P-ISSN 2586-9000
E-ISSN 2586-9027
Homepage : https://tci-thaijo.org/index.php/SciTechAsia
Science & Technology Asia
Vol.29 No.1 January - March 2024
Page: [208-214]
Original research article

Synchronous Colonic Neuroendocrine Tumor and Adenocarcinoma: A Case Report with Literature Review

Naree Pluthikarmpae[1,*], Chatchanok Paoin[2]

[1]*Department of Pathology, Suranaree University of Technology Hospital, Suranaree University of Technology, Nakhon Ratchasima 30000, Thailand*
[2]*Department of Internal Medicine, Institute of Medicine, Suranaree University of Technology, Nakhon Ratchasima 30000, Thailand*

Received 5 May 2023; Received in revised form 19 November 2023
Accepted 12 January 2024; Available online 31 March 2024

ABSTRACT

Multiple primary malignancies are categorized as synchronous and metachronous tumors, depending on the different rules of international institutions. The synchronous occurrence of a colonic neuroendocrine tumor with adenocarcinoma is rare. We present a case involving a synchronous colonic neuroendocrine tumor and adenocarcinoma. Our patient is a 68-year-old male with a positive stool occult blood test from a check-up examination. A biopsy of an unknown location from a colonoscopy revealed a moderately differentiated adenocarcinoma. His whole-abdominal computed tomography (CT) scan showed focal eccentric thickening with solid enhancement of the hepatic flexure colon. The patient underwent a right hemicolectomy. Macroscopic examination revealed an ulceroproliferative mass at the hepatic flexure and a submucosal mass at the cecum. The mass at the hepatic flexure exhibited villous, back-to-back, and cribriform glands composed of columnar cells with some tumor cells floating in extracellular mucin that were positive for CK20 and CDX2 immunostaining, diagnosed as a well-differentiated adenocarcinoma with mucinous features. The mass at the cecum revealed nest, trabecular, and glandular patterns of monotonous cuboidal to polygonal cells that tested positive for synaptophysin, chromogranin A, and CDX2 immunostaining, diagnosed as a well-differentiated neuroendocrine tumor. Many hypotheses have been proposed regarding the pathogenesis of neuroendocrine neoplasms with other primary malignancies. In our opinion, a genetic abnormality of common cell origin might be one of the possible etiologies of our case due to the common endodermal origin and the positivity of CDX2. We recommend that close surveillance for synchronous tumors in patients with colorectal neuroendocrine tumors might be helpful.

Keywords: Adenocarcinoma; Colon; Neuroendocrine tumor; Synchronous tumor

***Corresponding author:** naree.pl@g.sut.ac.th

1. Introduction

Multiple primary malignancies are tumors that occur together in one patient. The definitions and rules applied to count multiple primary malignancies vary among institutions [1-3]. The incidence of gastrointestinal neuroendocrine tumors with multiple primary malignancies was 12-54% [4-9]. Tichansky et al. [4] reported that the rates of synchronous and metachronous cancers of colorectal neuroendocrine tumors were 8.0% and 22.6%, respectively. The most common site of multiple primary malignancies was the gastrointestinal tract [4, 5, 8]. The most common histology was adenocarcinoma of the large intestine [5]. The rate of occurrence of gastrointestinal neuroendocrine tumors with synchronous colorectal adenocarcinoma ranged from 1% to 8% [7].

We report a case of a 68-year-old male with adenocarcinoma at the hepatic flexure with an incidental finding of a well-differentiated neuroendocrine tumor in the cecum.

2. Case Report

The patient, a 68-year-old male, tested positive for occult blood in a check-up examination. His underlying diseases included type 2 diabetes mellitus, hyperlipidemia, asymptomatic hyper-uricemia, and benign prostatic hyperplasia. The patient had no family history of cancer. He had no gastrointestinal symptoms, cough, dyspnea, weight loss, fever, palpitation, or sweating. His complete blood count and liver function test results were unremarkable. Colonoscopy performed at the previous hospital showed masses in the ileocecal valve, transverse, splenic flexure, and hepatic flexure colon. A biopsy from an unknown location from colonoscopy revealed a moderately differentiated adenocarcinoma. A whole-abdominal computed tomography (CT) scan showed focal eccentric thickening with solid enhancement of the hepatic flexure colon with multiple right and middle colic lymph nodes measuring up to 1.2 cm. The patient underwent a right hemicolectomy. A mass at the hepatic flexure with positive mesenteric lymph nodes was intraoperatively observed. No liver, peritoneal, or pelvic nodules were identified. Macroscopic examination revealed a submucosal rubbery gray-white mass in the cecum and an ulceroproliferative rubbery light-brown mass in the hepatic flexure colon. The mass at the cecum showed nest, trabecular, and glandular patterns of monotonous cuboidal to polygonal cells with round to oval nuclei, salt-and-pepper chromatin, and eosinophilic cytoplasm (Figs. 1A-1B). The mitotic rate was 2.2/2 mm^2. Necrosis was not observed. The tumor cells invaded the muscularis propria. Lymphovascular and perineural invasions were identified. The tumor cells were positive for synaptophysin, chromogranin A, and CDX2 immunostaining (Figs. 1C-1E). The Ki-67 index was 4.6%. The diagnosis was a well-differentiated neuroendocrine tumor, G2. The mass at the hepatic flexure revealed villous, back-to-back, and cribriform glands composed of columnar cells with enlarged hyperchromatic to vesicular nuclei (Fig. 2A). Some glands of tumor cells floated in extracellular mucin (Fig. 2B). The tumor cells invaded the muscularis propria. Immunostaining for CK20 and CDX2 was positive but the CK7 staining was negative (Figs. 2C-2D). The diagnosis was a well-differentiated adenocarcinoma with the mucinous feature. One regional lymph node was involved by well-differentiated neuroendocrine tumor cells that were positive for synaptophysin, chromogranin A, and CDX2. Immunohistochemistry for mismatch repair proteins showed no loss of nuclear expression. The remaining small intestine and colon revealed four tubular adenomas with low grade dysplasia and three tubulovillous adenomas with low grade dysplasia. At seven months postoperatively, he was asymptomatic. Serum carcinoembryonic antigen (CEA) was

normal. The chest and whole abdominal CT scan showed no local recurrence, lymphadenopathy, or distant metastasis.

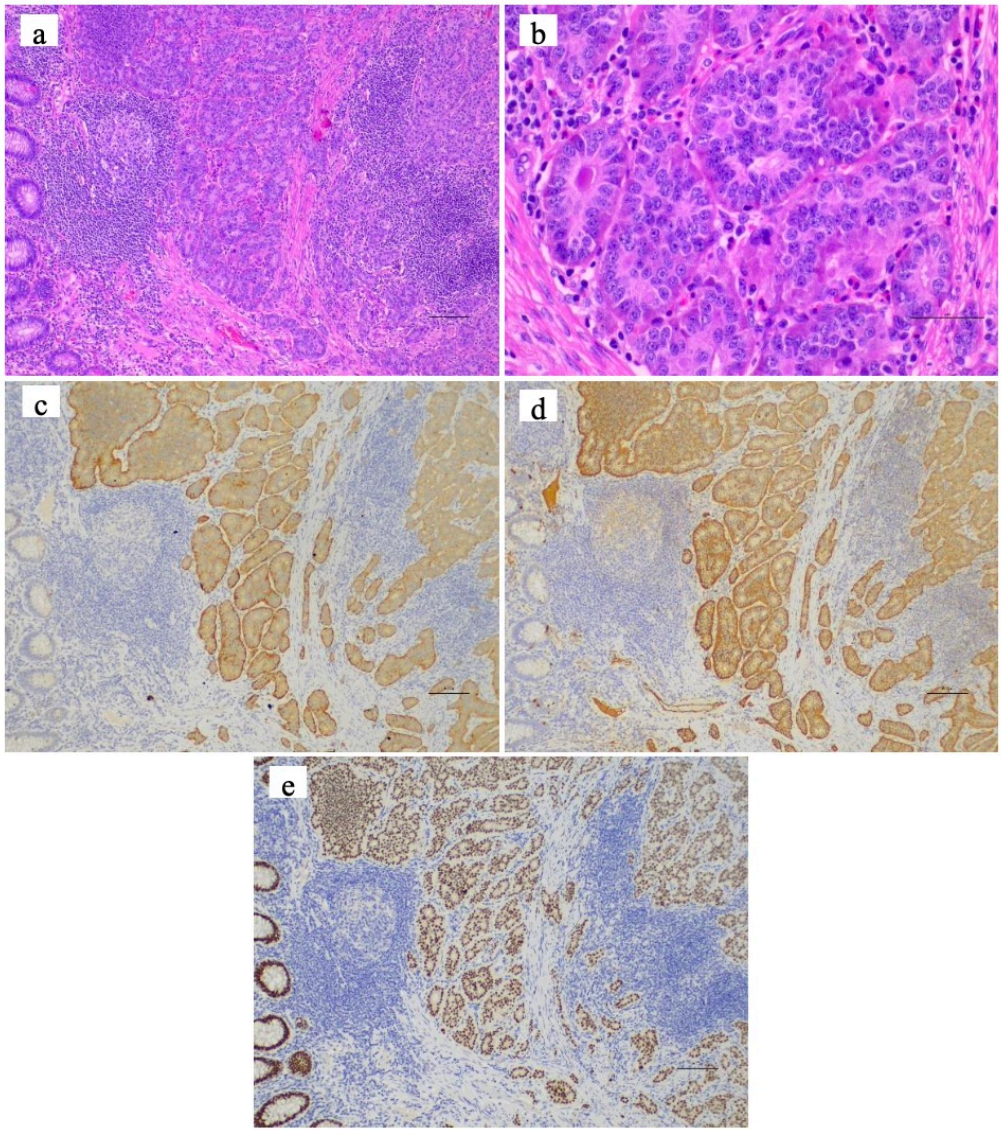

Fig. 1. Well-differentiated neuroendocrine tumor at the cecum (a) The histologic examination reveals nest, trabecular, and glandular patterns of monotonous cuboidal to polygonal cells (hematoxylin and eosin, 100x). (b) Tumor cells exhibit round to oval nuclei, salt-and-pepper chromatin, and eosinophilic cytoplasm (hematoxylin and eosin, 400x). (c) Tumor cells show positivity for synaptophysin (immunohistochemical staining, 100x). (d) Chromogranin A staining displays positive results in tumor cells (immunohistochemical staining, 100x). (e) Positive immunostaining for CDX2 is observed in tumor cells (immunohistochemical staining, 100x).

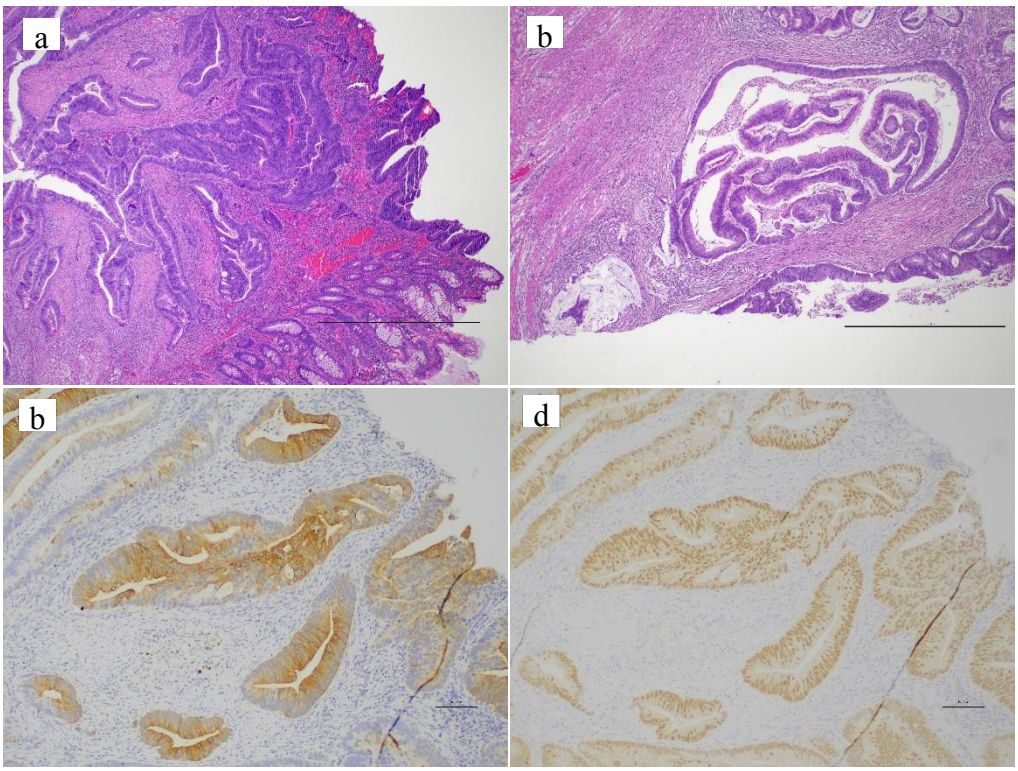

Fig. 2. Well-differentiated adenocarcinoma with mucinous feature at the hepatic flexure (a) The histologic examination reveals cribriform glands of tumor cells (hematoxylin and eosin, 40x). (b) Some tumor cells float in extracellular mucin (hematoxylin and eosin, 40x). (c) Tumor cells exhibit positivity for CK20 (immunohistochemical staining, 100x). (d) Positive immunostaining for CDX2 is observed in tumor cells (immunohistochemical staining, 100x).

3. Discussion

The Surveillance, Epidemiology, and End Results (SEER) Program Code Manual of the National Cancer Institute, USA, uses three rules that include site differences, histologic type differences, and time interval of occurrence [1]. Each site category and subcategory, according to the International Classification of Diseases for Oncology 2 (ICD-O-2), is counted independently [1]. Each site of the colon is considered a separate site [1]. Primary malignancies that occur in less than two months separately are defined as synchronous cancers [1]. The Standards and Guidelines for Cancer Registration in Europe mentions that the International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC) rules of multiple primary tumors do not depend on time intervals [2]. Tumors that occur in one organ or a pair of organs or tissues are considered one tumor, except for lymphoma, leukemia, Kaposi sarcoma, and mesothelioma, in which case tumors are counted only once [2]. Tumors with different histology at the same site are counted individually [2]. The Eighth Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual defines tumors in the same organ that are diagnosed not more than four months apart or those that are identified at the time of surgery for the therapy of the first cancer as synchronous cancers [3]. Tumors in the same organ that are diagnosed more than four months away from each other are considered metachronous cancers [3]. According to the rules of the three international institutions

mentioned earlier, our case was classified as synchronous tumors.

Many hypotheses have been proposed on the pathogenesis of neuroendocrine tumors with other primary malignancies, such as genetic abnormalities of common cell origin [4, 10, 11], environmental factors [6, 10], and peptides and growth factors secreted from neuroendocrine tumors [5, 8, 10, 11]. De Santa Barbara et al. [12], who studied intestinal epithelium development and differentiation reported that vertebrate gut epithelial lining derived from endoderm and the stem cells in the middle of crypt differentiated to enterocytes, enteroendocrine cells, Paneth cells, and goblet cells. Andrew et al. grafted the quail endoderm with chick mesoderm and chick endoderm with quail mesoderm to chorioallantoic membranes of chick embryos. Gut endocrine cells from the combination of quail endoderm with chick mesoderm showed quail nuclei and revealed chick nuclei from the combination of chick endoderm with quail mesoderm [13]. Cox et al. [14] cloned adenocarcinoma of the colon on rats that consequently developed eleven tumors, composed of neuroendocrine tumors (carcinoid), adenomatous, and undifferentiated components. Goldenberg et al. [15] had transplanted a human neuroendocrine tumor (carcinoid tumor) of the transverse colon on cheek pouches of hamsters that subsequently showed tumors composed of signet-ring cells that were not positive for enterochromaffin granule staining. These studies suggest that both colonic epithelium and enteroendocrine cells, which are the origins of colonic adenocarcinoma and neuroendocrine tumors, respectively, are derived from the endoderm.

Caudal type homeobox 2 (CDX2) is the protein-encoding gene that regulates intestinal development. Immunohistochemistry for CDX2 is expressed in the nuclei of normal intestinal epithelium and is usually positive in colorectal adenocarcinoma. CDX2 is also positive in normal endocrine cells of the intestinal tract [16, 17]. Beck [18], who reviewed CDX2 knockout studies, summarized that the CDX2 gene plays a major role in the differentiation of the midgut endoderm. La Rosa et al. [16] reported that CDX2 is expressed in well-differentiated endocrine tumors from the duodenum, ileum, appendix, right side of the colon, and pancreas and is weakly expressed in pheochromocytoma from the adrenal gland but is not expressed in well-differentiated endocrine tumors of the lung, thyroid gland, parathyroid gland, carotid body, and ear. Barbareschi et al. [17] studied CDX2 gene product expression in neuroendocrine tumors and found that CDX2 was highly positive in well-differentiated neuroendocrine tumors of the ileum and appendix, weakly positive in well-differentiated neuroendocrine tumors of the stomach, duodenum, rectum, and pancreas, and negative in well-differentiated neuroendocrine tumors of the lung. Several previous studies revealed that CDX2 expression was positive in well-differentiated neuroendocrine tumors of the intestinal tract, mainly in the midgut [16, 17, 19-22], and pancreas [16, 17, 19, 20], but negative in well-differentiated neuroendocrine tumors of the lung [16, 17, 19-22]. In contrast, CDX2 expression was found in neuroendocrine carcinomas from various sites and was not specific to the intestine [16, 17]. These studies support that CDX2, which regulates intestinal development, is associated with the occurrence of neuroendocrine tumors of the midgut and pancreas and colonic adenocarcinoma.

4. Conclusion

The genetic abnormality of common cell origin might be one of the possible etiologies of our synchronous well-differentiated neuroendocrine tumor and adenocarcinoma of the colon based on the common endodermal origin of the colonic epithelial and endocrine cells and the

positivity of CDX2 staining. If a large number of cases of midgut neuroendocrine tumors with colonic adenocarcinoma can be collected, further genetic studies may be helpful in establishing the pathogenesis of these tumors. We recommend that close surveillance for synchronous tumors, especially those of the gastrointestinal tract, in patients with colorectal neuroendocrine tumors could be beneficial.

Acknowledgements

The authors would like to express their appreciation to Suranaree University of Technology Hospital for providing research funding, and Dr. Napasorn Orathiawan for generously providing the light microscope used for photographing the figures in this study.

References

[1] Program S. The SEER Program code manual: Third edition, Jan. 1998. [Bethesda, Md. ?] : Cancer Statistics Branch, Surveillance Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Dept. of Health and Human Services, 1998.; 1998.

[2] Tyczynski JE, Démaret E, Parkin DM. Standards and Guidelines for Cancer Registration in Europe: International Agency for Research on Cancer; 2003.

[3] Edge SB. AJCC cancer staging manual 8th ed. 8th ed. American Joint Committee on C, editor. New York: Springer; 2017.

[4] Tichansky DS, Cagir B, Borrazzo E, Topham A, Palazzo J, Weaver EJ, et al. Risk of second cancers in patients with colorectal carcinoids. Dis Colon Rectum. 2002;45(1):91-7.

[5] Habal N, Sims C, Bilchik AJ. Gastrointestinal carcinoid tumors and second primary malignancies. J Surg Oncol. 2000;75(4):310-6

[6] Brown NK, Smith MP. Neoplastic diathesis of patients with carcinoid. Report of a case with four other neoplasms. Cancer. 1973;32.

[7] Rivadeneira DE, Tuckson WB, Naab T. Increased incidence of second primary malignancy in patients with carcinoid tumors: case report and literature review. J Natl Med Assoc. 1996;88(5):310-2.

[8] Parra- Medina R, Moreno- Lucero P, Jimenez- Moreno J, Parra- Morales AM, Romero- Rojas A. Neuroendocrine neoplasms of gastrointestinal tract and secondary primary synchronous tumors: A systematic review of case reports. Casualty or causality? PLoS One. 2019;14(5):e0216647.

[9] Saha S, Hoda S, Godfrey R, Sutherland C, Raybon K. Carcinoid tumors of the gastrointestinal tract: a 44- year experience. South Med J. 1989;82(12):1501-5.

[10] Lancellotti F, Solinas L, Telesco D, Sagnotta A, Belardi A, Balsamo G, et al. A rare case of metachronous neuroendocrine tumor after a colorectal adenocarcinoma: qualitative critical review of synchronous and metachronous gastrointestinal NET. Clin J Gastroenterol. 2021;14(1):115-22.

[11] Shenoy S. Gastrointestinal carcinoids and colorectal cancers: is it a paracrine effect? Tumori. 2013;99(4):e141-3.

[12] de Santa Barbara P, van den Brink GR, Roberts DJ. Development and differentiation of the intestinal epithelium. Cell Mol Life Sci. 2003;60(7):1322-32.

[13] Andrew A, Kramer B, Rawdon BB. The embryonic origin of endocrine cells of the gastrointestinal tract. General and Comparative Endocrinology. 1982;47(2):249-65.

[14] Cox WF, Jr., Pierce GB. The endodermal origin of the endocrine cells of an

adenocarcinoma of the colon of the rat. Cancer. 1982;50(8):1530-8.

[15] Goldenberg DM, Fisher ER. Histogenetic relationship between carcinoids and mucin- secreting carcinomas of colon as revealed by heterotransplantation. Br J Cancer. 1970;24(3):610-4.

[16] La Rosa S, Rigoli E, Uccella S, Chiaravalli AM, Capella C. CDX2 as a marker of intestinal EC- cells and related well-differentiated endocrine tumors. Virchows Arch. 2004;445(3):248-54.

[17] Barbareschi M, Roldo C, Zamboni G, Capelli P, Cavazza A, Macri E, et al. CDX- 2 homeobox gene product expression in neuroendocrine tumors: its role as a marker of intestinal neuroendocrine tumors. Am J Surg Pathol. 2004;28(9):1169-76.

[18] Beck F. Homeobox genes in gut development. Gut. 2002;51(3):450-4

[19] Yang MX, Coates RF, Ambaye A, Cortright V, Mitchell JM, Buskey AM, et al. NKX2. 2, PDX- 1 and CDX- 2 as potential biomarkers to differentiate well-differentiated neuroendocrine tumors. Biomark Res. 2018;6:15.

[20] Srivastava A, Hornick JL. Immunohistochemical staining for CDX-2, PDX- 1, NESP- 55, and TTF- 1 can help distinguish gastrointestinal carcinoid tumors from pancreatic endocrine and pulmonary carcinoid tumors. Am J Surg Pathol. 2009;33(4):626-32.

[21] Lin X, Saad RS, Luckasevic TM, Silverman JF, Liu Y. Diagnostic value of CDX- 2 and TTF- 1 expressions in separating metastatic neuroendocrine neoplasms of unknown origin. Appl Immunohistochem Mol Morphol. 2007;15(4):407-14.

[22] Jaffee IM, Rahmani M, Singhal MG, Younes M. Expression of the intestinal transcription factor CDX2 in carcinoid tumors is a marker of midgut origin. Arch Pathol Lab Med. 2006;130(10):1522-6.