AFP (alpha fetoprotein): Who are you in gastrology?

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ABSTRACT

AFP-producing (hepatoid differentiation) gastric cancer (GC) initially reported in 1970 plays an important role in the field of gastrology, which should be distinguished from other solid-type GCs owing to their different biological behavior. This review article aims to summarize the literature related to the role of AFP in gastric cancer and to unveil the underlying mechanism by which AFP-production impacts prognosis of GC patients. The prima facie evidence demonstrated that AFP-producing GC is more aggressive and characterized by a high incidence of venous invasion, lymphatic invasion, and metachronous and synchronous liver metastasis compared with AFP-non producing GC. Furthermore, distant metastasis was frequently observed, leading to a poorer overall prognosis. The underlying molecular mechanism is still obscure and optimal regimen remains undefined well. Nevertheless, our present study advances the knowledge of AFP-producing GC in the field of gastrology. AFP-positivity should be highlighted and an a priori enhancer intervention is needed to improve prognosis in future clinical practice. Personalized medication is strongly suggested.

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Introduction

Alpha fetoprotein (AFP) as an oncogenic glycoprotein is normally expressed during gestation, which was originally identified in the human fetus in 1956 [1]. AFP can be synthesized by yolk sac, fetal liver, and some gastrointestinal cells. A rise of serum AFP level is routinely taken into account for abnormality in adults and frequently utilized as a suitable biomarker for yolk sac tumor, tumors of gonadal origin, hepatocellular carcinoma (HCC), and certain gastric carcinomas (GCs) [2].

Gastric cancer is the second most common cause of cancer death, and the fourth common cancer worldwide [3]. AFP-producing (hepatoid differentiation) GC is a rare form of stomach malignancy and was initially reported by Bourreille et al. in 1970 [4]. AFP-producing GC is a variant of adenocarcinoma with high malignancy [5]. Indeed, it comprises two morphological subtypes: clear cell and hepatoid [2]. Histologic types can be classified into yolk sac tumor, enteroblastic (ENT), hepatoid (HPT), and common (COM) adenocarcinoma types. The tumor phenotypes can be divided into gastric, intestinal, and gastrointestinal types based on immunohistochemical analysis (Table 1) [6]. Most cases are shown as an intestinal phenotype. In histology, the primary type of mucosal lesion is COM and/or ENT. HPT only appears in invasive lesions. These findings imply that mucosal COM type may be differentiated into HPT and ENT during the process of tumor proliferation and invasion, acquiring AFP-producing ability [6].

The incidence of AFP-producing GC is approximately 1.3%–15% in GC, which is characterized by its poor overall prognosis with a high incidence of venous invasion, lymphatic invasion, and metachronous and synchronous liver metastasis compared with AFP-non producing GC [8]. Metachronous solitary adrenal gland and pulmonary metastases [9] and cerebral metastasis [10] of AFP-producing GC may also be observed. Furthermore, it could relatively rarely be manifested by meningitis carcinomatosa after liver metastasis was reduced by 6 courses of chemotherapy [11].

Production of AFP implies enteroblastic or hepatoid differentiation of gastric cancer cells [5]. Although a series of studies on AFP-producing GC appear in recent years, the impact of peripheral AFP on the prognosis and sensitivity of chemotherapy of GC patients remains obscure. The deleterious sequela of elevated serum AFP level are to be systematically analyzed. Herein, it is of great interest in reviewing...
and summarizing the effect of peripheral AFP on the GC patients based on published data to better understand AFP-related cancer biology, provide better healthcare planning for AFP-producing patients, and improve their prognosis.

**Manifestation of AFP-producing gastric cancer**

The clinical presentation of AFP-producing gastric cancer is similar with the one of common type of GC such as a poor complexion and appetite [11], abdominal distension, epigastric pain and fullness [12–16]. Physical examination may exhibit anemic conjunctiva and slight pretilial edema owing to low level of serum hemoglobin and albumin [11]. Elastic and firm liver may be palpable below the right costal margin when hepatic metastasis occurs [13]. The laboratory data may display an increase of serum level of other tumor markers including des-gamma-carboxy prothrombin (DCP), CEA, and hCG [13,16–18]. Serum CA19-9 level is infrequently elevated [16]. Ki67 staining may be positive in the tumor tissue [19]. Combined use of peripheral biomarkers will increase diagnostic sensitivity of gastric cancer [20]. Multiple metastatic nodules in the liver are often observed in the abdominal CT or MR imaging [21,22]. Liver metastases can be rapidly enlarged and even ruptured [19]. Therefore, AFP-producing GC at early stage is rarely found. The patients died of hepatic metastasis even if AFP-producing early GC (type 0 Ila and Ilc tumor) was identified [12].

**Difference of biological behavior between AFP- and AFP-non producing GCs**

Accumulating evidences have revealed a dramatic difference of clinicopathological characteristics and clinical outcomes between AFP- and AFP-non producing GCs. Overall, AFP-producing GC characterized by more aggressive behavior results into a poorer prognosis [8]. It rapidly progresses and frequently metastasizes into the liver and its regional lymph nodes [21]. Tumor recurrence was frequently observed in those AFP-producing patients and even those submucosal GC patients who had successfully received gastrectomy with lymph node dissection (D2 or D3). Differently, no recurrence was found in AFP-negative GC patients even if second-station metastasis of lymph node appeared [22]. In the seronegative and histopositive AFP-producing patient, lymph node metastasis was still found although no apparent swelling of lymph node was shown by preoperative diagnostic imaging [17]. Compared with AFP-non producing GC, the proportion of early GC is significantly lower (4% vs. 30.1%), whereas the proportion of advanced GC (96% vs. 69.9%) is remarkably higher among AFP-producing GC patients [7]. Indeed, multivariate analysis exhibited that AFP positivity can be a new independent prognostic factor in GC patients [22]. Furthermore, liver metastasis was frequently observed (90.9%, 10/11) by Hirajima et al., which was considered to be the only independent prognostic factor (HR = 17.6, p = 0.0081) for AFP-producing GC patients [8]. Dr. Lin et al. reported that the incidence of lymph node and liver metastasis was statistically higher (91.4% vs. 60.7%, and 27.6% vs. 4.4%). Nevertheless, the underlying mechanism of tendency of these metastases remains unclear. The 1-, 3-, and 5-year survival rates were 15.4%, 7.7%, and 0% respectively among those GC patients with serum AFP greater than 300 ng/mL. The 1-, 3-, 5-, and 10-year survival rates were 46.7%, 28.9%, 17.8%, and 13.3% respectively among GC patients with serum AFP greater than 20 ng/mL, but 300 ng/mL or less [7].

**Molecular characteristics of AFP-producing gastric cancer**

To further clarify the biological behavior of AFP-producing GC, analysis of gene expression was performed for gastric cancer specimens. The findings exhibited that SALL4 protein was expressed among 95% of AFP-producing gastric carcinoma or hepatoid gastric carcinoma. Both Glypican 3 and AFP (hepatocyte markers) rather than NCAM/CD56 (putative hepatic stem/progenitor markers) could be detected in all AFP-producing GC [2]. Indeed, SALL4 is a novel embryonic stem cell and germ cell marker, which was identified in the immature teratomas and acts for maintaining the pluripotent and self-renewal properties of embryonic stem cells [23]. Detection of SALL4 expression can be utilized to diagnostically distinguish AFP-producing GC from hepatocellular carcinoma [23].

In gastric cancer expression of GATA4 is epigenetically diminished by hypermethylation of the primer region. However, in AFP-producing GC, GATA4 expression is relatively silenced. 3/8 cases were positively shown by immunohistochemical analysis. No GATA4 methylation was detected in any of the AFP-producing GC by using methylation-specific PCR, whereas methylation was concurrently found with GATA4 expression in common GC. The underlying silencing mechanism of GATA4 methylation in AFP-producing GC is involved in histone modification (deacetylation) [5]. Compared with AFP-negative GC, a higher frequency of c-Met expression was detected in the AFP-producing GC (p < 0.01), which is known to regulate cell proliferation and migration. Hepatocyte growth factor (HGF) as a ligand for c-Met receptor is strongly associated with malignant invasive property and development of distant metastases. In addition, it was found that the frequency of VEGF-C expression in the AFP-positive GC was significantly higher than that in the AFP-negative GC (p < 0.01). The microvessel density in the AFP-producing GC was also higher than that in the AFP-negative GC [24]. Therefore, the increased frequency of microvessel density and augmented expression of c-Met/HGF and VEGF-C may have a large measure explain for the poorer prognosis of AFP-producing GC [24–26].

**Table 1**

<table>
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<th>Publication year</th>
<th>Reference</th>
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**Regulation of AFP-production in gastric cancer**

Since in the fetal liver liver-enriched nuclear factors (LENFs) are germane to the transcriptional regulation of AFP expressions of LENFs (C/EBP (CCAT enhancer binding protein)-alpha, -beta, HNF (hepatocyte nuclear factor)-1α, -1β, and -4α) were studied [27]. The findings displayed that compared with AFP-non producing GC, the liver activating protein (LAP) as an activating isoform of C/EBP-beta was remarkably expressed, and that the expression level of the liver inhibitory protein (LIP) (an inhibitory isoform of C/EBP-beta) was significantly lower in AFP-producing GC. It implies that isoforms of C/EBP-beta play an important role in regulating phenotype of AFP-GC [27].

Interestingly, it was also found that absence of ATBF1 caused AFP gene expression in gastric cancer, which is a transcription factor binding to an AT rich region in the AFP regulatory element. ATBF1 could downregulate AFP gene expression. Furthermore, a negative correlation between the expression of AFP and ATBF1 was clearly
observed in GC. Chloramphenicol acetyltransferase (CAT) assay revealed this direct suppression of AFP gene expression by ATBF1 [28].

Treatment for AFP-producing gastric cancer

With respect to common gastric cancer, currently surgery remains the primary therapeutic strategy although chemical and biological drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and trastuzumab are being developed and used in clinical practice [29,30]. Owing to the aggressive feature of AFP-producing GC, radical resection is normally encouraged to perform, whereas palliative resection is used for the cases with distant metastasis. Adjuvant chemotherapy may be adopted to enhance the efficacy of surgical therapy [31]. Although cisplatin resistance of AFP-producing GC was observed in clinic, rapamycin may be used as a potential supplemental agent for improving therapeutic effectiveness. Rapamycin, an inhibitor of the mammalian target of rapamycin complex 1 (mTORC1), plays a role in the pivotal kinase pathway. It is capable of intensifying the cytotoxic action of cisplatin [32].

It is known that AFP-producing GC is resistant to chemotherapy [33], which is partially caused by overexpression of p-glycoprotein in cancerous tissue [34]. To date, no consistent regimen for AFP-producing GC has been achieved. A personalized one is de facto suggested. For instance, a short-term response was achieved by using cisplatin/irinotecan chemotherapy [35]. The different case showed that total gastrectomy even with splenectomy may be performed to treat AFP-producing GC with liver metastases (pathological stage IV). Thereafter, the patient should receive combination chemotherapy including compound tegafur and oteracil potassium sustained capsules (S-1) at a dose of 100 mg/d for 2 weeks and discontinuation for 1 week and paclitaxel at a dose of 80 mg on days 1 and 8. Serum AFP level was remarkably altered with a 10-fold decrease and liver metastasis was regressed. As serum level of AFP was increased, S-FU (500 mg/day for 7 days) and paclitaxel (120 mg weekly) at weekly intervals were given. After one course, monotherapy with paclitaxel (120 mg) was continued for 6 weeks. Serum AFP decreased markedly and liver metastases disappeared [15]. Intriguingly, the data from a covery of AFP-producing patients revealed that FLEEP chemotherapy (combined use of 5-fluorouracil, leucovorin, etoposide, and cis-diaminedichloroplatinum) was significantly effective for stage IV AFP-producing GC compared with stage IV AFP-negative GC. Preoperative FLEEP chemotherapy could downstage GC, resulting in a better prognosis of AFP-producing GC [36]. With regard to an unresectable AFP-producing GC of the esophago-gastric junction with multi–metastatic lesions of the liver, a regimen of capecitabine (1000 mg/m² twice daily; days 1–14; repeated day 22) and oxaliplatin (130 mg/m²; day 1; repeated day 22)-based combination chemotherapy was successfully administered. Four weeks later, serum AFP level was pronouncedly altered (with a 9-fold decrease). Furthermore, MRI imaging displayed a remarkable regression and even disappearance of liver metastases and lymph nodes. As a result, a long-lasting major remission was achieved in a survival of 18.5 months without surgical therapy [37]. Therefore, prediction of chemotherapeutic sensitivity is to be studied, which will guide our provision for personalized regimen.

Noticeably, one AFP-producing GC case with metachronous liver metastasis was successfully treated by a distal gastrectomy and a partial hepatectomy of S6 and S8. After the operation, the patient’s serum AFP level remained within normal limits for one year without any chemotherapy [38].

Future direction

As personalized medicine is rapidly advancing [39], categorization of gastric cancer patients is per se required in clinical practice. AFP-producing GC is one group characterized by higher malignancy, which demands aggressive therapeutic strategies. To prevent recurrence, early use of immunohistochemical staining of AFP for each specimen is mandatory apart from detection of peripheral AFP level [12]. Furthermore, sub-grouping of AFP-producing GC may be given since the prognosis is poorer in those with higher levels of AFP (>300 ng/mL). Seronegative and histopositive AFP-producing GC as an early form of aggressive cancer should be taken into account for special analysis and personalized treatment [17]. Refinement may also be utilized by using well-known specific biomarkers. For instance, hepatocyte paraffin-1 ( HepPar1) or des-gamma-carboxy prothrombin (DGP) positivity or negativity can be supplemented to AFP-producing GC [13,16]. The etiology of this type is strongly associated with Helicobacter pylori (HP) infection although their causative relationship is still obscure [16]. The AFP-producing GC with high peripheral levels of human chorionic gonadotropin (hCG) and carcinoembryonic antigen (CEA) is likely to be a poorer differentiation of adenocarcinoma and metastasizes to both ovary and liver [18]. The biological mechanisms of these two cases are different and to be further investigated separately. The acquisition of AFP-production, the reason for poor prognosis of AFP-producing GC, and molecular pathologic analysis are also necessary to be studied [6]. In addition, suitable biomarkers for predicting chemotherapeutic sensitivity are to be identified, which will guide our provision for personalized regimen.

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Conflict of interest

There is no any conflict of interest.

References


