



A *EWSR1-CREM*-rearranged gastric mesenchymal tumor accompanied by gastritis cystica profunda and with probable benign behavior: a case report

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Abstract: Genomic rearrangements involving *EWSR1* and the *CREB* family of transcription factors are increasingly detected in an array of mesenchymal neoplasms, most of which are malignant. 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. Herein, we report a peculiar case in which an *EWSR1-CREM*-rearranged gastric mesenchymal tumor was admixed with GCP in a 64-year-old woman. All layers of the gastric wall were invaded, although no lymph node or neural invasion, or tumoral vascular emboli was noted. The mass showed readily distinguishable epithelial and mesenchymal components. The epithelial component consisted mainly of glandular structures with some showing metaplastic growth. The epithelial cells showed focally atypical hyperchromatic nuclei, slightly eosinophilic cytoplasm, and infrequent mitosis. The mesenchymal component consisted of monomorphic, ovoid-shaped cells with scanty cytoplasm, regular nuclei, and rare mitotic figures. Immunohistochemically, the epithelial cells were uniformly positive for cytokeratins, and the mesenchymal neoplasm showed focal positivity for CD10, CD117 and CD56. An *EWSR1-CREM* fusion was identified with genomic profiling and confirmed with fluorescence in situ hybridization (FISH) in the tumor. Given the low mitotic activity, absence of nodal or distant spread and vascular or neural invasion, and disease-free status at 28-month follow-up, both lesions were likely benign. To our knowledge, this is the first to report an *EWSR1-CREM* fusion in a gastric mesenchymal tumor with accompanying GCP.

Keywords: Gastric mesenchymal tumor; gastritis cystica profunda (GCP); *EWSR1-CREM* gene fusion; case report; next-generation sequencing

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Introduction

Recurrent genomic arrangements represent a significant molecular characteristic in approximately one-third of sarcomas (1). A significant group of the fusions that lack tumor type-specificity are those involving *Ewing sarcoma breakpoint region 1* (*EWSR1*) and genes of the CREB family of transcription factors (*CREB*, *ATF1*, and *CREM*), which have been reported in a wide spectrum of mesenchymal

tumors, 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). GCP is difficult to diagnose preoperatively owing to nonspecific symptoms and radiographic appearances, 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 (ADC) was partially within GCP. Therefore, GCP is generally regarded as a precursor of gastric tumor (6,8). There are currently 5 patients reported to have gastric cancer arising from or associated with GCP, all of which ADCs (*Table 1*) (9-13).

Herein, we report a peculiar case that showed an admixture of GCP and *EWSR1-CREM*-rearranged gastric mesenchymal neoplasm. Given the patient's disease-free status at 28 months post-surgery, it was more likely that both lesions were benign. For comprehensive characterization of this admixture, we performed multiple analyses on the surgical specimen, including histologic examination, immunohistochemistry (IHC), next-generation sequencing, fluorescence in situ hybridization (FISH), and follow-up phone calls to track survival outcomes. We present the following case in accordance with the CARE reporting checklist (available at <https://tc.amegroups.com/article/view/10.21037/tcr-21-2331/rc>).

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 (*Figure 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 (*Figure 2B,2C*). 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 (*Figure 2D*).

On IHC, 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 (*Figure 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, Guangzhou, China) revealed an *EWSR1-CREM* (E15:C7) fusion, which was further confirmed by FISH using both fusion and split-apart probes (*Figure 4*). Furthermore, this fused gene appeared to be detectable exclusively in the mesenchymal component.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In summary, we report a gastric fundic mass consisting of readily distinguishable epithelial and mesenchymal

Table 1 Case reports in which GCP either co-occurred with or resembled gastric neoplasms

Ref.	Age	Sex	Prior gastric surgery	Symptom	Involved gastric layer(s)	Gastric tumor	GCP IHC	Treatment	Survival outcome
(9)	63	M	No	Abdominal pain	Mucosa	ADC	KCNE2, ER	Distal gastrectomy	NR
(10)	55	M	No	No stomach or intestinal symptoms	Submucosa	ADC	NR	Endoscopic submucosal dissection	AWED, 39 months
(11)	45	M	No	Epigastric abdominal pain and black stool	Mucosa, submucosa	ADC	NR	Total gastrectomy with esophagojejunostomy, abdominal lymphadenectomy, feeding jejunostomy, and bilateral vagotomies	NR
(12)	51	M	No	Abdominal pain	Submucosa, muscularis propria, subserosa	ADC	Ki-67, p53, p21WAF1/CIP1	Total gastrectomy	AWED, 10 years
(13)	83	F	Gastrojejunostomy 50 years prior	Epigastric discomfort	Mucosa, submucosa	ADC, signet ring cell carcinoma	Ki-67	Distal gastrectomy, regional lymphadenectomy	AWED, 46 months
(14)	67	M	No	Melena, ulcerated bleeding	Submucosa, muscularis propria	No tumor observed. GCP lesion mimicked GIST in GI tract bleeding and endoscopic ultrasonography	NR	Surgical resection of the lesion	NR
(15)	61	M	No	None	Mucosa, submucosa, muscularis propria	No tumor observed. GCP lesion mimicked solid submucosal tumors in radiologic evaluation	CD68	Laparoscopic wedge resection	AWED. Duration not reported

GCP, gastritis cystica profunda; IHC, immunohistochemistry; ADC, adenocarcinoma; NR, not reported; AWED, alive with no evidence of disease; GIST, gastrointestinal stromal tumor; GI, gastrointestinal.

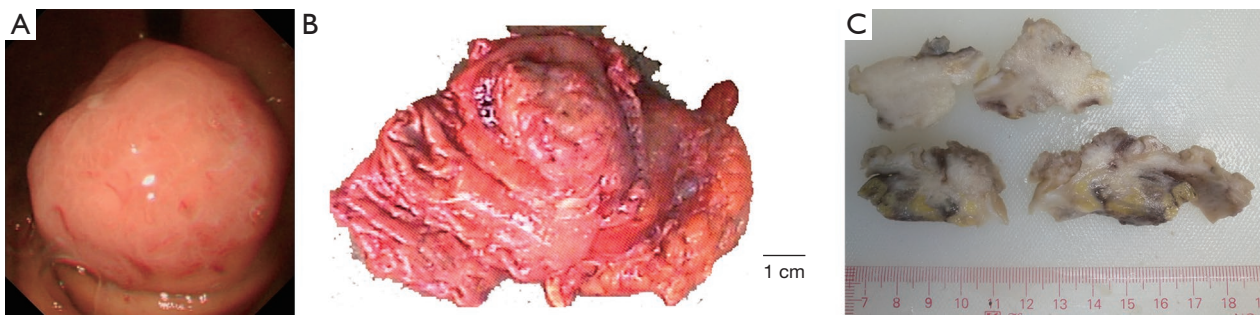


Figure 1 Macroscopic appearance of the gastric tumor described in this case. (A) Gastroscope showed a reddish protruding lesion with smooth surface in the cardia. (B) A large polypoid tumor with a broad base was resected by partial gastrectomy. (C) On the cut surface, the tumor has a grey appearance without clear margin.

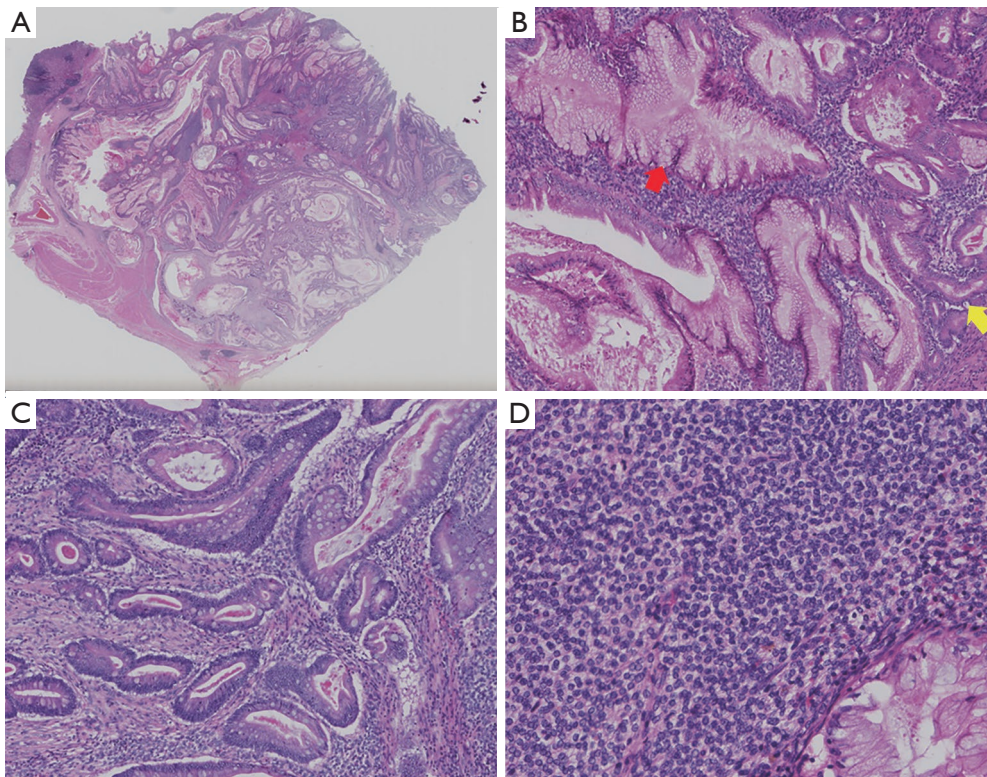


Figure 2 Histologic features of the gastric neoplasm described in this report. (A) The lesion was located in the gastric mucosa and muscularis propria; note the residual fundic mucosa. (B) The tumor was composed of irregular glands and mesenchymal components; the glands were lined by the columnar cells 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) $\times 200$ magnification or (B-D) $\times 400$ magnification.

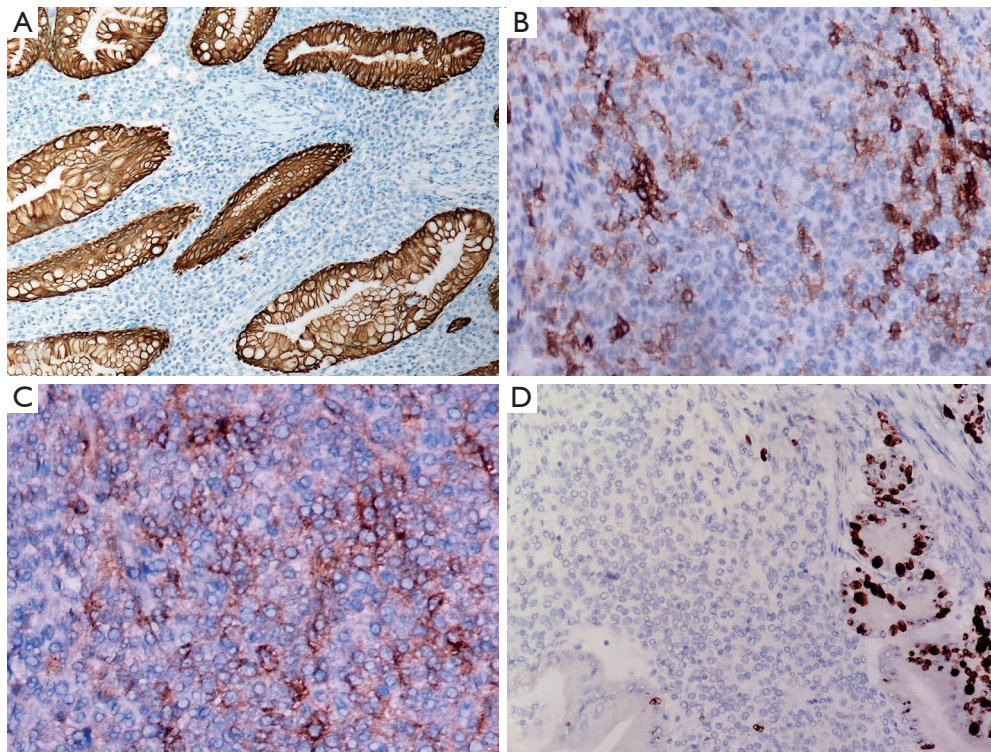


Figure 3 Immunohistochemical features of the gastric tumor. (A) The epithelial component was positive for cytokeratins, whereas the mesenchymal component showed focal positivity for (B) CD10 and (C) CD117. (D) There was very low Ki-67 index (1%) in the mesenchymal component. All figures are shown at $\times 400$ magnification.

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 (16). Also, all three patients displayed patchy positivity for S-100 and negativity for CD117 on IHC, further excluding a CCSLGT diagnosis (17). 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 (17). Furthermore, DOG-1 immunoreactivity is reported in 87–97% GISTs (18) and CD34 in 60–70% (17), 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 (17). Recent years have also seen an explosion in the histological spectrum of mesenchymal tumors with *EWSR1/FUS-CREB* family fusions (2–4,19). Shibayama *et al.* (19) reported 8 cytokeratin-positive intra-abdominal malignancies harboring *EWSR1/FUS-CREB* fusions. Among these cases, one was strikingly reminiscent to ours in that a gastric submucosal mesenchymal neoplasm was admixed with dilated epithelial structures

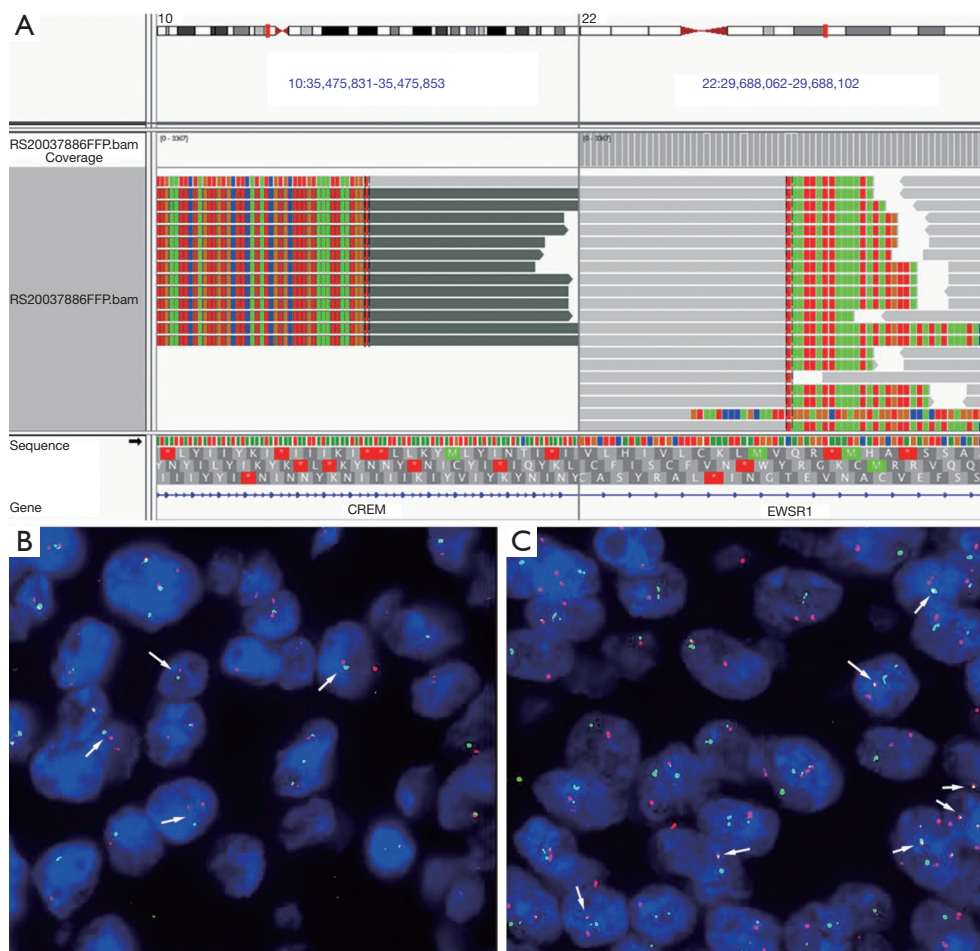


Figure 4 *EWSR1-CREM* gene fusion was identified by sequencing and confirmed by FISH. (A) A fusion between *EWSR1* exon 15 (22:29688210) and *CREM* exon 7 (10:35475834) was identified by next-generation sequencing. (B) *EWSR1* break-apart FISH and (C) two-color FISH with *EWSR1* (green) and *CREM* (red) probes both confirming the *EWSR1-CREM* fusion (arrows). Magnification: $\times 1,000$. FISH, fluorescence in situ hybridization.

that invaginated from the mucosa. *EWSR1-CREB* fusion was detected with 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 cytomorphology, 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 Shibuya and

colleagues, Argani *et al.* (4) also described 13 *EWSR1/FUS-CREB*-rearranged malignant epithelioid neoplasms, most of which located intra-abdominally or expressing epithelial markers cytokeratin and/or EMA. An interesting finding was an *EWSR1-CREM* fusion that attaches *CREM* exon 7 to *EWSR1* exon 15, the same composition as with this case. One of the *EWSR1-CREM*-rearranged tumors was intra-abdominal and inseparable from gastric fundus, although it was not specified which breakpoints were detected. Since *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 *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.

GCP 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 *H. pylori* infection, suggesting association with insult to the gastric mucosa (6,10). Highly suspected as precancerous, GCP was simultaneously found together with gastric ADC in 5 cases (9-13). There therefore appears to be an association among mucosal insult, GCP, and neoplastic growth. 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. On the other hand, evidence is still amassing as to the association between surgical resection and GCP (20), and a recent study observed GCP and ADC 50 years after gastrojejunostomy at the anastomotic site (13). It is therefore advisable to monitor disease recurrence on a regular basis.

To our knowledge, this is the first to report an *EWSR1-CREM* fusion in a gastric mesenchymal tumor with accompanying GCP. However, due to its anecdotal nature, this case is limited answering the questions it raises. First, it remains to be elucidated whether the GCP and mesenchymal tumor were associated in etiology. Additionally, it is of interest to clarify whether this admixture represents a novel of class of gastric mesenchymal tumors and, if yes, questions such as its epidemiology, symptoms, prognosis, and treatments would warrant further investigations. A review of previous cases may be in order, since there have been isolated reports of GCP mimicking GIST (14) or solid submucosal tumor (15) (Table 1).

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2331/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2331/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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