Clinical significance of combined determination of serum PG Ⅰ, PG Ⅱ and GAS for diagnosis of gastric cancer

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Abstract To evaluate the clinical value of combined determination of serum PG Ⅰ, PG Ⅱ and GAS for early diagnosis of gastric cancer, the serum levels of PG Ⅰ, PG Ⅱ and GAS in 190 healthy controls and 129 patients with gastric disorders were measured by RIA. The 129 patients include 68 cases of gastric cancer. The results showed that the serum levels of PG Ⅰ and PG Ⅰ/PG Ⅱ ratio in gastric cancer patients were obviously lower than those in healthy controls, while comparing with controls, the serum GAS levels were significantly higher. The diagnostic accuracy of the determinations for gastric cancer was evaluated by receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) levels of serum PG Ⅰ, PG Ⅰ/PG Ⅱ ratio and GAS were 0.833, 0.842 and 0.851, respectively. As serum PG Ⅰ or PG Ⅰ/PG Ⅱ ratio or GAS were combined, the sensitivity and specificity of determination for gastric cancer diagnosis were 94.2% and 73.4%, respectively. All these results indicated that the combined determination of serum PG Ⅰ, PG Ⅱ and GAS levels may be used as a tool for primary screening of gastric cancer.

Key words Gastric cancer, Pepsinogen, Gastrin, Radioimmunoassay
CLC numbers R730.43, R817.4

1 Introduction

In our country, gastric cancer is one of the most serious diseases threatening people health. Early diagnosis is considered to be an effective method to decrease the death ratio caused by gastric cancer. Today, however, effective early diagnosis method is still lacking. Our previous studies demonstrated that it was a helpful method for the early diagnosis of gastric cancer to determine the serum levels of pepsinogen Ⅰ (PG Ⅰ) and pepsinogen Ⅱ (PG Ⅱ).[1] Stemmermann and his colleagues, however, pointed out that though serum PG Ⅰ and PG Ⅱ could be selected as early diagnostic markers for gastric cancer, it was very difficult to obtain satisfactory specificity and sensitivity.[2] Gastrin(GAS) is another basic secreting element of stomach mucosa and its serum levels can also reflect the morphological and functional status of stomach mucosa. In the present study, we tried to establish a combined diagnostic method by adding GAS to PG Ⅰ and PG Ⅱ and evaluate its specificity and sensitivity in the early diagnosis of gastric cancer.

2 Materials and methods

2.1 Blood samples

Healthy controls: serum samples were obtained from 190 subjects free from upper abdominal complaints and without evidences of gastroduodenal disorders, liver diseases and renal diseases after health examination.

Patients: 129 patients with various gastric disorders were included in the study. By criteria based on endoscope and pathology, they were classified into five diagnosis groups and summarized as follows: 25 patients with duodenal ulcer, 15 patients with gastric ulcer, 21 patients with atrophic gastritis, 68 patients with gastric cancer including 5 patients with stomach cardia cancer.

2.2 Methods

Blood samples were obtained in the early morn-

Supported by the Society Development Fund of Jiangsu Province (No.BS94012)
Received date: 2005-01-21

ing, kept for 30 min at room temperature, and centrifuged at 3000 r/min for 15 min at 4℃. The separated sera were kept at −20℃ until use. The serum levels of PG Ⅰ, PG Ⅱ and GAS in 190 healthy controls and 129 gastric patients were measured by radio-immunoassay (RIA). RIA kits for serum PG Ⅰ and PG Ⅱ were established by our institute.[3] RIA kit for GAS was purchased from North Immunoreagent Institute of Beijing. Determinations were carefully performed according to the kit protocol.

The results were displayed as Mean±SD. Statistical significance was determined by *t*-test. The ROC curve analysis was performed on SPSS 11.5 software. AUC was used to evaluate the diagnostic accuracy.

3 Results

3.1 Serum PG Ⅰ, PG Ⅱ, PG Ⅰ/PG Ⅱ ratio and GAS in healthy controls and patients with various gastric disorders

The mean serum levels of PG Ⅰ, PG Ⅱ, the PG Ⅰ/PG Ⅱ ratio and GAS in patients with different gastric diseases and healthy controls are shown in Table 1. In patients with gastric cancer, compared with healthy controls, the mean serum levels of PG Ⅰ and the PG Ⅰ/PG Ⅱ ratio were significantly lower, while, on the contrary, the mean serum levels of GAS were significantly higher. On the mean serum levels of PG Ⅰ, no significant difference was observed between patients with stomach cardia cancer and healthy controls. In patients with duodenal ulcer and gastric ulcer, comparing with healthy controls, the mean serum levels of PG Ⅰ and PG Ⅱ increased significantly, while the mean serum levels of GAS were just moderately elevated. Interestingly, compared with healthy controls, serum PG Ⅱ levels in patients with gastric cancer had no obvious difference, while, in patients with stomach cardia cancer, the levels increased.

3.2 Accuracy evaluation of determining serum PG Ⅰ, PG Ⅰ/PG Ⅱ ratio and GAS for diagnosis in gastric cancer

ROC curve analysis was used to evaluate the diagnostic accuracy of serum PG Ⅰ, PG Ⅰ/PG Ⅱ ratio and GAS for gastric cancer. AUC levels of determinations on serum PG Ⅰ, PG Ⅰ/PG Ⅱ ratio and GAS, as shown in Fig.1 and Fig.2, were 0.833, 0.842 and 0.851, respectively.

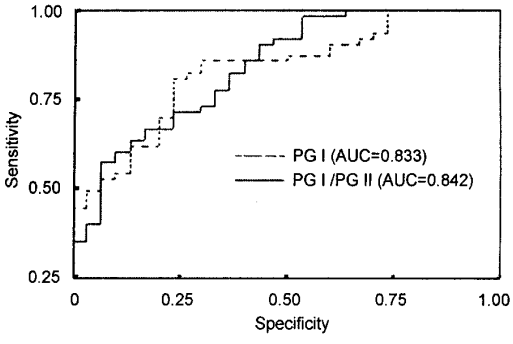

Fig.1 ROC curves of serum PG Ⅰ and PG Ⅰ/PG Ⅱ ratio.

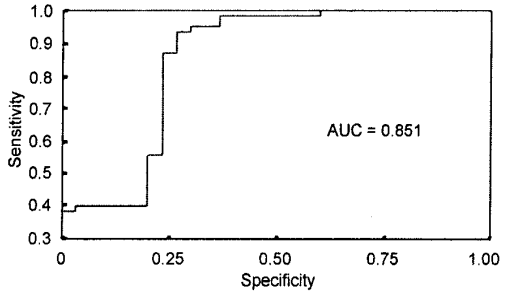

Fig.2 ROC curve of serum GAS.

Table 1 Serum PG Ⅰ, PG Ⅱ, PG Ⅰ/PG Ⅱ ratio and GAS in healthy controls and patients with various disorders (Mean±SD)

Diagnosis	*n*	PG Ⅰ (μg/L)	PG Ⅱ (μg/L)	PG Ⅰ / PG Ⅱ ratio	GAS(ng/L)
Healthy controls	190	54.4±15.4	22.6±11.5	3.0±2.0	55.1±35.7
Duodenal ulcer	25	78.7±28.3[a]	36.9±15.5[a]	1.9±0.4	79.5±74.5
Gastric ulcer	15	61.2±22.7[a]	30.6±28.4[a]	2.1±1.1	70.1±29.7
Atrophic gastritis	21	47.2±16.0[b]	25.1±16.8	2.4±1.1	68.2±25.6
Gastric cancer	63	30.0±18.2[a]	19.3±9.8	1.6±0.5[a]	118.7±54.9[a]
Stomach cardia cancer	5	43.5±31.1[b]	31.0±7.7[a]	1.5±1.1[a]	120.4±92.6[a]

Note: a) compared with controls $P<0.01$; b) compared with controls $P<0.05$

3.3 Sensitivity and specificity of single and combined determinations on serum PG Ⅰ, PG Ⅰ /PG Ⅱ ratio and GAS for diagnosis in gastric cancer

Table 2 shows the sensitivity and specificity of different determinations for gastric cancer diagnosis when serum PG Ⅰ, PG Ⅰ /PG Ⅱ ratio and GAS were used separately or in different combination. Apparently, when serum PG Ⅰ, PG Ⅰ /PG Ⅱ ratio and GAS were used separately to perform gastric cancer diagnosis, the determination's specification was higher, but their sensitivity was very low. By contrast, as serum PG Ⅰ or PG Ⅰ /PG Ⅱ ratio or GAS were combinedly determined, the high sensitivity and satisfactory specificity were obtained, which were 94.2% and 73.4%, respectively.

Table 2 Sensitivity and specificity for gastric cancer diagnosis using single or various combined determinations

Determination	Sensitivity(%)	Specificity(%)
Single determinations:		
PG Ⅰ <35μg/L	54.9	89.3
PG Ⅰ /PG Ⅱ ratio<1.5	61.8	83.9
GAS >90ng/L	40.0	81.0
Combined determinations:		
PG Ⅰ <35μg/L and PG Ⅰ /PG Ⅱ ratio<1.5	28.4	96.4
PG Ⅰ <35μg/L or PG Ⅰ /PG Ⅱ ratio<1.5	71.6	83.0
PG Ⅰ <35μg/L or PG Ⅰ /PG Ⅱ ratio<2.0	81.4	63.4
PG Ⅰ /PG Ⅱ ratio<1.5 or GAS >90ng/L	70.0	63.0
PG Ⅰ <35μg/L or GAS >90ng/L	92.1	61.0
PG Ⅰ <35μg/L or PG Ⅰ /PG Ⅱ ratio<1.5 or GAS >90ng/L	94.2	73.4

4 Discussion

Human pepsinogens originating from the stomach mucosa are classified into two biochemically and immunochemically distinct groups, namely serum PG Ⅰ and PG Ⅱ. PG Ⅰ and PG Ⅱ are derived from different parts of gastroduodenal mucosa, that is, the former only from peptic cells in oxyntic gland mucosa and the latter from these cells in pyloric glands and Brunner's glands. They are not only secreted into the gastric lumen, but also enter the blood circulation. Their serum levels are tightly correlated with the morphological and functional status of stomach mucosa.[4]

Atrophic gastritis was regarded as the precursor of gastric cancer. It has been reported that in more than eighty percent patients with gastric cancer, atrophic gastritis could be found, and about ten percent atrophic gastritis finally developed to gastric cancer. Atrophic gastritis can cause the destruction of peptic cells and influence the synthesis and secretion of PG Ⅰ, then, ultimately, make the serum PG Ⅰ levels decreased significantly. In our present study, we also observed that in a part of patients with severe atrophic gastritis the levels of PG Ⅰ were significantly lower compared with normal controls. Furthermore, our results demonstrated that the serum PG Ⅰ levels could also be influenced by the site of gastric cancer. In patients with stomach cardia cancer, comparing with normal controls, the decrease of serum PG Ⅰ levels was not so significant as that in patients with other gastric cancer. No significant difference was found on the PG Ⅱ levels between gastric cancer patients and normal controls. That may be attributed to the wider distribution of PG Ⅱ secreting cells in stomach mucosa. In patients with peptic ulcer, the serum levels of PG Ⅰ and PG Ⅱ were significantly higher, which might be caused by increased synthesis, enhanced secretion and more chance to penetrate into blood.

GAS is another basic secreting element of stomach mucosa and its serum levels can also reflect the morphological and functional status of stomach mucosa. In patients with gastric cancer, the gastric cancer cells can secrete GAS in autocrine and paracrine

manner, which can stimulate the proliferation of the gastric tumor cells through the GAS receptor (GR) mainly expressed on the gastric cancer cells. The serum GAS levels in gastric cancer were significantly higher than those in other gastric diseases.

On early stage, the symptom of gastric cancer is very similar to that of common gastric diseases. Until now, high specific diagnostic methods for gastric cancer are still lacking. That is one of the most important reasons which cause some patients with gastric cancer cannot be timely diagnosed on early stage. For example, though we can detect 50% CEA positive in patients with gastric cancer by sampling stomach fluid,the positive ratio will decrease to 4.5% when serum is sampled.[5]

Screening of gastric cancer, which impels us to find and treat the disease as early as possible, is an effective method to low the death ratio caused by the cancer. Since serum PG Ⅰ, PG Ⅱ and GAS are secreted by different cells in stomach mucosa, and their levels in serum are influenced by the focus and the invaded area of the cancer, the specificity and sensitivity of the single determination are very limited. ROC curves analysis showed that the AUC levels of single determinations on serum PG Ⅰ, PG Ⅰ /PG Ⅱ ratio and GAS were 0.833, 0.842 and 0.851, respectively. The above results show that the single determinations had moderate sensitivity and specificity for the diagnosis of gastric cancer. But the combined determination (PG Ⅰ <35μg/L or PG Ⅰ /PG Ⅱ ratio<1.5 or GAS>90ng/L), as shown in our present study, has not only high sensitivity (94.2%), but also satisfactory specificity (73.4%). So we demonstrate that the combined determination is an effective method to screen the high risk group of gastric cancer, and to elevate the diagnostic accuracy of gastric cancer in the end.

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