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Case Report

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Gastric Clear Cell Adenocarcinoma Derived from Papillary Adenocarcinoma and its Molecular Alterations

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Abstract

Introduction: Although clear cell carcinoma has been reported in the gastrointestinal tract, such as the colon, clear cell adenocarcinoma (CCA) is a rare histological variant of gastric adenocarcinoma. It may be important for pathologists to distinguish CCA from clear cell metastatic lesions arising from other organs, especially the kidney. Even more importantly, the molecular alterations occurring in CCA should be identified.

Case Report: Here, we present a rare case of gastric CCA with a papillary adenocarcinoma (PA) component and evaluated the molecular alterations in the CCA (submucosal lesion) and PA (intramucosal lesion) components separately. MUC2, MUC5AC, MUC6, and CD10 expression was observed immunohistochemically in both components. According to the findings, the phenotype was considered the gastric and intestinal phenotypes (mixed type). Although CDX2 was diffusely expressed in the PA component, its expression was more sporadic in the CCA component. Using a customized gene panel, p53 was overexpressed in both components, suggesting mutation of TP53 (P152L (cCg>cTg) in exon 5, missense mutation).

Conclusions: Although the specific molecular profile of gastric CCA was not identified in the present case, gastric CCA is a unique histological variant of gastric cancer in terms of the clinicopathological findings. Word count, 193.

Keywords: Clear Cell Adenocarcinoma; Gastric Cancer; Mucin; Papillary Adenocarcinoma; TP53 Mutation.

Introduction

Clear cell adenocarcinoma (CCA) is a rare variant of gastric adenocarcinoma [1-4]. CCAs are usually found in the kidney; however, they have also been reported in the digestive tract and even in gastric cancer [1-4]. To date, only a few cases of gastric CCA have been reported [1-4]. Macroscopically, CCA often presents as a bulging or polypoid mass at the gastroesophageal junction [3]. In particular, CCA is more commonly seen in papillary adenocarcinoma (PA) in elderly patients [2]. Tubules and papillae are lined by clear cells, which represent the clear cytoplasm of the tumour [2]. In addition, this type of gastric adenocarcinoma has a poor prognosis, compared with conventional gastric adenocarcinomas [1]. Although differentiation of gastric CCA from metastatic renal CCA in the stomach contributes to accurate diagnosis and appropriate treatment [1-4], molecular identification of gastric CCA is important from not only a pathological but also clinical aspect. Here, we describe a rare case of gastric CCA including the pathological findings and molecular alterations.

Clinical Report

Clinical Summary

A 63-year-old man with no clinical symptoms presented to the Department of Gastroenterology, Southern Tohoku General Hospital (Japan) for endoscopic examination. Endoscopic examination of the upper gastrointestinal tract revealed a depressed lesion with an irregular surface in the lesser curvature of the middle gastric body. The lesion was suspected to be early gastric cancer due to the endoscopic findings. Thus, the region was biopsied for definitive histological diagnosis, and the biopsy identified PA. Computed tomography did not show massive lymph node swelling around the stomach, suggesting no lymph node metastasis. In addition, laboratory data including tumour marker (AFP, CEA, and CA19-9) levels were within normal ranges. Although submucosal invasion was suspected based on the endoscopic findings, endoscopic submucosal dissection (ESD) was selected due to patient preference. A serum antibody test for Helicobacter pylori was performed. The antibody test was negative at the time of consultation.

Pathological findings in the resected stomach specimen

Macroscopically, a depressed lesion measuring 14 × 29 mm was observed in the resected specimen (Figure 1a). Histologically, the ESD specimen consisted of two components, PA and CCA, characterized by marked cytoplasmic clear cell changes in the depressed lesion (Figure 1b). The neoplastic glands had invaded into the submucosa, which was devoid of lymphatic and vascular invasion. The mucosal lesion comprised irregularly branched papillary neoplastic glands with high nuclear pleomorphism and mitotic activity (Figure 1c). The lesion was histologically diagnosed as PA (Figure 1d). In the submucosal lesion, the carcinoma was composed of polygonal tumour cells with marked clear cytoplasm and small round-like nuclei occasionally with obscure nucleoli and low mitotic activity (Figure 1e, f). The tumour cells showed mainly tubular structures (Figure 1e). A transitional area between the two components was clearly observed (Figure 1f and 1h). In addition, tumor necrosis and hemorrhage were not seen in either component. Although the Periodic acid–Schiff (PAS) reaction was focally positive in the PA component, it was negative in the CCA component. In addition, the PAS reaction was not digested in PA component. Thus, glycogen had not accumulated in the tumour cytoplasm. Alcian Blue staining was negative in both components. Finally, atrophic gastric mucosa with intestinal metaplasia was observed in the background mucosa of the lesion. Based on the pathological findings of the ESD specimen, we performed gastrectomy. No residual cancer tissue was identified in the resected specimens of the stomach. In addition, lymph node metastasis was not detected.

Molecular examination

Immunohistochemical staining of the tumour cells was performed using the Leica BOND system. Expression of MUC2, MUC5AC, and MUC6 was positive in both components (Figure 2a–f). In addition, expression of CD10 was focally positive (along the brush border) in both components. Therefore, the tumor was considered to exhibit the gastric and intestinal phenotypes (mixed phenotype) in both components (Figure 2g, h). According to the findings, the clear cell change was caused by accumulation of gastric and intestinal mucins. Adipophilin was not expressed in either component, suggesting that the clear cell change was not caused by fat deposits. Intranuclear expression of CDX2 was diffuse in the PA component and lower in the CCA component (Figure 2i, j). The ki-67 proliferation index was 76.8% and 4.80% in the PA and CCA components, respectively (Figure 2k, l). Overexpression of p53 was found in both components (Figure 2m, n). No intranuclear accumulation of β-catenin or expression of AFP, SAL4, or glypican-3 was detected in either component. Finally, expression of MLH1/PMS2 was also observed in both components. The immunohistochemical results are shown in Table 1. Multiple mutations in cancer-related genes were examined to determine the mutation profile of the tumor cells using a customized gene panel containing 28 genes (APC, BRAF, TP53, CDKN2A, MET, ATM, MLH-1, PMS2, HRAS, AXIN2, BAX, DCC, MSH2, POLE, RNF43, PTEN, EPCAM, MSH6, BUB1B, RHOA, KRAS, NRAS, SMAD4, CDK4, PIK3CA, STK11, TGFBR2, and EGFR) (Next Generation Sequencing; Illumina). Although no mutation was found in the other 27 genes, TP53 mutation was found in both components (P152L (cCg>cTg) exon 5, missense).

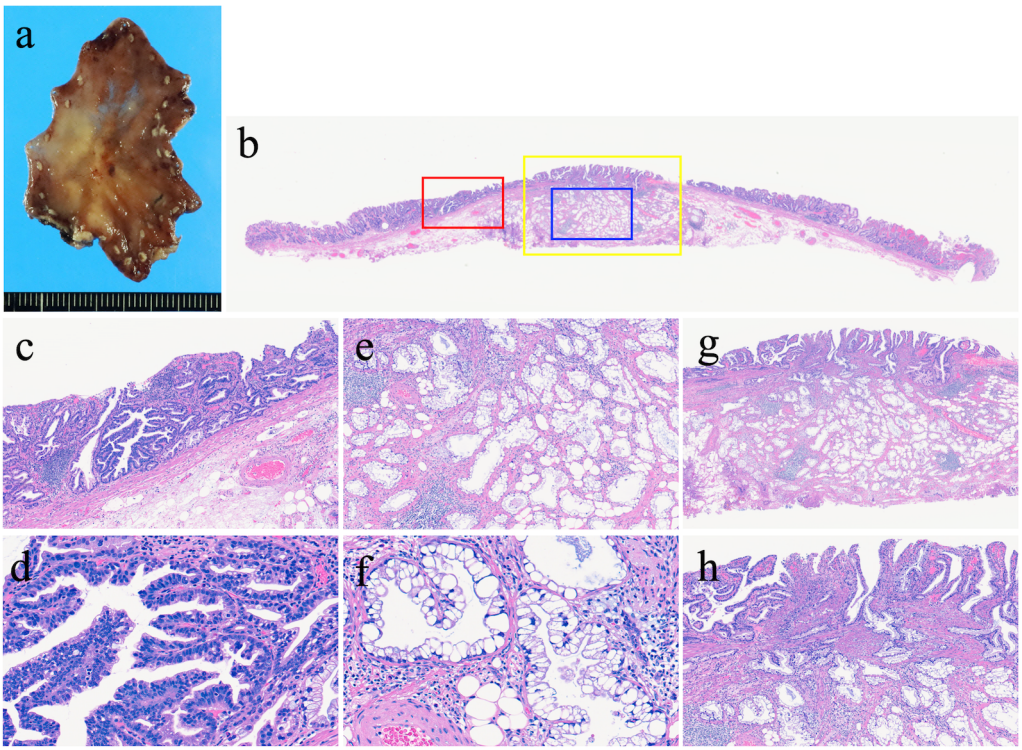

Figure 1: Macroscopic and histological features of gastric clear cell adenocarcinoma. a. A depressed lesion with an irregular surface located at the lesser curvature of the middle gastric body. b. Histological loupe finding of the lesion. The red, blue, and yellow squares indicate an intramucosal lesion, a submucosal lesion, and both lesions, respectively. c. Low-power view of papillary adenocarcinoma involved mainly in the intramucosal region. d. High-power view of clear cell adenocarcinoma that had invaded into the submucosal layer. e. Intermediate-power view of clear cell adenocarcinoma. f. High-power view of clear cell adenocarcinoma. g. Transitional area between the papillary adenocarcinoma and clear cell adenocarcinoma components. h. High-power view of the transitional area.

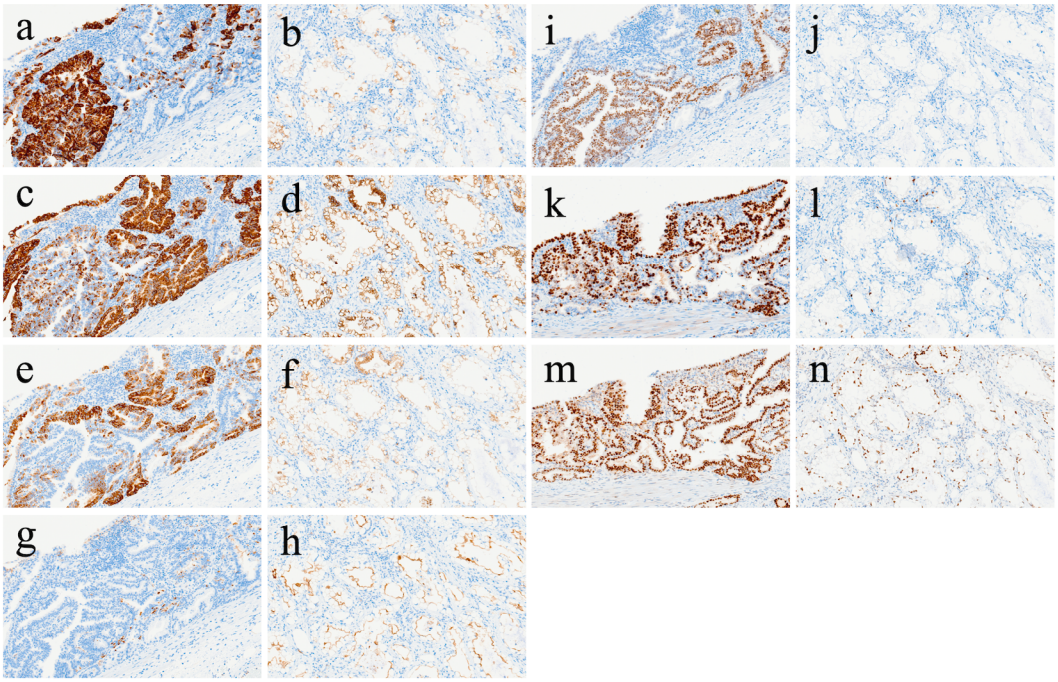

Figure 2: Immunohistochemical expression in the present case. a. MUC2 in papillary adenocarcinoma. b. MUC2 in clear cell adenocarcinoma. c. MUC5AC in papillary adenocarcinoma. d. MUC5AC in clear cell adenocarcinoma. e. MUC6 in papillary adenocarcinoma. f. MUC6 in clear cell adenocarcinoma. g. CD10 in papillary adenocarcinoma. h. CD10 in clear cell adenocarcinoma. i. CDX2 in papillary adenocarcinoma. j. CDX2 in clear cell adenocarcinoma. k. Ki-67 in papillary adenocarcinoma. l. Ki-67 in clear cell adenocarcinoma. m. p53 overexpression in papillary adenocarcinoma. n. p53 overexpression in clear cell adenocarcinoma.

Staining	Conventional type	Clear cell type
PAS	Focal positive	Negative
D-PAS	Focal positive	Negative
AB	Negative	Negative
Adipophilin	Negative	Negative
MUC2	Positive	Focal positive
MUC5AC	Positive	Positive
MUC6	Positive	Positive
CD10	Focal positive	Positive
CDX2	High expression	Low expression
Ki-67	76.80%	2.70%

p53	Positive	Positive
β-catenin	Negative	Negative
MLH1/PMS2	Positive	Positive
AFP	Negative	Negative
SAL4	Negative	Negative
Glypican-3	Negative	Negative

Table 1: Immunohistochemical findings of the present case.

Discussion

Epithelial clear cell change is a characteristic cytoplasmic change that has attracted attention [1-5]. CCA may not be a single entity considering the molecules that accumulate in the tumour cytoplasm. Tumour cells can be classified into three types according to the type of cytoplasmic molecules that have accumulated, i.e., glycogen, fat, and mucin [3,4]. In the present case, glycogen and fat did not accumulate in the tumour cytoplasm because of a negative PAS reaction and negative adipophilin expression. Considering the abovementioned findings, gastric and intestinal mucins were produced in the cytoplasm of both components. These results may be supported by a previous study that gastric CCAs characterized by mucin production are associated with expression of MUC2, MUC5AC, and MUC6 [5].

Among gastric CCAs, AFP-producing gastric carcinoma with enteroblastic-like differentiation is a representative type of gastric cancer and is histologically diagnosed as hepatoid carcinoma [6,7]. On the other hand, a previous study showed that CCA originating from PA is classified as an AFP-producing adenocarcinoma [8]. Thus, CCA can be also classified as AFP-producing and non-AFP-producing types. AFP-producing CCA is glycogen-rich CCA [7], whereas non-AFP-producing CCA may be associated with mucin-producing CCA. In addition, a previous study showed that the prognosis of CCA patients is poor [1,2], and this may suggest a poor prognosis of AFP-producing CCA as well.

CDX2 is a homeobox caudal protein family member encoded by the CDX2 gene that likely plays a role in intestinal epithelial differentiation and proliferation via transcriptional activation of intestine-specific proteins, such as MUC2, sucrase-isomaltase, and carbonic anhydrase I [9]. CDX2 is frequently expressed in intestinal-type gastric epithelial neoplasia; however, CDX2 has not been well examined in gastric CCA. In the present case, reduced CDX2 expression was found in the CCA component compared with the PA component. This finding might suggest that CCA is progressive type from differentiated type [10], based on a previous hypothesis that CDX2 has a tumor suppressive role in human colorectal carcinogenesis [11], and this might also apply to gastric carcinogenesis. The different CDX2 expression between the PA and CCA components may provide novel insight into the carcinogenesis of gastric CCA.

p53 overexpression has been reported in 37.8–54% of gastric cancer cases [12]. According to previous studies, overexpression of p53 is generally associated with worse patient prognosis and with well-known prognostic factors such as vascular invasion and lymph node metastasis [12]. The association between TP53 mutation and gastric CCA has not been well examined. Akazawa et al. reported that TP53 was the most frequently mutated gene in AFP-producing gastric CCA [13]. On the other hand, Uesugi et al. showed that TP53 mutation is frequently found in gastric PA [14]. In the present case, p53 overexpression and TP53 mutation were found in both the PA and CCA components. Although this finding suggests that TP53 mutation played an important role in early carcinogenesis in the present case, such mutation might be characteristic of not only CCA but also PA. In addition, no distinct mutation associated with CCA development was identified using the gene panel in the present case. Unfortunately, the mutation profile of gastric CCA remains unknown.

Interestingly, a low ki-67 proliferation index was found during the transformation from PA to CCA. However, TP53 mutation, which potentially contributes to high proliferative activity [12], was found in both components in the patient. Thus, the reason for the low ki-67 proliferation index during the progression from PA to CCA remains unknown. Further examination regarding the association between TP53 mutations and a low ki-67 proliferation index is needed in the near future.

Conclusions

We investigated the CCA and PA components separately in a case of gastric CCA. The accompanying PA cells helped us evaluate the atypia of the clear cells, given that small-sized nuclei may be mistaken for low-grade nuclear atypia. Diffuse cytoplasmic staining of MUC2, MUC5AC, and MUC6 suggested that the clear cell component might contain gastric and intestinal mucins. In

addition, CD10 expression along the brush borders of clear cells was found, also suggesting a small intestinal phenotype. We verify the well-known causes of clear cytoplasm, namely accumulation of mucin. Finally, we examined the mutation profile of CCA. However, only TP53 mutation was identified in the present case. Further studies may be needed to identify molecular alterations in the transformation of PA into CCA.

Declarations

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Contributions: TS contributed to the preparation of the manuscript. NU helped create the figures and tables and perform the molecular analysis. KH, NT, HY, RY, and MH provided clinical support during the preparation of the manuscript. MS and NY helped interpret the pathological findings.

Availability of data and material: The datasets analyzed in the current study are available from the corresponding author upon reasonable request.

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