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Clinicopathological characteristics of signet-ring cell carcinoma derived from gastric fovelar epithelium

Zhi Shang Zhang[1] | Wei Yi Deng[1] | Si Lin Huang[1] | Bin Feng Yang[2] | Fang Heng Zhu[2] | Bo Jiang[3] | Su Nan Wang[4] | Yang Kun Wang[5]

[1]Department of Pathology, Shenzhen Hospital of Southern Medical University, Shenzhen, Guangdong Province, China

[2]Department of Pathology, Xinxiang Central Hospital, Xinxiang, Henan Province, China

[3]Department of Pathology, The 990th Hospital of the PLA Joint Logistics Support Force, Zhumadian, Henan Province, China

[4]Shenzhen Polytechnic, Shenzhen, Guangdong Province, China

[5]Department of Pathology, Foresea Life Insurance Guangzhou General Hospital, Guangzhou, Guangdong Province, China

Correspondence
Su Nan Wang, Shenzhen Polytechnic, Xili Lake, Xilihu Town, Nanshan District, Shenzhen, Guangdong Province 518055, China.
Email: wangsunan_k@163.com

Yang Kun Wang, Department of Pathology, Foresea Life Insurance Guangzhou General Hospital, No. 703 Xincheng Avenue, Zengcheng District, Guangzhou, Guangdong Province 511300, China.
Email: dr.wyk@163.com

Objective: We aimed to investigate the immunophenotype, differential diagnosis, and clinicopathological characteristics of signet-ring cell carcinoma (SRCC) derived from gastric foveolar epithelium.

Methods: Clinical characteristics, endoscopic findings, histopathological features, and follow-up data of seven cases of SRCC derived from gastric foveolar epithelium with small intramucosal lesions were analyzed.

Results: Seven patients with a mean age of 38.3 years were diagnosed with SRCC derived from gastric foveolar epithelium and small intramucosal lesions, all of them were negative for *CDH-1* germline mutation. The glands proliferated and expanded, and then morphologically transformed into signet-ring cells and formed clonal hyperplastic SRCC, which expanded laterally along the gastric foveolar cells to a length of 3–6 mm. Periodic acid Schiff staining was positive, while CK7 and MUC6 were negative, in all cases. Ki-67-positive cells ranged 37%–60%. During a follow-up period of 6–30 months, no patients experienced tumor recurrence or metastasis.

Conclusions: SRCC derived from gastric foveolar epithelium is originated from the proliferative region of the bottom of the gastric pit and gland neck. It is easily missed diagnosed or misdiagnosed as it grows laterally along the gastric foveolar cells. Biological behavior, genetics, and etiology of such SRCC, as well as the clinicopathological characteristics, need to be further studied.

KEYWORDS
gastric foveolar epithelial cells, immunohistochemistry, pathology, signet ring cell carcinoma

1 | INTRODUCTION

Signet-ring cell carcinoma (SRCC) is a highly malignant gastric adenocarcinoma that often invades the whole stomach wall. SRCC is usually diagnosed at the advanced stage.[1–3] Recent studies have demonstrated that gastric and intestinal immunophenotypes are related to patient prognosis and biological behavior.[4–6]

According to its morphology, gastric cancer can be classified into SRCC and intestinal-type gastric cancer (Lauren classification). According to the lesion site, gastric SRCC can be further divided as tumors derived from the gastric foveolar epithelial cells (surface mucous epithelium), the pyloric gland, and the fundic gland. Intestinal-type gastric cancer, based on the Lauren classification, can be classified into tumors derived from

absorptive epithelial cells and goblet cells according to the lesion location.[7]

SRCC is similar to intestinal-type gastric cancer in the Lauren classification, which arises from the gastric mucosal epithelium.[8] Histologically, there are three to five glands opening on the bottom of the gastric pit that form the basic structural unit of the gastric mucosa (the gastric unit). Additionally, its structure is of monoclonal origin.[9] The gastric unit is composed of gastric foveolar epithelium and gastric glands (composing of isthmus, gland neck, and the basal part).

The cells in the isthmus of the gastric gland and the upper part of the gland neck are considered to be the proliferation area, from which SRCC is originated.[10] However, this area contains a variety of poorly differentiated cells with irregular structures; therefore, it is unclear from which particular cells in the proliferation area SRCC originates.[11,12]

In this study, we summarized the clinicopathological characteristics of seven cases with SRCC derived from gastric foveolar epithelium and small (<5 mm) intramucosal lesions and reviewed the features of previously reported SRCC cases involving the gastric foveolar epithelium (ie, the surface mucous epithelium),[13–17] aiming to improve the understanding of this type of SRCC.

2 | PATIENTS AND METHODS

2.1 | Characteristics of the patients

Seven cases with gastric SRCC derived from foveolar epithelium with small intramucosal lesions diagnosed under gastroscopy and confirmed by histopathological findings of biopsy specimens between January 2017 and December 2019 at the Department of Pathology of Shenzhen Hospital of Southern Medical University (Shenzhen, Guangdong Province, China), Xinxiang Central Hospital (Xinxiang, Henan Province, China), and the 990th Hospital of the PLA Joint Logistic Support Force (Zhumadian, Henan Province, China) were retrospectively identified and included in the analysis. All patients had a family history of gastric cancer in the first and second generations, and were tested for *CDH-1* germline mutations. Three cases underwent endoscopic submucosal dissection (ESD), whereas the other four cases underwent local resection within 20–40 days after the diagnosis was made. All specimens were fixed with 10% neutral buffered formalin for 8–48 h within 30 min after the lesion was resected; the volume of formalin used to that of the tissue specimen was 10:1. According to the standardized sampling and preparation of gastric ESD specimens,[18,19] hematoxylin and eosin (HE) staining and immunohistochemical (IHC) staining were performed.

2.2 | IHC staining

The tissue slides were deparaffinized, hydrated, and rinsed with distilled water using the EnVision two-step method, and were then placed in the tris-buffered saline (TBS) for 10 min. Endogenous peroxidase was inactivated by using blocking buffer for 5 min, and each slide was then treated with TBS for 10 min. Each slide was incubated with primary antibodies (CKpan, CK7, CK20, carcinoembryonic antigen [CEA], villin, CDX2, MUC1, MUC2, MUC5AC, MUC6, p53, Ki-67, and *Helicobacter pylori* [*H. pylori*]; Maixin Biotech, Fuzhou, Fujian Province, China) for 30 min at room temperature. After washing with TBS for 10 min, each slide was then incubated using the EnVision two-step method. After washing with TBS for 10 min, the secondary antibody was applied for 10 min. The chromogenic substrate solution was incubated for 10 min and then washed with distilled water. 3,3′-diaminobenzidine (DAB) was used for color development, and HE was used for redyeing. Adjacent non-cancerous tissue sample was used as the positive control, while the phosphate-buffered saline (PBS) buffer was used as the negative control (instead of the primary antibody). The working system was purchased from Shenzhen Dameng Biomedical Technology (Shenzhen, Guangdong Province, China). The operative procedures were performed strictly in accordance with the manufacturer's instructions. The Ki-67 index was calculated as the number of Ki-67-positive cells per 100 tumor cells.

2.3 | Follow-up

All patients were followed up after they were discharged from the hospital till June 2020 (anywhere from 6 to 30 months). Follow-up was conducted via telephone or in-person visit to evaluate tumor recurrence, long-term outcome and patient survival.

3 | RESULTS

3.1 | Clinical characteristics of the patients

Seven patients aged 26–51 years (mean age 38.3 y) who were diagnosed as SRCC derived from gastric foveolar epithelium with small intramucosal lesions based on gastroscopic findings and histopathological results via biopsy were retrospectively included for analysis. Clinical manifestations of the patients included dull pain and discomfort of the upper abdomen, slight fullness, belching, and acid reflux. All cases were negative for *CDH-1* germline mutation. Lesions in three patients were resected by ESD, and those in the other four patients were managed by local resection within 20–40 days after the diagnosis (Table 1); the resected margins were negative for tumor invasion.

3.2 | Hipathological features

SRCC was originated from gastric fundus in one case, the body of the stomach in three cases, and the gastric antrum in three cases, respectively. Histopathology showed that the mucinous glands in the upper part of the gland neck were increased in five cases (Figure 1A), with signet-ring cells presenting outside the slightly dilated glands (Figure 1B).

TABLE 1 Clinicopathological characteristics and follow-up of signet-ring cell carcinoma derived from gastric foveolar epithelium

Case no.	Age (y)	Sex	Lesion site	Early cancer treatment	Histological features	Staining and immunophenotype	*Helicobacter pylori*	P53 pattern	Follow-up (mo)
1	26	F	Body of the stomach	ESD	The proliferative area grew laterally, of 6 mm in length, with mucosal erosion. Signet-ring cells were seen	Positive for PAS, MUC5AC, CKpan, CK20, CEA, villin, CDX2, MUC2; weakly positive for p53 and MUC1; negative for CK7 and MUC6. Ki67-positive cells were 60%	+	Mutant	28
2	51	F	Body of the stomach	ESD	The proliferative area was expanded laterally, of 4 mm in length, with mucosal erosion. No signet-ring cells were found	Positive for PAS, MUC5AC, CKpan, CK20, CEA, villin, CDX2, p53; weakly positive for MUC1; negative for CK7, MUC2, MUC6. Ki67-positive cells were 40%	-	Mutant	30
3	43	M	Gastric antrum	Local resection	The proliferative region is transversely expanded, of 3 mm in length, with local depression. Signet-ring cells were seen	Positive for PAS, MUC5AC, CKpan, CK20, CEA, villin, CDX2, MUC2; weakly positive for p53; negative for CK7, MUC1, MUC6. Ki67-positive cells were 54%	+	WT	27
4	39	M	Gastric antrum	Local resection	The proliferative region was transversely expanded, of 5 mm in length, and partially depressed. Signet-ring cells were seen	Positive for PAS, MUC5AC, CKpan, CK20, CEA, villin, CDX2, MUC2; negative for CK7, MUC1, p53, MUC6. Ki67-positive cells were 37%	-	WT	14
5	34	F	Gastric fundus	ESD	The proliferative region was transversely expanded, of 6 mm in length, with local depression. No signet-ring cells were found	Positive for PAS, MUC5AC, CKpan, CK20, CEA, villin, CDX2; negative for CK7, p53, MUC2, MUC1, MUC6. Ki67-positive cells were 57%	-	Mutant	11
6	47	M	Body of the stomach	Local resection	The proliferative region is laterally expanded, of 4 mm in length, with local depression. Signet-ring cells were seen	Postivie for PAS, MUC5AC, CKpan, CK20, CEA, villin, CDX2, p53; weakly positive for MUC1; negative for CK7, MUC2, MUC6. Ki67-positive cells were 48%	-	Mutant	23
7	28	F	Gastric antrum	Local resection	The proliferative area was transversely expanded, of 5 mm in length, with mucosal erosion. Signet-ring cells were seen	Positive for PAS, MUC5AC, CKpan, CK20, CEA, villin, CDX2, MUC2; weakly positive for p53; negative for CK7, MUC1, MUC6. Ki67-positive cells were 44%	+	WT	6

Abbreviations: CEA, carcinoembryonic antigen; CK, cytokeratin; F, female; M, male; PAS, periodic acid Schiff; WT, wild-type; +, positive; -, negative.

Single or multiple signet-ring cells, transformed from columnar cells, presented among mucous neck cells. They were round in shape and large in volume, with a diameter of once to twice the peripheral columnar epithelium and a crescent-shaped nucleus (Figure 2A). These cells originated from the area between the normal mucous neck cells and gradually moved outside the gland (Figure 2B). After differentiation and transformation, the cells presented with independent monoclonal proliferation (Figure 2C). Multiple immature signet-ring cells were observed in the proliferative zone; however, there were no mature signet-ring dysplastic cells (Figure 2D).

The growth pattern and size of the SRCC are summarized in Table 1. Inflammatory cells, such as lymphocytes, plasma cells, neutrophils infiltration in the stroma, and lymphoid follicles in the stroma, were observed. There was no fibrous connective tissue proliferation, or mucus and intestinal metaplasia. In these seven cases with SRCC derived from gastric foveolar epithelium, transverse expansion was seen in one-third of the opening side of gastric fundic mucosa (Figure 3A), with a length of 3–6 mm.

Among the seven cases, three presented with gastric mucosal erosion or mucosal ulcer (Figure 3B), and the other four had local mucosal depression caused by mucosal thinning (Figure 3C). Three (42.9%) of the cases were infected with *H. pylori* (Figure 4A), which was confirmed by IHC staining (Figure 4B).

Five types of cytological morphology were observed: (a) typical signet-ring cells were round, of 15–30 μm in diameter, vacuolated, with mucus in the cytoplasm being reddish. The nuclei were eccentric, with a signet-ring or crescent shape (Figure 5A). (b) Immature signet-ring cells were round or irregular in shape, and the cytoplasm was strongly eosinophilic. The nucleus was irregular, round, oval, or eccentric, with a ratio of nucleus to cytoplasm of 1:1–3. The chromatin of the nucleus was bichromatic (Figure 5B). (c) The highly proliferative signet-ring cells were round or oval, had a uniform cytoplasm, and

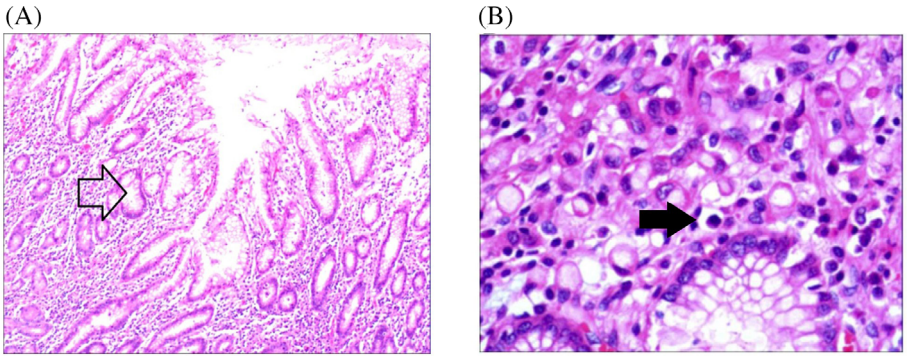


FIGURE 1 Signet-ring cell carcinoma derived from gastric foveolar epithelium. A, Mucinous glands increased in the upper part of the neck (arrowhead; HE stain, ×100). B, Signet-ring cells outside the slightly dilated glands (arrowhead; HE stain, ×200)

were slightly stained with a bichromatic mucus. The nuclei were large and eccentric, with prominent nucleoli (Figure 5C). (d) The non-nucleus vacuole signet-ring cells (vacuolated caused by the cut surface during tissue slicing) maintained the outline of the cytoplasm and the light-red-stained mucus in the cytoplasm (Figure 5D). (e) The degenerative signet-ring cells had a larger cell volume, ranging 20–40 μm (up to 50 μm), with a capsule or incomplete capsule. The nucleus was small and lightly stained gray, or there was no nucleus (Figure 5E).

3.3 | Periodic acid Schiff (PAS) and IHC staining

All of the seven cases were positive for PAS staining (Figure 6A). Additionally, IHC staining showed that MUC5AC (Figure 6B), CKpan, CK20 (Figure 6C), CEA, villin (Figure 6D), and CDX2 were positive in all seven cases. Four cases were MUC2-positive (Figure 6E), while MUC1 was weakly positive in three cases and negative in the other four cases. P53 was positive in two cases, weakly positive in three cases, and negative in the other two cases. All cases were negative for CK7 and MUC6. The percentage of Ki-67-positive cells in the seven cases ranged 37%–60% (Figure 6F and Table 1). The highly proliferative signet-ring cells corresponded to the Ki-67-positive cells.

3.4 | Follow-up

During a follow-up period of 6–30 months, no patients experienced tumor recurrence or metastasis.

4 | DISCUSSION

SRCC is usually diagnosed at an advanced stage. One reason might be that the pathological formation mechanisms and the histomorphological features of precancerous lesions of SRCC remain unclear.[20–22] Small lesions in the lamina propria have been reported to be difficult to diagnose under endoscopy. The incidence of lymph node metastasis in early SRCC is much lower than that in moderately and poorly differentiated carcinomas. When a SRCC invades the submucosa, tumor cells spread rapidly and widely.[23] Early diagnosis is difficult to be made in patients with *CDH-1* mutation.

Early SRCC is often not visible under endoscopy. Advanced hereditary diffuse gastric cancer is characterized by its rapid spread. A histological examination of the entire, generally normal, gastric mucosal specimens obtained by preventive gastrectomy is still the standard practice for asymptomatic carriers of *CDH-1* mutation. Close inspection can identify over 90% of SRCC, mainly multifocal and intramucosal carcinomas, as well as those in situ.

In this study, seven cases of *CDH-1* germline mutation-negative SRCC derived from gastric foveolar epithelium with small intramucosal lesions were analyzed. Lymph node metastasis or submucosal tumor involvement was not observed after ESD or local resection of the lesions. Moreover, there was no recurrence during a follow-up period of 6–30 months. SRCC derived from gastric foveolar epithelium originates from the isthmus of the gastric gland and the proliferation area of the upper part of the gland neck. The characteristic for the distinguishment of SRCC derived from gastric foveolar epithelium from other SRCC is that signet-ring cells could be seen in the isthmus at the initial stage.

At first, there are more glands in the gland neck with slight expansion, and signet-ring cells present between the mucous neck cells. The shape of the cells changes from columnar to round, and their volume increases with the diameter being 1–2 μm longer than the peripheral columnar epithelium. The nucleus is crescent-shaped. The signet-ring cells then gradually move outside the gland, and are transformed, differentiated, and proliferated to form an independent monoclonal proliferation. The transformed clonal SRCC cells mainly distribute in the area of the first-third of the fundic gland mucosa, showing transverse expansion and a "creeping" spread in the foveolar stroma of the stomach. Because of the enlargement and retention of the proliferative region, cell growth and differentiation of normal gastric mucosa are inhibited, resulted in gland atrophy in the lamina propria of the gastric mucosa and the formation of local mucosal invagination.

Six aspects for the diagnosis of SRCC were proposed. At the early stage of the disease, the glands in the gastric foveolar epithelium proliferate and expand, and signet-ring cells could be seen in most cases. The cancer cells extend laterally along the gastric foveolar cells to the length of 3–6 mm. The morphology of signet-ring cells can be divided into the typical signet-ring cells, immature signet-ring cells,

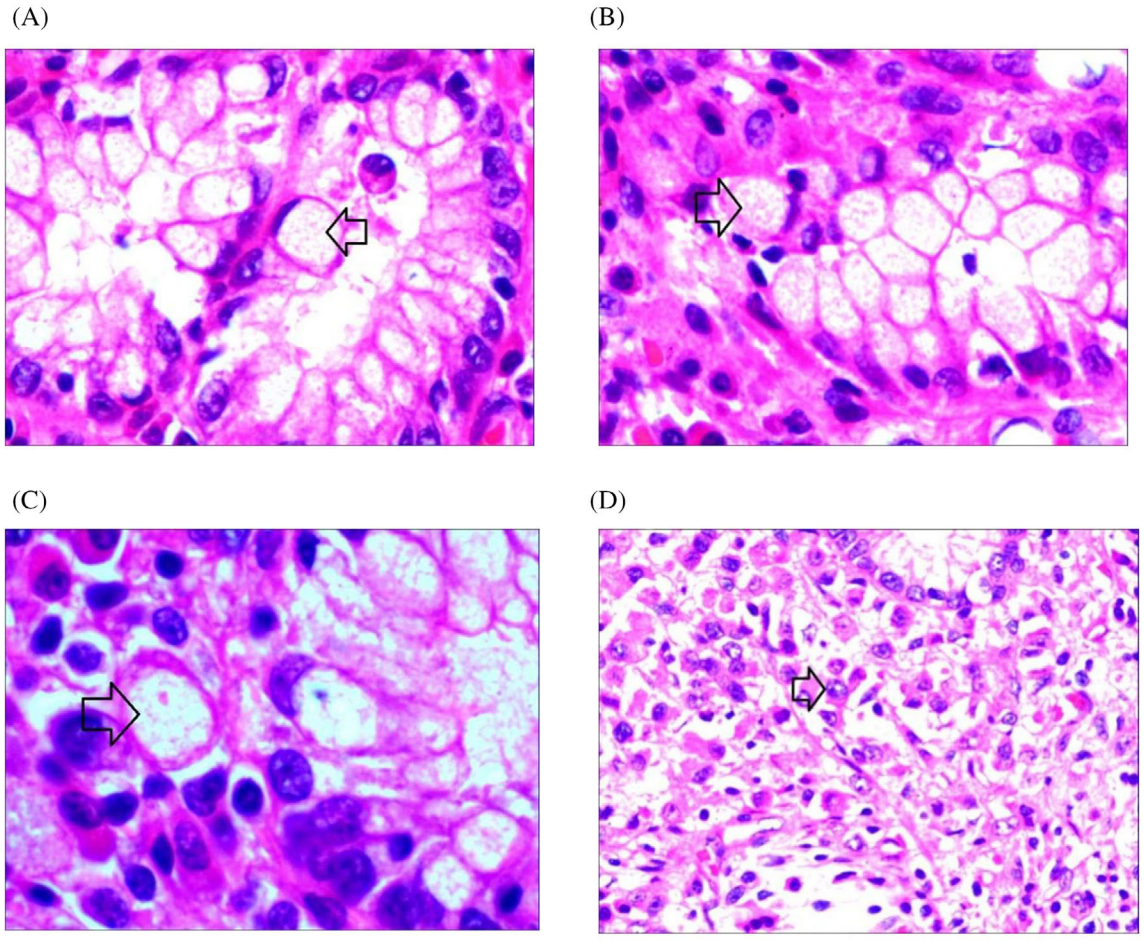


FIGURE 2 Signet-ring cell carcinoma derived from gastric fovea epithelium. A, In the area between the cells of the mucinous gland, the cells were round and enlarged in volume (arrowhead). The diameter of the cells was once to twice that of the surrounding columnar epithelium, and the nucleus was crescent shaped (HE stain, ×400). B, Signet-ring cells moved outside the gland (arrowhead; HE stain, ×400). C, Signet-ring cells located in the stroma (arrowhead; HE stain, ×400). D, A large number of immature signet-ring cells in the proliferative zone (arrowhead), but no signet-ring dysplastic cells (HE stain, ×200)

highly proliferative signet-ring cells, non-nucleus vacuole signet-ring cells, and degenerative signet-ring cells. Less than half (42.9%) of our cases were accompanied by *H. pylori* infection. The cancer cells located in the proliferative region inhibit normal differentiation of gastric glands, resulted in gland atrophy of the lamina propria and local mucosal invagination. PAS staining was positive for all of our cases, together with positive staining of MUC5AC, CKpan, CK20, CEA, villin, and CDX2. Lauren intestinal-type gastric cancer is positive for MUC2, CDX-2, and CD10; however, SRCC of gastric foveolar epithelium is positive for MUC1, MUC5AC, and MUC6. In addition, SRCC of gastric foveolar epithelium is more prevalent in women and young individuals, and is associated with *H. pylori* infection.

More than half of the world's population is infected with *H. pylori*, most of whom are asymptomatic. Approximately 10% of *H. pylori*-infected population develop peptic ulcer, atrophic gastritis, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma.[19,24–26] An increasing amount of evidence has shown that the *H. pylori* strain, the host, the presence of cyclobacteria and other factors jointly determine disease occurrence and development.[27]

As an important part of the micro-ecological environment in the stomach, gastric flora maintains the balance of gastric environment through a variety of regulatory pathways. Change in bacterial community structure leads to dysbiosis and disease development.[28] World Health Organization has classified *H. pylori* as a pathogen of gastric cancer, and *H. pylori* eradication can prevent gastric cancer.[29] Because *H. pylori* adheres to and selectively destroys the cytoplasm of the mucous cells, the cytoplasm is swollen and vacuolated, and the degenerated epithelial cells rupture, leading to gastric mucosal erosion or ulcers.[30] In cases of *H. pylori* infection in SRCC of gastric foveolar epithelium, *H. pylori* is often located in the neck of the gland, from which this type of SRCC originates. To determine whether *H. pylori* infection can directly lead to the spread and transformation of the cells in the proliferating area as well as the occurrence of SRCC derived from gastric foveolar epithelium, the processes and growth mechanisms require further study.

Another important factor contributing to the low rate of early diagnosis of gastric SRCC is that it is easily missed diagnosed and misdiagnosed. This is especially true in that the differentiation stage of

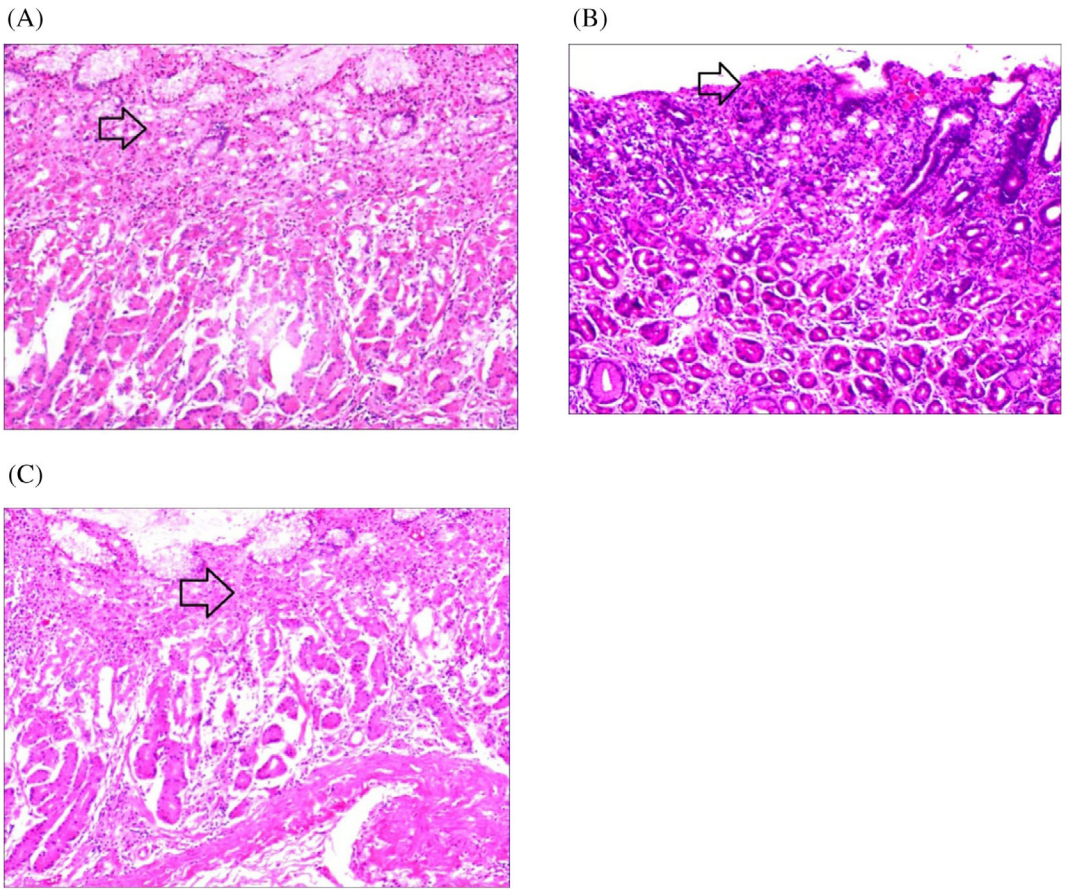
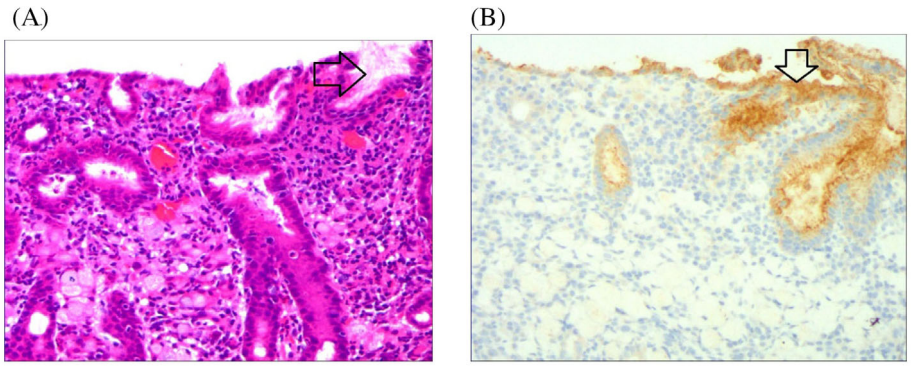


FIGURE 3 Histological morphology of signet-ring cell carcinoma derived from gastric foveolar epithelium. A, Cancer cells (arrowhead) were located in the proliferative zone of the gastric fundus and the gland neck. One-third of the opening side of gastric fundic mucosa showed transverse expansion; B, Gastric mucosal erosion or small ulcer (arrowhead) on the surface of gastric mucosa. C, Local mucosal depression (arrowhead) caused by mucosal thinning. HE stain, ×40

FIGURE 4 A, Signet-ring cell carcinoma derived from gastric foveolar epithelium (arrowhead) with *Helicobacter pylori* infection and infiltration of inflammatory cells such as interstitial lymphocytes, plasma cells, and neutrophils (HE stain). B, *Helicobacter pylori* (brown; arrowhead) (EnVision two-step method). Magnification, ×200



SRCC of gastric foveolar epithelium is usually not detected early enough.

Through the analysis of seven cases of early SRCC, we summarized the location, growth mode, distribution, differentiation, and morphological characteristics of five types of SRCC cells, along with the histopathological and differential diagnosis of SRCC derived from gastric foveolar epithelium.

Investigation of the pathogenesis and development of SRCC together with the mechanisms are vital for the establishment of management strategies of the disease. Studies with large sample sizes and long follow-up period are urgently warranted. In addition, the biological behavior, genetics, and etiology of SRCC derived from gastric foveolar epithelium, as well as the clinicopathological characteristics, need to be further studied.

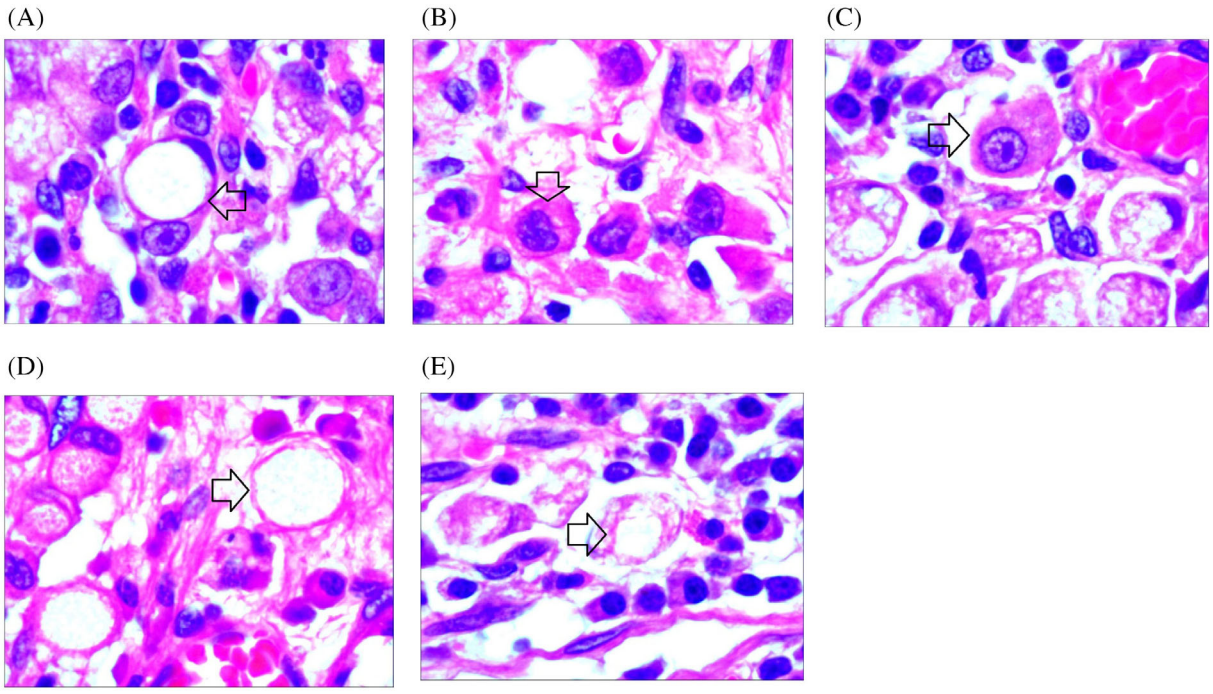


FIGURE 5 A, Typical signet-ring cells (round cell of 15–30 μm in diameter) (arrowhead) with reddish mucus in the cytoplasm, nucleus deviation, signet-ring shaped, or crescent-shaped nucleus. B, Immature signet-ring cells (arrowhead) were round or irregular in shape and strongly eosinophilic in the cytoplasm; the nucleus was irregular, round or oval, eccentric, with a ratio of nucleus to cytoplasm of 1:1–3; the chromatin of nucleus was bichromatic. C, Highly proliferative signet-ring cells (arrowhead) were round or oval with uniform cytoplasm and stained with bicolor mucus. The nuclei were large and eccentric, with prominent nucleoli. D, This type of signet-ring cells (arrowhead) were presented by the cut surface during the slicing, which kept the outline of the cytoplasm. The cytoplasm was stained with light red mucus. E, The cell volume of degenerative signet-ring cells (arrowhead) ranged 20–40 μm (up to 50 μm), with capsule or incomplete capsule, small and light stained nucleus, dark or no nucleus. HE stain, ×600

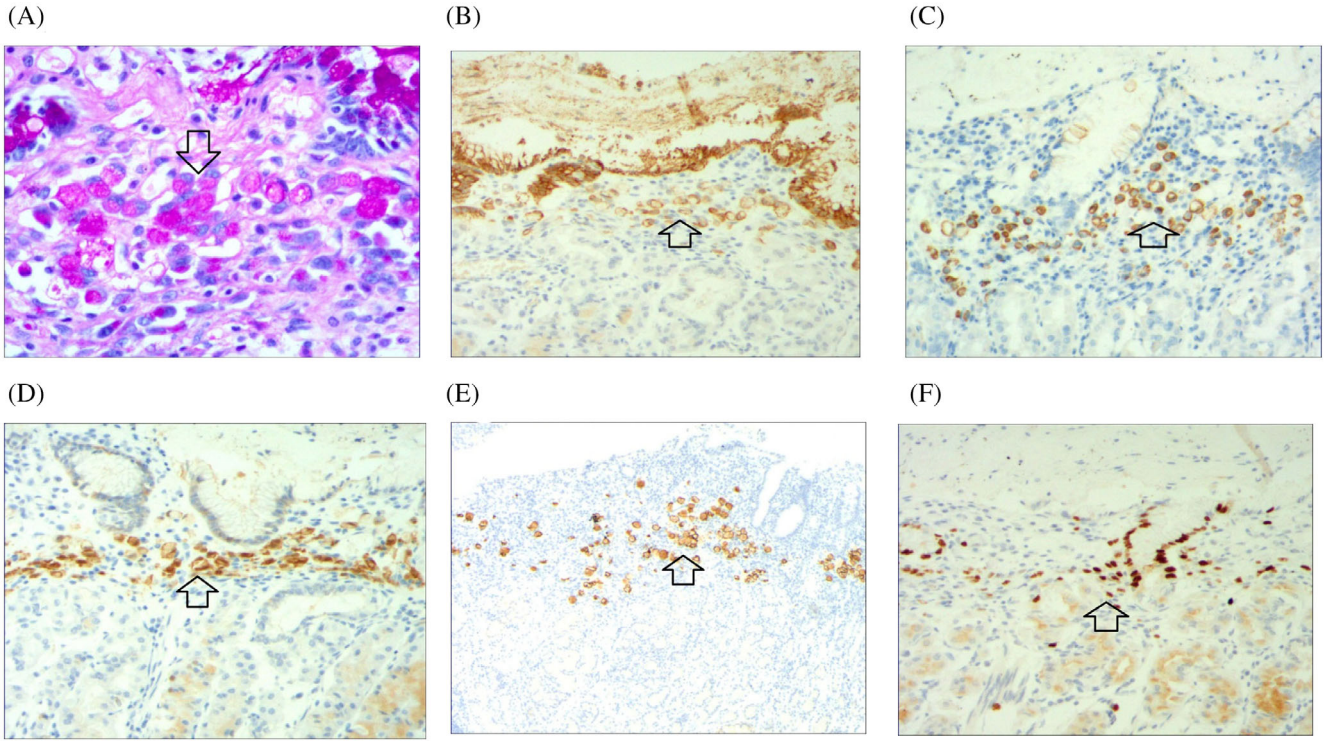


FIGURE 6 A, Signet-ring cell carcinoma was purplish red with special staining of periodic acid Schiff (PAS). The signet-ring cells were positive for B, MUC5AC, C, CK20, D, villin, and E, MUC2 (arrowhead; EnVision two-step method). F, The number of Ki-67-positive cells (arrowhead) was 44% (EnVision two-step method). Magnification, ×200.

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CONFLICT OF INTEREST

None.

ORCID

Yang Kun Wang https://orcid.org/0000-0002-5550-7058

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