A Case of Gastric Amphicrine Signet-Ring Cell Carcinoma

Clinical Pathology
Volume 12: 1–3

DOI: 10.1177/2632010X19880535

Yuki Hanamatsu[1], Chiemi Saigo[1], Nami Asano[2], Yusuke Kito[1], Kazuhiko Nakada[3], Yohei Takeda[3] and Tamotsu Takeuchi[1]

[1]Department of Pathology and Translational Research, Gifu University School of Medicine, Seki, Japan. [2]Department of Pathology, Chuno Kosei Hospital, Seki, Japan. [3]Department of Surgery, Chuno Kosei Hospital, Seki, Japan.

ABSTRACT: "Amphicrine" (in Greek, *amphi-* means "both" or "double") refers to cells that synchronously exhibit the endocrine and exocrine phenotypes. Gastric amphicrine carcinoma is very rare, and only a few case reports are found in the English literature; thus, its pathobiological features remain unclear. Here, we report a case of amphicrine gastric carcinoma. A woman in her sixth decade of life presented with anemia and underwent upper endoscopy, followed by histopathological examination of biopsy specimens. She appeared to have gastric cancer with a tumor measuring 5.0 cm × 4.0 cm in size. Subsequently, the patient underwent total gastrectomy with lymph node dissection. Histopathological examination revealed a poorly cohesive carcinoma that sparsely coexisted with signet-ring cell carcinoma cells with regional lymph node metastasis. Interestingly, synaptophysin immunoreactivity with the coexistence of Alcian blue was found in individual signet-ring cell carcinoma cells. Furthermore, the present amphicrine carcinoma cells immunohistochemically expressed CD44 variant 9, a functional cancer stem cell marker. We believe that the present case findings may support the idea of multipotent stem cells being an origin of amphicrine gastric cancers.

KEYWORDS: Amphicrine tumor, gastric cancer, CD44v9, multipotent stem cell

RECEIVED: July 24, 2019. **ACCEPTED:** September 12, 2019.

TYPE: Case Report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Chiemi Saigo, Department of Pathology and Translational Research, Gifu University School of Medicine, Seki 501-1194, Gifu, Japan.
Email: gifuapthology@aol.com

Feyrter[1] first proposed the concept of the "endocrine epithelial system" to indicate the coexistence of endocrine and exocrine secretory products in single cells. Later, Ratzenhoffer and Leb[2] advocated the use of the word "amphicrine" (Gk: *amphi-* means "both" or "double") to refer to cells that synchronously exhibit the endocrine and exocrine phenotypes. Investigators have reported the amphicrine phenotype in physiological and pathological cells, including those present in tumors of the gastrointestinal tract. However, few reports have described amphicrine differentiation in gastric cancer.[3-5] Therefore, the pathobiological and clinicopathological features of amphicrine gastric cancer remain unclear. Here, we report a case of amphicrine gastric cancer.

A woman in her sixth decade of life underwent follow-up for 10 years after surgical treatment for breast cancer. She had no signs of *Helicobacter pylori* on a urea breath test or history of intake of any proton pump inhibitors. She presented with anemia and had undergone upper endoscopy.

She appeared to have a gastric tumor in the corpus. Tissue specimen biopsy revealed a poorly cohesive carcinoma that sparsely coexisted with signet-ring cell carcinoma cells. Subsequently, the patient underwent total gastrectomy with lymph node dissection. The resected tumor measured 5.0 cm × 4.0 cm in size (Figure 1). The tumor had extended to the surface of the serosa with regional lymph node metastasis. The patient was accordingly diagnosed with $T_{4a}N_2M_0$, Stage-IIIA (8th edition of tumor–node–metastasis staging by the American Joint Committee on Cancer/Union for International Cancer Control) gastric cancer.

In surgically resected tissue specimens, a poorly cohesive carcinoma harboring 2 distinct phenotypes of signet-ring cell carcinoma cells were detected—cells with eosinophilic and somewhat granular cytoplasm (Figure 2A) or pale cytoplasm (Figure 2B). We also observed a carcinoid-like tumor cell nest around the signet-ring cells (Figure 2C).

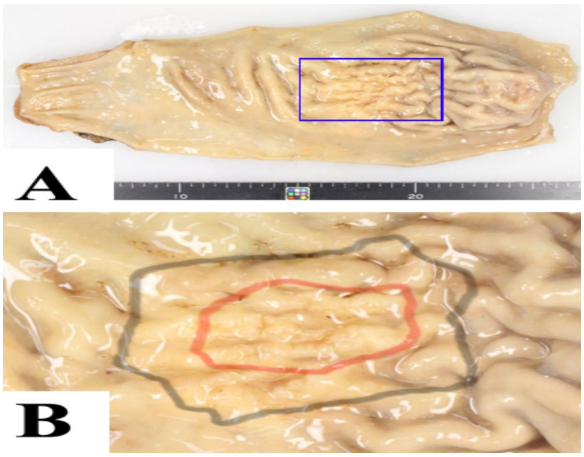

Figure 1. Because the present tumor was located in the greater curve of the corpus, the resected stomach was opened along the lesser curvature of the stomach. The tumor was found in the corpus within the square range highlighted by the blue line (A). Histopathological examination revealed that a carcinoid-like tumor cell nest was located in the center of the tumor, within the red circle, while signet-ring cell carcinoma cells were distributed in the whole area of the tumor, within the black circle (B).

Subsequently, we performed immunohistochemical staining using a specific antibody against synaptophysin, an integrated part of the neuroendocrine secretory granule membrane, which is broadly used as a protein marker for neuroendocrine cells.[6]

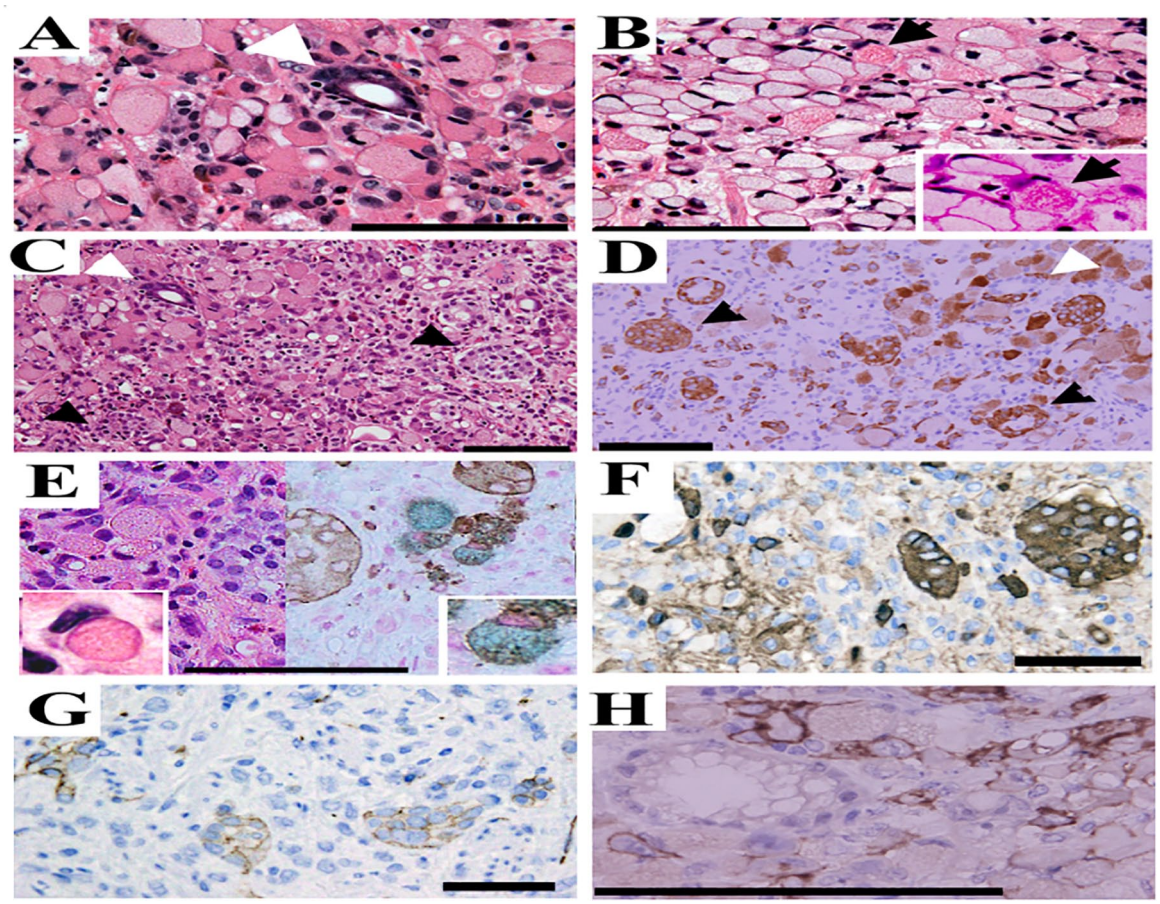

Figure 2. Poorly cohesive carcinoma harboring 2 distinct phenotypes of signet-ring cell carcinoma cells—cells with eosinophilic and somewhat granular cytoplasm (A and B). Note the signet-ring cell carcinoma with eosinophilic granules indicated by black arrow. We also observed a carcinoid-like tumor cell nest (black arrowheads) around the signet-ring cells (C). Note the synaptophysin immunoreactivity in the carcinoid-like nested tumor cells (black arrowheads) and also in the signet-ring cell carcinoma cells (D). We confirmed the coexistence of synaptophysin immunoreactivity and Alcian blue (pH 2.5) staining in individual signet-ring cell carcinoma cells, which harbored eosin-stained abundant granular cytoplasm in a mirror image tissue section (E). Both chromogranin and CD56 immunoreactivity were found in cancer cells (F and G, respectively). Interestingly, the CD44v9 immunoreactivity was found in the present gastric cancer cells (H). Scale bar: 100 μm. White arrow indicates the same tubular structure to facilitate quick understanding of tissue location.

Immunohistochemical staining was performed as previously reported.[7] Notably, both carcinoid-like nested tumor cells and signet-ring cell carcinoma cells were stained by anti-synaptophysin antibody (Figure 2D). As expected, signet-ring cell carcinoma cells exhibited periodic acid–Schiff and/or Alcian blue (AB) (pH 2.5) positivity. We confirmed the coexistence of synaptophysin immunoreactivity and AB staining in individual signet-ring cell carcinoma cells, which harbored eosin-stained abundant granular cytoplasm (Figure 2E). In addition, we also found chromogranin and CD56 immunoreactivity in the present cancer cells (Figure 2F and G). These findings indicated that the poorly cohesive carcinoma contained amphicrine signet-ring cell carcinoma cells with eosinophilic cytoplasm.

CD44 variant 9 (CD44v9) marks a population of cancer stem cells, which are able to form tumors as well as regenerate the original tumor heterogeneity.[8] Subsequently, immunohistochemical staining was performed using specific antibody to CD44v9 (Cat No. CAC-LKG-M001, Cosmo Bio, Tokyo, Japan). Interestingly, we found CD44v9 immunoreactivity in signet-ring cell carcinoma cells (Figure 2H). The presence of CD44v9-expressing cells might suggest that the present amphicrine cell would have a phenotype of progenitor cell. To our knowledge, this is also the first report of amphicrine signet-ring cell carcinoma with eosinophilic cytoplasm.

Acknowledgements

The authors wish to thank Ms Reiko Shinoda for her technical assistance.

Author Contributions

All authors were involved in the diagnosis or treatment of the patient. YH, CS, and TT drafted the manuscript.

ORCID iD

Chiemi Saigo https://orcid.org/0000-0002-1537-0093

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