ORIGINAL ARTICLE

Gastric Adenocarcinoma of Fundic Gland Type – Spectrum of Morphological and Immunohistochemical Patterns

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ABSTRACT

Background and Objective: Fundic gland adenocarcinoma of stomach is a distinct entity. This study investigated the clinico-pathological features, diagnosis and differential diagnosis of gastric adenocarcinoma of fundic gland type (GA-FG).

Methods: A total of 16 cases of GA-FG were collected, their clinical characteristics were analyzed, histopathological and immunophenotypic characteristics were observed, and the relevant literature was reviewed.

Results: There was no typical clinical manifestation of GA-FG. 16 patients were basically hospitalized with abdominal discomfort. Histopathology of GA-FG showed the diffuse multilayering and nuclear stratification with mild cytologic atypia and minimal stromal reaction even in invasive front.

Conclusion: Adenocarcinoma of gastric fundus is a novel histologic type of gastric cancer. Its diagnosis is mainly based on the patho-morphological characteristics with supporting immunohistochemistry. The prognosis is good, and it needs long-term follow-up.

KEYWORDS: Gastric neoplasms; Gastric adenocarcinoma; Fundic gland type, Immunohistochmistry; Diagnosis.

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INTRODUCTION

Gastric cancer is the fifth leading cause of death in the world.[1] The clinical prognosis of patients with common types of gastric cancer is generally poor, but the biological behavior of gastric adenocarcinoma of the fundic gland type (GA-FG) may be different from that of the conventional histologic subtype. The GA-FG has recently been accepted as a distinct type of gastric cancer. Japanese scholar Tsukamoto[2] first reported the tumor in 2007. Ueyama[3] reported 10 cases in 2010 and gave a more detailed description of this tumour. As of 2018,[4] 111 cases have been reported in scientific literature most of which are reported by East Asian countries. Mostly the published literature is in the form of case reports. This paper presents the patho-morphological and immunohistochemical diagnosis of 16 cases of gastric adenocarcinoma of the GA-FG with review

of the relevant literature to raise the clinicians' and pathologists' awareness of the tumor for subsequent reduced misdiagnosis and over-diagnosis.

METHODS

The study protocol was approved in compliance with the regulations and guidelines of Jinhu County People's Hospital Institutional and Ethical Committee vide Letter No.20200328. Informed consent was obtained from all individual participants included in the study. A total of 16 cases of gastric adenocarcinoma of the fundic gland type diagnosed by the Department of Pathology, Nanjing Drum Tower Hospital and Jinhu County People's Hospital in Jiangsu province of China were collected from 2017 to 2019, all of which were endoscopic submucosal dissection (ESD) specimens. These specimens were fixed by 4% neutral formaldehyde followed by paraffin blocks preparation and Haematoxylin & Eosin staining. Immunohistochemical staining was performed with strept-avidin-biotin method (Lab Vision Secondary Detection Kit). Briefly, the sections were de-paraffinised for twenty minutes to block endogenous peroxidase activity. Prior to antibody incubation, antigen retrieval was applied with citrate buffer at a Ph 6.0. Subsequently, slides were incubated withMUC6、pepsinogen-I, H+/K+-ATPase, Synaptophysin (SYN), Ki67, β-catenin, MUC5AC, MUC2, CD31, D2-40. All antibodies were purchased from Abcam, USA. Di'aminobenzidine (DAB) was applied as chromogen. Finally, the sections were counterstained with haematoxylin solution for one minute and mounted for observation under microscope.

STATISTICAL ANALYSIS

The study data was computed by using statistical package of social sciences (SPSS) version 22.0 (Chicago, IL, USA). Mean and standard deviations were used for quantitative variables while frequencies and percentages were given for qualitative variable.

RESULTS

As regards gender, there were 05 males (31%) and 11 females (69%) with age and clinical characteristics listed in Table-1. Endoscopic findings of these cases (Fig:1) showed that all tumors were located in the upper third of the stomach. Eleven (69%) tumors were macroscopically identified as submucosal tumor (SMT) of stage 0-IIa (superficial elevated type), four (25%) were macroscopically identified as SMT stage 0-IIc (superficial ulcer/depression type) and one (6%) case was identified as stage 0-IIb (superficial flat type). None of these cases had any history of helicobacter pylori infection in the past.

Microscopically, all 16 cases were of similar histopathologic features comprising of variety of cell types with chief cell predominant, parietal cell predominate and admixture of both cell types seen. The deeper glandular structures formed a so-called "endless glands" pattern.[4] No necrosis or brisk mitoses was evident. The glandular tumour cells showed minimal atypical changes and inconspicuous nucleoli in the neoplastic chief and parietal cells. The intervening stroma showed edematous and myxoid changes with prominent desmoplasia in a couple of cases only (Fig:2A-B). Immunohistochemical markers used were as follows: pepsinogen-I (Fig:2C) for chief cells, H+/K+-ATPase (Fig:2D) for acidic chief cells, MUC6 (Fig:2E) for mucous necks cells or pyloric gland cells, β-catenin (Fig:2F) showed positive reaction, SYN (Fig:2G) showed mottled weak (+), while Ki67 (Fig:2H) proliferation index was about 5%. In addition, MUC5AC (Fig:2I) was positive for foveolar cells while MUC2 (Fig:2J) wasnegative and CD31 and D2-40 showed no vascular invasion (Fig:2K-L).

Table-1: Characteristics of 16 cases.

	Age(yr)/sex	*HP infection*	*Location*	*Size(mm)*	*Macroscopic feature*	*Depth(μm)*	*Lymphatic/venous invasion*
1.	40/Female	Negative	Cardia part	5	IIa	50	(-)/(-)
2.	51/Male	Negative	Body of stomach	3	IIa	80	(-)/(-)
3.	68/Female	Negative	Fundus of stomach	8	IIa	40	(-)/(-)
4.	67/Female	Negative	Body of	6	IIa	40	(-)/(-)

			stomach				
5.	56/Male	Negative	Body of stomach	5	IIa	50	(-)/(-)
6.	56/Female	Negative	Body of stomach	4	IIc	80	(-)/(-)
7.	50/Female	Negative	Body of stomach	8	IIa	50	(-)/(-)
8.	79/Male	Negative	Fundus of stomach	5	IIa	50	(-)/(-)
9.	80/Female	Negative	Cardia part	8	IIa + IIc	40	(-)/(-)
10.	62/Male	Negative	Fundus of stomach	5	IIa	80	(-)/(-)
11.	53/Female	Negative	Body of stomach	6	IIa	50	(-)/(-)
12.	45/Female	Negative	Body of stomach	5	IIc	60	(-)/(-)
13.	74/Female	Negative	Cardia part	6	IIa	50	(-)/(-)
14.	82/Male	Negative	Cardia part	8	IIc	80	(-)/(-)
15.	45/Female	Negative	Fundus of stomach	6	IIa	50	(-)/(-)
16.	36/Female	Negative	Body of stomach	8	IIc	40	(-)/(-)

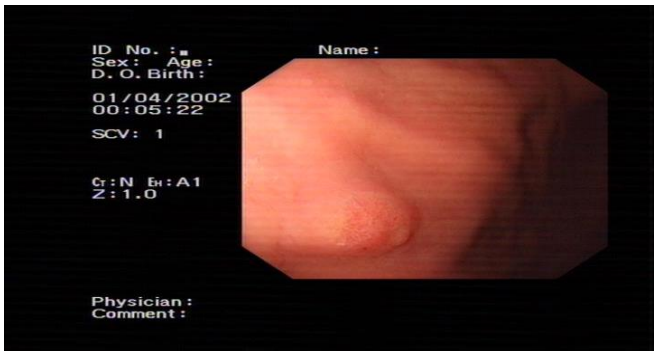

Figure-1 A flat bulge with a diameter of 0.5cm is seen on the anterior wall of the stomach on endoscopy.

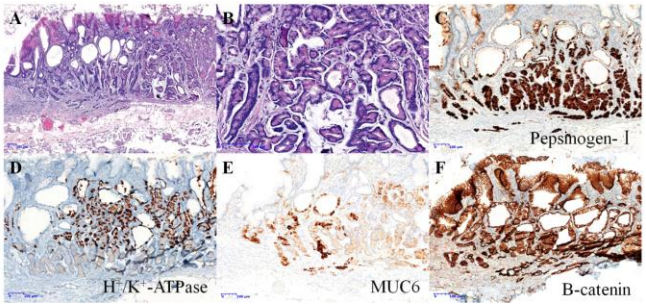

Figure-2-A: Tumor cells with glands arranged disorderly and invade the submucosa. **B:** Tumor cells are composed of gastric gland chief cells and parietal cells. **C:** Tumor cells are pepsinogen-I diffusely positive. **D:** Tumor Cell H + / K + -ATPase positive. **E:** Tumor cell MUC6positive. **F:** Tumor cell β-catenin positive.

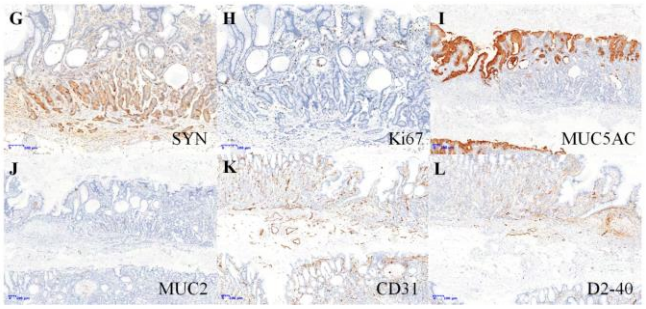

Figure-2G: Tumor cells SYN mottled weakly positive. **H:** Tumor cell Ki67 proliferation index (5%). **I:** MUC5AC was positive for luminal margin cells. **J:** MUC2 negative in tumor cells. **KL:** CD31 and D2-40 show no venous and/or lymphatic invasion.

DISCUSSION

Gastric adenocarcinoma of the fundic gland type is a tumor arising directly from the gastric epithelium with no intestinal metaplasia reported so far.[5,6] Etiology, the occurrence of conventional gastric adenocarcinoma is attributed to many factors, both environmental and genetic factors, such as chronic Helicobacter *pylori* (HP) infection leading to intestinal metaplsia and mucosal atrophy playing a key role in carcinogenesis.[7] In contrast, the HP infection rate of gastric adenocarcinoma of the fundic gland type patients is reported to be only 30 – 40% while the associated inflammation, intestinal metaplasia and atrophy are not significant features.[4] These characteristics are basically consistent with the 16 cases reported in this paper,

suggesting that gastric adenocarcinoma of the fundic gland type may be different from common gastric adenocarcinoma in its etiology. American scholars believe the tumor is called adenosinoma, while Japanese scholars call it as gastric adenocarcinoma. The fifth edition[8] of the 2019 WHO Digestive System Tumor Classification reports it to be located in the mucosal layer infiltrating the sub-mucosa. So this brings a challenge to the hsitopathologist to rule out the possibility of invasion in an otherwise fundic or oxyntic cell adenoma. Long-term use of proton pump inhibitors (PPI) has been found to be associated with gastric fundic gland polyps (FGP), but it is not clear whether PPI is associated with GA-FG. Eight of the 12 gastric adenocarcinoma of the fundic gland type patients reported by Chan[9] and others had a history of taking drugs, including PPI and H-2 blockers. However, these findings yet need to be validated for any significant association. There is a limited data available for the molecular genetics of this tumour type. Nomura et al.[10] in a study of 26 cases of GA-FG type found a positive β-catenin immunohistochemical staining in 80% (22/26) cases while 13 cases showed mutations in GNAS, CTNNBl, AXINl/2, APC genes, 5 showed mutations in GNAS only suggesting that GNAS mutations play a role in wnt-β-catenin signaling pathway. GNAS mutation may be related to submucosal infiltration and larger tumor volume of GA-FG type, but because of the few reported cases, it is still needs further validation. In contrast, there is no or rare GNAS mutation in conventional gastric adenocarcinoma.

Among the different subtypes of gastric adenocarcinoma of the fundic gland type, the superficial elevated type is the most common, followed by flat type while the superficial ulcer type is rare.[11] None of our 16 cases showed lymphovascular invasion. Low Ki 67 proliferation index (< 5%) also reflects an indolent course.

CONCLUSION

Gastric adenocarcinoma of the fundic gland type is a novel histologic subtype of low-grade malignant gastric cancers having unique clinicopathological characteristics. Its biological behavior is better than the conventional gastric adenocarcinoma with low frequency of reported recurrence. The prognosis stays good with endoscopic submucosal dissection and endoscopic mucosal resection as main treatment modalities however long-term follow-up is required.

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LIMITATIONS OF THE STUDY

This study does not show data related to surgical treatments and their outcomes. More studies with follow up are required to develop national databases in each country.

CONFLICT OF INTEREST

None to declare.

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REFERENCES

1. Venerito, M, Link, A, Rokkas, T, Malfertheiner, P. Review: gastric cancer—Clinical aspects. Helicobacter. 2019; 24 (Suppl. 1): e12643. DOI: https://doi.org/10.1111/hel.12643
2. Tsukamoto T, Yokoi T, Maruta S, Ktamura M, Yamamoto T, Ban H, et al. Gastric adenocarcinoma with chief cell differentiation. Pathol Int. 2007; 57 (8): 517-22. DOI:10.1111/j.1440-1827.2007.02134.x.
3. Ueyama H, Yao T, Naksahima Y, Hirakawa K, Oshiro Y, Hirahashi M, et al. Gasric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma. Am J Surg Pathol. 2010; 34 (5): 609-19. DOI:10.1097/PA.0b013e31811d94d53.
4. Benedict MA, Lauwers GY, Jain D. Gasric adenocarcinoma of fundic gland type: update and

literature review. Am J Clin Pathol. 2018; 149 (6): 461-73. DOI:10.1093/ajcp/aqy019.
5. Kushima R, Sekine S, Matsubara A, Taniguchi H, Ikegami M, Tsuda H. Gastric adenocarcinoma of the fundic gland type shares common genetic and phenotypic features with pyloric gland adenoma. Pathol Int. 2013; 63 (11): 318-25. DOI: 10.1111/pin.12070.
6. Ueyama H, Matsumoto K, Nagahara A, Hayashi T, Yao T, Watanabe S, et al. Gastric adenocarcinoma of the fundic gland type (chief cell predominant type). Endoscopy. 2014; 46 (2): 153-7. DOI:10.1055/s-0033-1359042.
7. Nagini S. Carcinoma of the stomach: a review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol. 2012; 4 (7): 156-9. DOI:10.4251/wjgo.v4.i7.156.
8. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumors of the digestive system. Histopathology. 2020; 76 (2): 182-8. DOI:10.1111/his.13975.
9. Chan K，Brown IS，Kyle T, Lauwers G Y, Kumarasinghe MP. Chief cell-predominant gastric polyps: a series of 12 cases with literature review. Histopathology. 2016; 68 (6): 825-33. DOI:10.1111/his.12859.
10. Nomura R，Saito T, Mitomi H, Hidaka Y, Lee S, Watanabe S, et a1. GNAS mutation as an alternative mechanism of activation of the Wnt/beta caten in signaling pathway in gastric adenocarcinoma of the fundic gland type. Hum Pathol. 2014; 45 (12): 2488-96. DOI:10.1016/j.humpath.2014.08.016.
11. Manabe S, Mukaisho K, Yasuoka T, Usui F, Matsuyama T, Hirata I, et al. Gastric adenocarcinoma of the fundic gland type spreading to heterotopic gastric glands. World J Gastroenterol. 2017; 23 (38): 7047-53. DOI:10.3748/wjg.v23.i38.7047.

Author's Contribution

LW, JJ: Conception and design of study, acquisition of data and drafting of manuscript with critical input.

GC, LL, MC: Acquisition of data, drafting of manuscript with critical input.

ALL AUTHORS: Approval of the final version of the manuscript to be published.