

Gastric calcifying fibrous tumor: A clinicopathological study of nine cases

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Abstract. The aim of the present study was to analyze the clinicopathological characteristics presented in 9 cases of gastric calcifying fibrous tumor (CFT), and investigate the expressions and clinical implications of G protein-coupled estrogen receptor (GPER), estrogen receptor (ER) and vimentin in gastric CFTs. The clinical and pathological information of 9 patients with CFTs was investigated retrospectively. Subsequently, the expression of GPER, ER and vimentin were examined using immunohistochemistry, and a literature search for gastric CFT was conducted. The 9 patients were 40-71 years old with a mean age of 52.22 years, including 6 female and 3 male patients. Pathological features included dense hyalinized collagen fibers with a psammomatous body or dystrophic calcification, and the infiltration of scattered lymphocytes and plasma cells. Immunohistochemically, all cases expressed vimentin and GPER, whereas ER expression was negative. Using a database research, 25 studies regarding gastric CFT were identified, including 48 cases with a sex ratio (female:male) of 1.4:1. In addition, the number of female patients was twice the number of male patients in patients <50 years old, whereas the number was almost equal between women and men ≥50 years of age. Gastric CFT is a benign lesion with a good prognosis and a predilection for female patients, particularly premenopausal women. Estrogen may serve a role in this female predominance, and this may be mediated by GPER rather than ER.

Introduction

Calcifying fibrous tumor (CFT) was first described as a 'childhood fibrous tumor with psammoma bodies' by Rosenthal and

Abdul-Karim (1) in 1988, but later studies demonstrated it may also occur among the adult population (2,3). CFT is a rare but distinctive entity; it is a benign lesion that consists of abundant hyalinized collagen with psammomatous or dystrophic calcifications (4). CFTs primarily originate from the soft tissue, e.g. pleura and abdominal viscera; the stomach only rarely participates (5). CFT confined to the gastric wall is a rare and benign lesion, which usually presents without any gastrointestinal symptoms and is often detected incidentally (5). Gastric CFT is less likely to cause serious complications such as perforation or obstruction. In spite of its benign course and good prognosis, with known histological and immunohistochemical features, the exact pathogenic mechanism of this lesion remains elusive. Gastric CFT should be carefully differentiated from other spindle cell mesenchymal lesions involved in the stomach, such as inflammatory myofibroblastic tumor, sclerosing calcified gastrointestinal stromal tumor, schwannoma and IgG4-related sclerosing disease. Furthermore, given the rarity of gastric CFT (less than 50 cases reported to date), it is important to enhance the understanding of this lesion among clinicians. Therefore, the present study focused on exploring its clinical and pathological features by presenting 9 cases of gastric CFT, and reviewing previous English language articles regarding gastric CFT to determine whether this kind of tumor has a sex predilection. Furthermore, the current study aimed to analyze the possible association between female predominance and expression of G protein-coupled estrogen receptor (GPER).

Subjects and methods

The clinical information, relevant biochemical indicators [blood routine, tumor markers, C reactive protein, hepatitis B virus and *Helicobacter pylori* (HP)] and pathological features (gross examination and microscopic findings) of 9 patients with gastric CFT who had been admitted to the Department of Gastroenterology and Gastrointestinal Surgery at the Renmin Hospital of Wuhan University (Wuhan, China) between January 2015 and July 2018 were retrospectively reviewed. The present protocol was approved by the Institutional Review Board of the Renmin Hospital of Wuhan University, and all patient data was handled confidentially. All patients included in the present study provided written informed consent. The tumor slides from the 9 cases were collected from the Department of Pathology of the Renmin Hospital of Wuhan University. In

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addition, literature databases up to July 2018 were searched, including PubMed (www.ncbi.nlm.nih.gov/pubmed), Embase (www.embase.com), Scopus (www.scopus.com) and Google Scholar (scholar.google.com), for previously published English language articles regarding gastric CFT case reports or case series. The search terms were 'calcifying fibrous tumor AND gastric', and 'calcifying fibrous pseudotumor AND gastric'. Two authors reviewed potential studies, and any discrepancies were resolved by a third author.

Tumor specimens resected by endoscopic submucosal dissection (ESD) or gastric wedge excision (GWE) were fixed in 10% formalin solution for 4 h at room temperature and embedded in paraffin using routine methods. Deparaffinized sections with 4 μ m thickness were used for staining with hematoxylin and eosin (5 min for hematoxylin and 1 min for eosin). Immunohistochemical techniques were conducted according to the SP method as described previously (6). Deparaffinized sections with 4 μ m thickness were quenched in 3% H₂O₂, then subjected to antigen retrieval in boiling citric acid (pH 6.0) for 15 min and washed with PBS. Following incubation overnight with primary antibodies against GPER (ab39742; 1:200), estrogen receptor (ER; ab17230; 1:200) or vimentin (ab24525; 1:5,000; all from Abcam, Cambridge, UK) at 4°C, the sections were incubated for 15 min at room temperature with horseradish peroxidase-labeled polymer-conjugated secondary antibodies (MaxVision™ kits; Maxim Bio, Fujian, China). The specimens were then incubated for 1 min at room temperature with diaminobenzidine (Maxim Bio). Finally, the sections were counterstained at room temperature with hematoxylin for 30 sec.

Results

Clinical characteristics of the 9 cases. Six patients (cases 4-9) originally attended the hospital for a check-up for non-specific symptoms, such as belching or a bloated abdomen. Among the 9 cases, there were 6 female patients and 3 male patients (2:1). The age of the patients ranged from 40-71 years, with a mean age of 52.22 years. A total of 6 tumor cases (cases 1, 2, 5, 6, 7 and 8) originated from the gastric body, whereas the remaining 3 originated from the fundus of the stomach (cases 3, 4 and 9; Table I). Cases 1 and 9 were concomitant with reflux esophagitis, case 2 was accompanied with duodenal ulcer, and erosive hemorrhagic gastritis and hypertension were reported in case 3. Furthermore, type 2 diabetes and superficial gastritis were diagnosed in cases 6 and 8, respectively. No patients were reported to suffer from autoimmune disorders. The details of smoking, alcohol consumption and body mass index are listed in Table I.

Laboratory tests. No abnormalities were evident in routine and tumor marker blood tests [including carcinoembryonic antigen, α -fetoprotein, carbohydrate antigen (CA)19-9 and CA-125]. Cases 1 and 2 presented with chronic hepatitis B virus (HBV) infection, and cases 1, 3 and 8 were positive in the ¹³C breath test and diagnosed with HP infection (Table II). Furthermore, C-reactive protein (CRP) levels were slightly elevated in 5 cases (cases 1, 2, 3, 7 and 8).

Gross examination and microscopic findings. Sections from all 9 cases revealed well-defined lumps; each section contained

an isolated nodular lesion covered by intact mucosa. The maximum diameter ranged from 1.3-2.5 cm, with a mean of 1.81 cm. A total of 4 tumors (cases 2, 3, 4 and 8) were located in the lamina propria, with extension to the submucosa, whereas the remaining 5 cases (1, 5, 6, 7 and 9) occurred in the submucosa (Table I).

Microscopically, the common characteristics of the 9 cases included considerable hypocellular sclerosis and wavy storiform coarse collagen infiltrated with scattered or patchy mononuclear inflammatory cells. Six cases (cases 1, 2, 4, 5, 6 and 9) exhibited a predominance of dense hyaline fibrous tissue infiltrated with many inflammatory cells and multifocal dystrophic calcifications. Psammomatous and dystrophic calcifications are indicated in Fig. 1.

Immunohistochemical staining. From the immunohistochemical examination of gastric CFT specimens, lesional cells were determined to be positive for vimentin and GPER expression. However, all 9 cases were negative for ER expression (Fig. 2).

Treatment and follow-up. A total of 8 patients were treated with ESD; only 1 patient (case 6) underwent partial gastrectomy. Following ESD or surgical treatment, all patients recovered fully. None of the 9 patients available to follow-up (mean follow-up time, 13.11 months; range, 4-25 months) have experienced local recurrence (Table I).

Literature search. In total, 25 previous studies regarding gastric CFT were identified, including 39 individual cases (Table III) (7-31). At present, there are 48 cases of gastric CFT reported in the English language literature, including the 9 cases from the present study. Among the 48 cases of gastric CFT, there were 28 female and 20 male patients, a sex ratio of 1.4:1. The number of female patients was more than twice that of the male patients in the patients <50 years of age (17 vs. 8), whereas the number was almost equal between women and men \geq 50 years of age (11 vs. 12; Fig. 3). Regarding geographical distribution of the gastric CFT patients, Asia ranked the highest (including 17 patients in China, 4 in Korea, 3 in Japan, 1 in Kuwait, 1 in Turkey and 1 in Pakistan), followed by Europe (7 patients in Germany, and 1 in each of Greece, Slovakia, Switzerland, France and Italy), whereas only 9 cases occurred in North America (8 patients in the USA and 1 in Canada). According to the distribution of these 48 cases, it appears that people from Asia, especially from East Asia, are more likely to suffer from this disease than people from Europe or North America, potentially due to ethnic or regional differences.

Discussion

To the best of our knowledge, the present study reported the largest case series on gastric CFTs to date. Among the 9 gastric CFT patients included in this study, 3 were infected with HP, and 2 with HBV. Due to the extremely low incidence of this type of tumor, there is no previous research considering the association between the occurrence of gastric CFT and HP or HBV. In addition, the distribution of the 48 reported cases indicated that people from East Asia may be more likely to suffer from this disease compared with people from Europe or

Table I. Clinicopathologic features of 9 cases of gastric calcifying fibrous tumor.

Case no.	Age (years)	Sex	Smoking	Drinking	BMI (Kg/m ²)	Concomitant disease	Site	Layer	Size (cm)	Treatment	Complications	Follow-up (months)
1	44	Female	No	No	22.89	Reflux esophagitis	Body	Submucosa	1.5x1.0x0.8	ESD	None	25
2	50	Female	No	No	27.06	Duodenal ulcer	Body	Lamina propria	1.5x1.5x1.0	ESD	Celiacgia	14
3	42	Female	No	Yes	23.81	Erosive hemorrhagic gastritis hypertension	Fundus	Lamina propria	1.3x0.8x0.6	ESD	None	23
4	61	Male	Yes	Yes	17.90	None	Fundus	Lamina propria	2.5x2.0x1.5	ESD	None	17
5	46	Female	No	No	21.33	None	Body	Submucosa	1.7x1.5x0.2	ESD	None	11
6	71	Male	No	No	20.24	Diabetes	Body	Submucosa	2.0x1.5x0.5	GWE	Celiacgia	9
7	54	Female	No	No	23.44	None	Body	Submucosa	2.0x1.5x1.5	ESD	None	9
8	62	Male	Yes	Yes (alcoholism)	27.34	Superficial gastritis	Body	Lamina propria	2.0x1.2x0.4	ESD	None	6
9	40	Female	No	No	19.52	Superficial gastritis	Fundus	Submucosa	1.8x1.3x0.8	ESD	None	4

ESD, endoscopic submucosal dissection; GWE, gastric wedge excision; BMI, body mass index.

Table II. Laboratory tests of 9 cases of gastric calcifying fibrous tumor.

Case no.	Blood routine	Tumor markers ^a	CRP	HBV	HP
1	-	-	↑	+	+
2	-	-	↑	+	N
3	-	-	↑	N	+
4	-	-	-	N	N
5	-	-	-	N	N
6	-	-	-	N	N
7	-	-	↑	N	N
8	-	-	↑	N	+
9	-	-	-	N	N

^aTumor markers consist of carbohydrate antigen 125, carbohydrate antigen 19-9, α -fetoprotein and carcinoembryonic antigen. CRP, C-reactive protein; HBV, hepatitis B virus; HP, *H. pylori*; -, in normal range; ↑, beyond normal range; +, positive result; N, negative result.

North America. Whether this is a coincidence requires further exploration.

At present, the etiology and pathogenesis of CFT confined to the gastric wall remain elusive (5,11-14). In a previous study, cases of CFT following trauma were reported, and it has been speculated that gastric CFT may represent a localized inflammatory fibrosclerosis in response to tissue injury affecting the stomach (32). However, no prior history of any trauma or tissue injuries to the stomach, such as ulcers or perforation, were identified in the present 9 cases. Furthermore, previous studies have indicated that these tumors are true neoplasms, with the potential for non-destructive local recurrence (33), rather than a reactive process resulting from abnormal tissue healing (5,7). It has also been suggested that this lesion results from an immunoglobulin (Ig)G4-associated disorder (34,35); gastric CFTs may represent a stage of an IgG4-associated disorder, and steroid therapy should be included in clinical management prior to GWE or ESD (18). However, among the present 9 cases, none of the patients presented with autoimmune disorders such as primary biliary cirrhosis, chronic atrophic gastritis, inflammatory bowel disease or IgG4-associated pancreatitis.

The present study demonstrated that gastric CFT may have a female predominance (female:male, 2:1), which is consistent with the previous literature (1.27:1) (5,13). Including the 9 cases in the current study and the 39 from previous studies, the sex ratio is 1.4:1. Following age stratification, a marked difference was identified in the sex ratio of patients above or below age 50. This suggests that this rare tumor is more common in female patients, particularly premenopausal women. Based on the marked difference in sex ratio before and after age 50, it is speculated that estrogen may serve a role in the occurrence and progression of gastric CFT.

As estrogen exerts its effects via binding GPER or ER, the ER and GPER expression status of the patient samples was detected with immunohistochemistry. Immunostaining was performed on samples from 9 cases; cells from the lesions exhibited positive immunoreactivity for GPER, but no immunoreactivity for ER.

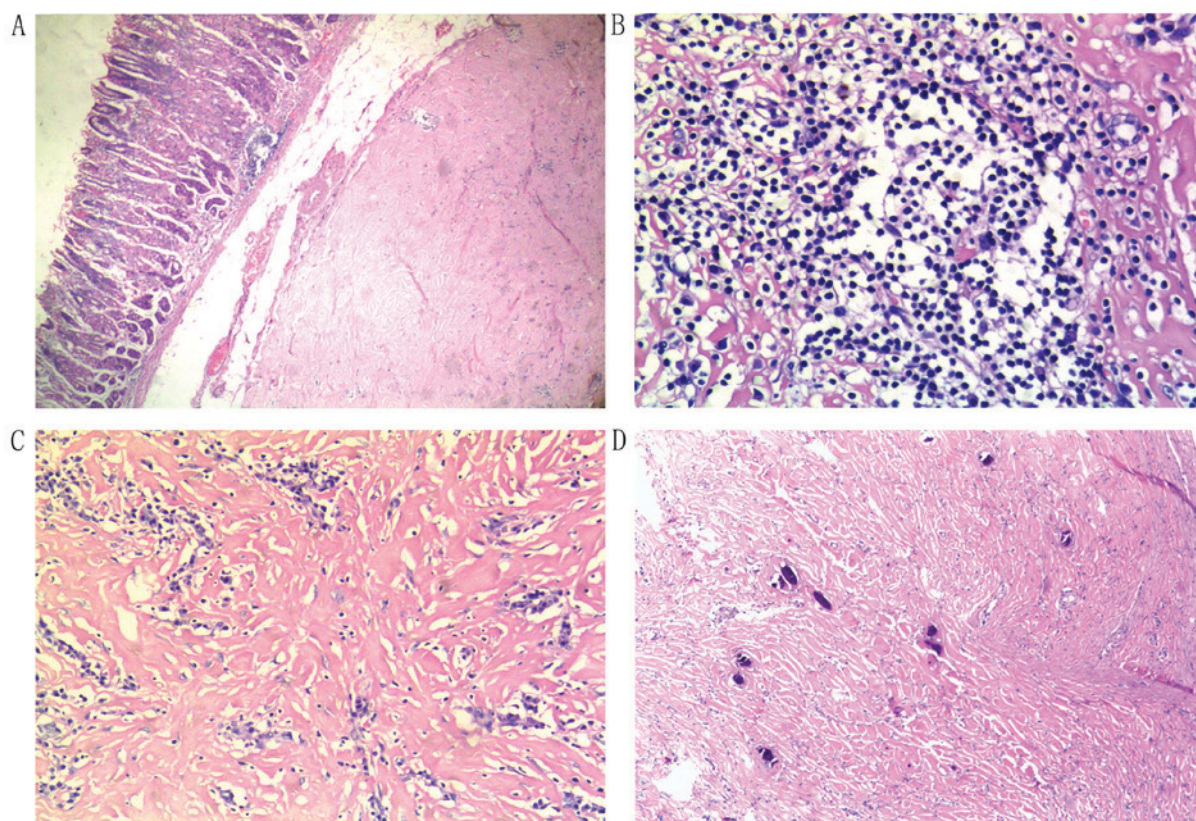


Figure 1. Microscopic features of gastric calcifying fibrous tumor. (A) The mass was well-circumscribed and located in the lamina propria (H&E staining; original magnification, x40). (B and C) Lymphoplasmacytic inflammatory infiltrate was present throughout the tumor and focally formed lymphoid follicles (H&E staining; B, original magnification, x200; C, original magnification, x100). (D) Psammoma and dystrophic bodies are visible in this case (H&E staining; original magnification, x100). H&E, hematoxylin and eosin.

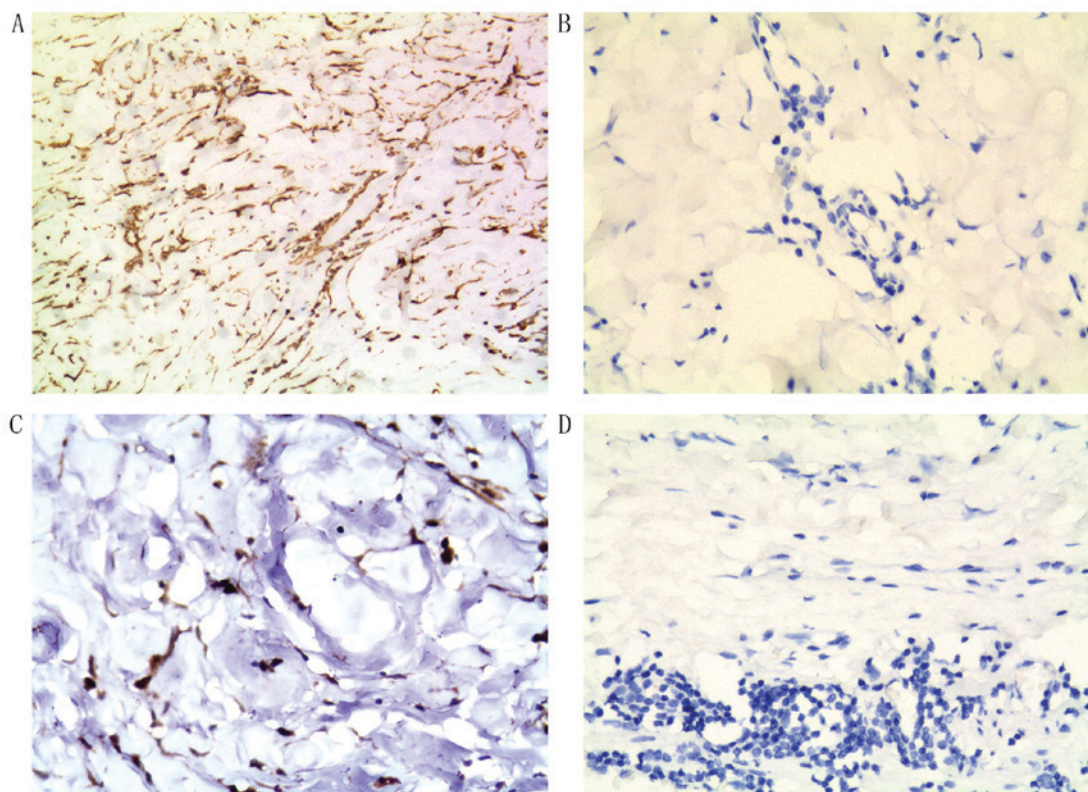


Figure 2. Immunohistochemical features of gastric calcifying fibrous tumor (hematoxylin and eosin staining; original magnification, x200). (A) Vimentin expression was positive; (B) estrogen receptor expression was negative; (C) G protein-coupled estrogen receptor expression was positive. (D) Immunohistochemical negative control.

Table III. Clinicopathologic features of 39 cases of gastric calcifying fibrous tumor from previous studies.

Author	Case no.	Country	Age (years)	Sex	Site	Layer	Size (cm)	Treatment	(Refs.)
Tanaka <i>et al</i>	10	Japan	43	Female	NA	Submucosa	NA	Local excision	(7)
Liu and Song	11	China	32	Male	Body	Submucosa	3.0x2.0x2.0	Local excision	(8)
Nascimento <i>et al</i>	12	USA	64	Male	NA	NA	1.1	Local excision	(9)
Nascimento <i>et al</i>	13	USA	65	Female	NA	NA	0.8	Local excision	(9)
Kitamura <i>et al</i>	14	Japan	44	Female	Body	Submucosa	3x2.6x2.4	LWGR	(10)
Yun <i>et al</i>	15	Korea	59	Male	Fundus	Lamina propria	3.9x2.7	LWGR	(11)
Agaimy <i>et al</i>	16	Germany	51	Male	Body	Lamina propria	2.0	Local excision	(12)
Agaimy <i>et al</i>	17	Germany	77	Female	Body	Lamina propria	1.0	Local excision	(12)
Agaimy <i>et al</i>	18	Germany	59	Female	Body	Lamina propria	3.0	Local excision	(12)
Agaimy <i>et al</i>	19	Germany	53	Male	Antrum	Muscularis mucosae	2.0	Local excision	(12)
Agaimy <i>et al</i>	20	Germany	40	Male	Body	Lamina propria	2.0	Local excision	(12)
Agaimy <i>et al</i>	21	Germany	42	Female	Body	Lamina propria	3.0	Local excision	(12)
Agaimy <i>et al</i>	22	Germany	51	Male	Body	Lamina propria	2.2	Local excision	(12)
Pezhouh <i>et al</i>	23	USA	70	Female	NA	Submucosa	1.3	NA	(13)
Pezhouh <i>et al</i>	24	USA	39	Male	NA	Submucosa	1.5	NA	(13)
Pezhouh <i>et al</i>	25	USA	51	Female	NA	Serosa	0.5	NA	(13)
Pezhouh <i>et al</i>	26	USA	40	Female	NA	Submucosa	2.5	NA	(13)
Pezhouh <i>et al</i>	27	USA	65	Female	NA	Submucosa	1.5	NA	(13)
Shi <i>et al</i>	28	China	58	Female	Body	Lamina propria	2.3	ESD	(14)
Shi <i>et al</i>	29	China	46	Female	Body	Lamina propria	1.0	ESD	(14)
Shi <i>et al</i>	30	China	61	Male	Body	Lamina propria	2.0	EFR	(14)
Shi <i>et al</i>	31	China	53	Male	Antrum	Lamina propria	2.5	EFR	(14)
Fan <i>et al</i>	32	China	49	Male	Body	NA	2.0x2.5	Local excision	(15)
Ogasawara <i>et al</i>	33	Japan	37	Female	Body	Lamina propria	1.0	ESD	(16)
George and Abdeen	34	Kuwait	27	Female	Fundus	Submucosa	1.5x1x0.5	Surgery	(17)
Zhang <i>et al</i>	35	China	55	Female	Body	Submucosa	2.0	ESD	(18)
Vasilakaki <i>et al</i>	36	Greece	60	Male	Body	Lamina propria	1.0x0.8	Local excision	(19)
Attila <i>et al</i>	37	Canada	47	Female	Body	Mucosa	2.0x2.0	LWGR	(20)
Elpek <i>et al</i>	38	Turkey	25	Man	Body	Submucosa	1x0.9x0.5	Urgent surgery	(21)
Puccio <i>et al</i>	39	Italy	49	Female	Body	NA	NA	LWGR	(22)
Štofíková <i>et al</i>	40	Slovakia	68	Female	Body	Submucosa	3.2	Local excision	(23)
Abbadessa <i>et al</i>	41	USA	17	Male	NA	NA	NA	LWGR	(24)
Lee <i>et al</i>	42	Korea	49	Man	Body	Submucosa	3.0	Laparoscopic and endoscopic excision	(25)
Liu <i>et al</i>	43	China	37	Female	NA	NA	NA	Endoscopic resection	(26)
Lee <i>et al</i>	44	Korea	5	Female	Fundus/body	NA	4.0x3.0	Total excision	(27)
Delbecque <i>et al</i>	45	Switzerland	63	Male	Body	Submucosa	2x1.5x1.5	Local excision	(28)
Azam <i>et al</i>	46	Pakistan	13	Male	Fundus	NA	8.0x6.0x6.0	Surgery	(29)
Chatelain <i>et al</i>	47	France	50	Female	Body	NA	2.0	Local excision	(30)
Jang <i>et al</i>	48	Korea	43	Female	Body	Submucosa	3.0x2.0	LGWR	(31)

LWGR, laparoscopic gastric wedge resection; ESD, endoscopic submucosal dissection; EFR, endoscopic full thickness resection; NA, not available.

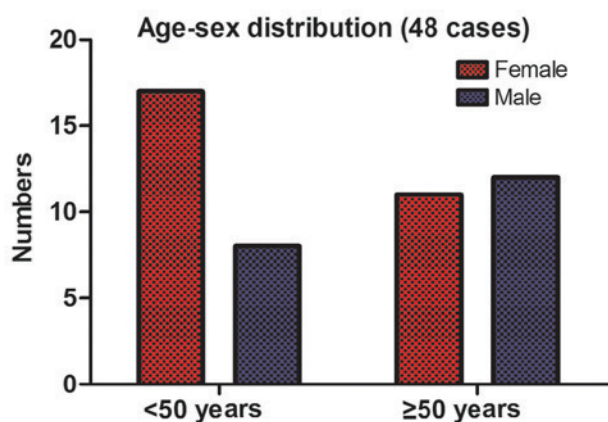


Figure 3. Age-sex distribution of all 48 reported gastric calcifying fibrous tumor cases. The number of female patients was twice that of male patients <50 years of age, whereas the number was almost equal between women and men ≥50 years of age.

ER, also known as classical steroid receptor, is a ligand-activated nuclear transcription factor that recognizes cis-acting hormone response elements in the promoters of hormonally regulated genes (36). The present results revealed that the ER mediation of the classical genomic signal pathway was not associated with the potential effects of estrogen on the pathogenesis of gastric CFTs. Thus, any effects of estrogen on this tumor are likely to be mediated by an alternative pathway. GPER is a membrane-associated estrogen receptor that can mediate both the rapid estrogen and traditional genomic estrogen response signal pathways (36). A previous study demonstrated that estrogen exerts its physiological effects through GPER in normal stromal cells (37). Furthermore, the activation of GPER signaling by estrogen has been reported to stimulate the formation of fibers in fibroblasts (38). Therefore, it can be hypothesized that the activation of GPER by estrogen may promote the formation of fibers, and even fibrosis, in the stomach. However, more basic research regarding the effects of estrogen in gastric CFTs will be required in the future to confirm this hypothesis.

Gastric CFT is a benign lesion with a good prognosis that demonstrates a predilection for female patients, especially premenopausal women. Estrogen mediated by GPER rather than ER may serve a role in this female predominance. The association between gastric CFTs and HP or HBV infection remains to be elucidated in high-calibrated studies.

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Availability of data and materials

The data generated during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ST and WD conceived and designed the present study; XP performed the literature review; ZZ assessed the immunohistochemical results; ST wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the Renmin Hospital of Wuhan University (Wuhan, China). All patients included in this study provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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