Tumor Res., 8, 171-177, 1973

Alpha-fetoprotein content in tissues from patients with gastric cancer

H. KITAOKA, N. HATTORI, T. MUKOJIMA, H. OHKURA, N. NAKAYAMA and H. OKADA

National Cancer Center Hospital and National Cancer Center Research Institute
Tokyo, Japan

SUMMARY

The alpha-Fetoprotein (α-FP) content in gastric carcinoma tissues and in surrounding intact gastric mucosae and also in metastatic lesions were measured by the radioimmunoassay method. The results obtained by this method are summarised as follows;

1. In cases with higher titers of α-FP in gastric cancer nests than those in intact gastric mucosae, the available evidence indicates that gastric carcinoma, especially of the intestinal type is the source of α-FP synthesis. Relevant cases were 7 out of 25 cases.
2. In 10 out of 25 cases, the concentration of α-FP in the surrounding intact gastric mucosae was higher than that in primary gastric carcinoma nests.
3. Eight out of 25 cases showed approximately equal contents of α-FP in cancer nests, as in intact gastric mucosae and in sera. Most of them histologically revealed undifferentiated adenocarcinoma of the diffuse type.

INTRODUCTION

A considerable number of articles on α-FP production of hepatoma are available[3,10], but little work has been done on α-FP synthesis in gastric carcinoma. As far as we know, the work reported here is the first designed in Japan to elucidate the higher possibility of α-FP secretion in gastric carcinoma cells.

Sera obtained from 373 patients with gastric carcinoma reveal a 3.5% of positive α-FP, especially much higher values in cases with liver metastasis by the single-radial immunodiffusion method of Mancini.

In contrast, in 100 cases with negative α-FP by the Mancini method, about 44% of cases contains α-FP beyond the lower limit of positive threshold (20 ng/ml) by the radioimmunoassay method. Elevation of serum α-FP

value beyond the physiological limits is cleary detected by the radioimmunoassay method with a high incidence of 13 times as much as that of the Mancini method.

The site of α-FP synthesis has not been determined as yet in metastatic lesions from gastric cancer. To obtain information concerning the probable site of its synthesis, α-FP content of gastric carcinoma nests was determined by radioimmunoassay.

METHODS

The method is as follows: by opening the resected stomach, carcinoma tissue specimens were isolated and prepared. Intact mucosal tissues were also collected for contrast. Both specimens were immediately frozen. They were homogenized with veronal buffered saline when used. The crude homogenate was centrifuged and the clear supernatant was used for α-FP evaluation.

RESULTS

The results obtained in 25 cases of gastric carcinoma are classified into 3 groups as shown in Table 1.

Table 1. *Alpha-fetoprotein content in tissues from gastric cancer patients (radioimmunoassy)*

α-FP content (ng/ml)	Number of cases		Total
	Intestinal Type	Diffuse Type	
Ca>M	5	2	7
Ca<M	5	5	10
Ca=M	3	5	8
total	13	12	25

Group I (Ca>M) indicates that the α-FP content in gastric carcinoma nests (Ca) is much higher than that in intact mucosal tissues (M). The α-FP titer of tumor extracts invariably showed higher values than that of sera.

Group II (Ca<M) indicates that the concentration of α-FP in carcinoma nests is less than that in intact mucosal areas. Adjacent areas to gastric carcinoma revealed higher concentrations of α-FP than that in areas apart from carcinoma lesions.

Group III (Ca=M) represents cases that reveal approximately equal contents in each area.

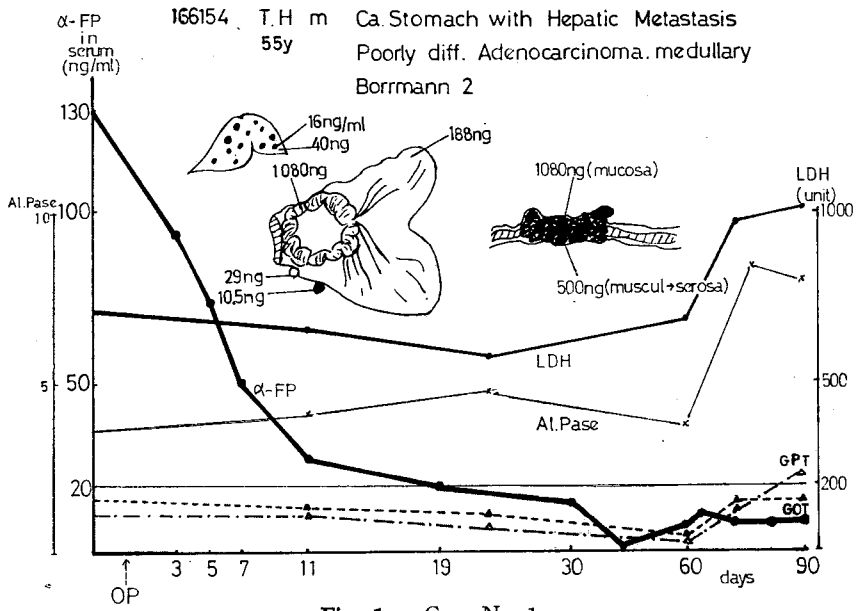

Fig. 1. Case No. 1.

From their histological pictures, intestinal type of differentiated adenocarcinoma is frequently noted in Group I. The majority of Group III showed a diffuse type of undifferentiated adenocarcinoma.

A typical example of Group I is presented in Fig. 1. The operation specimen reveals gastric carcinoma occupying the pyloric canal on the lesser curvature, with superficial ulceration surrounded by slightly elevated tumor margins.

The α-FP content in both hepatic metastasis and lymphnode metastasis are markedly lower than in primary lesion of cancer. Namely, the concentration of α-FP in gastric carcinoma is about 70 times or 100 times higher than that in metastases. The serial values of serum α-FP rapidly decrease after the operation and remain within physiological limits for about one and half months. However, progressive metastatic lesions in the liver continued to remain ; this was shown by autopsy 5 months after the operation.

Histologically, the primary lesion reveals typical tubular adenocarcinoma in some areas. There are also rather solid nests mainly composed of polyhedral cells with clear cytoplasm and giant bizarre nuclei. The appearence of these cells is one of the characteristics observed in gastric carcinoma with positive α-FP detected by the Mancini method[6]. Metastases to the liver and the regional lymphnodes histologically reveal differentiated tubular adenocarcinoma.

In another case of Group I, metastatic foci in regional lymphnodes

showed an excessive high titer of α-FP; grossly and histologically, there are no apparent differences between this case and the others. Serum α-FP was within normal limits approximately 2 weeks after the operation.

Based on the findings of these two examples selected from Group I, it seems reasonable to assume a high probability of α-FP synthesis in gastric carcinoma cells, especially in Group I.

The relationship between the α-FP content in gastric mucosa and intestinal metaplasia is schematically presented in Fig. 2. The abscissa indicates the degree of intestinal metaplasia. Degree A means maximum diffuse severe intestinal metaplasia. On the other hand, degree E indicates non-metaplastic mucous membrane. Degree B, C and D show a gradual decrease of this intensity, respectively. The dark solid circles indicate differentiated adenocarcinoma. The open circles indicate undifferentiated

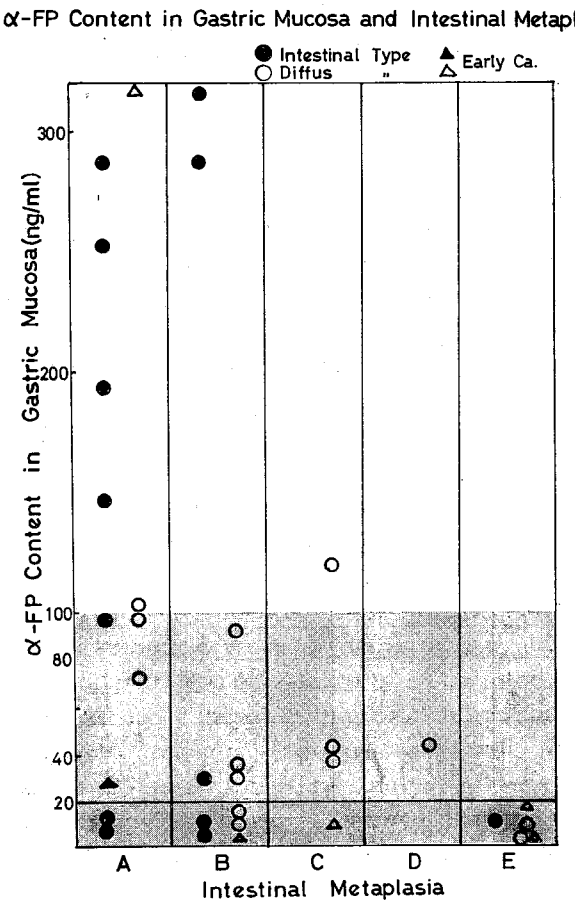

Fig. 2.

adenocarcinoma. And cases with undifferentiated adenocarcinoma show relatively low concentrations of α-FP in gastric mucosa.

The carcinoma cases with a higher α-FP content than that of intact mucosa above 100 ng/ml generally reveal differentiated adenocarcinoma of the intestinal type. A majority of cases with diffuse type of undifferentiated adenocarcinoma show a low concentration of α-FP under 100 ng; and in most of them, the α-FP content of carcinoma is equal to or less than that of intact mucosa.

On the basis of these observation, it may be surmized that a pathway through the intestinal metaplasia process may well have an intense connection with the development of differentiated adenocarcinoma of the intestinal type. In other words, there is a possibility that differentiated and undifferentiated adenocarcinoma of the stomach may be based on a different histogenesis.

The patterns of serial values in serum α-FP after operations are divided into 3 types. A rapid descending pattern is frequently noted in cases of carcinoma with a higher α-FP content than intact areas.

Carcinoma with an α-FP content which equals or is less than that of intact mucosal tissues reveal the latter two patterns showing a minimum fluctuation or stationary values within normal limits.

Based on these results, it may be said that α-FP may be secreted by carcinoma cells in primary or metastatic lesions of certain patients with gastric carcinoma.

DISCUSSION

After the measurement of protein contents in tissue extracts by the Lowry-Folin method, titration of α-FP expressed in ng/ml by re-calculation of α-FP to the soluble protein fraction showed a parallel relation of values presented in this report. The results positively suggest a high possibility of α-FP synthesis in gastric cancer of either primary focus or metastatic lesions, which histologically revealed well-differentiated tubular adenocarcinoma of the intestinal type. The first case report of gastric carcinoma with positive α-FP was presented by Bourreille in 1970[2]. Although, further studies on this problem have been carried out by many researchers[1,7], the measurement of α-FP gastric carcinoma tissues was made for the first time by Montplaisir[9] in 1973. His data revealed concentrations of α-FP 4 to 6 times higher in liver metastasis than in the serum and gastric extracts. Montplaisir's case might be compatible with other cases disclosing an intimate correlation of cancer progression with elevation of serum α-FP concentration.

In case reports of ovarian teratocarcinoma described by Mawas et al (1969)[8] and by Esterhay et al (1973)[4], progressively decreasing levels of α-FP were observed even with metastatic or recurrent lesions after effective surgical treatment; the same was noted in Case No. 1 presented in this paper. Esterhay proposed that the reduction of α-FP synthesis depended upon the histological maturation of neoplasms. In Case No. 1, the α-FP content in primary gastric carcinoma nests showing histologically undifferentiated adenocarcinoma was much higher than that in metastatic lesions of the liver or the regional lymphnodes with histology revealing a well-differentiated adenocarcinoma. This has led to the belief that α-FP synthesis might originate in immature gastric carcinoma cells.

Gitlin's report (1972)[5] of α-FP content in human embryos and fetuses measured with ^{14}C-labeled amino acids, revealed that α-FP production possibly originated in the gastrointestinal tract. One of the results in which α-FP activity in adjacent gastric intact tissues to tumor lesions showed higher values than that in gastric cancer nests may result in the evaluation based on data such as reported by Gitlin.

The data concerning the relationship between intestinal metaplasia and α-FP values in intact gastric mucosae adjacent to cancer with the results where α-FP values in gastric cancer of a histologically intestinal type were higher than those in gastric carcinoma of diffuse type lead to the following suggestions regarding gastric carcinogenesis based on the concept of re-activation of α-FP synthesis in the stomach. (1) In the process of malignant transformation of gastric mucosal cells, they re-acquire their activity of α-FP synthesis by a partial immaturation toward the embryonal phase. (2) Latent capability of α-FP production is excessively exhibited especially in gastric carcinoma of the intestinal type. (3) Re-activation of α-FP synthesis indicates one of the functional premalignant changes. (4) α-FP activity in intact gastric mucosae is induced in the developmental process of gastric cancer. Parallel or reserve reciprocal contrasts of α-FP values in gastric carcinoma nests and intact mucosal areas might lead to a new aspect of analytical progress or to the prognosis of gastric cancer.

Acknowledgment

This study was supported by a grant in aid for developmental research for cancer supplied by the Ministry of Health and Welfare, Japan.

REFERENCES

1. ALPERT, E., PINN, V. W., and ISSELBACHER, K. J.: Alpha-fetoprotein in a patient with gastric carcinoma metastatic to the liver. *New. Engl. J. Med.*, **285**, 1058 (1971).
2. BOURREILLE, J., METAYER, P., SAUGER, F., MATRAY, F. and FONDIMARE, A.: Exist-

ence d'alpha-foeto protéine au cours d'un cancer secondaire du foie d'origine gastrique. *Presse Med.*, **78**, 1277 (1970).

3. ENGELHARDT, N. V., GOUSSEV, A. I., SHIPOVA, L. Ja., and ABELER, G. I.: Immunofluorescent study of alpha-foetoprotein (α-fp) in liver and liver tumours. I. Technique of α-fp localization in tissue sections. *Int. J. Cancer.* **7**, 198 (1971).
4. ESTERHAY, R. J. Jr., SHAPIRO, H. M., SUTHERLAND, J. C., McINTIRE, K. R. and WIERNIK, P. H.: Serum alpha fetoprotein concentration and tumor growth dissociation in a patient with ovarian teratocarcinoma. *Cancer* **31**, 835 (1973).
5. Gitlin, D., PERRICELLI, A. and GITLIN, G. M.: Synthesis of α-fetoprotein by liver, yolk sac, and gastrointestinal tract of the human conceptus. *Cancer Res.*, **32**, 979 (1972).
6. KITAOKA, H., HATTORI, N. and MUKOJIMA, T,: Alpha fetoprotein and metastatic carcinoma. *Igaku no Ayumi*, **79**, 129 (1971). (in Japanese)
7. KOZOWER, M., FAWAZ, K. A., MILLER, H. M. and KAPLAN, M. M.: Positive alpha-fetoprotein in a case of gastric carcinoma. *New. Engl. J. Med.*, **285**, 1059 (1971).
8. MAWAS, C., KOHEN, M., LEMERLE, J., BUFFE, D., SCHWEISGUTH, O. and BURTIN, P.: Serum α_1 foeto-protein (fetuin) in children with malignant ovarian or testicular teratomas. Preliminary results. *Int. J. Cancer*, **4**, 76 (1969).
9. MONTPLAISIR, S., RABIN, B., PELLETIER, M., ROSE, N. R. and ALPERT E.: Alpha$_1$-fetoprotein content of gastric carcinoma and hepatic metastases. *Amer. J. Dig. Dis.*, **18**, 416 (1973).
10. SMITH, J. A., FRANCIS, T. I., EDINGTON, G. M. and WILLIAMS, A. O.: Immunofluorescent localization of human alpha feto-protein in fetal and neonatal livers and cultured cells from hepatocellular carcinoma. *Brit: J. Cancer*, **25**, 343 (1971).