Serum tumor markers not useful in screening patients with pancreatic mucinous cystic lesions associated with malignant changes

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BACKGROUND: Serum cancer antigen 19-9 (CA19-9) provides additional information about mucinous cystic pancreatic neoplasm (MPN). This study was undertaken to assess both CA19-9 and carcinoembryonic antigen (CEA) serum concentrations in consecutive patients affected by MPNs and other chronic benign and malignant pancreatic diseases. We also evaluated whether serum CA19-9 and CEA determinations provide additional information such as the presence of invasive carcinoma in MPN patients.

METHODS: Serum CA19-9 and CEA from 91 patients with pancreatic diseases were tested by commercially available kits at the time of diagnosis. The upper reference limit of serum CA19-9 was 37 U/mL and that of serum CEA was 3 ng/mL.

RESULTS: Thirty-five patients was diagnosed with chronic pancreatitis (CP), 32 with MPN, and 24 with pancreatic ductal adenocarcinoma (PDAC) confirmed histologically. Surgery was carried out in 5 CP patients, in 10 MPN patients (7 of them had severe dysplasia), and 9 PDAC patients. Serum CA19-9 activity was high in 12 (34.3%) CP patients, in 7 (21.9%) MPN patients, and in 12 (50.0%) PDAC patients (P=0.089). High serum CEA concentrations were noted in 6 (17.1%) CP patients, in 6 (18.8%) MPN patients, and in 12 (50.0%) PDAC patients (P=0.010). In the 7 MPN patients associated with histologically confirmed severe dysplasia, 3 (42.9%) patients had elevated serum activity of serum CA19-9, and 2 (28.6%) patients had high levels of CEA.

CONCLUSION: Serum determination of oncological markers is not useful in selecting MPN patients with malignant changes.

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KEY WORDS: cancer antigen 19-9; carcinoembryonic antigen; cystic pancreatic neoplasms; chronic pancreatitis; pancreatic ductal adenocarcinoma; laboratory assessment

Introduction

Mucinous cystic pancreatic neoplasms (MPNs) are a heterogeneous group of tumors characterized by mucin production.[1] The following types of cystic neoplasms account for approximately 90% of all cystic tumors of the pancreas: intraductal papillary mucinous neoplasms (IPMNs) involving either the main pancreatic duct, branch duct or both (mixed IPMNs), mucinous cystic neoplasms (MCNs), serous cystic neoplasms (SCNs) and pseudopapillary neoplasms. In fact, the MPNs requiring particular clinical consideration due to the possibility of malignant progression are IPMNs and MCNs.[2] A previous history of diabetes, especially with insulin use, chronic pancreatitis (CP) and a family history of pancreatic ductal adenocarcinoma (PDAC) are the risk factors for the development of IPMNs, and these findings suggest an overlap between certain risk factors for PDAC and IPMNs.[3] In addition, no serum markers exist to differentiate pancreatic cystic lesions from CP and PDAC. Previously, we reported that IPMNs have serum vascular endothelial growth factor receptor-2 (VEGFR-2) levels different from those in PDAC patients. However, we also found that serum VEGFR-2 cannot be routinely utilized to differentiate IPMNs from PDACs because the values are overlapped in the two groups of patients.[4] Serum transforming growth factor-beta1 level was also found to be elevated in IPMNs patients and in

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PDAC patients, suggesting a high apoptotic activity in IPMNs and PDAC patients. But we found that the values of these markers are similar in IPMNs and PDAC patients.[5] Determination of serum leptin level was also suggested to be able to differentiate benign from malignant pancreatic diseases.[6] Others[1] found that even if serum cancer antigen 19-9 (CA19-9) is not a marker of cystic pancreatic neoplasm, its determination provides additional information within the diagnostic work-up since a positive result is associated with the presence of an invasive carcinoma. We thus evaluated the behavior of serum CA19-9 in consecutive patients with pancreatic diseases, such as MPNs, CP and PDAC. In addition, serum carcinoembryonic antigen (CEA) level was also determined in the three groups of patients. Moreover, whether serum CA19-9 and CEA determinations provide additional information about the presence of invasive carcinoma in MPN patients was also studied.

Methods

Ninety-one consecutive patients with pancreatic diseases (54 males, 37 females, mean age 61.6 years, range 28-88) were investigated (Table 1).

Serum CA19-9 and CEA levels were determined using commercially available kits in all patients at the time of diagnosis. Serum CA19-9 level was determined using an immunometric technique (VITROS CA19-9, Ortho-Clinical Diagnostics, High Wycombe, UK) with the detection limit of 1.4 U/mL, linearity 1.4-1000 U/mL, within-run coefficient of variation (CV) 0.8%-1.2%, and total imprecision CV 2.6%-3.4%. The upper reference limit of CA19-9 was 37 U/mL. CEA, a glycoprotein with a molecular weight of approximately 180 000 dalton was tested using an immunometric immunoassay technique (VITROS CEA, Ortho-Clinical Diagnostics). The detection limit of this test was 0.31 ng/mL, linearity 0.31-400 ng/mL, within-run CV 1.5%-2.2%, and total imprecision CV 2.7%-3.9%. The upper reference limit of CEA was 3 ng/mL.

Table 1. Clinical characteristics of the 91 patients in the three groups (*n*, %)

	CP (*n*=35)	MPN (*n*=32)	PDAC (*n*=24)	Overall (*n*=91)	*P* value*
Gender					**0.039**
Male	26 (74.3)	14 (43.8)	14 (58.3)	54 (59.3)	
Female	9 (25.7)	18 (56.3)	10 (41.7)	37 (40.7)	
Pain	13 (37.1)	1 (3.1)	23 (95.8)	37 (40.7)	**<0.001**
Diabetes	12 (34.3)	3 (9.4)	11 (45.8)	26 (28.6)	**0.007**
Jaundice	0	2 (6.3)	17 (70.8)	19 (20.9)	**<0.001**
Surgery	5 (14.3)	10 (31.3)	9 (37.5)	24 (26.4)	0.103

The *P* values indicate the differences among the three groups of patients studied. CP: chronic pancreatitis; MPN: mucinous cystic pancreatic neoplasms; PDAC: pancreatic ductal adenocarcinoma. *P* values take into account the comparison among the three groups.

Statistical analysis

Descriptive data were expressed as absolute numbers, relative percentages, means and standard deviations. Serum CA19-9 and CEA levels were evaluated by the Kolmogorov-Smirnov test; they were not normally distributed in our population; thus, for continuous variables, a non-parametric test, the Mann-Whitney *U* test, was used to analyze the data. For categorical variables, Fisher's exact test and the Chi-square test were used as appropriate. *P* values less than 0.05 were considered statistically significant.

Results

The 91 patients with pancreatic diseases were divided into three groups. Group 1 comprised 35 CP patients (26 males and 9 females) including 15 patients with calcifications, 1 patient with pseudocyst, 12 patients with exocrine pancreatic insufficiency, and 12 patients with diabetes mellitus, of whom 13 patients were studied during a flare-up of the disease. Group 2 comprised 32 MPN patients (14 males and 18 females), in whom 2 patients had main duct IPMNs, 2 mixed type IPMNs, 2 MCNs, and 26 branch duct IPMNs. Pain was found in only one (3.1%) MPN patient. Diabetes was found in 3 (9.4%) MPN patients and jaundice in 2 (6.3%) MPN patients; surgery was performed in 10 (31.3%) of the 32 MPN patients, and 7 (21.9%) of them had severe dysplasia. Group 3 comprised 24 patients with histologically confirmed PDAC (14 males and 10 females). Pain occurred in 23 (95.8%) patients, diabetes mellitus in 11 (45.8%), jaundice in 17 (70.8%); and 9 (37.5%) patients underwent surgery. As expected, CP patients were mostly males whereas pain and jaundice were present in most PDAC patients; surgery was carried out mainly in MPN and PDAC patients.

The individual circulating levels of CA19-9 and CEA are illustrated in Figs. 1 and 2. Both CP and MPN patients had similar serum levels of CA19-9 and CEA, whereas serum levels of the two markers in patients with CP and MPN were significantly lower than those of PDAC patients.

Jaundice, pain, diabetes and surgery are taken into consideration (Table 2). It was found that patients with jaundice had serum levels of CA19-9 and CEA significantly higher than those without jaundice, and patients with pain had serum CEA levels significantly higher than those without pain. When the groups were considered