Alpha-Fetoprotein Producing Breast Cancer Cells: Case Report and Review of Literature

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Abstract: *Aim*: In this paper we report a rare case of breast carcinoma followed by liver metastasis associated to alpha fetoprotein (AFP) secretion by tumor cells.

Methods: Carcino-embryonic antigen (CEA), carbohydrate antigen (CA) 15-3, serum AFP and AFP immunohistochemistry staining were detected using commercial kits in 44 year-old woman with breast cancer.

Results: CEA and CA 15-3 were within normal limits. AFP baseline was 14000 ng/l. There was no chronic hepatic viral disease. Biopsy revealed invasive carcinoma ductal cells. Histologic examination of the tumor showed invasive carcinoma, nuclear grade was 2, the tumour cells were negative for oestrogen and progesterone receptor positive for Her-2/neu. The immunohistochemistry stainig for AFP revealed positive reactivity. After chemotherapy, AFP level was within the normal range and abdominal ultrasonography showed a partial response evaluated at 50 %. The patient was in good condition at the time of our report (May 2013).

Conclusion: We presume that the increased serum AFP level is responsible for the cancer evolution with good prognosis for breast cancer and poor one for gastric cancer and colon cancer.

Keywords: Alpha-fetoprotein, Breast cancer, Colon cancer.

BACKGROUND

High blood levels of alpha fetoprotein (AFP) are commonly associated to hepatocellular carcinoma or embryonic cell carcinoma. However AFP secretion was reported in neoplasms of several other organs such as gastrointestinal tract, pancreas and gallbladder. These organs are derived from the primitive foregut which produces AFP during the fetal period [1]. AFP producing breast cancer is extremely rare.

In this paper we report a rare case of breast carcinoma followed by liver metastasis associated to alpha fetoprotein secretion by tumor cells.

CASE REPORT

A 44 year-old woman visited our hospital in July 2006, for a palpable right breast nodal. Mamography demonstrated an irregular-shaped tumor in the upper outer quadrant measured 15 mm without lymphadenopathy. No metastases were noted. No hepatitis B or C antigens were detected. Carcino-embryonic antigen (CEA) and carbohydrate antigen (CA) 15-3 were within normal limits. AFP baseline was 14000 ng/ml (Table **1**). Biopsy revealed invasive carcinoma ductal cells. In August 2006 the patient underwent a radical mastectomy with axillary lymph node dissection. Histologic examination of the tumor showed invasive carcinoma, nuclear grade was 2, the tumour cells were negative for oestrogen and progesterone receptor positive for Her-2/neu (Figure **1**). The immunohistochemistry stainig for AFP revealed positive reactivity in breast cancer cells (Figure **2**). The patient received adjuvant chemotherapy and radiotherapy treatment during 1 year of herceptin adjuvant. AFP level became very low (3ng/ml, Table **1**). Treatment achieved in March 2008. The patient was regularly followed up. In September 2008, she complained of a pain in the hypochondria. Abdominal ultrasonography revealed multiple metastatic secondary liver lesions which were confirmed by magnetic resonance imaging. No metastases were noted in other sites. CA15-3 was normal. Although AFP considerably decreased to 14 ng/ml (Table **1**), it remained beyond the normal range (greater than 2ng/ml). The patient received palliative chemotherapy. After 3 cycles of chemotherapy, the serum AFP level was within the normal range and abdominal ultrasonography showed a partial response evaluated at 50 %. The patient was in good condition at the time of our report (May 2013).

MATERIAL AND METHODS

Serum levels of CEA, CA15-3 and AFP were measured based on microparticle enzyme immunoassay technique using the AxSYM system (Abbott Laboratories, Abbott Park, IL, USA).

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Table 1: Serum AFP Concentrations During Patient's Follow Up

Period	State	AFP concentration (ng/ml)
July 2006	Baseline	14 000
September 2006	After surgery	7 000
January 2007	After chemotherapy	3
March 2008	After adjuvant treatment	3
September 2008	Relapse	14
January 2009	After 3 chemotherapy cycles	2

For immunohistochemical staining of AFP, tissue was deparaffinized, rehydrated and boiled in target retrieval solution (DAKO, Carpinteria, CA) to improve staining. The section was incubated with rabbit antiserum for AFP. Immunoreactive products were detected using DAKO Envision+.

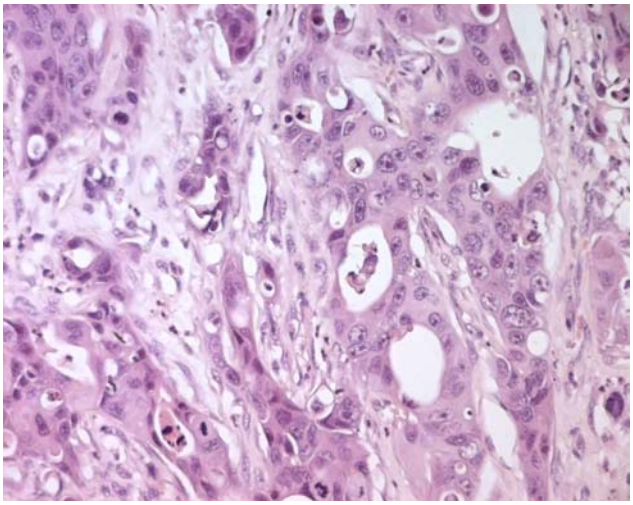

Figure 1: Moderate invasive ducta carcinoma of the breast (HE x 250).

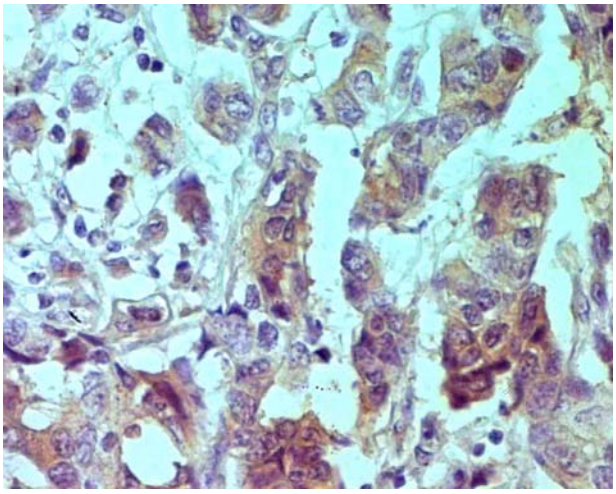

Figure 2: Immunoreactive positivity for alpha fetoprotein (immunohistochemistry, original magnification x400).

DISCUSSION

AFP plays many important physiological functions. Firstly it binds and transports ligands. Secondly it is a growth regulator as enhancer or inhibitor. This function is dose-dependent [2]. AFP suppresses both ontogenic and oncogenic growth in cell culture and various animal models. Moreover AFP is considered as an anticancer drugs-ligand carrier. In fact, target tumor cells overexpress binding AFP receptors which increase antitumor efficiency. Finally AFP can be employed to chemoprevent breast cancer [3]. AFP has been shown to inhibit the growth of human breast cancer in mice [4] and prevent the development of carcinogen-induced mammary cancers in rats [5]. It was also showed that AFP increases the antitumour effect of tamoxifen in rats [6]. Interestingly, Zhang *et al.* found that the suppressor of the alpha fetoprotein gene, the AT motif-binding factor 1 (ATBF1) gene was well expressed in low risk breast cancer [7]. They also found that patients expressing high levels of ATBF1 mRNA tended to have a better prognosis than those expressing low levels. In our case, the secretion of AFP was simultaneously associated with good outcome after palliative chemotherapy. Thus we hypothesized that AFP secretion improved the treatment effect in our patient. Our immunohistochemistry results clearly demonstrated that AFP was secreted by breast cancer cells and not liver cancer cells. In addition, in liver metastasis state, AFP concentration was within normal range. Our findings are in agreement with Sarui *et al*. [8]. Similar case was reported by Bartram *et al*. [9].

Mizejewski elegantly described the mechanism of AFP derived Growth Inhibitor Peptides (GIP-34 and GIP-8) [10]. In fact GIP-34 is cell penetrating peptide which gains the entrance and self cork-screwing into bilipid cancer cell membranes. This displays an overall net negative cell surface by switching sphingomyelin and/or phosphatidylcholine for phosphatidylserine. Thus shifting a negative charge to the cancer cell

apical surface. The negative-charged cell surface not only flags cells for targeted apoptosis, but also designates the cell as a candidate for cell penetration, and transmembrane passage. Another mechanistic action worth noting is that AFP-GIP-34 affects dependant voltage-gated K+-channels [10].

Previous reports demonstrate gastric cancer cells to produce AFP. It is considered as a distinct entity with a frequency of 2% to 6% of all gastric tumours [11]. This entity is distinctly considered in patients with liver lesions and an elevated AFP without risk factors of hepatocellular carcinoma or patients with associated gastric symptoms. In most cases patients with AFP secreting cancers had poor prognosis. This cancer have higher malignant potential (high proliferative activity, weak apoptosis, rich neovascularization and higher frequency of c-Met expression) compared to AFP-negative cancers [12]. Even if the tumour is an early cancer, AFP-producing cancer has a tendency to be associated with liver metastasis [13, 14]. Marx *et al.* reported three cases of gastric cancers with hepatic metastases secreting AFP [15]. The prognosis of gastric cancer tends to be poor with a high frequency of synchronous metastasis when AFP secretion exists. Furthermore, when liver metastases were metachronous, a shorter interval was reported [12]. Our patient developed liver metastasis six months after the treatment achievement. Only few cases were reported to have long survival period after the first diagnosis of gastric cancer [16, 17].

AFP-producing colorectal carcinoma generally has a poor prognosis [18] because of the frequent occurrence of blood-borne metastasis. All the reported cases have extensive liver and/or lung metastases at the time of diagnosis. A recent study demonstrated that AFP was localized in the colon rat mesenchyme cells [19].

Rare cases of acinar cell carcinomas of the pancreas, and of primary gallbladder carcinoma were found to express AFP [20, 21].

CONCLUSION

We presume that the increased serum AFP level is responsible for the cancer evolution with good prognosis for breast cancer and poor one for gastric cancer and colon cancer.

STATEMENT OF CONFLICTS OF INTEREST

Authors confirm that there are no conflicts of interest.

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