminal circumference in the ascending colon; B: About a 1.5 cm sized sessile polyp in the sigmoid colon.



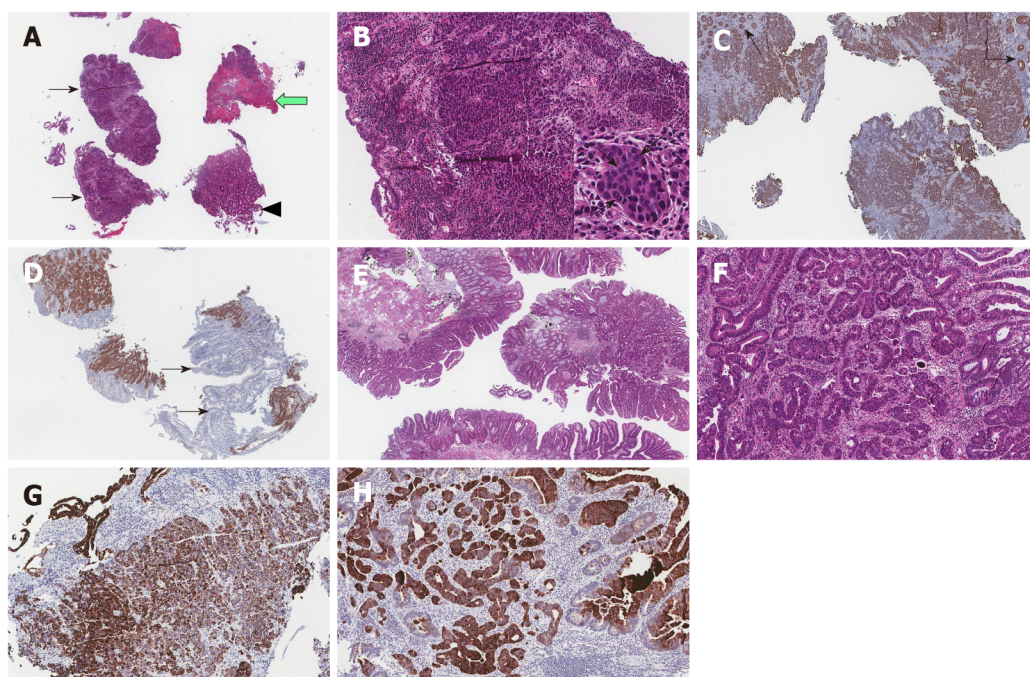
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Figure 2 Abdominopelvic computed tomography and chest computed tomography images. A: Low density lesion of about 8.7 cm in the left lobe of the liver, and several smaller lesions in the right lobe of the liver (arrow); B: Left supraclavicular lymph node enlargement (line).

The prognosis of colorectal LCNEC is poor. Colorectal LCNEC is a highly aggressive neoplasm with a high mortality rate[10], and 36% of LCNEC patients had distant metastasis at the time of diagnosis. The liver is the most involved organ in metastatic disease[11]. In this case, multiple metastatic lesions in the liver, lungs, bones, peritoneum and lymph nodes were noted at the diagnosis.

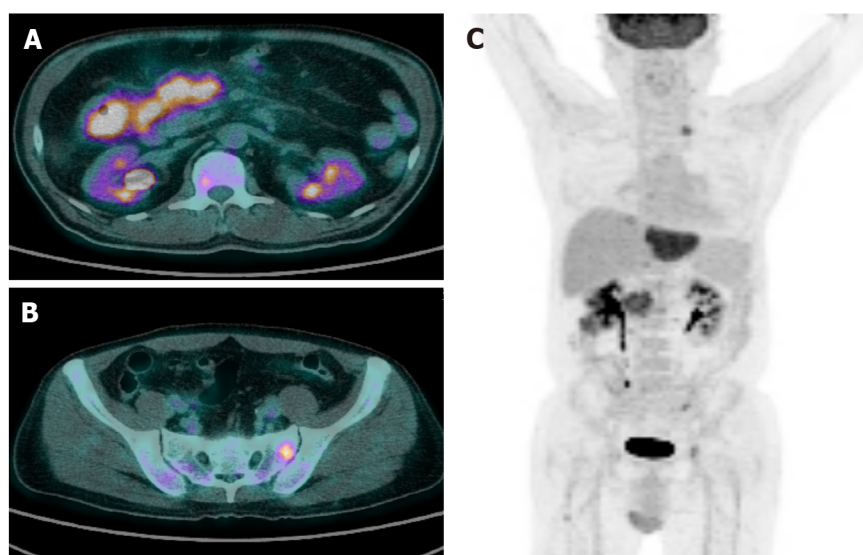
LCNEC with synchronous or metachronous adenocarcinoma in the colon has been reported only in a few cases. The pathophysiological association between neuroendocrine carcinoma and adenocarcinoma is still unclear. Some suggest a possible association in the pathogenesis of the colorectal NET and adenocarcinoma[12,13]. CK20 is known as a common marker in colorectal adenocarcinoma. Kato *et al* [13] reported a CK20 positive colonic LCNEC which is accompanied by synchronous colorectal adenocarcinoma. This report suggested different types of gastrointestinal neoplasm might originate from a common stem cell clone which might share a similar genetic mutation(s) during early oncogenesis. In our case, an immunohistochemical stain for CK20 was performed on the colonic LCNEC and adenocarcinoma, and both were confirmed to be immunoreactive (Figures 3G and 3H), supporting the theory of Kato *et al* [13]. Therefore, when LCNEC of the colon is diagnosed, it can be accompanied by synchronous or metachronous colonic adenocarcinoma and a close examination of the remaining colon is required. In addition, colonoscopy follow-up should be considered.

The primary treatment of colorectal LCNEC is surgery if R0 resection is possible[14]. When complete resection is impossible, a debulking procedure and cytoreductive therapy or systemic chemotherapy should be considered[15]. LCNEC is similar to small cell neuroendocrine carcinoma (SCNEC) in histogenesis, biology and clinical behavior. For patients with locally advanced or metastatic disease, extrapolation from the treatment paradigms for both non-SCNEC and SCNEC, with chemoradiation and chemotherapy in stage III, and chemotherapy and palliative radiation in stage IV, seems reasonable. Regarding drug choice for systemic chemotherapy, regimens based on efficacy in SCNEC such as etoposide and a platinating agent are preferred[16]. There are no established guidelines for patients diagnosed with LCNEC with synchronous adenocarcinoma of the colon, but chemotherapy can be considered depending on which disease is predominant. In this case, LCNEC was considered a more predominant lesion than adenocarcinoma and a chemotherapy with a combination of cisplatin and etoposide was considered, but the patient refused.



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Figure 3 Histologic and immunohistochemical findings of colonic large cell neuroendocrine carcinoma. Histologic findings of colonic adenocarcinoma. Immunohistochemical stain for CK20 in both colonic large cell neuroendocrine carcinoma and colonic adenocarcinoma. A: Low power view of biopsy specimen reveals several tissue fragments mainly consisted of tumor (black arrows), ulcer debris (white arrow), and non-neoplastic colonic mucosa (arrowhead) (HE, $\times 20$); B: Medium power view displays invasive tumor cells forming organoid structures such as cords or small nests (HE, $\times 100$). Tumor cells display severe atypia and have round nuclei, sometimes with prominent nucleoli (arrows), and moderate amounts of cytoplasm, with high mitotic rate (Inset, HE, $\times 400$); C: Infiltrating tumor cells are identified by immunohistochemical stain for cytokeratin (CK, $\times 100$). Note the non-neoplastic mucosal glands (arrows) that are separated from the tumor; D: Tumor cells show strong immunoreactivity for neuroendocrine marker (synaptophysin, $\times 100$). Note the non-neoplastic mucosal glands (arrows) are negative for neuroendocrine marker; E: Low power view of biopsy specimen reveals colonic epithelial proliferative lesion forming tubular and papillary structures (HE, $\times 20$); F: Medium power view displays invasive growth of tumor cells that form irregular branching and budding of glands (HE, $\times 100$); G: Infiltrating tumor cells of colonic large cell neuroendocrine carcinoma are immunoreactive for CK20 ($\times 100$); H: Invasive tumor glands of colonic adenocarcinoma are also immunoreactive for CK20 ($\times 100$).



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Figure 4 Positron emission tomography images. A: Abnormal fluorodeoxyglucose uptake at the ascending colon with enlarged lymph nodes at the adjacent mesentery; B and C: Hematogenous metastasis in the liver, lung, bones, peritoneum, supraclavicular lymph node.

CONCLUSION

In conclusion, we report on a case of silent LCNEC of the colon despite the advanced state and

synchronous adenocarcinoma, suggesting the possibility of an association between the two types of primary colon cancer. In patients diagnosed with LCNEC in the colon, there is a possibility of synchronous or metachronous adenocarcinoma after surgical treatment, so appropriate screening tests are required. Further studies are needed on the pathogenesis of the two primary cancers.

FOOTNOTES

Author contributions: Baek HS analyzed clinical data and drafted the manuscript; Lee ST, Kim SW, Seo SY advised and reviewed the manuscript; Park HS performed the pathologic review.

Informed consent statement: Informed written consent was obtained from the patient regarding the publication of this report and accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang JJ

L-Editor: Filipodia

P-Editor: Wang JJ

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