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# Gastric Small Cell Neuroendocrine Carcinoma With Loss of Epithelial Markers Expression

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**Abstract.** *Background/Aim: Given that gastric small cell neuroendocrine carcinoma (SCNEC) is notably more aggressive than conventional adenocarcinoma, and a platinum-based regimen aligned with the treatment for pulmonary SCNEC is advocated when chemotherapy is needed, ensuring an accurate pathological diagnosis is paramount. Case Report: A 63-year-old man, examined for melena, underwent gastroscopy which revealed a total circumferential Borrmann type 3 lesion extending from the pylorus to the antrum of the stomach. He underwent a distal gastrectomy with D2 lymphadenectomy. The microscopic examination revealed SCNEC with a minor adenocarcinoma component. Immunohistochemically, the SCNEC was diffusely positive for synaptophysin, CD56, and INSM1, very focally positive for chromogranin A, and negative for leukocyte common antigen, CD3, and CD20. A significant observation in this case was the complete negativity for epithelial markers including keratin (CK7, CK8, CK20, CAM5.2, and AE1/AE3) and epithelial membrane antigen. Conclusion: Diffuse positivity for neuroendocrine markers, negativity for other lineage markers, and a transition from the adenocarcinoma component, if present, serve as significant diagnostic clues for gastric SCNEC with loss of epithelial markers expression. SCNEC should not be excluded solely based on the negative result for epithelial markers.*

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Gastric neuroendocrine neoplasms comprise well-differentiated neuroendocrine tumors (formerly referred to as carcinoid tumors) and poorly differentiated neuroendocrine carcinomas (NECs). NECs represent less than 1% of gastric malignancies and are classified into small cell NEC (SCNEC) or large cell NEC, depending on their morphology (1). Given that gastric SCNEC is notably more aggressive than conventional adenocarcinoma, and a platinum-based regimen aligned with the treatment for pulmonary SCNEC is advocated when chemotherapy is needed, ensuring an accurate pathological diagnosis is paramount (2). Here, we report an unusual case of gastric SCNEC that is immunohistochemically negative for epithelial markers.

## Case Report

A 63-year-old man was referred to our hospital for a melena examination. His medical history included hypertension, type 2 diabetes mellitus, hyperlipidemia, chronic kidney disease, and a kidney donor. Gastroscopy revealed a total circumferential Borrmann type 3 lesion extending from the pylorus to the antrum of the stomach. Gastric cancer was suspected from the biopsy of the lesion, leading to a distal gastrectomy with D2 lymphadenectomy.

Macroscopically, the lesion measured 65×55 mm in size (Figure 1A). Microscopic examination revealed gastric cancer consisting of an intramucosal adenocarcinoma component and a submucosal poorly differentiated component that invaded the muscularis propria (Figure 1B). The latter was predominant, and the former measured 3 mm in size. Although both components were proximate, no continuity was observed. The adenocarcinoma component was of a well-differentiated type (Figure 1C). The poorly differentiated component, composed of small round or angulated cells with a high nuclear to

cytoplasmic ratio, fine granular, and hyperchromatic nuclei, inconspicuous nucleoli, and brisk mitotic activity, exhibited solid sheet growth with necrosis, resembling SCNEC (Figure 1D). Given the small size of the adenocarcinoma component and the lack of continuity between it and the poorly differentiated component resembling SCNEC, and considering that this was an early-stage case of gastric SCNEC, immunohistochemistry was performed to rule out a collision tumor composed of adenocarcinoma and malignant lymphoma. Immunohistochemically, the poorly differentiated component resembling SCNEC was positive for synaptophysin, CD56, and INSM1, focally positive for chromogranin A, and negative for keratin (CK7, CK8, CK20, CAM5.2, and AE1/AE3) and epithelial membrane antigen (EMA), while the adenocarcinoma component was positive for keratin (CK7, CK8, CAM5.2, and AE1/AE3), focally positive for keratin (CK20) and EMA, and negative for synaptophysin, chromogranin A, CD56, and INSM1 (Figure 1E-G). Both components were negative for vimentin, leukocyte common antigen (LCA), CD3, and CD20. The results of immunohistochemical staining for each component are summarized in Figure 1H. *In situ* hybridization for Epstein–Barr virus-encoded small RNA was negative. Although the loss of expression of epithelial markers is unusual for SCNEC, the poorly differentiated component was diagnosed as SCNEC based on neuroendocrine morphology, diffuse positivity for neuroendocrine markers, and the absence of other lineage markers. Since the adenocarcinoma component constituted less than 10% of the tumor, the classification of mixed neuroendocrine-non-neuroendocrine neoplasm was not applicable. Vascular invasion was noted, but no regional lymph node metastasis was detected. The pathologic stage of the gastric cancer was established as pT2, pN0, cM0, stage IB, according to the Union for International Cancer Control/American Joint Committee on Cancer 8$^{th}$ edition. He underwent four cycles of etoposide and cisplatin chemotherapy, and no evidence of recurrence or metastasis was detected 8 months after surgery.

## Discussion

Gastric SCNEC is composed of small round, ovoid, angulated, or spindle-like cells with minimal cytoplasm, hyperchromatic nuclei, and frequent mitoses, and exhibits growth in solid sheets with multifocal necrosis (3, 4). Although typical SCNEC can often be diagnosed based on morphology, immunohistochemistry is frequently employed for atypical cases or those posing diagnostic challenges, particularly when dealing with a limited amount of tumor tissue in biopsy specimens. More than 85% of gastric NEC cases are classified as stage III or IV; however, our current case was diagnosed at an early stage (5). Furthermore, due to the minimal size of the adenocarcinoma component and a lack of continuity with the SCNEC component, we conducted immunohistochemistry for confirmation. This was to exclude the possibility of a collision tumor, a rare confluence of adenocarcinoma and malignant lymphoma, as described in the literature (6, 7). Keratins, also known previously as cytokeratins, are intermediate filament-forming proteins that constitute the primary cytoskeletal components of epithelial cells (8). With fifty-four types of keratins known, each displaying highly specific expression patterns correlated with cellular differentiation, broad-spectrum keratin antibody cocktails serve as crucial tools in detecting epithelial differentiation within surgical pathology (8). AE1/AE3 is one of the most widely used broad-spectrum keratin antibody cocktails. It reacts with keratin K1-K8, K10, K14-16, and K19, exhibiting high sensitivity in detecting carcinomas in nearly all organs, with exceptions including hepatocellular, adrenal cortical, and certain renal cell carcinomas (9, 10). CAM5.2 is an antibody that reacts with keratin K8 and weakly with K7, demonstrating high sensitivity towards the vast majority of carcinomas and is commonly employed in screening for epithelial differentiation (9, 11). EMA, also known as cell surface-associated mucin 1, is a membrane-associated protein belonging to the mucin gene family. It is expressed on the apical surface of almost all glandular and ductal epithelial cells and is commonly found in most adenocarcinomas (9). Positive rates of AE1/AE3, CAM5.2, and EMA for gastric adenocarcinoma are 100%, while those for gastric SCNEC are 87%, 93%, and 67% respectively (12, 13). This indicates that a negative result for broad-spectrum epithelial markers does not necessarily exclude gastric SCNEC. Li *et al*. reported a case of gastric SCNEC that was negative for both keratin (AE1/AE3 and CAM5.2) and EMA, similar to the present case, in a series of 15 gastric SCNECs (13). The current case exhibited no reactivity for CK7, CK8, CK20 (reactive for keratin K7, K8, and K20 respectively) in addition to AE1/AE3, CAM5.2, and EMA. We previously reported a case of large cell neuroendocrine carcinoma in the sigmoid colon, characterized by a discohesive component resembling undifferentiated carcinoma and showing decreased expression of keratin (14). The present case further demonstrates that NEC can display lost or decreased expression of epithelial markers while maintaining its neuroendocrine morphology. Although the frequency of gastric SCNEC being completely negative for several epithelial markers is considered to be low, such a case can present a potential diagnostic pitfall. Diffuse positivity for neuroendocrine markers, negativity for other lineage markers, and a transition from the adenocarcinoma component, if present, serve as significant diagnostic clues for gastric SCNEC with loss of epithelial markers expression.

To summarize, we reported an unusual case of gastric SCNEC that is immunohistochemically negative for several epithelial markers. From a practical perspective, it is crucial for diagnostic pathologists to understand such cases to reach

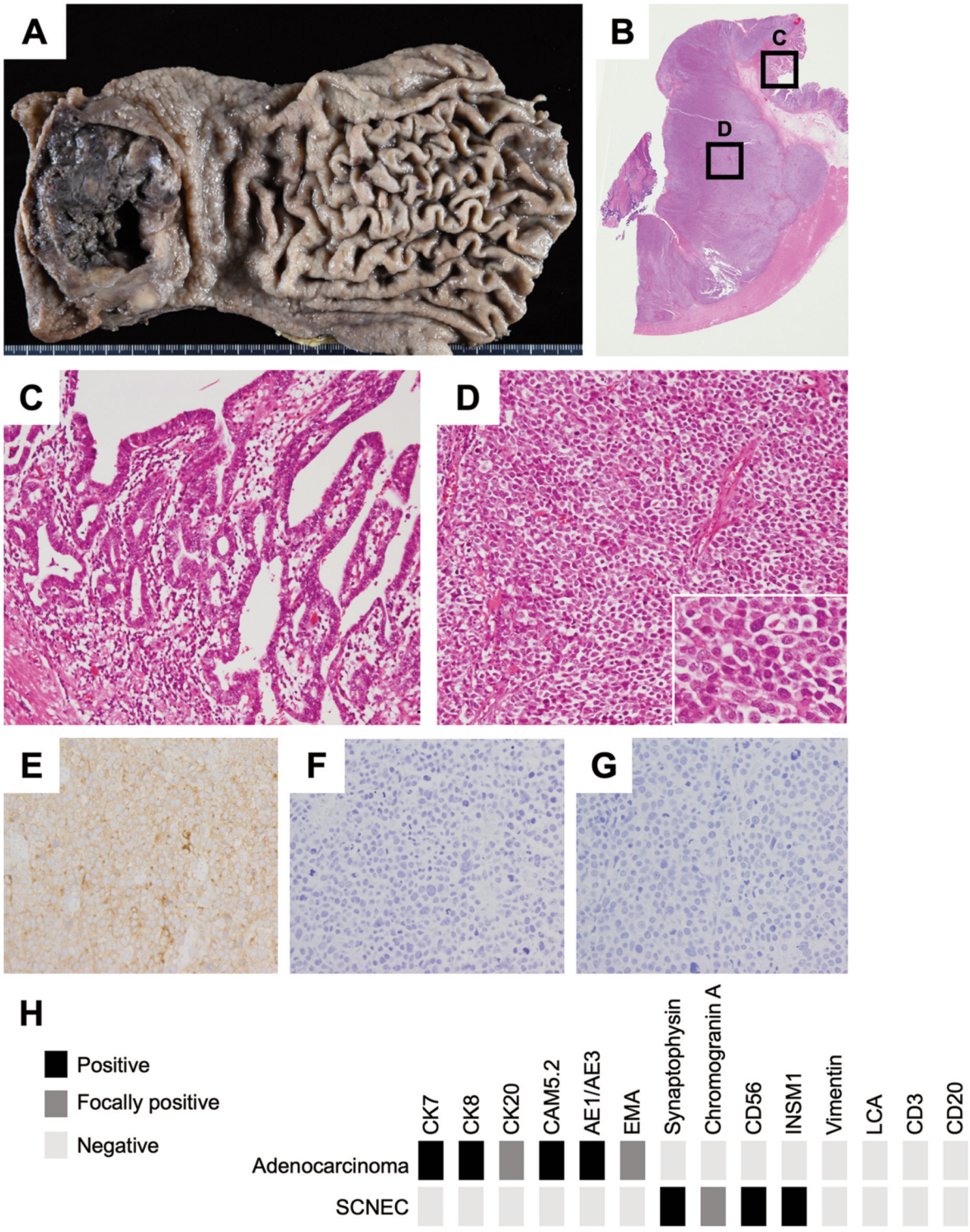


Figure 1. *Pathological findings. A) Macroscopic examination reveals a total circumferential Borrmann type 3 lesion extending from the pylorus to the antrum of the stomach. B) A loupe image shows gastric cancer consisting of an intramucosal adenocarcinoma component (C) and a submucosal poorly differentiated component that invades the muscularis propria. C) Microscopic examination reveals that the adenocarcinoma component is of a well-differentiated type. D) The poorly differentiated component, composed of small round or angulated cells with a high nuclear to cytoplasmic ratio, fine granular, and hyperchromatic nuclei, inconspicuous nucleoli, and brisk mitotic activity, exhibits solid sheet growth with necrosis, resembling SCNEC. The inset shows a high magnification image. E-G) Immunohistochemical findings show that the poorly differentiated component is positive for synaptophysin (E) and negative for both keratin (AE1/AE3) (F) and EMA (G). H) Results of the immunohistochemical staining for each component.*

an accurate diagnosis. SCNEC should not be excluded solely based on the negative result for epithelial markers.

## Conflicts of Interest

All Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

RY designed the study and drafted the manuscript and histological images. SU, KY, and SH provided clinical details. YK edited and reviewed the manuscript. All Authors gave final approval for publication.

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## References

1 Niederle MB, Hackl M, Kaserer K, Niederle B: Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. Endocr Relat Cancer 17(4): 909-918, 2010. DOI: 10.1677/ERC-10-0152

2 Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, Sedlackova E, Toumpanakis C, Anlauf M, Cwikla JB, Caplin M, O'Toole D, Perren A Vienna Consensus Conference participants: ENETS Consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology 103(2): 186-194, 2016. DOI: 10.1159/000443172

3 Gonzalez RS: Diagnosis and management of gastrointestinal neuroendocrine neoplasms. Surg Pathol Clin 13(3): 377-397, 2020. DOI: 10.1016/j.path.2020.04.002

4 Mastracci L, Rindi G, Grillo F, Solcia E, Campora M, Fassan M, Parente P, Vanoli A, La Rosa S: Neuroendocrine neoplasms of the esophagus and stomach. Pathologica 113(1): 5-11, 2021. DOI: 10.32074/1591-951X-229

5 Vanoli A, La Rosa S, Miceli E, Klersy C, Maragliano R, Capuano F, Persichella A, Martino M, Inzani F, Luinetti O, Di Sabatino A, Sessa F, Paulli M, Corazza GR, Rindi G, Bordi C, Capella C, Solcia E: Prognostic evaluations tailored to specific gastric neuroendocrine neoplasms: analysis of 200 cases with extended follow-up. Neuroendocrinology 107(2): 114-126, 2018. DOI: 10.1159/000489902

6 Kobayashi K, Furukawa K, Ishikawa E, Mitsuma A, Funasaka K, Kakushima N, Furune S, Ito N, Wada H, Hirose T, Muroi K, Suzuki T, Suzuki T, Hida E, Hirai K, Shibata H, Koya T, Nakamura M, Kawashima H, Miyahara R, Fujishiro M: Collision tumors of gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. Intern Med 60(15): 2419-2424, 2021. DOI: 10.2169/internalmedicine.6124-20

7 Liu L, Zhao H, Sheng L, Yang P, Zhou H, Wang R: Collision of lymphoepithelioma-like carcinoma with diffuse large B-cell lymphoma of the stomach: a case report. Anticancer Res 37(8): 4569-4573, 2017. DOI: 10.21873/anticanres.11855

8 Schweizer J, Bowden PE, Coulombe PA, Langbein L, Lane EB, Magin TM, Maltais L, Omary MB, Parry DA, Rogers MA, Wright MW: New consensus nomenclature for mammalian keratins. J Cell Biol 174(2): 169-174, 2006. DOI: 10.1083/jcb.200603161

9 Ordóñez NG: Broad-spectrum immunohistochemical epithelial markers: a review. Hum Pathol 44(7): 1195-1215, 2013. DOI: 10.1016/j.humpath.2012.11.016

10 Cooper D, Schermer A, Sun TT: Classification of human epithelia and their neoplasms using monoclonal antibodies to keratins: strategies, applications, and limitations. Lab Invest 52(3): 243-256, 1985.

11 Smedts F, Ramaekers F, Robben H, Pruszczynski M, van Muijen G, Lane B, Leigh I, Vooijs P: Changing patterns of keratin expression during progression of cervical intraepithelial neoplasia. Am J Pathol 136(3): 657-668, 1990.

12 Pan CC, Chen PC, Tsay SH, Ho DM: Differential immunoprofiles of hepatocellular carcinoma, renal cell carcinoma, and adrenocortical carcinoma. Appl Immunohistochem Mol Morphol 13(4): 347-352, 2005. DOI: 10.1097/01.pai.0000146525.72531.19

13 Li AF, Li AC, Hsu CY, Li WY, Hsu HS, Chen JY: Small cell carcinomas in gastrointestinal tract: immunohistochemical and clinicopathological features. J Clin Pathol 63(7): 620-625, 2010. DOI: 10.1136/jcp.2010.077024

14 Yamada R, Nakahara O, Takamori H, Komohara Y, Fujiwara M: Large cell neuroendocrine carcinoma with discohesive growth pattern of the sigmoid colon resembling undifferentiated carcinoma. Pathol Int, 2023. DOI: 10.1111/pin.13384

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