Case report: A EWSR1-CREM-Rearranged Gastric Mesenchymal Tumor Accompanied by Gastritis Cystica Profunda and with Probable Benign Behavior

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Case Report

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Abstract

Background:

Genomic rearrangements involving EWSR1 and the CREB family of transcription factors are increasingly detected in an array of mesenchymal neoplasms, including clear cell sarcoma-like tumors of the gastrointestinal tract (CCSLGT), a gastrointestinal malignancy. Gastritis cystica profunda (GCP) is a rare disease characterized by cystic dilatation of gastric glands into the submucosa and generally regarded as a precursor to tumor.

Case presentation:

Herein, we report a peculiar case in which a EWSR1-CREM-rearranged gastric mesenchymal tumor was admixed with GCP in a gastric fundic mass in a 64-year-old woman. Histologically, the mass showed readily distinguishable epithelial and mesenchymal components. All layers of the gastric wall were invaded, although no lymph node or neural invasion, or tumoral vascular emboli was noted. The epithelial component consisted of foveolar-type glands interspersed with pyloric-type ones, with glands showing metaplastic growth. Most glands were elongated with irregular contour, with some forming cystic structures containing eosinophilic secretory material. The epithelial cells showed focally atypical hyperchromatic nuclei, inconspicuous nucleoli, slightly eosinophilic cytoplasm, and infrequent mitosis. The mesenchymal component consisted of monomorphic, ovoid-shaped cells often arranged in sheets surrounding the glands. These cells displayed scanty cytoplasm, regular nuclei, and rare mitotic figures. Immunohistochemically, the epithelial cells were uniformly positive for cytokeratins and negative for markers of neuroendocrine differentiation, and the mesenchymal neoplasm showed focal positivity for CD10, CD117 and CD56 as well as negativity for cytokeratin, neuroendocrine markers, DOG-1, CD34, SMA, desmin, HMB-45, Melan A, and S-100. An EWSR1-CREM fusion was identified with genomic profiling and confirmed with fluorescence in situ hybridization in the tumor. Given the low mitotic activity, absence of nodal or distant spread and vascular or neural invasion, and the disease-free status at 28-month follow-up, both lesions were likely benign.

Conclusions:

To our knowledge, this is the first to report a EWSR1-CREM fusion in a gastric mesenchymal tumor with accompanying GCP. Whether this case suggests a novel entity or falls into one of proposed classes awaits report of more similar cases and insights into the relationship between GCP pathogenesis and oncogenesis.

Background

Recurrent genomic rearrangements represent a significant molecular characteristic in approximately one-third of sarcomas (1). While many of these alterations are tumor-type specific, some show marked promiscuity. A significant group of the latter class are fusions involving Ewing sarcoma breakpoint region
1 (EWSR1) and genes of the CREB family of transcription factors (CREB, ATF1, and CREM). A wide spectrum of mesenchymal tumors have been reported to harbor one of these three fusions, including clear cell sarcomas (CCSs), CCS-like tumors of the gastrointestinal tract (CCSLGT), angiomatoid fibrous histiocytoma (AFH) with intracranial predilection, pulmonary myxoid sarcoma, and malignant epithelioid neoplasm with predilection for mesothelial-lined cavities, among which only CCSLGT is located in the gastrointestinal (GI) tract (2–4).

Gastritis cystica profunda (GCP) is a rare disease first described in 1972 (5). GCP is characterized by hyperplasia and cystic dilatation of gastric glands that extend into the submucosa (6). The cystic expansion may also occur in the mucosa and/or muscularis propria in some cases, while in others the mucosa may appear normal (6, 7). The nonspecific symptoms and radiographic appearances make it difficult to diagnose GCP preoperatively, and most of the 52 patients reported so far underwent surgical excision. There is currently no evidence of recurrence or metastasis, suggesting a benign course (6). However, GCP was reported to show elevated proliferation and DNA repair and occur in 3% gastric carcinomas (6), and several cases have shown early gastric cancer associated with GCP, including three in which an adenocarcinoma was partially within GCP. Therefore, GCP is generally regarded as a precursor of gastric tumor (8–10).

Herein, we report a peculiar case that showed an admixture of GCP and EWSR1-CREM-rearranged gastric mesenchymal neoplasm. Given the low mitotic activity, absence of nodal or distant spread and vascular or neural invasion, and the fact that patient was alive with no evidence of disease at 28 months after surgical excision, it was more likely that both lesions were benign.

**Case Presentation**

A 69-year-old woman visited our hospital with complaints of dizziness and fatigue for the previous two months. Past medical history was significant for chronic type II diabetes, which was kept under control with novolin 30R. The patient had not received gastric surgery before. Blood test showed low levels of hemoglobin (87 g/l), mean corpuscular volume, and mean corpuscular hemoglobin. Gastroscopy revealed in the fundus an unencapsulated mass with smooth surface distinctly separated from the surrounding tissues (Figure 1A). Colonoscopy was unremarkable. Laparoscopic partial gastrotomy was subsequently performed in Apr 2019 to remove the polypoid mass, which measured 8 cm in greatest dimension and showed a gray, firm cut surface (Figures 1B & 1C). The patient was alive with no evidence of recurrence or metastasis at 28 months follow-up after surgery.

Histologically, the mass showed readily distinguishable epithelial and mesenchymal components. All layers of the gastric wall were invaded, although no lymph node or neural invasion, or tumoral vascular emboli was noted. At the periphery were residual gastric oxyntic gland mucosa (Figure 2A). The epithelial component consisted of MUC5AC-expressing, foveolar-type glands interspersed with MUC6-expressing, pyloric-type glands. Some glands showed metaplastic growth, indicated by the admixture of foveolar-type, pyloric-type, and goblet cells. Most glands were elongated with irregular contour, with some forming
cystic structures containing eosinophilic secretory material. The epithelial cells showed focally atypical hyperchromatic nuclei, inconspicuous nucleoli, slightly eosinophilic cytoplasm, and infrequent mitosis (Figures 2B & 2C). The mesenchymal component consisted of monomorphous, ovoid-shaped cells often arranged in sheets surrounding the glands. These cells displayed scanty cytoplasm, regular nuclei, and rare mitotic figures (Figure 2D).

On immunohistochemistry, the epithelial cells were uniformly positive for cytokeratins and negative for markers of neuroendocrine differentiation (Figure 3A). The mesenchymal cell showed focal positivity for CD10 and CD117 (Figures 3B & 3C), focal, patchy positivity for CD56, negativity for cytokeratin, neuroendocrine markers, DOG-1, CD34, SMA, desmin, HMB-45, Melan A, and S-100. Ki-67 index was low in the mesenchymal cells (1%; Figure 3D). Interestingly, genomic profiling with a targeted panel of 520 cancer-related genes (OncoScreen Plus, Burning Rock, China) revealed a $EWSR1$-$CREM$ (E15:C7) fusion, which was further confirmed by fluorescence in situ hybridization using both fusion and split-apart probes (Figure 4). Furthermore, this fused gene appeared to be detectable exclusively in the mesenchymal component.

**Discussion and Conclusions**

In summary, we report a gastric fundic mass consisting of readily distinguishable epithelial and mesenchymal components. The epithelial cells showed morphology and immunophenotype consistent with metaplasia and downgrowth of gastric glands into the submucosa, suggesting GCP. The mesenchymal component was comprised of ovoid-shaped cells harboring $EWSR1$-$CREM$ fusion. Given the absence of lymph node, vascular or neural invasion, low mitotic activity, and disease-free status at 28-month follow-up, the GCP and mesenchymal tumor were likely benign.

A panel of mesenchymal tumors of the GI tract was considered for the mesenchymal component. CCSLGT was considered based on the anatomic site and presence of $EWSR1$-$CREM$ fusion. However, CCSLGT is a malignant entity that occurs mostly in young adults. In a series of 3 CCSLGT cases that harbored $EWSR1$-CREB family fusion, the patient age ranged 24-29, and one developed lung metastasis and died after 2 years (11). Also, all three patients displayed patchy positivity for S-100 and negativity for CD117 on immunohistochemistry, further excluding a CCSLGT diagnosis (12). The immunostaining results in this case agreed with gastrointestinal stromal tumor (GIST) on CD117 positivity and S-100 negativity. However, CD117 negativity occurs in up to 18% of gastric GISTs, making it a less specific marker (12). Furthermore, DOG-1 immunoreactivity in reported in 87%-97% GISTs (13) and CD34 in 60-70% (12), both of which were lacking in this case. Morphologically, most GISTs are composed of either short fascicles of spindle cells or round, epithelioid cells arranged in nests, which contrasts with the ovoid cells arranged in sheets in this case. Other tumor types, such as smooth muscle neoplasms and tumors with fibroblastic/myofibroblastic, neural, or melanocytic differentiation, were excluded by respective negative immunostaining for SMA, desmin, neuroendocrine markers, and melanocytic markers in this case (12). Recent years have also seen an explosion in the histological spectrum of mesenchymal tumors with $EWSR1$/FUS-CREB family fusions (2–4, 14). Shibyama et al. reported 8 cytokeratin-positive intra-
abdominal malignancies harboring \textit{EWSR1/FUS-CREB} fusions (14). Among these cases, one was strikingly resemblant to ours in that a gastric submucosal mesenchymal neoplasm was admixed with dilated epithelial structures that invaginated from the mucosa. \textit{EWSR1-CREB} fusion was detected with fluorescence in situ hybridization (FISH), and the tumor also showed low mitotic activity. There were, however, peripheral lymphoid cuffing and prominent hemorrhagic pseudoangiomatous spaces suggested of AFH. In addition to cytokeratin positivity, the tumor also showed other discrepancies such as epithelioid cytormorphology, diffuse SMA positivity, and possibly a more aggressive clinical course. Interestingly, 2 subsequent specimens resected in the abdominal cavity at recurrence displayed similar histology but without the epithelial inclusions, suggesting the GCP-like structure as a completely independent or stomach-specific phenomenon. However, conclusive elucidation awaits further research.

In addition to the case series by Shibyama and colleagues, Argani et al. also described 13 \textit{EWSR1/FUS–CREB}-rearranged malignant epithelioid neoplasms, most of which located intra-abdominally or expressing epithelial markers cytokeratin and/or EMA (4). An interesting finding was a \textit{EWSR1-CREM} fusion that attaches \textit{CREM} exon 7 to \textit{EWSR1} exon 15, the same composition as with this case. One of the \textit{EWSR1-CREM}-rearranged tumors was intra-abdominal and inseparable from gastric fundus, although it was not specified which breakpoints were detected. Since \textit{EWSR1} exon 15 is a highly rare breakpoint, this similarity may reflect shared molecular basis between these cases and ours despite immunohistochemical and clinical differences. As new \textit{EWSR1/FUS–CREB}-rearranged mesenchymal tumors are detected and new classes proposed at a rapid pace, it is possible that this case falls into one of the recorded classes, although more insights into the relationship between the pathogenesis of GCP and the mesenchymal neoplasm are warranted.

Gastritis cystica profunda was previously associated with a history of gastric surgery, although a recent review found GCP occurring approximately equal percentages of patients with (52\%) and without surgery (48\%) (6). However, GCP was observed in animals after gastrectomies or predisposition to \textit{H. pylori} infection, suggesting association with insult to the gastric mucosa (6, 9). Highly suspected as precancerous, GCP was reported in 3 cases as the background from which early gastric adenocarcinoma arose (8–10). In this case, it is unknown whether GCP and mesenchymal neoplasm developed independently from one other or in concert, although considering the rarity of both entities and the precancerous nature of GCP, the two lesions may be pathogenetically connected.

To our knowledge, this is the first to report a \textit{EWSR1-CREM} fusion in a gastric mesenchymal tumor with accompanying GCP. Whether this case suggests a novel entity or falls into one of proposed classes awaits report of more similar cases and insights into the relationship between GCP pathogenesis and oncogenesis.

\textbf{Abbreviations}

\textit{EWSR1}, Ewing sarcoma breakpoint region 1. \textit{CREB}, cAMP-responsive element-binding protein 1. \textit{CREM}, cAMP-responsive element modulator. GCP, gastritis cystica profunda. CCSLGT, clear cell sarcoma-like
tumors of the gastrointestinal tract. DOG-1, discovered on GIST-1. SMA, smooth muscle antigen. HMB-45, human melanoma black 45. CCS, clear cell sarcoma. AFH, angiomatoid fibrous histiocytoma. GI, gastrointestinal. FISH, fluorescence in situ hybridization.

Declarations

_Ethics approval and consent to participate_

All procedures performed in studies involving human participants were in accordance with the ethical standards with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

_Consent for publication_

The patient has provided written informed consent for participating in the study.

_Availability of data and materials_

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

_Competing interests_

The authors have no competing interests to declare.

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_Authors’ contributions_

QC and HW performed histopathologic review, analyzed the data, drafted the manuscript, and prepared the figures. HW performed histopathologic review, drafted the manuscript, and provided critical feedback. YC, ZX, and JC provided critical feedback. ZL provided supervision, critical feedback, and administrative support.

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Figures

Figure 1

Macroscopic appearance of the gastric tumor described in this case. (A) Gastroscopy showed a reddish protruding lesion with smooth surface in the cardia. (B) A large polypoid tumor with a broad base was resected by partial gastrectomy. (C) On the cut surface, the tumor has a grey appearance without clear margin.

Figure 2

Histologic features of the gastric neoplasm described in this report. (A) The lesion was located in the gastric mucosa and muscularis propria; note the residual fundic mucosa. (B) The tumor was composed of irregular glands and mesenchymal components; the glands were lined by the columnar cells with an apical mucin cap and basally oriented nuclei (red arrow) or by the low columnar epithelia featuring a defined ground-glass appearance with lightly eosinophilic cytoplasm (yellow arrow). (C) Focally, intestinal-type glands exhibited disturbed architecture, crowded nuclei and slightly elevated nucleus/cytoplasm ratio. (D) The mesenchymal component consisted of bland oval cells with scanty cytoplasm and monomorphic nuclei. A-D, Hematoxylin and eosin staining at (A) 200× magnification or (B-D) 400× magnification.
**Figure 3**

Immunohistochemical features of the gastric tumor. (A) The epithelial component was positive for cytokeratins, whereas the mesenchymal component showed focal positivity for (B) CD10 and (C) CD117. (D) There was very low Ki-67 index (1%) in the mesenchymal component. All figures are shown at 400× magnification.
Figure 4

EWSR1-CREM gene fusion was identified by sequencing and confirmed by fluorescence in situ hybridization (FISH). (A) A fusion between EWSR1 exon 15 (22:29688210) and CREM exon 7 (10:35475834) was identified by next-generation sequencing. (B) EWSR1 break-apart FISH and (C) Two-color FISH with EWSR1 (green) and CREM (red) probes both confirming the EWSR1-CREM fusion (arrows).