α-Fetoprotein-positive hepatoid adenocarcinoma of the stomach and a new classification: A case report

ZHEN-YU YE[1,2], CHUAN-HAI XU[3], WANG CHEN[4], ZHONG-MING SHAO[3], XUE ZHAO[5], JIN-LING TANG[6], XIANG-SU LI[2], XIN WANG[2], CHAO-NAN WANG[5], QING-QING YANG[2,7], YANG HUANG[2,7], XUE-YI XIAO[2,7], XU-DONG WU[1,2] and QI-BIAO WU[1]

[1]Faculty of Chinese Medicine, Macau University of Science and Technology, Taipa 999078, Macau SAR, P.R. China; [2]Department of Gastroenterology, Yancheng No. 1 People's Hospital, Yancheng, Jiangsu 224005, P.R. China; [3]Department of Pathology, Yancheng No. 1 People's Hospital, Yancheng, Jiangsu 224005, P.R. China; [4]Department of Medical Imaging, Yancheng No. 1 People's Hospital, Yancheng, Jiangsu 224005, P.R. China; [5]Department of General Medicine, Yancheng No. 1 People's Hospital, Yancheng, Jiangsu 224005, P.R. China; [6]Gastrointestinal Endoscopy Center, Yancheng No. 1 People's Hospital, Yancheng, Jiangsu 224005, P.R. China; [7]Department of Gastroenterology, Yancheng Clinical College of Xuzhou Medical University, Yancheng, Jiangsu 224005, P.R. China

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Abstract. α-Fetoprotein (AFP)-producing gastric carcinoma (AFPGC) is a rare subtype of gastric cancer (GC) with controversial classification methods. Hepatoid adenocarcinoma of the stomach (HAS) is another rare subtype of GC. Its definition intersects with that of AFPGC, but it is much rarer. The present report describes the case of an elderly patient with GC and AFPGC and HAS features in a serum test and pathology, respectively, and proposes a new classification of GC subtypes based on histological and AFP-producing features. A 75-year-old woman presented with a history of polydipsia and polyuria for over a decade and dizziness for 1 day. Serum AFP levels gradually elevated from 183.70 to 397.70 ng/ml in 1 month after the patient's first clinic visit. Subsequent pathological findings from endoscopic biopsy samples confirmed a hepatoid focus with positive immunohistochemical staining for AFP. The patient underwent a laparoscopic-assisted radical total gastrectomy and esophagojejunal Roux-en-Y anastomosis, and the serum AFP levels decreased to the normal range after the surgery. The present case indicates the diagnostic value of both the serum AFP level and pathological examinations in the diagnosis of AFPGC and HAS, and also highlights the contemporary circumstances of the vague classification based on different criteria for these two subtypes. Furthermore, the present report proposes a new classification considering both histological and AFP-producing features (using both serum biomarkers and immunohistochemistry tests) to cover all cases encompassed by AFPGC and HAS under all definition methods. This new method would give more precise diagnoses and add value to the subsequent treatment decision-making.

Correspondence to: Professor Xu-Dong Wu, Department of Gastroenterology, Yancheng No. 1 People's Hospital, 166 Yulong Road West, Yancheng, Jiangsu 224005, P.R. China
E-mail: hnjsycwxd@163.com

Professor Qi-Biao Wu, Faculty of Chinese Medicine, Macau University of Science and Technology, Avenida Wai Long, Taipa 999078, Macau SAR, P.R. China
E-mail: qbwu@must.edu.mo

Abbreviations: AFP, α-fetoprotein; AFPGC, AFP-producing gastric carcinoma; AFPHAS, AFP-positive hepatoid adenocarcinoma of the stomach; AFPNAS, AFP-positive non-hepatoid adenocarcinoma of the stomach; CDX, caudal type homeobox; CK, cytokeratin; CT, computed tomography; GC, gastric cancer; GI, gastrointestinal; HAS, hepatoid adenocarcinoma of the stomach; Hep Par, hepatocyte paraffin; IHC, immunohistochemistry; OB, occult blood; T2DM, type 2 diabetes mellitus; WHO, World Health Organization

Key words: stomach neoplasms, AFP-positive adenocarcinoma, hepatoid adenocarcinoma, classification

Introduction

Gastric cancer (GC) is now widely recognized as one of the most common cancer types, with the sixth highest incidence (5.6%) and causing the third most cancer deaths (7.7%) worldwide (1). As a rare subtype of GC, α-fetoprotein (AFP)-producing gastric carcinoma (AFPGC) was first described by Bourreille *et al* (2) in 1970. AFP is typically considered an ideal clinical serum biomarker for screening and monitoring hepatocellular carcinoma, noncancerous liver diseases, yolk sac tumors and tumors of gonadal origin (3-8). The elevation of serum AFP levels has also been observed in certain other types of cancers, including cancer of the stomach, lung, pancreas, colon and bladder (9-15). Among all these organs, the stomach is believed to be the most common site of occurrence (16-18). The proportion of AFPGC among all GC cases is controversial: Reports usually estimate it to be between 1.3-7.1%, (17,19-22), whilst certain data suggest it is as high as 15% (23).

Hepatoid adenocarcinoma of the stomach (HAS), another rarer subtype of GC, was first described by Ishikura *et al* (24,25) in the 1980s to describe GC cases with hepatoid features. The proportion of HAS among all GC cases was previously estimated to be between 1.7-15.0‰ (26,27).

Several factors have been noted to have a significant impact on the increased risk of developing GC, including family history, diet, alcohol consumption, smoking, *H. pylori* and Epstein-Barr virus infections (28). There is no further evidence indicating that specific non-genetic factors are more inclined to predispose to specific subtypes such as AFPGC or HAS.

For all subtypes of GC, surgical resection remains the primary treatment strategy, including conventional surgery and endoscopic resection for early-stage lesions. Postoperative adjuvant radiotherapy, chemotherapy and targeted therapy are also utilized as supplementary treatment modalities (29).

The present report provides a description of the clinical and pathological findings, upper gastrointestinal endoscopy and enhanced chest-abdominal computed tomography (CT) images, and the outcome of surgery for an elderly patient with GC, and AFPGC and HAS features in serum test and pathology, respectively. As there are certain contemporary inconsistencies in the definitions of AFPGC and related concepts, the present report also proposes a new classification method for relevant diseases and pertinent literature is reviewed.

Case report

A 75-year-old woman presented to the General Clinic, Yancheng No. 1 People's Hospital (Yancheng, China) in November 2023 (day 0), with a chief complaint of dizziness for 1 day and a history of polydipsia and polyuria for over a decade. The patient was admitted to the ward of the Department of General Medicine with an initial diagnosis of type 2 diabetes mellitus (T2DM) and hypertension. Routine laboratory tests on admission suggested a positive fecal occult blood (OB) test, positive serum *H. pylori* IgG antibodies and positive *H. pylori* current infection marker. The patient also had mild anemia with a blood hemoglobin level of 91 g/l (reference range, 130-175 g/l). Further gastrointestinal (GI) tumor marker tests indicated an elevated serum AFP level of 183.70 ng/ml (reference range, 0-7 ng/ml). The results of other related laboratory tests, including liver function tests, Hepatitis B indicators and other GI tumor markers, were all within normal limits. Abdominal CT also revealed no significant hepatic abnormalities. Following treatment for acid suppression and gastric protection with omeprazole and sucralfate, the fecal OB test turned negative. The patient was discharged upon their request as the symptoms had subsided.

Follow-up at 1-month post-discharge (day 27) revealed a marked increase in serum AFP to 314.15 ng/ml at Qingdun Town Healthcare Center (Yancheng, China). A total of 2 weeks later, the patient presented to the General Clinic at Yancheng No. 1 People's Hospital again and was readmitted to the ward of the Department of General Medicine in December 2023 (day 43). Further tests indicated an ulteriorly elevated serum AFP level at 397.70 ng/ml. An upper gastrointestinal endoscopy revealed irregular elevations and depressions from the esophagus (40 cm from incisors) to the cardia, covered with a white coating on the surface presumably mainly made up of necrotic tissue and mucus, with a crater-like elevated nodule, indicating the presence of ulcerative GC (Borrmann II). The lesion tissue was brittle and prone to hemorrhage (Fig. 1). The endoscopic diagnosis indicated esophageal cardia cancer. Subsequent enhanced chest-abdominal CT demonstrated thickening and enhancement of the gastric wall lateral to the lesser curvature of the cardia and gastric fundus, further clarifying the extent of the lesion (Fig. 2). Endoscopic biopsy sample collected was fixed with 4% formaldehyde solution for 6 h at 25˚C. Paraffin-embedded tissue sections (4 μm) were deparaffinized with xylene and rehydrated with a series of anhydrous ethanol, 95% ethanol, 70% ethanol and PBS. For pathological examination, part of the sections were stained with hematoxylin for 3 min at 25˚C and eosin for 45 sec at 25˚C. For immunohistochemistry (IHC), part of the sections underwent blocking of endogenous peroxidase using 3% hydrogen peroxide for 10 min at 25˚C, followed by blocking of unspecific protein binding using 5% bovine serum albumin (cat. no. GC305010; Servicebio Ltd) for 1 h at 37˚C. IHC sections underwent heat-mediated antigen retrieval with sodium citrate buffer (pH=6) for 10 min at 97˚C and were then incubated overnight at 4˚C with AFP antibody (1:100 dilution; cat. no. RMA-1069; Maxim Biotechnologies, Ltd), hepatocyte paraffin (Hep Par) 1 antibody (1:100 dilution; cat. no. MAB-1034; Maxim Biotechnologies, Ltd), cytokeratin (CK)19 antibody (1:100 dilution; cat. no. MAB-0829; Maxim Biotechnologies, Ltd) or caudal type homeobox (CDX)2 antibody (1:100 dilution; cat. no. RMA-0631; Maxim Biotechnologies, Ltd). Subsequently, IHC sections were treated with HRP-conjugated goat anti-rabbit IgG (H+L) (1:200 dilution; cat. no. GB23303; Servicebio Ltd) as the secondary antibody for 20 min at 25˚C, and visualization was performed using a DAB color development kit (cat. no. G1212-200T; Servicebio Ltd), followed by counterstaining using hematoxylin for 3 min at 25˚C. All sections were sealed with neutral

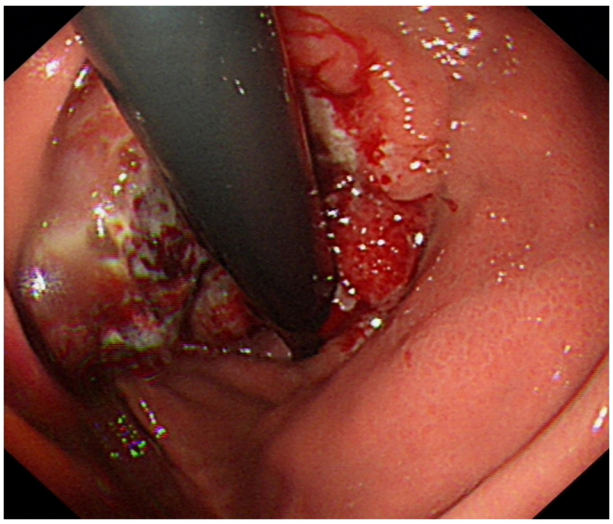

Figure 1. Endoscopy image. Irregular elevations and depressions from the esophagus (40 cm from incisors) to the cardia, covered with white coating on the surface presumably mainly made up of necrotic tissue, mucus, etc., with a crater-like elevated nodule, indicating the presence of ulcerative GC (Borrmann II). The lesion tissue was brittle and prone to hemorrhage.

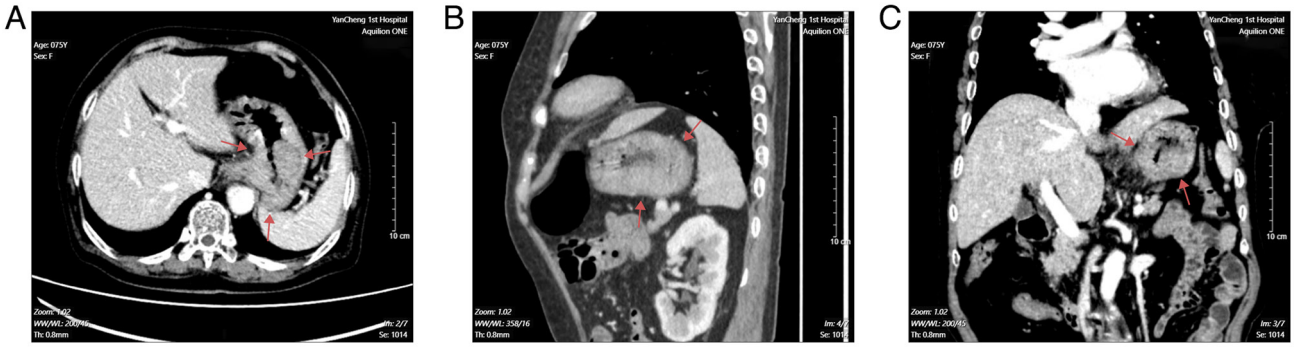

Figure 2. Images from enhanced chest-abdominal CT. (A) Cross-sectional, (B) sagittal plane and (C) coronal images. An irregular soft tissue mass can be seen on the greater curvature side of the cardia-gastric body, involving part of the lesser curvature side. The mass shows inhomogeneous enhancement. Localized mucosal-like enhancing structures disappear, and the fat space on the plasma surface of the lesser curvature is blurred. A lymph node shadow of ~11x6 mm can be seen. Images from multiple angles suggest the approximate extent of the lesion. The arrows point out areas of thickening and protrusion of the stomach wall.

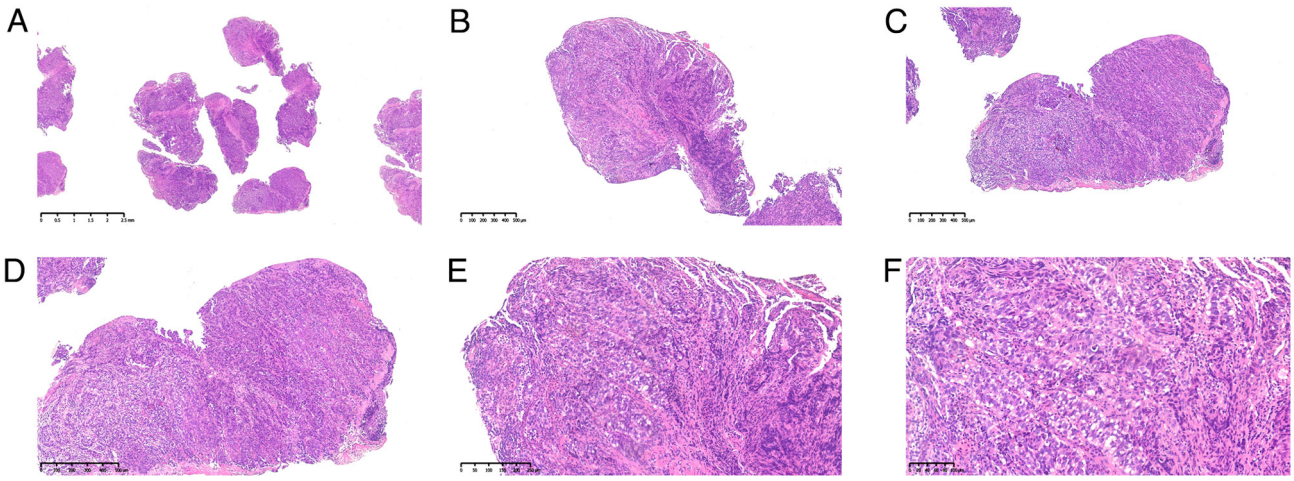

Figure 3. Pathological images. Hematoxylin and eosin stain at the following magnifications: (A) x60, (B) x200, (C) x200, (D) x280, (E) x500 and (F) x800. Under low magnification (A-C), the tumor cells demonstrate infiltrative growth, and the histological pattern consists of a combination of tubular adenocarcinoma and solid arrangement, with a gradual migratory process between the two. Under high magnification (D-F), the cancer cells are large, with plentiful cytoplasm appearing either eosinophilic or hyaline and containing visible intracytoplasmic vacuoles. The nuclei of these cells are either round or irregular in shape. The medullary or striated structures comprise eosinophilic polygonal cells, and the cancer cells exhibit different degrees of differentiation towards hepatocytes. The interstitium is rich in blood vessels and sinuses, with narrow fibrous interstitial compartments.

resin and scanned with a digital slide scanner (NanoZoomer S20; Hamamatsu Photonics KK). Pathological examination confirmed the diagnosis of poorly differentiated cancer and focal tissue showed liver-like features (Fig. 3). IHC results revealed that the endoscopic biopsy samples were immunopositive for AFP (partial), Hep Par 1 (focal), CK19 (patchy) and CDX2 (homogeneous) (Fig. 4). Based on the elevation in serum AFP and positive AFP staining outcome, the patient was diagnosed with AFPGC. Furthermore, based on the liver-like pathology features, the patient was diagnosed with HAS.

The patient showed no obvious GI-related symptoms throughout the whole observation period before surgery. The patient was then referred to Jiangsu Provincial People's Hospital (Nanjing, China) for radical gastric cancer surgery and the discharge record for this hospitalization was obtained from the patient through a follow-up visit. The patient underwent a 3D laparoscopic-assisted radical total gastrectomy and esophagojejunal Roux-en-Y anastomosis in January 2024 (day 56). The postoperative pathologic resection specimen revealed a lesion located in the lesser curvature of the cardia with a lesion size of 6.5x6.0x2.0 cm, which was styled as Borrmann III in vision and low-differentiated (G3) diffuse tubular adenocarcinoma [International Classification of Diseases for Oncology type 8211/3 (30); T3N0M0 (31)] in the histology. The lesion infiltrated the sub-plasma layer, cancer emboli were seen in the vasculature, there was no clear invasion of nerves, no cancer metastasis in the lymph nodes, and no cancer involvement in the fatty-fibrous connective tissue (data not shown). IHC results revealed that the postoperative resection specimen was immunopositive for human epiderminal growth gator receptor 2 (2+), Ki67 (90%+), postmeiotic segregation increased 2 (partial), MutL homolog 1, MutS homolog (MSH)2, MSH6, AFP, Sal-like protein 4 (partial) and Glypican-3, and negative for *in situ* hybridization Epstein-Barr encoding region and p53 (data not shown). Post-surgery, the serum AFP level reduced to the normal range (Fig. 5).

The patient was followed up with remotely by telephone in April 2024 (day 148). At the time of this follow-up, the patient was alive and in good postoperative condition.

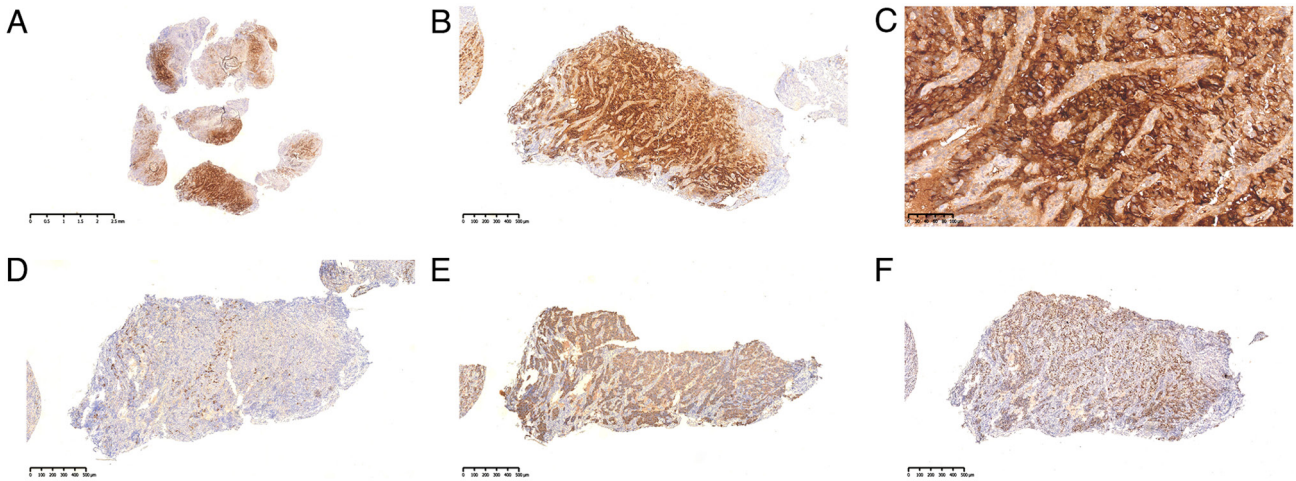

Figure 4. Immunohistochemistry images. AFP stain at the following magnifications: (A) x60, (B) x200 and (C) x800. (D) Hep Par 1 stain (magnification, x200). (E) CK19 stain (magnification, x200). (F) CDX2 stain (magnification, x200). (A-C) Strong cytoplasm AFP staining can be seen in partial tissues, (D) strong cytoplasm Hep Par 1 staining can be seen in focal tissues, (E) strong cytoplasm CK19 staining can be seen in sample tissues and (F) strong nuclear CDX2 staining can be seen in sample tissues. AFP, α-fetoprotein; Hep Par, hepatocyte paraffin.

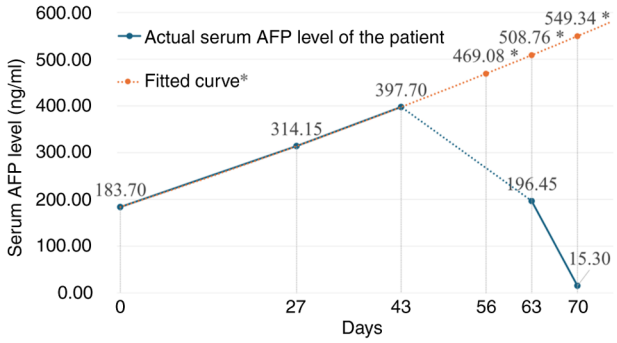

Figure 5. Changes in the serum AFP level of the patient. The serum AFP levels showed a near-linear increase before the surgery and they reduced to normal after the surgery. A fitted curve was added to see what would happen if the surgery was not performed. A binomial fit was used, $y=0.0091x^2 + 4.5864x + 183.7$. AFP, α-fetoprotein.

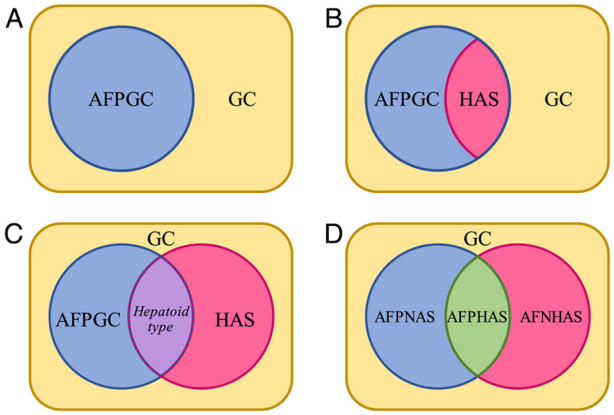

Figure 6. History of changes in the relationship between AFPGC and HAS. (A) Bourreille *et al* (2) proposed the original definition of AFPGC in 1970. (B) Ishikura *et al* (24,25) proposed the original definition of HAS as a subtype of AFPGC in the 1980s. (C) Expansion of the definition of HAS. The expanded HAS concept now encompasses non-AFPGC components in addition to its original scope. Some researchers redefined this cross part of AFPGC and expanded HAS (the range of the original HAS concept) as the hepatoid type (16,37), but certain researchers considered this component no longer part of AFPGC (39). (D) The proposal in the present report of a separate definition of AFPNAS, AFPHAS and AFNHAS assigned to each component to avoid misunderstandings and disagreements resulting from differences in definitions. AFP, α-fetoprotein; AFPGC, AFP-producing gastric carcinoma; HAS, hepatoid adenocarcinoma of the stomach; AFPNAS, AFP-positive non-hepatoid adenocarcinoma of the stomach; AFPHAS, AFP-positive hepatoid adenocarcinoma of the stomach; GC, gastric cancer.

Discussion

Since the first report in 1970, the definition of AFPGC has remained ambiguous. In the original case reported by Bourreille *et al* (2), AFPGC was initially defined as GC with excessive serum AFP levels. With the further development of IHC techniques, certain researchers preferred to redefine AFPGC as one type of GC with positive IHC staining for AFP (32). To resolve this divergence, recent guidelines have suggested that AFPGC be defined as GC with both elevated serum AFP levels and positive IHC staining for AFP (33). However, a recent case reported, in which there were GC-related serum AFP elevation and negative IHC staining for AFP, has challenged the definitions from the guidelines (34).

In the present case, as the pathological findings revealed hepatoid features, there was another related disease to discuss. HAS is another rare but aggressive GC-related disease; HAS was first reported by Ishikura *et al* (24,25) in the 1980s after the observation of certain AFPGC cases with hepatoid features. Subsequent studies have reported that AFP expression is not necessarily observed in certain cases of HAS, further relaxing the definition of HAS as GC with foci of hepatocellular differentiation (Fig. 6) (18,35).

Due to the many histological overlaps between AFPGC and HAS, this ambiguous space of definition often confuses the two, and this confusion has already led to their misuse in certain cases (36). Indeed, it is essential to further clarify the distinction between AFPGC and HAS. During fetal development, AFP is rationally synthesized not only by the liver but also by the yolk sac and gastrointestinal tract. Therefore, the tissues producing AFP in GC can also have

Table I. Serum positivity according to the level of serum α-fetoprotein.

Serum AFP level, ng/ml	n≤20	20<n≤100[a]	100<n≤300[b]	n>300[c]
Serum-positivity grade	S0	S1+	S2+	S3+

[a]A total of 20 ng/ml was used as the cutoff to include more early or low expression cases; [b]100 ng/ml was used as the cutoff to identify a typical rise in serum AFP level; [c]300 ng/ml was used as the cut-off to distinguish very high levels of serum AFP. AFP, α-fetoprotein.

Table II. Tissue positivity according to the immunohistochemistry staining intensity.

		Faint			
Staining intensity	Complete absence	<10% tumor cells	>10% tumor cells	Moderate	Strong
Tissue-positivity grade	T0		T1+	T2+	T3+

different morphologies. Motoyama *et al* (37) first advocated the typing of AFPGC based on histological features. They proposed three subtypes: i) Hepatoid type; ii) yolk sac tumor-like type; and iii) fetal gastrointestinal type, which has also been referred to as enteroblastic type in classifications by Kinjo *et al* (16). This classification further highlights the differences and connections between AFPGC and HAS. After finding certain cases that showed only features of common adenocarcinoma, Kinjo *et al* (16) proposed a fourth type, the common adenocarcinoma type, in 2012. These four subtypes can appear alone or in combination. Recently, a rare case of adenocarcinoma coexisting with squamous cell carcinoma has been reported (34). This may require an expansion of the existing classification.

The diagnosis of AFPGC is extremely heterogeneous and a single diagnosis of only AFPGC may result in a loss of critical information. Certain researchers have tried to eliminate the concept of AFPGC and advocated for a diagnostic system based on histological criteria instead (38), and this viewpoint was supported by the fifth edition of the World Health Organization (WHO) classification of tumors, which includes only HAS and not AFPGC (30).

However, it should be noted that the distinction between AFP-positive and -negative types remains critical when identifying histological type. Chen *et al* (39) revealed that a group with higher AFP expression had a higher frequency of liver metastasis and worse overall survival compared with those with lower AFP expression among patients with HAS. Moreover, a large-scale epidemiological study has reported the importance of serum AFP levels in patients with GC (40). Therefore, the present report proposes a new classification method to take both histological and AFP-producing features into account. GCs with an elevation in serum AFP levels are defined as serum-positive, and those with positive results in IHC staining for AFP in pathological tissues as tissue-positive. Either serum-positive or tissue-positive should be considered as AFP-positive, and specific serum and IHC manifestations should be marked in the diagnosis. The criteria for serum AFP positivity are widely defined by different values in different studies. Generally, a serum AFP level of >20 ng/ml can be considered as clinically significant and serum AFP positive (40,41). However, certain researchers preferred 100 ng/ml as the cutoff (21,39,42). Nevertheless, there is insufficient evidence for any of the two cutoffs. Considering both cutoffs may be a better option to avoid including cases with physiological variations or focusing too late on potential cases. In many studies, a cutoff value of 300 ng/ml is also used to distinguish very high levels of AFP from others (41,43). Therefore, 20, 100 and 300 ng/ml could be used as cutoffs to grade serum AFP levels, which may be helpful to include more cases previously missed and eliminate the confusion introduced by different definitions of AFP positive cases (Table I). Similarly, a grading system to assess the IHC staining results of AFP is also proposed (Table II). The four-level grading method based on staining intensity is a novel, simple and reproducible method widely used to evaluate or interpret the IHC staining results of many indicators (44-47).

Under the aforementioned definition of AFP positivity, the concepts of AFPGC and HAS were combined to introduce three related new diagnoses: i) AFP-positive hepatoid adenocarcinoma of the stomach (AFPHAS); ii) AFP-positive non-hepatoid adenocarcinoma of the stomach (AFPNAS); and iii) AFP-negative hepatoid adenocarcinoma of the stomach (AFNHAS). This new diagnostic classification would be able to cover all cases encompassed by AFPGC and HAS under all definition methods and establish a fixed definition for each case. This may help prevent confusion and data misapplication in statistical analysis arising from similar cases being classified under different diagnoses with different definition methods.

Furthermore, if further evidence shows that other histological types significantly differ in prognosis or other aspects, AFPNAS may be further categorized into more specific diagnosis groups, including but not limited to AFP-positive yolk-sac-tumor-like adenocarcinoma of the stomach, AFP-positive fetal-gastrointestinal adenocarcinoma of the stomach and AFP-positive common adenocarcinoma of the stomach. AFP-negative cases with other histological types can also be categorized as AFP-negative yolk-sac-tumor-like adenocarcinoma of the stomach, AFP-negative fetal-gastrointestinal adenocarcinoma of the stomach and AFP-negative

common adenocarcinoma of the stomach. If needed, AFP-positive squamous-cell carcinoma of the stomach and AFP-negative squamous-cell carcinoma of the stomach can also be discussed.

In the present case, the patient was finally diagnosed as AFPHAS (S3+T3+) according to the proposed new classification system. Several existing meta-analyses (48,49) have conducted preliminary statistical evaluations of various pathologic features, serum AFP levels and survival rates in patients. It is anticipated that a new classification could be further implemented into these data to reveal the impact of serum AFP grading and newly proposed subtypes on patient prognosis. Unfortunately, due to the paucity of literature focusing on differences in the degree of AFP staining in tissues, assessing the impact of tissue AFP grading on patient prognosis remains a task of future work to consider after the present report.

Generally, existing published data is limited by small sample sizes in individual studies and a lack of AFP-level grading. Therefore, whilst these studies (40,41,50) suggest that AFP levels and pathological type impact prognosis, the exact extent of this impact remains unclear. The new classification system proposed in the present report could enable researchers to further categorize both reported and unreported cases, which will allow the exploration of the specific influence of AFP levels and pathological type on survival expectations in patients with GC in more depth. Ultimately, this could help clinicians refine a more precise assessment of the survival expectations of patients, and possibly influence future decisions regarding additional postoperative treatment options.

There is often a genetic factor in the development of cancer, and this may be true for AFPGC cases as well. A whole-exome sequencing study (51) revealed the association between certain genes and AFPGC that AFPGC cases with mutations of multiple genes such as cyclin E (CCNE) 1, Cyclin D1, EGFR, Erb-b2 receptor tyrosine kinase (ERBB) 2, ERBB3, ERBB4, Aurora kinase A, AXL receptor tyrosine, B-cell lymphoma 6, breast cancer gene 2, vascular endothelial growth factor receptor 1, fibroblast growth factor receptor 2, cellular myelocytomatosis oncogene and myeloid cell leukemia 1, tend to have a worse OS rate and exhibit more aggressive behavior than normal GC subtypes, due to the activation of core signal pathways such as RTK/RAS/PI(3)K, p53/cell cycle and JAK/STAT. Based on these findings, CCNE1- and ERBB2-targeted medications may have potential in future AFPGC therapy, which may help to offer differentiated options for patients with AFPGC beyond conventional GC therapies. Unfortunately, the study (51) only used tissue IHC positivity as the inclusion criterion, it did not differentiate between histological types and it omitted serum-positive-only cases. With the new proposed classification system in the present report, researchers in the future could further refine the relationships between mutations, pathways and pathological typing.

Moreover, the patient in the present case was infected with *H. pylori* and had a history of T2DM. *H. pylori* is categorized as a group 1 carcinogen by the WHO and is now widely recognized as a primary risk factor for GC (52-55). It is not fully elucidated how *H. pylori* causes GC, but studies have revealed that the mechanism is related to multiple virulence factors, including cytotoxin-associated gene A, vacuolating cytotoxin A and outer membrane proteins (56,57). Only one previous study explored whether *H. pylori* serves a different role in different GC subtypes, and this study failed to demonstrate an association between the *H. pylori*-positive rate and the presence of AFP-positive or hepatoid features in patients with GC (58). Furthermore, compared with *H. pylori*, the effect of T2DM on the development of GC does not seem to be precise. Certain earlier studies reported an increased risk of GC with pre-existing T2DM (59-61). However, recent research highlight that different study types can lead to different conclusions on this issue. Statistical significance between T2DM history and GC risk has not been demonstrated in prospective studies (62). In addition, a later large-scale study reported that T2DM is unrelated to GC overall but may be associated with excess cardia GC risk (63). In the present case, the tumor was located around the cardia of the patient. If the patient had been able to eradicate *H. pylori* earlier and received more regular glucose management, they may have been not developed GC. This demonstrates the importance of routine screening for *H. pylori* and long-term regular glucose monitoring in the primary health care system.

In conclusion, the present report describes the case of an elderly patient with AFPGC and HAS with hepatoid features in the tumor and with both elevated serum AFP levels and positive IHC AFP staining. Although the case could have been diagnosed as both AFPGC and HAS using any existing definition, it was found that the current parallelism of conflicting definition methods of AFPGC and HAS was already a barrier to scientific progress. Therefore, the present report proposed a new classification considering both histological and AFP-producing features, and both expressing features in serum and tissue, to eliminate this obstacle, covering all cases encompassed by AFPGC and HAS under all definition methods and establishing a fixed definition for each case. Moreover, there is currently minimal variation in the treatment approaches for most types of GC, including AFPGC and HAS. Nonetheless, it is crucial to recognize that both AFP level (41) and pathological type (50) serve as independent prognostic factors for GC. The new classification proposed in the present report not only holds significance for pathologists but also extends its relevance to other clinicians by highlighting the importance of AFP levels and pathological type in GC cases. This dual focus is anticipated to remarkably enhance the precision of survival prognosis evaluations. Furthermore, it carries the potential to impact subsequent choices concerning adjunctive postoperative treatments, thereby broadening the scope of personalized patient care strategies in gastric oncological settings. However, further studies are required to elucidate the associations between each specific subtype and genetic-environmental factors such as genes, *H. pylori* infection and chronic health history, under the new classification method proposed.

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Availability of data and materials

The data generated in the present study are not publicly available due to patient privacy protection but may be requested from the corresponding author.

Authors' contributions

ZYY proposed the new classification and drafted the manuscript. CHX and ZMS performed the pathology and IHC examinations and prepared Figs. 3 and 4. WC performed the CT scan and prepared Fig. 2. XZ and CNW developed the treatment plan for the patient, collected the clinical history, and wrote part of the manuscript text. JLT and XDW performed the endoscopy and prepared Fig. 1. XSL and XW searched for relevant literature and refined the new classification. QQY, YH and XYX performed the followed-up of the patient, obtained the post-discharge record from the patient and analyzed patient data. XDW and QBW conceived the idea, refined the new classification and contributed to supervision. ZYY and XDW checked and confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Patient consent for publication

Written informed consent was obtained from the patient for the case information and images to be published in the present case report.

Competing interests

The authors declare that they have no competing interests.

Authors' information

ORCID of Authors:
Dr Zhen-yu Ye, https://orcid.org/0000-0001-5068-2204
Prof Xu-dong Wu, https://orcid.org/0000-0002-2881-954X
Prof Qi-biao Wu, https://orcid.org/0000-0002-1670-1050

References

1. Chhikara BS and Parang K: Global cancer statistics 2022: The trends projection analysis. Chem Biol Lett 10: 451, 2023.
2. Bourreille J, Metayer P, Sauger F, Matray F and Fondimare A: Existence of alpha-fetoprotein during gastric-origin secondary cancer of the liver. Presse Med (1893) 78: 1277-1278, 1970 (In French).
3. Daniele B, Bencivenga A, Megna AS and Tinessa V: Alpha-fetoprotein and ultrasonography screening for hepatocellular carcinoma. Gastroenterology 127 (5 Suppl 1): S108-S112, 2004.
4. O'Conor GT, Tatarinov YS, Abelev GI and Uriel J: A collaborative study for the evaluation of a serologic test for primary liver cancer. Cancer 25: 1091-1098, 1970.
5. Babalı A, Çakal E, Purnak T, Bıyıkoğlu I, Cakal B, Yüksel O and Köklü S: Serum α-fetoprotein levels in liver steatosis. Hepatol Int 3: 551-555, 2009.
6. Motoyama T, Watanabe H, Yamamoto T and Sekiguchi M: Production of alpha-fetoprotein by human germ cell tumors in vivo and in vitro. Acta Pathol Jpn 37: 1263-1277, 1987.
7. Ezaki T, Yukaya H, Ogawa Y, Chang YC and Nagasue N: Elevation of alpha-fetoprotein level without evidence of recurrence after hepatectomy for hepatocellular carcinoma. Cancer 61: 1880-1883, 1988.
8. Ganjei P, Nadji M, Albores-Saavedra J and Morales AR: Histologic markers in primary and metastatic tumors of the liver. Cancer 62: 1994-1998, 1988.
9. Yasunami R, Hashimoto Z, Ogura T, Hirao F and Yamamura Y: Primary lung cancer producing alpha-fetoprotein: A case report. Cancer 47: 926-929, 1981.
10. Saito S, Hatano T, Hayakawa M, Koyama Y, Ohsawa A and Iwamasa T: Studies on alpha-fetoprotein produced by renal cell carcinoma. Cancer 63: 544-549, 1989.
11. Yamagata T, Yamagata Y, Nakanishi M, Matsunaga K, Minakata Y and Ichinose M: A case of primary lung cancer producing alpha-fetoprotein. Can Respir J 11: 504-506, 2004.
12. Matsueda K, Yamamoto H, Yoshida Y and Notohara K: Hepatoid carcinoma of the pancreas producing protein induced by vitamin K absence or antagonist II (PIVKA-II) and alpha-fetoprotein (AFP). J Gastroenterol 41: 1011-1019, 2006.
13. Itoh T, Kishi K, Tojo M, Kitajima N, Kinoshita Y, Inatome T, Fukuzaki H, Nishiyama N, Tachibana H and Takahashi H: Acinar cell carcinoma of the pancreas with elevated serum alpha-fetoprotein levels: A case report and a review of 28 cases reported in Japan. Gastroenterol Jpn 27: 785-791, 1992.
14. Kato K, Matsuda M, Ingu A, Imai M, Kasai S, Mito M and Kobayashi T: Colon cancer with a high serum alpha-fetoprotein level. Am J Gastroenterol 91: 1045-1046, 1996.
15. Yachida S, Fukushima N, Nakanishi Y, Akasu T, Kitamura H, Sakamoto M and Shimoda T: Alpha-fetoprotein-producing carcinoma of the colon: Report of a case and review of the literature. Dis Colon Rectum 46: 826-831, 2003.
16. Kinjo T, Taniguchi H, Kushima R, Sekine S, Oda I, Saka M, Gotoda T, Kinjo F, Fujita J and Shimoda T: Histologic and immunohistochemical analyses of α-fetoprotein-producing cancer of the stomach. Am J Surg Pathol 36: 56-65, 2012.
17. Liu X, Cheng Y, Sheng W, Lu H, Xu Y, Long Z, Zhu H and Wang Y: Clinicopathologic features and prognostic factors in alpha-fetoprotein-producing gastric cancers: Analysis of 104 cases. J Surg Oncol 102: 249-255, 2010.
18. Nagai E, Ueyama T, Yao T and Tsuneyoshi M: Hepatoid adenocarcinoma of the stomach. A clinicopathologic and immunohistochemical analysis. Cancer 72: 1827-1835, 1993.
19. Wang D, Li C, Xu Y, Xing Y, Qu L, Guo Y, Zhang Y, Sun X and Suo J: Clinicopathological characteristics and prognosis of alpha-fetoprotein positive gastric cancer in Chinese patients. Int J Clin Exp Pathol 8: 6345-6355, 2015.
20. Hirajima S, Komatsu S, Ichikawa D, Kubota T, Okamoto K, Shiozaki A, Fujiwara H, Konishi H, Ikoma H and Otsuji E: Liver metastasis is the only independent prognostic factor in AFP-producing gastric cancer. World J Gastroenterol 19: 6055-6061, 2013.
21. Kono K, Amemiya H, Sekikawa T, Iizuka H, Takahashi A, Fujii H and Matsumoto Y: Clinicopathologic features of gastric cancers producing alpha-fetoprotein. Dig Surg 19: 359-365, 2002.
22. Chang YC, Nagasue N, Abe S, Taniura H, Kumar DD and Nakamura T: Comparison between the clinicopathologic features of AFP-positive and AFP-negative gastric cancers. Am J Gastroenterol 87: 321-325, 1992.
23. Sun N, Sun Q, Liu Q, Zhang T, Zhu Q, Wang W, Cao M and Zang QI: α-fetoprotein-producing gastric carcinoma: A case report of a rare subtype and literature review. Oncol Lett 11: 3101-3104, 2016.
24. Ishikura H, Fukasawa Y, Ogasawara K, Natori T, Tsukada Y and Aizawa M: An AFP-producing gastric carcinoma with features of hepatic differentiation. A case report. Cancer 56: 840-848, 1985.
25. Ishikura H, Kirimoto K, Shamoto M, Miyamoto Y, Yamagiwa H, Itoh T and Aizawa M: Hepatoid adenocarcinomas of the stomach. An analysis of seven cases. Cancer 58: 119-126, 1986.
26. Lin JX, Wang ZK, Hong QQ, Zhang P, Zhang ZZ, He L, Wang Q, Shang L, Wang LJ, Sun YF, *et al*: Assessment of clinicopathological characteristics and development of an individualized prognostic model for patients with hepatoid adenocarcinoma of the stomach. JAMA Netw Open 4: e2128217, 2021.

27. Shi J, Liu L and Chen YP: Research progress of prognostic analysis and clinicopathological characteristics of hepatoid adenocarcinoma of the stomach. Zhonghua Zhong Liu Za Zhi 43: 104-107, 2021 (In Chinese)
28. Machlowska J, Baj J, Sitarz M, Maciejewski R and Sitarz R: Gastric cancer: Epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci 21: 4012, 2020.
29. Wang FH, Zhang XT, Tang L, Wu Q, Cai MY, Li YF, Qu XJ, Qiu H, Zhang YJ, Ying JE, *et al*: The Chinese society of clinical oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2023. Cancer Commun (Lond) 44: 127-172, 2024.
30. WHO Classification of Tumours Editorial Board: WHO classification of tumours. Digestive System Tumours. 5th edition. World Health Organization, Lyon, 2019.
31. Amin MB, Edge SB, Greene FL and Brierley JD (eds): AJCC cancer staging manual. 8th edition. Springer, New York, NY, 2017.
32. Kodama T, Kameya T, Hirota T, Shimosato Y, Ohkura H, Mukojima T and Kitaoka H: Production of alpha-fetoprotein, normal serum proteins, and human chorionic gonadotropin in stomach cancer: Histologic and immunohistochemical analyses of 35 cases. Cancer 48: 1647-1655, 1981.
33. Chinese Medical Association Oncology: Clinical diagnosis and treatment guideline of gastric cancer of Chinese Medical Association (2021 edition). Natl Med J Chin 102: 1169-1189, 2022 (In Chinese)
34. Sun L, Wei JJ, An R, Cai HY, Lv Y, Li T, Shen XF, Du JF and Chen G: Gastric adenosquamous carcinoma with an elevated serum level of alpha-fetoprotein: A case report. World J Gastrointest Surg 15: 2357-2361, 2023.
35. Trompetas V, Varsamidakis N, Frangia K, Polimeropoulos V and Kalokairinos E: Gastric hepatoid adenocarcinoma and familial investigation: Does it always produce alpha-fetoprotein?. Eur J Gastroenterol Hepatol 15: 1241-1244, 2003.
36. Jiao XH, Dong LC, Tian GL, Zheng YY and Shao YY: 2 cases of alpha-fetoprotein-elevated gastric cancer and literature review. J Qiqihar Med Univ 23: 175, 2010 (In Chinese).
37. Motoyama T, Aizawa K, Watanabe H, Fukase M and Saito K: Alpha-fetoprotein producing gastric carcinomas: A comparative study of three different subtypes. Acta Pathol Jpn 43: 654-661, 1993.
38. Yang XS, Wang AQ, Wu Y, Li Z, Bu Z and Ji J: Hepatoid adenocarcinoma of stomach: Current research, progress, and controversy. Chin J Clin Oncol 50: 679-684, 2023 (In Chinese)
39. Chen EB, Wei YC, Liu HN, Tang C, Liu ML, Peng K and Liu T: Hepatoid adenocarcinoma of stomach: Emphasis on the clinical relationship with alpha-fetoprotein-positive gastric cancer. Biomed Res Int 2019: 6710428, 2019.
40. Chen Y, Qu H, Jian M, Sun G and He Q: High level of serum AFP is an independent negative prognostic factor in gastric cancer. Int J Biol Markers 30: e387-e393, 2015.
41. Lin HJ, Hsieh YH, Fang WL, Huang KH and Li AF: Clinical manifestations in patients with alpha-fetoprotein-producing gastric cancer. Curr Oncol 21: e394-e399, 2014.
42. Ooi A, Nakanishi I, Sakamoto N, Tsukada Y, Takahashi Y, Minamoto T and Mai M: Alpha-fetoprotein (AFP)-producing gastric carcinoma. Is it hepatoid differentiation?. Cancer 65: 1741-1747, 1990.
43. Gong W, Shou D and Gong P: Extremely high expression of serum alpha-fetoprotein level of gastric adenocarcinoma: A rare case with an unexpected well-prognosis. Springerplus 5: 2056, 2016.
44. Yu J, Kane S, Wu J, Benedettini E, Li D, Reeves C, Innocenti G, Wetzel R, Crosby K, Becker A, *et al*: Mutation-specific antibodies for the detection of EGFR mutations in non-small-cell lung cancer. Clin Cancer Res 15: 3023-3028, 2009.
45. Simonetti S, Molina MA, Queralt C, de Aguirre I, Mayo C, Bertran-Alamillo J, Sanchez JJ, Gonzalez-Larriba JL, Jimenez U, Isla D, *et al*: Detection of EGFR mutations with mutation-specific antibodies in stage IV non-small-cell lung cancer. J Transl Med 8: 135, 2010.
46. Hofman P, Ilie M, Hofman V, Roux S, Valent A, Bernheim A, Alifano M, Leroy-Ladurie F, Vaylet F, Rouquette I, *et al*: Immunohistochemistry to identify EGFR mutations or ALK rearrangements in patients with lung adenocarcinoma. Ann Oncol 23: 1738-1743, 2012.
47. Guo R, Ma L, Bai X, Miao L, Li Z and Yang J: A scoring method for immunohistochemical staining on Ki67. Appl Immunohistochem Mol Morphol 29: e20-e28, 2021.
48. Li XD, Wu CP, Ji M, Wu J, Lu B, Shi HB and Jiang JT: Characteristic analysis of α-fetoprotein-producing gastric carcinoma in China. World J Surg Oncol 11: 246, 2013.
49. Su JS, Chen YT, Wang RC, Wu CY, Lee SW and Lee TY: Clinicopathological characteristics in the differential diagnosis of hepatoid adenocarcinoma: A literature review. World J Gastroenterol 19: 321-327, 2013.
50. Jiang J, Ding Y, Lu J, Chen Y, Chen Y, Zhao W, Chen W, Kong M, Li C, Teng X, *et al*: Integrative analysis reveals a clinicogenomic landscape associated with liver metastasis and poor prognosis in hepatoid adenocarcinoma of the stomach. Int J Biol Sci 18: 5554-5574, 2022.
51. Lu J, Ding Y, Chen Y, Jiang J, Chen Y, Huang Y, Wu M, Li C, Kong M, Zhao W, *et al*: Whole-exome sequencing of alpha-fetoprotein producing gastric carcinoma reveals genomic profile and therapeutic targets. Nat Commun 12: 3946, 2021.
52. Crowe SE: Helicobacter pylori infection. N Engl J Med 380: 1158-1165, 2019.
53. Bornschein J, Selgrad M, Warnecke M, Kuester D, Wex T and Malfertheiner P: H. pylori infection is a key risk factor for proximal gastric cancer. Dig Dis Sci 55: 3124-3131, 2010.
54. Kumar S, Metz DC, Ellenberg S, Kaplan DE and Goldberg DS: Risk factors and incidence of gastric cancer after detection of Helicobacter pylori infection: A large cohort study. Gastroenterology 158: 527-536.e7, 2020.
55. Shirani M, Pakzad R, Haddadi MH, Akrami S, Asadi A, Kazemian H, Moradi M, Kaviar VH, Zomorodi AR, Khoshnood S, *et al*: The global prevalence of gastric cancer in Helicobacter pylori-infected individuals: A systematic review and meta-analysis. BMC Infect Dis 23: 543, 2023.
56. Alipour M: Molecular mechanism of Helicobacter pylori-induced gastric cancer. J Gastrointest Cancer 52: 23-30, 2021.
57. Takahashi-Kanemitsu A, Lu MX, Knight CT, Yamamoto T, Hayash T, Mii Y, Ooki T, Kikuchi I, Kikuchi A, Barker N, *et al*: The Helicobacter pylori CagA oncoprotein disrupts Wnt/PCP signaling and promotes hyperproliferation of pyloric gland base cells. Sci Signal 16: eabp9020, 2023.
58. Liu DR, Li BB, Yan B, Liu L, Jia Y, Wang Y, Ma X and Yang F: The clinicopathological features and prognosis of serum AFP positive gastric cancer: A report of 16 cases. Int J Clin Exp Pathol 13: 2439-2446, 2020.
59. Ge Z, Ben Q, Qian J, Wang Y and Li Y: Diabetes mellitus and risk of gastric cancer: A systematic review and meta-analysis of observational studies. Eur J Gastroenterol Hepatol 23: 1127-1135, 2011.
60. Yoon JM, Son KY, Eom CS, Durrance D and Park SM: Pre-existing diabetes mellitus increases the risk of gastric cancer: A meta-analysis. World J Gastroenterol 19: 936-945, 2013.
61. Sekikawa A, Fukui H, Maruo T, Tsumura T, Okabe Y and Osaki Y: Diabetes mellitus increases the risk of early gastric cancer development. Eur J Cancer 50: 2065-2071, 2014.
62. Bae JM: Diabetes history and gastric cancer risk: Different results by types of follow-up studies. Asian Pac J Cancer Prev 23: 1523-1528, 2022.
63. Dabo B, Pelucchi C, Rota M, Jain H, Bertuccio P, Bonzi R, Palli D, Ferraroni M, Zhang ZF, Sanchez-Anguiano A, *et al*: The association between diabetes and gastric cancer: Results from the stomach cancer pooling project consortium. Eur J Cancer Prev 31: 260-269, 2022.