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Research Article

Using Tumor Registration Information to Identify Neuroendocrine Carcinomas of the Stomach

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Abstract

Objective: To identify neuroendocrine carcinomas of the stomach using tumor registration data.

Design: Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute from 2000-2015. Linear plots, double logarithmic plots, and frequency density plots compared age of diagnosis and age specific incidence rates of gastric adenocarcinomas, NOS; intestinal type carcinomas; diffuse type carcinomas; signet ring cell carcinomas; and carcinoids.

Results: Adenocarcinomas, NOS were most frequently reported. Double logarithmic plots of age at diagnosis and age specific incidence rates generated near parallel rates for adenocarcinomas, NOS and intestinal type carcinomas indicating that the carcinogenic pathways of these tumors were similar. The rates for diffuse carcinomas and signet ring cell carcinomas were graphically related but different from adenocarcinomas. The rates for signet ring cell carcinomas and diffuse type carcinomas were approximately parallel to carcinoid tumors on double logarithmic plots even though incidence rates were different. The age frequency density plot for signet ring cell carcinomas was isomorphic with the plot for diffuse carcinomas and carcinoid tumors, but not with adenocarcinomas, NOS or intestinal type carcinomas.

Conclusions: Compared to carcinoids of the stomach, the graphical patterns indicate that diffuse types of gastric cancers and signet ring cell carcinomas are neuroendocrine tumors, which explains the expression of neuroendocrine related markers in these tumors.

Keywords: Gastric cancer; Neuroendocrine tumor; Cancer registration; Pathology

Introduction

Pathologists have long observed that malignant tumors of the gastrointestinal tract occasionally express varying proportions of glandular epithelial cells, signet ring cells, and endocrine cells [1-25]. For this report, we took advantage of tumor registry data to demonstrate that diffuse types of gastric cancer and signet ring cell carcinomas are neuroendocrine tumors in addition to gastric carcinoids. Our analysis, which involves double logarithmic plots of incident data, was used historically to investigate the increase in the rate of cancer with age [26,27]. In this study, we used log-log plots to compare the age specific incident rates of selected histopathological tumor types found in the stomach. These results may have relevance for gastric tumors often described as mixed or composite exocrine-neuroendocrine carcinomas.

Materials and Methods

Data were obtained from the SEER (Surveillance, Epidemiology, and End Results) Program of the National Cancer Institute. Age adjusted incident rates (2000 U.S. standard population) were calculated for gastric adenocarcinomas, NOS (Not Otherwise Specified), intestinal type adenocarcinomas, diffuse type carcinomas, signet ring cell carcinomas, and carcinoids and expressed as the number of cases per 100,000 persons per year. Age adjustment avoids the confounding with the variable distribution of age in different geographical regions covered by SEER. The size of the SEER database allows for the analysis of individual histopathological tumor types. Age-adjusted rates calculated at 5-year intervals for these individual cancers were plotted on linear as well as on double logarithmic scales. Data were obtained from SEER Registry 18 from 2000-2015. Initiated in 1973, SEER now covers approximately 35% of the population. Cases from all racial/ethnic groups and men and women were combined. Cases identified by death certificate or autopsy only were excluded. Data listed in SEER represents the diagnosis submitted by the attending pathologist. Our analysis was limited to cases less than 85 years since patients more than 85 years at time of diagnosis were assigned by SEER to a single category (85+) and not stratified by 5-year age intervals.

Histopathologic codes

In SEER, the histopathologic types of cancers are coded from pathology reports according to the *International Classification of Diseases for Oncology* (ICD-O)published by the World Health Organization (2000). Only codes for malignant tumors were used. Table 1 lists the ICD-O codes, number of cases available for each code, and the histopathologic tumor types. The ICD-O does contain

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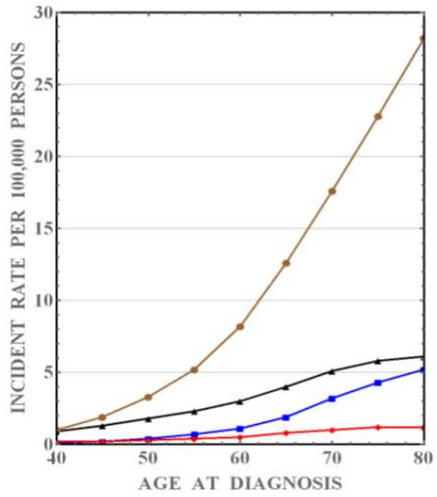

Figure 1: Age specific incident rates for gastric adenocarcinomas, NOS (brown), intestinal type carcinomas (blue), signet ring cell carcinomas (black), and for the diffuse type of carcinoma (red). Data taken from the SEER Program 2000-2015.

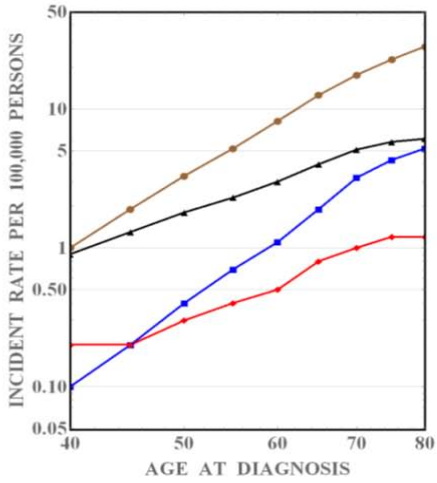

Figure 2: Log-log plots for the age specific incident rates shown in Figure 1 for gastric adenocarcinomas, NOS (brown), intestinal type carcinomas (blue), diffuse type of carcinoma (red), and for signet ring cell carcinoma (black). The plots for adenocarcinomas, NOS and intestinal type carcinomas are nearly parallel whereas the log-log plot for signet ring cell carcinomas and the diffuse type have a different slope. The different slopes for signet ring cell carcinoma and the diffuse type imply different carcinogenic pathways than for adenocarcinomas, NOS, and intestinal type carcinomas.

a code assigned for "mixed adenocarcinoma-carcinoid tumors." However, only 39 cases have been reported. Secondary slide review of the histopathological data recorded in SEER is not possible.

Data analysis

Log-log transformation: Investigators have taken advantage of logarithmically scaled plots of population data to study both rates and origins of human cancer [26,28]. With double log plots, a straight line is obtained whose slope represents the aggregated summation of all cellular and molecular events occurring during carcinogenesis. Double log plots were constructed as the log-age at presentation versus the log-specific incident rate of cancer. For log-log plots, the natural

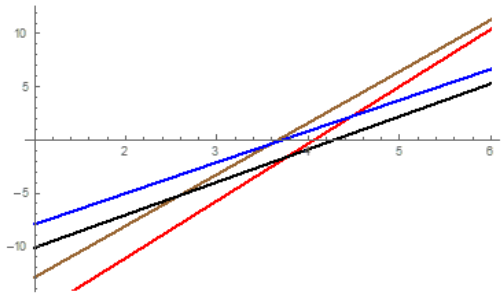

Figure 3: Optimal linear mathematic fit for the rates in Figure 2 showing the relationship when the log-log plot is re-plotted as the best linear fits according to the equation for a straight line, that is, y=mx+c. Lines correspond to the data produced in the log-log plot (Figure 2) and reveal different slopes for adenocarcinoma, NOS, and the intestinal type compared to the diffuse type and to signet ring cell tumors. Adenocarcinoma, NOS=brown, signet ring cell carcinoma=blue, intestinal type =red, and the diffuse type=black.

logarithm was used as base. All calculations were accomplished using Mathematica® a commercial computer program (Wolfram Research, Champagne, Illinois).

Log-log plots were generated as follows: Let I_A denote the incidence of cancer for histopathological type A and I_B denote the incidence for type B. If the plots of incidence rates against age are two straight lines in the log-log scale for two cell types, we have

$$\log\left(I_A\left(Age\right)\right) = r\log\left(Age\right) + C_A \left(I_A\left(Age\right) = Age^r e^{C_A}\right)$$

$$\log\left(I_B\left(Age\right)\right) = r\log\left(Age\right) + C_B \left(I_B\left(Age\right) = Age^r e^{C_B}\right)$$

where r denotes the common slope and C_A and C_B denote the intercepts for tissue A and tissue B, respectively. Both I_A and I_B increase polynomially in degree r with age. Furthermore,

$$I_A\left(Age\right) / I_B\left(Age\right) = e^{C_A - C_B}$$

That is, I_A and I_B are proportional by a constant $e^{C_A - C_B}$.

If two plots are not straight lines but have equal distance, we have,

$$\log\left(I_A\left(Age\right)\right) = \log\left(I_B\left(Age\right)\right) + C$$

Then we have,

$$I_A\left(Age\right) / I_B\left(Age\right) = e^C$$

Age Frequency Density: To evaluate age distributions, the age frequency density for age at diagnosis was compared for each year until age 100 using linear scales. These plots represent the relative frequency of the age at diagnosis for each year for each cancer type with a total probability of 1.0 for the population.

Results

Incident rates

The age specific incident rates for 4 gastric cancers reported as adenocarcinoma, NOS, intestinal type carcinoma, diffuse type carcinoma, and signet ring cell carcinoma were calculated and plotted at 5-year intervals to age 85 (Figure 1). Cases reported as adenocarcinomas, NOS were clearly most common. Variations in the reported incidence of all 4 cancers were expected. In Figure 2, the log-log plots of the incidence rates (plotted in Figure 1)are compared for the 4 histopathologic types. On a log-log plot (Figure 2), linear rate

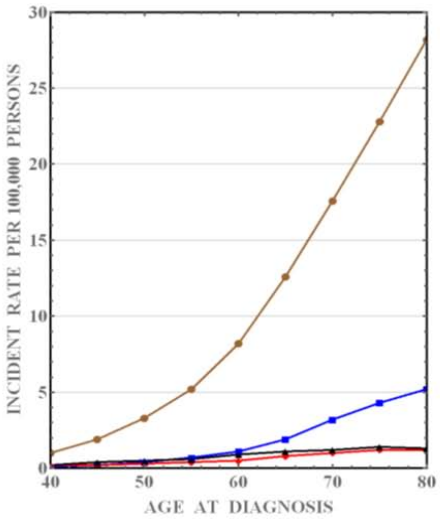

Figure 4: Age specific incident rates for gastric adenocarcinomas, NOS (brown), intestinal type carcinomas (blue), diffuse type of carcinoma (red), and carcinoids (black). Data taken from the SEER Program 2000-2015.

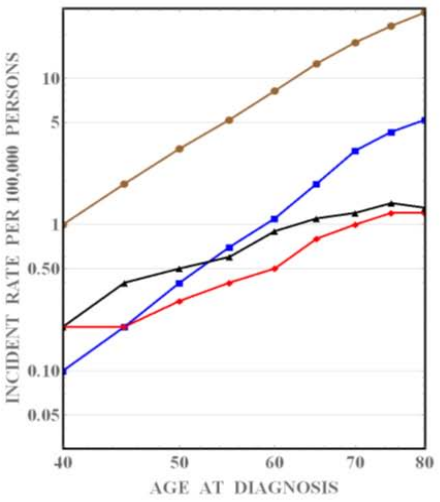

Figure 5: Log-log plots of the age specific incident rates shown in Figure 4 for gastric adenocarcinomas, NOS (brown), intestinal type carcinomas (blue), diffuse type carcinomas (red), and carcinoids (black). The lines for adenocarcinomas, NOS and intestinal type carcinomas are nearly parallel whereas the log-log plot for carcinoids and the diffuse type have different slopes. The plots for carcinoids and the diffuse type are considered proportional. The slopes for carcinoids and the diffuse type indicate different carcinogenic pathways than for adenocarcinomas and intestinal type carcinomas.

patterns indicate that age specific rates are increasing exponentially since relatively straight lines were generated. Note that rates (Figure 2) for adenocarcinomas and intestinal type carcinomas are proportional when plotted as logarithms whereas the rates for the diffuse type and for signet ring cell carcinomas have different slopes when plotted as logarithms. Figure 3 shows the mathematical optimal linear fits for the log-log plots shown in Figure 2, graphically confirming that rates for adenocarcinomas and intestinal type carcinomas are different from the diffuse type and signet ring cell carcinomas.

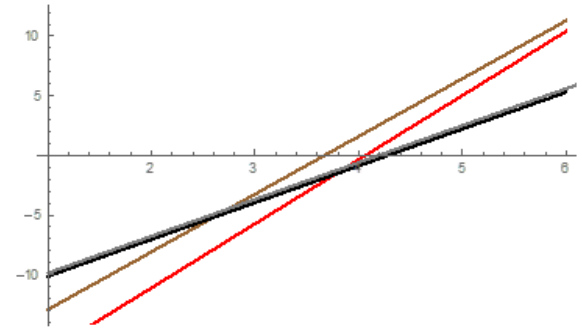

Figure 6: Optimal linear mathematic fits for the rates in Figure 5 showing the relationship when the log-log plot is re-plotted as best linear fit according to the equation for a straight line, that is, y=mx+c. Lines correspond to the data produced in the log-log plot (Figure 5) and indicate that adenocarcinomas, NOS and intestinal type carcinomas have significantly different slopes than the diffuse type and carcinoids. Adenocarcinoma, NOS=brown, diffuse type=gray, intestinal type =red, and carcinoids=black. Note that the lines for the diffuse type and for carcinoids overlap.

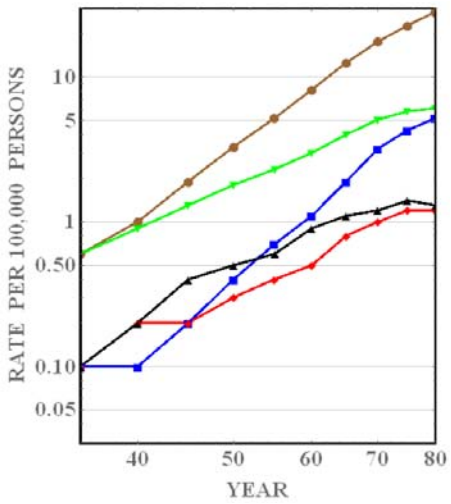

Figure 7: Log-log plots of 5 cancers. Adenocarcinomas, NOS (brown), intestinal type (blue), signet ring cell carcinomas (green), diffuse types (red), and carcinoids (black). The plots for adenocarcinomas, NOS and the intestinal type do not follow the plots for the other three cancers, since their slopes are different but follow the slope for carcinoid tumors. Well-behaved straight lines cannot be attained when the total number of cases is less than 5,000 due to variations of diagnosis within each 5-year age group.

Figure 4 compares age specific incident rates of adenocarcinomas, NOS, and intestinal type carcinomas with the diffuse type and with carcinoids. Figure 5compares the log-log plots for the same tumor types. The rates are considered proportional for the diffuse type and carcinoids even though the number of cases is relatively low, especially below age 45, and, therefore, do not generate ideal straight lines. Figure 6 shows the optimal mathematical linear fits for the log-log plots comparing the incident rates of adenocarcinomas, NOS and intestinal types with the diffuse type and carcinoids of the stomach. Thus, diffuse types and carcinoids constitute a different population than adenocarcinomas, NOS and intestinal type carcinomas because they develop at significantly different rates. Figure 7 compares the rate, plotted as a log, for adenocarcinoma, NOS with the rates for

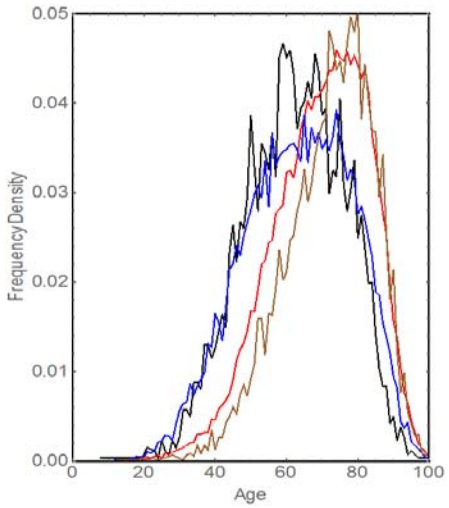

Figure 8: Frequency density analysis. The frequency density for carcinoids (blue) and signet ring cell carcinomas (black) is isomorphic indicating the these tumors primarily arise within the same age group. The red curve represents the frequency density for adenocarcinomas of the stomach and the brown curve the frequency density for intestinal type carcinomas. The density analyses for adenocarcinomas, NOS and intestinal type carcinomas is shifted to the older age groups.

signet ring cell carcinomas, diffuse type, and carcinoids also plotted as logs.

Age frequency density

The age frequency density was isomorphic for signet ring cell carcinomas and carcinoids whereas the frequency density for adenocarcinomas, NOS and intestinal type carcinomas was shifted to the right into the older age groups (Figure 8). Therefore, the age frequency indicates that the age distribution of signet ring cell carcinomas and carcinoids is congruent and differs from that of adenocarcinomas and intestinal type carcinomas. Although the data are not shown, the age frequency distribution for diffuse type carcinomas overlapped with the signet ring cell type and carcinoids. The mean age at diagnosis for diffuse type carcinomas is 64.2 years, signet ring cell carcinomas 63.2 years and for carcinoids it is 62.1. For adenocarcinomas, NOS it is 69.7 and for intestinal types it is 72.1 years.

Discussion

Human data can have many deficiencies and, therefore, should be carefully interpreted. Using tumor registry information to analyze specific histopathological tumor types may be justifiably questioned, since a registry accrues cases with input from multiple pathologists, from multiple institutions, and from different geographical regions. This diversity could lead to variations in interpretation and reporting, which should be acknowledged. Although this diversity which is based on the subjective interpretation of tumor types must be considered, our conclusions were based on the different angles of the slopes in the log-log plots and not on the number of incorrect or correct diagnoses reported. The slopes do not depend on the number of cases reported or accuracy of diagnosis, but on the mix of cancer types reported and the detailed coding structure of ICO-O. Because of the potential for error, relatively large numbers of cases which are found

Table 1:

ICD-O Code	Tumor Type	No. of Cases
8140	Adenocarcinoma, NOS	42,416
8144	Intestinal Type Carcinoma	6,598
8490	Signet Ring Cell Carcinoma	15,637
8240	Carcinoid, NOS	4,025
8145	Diffuse Type Carcinoma	2,966

in tumor registries are usually required to generate the slopes. For example, if the diffuse type of gastric cancer is incorrectly reported as adenocarcinoma and all the tumors are assigned the ICD-O code number for adenocarcinoma, then a single slope representing both cancers would be generated because of a single code number for adenocarcinoma despite the relative number of cases. If, on the other hand, some cases were properly reported as the diffuse type and assigned the appropriate ICD-O code, then the slopes would be different if the tumor types developed at different rates indicating different types of cancer.

Our conclusion that the diffuse type of gastric carcinoma and signet ring cell carcinomas are neuroendocrine tumors depends on observations made 65 years ago that age of diagnosis and age specific incidence rates generated straight lines when plotted as logarithms [26]. It was also observed that rates of cancer increased approximately 6 times faster than age [26]. These observations led to the hypothesis that cancer required a series of "hits" which led to the concept for the multistage process of carcinogenesis [26]. If these "hits" were similar for neuroendocrine cell tumors and adenocarcinomas of the stomach, then these two populations of tumor cells should have near parallel curves in the log-log plots, which was not observed. On the other hand, due to similar parallel rates in the log-log plots, cancers reported as adenocarcinomas, NOS are pathogenically similar to cancers more precisely reported as intestinal type. Based on our results, gastric cancers reported as the diffuse type, signet ring cell type, or carcinoids are neuroendocrine tumors.

The relationship between carcinomas and neuroendocrine tumors of the stomach has been controversial. The initial description of a mixed tumor containing exocrine and neuroendocrine elements was published almost 100 years ago in 1924 [29]. Signet ring cell carcinomas arising in the stomach are usually associated with the diffuse type of gastric cancer. Moreover, pathologists have documented that carcinomas arising in other parts of the gastrointestinal tract may contain mixed cell types some of which express electron-dense granules specific for neuroendocrine cells [30].

Pathologists have speculated on the origin and significance of these unusual mixed tumors. Various descriptive terms have been applied such as collision tumors, mixed tumors, amphicrine tumors, composite glandular-endocrine tumors, argentaffin cell adenocarcinoma, and assorted combinations [19]. Various classifications have been proposed often based on clinical outcome, proportions of different tumor types, or extent of differentiation of individual components [31,32]. In recognition of these mixed-cell carcinomas, the WHO in 2010 formally designated these tumors as "mixed adeno neuroendocrine carcinomas" (MANECs). By definition, each component of a mixed adeno neuroendocrine

carcinoma should represent at least 30% of the tumor [19,33].

It has been proposed that in log-log plots the slope is a biological constant characteristic of the tissue in which the cancer has been initiated [28]. Furthermore, the slope represents the aggregated accumulation of all molecular and cellular events occurring during carcinogenesis regardless of the number of "hits". Since we observed that:1) the slopes in the log-log plots for adenocarcinomas and intestinal types of gastric cancers are different from the slopes for the diffuse types of gastric cancer including signet ring cell tumors and carcinoids, thereby indicating different mechanisms of malignant transformation, 2) the graphical patterns revealed that log-log plots for the diffuse types and signet ring cell carcinomas were congruent with carcinoids, and 3) the age frequency density distribution was isomorphic for the diffuse types of cancer, signet ring cell tumors and carcinoids. Furthermore, the observation that endocrine related tumors originate at an earlier age than adenocarcinomas may argue against these tumors arising from a common cell of origin followed by divergent differentiation, an argument that has been frequently considered.

Perhaps it should be noted that our conclusions are consistent with histochemical observations. It has been proposed that signet ring cells are derived from neurological and neuroendocrine cells based on expression of synaptophysin and chromogranin A [1,34]. Furthermore, enterochromaffin-like cells (ECL) were found in 40% of diffuse gastric carcinomas but were not found in intestinal type tumor cells [2]. Others have concluded that neuroendocrine and especially ECL cell-derived tumors were more frequent in the stomach than previously suspected [35]. Signet ring cells often lack neutral and acid mucins, which is usually consistent with cells showing neuroendocrine differentiation [20,22].

Histopathologic data collected by tumor registries may provide additional research opportunities, since studies can be conducted on large cohorts. Previously, we showed that log-log plots were able to define carcinogenic fields and that carcinoids of the lung do not develop at the same rate as other lung cancers [36,37]. Our conclusions about gastric mixed tumors may apply to goblet cell carcinomas of the appendix and other tissues in which mixed exocrine-neuroendocrine tumors have been reported, although this requires investigation [35,38].

In summary, graphical analysis of tumor registry data indicates that gastric cancers reported as adenocarcinomas, NOS are pathogenically similar to cancers reported as intestinal type. In contrast, diffuse type of gastric cancers and signet ring cell types are neuroendocrine tumors similar to gastric carcinoids, which may explain the presence of neuroendocrine markers occasionally found in these carcinomas. Perhaps, all gastric tumors containing neuroendocrine elements belong to the diffuse type, including mixed tumors.

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References

1. Bakkelund K, Fossmark R, Nordrum I, Waldum H. Signet ring cells in gastric carcinomas are derived from neuroendocrine cells. J Histochem Cytochem. 2006; 54: 615-621.
2. Waldum HL, Aase S, Kvetnoi I, Brenna E, Sandvik AK, et al. Neuroendocrine differentiation in human gastric carcinoma. Cancer. 1998; 83: 435-444.
3. Ulich TR, Kollin M, Lewin KJ. Composite gastric carcinoma: report of a tumor of the carcinoma-carcinoid spectrum. Arch Pathol Lab Med. 1988; 112: 91-93.
4. Fujiyoshi Y, Kuhara H, Eimoto T. Composite glandular-endocrine cell carcinoma of the stomach. Report of two cases with goblet cell carcinoid component. Pathol Res Pract. 2005; 200: 823-829.
5. Ali MH, Davidson A, Azzopardi JG. Composite gastric carcinoid and adenocarcinoma. Histopathology. 1984; 8: 529-536.
6. Rayhan N, Sano T, Qian ZR, Obari AK Hirokawa M. Histological and immunohistochemical study of composite neuroendocrine-exocrine carcinomas of the stomach. J Med Invest. 2005; 52: 191-202.
7. Jain D, Eslami-Varzaneh F, Takano A. Ayer U, Umashankar R, Muller R, et al. Composite glandular and endocrine tumors of the stomach with pancreatic acinar differentiation. Am J Surg Pathol. 2005; 29: 1524-1529.
8. Adhikari D, Conte C, Eskreis D, Urmacher C, Kahn E. Combined adenocarcinoma and carcinoid tumor in atrophic gastritis. Ann Clin Lab Sci. 2002; 32: 422-427.
9. Blumenfeld W, Chandhoke KD, Sagerman P, Turi GK. Neuroendocrine differentiation in gastric adenocarcinomas. An immunohistochemical study. Arch Pathol Lab Med. 1996; 120: 478-481.
10. Lee EJ, Park SM, Maeng L, Lee A, Kim KM. Composite glandular-endocrine cell carcinomas of the stomach: Clinicopathologic and methylation study. APMIS. 2005; 113: 569-576.
11. Yamashina M, Flinner RA. Concurrent occurrence of adenocarcinoma and carcinoid tumor in the stomach: a composite tumor or collision tumors? Am J Clin Pathol. 1985; 83: 233-236.
12. Yang GC, Rotterdam H. Mixed (composite) glandular-endocrine cell carcinoma of the stomach. Report of a case and review of literature. Am J Surg Pathol. 1991; 15: 592-598.
13. Soga J, Tazawa K Aizawa O, Wada K Tuto T. Argentaffin cell adenocarcinoma of the stomach: An atypical carcinoid? Cancer. 1971; 28: 991-1003.
14. Azzopardi JG, Pollock DJ. Argentaffin and argyrophil cells in gastric carcinoma. J Pathol Bacteriol. 1963; 86: 443-451.
15. Black WG, Haffner HE. Diffuse hyperplasia of gastric argyrophilic cells and multiple carcinoid tumors: a historical and ultrastructural study. Cancer. 1968; 1080-1099: 1968.
16. Kim KM, Kim MJ, Cho BK, Choi SW, Rhyu MG. Genetic evidence for the multi-step progression of mixed glandular-neuroendocrine gastric carcinomas. Virchows Arch. 2002; 440: 85-93.
17. Waldum HL, Haugen OA, Isaksen C Mecsei R, Sandvik AK. Are diffuse gastric carcinomas neuroendocrine tumours (ECLomas)? Europ J Gastroenterol Hepatol. 1991: 3: 245-249.
18. Aoyagi K, Kizaki J, Isobe T, Akagi Y. A case of gastric cancer with neuroendocrine carcinoma, signet ring cell carcinoma components and intramural metastases. Am J Case Rep. 2016; 17: 274-279.
19. La Rosa S, Marando A, Sessa F, Capella C. Mixed adenoneuroendocrine carcinomas (MANECs) of the gastrointestinal tract: An update. Cancers. 2012; 4: 11-30.

20. Morii S, Oka K, Hakozaki H, Nihei T, Mori N. CEA-producing mucin-negative gastric signet ring cell carcinoma with neuroendocrine markers: A case report. J Clin Gastroenterol. 1999; 29: 82-85.

21. Nugent SL, Cunningham SC, Alexiev BA, Bellavance E, Papadimitriou JC, Hanna N. Composite signet-ring cell/neuroendocrine carcinoma of the stomach with a metastatic neuroendocrine carcinoma component: a better prognosis entity. Diagn Pathol. 2007; 2: 43-50.

22. Sugihara A, Nakasho K, Yamada N, Nakagomi N, Tsujimura T, et al. Neuroendocrine differentiation of periodic-acid Schiff and alcian blue-negative signet ring cell-like cells and tubular adenocarcinoma cells with a gastric cancer. Scand J Gastroenterol. 2004; 8: 795-800.

23. Bartley AN, Rashid A, Fournier KF, Abraham SC. Neuroendocrine and mucinous differentiation in signet ring cell carcinoma of the stomach: evidence for a common cell of origin in composite tumors. Human Pathol. 2011; 42: 1420-1429.

24. Klappenbach RS, Kurman RJ, Sinclair CF, James LP. Composite carcinoa-carcinoid tumors of the gastrointestinal tract. A morphologic, histochemical, and immunocytochemical study. Am J Clin Pathol. 1985; 84: 137-143.

25. Prade M, Bara J, Gadenne C, Bognel C. Charpentier M, et al. Gastric carcinoma with argyrophilic cells-light microscopic, electron microscopic, and immunohistochemical study. Hum Pathol. 1982; 13: 588-592.

26. Armitage P, Doll R. The age distribution of cancer and a multistage theory of carcinogenesis. Br J Cancer. 1954; 8: 1-12.

27. Nordling CO. A new theory on the cancer-inducing mechanism. Br J Cancer. 1953; 7: 68-72.

28. Cook PJ, Doll R, Fellingham SA. A mathematical model for the age distribution of cancer in man. Int J. Cancer. 1969; 4: 93-112.

29. Cordier R. Les cellules argentaffines dans les tumeurs intestinalis. Arch Int Med Exp. 1924; 1-5.

30. Warner TF, Seo IS. Goblet cell carcinoid of appendix: ultrastructural features and histogenetic aspects. Cancer. 1979; 44: 1700-1706.

31. Lewin K. Carcinoid tumors and the mixed (composite) glandular-endocrine cell carcinomas. Am J Surg Pathol. 1987; 11: 71-86.

32. Lewin KJ, Appelman HD. Tumors of the esophagus and stomach, In J Rosai, LH Sobin (eds), Atlas of Tumor Pathology, 3rd series, Fascicle 18, Armed Forces Institute of Pathology, Washington, DC, pp 351-352, 1996.

33. Rindi G, Arnold R, Bosman FT, Capella C, Klimstra DS, Kloppel G, et al. Nomenclature and Classification of Neuroendocrine Neoplasms of the Digestive System, In *WHO Classification of Tumours of the Digestive System*, 4th edition, IARC Press, Lyon, pp13-14, 2010.

34. Qvigstad G, Sandvik AK, Brenna E, Ases S, Waldum HL. Detection of chromogranin A in human gastric adenocarcinomas using a sensitive immnohistochemical technique. Histochem J. 2000; 32: 551-556.

35. Brathwaite S, Rock J, Yearsley MM, Bekaii-Saab T, Wei L, Frankel WL, et al. Mixed adeno-neuroendocrine carcinoma: An aggressive clinical entity. Ann Surg Oncol. 2016: 23: 2281-2286.

36. Henson DE, Schwartz AM, Nsouli H, Albores-Saavedra J. Carcinomas of the pancreas gallbladder, extrahepatic bile ducts, and ampulla of Vater share a field for carcinogenesis. Arch Pathol Lab Med. 2009; 133: 67-71.

37. Schwartz AM, Henson DE. Analysis of Surveillance, Epidemiology, and End Results Database for carcinoid tumors. Chest. 2015; 148: e104-105.

38. Capella C. LaRosa S, Uccella S, Billo P, Cornaggia M. Mixed endocrine-exocrine tumors of the gastrointestinal tract. Semin Diagn Pathol. 2000; 17: 91-103.

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