

The Role Of Tumor Markers In The Diagnosis And Follow Up In Patients With Pancreatic Cancer

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Summary:

Background: To shade a light on certain tumor markers and their sensitivity and specificity in determination of pancreatic cancer.

Patients & Methods :- A total of 35 patients with pancreatic cancer were studied between June 2003 and April 2004 in Specialized Surgical - Baghdad Teaching Hospital . These patients were compared with other 25 non malignant G.I diseases patients as well as 35 healthy controls . The serum was estimated for CAI 9-9 , and CEA by ELFA (Enzyme Linked Fluorescent Assay) method and CPR by ELISA method.

Results :- Five patients with pancreatic cancer were excluded from this study because they were beyond surgery. The results show that there is significant differences between serum level of CAI 9-9 in pancreatic cancer patients as compared with the non malignant G.I disease patients group and control (P< 0.05). While for the determination of CEA there is also significant difference between the pancreatic patients group as compared with the non malignant G.I patients group and control group (P< 0.05). As for the result of CRP there is also significant difference between the pancreatic patients group and the non malignant G.I patients group and control group (P< 0.05) .

Conclusion :- Significant differences were found in the result of the tumor markers CA 19-9 , CEA , and CRP studied in patients with pancreatic cancer as compared with the other non malignant G.I patients and controls . The sensitivity for using all the mentioned parameters was 90% were as the specificity was 75%.

Key words: Pancreatic tumors, CA 19-9, CEA, CRP

Introduction :

Pancreatic cancer, is the fifth most common cause of cancer mortality in both Europe and North America [1] .

The disease is difficult to diagnose in its early stages , and most patients have incurable disease by the time they present with the symptoms . The over all 5- year survival rate for this disease is less than 5% [1, 2] .

Pancreatic cancer can arise from both the endocrine and exocrine portions of pancreas . Of pancreatic tumors, 95% develop from the exocrine portions of the pancreas , including the ductal epithelium , acinar cells, connective tissue, and lymphatic tissue. Approximately 75% of all pancreatic carcinomas occur within the head or neck of the pancreas [2] .

As in other organs , chronic inflammation is a predisposing factor in the development of pancreatic cancer. Patients with chronic pancreatitis from alcohol , especially those with familial forms , have much higher incidence and an earlier age of onset of pancreatic cancer. Beside that cigarette smoking, coffee drinking, high dietary fat, diabetes mellitus , and exposure to certain carcinogen in chemical and metal industries have been suggested as a risk factor [2,3,4] .

Although a variety of tumor markers are available for the diagnosis of pancreatic cancer, their sensitivity and specificity have not yet been ideal serum CA 19-9, CA 242, CA -50 and CA 72-4 are the preferred tumor markers to be used in the diagnosis and follow -up of the patients[5]

CAI 9-9 - The carbohydrate antigen 19-9, is changed to a sialyted oligosaccharide that is most commonly found or circulating mucins in cancer patients . Its molecular weight 210,000 Dalton [2] .

Although CAI 9-9 test was first developed for use in detecting colorectal cancer, it is more sensitive to pancreatic cancer. It is now considered the best tumor marker for patients with the cancer of pancreas . It will not usually detect very early disease but is used to observe patients being treated for advanced disease . if the CAI 9-9 blood level is high in newly diagnosed patients , this usually means the disease is advanced . Abnormal level are above 37 U/ml. [6,7] .

Increased concentrations of CAI 9-9 are not however specific for adenocarcinoma of the pancreas, high levels can also be found in other gastrointestinal (GIT) malignancies (especially with advanced disease) as well as in various benign disorders (e.g., both chronic and acute pancreatitis , cirrhosis, cholangitis and hepatocellular jaundice) [8].

Monthly CAI 9-9 measurement appear to be justified for monitoring response to therapy and tailoring treatment decisions [9] .

CEA, is a glycoprotein consisting of - 60% carbohydrate and a molecular mass of - 180 - 200

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Dalton. [10] . CEA exhibits considerable heterogeneity, which appears to be attributable to variations in its carbohydrate chain. Most of the carbohydrate is composed of mannose, galactose , N- acetylglucosamine , fructose , and sialic acid [10] . CEA is attached to the cell membrane by a glycosyl phosphotidyl inositol anchor and probably is released as a soluble form by a phospholipase C or phospholipase D [11] .

It is normally found in fetal tissue and also produced by the cancerous cells of the large intestine , liver , stomach , pancreas , melanoma , lymphoma , cervix , bladder , kidney , thyroid and the ovary . CEA is also produced by some of the breast and the lung cancers [5] . CEA can be considered an intercellular adhesion molecule , in contradistinction to the Ca ⁺² and temperature - dependent cadherine [12] .

The reference range is less than or equal to 2.5 - 5.0 ng/ml. Only 40 – 45 of patients with pancreatic carcinoma have elevation in CEA levels [2] .

C- reactive protein (CRP) is the archetypal positive acute-phase protein (APP) in human and widely used as a marker for the acute-phase response in clinical practice. At diagnosis - 40% of patients with pancreatic cancer exhibit an elevated serum level of CRP . This proportion increase to - 80% as patients approach the time of death [13] .

It has been shown that the acute - phase protein response to be associated with hypermetabolism, accelerated weight loss, and poor survival in patients with advanced cancer [14] .

The acute - phase protein characterized by elevated circulating concentration of so - called positive acute - phase protein, such as CRP . The circulating concentrations of such protein depend on the rate of synthesis (largely in the liver) , degradation, and transcapillary escape [14] .

Since pancreatic tumors are not uncommon the aim of this study is to shade a light on the sensitivity and specificity of tumor markers that are related to this disease.

Material and Method :

Blood samples were collected from 35 patients with pancreatic carcinoma , these samples were compared with 25 sample from patients with non malignant G.I diseases patients.

The non malignant G.I diseases were chronic cholecystitis , duodenal ulcer , gastric ulcer , cholangitis , diverticulitis , and chronic gastritis .

Normal blood samples were obtained from 35 apparently healthy blood donor persons who were considered as controls .

All the patients were attending the GIT center / Medical city between June 2003 and April 2004

The samples were estimated for CA19-9, CEA, and CRP. The method used for estimation of CAI 9-9 , CEA was ELFA - Enzyme Linked Fluorescent Assay - by kit supplied by bio Meireux in the first

referral private lab. for tumor markers. As for estimation of CRP was by ELISA - Enzyme Linked Immunoassay methods, using BioRad EIA reader model 550, using CRP kit provided by Biocheck-USA..

Statistical Method:

ANOVA test was used to show the difference between variables, as well unpaired student T-test.

Results :

A total of 95 individuals were studied, 35 apparently normal blood donor individuals used as controls, 25 patients with non malignant G.I diseases, and 35 patients with pancreatic cancer five of those patients were beyond surgery and their CAI 9-9 was above 70 IU/ml and CEA above 60 ng/ml so they were excluded from this study

The mean age of the subjects ± SEM were 53.56 ± 2.41 , 53 ± 2.76, 62.2 ± 2.95 years respectively,(table I).

Table I : Age and gender in normal healthy individuals , patients with non malignant G.I diseases , and patients with pancreatic carcinoma .

<i>Individual characteristics</i>	<i>Control</i>	<i>Non malignant G.I. diseases</i>	<i>Pancreatic carcinoma</i>
<i>Age (Mean)years± (SEM)</i>	<i>53.5 ± 2.41</i>	<i>53.0 ± 2.76</i>	<i>62.21 ± 2.95</i>
<i>Gender</i>			
<i>Male</i>	<i>20</i>	<i>16</i>	<i>11</i>
<i>Female</i>	<i>15</i>	<i>9</i>	<i>19</i>

Serum CAI 9-9 values in controls, non malignant G.I diseases patients group , and pancreatic cancer patients group were shown in table II , that there was insignificant difference between the non malignant G.I diseases patients group and control group (P> 0.05) and significant differences between the pancreatic cancer patients group and the control group (P<0.05).

Serum CEA in pancreatic cancer patients was compared with non malignant G.I diseases patients and control The results indicated that there was insignificant difference between the

non malignant G.I group and the control group ($P > 0.05$), while there was significant difference between the pancreatic cancer patients group and the control group ($P < 0.05$). Serum CRP showed more or less similar results regarding the non malignant G.I diseases and pancreatic cancer patients in comparison with control group (table II).

Table II : Serum determination of CA19-9 and CEA in healthy individuals, patients with non malignant G.I diseases, and pancreatic carcinoma.

Study groups	No. of individuals	Mean	± SEM	P ANOVA
Serum level of CA19-9 (IU/ml)				
Controls	35	10.20	4.32	
Non malignant G.I diseases	25	42.37	8.14	$P > 0.05$
Pancreatic cancer	30	197.16	37.52	$P < 0.05$
Serum level of CEA (ng/ml)				
Controls	35	1.83	0.58	
Non malignant G.I diseases	25	3.01	0.73	$P > 0.05$
Pancreatic cancer	30	24.52	13.63	$P < 0.05$
C-REACTIVE PROTEIN(mg/L)				
control	35	2.89	1.76	
Non Malignant C.I Disease	25	4.61	2.88	$P > 0.05$
Pancreatic Cancer	30	98.96	24.96	$P < 0.05$

In general, the results showed that there was insignificant difference between the non malignant G.I diseases patients group and control group ($P > 0.05$) although CA19-9, CEA & CRP were higher levels in the non malignant GI diseases.

The tumor markers showed significant difference between the pancreatic cancer patients group and the control group ($P < 0.05$), (table II).

The sensitivity and specificity of the three tumor

markers CAI 9-9, CEA and CRP were calculated according to the cutoff values of the three markers (Mean \pm 2 SEM) The sensitivity and the specificity were 90% & 75% respectively if the three tumor markers were measured, while less sensitivity and specificity if one or two tumor markers were measured table III).

Table III :- The sensitivity and specificity of CA 19-9, CEA, and CRP in pancreatic cancer.

	Sensitivity	Specificity
CA19-9	62 %	65 %
CEA	40 %	60 %
CRP	80 %	40 %
CEA + CRP	80 %	72%
CEA + CA19-9	83 %	73%
Ca19-9 + CEA + CRP	90 %	75%

Discussion :

The clinical presentation of pancreatic cancer is often indistinguishable from other pancreatic diseases; Patients with tumors of body or tail of pancreas usually present with abdominal pain weight loss, anemia and abdominal mass which is usually at the late stage of the disease and more often with metastases, while those with tumors of the head of pancreas present with painless and progressive jaundice, thus tumor markers is one of the diagnostic aids for this tumor [1,2].

A variety of tumor markers could be found in the serum of patients with pancreatic cancer as CEA, CA 19-9, CA 242 [16], CA-50 and CA 72-4 [5] that those tumor markers were used in diagnosis and follow-up of operated cases of pancreatic tumors. Serum concentration of CAI 9-9 were elevated particularly in patients with pancreatic cancer but also in patients with other G.I cancers or some benign G.I diseases [17], this was comparable to the present study.

The sensitivity of CAI 9-9 in pancreatic cancer was 60 - 95 % and its specificity was 57 - 90 % [5,18], Baurfi et al. in 1996 [19] had reported a higher sensitivity of CA19-9 that was 85.7 %, while in the this study the sensitivity was 62 % and specificity was 65 %, and this agreed more or less with the previous studies.

These results confirmed that CAI 9-9 measurement could be used for diagnosis as well as for prediction of resection, survival rate after surgery and recurrences [6], though this was of no value for early detection of this malignancy [18].

The lack of absolute specificity results were due

to several factors as, tumors of non - pancreatic origin might cause an increase in CAI 9-9 serum level , benign disease of the pancreobiliary tree (chronic pancreatitis and obstructive jaundice) might cause significant increase as well , an altered hepatic function , whether was caused by cancer or a benign disease might give rise to increase serum CA19-9 level , due to its reduced molecular clearance, that occurred mainly through the hepatic metabolism.[5,20]

Serum CEA was less sensitive and less specific, in this study their results were 40 % and 60 % respectively and these results were explained as the circulating CEA level in a given patient was the end result of various factors , including the level of gene expression, the rate of CEA synthesis, its subsequent release by the tumor, the half-life of CEA in the circulation , the degree of necrosis and vascularization of the tumor, as well as the rate of CEA catabolism by the liver. Despite the complexity of the synthesis, the CEA assay had taken an important role in the management of patients with cancer [12] .

Five patients in this study who had serum CEA above 60 ng/ml and CA 19-9 above 70 IU/ml were excluded from this study because the tumor was beyond surgery i.e the patients with such CEA & CA 19-9 levels should be considered before laprotomy.

There was a wide variation for proper selection of the most specific and sensitive tumor markers for pancreatic cancer and gastrointestinal cancers some studies showed that CEA,CA 19-9 and CA 72-4 improved the diagnostic accuracy in GIT malignancies compared with these marker alone [21]

The sensitivity and specificity of CRP , in this study were 80 % and 40 respectively .

It has been explained that the acute-phase protein response was a useful prognostic indicator for patients with unresectable pancreatic cancer. Moreover, the metabolic disturbances associated with an acute-phase protein response of patients with pancreatic cancer might be worthwhile therapeutic target . The mechanism by which a systemic inflammatory response might impact on cancer - specific survival is not clear. However , it is known that as part of the systemic inflammatory response to the tumor there is a release of pro-inflammatory cytokines and growth factors , which have profound catabolic effect on host metabolism [1,14,21] .

In conclusion the tumor markers CAI 9-9 , CEA, and CRP in patients with pancreatic cancer had sensitivity of 90% if measured together while 75% specificity, they could be considered as good predictors for such malignancy that might prevent delay in diagnosis . High level of the multiple panel of CEA,CA19-9 and CRP could spare patients a major exploratory laparotomy.

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