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Clinical characteristics and treatments of patients with alpha-fetoprotein producing gastric carcinoma

Minireview

W. GONG[1,2,#], Y. SU[3,#], A. LIU[1], J. LIU[1], D. SUN[4], T. JIANG[5], J. XIANG[1], C. CHI[6], P. SUN[1,*]

[1]Department of Oncology, Yuhuangding Hospital of Yantai, Yantai, Shandong Province 264001, China; [2]Shandong University, Jinan, Shandong Province 250013, China; [3]Department of Radiotherapy, Yuhuangding Hospital of Yantai, Yantai, Shandong Province 264001, China; [4]Pathology Department, Yuhuangding Hospital of Yantai, Yantai, Shandong Province 264001, China; [5]Department of Oncology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong Province 266000, China; [6]Department of Clinical Laboratory, Yantai Yuhuangding Hospital Laishan Branch, Yantai, Shandong Province 264001

**Correspondence: sunping20039@hotmail.com*
[#]Contributed equally to this work.

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Alpha-fetoprotein (AFP) is a well-known tumor marker of hepatic carcinoma and yolk sac tumor. Alpha-fetoprotein producing gastric carcinoma (AFPGC) is a rare type of gastric cancer with high malignancy and poor prognosis, which makes it different from other types of gastric cancer. This rare gastric cancer patient subgroup is likely frequently misdiagnosed which may be related to lack of knowledge about the disease. The purpose of this article is to summarize the mechanism of AFP positive gastric cancer, classification, biological behavior and treatment, in order to assist clinical practitioners to detect AFPGC earlier and treat it better. Previous studies have shown that AFPGC has a complex pathophysiology mechanism. AFPGC is aggressive and characterized by stronger proliferation, neovascularization, lymphatic invasion and distant metastasis. Furthermore, so far there has been no standard treatment for patients with AFPGC. Nevertheless, our present study summarizes some effective treatments based on previous research. In conclusion, the present study demonstrates the importance of detecting AFP routinely in serum and tissues in gastric cancer cases, which will greatly improve the diagnosis rate of AFPGC, and in regards to treatment, surgery, chemotherapy, targeted therapy and interventional treatment may have positive impacts on AFPGC treatment outcome. However, further study with a larger sample is required to confirm the reliability and validity of these methods.

Key words: alpha-fetoprotein producing, gastric carcinoma, malignancy, prognosis, diagnosis, therapeutics

Gastric carcinoma is one of the ten common malignant tumors in China. Worldwide, gastric cancer mortality ranks No. 2, second only to lung cancer [1]. AFP is an oncofetal glycoprotein produced by the yolk sac and liver mainly during fetal development and to a lesser extent in the fetal gastrointestinal tract [2]. The highest serum AFP level occurs during 12–15 weeks of proliferation in pregnancy, and reduces to normal adult level about one year later. AFP is a specific marker for the diagnosis of hepatocellular carcinoma and yolk sac tumor. AFP also commonly increases in hepatitis, cirrhosis, hepatocellular carcinoma, yolk sac tumor, teratoma and reproductive system cancer and so on. When endoderm derived organs possessed to tumors such as gastrointestinal cancer, pancreatic cancer, gallbladder cancer and lung cancer, AFP may also increase to varying degrees. Bourreill etc. [3] reported the first case of AFP-positive gastric cancer with liver metastasis in 1970. AFPGC refers to the serum and gastric cancer tissue containing large amount of AFP with the exclusion of other possible hepatitis, cirrhosis, hepatocellular carcinoma and germ cell cancer and other diseases that may produce AFP. It is mainly diagnosed by high serum AFP levels and immunohistochemistry pathology. Immunohistochemical staining is necessary for the diagnosis of AFPGC. There are very few AFPGC cases with negative serological and positive immunohistochemistry staining [4], indicating the importance of histological examination in the diagnosis

of APFGC. Foreign literature shows AFPGC accounts for 1.3–15% of gastric cancer [5]. The incidence reported in China is lower than abroad. This very rare gastric cancer patient subgroup is likely frequently misdiagnosed, which may be related to clinically inadequate attention and the lack of routine investigation of AFP. Besides, it is reported that AFPGC is a highly aggressive tumor. Its 5-year survival rate and median survival time is lower than in other types of common gastric cancer. Awareness of this subgroup should be increased to improve early diagnosis and treatment and ultimately to improve patient prognosis.

Mechanism

Common specific markers of gastric cancer include CEA, CA199 and others. Then why does this type of gastric cancer has a high expression of AFP? One view tends to generate theory in which the stomach and liver tissues derive from endoderm, they evolve from the embryonic foregut in embryonic period, while there is a direct continuation of the foregut and yolk sac. The primitive cells can produce AFP. During gastric cancer process, because of an error occurring in cell differentiation, some suppressed genes are activated resulting in the potential for full expression of AFP. Its tissue morphology is similar to hepatocellular carcinoma tissue or yolk sac tumor [6]. SALL4 has been identified as a diagnostic marker of germ cell tumors, especially yolk sac tumors, in gonadal organs. SALL4 gene plays an important role during early embryonic development, organ formation and embryonic stem cell proliferation and maintenance of pluripotency. In order to clarify the significance of SALL4 as an oncofetal protein, Ushiku et al. [7] found by immunohistochemistry that SALL4 expression was closely associated with AFP expression in AFPGC, while both SALL4 and AFP expression are negative in normal gastric cancer. The result seems to reflect fetal gut differentiation in AFPGC, but we have not found in literature that SALL4 gene can promote the high expression of AFP. Besides, the authors also proved that SALL4 expression was completely negative in hepatoblastoma and hepatocellular carcinoma. The other view is that AFP comes from metastasizing liver tissues. In some AFPGC patients, AFP is negative in the absence of liver metastasis, and the level of AFP increases significantly in patients with liver metastasis, and the incidence of liver metastasis in AFPGC is higher than that in non-AFPGC patients. The hypothesis may be that the regeneration or proliferation of liver cells around liver metastases produce AFP. This suggests that the reason of high expression of AFP is multifactorial.

Classification

Motoyama et al. proposed a concept of histological type of AFPGC. They divided AFPGC into three subtypes: one is hepatic adenocarcinoma of stomach, the most common type; the second one is the fetus gastrointestinal type, whose histological morphology is similar to 3 months gestational histological tissue; the third one is like yolk sac tumor, which has tissues similar to liver and (or) yolk sac [8]. However, Li et al. proposed that AFPGC should be divided into four types: hepatoid type, fetal gastrointestinal type, yolk sac tumor type and mixed type.

Aggressive behavior and poor prognosis

AFPGC is highly invasive and has poorer biological behavior than other gastric cancer [9]. The median survival time of AFPGC patients is significantly shorter than that of other gastric cancers [10]. The 5-year survival rate of the AFP-positive group was significantly poorer than that of the AFP-negative group [11–12] (Table 1). It is mainly in middle-aged men that poorly differentiated adenocarcinoma commonly occurs in the antrum, and more performance for the advanced gastric cancer is Bormann II, Bormann III stage. It has the characteristics of stronger proliferation, lower cell apoptosis and more neovascularization compared with AFP negative gastric cancer [13]. It has a high transfer rate, and it is more associated with liver metastasis and lymphatic metastasis [14–16] (Table 2). Liver metastases are mostly diffuse with poor prognosis and survival of less than 1 year. The prognosis of AFPGC is related to tumor size, the depth of invasion, lymphatic metastasis, pathological stage, liver metastasis, vascular tumor invasion [17] and the expression of P21 [18]. A high level of serum AFP can also be used for evaluating the prognosis of gastric cancers whether in the presence or absence of liver metastasis [19]. Follow up of AFP levels in AFPGC may allow prediction of early treatment response and can be a better indicator than CEA for follow up in response evaluation [20]. AFP expression should also be used as a marker for the subsequent treatment in order to detect the progression or recurrence of disease earlier. In order to explain the different biological behavior with common gastric cancer, cellular factors such as Ki-67, c-Met, vascular endothelial growth factor-C, STAT3, hepatocyte growth factor and its receptor, have been investigated in AFP producing gastric adenocarcinoma and cell lines [21–23]. However, the exact molecular mechanism of the aggressive behavior is far from clear.

Treatment

At present, there is no standard treatment of AFPGC, common gastric cancer treatment is used as the reference standard. We have collected recent literature to present

Table 1. 5-year survival rate of AFPGC.

		5-year survival rate (%)	
	cases	AFP producing GC	AFP non-producing GC
Liu X, 2010 [11]	104	28	38
Liu X, 2015 [12]	65	4.7	16.5

Table 2. Comparison of clinicopathologic characteristics between AFP positive and negative groups.

	Chun H, 2016 [14] AFPGC			Wang D, 2015 [15] AFPGC			Liang H, 2016 [18] AFPGC		
	producing	non-producing	p-value	producing	non-producing	p-value	producing	non-producing	p-value
Tumor size (cm)	4	3.5	0.725	5.68	4.38	0.001	6.2	5.7	0.379
Vascular invasion (%)	22.85	7.89	0.002	82.2	66.7	0.032	87.5	86.67	0.598
Liver metastasis (%)	14.29	3.64	0.002	57.78	3.73	0	62.5	11.11	0.001
Lymph node metastasis (%)	68.57	48.86	0.023	77.78	63.67	0.037	75	88.89	0.1
Nerve invasion (%)	35.55	34.9	0.193	62.22	54.16	0.295			
Recurrence (%)	28.57	16.24	0.058				84.38	62.22	0.029

Table 3. Patients' treatment and outcome of AFPGC.

Author	Treatment	Long-term efficacy
Kim C, 2012 [24]	sorafenibin combination with capecitabine and cisplatin as a first line	ORR 62.5% PFS 10 months OS 14 months
Adachi Y, 2003 [25]	preoperative	5-year survival rate 22% OS 14 months
	radical operation	5-year survival rate 42% OS 24 months
Gan T, 2012 [26]	radical operation	1-year survival rate 51.7% 3-year survival rate 31% 5-year survival rate 10.3%
Galvez-Munoz E, 2009 [27]	Palliative total gastrectomy; palliative chemotherapy with cisplatin and capecitabine (6 cycles)	OS 8 months
Xie Y, 2015 [28]	Surgery for cure in 85%	OS 12 months
	Adjuvant chemotherapy offered in 12/16 (75%) resected patients	DFS 7 months
Kochi M, 2004 [29]	FLEP chemotherapy for AFPGC of stage IV	OS 15.8 months

ORR: objective response rate; PFS: progression free survival; OS: overall survival; DFS: disease free survival

patients' treatment of AFPGC [24–29] (Table 3). Radical surgery is a good means to extend patients' survival (30). If liver metastases are present, the removal of the liver is necessary [31]. The unresectable liver metastases can be considered for interventional therapy. Studies confirmed that patients with AFPGC should receive postoperative adjuvant chemotherapy regardless of the stage. LFEP (5-fu, leucovorin (LV), etoposide (vp-16) and cisplatin (DDP)) can be given to advanced patients who cannot be operated. The use of irinotecan has also been reported. More and more doctors use S-1 in the treatment of advanced AFPGC, which shows a good prospect [32]. It has been proved that the sensitivity of chemotherapy drugs differed from the Lauren types of AFPGC patients. Diffuse gastric cancer can benefit more from paclitaxel, S-1 and irinotecan [33]. At present, there is no large scale clinical research about APFGC-related targeted therapy. There are case reports of sorafenib, apatinib, trastuzumab that had efficacy in the treatment of AFPGC [34]. AFPGC treatment still needs further study and clinical data accumulation and analysis of randomized controlled trials in order to confirm which treatment is the most effective.

Conclusion

In summary, AFPGC is a rare, aggressive and malignant cancer with a high rate of missed diagnosis. It has the characteristics of stronger aggressive biological activity, later staging, lymph node metastasis, vascular invasion, liver metastasis, short survival and poor prognosis. All physicians should pay attention to this rare subgroup to improve its diagnosis and treatment. Physicians encountering high levels of AFP, following the general examination should consider the possibility of AFPGC, except for hepatocellular carcinoma, active liver disease, genitourinary system tumors and other diseases. For diagnosed gastric cancer the detection rate of this type is also low, mostly because serum APF is not routinely ordered, and the pathology laboratory rarely conducts AFP immunohistochemistry in gastric tissue. Therefore, it is recommended that physicians routinely exam the level of serum AFP in gastric cancer patients, especially in patients with liver metastasis, and that pathological specimens of routine AFP immunohistochemistry can greatly improve the detection rate of AFPGC. Clinicians can intervene early, provide more treatment measures and improve

prognosis. Both clinicians and pathologists should be familiar with the clinical and pathological features of the disease, in order to avoid misdiagnosis and missed diagnosis. In the process of tumor treatment and follow-up visit, AFP expression level should be closely monitored, because it is possible to evaluate the treatment effect, and indicate the tumor recurrence and metastasis. The treatment should consider a variety of methods, including surgery, chemotherapy, interventional therapy, targeted therapy, and there is a potential therapeutic option for this rare disease. As the number of cases is still limited, further randomized controlled trials are necessary to confirm the efficacy of the treatment for AFPGC.

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