# An Appearance of Mixed Large-cell Neuroendocrine Carcinoma and Hepatoid Carcinoma of Colon

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Vajira Med J. 2018; 62(3): 251-56
http://dx.doi.org/10.14456/vmj.2018.18

## Abstract

We present the first case of large-cell neuroendocrine carcinoma of the colon that combined with hepatoid adenocarcinoma without evidence of inflammatory bowel disease. The patient came to hospital to check up without any clinical symptoms. High serum alpha-fetoprotein (AFP) was found in this case. A clinician should realize that this rare tumor could be found in patient with intestinal mass along with high AFP level. Early diagnosis may improve outcome in this aggressive behavior and poor prognosis.

**Keyword**: Large cell neuroendocrine carcinoma, hepatoid adenocarcinoma, alpha-fetoprotein

# การพบ Large-cell neuroendocrine carcinoma ของลำไส้ใหญ่ร่วมกับ Hepatoid adenocarcinoma

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## บทคัดย่อ

รายงานนี้เป็นการรายงานผู้ป่วยรายแรกที่พบ large-cell neuroendocrine carcinoma ของลำไส้ใหญ่ร่วมกับ hepatoid adenocarcinoma โดยไม่พบหลักฐานของโรค Inflammatory bowel disease ร่วมด้วย ผู้ป่วยมาที่โรงพยาบาลเพื่อรับการตรวจสุขภาพประจำปีโดยไม่มีอาการผิดปกติใด ๆ การทดสอบทางห้องปฏิบัติการพบระดับ alpha-fetoprotein ในซีรั่มสูง ซึ่งนำไปสู่การตรวจอื่นเพิ่มเติม แพทย์ควรตระหนักถึงเนื้องอกหายากชนิดนี้ไว้ด้วยในกรณีที่ผู้ป่วยตรวจพบก้อนที่ลำไส้ร่วมกับการมีระดับ alpha-fetoprotein สูง การวินิจฉัยได้ในระยะแรก อาจให้ผลการรักษาที่ดีขึ้น

## Introduction

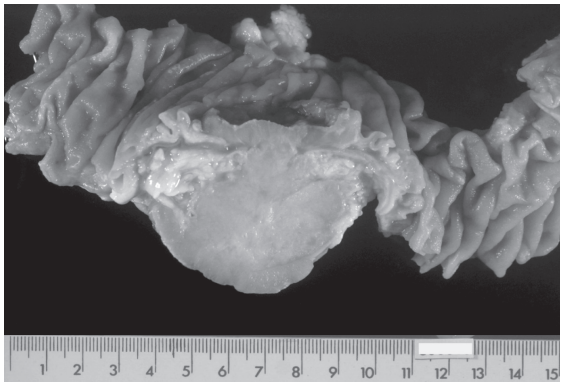
Gastroenteropancreatic neuroendocrine tumor (GEP-NETs) is a rare tumor entity. Most of them are well differentiated or grade 1 and 2, and have a favorable prognosis.[1,2] Poorly differentiated neuroendocrine carcinoma (NEC) including large cell subtype is extremely rare with reported incidence of approximately 0.1% to 3.9% of all colonic malignancies. [3,4]

Some GEP-NETs can be found along with a minor exocrine component of adenocarcinoma.[5-8] By the year 2010, World Health Organization (WHO ) has reported the criteria used to define mixed adenoneuroendocrine carcinomas (MANECs) was that the glandular portion must be distinct, and it comprises of more than 30% of total tumor volume.[9] In rare cases, the adenocarcinoma portion may have hepatoid feature that called hepatoid adenocarcinoma (HAC).[10-13] Only one case was reported to be NEC combined with hepatoid carcinoma in pancreas.[14] To date, no such a lesion had been found in colon. The present study described a woman with NEC combined with HAC of the colon without any evidence of inflammatory bowel disease (IBD).

## Case presentation

A 74-year-old woman, with underlying of chronic hepatitis B infection, sought for an annual health check-up in our hospital without any symptoms. Physical examination was unremarkable. Laboratory tests showed mild hyperlipidemia (LDL 171 mg/dL), HBV viral load 767 IU/ml and high alpha fetoprotein (AFP) level (266.5 mg/ml). Other laboratory tests including CBC, fasting blood sugar, serum creatinine, liver function test, urinalysis and carcinoembryonic antigen (CEA) were within normal limits. Ultrasound upper abdomen revealed unremarkable study. No significant lesion or tumor mass was found in the liver and pancreas. Colonoscopy revealed a large ulcer, sized 5 cm at the ascending colon.

She underwent extended right hemicolectomy and omentectomy without any significant morbidity. Gross pathology (Figure 1) showed a 4.5 cm irregular and indurated edges ulcer at hepatic flexure, 11 cm distal to the ileocecal valve and 6.5 cm from the colonic resection end. Cut sections of the colonic wall revealed a 5.5 cm area of infiltrating lesion extending from the ulcerated mucosa through the muscular coat of the bowel with nodular but intact serosal surface. Foci of tumor necrosis were seen. No gross tumor seeding of the omentum was found. Her clinical and pathologic findings were consistent with stage IIIB.

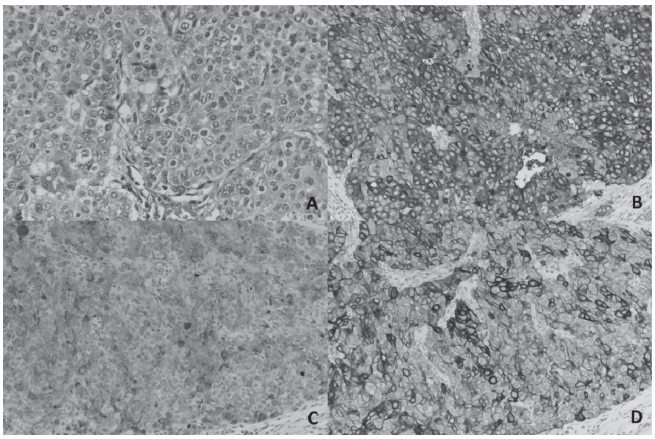


**รูปที่ 1:** An ulcerated mass at hepatic flexure, extending from the ulcerated mucosa into the pericolonic fat with nodular but intact serosal surface.

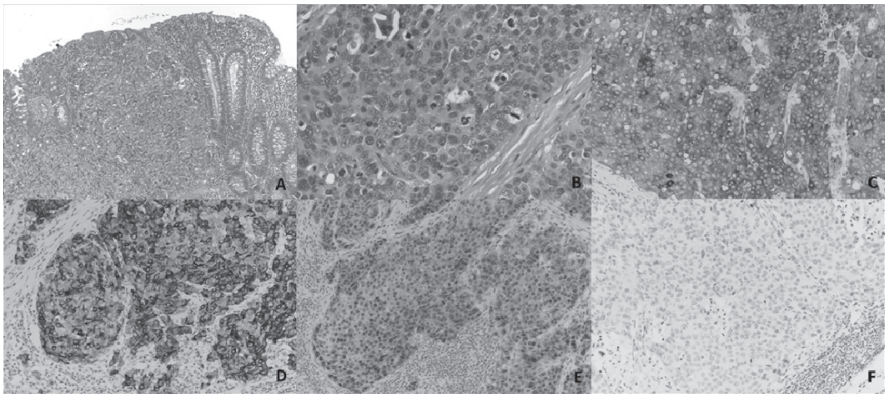
Histopathologic findings of colonic lesions showed infiltration of high-grade carcinoma from ulcer through the muscular wall, pericolic soft tissues and serosa. The tumor had various growth patterns of solid sheets and tumor clusters among delicate fibrovascular stroma. There was focal area of tumor, arranged in thick trabecular pattern with intervening delicate vessel, resembling thick hepatic cord with sinusoid. Tumor cell in this area revealed cuboidal shape with large amount of ample cytoplasm which was similar to the hepatocyte. These features along with high level of AFP, made a suspicion for hepatoid adenocarcinoma. However, these tumor areas were mingled to other area of high-grade carcinoma and these histologic features are not specific for those hepatoid adenocarcinoma. No distinct glandular pattern was displayed in the tumor. Extensive lymphovascular invasion of tumors were demonstrated. Metastasis was evidenced in 2 out of 31 dissected regional lymph nodes.

The provisional diagnosis was 'high-grade carcinoma' with differential diagnoses of poorly differentiated adenocarcinoma, neuroendocrine carcinoma and hepatoid adenocarcinoma. Among immunohistochemical study of CK7, CK20, CDX-2, synaptophysin, chromogranin A, CD56, NSE, Ki67, AFP, CEA, hepatocyte, glypican3, CK8/18 and CK19, positive expressions were found for: CDX-2, synaptophysin, chromogranin A, CD56, NSE, AFP, glypican3, CK8/18, CK19 and, Ki67 (30%). The suspicious area of hepatoid adenocarcinoma was positive for AFP, glypican3, CK8/18, and CK19 (Figure 2). Remaining tumor area revealed positive for CDX-2, synaptophysin, chromogranin A, CD56, NSE, CK8/18, and CK19 (Figure 3). Ki67 stain was positive in both areas.

The final pathologic diagnosis was large cell neuroendocrine carcinoma (LCNEC) combined with hepatoid carcinoma. Her serum level of AFP was declined to normal level within 1 month after surgery. Adjuvant chemotherapy was given. Colonoscopy was performed at 12 months after surgery. She was doing well at the time of this report without any evidence of disease 22 months after surgery.




**รูปที่ 2:** Tumor with trabecular pattern (A; 400x). The same tumor area with positive staining for AFP (B; 200x), Glypican 3 (C; 200x) and CK8/18 (D; 200x).




**รูปที่ 3:** Tumor with transitional zone (A; 100x). Pleomorphic tumor cells with high mitotic counts (B; 400x). The same tumor area with positive staining for synaptophysin (C; 200x), chromogranin A (D; 200x), CDX2 (E; 200x) and negative staining for CK20 (F; 200x).

## Discussion

Large-cell neuroendocrine carcinoma of colon is a rare type of neuroendocrine tumors.[3,4] It is regarded as poorly differentiated cancer with aggressive behavior. The prognosis is poor with early metastasis as shown by the evidences that more than 70% of the patients present with metastatic diseases.[3,4,15,16] Median survival rate was ranged from 5 months to 11 months. [3,4,15,16]

Large cell NEC of any locations including colon share similar morphological features as those found in lung. The morphologic features are initially described by Travis et al [17] and subsequently adopted by the World Health Organization (WHO). It is characterized by a) neuroendocrine pattern including an organoid, nesting, trabecular, rosette, and palisading pattern,[10] b) large cells with a polygonal shape, ample cytoplasm, coarse chromatin and frequent nucleoli, c) high mitotic rate (more than 20/10 high power fields) and/or more than 20% of Ki67 index along with frequent necrosis, and evidence of neuroendocrine features by immunohistochemistry (positive of at least 2 neuroendoendocrine markers: NSE, chromogranin A, synaptophysin and CD56) or electron microscopy (presence of dense secretory granule in the cytoplasm). [4,17]

Histomorphology of the tumor in this patient showed a high solid sheet, trabecular and focally nesting pattern with intervening delicate vessels. Distinct glandular pattern was not observed. Tumor cell showed pleomorphic nuclei, prominent nucleoli and moderate to large amount of ample cytoplasm. Mitotic figures were frequently noted (more than 20/10 HPFs). Immunohistochemical stains of neuroendocrine markers (synaptophysin, chromogranin A, CD56 and NSE) were positive whereas CK20 (which generally stained positive for adenocarcinoma) was negative, supporting a diagnosis of LCNEC.

With her clinical data of chronic hepatitis, laboratory findings of high serum AFP, unremarkable result of ultrasound upper abdomen and presence of trabecular pattern with intervening delicate vessels, resembling to thick hepatic cord with sinusoid, which could be features of hepatocellular carcinoma. We also performed other immunostains of AFP, CEA, hepatocyte, glypican3, CK8/18 and CK19. Positive staining for AFP, glypican3, CK8/18 and CK19, and negative staining of hepatocyte and CEA, suggested hepatoid carcinoma. Bourreille *et al.* were the first group who described hepatoid carcinoma as an AFP-producing tumor [18] with a few subsequent case reports.[19] This type of tumor is characterized by clinical high serum level of AFP, histomorphology mimic to hepatocellular carcinoma and positive staining for AFP, CEA, glypican3, CK18, CK19; and, less commonly positive staining for Hepatocyte and CK20. Hence, we concluded that our patient had tumor of mixed LCNEC and hepatoid carcinoma as shown by several findings described earlier.

Most cases of hepatoid carcinoma were described in stomach, followed by lung, gallbladder, pancreas, uterus and ovaries.[18] Four cases were found in the colon.[10-13] Three of them were associated with inflammatory bowel disease.[10-12] The hepatoid carcinoma is an aggressive tumor with poor prognosis. One literature review reported that approximately half of the patients died within the first 12 months after diagnosis.[19]

Our patient who had mixed components of LCNEC and hepatoid carcinoma had good outcomes and was in remission for nearly 2 years after diagnosis. This might be due to an early diagnosis of disease without any symptoms, and the treatment was successful.

In conclusion, we present the first case of LCNEC of the colon that combined with HAC without evidence of IBD. The prognosis was quite good. A close and long-term follow-up would be exercised.

## Summary

We present the first case of LCNEC of the colon that combined with HAC without evidence of IBD. The patient came to hospital to check up without any clinical symptoms. Abnormal laboratory test was high level of serum AFP. A clinician should be aware that this rare tumor could be found in patient with intestinal mass along with high AFP level.

Early diagnosis may improve outcome in this aggressive behavior and poor prognosis.

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