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α-Fetoprotein Producing Gastric Cancers - A Quick Review

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Abstract: A variety of malignancies other than yolk sac tumor and hepatocellular carcinoma also produce alpha fetoprotein, of which gastric adenocarcinoma is the most common. α-fetoprotein–producing gastric adenocarcinomas are rare, comprising about 1-6% of all gastric tumors. They can be subgrouped into three categories: gastric adenocarcinoma with yolk sac tumor differentiation, gastric adenocarcinoma with hepatoid differentiation and gastric adenocarcinoma with enteroblastic differentiation. These tumors have elevated alpha fetoprotein and have poorer prognosis than conventional gastric adenocarcinomas. Owing to rarity of the lesion, these tumors are less described. In this review article, we have briefly described pathogenesis, clinical features, morphological features and diagnostic cues of these AFP producing gastric cancers in order to avoid misdiagnosis leading to under treatment.

Key words: Alpha Fetoprotein · Gastric Adenocarcinoma · Hepatoid · Enteroblastic · Yolk Sac Tumor

INTRODUCTION

Epithelial tissues give rise to cancers or carcinomas that are responsible for more than 80% of cancer related deaths in the west. Adenocarcinomas arise from epithelial cells that secrete mucin and form glands. Adenocarcinomas are commonly seen in lower esophagus, stomach, intestines, breast, lung, liver, gall bladder, ovary and uterus. Gastric adenocarcinomas is one of the major contributors to cancer related mortality and is the second most common cancer in Asia [1-3].

Gastric carcinomas (GAC) are known to occasionally show hepatoid or yolk sac or fetal gut like differentiation. These cancers are considered as adenocarcinomas with embryonic features similar to the morphology of yolk sac tumor (YST) or adenocarcinomas with hepatocytes like morphology or resemble fetal gut epithelium. These gastric cancers show elevated alpha fetoprotein (AFP) and are known to have a worse prognosis than conventional gastric adenocarcinomas [4]. Motoyama *et al*. [5] discussed 9 cases of AFP producing gastric carcinoma. They classified these tumors into 3 subgroups that are hepatoid type, yolk sac tumor-like type and fetal gastrointestinal type. Hepatoid type is believed to be developed from liver cell metaplasia and yolk sac type from yolk sac metaplasia of a common lesion considered to be medullary adenocarcinoma that is poorly differentiated. The fetal gut type is considered to arise from the fetal gastrointestinal epithelium. Out of all three, the hepatoid subgroup was the most common and known to be aggressive than other types [5]. It is important to identify these AFP producing gastric cancers. In this review article, we have briefly described pathogenesis, clinical features, morphological features and diagnostic cues of these AFP producing gastric cancers.

Gastric Adenocarcinoma with Yolk Sac Tumor Differentiation: Gastric YST was first described by Gharcia, *et al*. in 1985. Since then, only a few cases are reported in the literature so far. Around 69% of gastric YSTs had adenocarcinoma component [6]. Most of these cases showed an elevated level of AFP. Pathogenesis of these tumors is not definitely known. One theory suggests forward differentiation of germ cells towards stomach epithelial cells and the other theory suggests retro differentiation of neoplastic stomach epithelial cells. Ooi, *et al*. [6] studied 5 cases of gastric adenocarcinoma with yolk sac differentiation. They believed that these tumors should be grouped under medullary tumors of the stomach with gut specific AFP.

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Microscopically these tumors show mixed features of yolk sac tumors with reticular patterned cells along with PAS positive hyaline globules and adenocarcinomatous areas with malignant glands. Occasional cases show choriocarcinoma differentiation along with yolk sac differentiation. These tumors are known to have bad prognosis and often present with lymph node or liver metastasis at initial diagnosis [6, 7]. Elderly patients are commonly affected and usually have advanced disease. Metastasis to the lung is also frequently recorded [8]. Chang *et al.* [9] studied three cases of AFP producing gastric adenocarcinomas with liver metastasis at presentation. The patients were aged between 59 and 65. Male to female ratio was 2:1. All three patients had poor prognosis [9]. The YST component of the tumor would be positive for low molecular weight cytokeratin, AE1/AE3, glypican 3, CD117, CD30, AFP, PLAP and OCT3/4 [10].

Gastric Adenocarcinoma with Hepatoid Differentiation: Hepatoid type of adenocarcinoma (HAC) is one of the rare types of extrahepatic carcinoma and morphologically looks like hepatocellular carcinoma (HCC) [11]. Other than stomach, it has also been reported in gallbladder, lungs, pancreas, esophagus, peritoneum and rectocolon. Embryologically the stomach and liver develop from anterior intestine which might be the reason for gastric cancers differentiating into liver like cells resulting in gastric adenocarcinoma with hepatoid differentiation (GACHD) [12, 13]. Affected patients range between 44 and 87 years of age. Male to female ratio is found to be 2.3:1. Abdominal pain, anemia and general fatigue are common clinical presentations. Most of the cases are advanced at presentation. AFP levels are elevated in about 70-80% of the patients and tend to be from less than 1 ng/ml to 700000 ng/ml. Distant spread to lymph nodes and liver is frequent [14, 15].

Morphologically, GACHDs have malignant hepatocyte like cells and also malignant glands often intermingled with each other. Adenocarcinoma cells often form papillae or tubules. Malignant hepatocytes like cells form nests or cord patterns and are highly vascular with rich interstitium. Immunohistochemically, other than AFP, tumor cells were seen to contain proteins including alpha-1 antitrypsin and albumin. AFP, CK19 and Gly3 are commonly seen to be positive in malignant hepatocyte looking cells [16, 17].

Another important point to know regarding GACHDs is the limitation of hepatocyte areas to deeper tumor tissue and hence the possibility of preoperative diagnosis of this variant by endoscopic biopsy is meagre. Also, note to be taken that identifying hepatoid differentiation on histopathology and immuno his to chemistry is mandatory for diagnosis regardless of the levels of serum AFP. If the GACHD patient had had liver metastasis at presentation which is not rare, it is important to distinguish these tumors from primary HCC. The latter usually has a history of cirrhosis and is present as a solitary lesion. Metastasis of HCC to the stomach is rare and the first layer of invasion would be the serosa of the stomach. Also, GACHD needs to be differentiated from other tumors such as germ cell tumors which also have elevated AFP levels. Prognosis of GACHD is worse and is known for its increased efficiency for distant spread and relapse. Overall survival of GACHD patients ranges from 10 to 18 months. AFP levels and TNM staging are positively related to prognosis [18].

Gastric Adenocarcinoma with Enteroblastic Differentiation: Gastric adenocarcinoma with enteroblastic differentiation (GACED) develops as a result of the imitation of fetal gastrointestinal epithelium by common tubular adenocarcinoma of the stomach [19]. 79% GACED patients were males and the common location was mainly middle and lower third of the stomach. Age of occurrence is older than conventional GACs. Percentage of lymphovascular invasion ranges from 72-76% and is significantly higher than conventional GACs. Lymph Node involvement was seen in 40% of GACEDs. Around 84% of the patients had advanced disease at presentation as opposed to 26-45% in conventional GACs. Also, 34% of GACED patients had metastatic liver lesions at initial diagnosis [20-23].

Earlier, Matsunou *et al*. [24] reported two cases and described morphology of GACEDs. The tumor usually contains tubules, papillary and gland patterns. Clear cell change, presence of glycogen, AFP and CEA expression and microvilli with core filaments attributed to enteroblastic differentiation on electron microscopy are other features of GACEDs. Areas of enteroblastic differentiation of GACED tend to occur in layers deeper to the mucosa through lymphovascular invasion which suggests that GACED might be an evolution from conventional GACs that could further differentiate into hepatoid type as a parallel process of invasion and spread [25, 26]. Immunohistochemically, enteroblastic lineage markers such as AFP, Glypican 3, SALL 4 were found to be positive in GACED, of which Glypin 3 was found to be most useful with a sensitivity of around 83%. GACED can be further classified as gastrointestinal or intestinal according to mucin production attributed to expression

of CD10, MUC6, MUC5AC and MUC2. GACED is known for frequent lymph nodes and liver metastasis owing to its affinity towards blood vessels. They are found to have worse prognosis than conventional GACs [27].

CONCLUSIONS

AFP producing GACs are rare malignant neoplasms observed in clinics and are prone to misdiagnosis. There have only been a few cases reported previously in the literature. Hence, in this review article, we have attempted to describe the pathogenesis, clinical features, morphological features and diagnostic cues of AFP producing GACs to enhance our understanding of this disease in an effort to decrease its misdiagnosis.

REFERENCES

1. Rocha, A. and S.M. Rocha, 2011. Myc gene amplification in gastric adenocarcinoma. Acad J. Cancer Res., 4(1): 18-23.
2. Praveen Kumar, V., S. Prasanthi, V.R.S. Lakshmi and M.V. Sai Santosh, 2010. Cancer Vaccines: A Promising Role in Cancer Therapy, Acad J. Cancer Res., 3(2): 16-21.
3. Shamsi, M., A. Hashyiani, R. Rajabi, A. Sharifi and S. Dejam, 2014. Knowledge and Some Factors Affected on Gastrointestinal Cancer Screening in the Women Iranian. World J. Med. Sci., 11(4): 445-451.
4. Yukio, M., R. Yasushi, S. Akihiro, M. Junya, K. Kazuki, A. Shinya, S. Sho, N. Masakatsu, A. Toru, H. Tsutomu, Y. Takanobu, S. Tsutomu, O. Takashi, Y. Norio, Y. Takaki, M. Munetaka, U. Tetsuo, F. Masashi, I. Shumpei and A. Hiroyuki, 2018. Long-term prognosis of α-fetoprotein-producing gastric cancer defined as immunohistochemichal expression. Journal of Clinical Oncology, 36(15 suppl): e16036.
5. Motoyama, T., K. Aizawa, H. Watanabe, M. Fukase and K. Saito, 1993. α-Fetoprotein-producing gastric carcinomas: a comparative study of three different subtypes. Acta Pathol. Jpn, 43: 654-661.
6. Ooi, A., I. Nakanishi, N. Sakamoto, Y. Tsukada, Y. Takahashi, T. Minamoto and M. Mai, 1990. α-fetoprotein (AFP)-producing gastric carcinoma. Is it hepatoid differentiation? Cancer, 65(8): 1741-1747.
7. Satake, N., M. Chikakiyo, T. Yagi, Y. Suzuki and T. Hirose, 2011. Gastric cancer with choriocarcinoma and yolk sac tumor components: case report. Pathology International, 61(3): 156-160.
8. Kim, Y.S., S.H. Kim, J.K. Seong, B.S. Lee, H.Y. Jeong and K.S. Song, 2009. "Gastric yolk sac tumor: a case report and review of the literature. Korean Journal of Internal Medicine, 24(2): 143-146.
9. Chang, Y.C., N. Nagasue, H. Kohno, H. Taniura, M. Uchida, A. Yamanoi, T. Kimoto and T. Nakamura, 1990. Clinicopathologic features and long-term results of afetoprotein-producing gastric cancer. Am. J. Gastroenterol., 85: 1480-1485.
10. Kao, C.S., M.T. Idrees, R.H. Young and T.M. Ulbright, 2012. Solid pattern yolk sac tumor: a morphologic and immunohistochemical study of 52 cases. American Journal of Surgical Pathology, 36(3): 360-367.
11. Kihn-Alarcón, A.J. and X.M. Xu, 2017. Mechanisms of radioresistance in hepatocellular carcinoma. Oncol. Transl. Med., 3: 165-170.
12. Ye, M.F., F. Tao, F. Liu and A.J. Sun, 2013. Hepatoid adenocarcinoma of the stomach: A report of three cases. World J. Gastroenterol., 19: 4437-4442.
13. Marchegiani, G., H.A. Gareer, Parisi, P. Capelli, C. Bassi and R. Salvia, 2013. Pancreatic hepatoid carcinoma: A review of the literature. Dig Surg., 30: 425-433.
14. Fakhruddin, N., H.F. Bahmad, T. Aridi, Y. Yammine, R. Mahfouz, F. Boulos, A. Awada and F. Farhat, 2017. Hepatoid adenocarcinoma of the stomach: A challenging diagnostic and therapeutic disease through a case report and review of the literature. Front Med., 4: 164-165.
15. Luo, H.F., H.J. Wang, G. Tan and Z. Wang, 2011. Hepatoid adenocarcinoma in stomach: a case report. Chinese-German J. Clin Oncol., 10: 297-299.
16. Ishikura, H., K. Kirimoto, M. Shamoto, Y. Miyamoto, H. Yamagiwa, T. Itoh and M. Aizawa, 1986. Hepatoid adenocarcinomas of the stomach: an analysis of seven cases. Cancer, 58: 119-126.
17. Kui, G.J., L.M. Yang and J.R. Meng, 2015. Gastrointestinal-like adenocarcinoma in 1 case. J.. Shanxi Med Univ (Chinese), 46: 1151-1152.
18. Li, X., G. Li and H. Li, 2015. Hepatoid adenocarcinoma of the stomach in 1 case. Cancer Prevent Treat (Chinese), 28: 301-302.
19. Nalini, B., K. Ajay, B. Mona and A. Nitesh, 2018. Gastric Adenocarcinoma with Yolk Sac Differentiation, Fungal Super Infection and A Large Solitary Liver Metastasis - A Histologic Conundrum. Trop Gastroenterol., 39(2): 113-116.

20. Maruyama, K., P. Gunvén, K. Okabayashi, M. Sasako and T. Kinoshita, 1989. Lymph node metastases of gastric cancer. General pattern in 1931 patients. Ann. Surg, 210: 596-602.
21. Maehara, Y., Y. Emi, H. Baba, Y. Adachi, K. Akazawa, Y. Ichiyoshi and K. Sugimachi, 1996. Recurrences and related characteristics of gastric cancer. Br. J. Cancer, 74: 975-979.
22. Selcukbiricik, F., E. Buyukunal, D. Tural, M. Ozguroglu, F. Demirelli and S. Serdengecti, 2013. Clinicopathological features and outcomes of patients with gastric cancer: a single-center experience. World J. Gastroenterol., 19: 2154-2161.
23. Isobe, Y., A. Nashimoto, K. Akazawa, I. Oda, K. Hayashi, I. Miyashiro, H. Katai, S. Tsujitani, Y. Kodera, Y.Y. Seto and M. Kaminishi, 2011. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. Gastric Cancer, 14: 301-316.
24. Matsunou, H., F. Konishi, R.E. Jalal, N. Yamamichi and A. Mukawa, 1994. α-fetoprotein-producing gastric carcinoma with enteroblastic differentiation. Cancer, 73: 534-540.
25. Kinjo, T., H. Taniguchi, R. Kushima, S. Sekine, I. Oda, M. Saka, T. Gotoda, F. Kinjo, J. Fujita and T. Shimoda, 2012. Histologic and immunohistochemical analyses of α-fetoprotein--producing cancer of the stomach. Am. J. Surg. Pathol., 36: 56-65.
26. Murakami, T., T. Yao, H. Mitomi, T. Morimoto, H. Ueyama, K. Matsumoto, T. Saito, T. Osada, A. Nagahara and S. Watanabe, 2016. Clinicopathologic and immunohistochemical characteristics of gastric adenocarcinoma with enteroblastic differentiation: a study of 29 cases. Gastric Cancer, 19: 498-507.
27. Matsumoto, K., H. Ueyama, K. Matsumoto, Y. Akazawa, H. Komori, T. Takeda, T. Murakami, D. Asaoka, M. Hojo, N. Tomita, A. Nagahara, Y. Kajiyama, T. Yao and S. Watanabe, 2016. Clinicopathological features of α-fetoprotein producing early gastric cancer with enteroblastic differentiation. World J. Gastroenterol., 22(36): 8203-8210.