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ORIGINAL RESEARCH

Histopathologic features of esophageal glands in the region of the gastroesophageal junction in Chinese patients with gastric cardiac cancer involving the esophagus

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Abstract: Esophageal glands (EGs) were implicated previously as a potential origin of carcinomas of the gastroesophageal junction (GEJ). The studies of histopathology on diseases in EGs, however, are scarce. In the present study, we systematically investigated EGs in 36 resection cases of gastric cardiac carcinomas involving the esophagus (GCE) in Chinese patients. All cases showed chronic inflammation in EGs and 14 (39%) with *Helicobacter pylori* infection. Hyperplasia, atrophy, and dysplasia were common in EGs and observed in 21 (58%), 14 (39%), and 28 (78%) cases, respectively. These changes were associated with various types of metaplasia, including intestinal (6, 17%), oncocytic (26, 72%), pancreatic acinar (11, 30%), and squamoid metaplasia (8, 22%). Oncocytic metaplasia was patchy, frequently replaced the entire lobule with dysplastic features. Pancreatic acinar metaplasia was present in superficial EGs as small acinar patches. Squamoid metaplasia was limited to the EG drainage ductile epithelium without keratin pearls or intercellular bridges; however, cytoplasmic vesicles and secretory vacuoles were common, suggesting dual differentiation. Dysplastic EGs featured architectural disarray with fused acini, cribriforming, abortive growth, and nuclear hyperchromasia, enlargement, and overlapping. The results demonstrate a spectrum of histopathologic changes in EGs and ductile epithelium, which is similar to those observed in GCE in Chinese patients.

Keywords: esophageal glands, esophagus, stomach, cancer, Chinese

Introduction

In the gastroesophageal junction (GEJ) region, esophageal glands (EGs) are unique and clustered at the distal end of the esophagus, but absent in the proximal stomach. Therefore, they are considered as the definitive histological evidence of the esophagus, especially in equivocal situations,[1,2] such as classification of tumors in the GEJ region.[3] Despite the strategic location and important physiological function of EGs,[1,2] their histopathologic profiles have not been systematically investigated. There are only a few case reports in the literature that describe dysplastic adenomatous changes in EGs.[4,5] Two recent case reports documented malignant proliferation of EGs, evolving into adenocarcinomas.[6,7] In our recent study of 41 cases of gastric cardiac carcinomas involving the esophagus (GCE) in Chinese patients,[8] we found that some well-differentiated carcinomas were located in the places where EGs lie in normal esophagi. These carcinomas showed a wide spectrum of histopathologic features, including multiple phenotypical differentiations and growth patterns within one cancer, which

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are not the features of GEJ carcinomas observed in American Caucasian patients.[9] We took advantage of this dataset to study the histopathologic features of the EGs associated with these carcinomas in Chinese patients.

Materials and methods

Patients

This retrospective study was carried out in 41 consecutive cases of gastric cardiac carcinomas in patients treated at the Nanjing Drum Tower Hospital over the period from May 2004 to March 2005. All patients were from a homogenous Chinese population whose tumors were diagnosed radiologically, endoscopically, and pathologically as gastric cardiac carcinomas invading through the GEJ into the distal esophagus. All tumors were surgically resected. The study protocol was approved by the Medical Ethics Committee of the Nanjing Drum Tower Hospital in Nanjing, China.

Specimens

The surgical resection specimens of GCE were processed according to a standard anatomical pathology specimen processing protocol. The GEJ was defined as the proximal end of the gastric longitudinal mucosal folds. All 41 tumors were located in the proximal stomach, up to 2 cm within the GEJ, and had invaded into the distal esophagus to various extents. Thus, these tumors were classified as Siewert type II GEJ carcinomas.[10] No frank macroscopic evidence of distal esophageal columnar metaplasia was identified in any case. All specimens were fixed in 10% buffered formalin solution overnight and then sampled. Multiple sections were taken from the tumors, the GEJ, and the esophageal and gastric walls adjacent to the tumor. Paraffin-embedded tissues were sectioned at 5 μm. Sections were stained with hematoxylin and eosin (H&E) and reviewed under a light microscope. In five cases, the carcinomas were poorly differentiated; in three cases they had destroyed the entire squamous columnar junction, and the diagnostic slides for EG analysis were not available in the remaining two. Thus, the current study was carried out in 36 cases with a total of 325 slides: nine per case on average (range: 2–21).

Esophageal gland (EG)

In the GEJ region, there are two types of EGs:[11]

Type one

Superficial EGs that are located underneath the squamous mucosa but above the muscularis mucosa, and concentrated in the area surrounding the esophageal squamous mucosal end (Figure 1, A and B). Histologically, superficial EGs are similar, if not identical, to gastric cardiac glands that are located in the most proximal stomach; both merge at the distal end of the esophagus. Therefore, superficial EGs are also known as esophageal cardiac-type glands if they reside underneath the squamous mucosa[11] (Figure 1, A, C, and D). The lengths of the gastric cardiac mucosa and of the superficial EG were measured on the sections. The lengths of the gastric cardiac mucosa were measured from the end of the esophageal squamous epithelium to the most distal cardiac glands available for assessment, while the lengths of the superficial EG were measured from the end of the esophageal squamous epithelium to the most proximal subepithelial superficial cardiac glands.

Type two

Deep EGs which are known as esophageal submucosal glands, and are located deeper, underneath the esophageal muscularis mucosa (Figure 1). The drainage duct of a deep EG penetrates upwards at a right angle through the muscularis mucosa, and communicates with the surface of esophageal squamous mucosa. Each deep EG is defined as an independent acinar lobule, with or without a drainage duct. The number of deep EGs per case was counted on the sections available for analysis. We recorded and analyzed the major pathologic changes within each EG, such as inflammation, hyperplasia, atrophy, cystic changes, and various types of metaplasia such as intestinal, oncocytic, squamoid, and pancreatic acinar metaplasia. The criteria for diagnosis of dysplasia included both cytological features such as nuclear

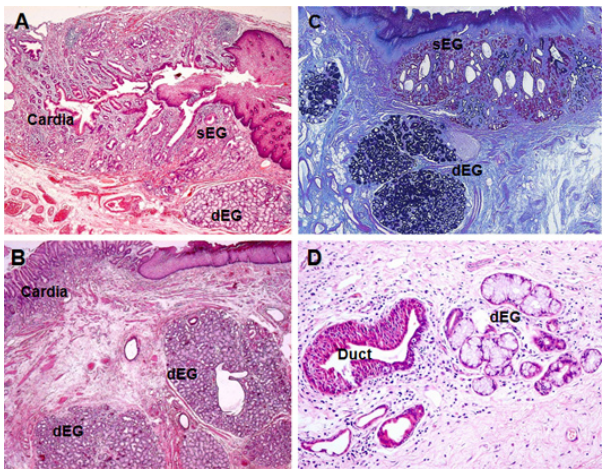

Figure 1 Microscopic images showing: **A**) The relationship between gastric cardiac mucosa, superficial esophageal glands (sEGs), and deep esophageal glands (dEGs). **B**) Hyperplastic changes in dEGs feature markedly enlarged lobule size. **C**) PAS-AB stain highlights intense acidic mucin (blue) in dEGs, and predominant neutral (red) and patchy acidic mucin in sEGs. **D**) Atrophic dEG with a drainage duct exhibits multilayered squamoid metaplasia. (Original × 20 in A, B, and C; and × 40 in D. H&E stains in A, B, and D; PAS-AB stain in C).

hyperchromasia, enlargement, overlapping, stratification, and prominent nucleoli, and architectural disarray such as glandular crowding, fusing, cribriforming, abortive irregularity, and anastomosis of dysplastic acini. No attempts were made to further subclassify dysplasia into low- and high-grade groups. Once abortive dysplastic glands or single cells had infiltrated into the stroma, the lesion was classified as invasive carcinoma.

Histochemical stains

Conventional periodic acid-Schiff – Alcian blue at pH 2.5 (PAS-AB) stains to detect goblet cells and mucinous vesicles and vacuoles were carried out on selected tissue sections. Routine Giemsa stain for *Helicobacter pylori* was performed with positive control for each run.

Immunohistochemistry

For select cases with a histological impression of pancreatic acinar metaplasia on H&E-stained sections, we performed routine immunohistochemical staining for the α-chymotrypsin protein antigen with the method described previously.[8] Briefly, paraffin-embedded tissue blocks were cut at 5 μm thickness. Sections were mounted and deparaffinized in fresh xylene and then re-hydrated in graded ethanol solutions from 100% down to 90%, 75%, and finally 50%. After subsequent washing in a phosphate-buffered saline (PBS) solution, sections were incubated with 3% H_2O_2 for blocking of endogenous peroxidases, and then incubated, first in heat-induced epitope retrieval (HIER) EDTA buffer (Dako Gene Company Ltd, Shanghai, China). The section was then incubated with a primary anti-α-chymotrypsin antibody (dilution 1:100; Zymed Lab, South San Francisco, CA) at 4°C over night. The sections were subsequently washed in PBS. The Dako Envision™ Dual Link Kit (Dako Gene Company Ltd) was used to visualize immunoreactive cells on the section after a brief histochemical reaction with 3,3′-diaminobenzidine and then hematoxylin counterstaining. Appropriate positive controls (pancreatic tissue) and negative controls (human tonsil and normal horse serum without the primary antibody) were run for each batch of slides.

Statistical analysis

Most statistical analyses were carried out with Microsoft Excel (Microsoft, Redmond, WA). Differences in patients, and in histopathological features were evaluated with the Chi-squared test and Fisher's exact test. Statistical significance was set at the 5% level.

Results

Patient demographic data

Of the 36 patients, 27 (75%) were male and 9 (25%) female. The male–female ratio was 3:1. Patient median age at diagnosis was 62 (± 10, SD) (range: 39–84) years. The average age of the male patients was slightly older (63 ± 12) than that of the females (60 ± 6), but the difference was not statistically significant.

EGs, cardiac and distal esophageal mucosa

Gastric cardiac mucosa was present in all cases with various lengths (range 0.1–1.9 cm; 0.62 ± 0.45). Superficial EGs were found in 30 (83%) cases (range 0.1–0.9 cm; 0.19 ± 0.19). Both gastric cardiac glands and superficial EGs were continuous, hyperplastic, tortuous, and frequently fused (Figure 1, A and B). In contrast, deep EGs were densely populated in the GEJ region (Figure 1B). Unlike the situation which is commonly seen in American Caucasian patients with esophageal adenocarcinomas,[9] in Chinese patients, these deep EGs were almost always underneath the squamous mucosa and rarely extended distally more than 1.0 mm into the proximal stomach (Figure 1, A–C). The median number of deep EGs was 12 (±10; range: 1–43) per case. This number may be underestimated because the entire GEJ was not examined histologically. In general, both superficial and deep EGs were lined with cuboidal epithelial cells with a vesicular, primarily mucinous cytoplasm in which large droplets of mucus occupied most of the cell cytoplasm and compressed the nucleus to the base. In contrast, deep EGs were multilobulated, and smoothly circumscribed (Figure 1, A–C). On PAS-AB stains, the cytoplasm of the superficial EGs was largely positive for neutral mucin, with patchy lobules showing acidic mucin, in contrast to the overwhelmingly intense acidic mucin stain in deep EGs (Figure 1C). The overall histopathologic changes in EGs were most conspicuous in the GEJ region and became less evident in the proximal portions of the esophagi that were available for evaluation.

The overlying esophageal squamous mucosa showed mild acanthosis, spongiosis, and occasional parakeratosis with mild chronic inflammation in most cases. No dysplasia or carcinoma *in situ* was detected. The classic Barrett esophageal mucosa with intestinal metaplasia was not identified.

Chronic inflammation, hyperplasia, and atrophy

As summarized in Table 1, chronic inflammation in EGs was present in all cases with predominant lymphoplasmacytic

Table 1 Summary of histopathology in superficial and deep esophageal glands

Histopathologic features	N	%*
Hyperplasia	21	58
Helicobacter pylori infection	14	39
Chronic inflammation	36	100
Atrophy, cystic changes	14	39
Metaplasia		
Intestinal	6	17
Oncocytic	26	72
Pancreatic acinar	11	30
Squamoid	8	22
Dysplasia	28	78

Notes: *The differences in disease frequency were statistically significant ($P < 0.001$) for chronic inflammation, oncocytic metaplasia, dysplasia than in other diseases.
Abbreviation: N, number.

infiltration (Figure 1) and some with *H. pylori* infection (Table 1). Occasionally, there were lymphoid follicles interspersed within or underneath the gastric cardiac-type mucosa at the GEJ (Figure 1A) and within superficial EGs. In general, gastric cardiac glands showed hyperplastic changes in villiform, serrated, or papillary configurations. In contrast, hyperplastic changes in deep EGs manifested as markedly enlarged EG lobules with dense vesicular mucin-containing acini. These hyperplastic deep EGs were arranged in high densities in the GEJ region (Figure 1, A–C) and were usually associated with scattered lymphoplasmacytic infiltration in the stroma. Some deep EGs showed marked atrophy, with much smaller lobule size, and reduced number of mucin acini (Figure 1D) or they exhibited cystic and/or oncocytic changes.

Dysplasia

In EGs, dysplastic changes in acinar epithelial cells were common (Table 1). Overall, EGs with dysplastic changes maintained architectural integrity, to some degree, and almost always featured fused acini with dysplastic nuclei. As shown in Figures 2 (B and C) and 3 (A–F), dysplastic nuclei were hyperchromatic and considerably enlarged. Nuclear polarity was maintained, and stratification with two or more layers of nuclei was rare. The nuclear membrane was thickened but smooth; the nuclear chromatin was pale-gray. Nucleoli were conspicuous (Figures 2B, 2C, 3B, and 3C). Mitosis or necrosis was rare (Figure 3F). The mucinous cytoplasm of EG epithelial cells was markedly reduced and thus the nuclear–cytoplasmic ratio was considerably increased. In some dysplastic acini, the cytoplasm became markedly vesicular and vacuolated (Figure 2C). These dysplastic changes were almost always associated with other diseases such as chronic inflammation, atrophy, and various types of metaplasia (Figures 2–5). Dysplastic EGs were frequently found adjacent to cancer tissue.

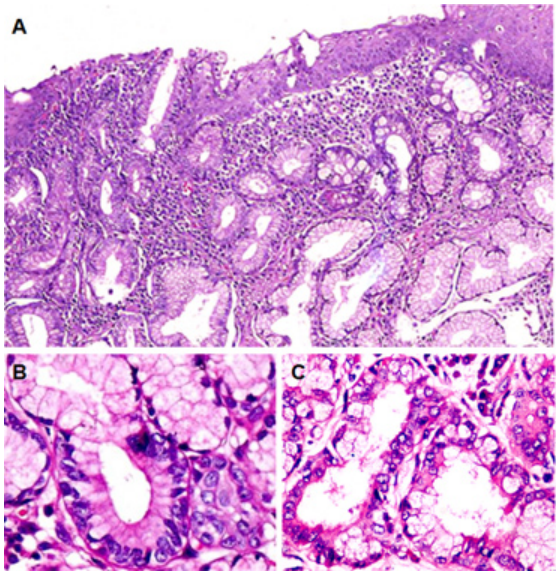

Figure 2 Microscopic images of sEGs showing: **A**) focal intestinal metaplasia, and **B**) dysplastic epithelial cells, with hyperchromic and markedly enlarged nuclei and reduced cytoplasm. Dysplastic acina fuses with adjacent nondysplastic acina. **C**) dysplastic acini feature vesicular cytoplasm. (Original × 40 in A, × 400 in B and C. H&E stain).
Abbreviations: H&E, hematoxylin & eosin; sEGs, superficial esophageal glands.

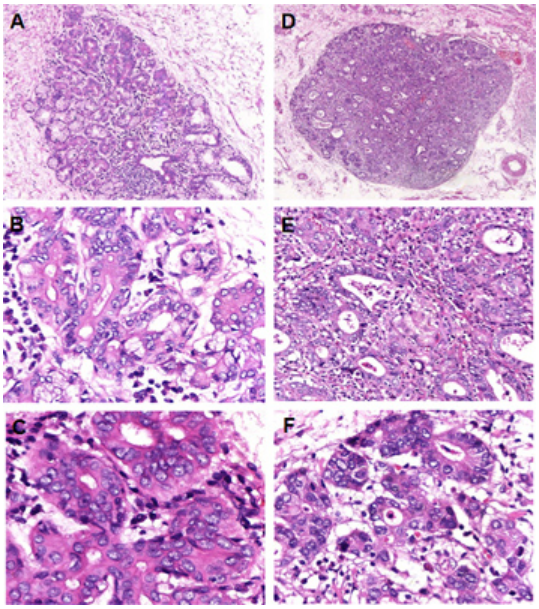

Figure 3 Microscopic images of two dysplastic dEGs. Left column: **A**) a dEG shows crowded, dysplastic acini with hyperchromatic nuclei associated with chronic inflammation. **B**) Dysplactic acini become irregular, fused, and cribriforming. **C**) Dysplastic mucin cells show markedly reduced vesicular cytoplasm and crowded, overlapped nuclei with prominent nucleoli. Right column (Another dEG): **D**) carcinoma *in situ* in a well-circumscribed contour. **E**) Malignant acini are irregular, fused, and microcystic. **F**) Abortive acini and mitotic figures are present. (Original × 20 in D, × 40 in A, × 200 in E, × 400 in B and F, and 600 in C. H&E stain).
Abbreviations: dEGs, deep esophageal glands; H&E, hematoxylin & eosin.

Intestinal metaplasia

Typical intestinal metaplasia with classic metaplastic goblet cells was infrequent in superficial EG (Figure 2A), was absent in deep EGs, and was usually associated with predominant lymphoplasmacytic infiltration, but not with active inflammation (Figure 2A, Table 1). Instead, hyperplastic superficial and deep EGs with markedly distended mucinous vesicular cytoplasm were common (Figure 2C).

Oncocytic metaplasia

In contrast to intestinal metaplasia, oncocytic metaplasia was very common in both superficial and deep EGs (Table 1, Figure 4). In superficial EGs and gastric cardiac glands, oncocytic metaplasia was usually clustered in the middle or lower portion of the epithelium. In deep EGs, it was in various parts of an EG lobule: it usually formed small patches in the center or at the periphery of a lobule, and occasionally involved the entire lobule (Figure 4B). However, oncocytic mass or oncocytoma was absent. The overall architecture of the EGs with oncocytic metaplasia was distorted to various degrees. Oncocytic metaplastic cells featured densely eosinophilic, fine, granular cytoplasm, and homogenous, centrally located, round nuclei with prominent nucleoli (Figure 4C). EG acini with oncocytic metaplasia were often atrophic, fused, forming cystic dilatation in a stroma rich in lymphoplasmacytic infiltrate (Figure 4). Some epithelial cells with oncocytic changes became dysplastic, with markedly enlarged nuclei, prominent nucleoli, and disruptive and discohesive growth, even forming single abortive acini or cells (Figure 4C).

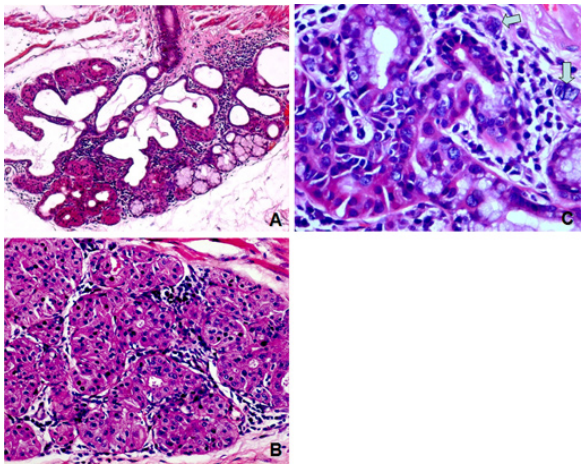

Figure 4 Microscopic images of dEGs featuring oncocytic metaplasia: **A**) a typical dEG with a drainage duct shows chronic inflammation, cystic atrophy, and evident oncocytic metaplasia. **B**) oncocytic metaplasia replace the entire lobule. **C**) In another case, acinar epithelial cells with oncocytic metaplasia show dysplastic changes and abortive, dysplatic acini (arrows). (Original × 40 in A, 100 in B, and × 400 in C. H&E stain).
Abbreviations: dEGs, deep esophageal glands; H&E, hematoxylin & eosin.

Pancreatic acinar metaplasia

Pancreatic acinar metaplasia in EGs was not uncommon (Table 1), was present mainly in superficial EGs, and intermingled with the cardiac-type mucinous glands (Figure 5). The disease featured small acinar nests in the middle or at the base of cardiac and superficial EGs, which were bordered abruptly with adjacent mucinous glands, and associated with mild chronic inflammation (Figure 5D). Cytologically, the EGs with pancreatic acinar metaplasia demonstrated a homogenous, basophilic cytoplasm in the basal portion, and an eosinophilic cytoplasm in the apical portion, with a centrally or basally located, uniformly round nuclei with distinct nucleoli (Figure 5, B and D). As shown in Figure 5C, these metaplastic acini were intensely immunoreactive to the anti-α-chymotrypsin protein antigen, confirming pancreatic acinar differentiation. In rare cases, metaplastic acini underwent dysplastic transformation with evident architectural disarray. Dysplastic nuclei became markedly enlarged, hyperchromatic, and pleomorphic with prominent nucleoli and scant, densely baso-eosinophilic cytoplasm (Figure 5D). These dysplastic nuclei bordered abruptly with the adjacent nondysplastic ones (Figure 5D); however, mitosis or necrosis was absent.

Squamoid metaplasia

Squamoid metaplasia was present only in the drainage ductile epithelium of deep EGs (Table 1, Figure 6). It was characterized by a multilayered epithelium with a distinct cytoplasmic

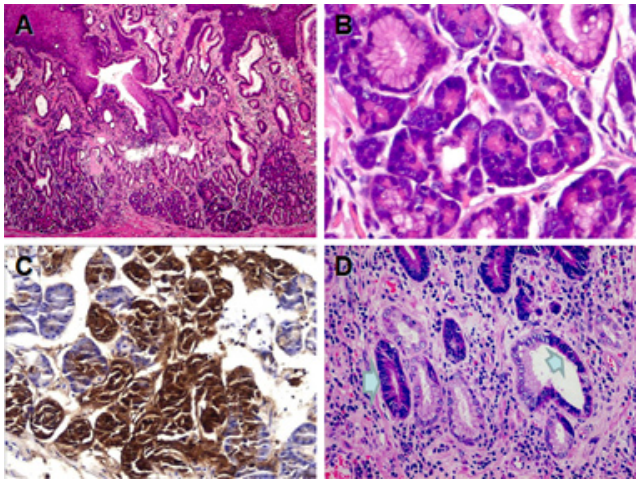

Figure 5 Microscopic images of sEGs. **A**) showing pancreatic acinar metaplasia present in the middle and lower portions of sEGs. **B**) At high magnification, metaplastic acinar cells demonstrate dark basal basophilic and apical eosinophilic cytoplasm and enlarged nuclei with thick nuclear members and prominent nucleoli. **C**) These metaplastic cells are intensely immunoreactive to the α-chymotrypsin protein antigen. **D**) In another case, metaplastic acini (arrows) become dysplastic with nuclear hyperchromatia, marked pleomorphism, sharp transition with adjacent benign glandular epithelial cells, and infiltrative growth. (Original × 20 in A; × 200 in D, and × 400 in B and C. H&E stain).
Abbreviations: H&E, hematoxylin & eosin; sEGs, superficial esophageal glands.

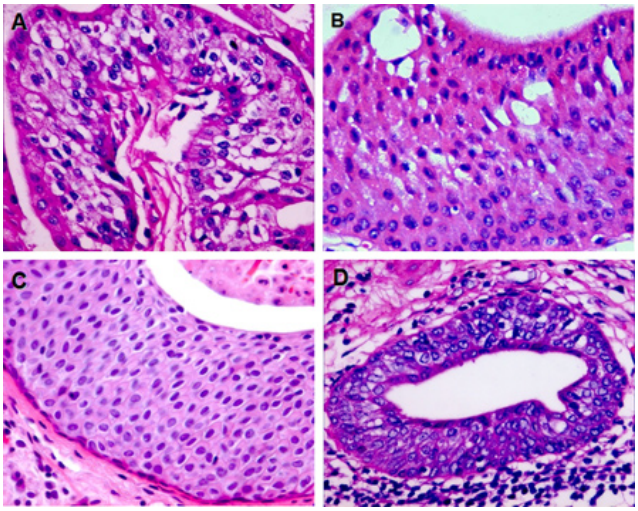

Figure 6 Microscopic images of multilayered squamoid metaplasia present in the ductile epithelium of dEGs: **A**) Ductile epithelial cells show squamoid metaplasia with clear cytoplasm. **B**) Squamoid epithelial cells show evident intra-cytoplasmic vesicles and vacuoles and the microvilli-lined luminal surface. **C**) Another dEG with metaplastic epithelial cells exhibiting irregular nuclear contour and conspicuous nuclear grooves, rendering a urothelioid appearance. **D**) In a rare case, squamoid metaplastic cells show dysplastic changes. (Original × 200 in A, B, C, and D. H&E stain).
Abbreviations: dEGs, deep esophageal glands; H&E, hematoxylin & eosin.

membrane, dense eosinophilic cytoplasm, irregular nuclear membrane, and inconspicuous nucleoli (Figure 6, A–C). The characteristic cytoplasmic keratin pearls and intercellular bridges were not apparent. These epithelial cells frequently showed vesicular cytoplasm with occasional large mucin-containing vacuoles and the microvilli-lined lumen (Figure 6B). In some cases, the cytoplasm became overtly vesicular and displayed a clear appearance (Figure 6A). Some metaplastic cells exhibited grooved nuclei and an irregular cell membrane, with a urothelioid appearance (Figure 6C). Dysplasia was occasionally observed, with enlarged, pleomorphic, and hyperchromatic nuclei in a disorganized, depolarized growth pattern (Figure 6D).

Discussion

In this study, we showed a wide spectrum of histopathology on diseases in both superficial and deep EGs within the GEJ region, in Chinese patients with GCE. The diseases of the EGs ranged from chronic inflammation, hyperplasia, and atrophy, to various types of metaplasia and dysplasia. We found that dysplastic changes in EGs were common, featuring architectural disarray, and fused acini, associated with chronic inflammation, and multiple differentiations, including intestinal, oncocytic, pancreatic acinar, and squamoid metaplasia in almost every case. Dysplastic epithelial cells in EGs exhibited prominent vesicular and vacuolar cytoplasm, and hyperchromatic, markedly enlarged nuclei with distinct nucleoli. The findings are in agreement with the hypothetical chronic inflammation–metaplasia–dysplasia–carcinoma sequence of carcinogenesis in gastric cancers.[12–14]

In humans and animals,[2,15] chronic inflammation in the GEJ region plays a key role in malignant transformation of epithelial cells into invasive carcinoma,[16–18] especially for pathogenesis of gastric cancer.[19–21] Our observations support this theory. In the present study, chronic inflammation was present in both superficial and deep EGs in all cases, most of which showed dysplastic changes. This may be related to the rampant *H. pylori* infection among Chinese patients.[22,23] The low prevalence of *H. pylori* infection described in this study may be related to the histochemical stain method used, which is not as sensitive as the combined serology test with histochemical stain for this bacterium.[19] In our study, despite the overwhelmingly high rate of chronic inflammation and dysplasia, the prevalence of intestinal metaplasia in EGs is lower than that reported in Germans (50%)[24] or in Japanese patients with esophageal squamous cell carcinomas (28%).[25] This discrepancy may result, at least in part, from differences in study materials. None of the previous investigators specifically studied the disease of EGs. Nevertheless, the value of goblet cells as the usual hallmark of intestinal metaplasia for predicting malignant transformation of columnar cells in the GEJ region has been challenged. Using more sensitive molecular and image cytometry methods, investigators found similar aneuploidy changes in both goblet and nongoblet cells in the GEJ region,[26] suggesting the existence of an unknown molecular pathway, or mechanism, for nongoblet glandular epithelial cells to undergo malignant degeneration in this region.

Dysplastic adenomatous changes in EGs have been described previously in several case reports from Japan,[4] China,[27] Saudi Arabia,[7] England,[6] and the United States.[5,28] The premalignant adenomatous changes in EGs may cause considerable difficulty for early endoscopic detection of dysplasia or early carcinoma of the GEJ or EGs because of the deeply seated nature of the tumor, which, unlike the similar adenomatous changes in the gastric or intestinal mucosa, is almost undetectable endoscopically in the proximal stomach below the GEJ. This becomes one of the factors for failure of early detection and poor prognosis of carcinomas originated in the proximal stomach.[8]

Oncocytic change in EGs is believed to be a normal variant.[29,30] In our study, this morphologic change was present in the majority of cases and not limited to the transitional region between mucin acini and the drainage duct of an EG lobule, as previously described.[29,30] Instead, oncocytic acini

were also present in other parts of an EG lobule and even replaced the entire lobule, which could not be explained as part of normal constituents.[30] Importantly, there is a consistent association of oncocytic changes in EGs with chronic inflammation, atrophy, and architectural disarray of an EG lobule. This line of morphologic evidence suggests that oncocytic changes in EG acini in the GEJ region of Chinese patients are abnormal and probably result from chronic irritation and inflammation. Therefore, oncocytic change in EGs should be classified as oncocytic metaplasia.

Pancreatic acinar metaplasia in the GEJ region is not uncommon but limited to gastric cardiac glands and superficial EGs. Its prevalence described in this study was similar to that (18%–24%) reported previously in biopsy specimens,[31–33] but much lower than that (61%) in surgically resected esophagi with the entire GEJ examined microscopically.[24] By comparison,[24,31–33] pancreatic acinar metaplasia is rare in the gastric fundus (0.16%) and antrum (0.8%).[31] Dysplasia in the acini with pancreatic acinar metaplasia also occurred. Taken together, our data may explain the reason why gastric carcinomas with pancreatic acinar differentiation are extremely rare in the distal stomach but frequent in the proximal.[8,9,31,38,39]

In this series, squamoid metaplasia was multilayered and present only in the ductile epithelium, not lobules, of deep EGs. Characteristically, these metaplastic epithelial cells did not exhibit typical features of squamous cell differentiation, but demonstrated glandular, secretory, and other peculiar morphologic features. These have not been reported previously but are consistent with multifunctionalities of these ductile epithelial cells, including secretion of bicarbonate ions[35] and immunoreactivity to the carcinoembryonic antigen protein.[30] These lines of evidence establish the morphologic basis for their dual or multiple functional rules.

Our study showed a wide spectrum of histopathologic changes in the same EGs and their ductile epithelium, which were similar to those described previously in carcinomas of the GEJ,[8,9,28,31,36] especially in Japanese and Chinese patients.[4,8,37,40] Prominent intracytoplasmic mucin-containing vesicles, vacuoles, and microvilli-lined lumens featured in EGs of the present study have been described previously in GEJ cancers[8,37] and metaplastic and dysplastic EG acini and ductile epithelial cells.[41] Further molecular investigation on rules of EGs in the pathogenesis of GEJ cancer is currently ongoing in our laboratory.

The major limitations of this study are primarily related to the retrospective nature of the study design. The prevalence of various diseases in EGs is certainly underestimated because of lack of microscopic examination of the entire GEJ. We are currently building a prospective data base for all surgical resection specimens on diseases involving the GEJ, which will overcome the suboptimal sampling problem and provide better tissue samples for future investigation of diseases involving the GEJ.

In conclusion, superficial and deep EGs adjacent to gastric cardiac carcinoma involving the esophagus in Chinese patients showed a wide spectrum of histopathologic changes, ranging from chronic inflammation, hyperplasia, and atrophy, to various types of metaplasia and dysplasia. The findings provide strong histopathologic evidence suggesting that GEJ cancer in Chinese patients may, at least in part, originate in gastric cardiac glands, EGs and their ductile epithelium.

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Disclosure

The authors report no conflict of interest in this work.

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