ORIGINAL ARTICLE

CA 19-9 to differentiate benign and malignant masses in chronic pancreatitis: is there any benefit?

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Abstract

Background The role of the tumor marker CA 19-9 in differentiating benign from malignant masses in chronic pancreatitis has not been extensively studied.

Aim This study aims at assessing the accuracy of CA 19-9 in differentiating inflammatory head masses in chronic pancreatitis from superimposed carcinomas on chronic pancreatitis.

Methods The data of 84 consecutive patients who had mass lesions in chronic pancreatitis were analyzed to determine the sensitivity, specificity and predictive values at cut-off values of 37, 100, 200 and 300 U/mL. Receiver operating characteristic (ROC) curves were used to assess the sensitivity and specificity.

Results There were 50 benign masses and 34 malignancies. The overall sensitivity and specificity of CA 19-9 for cancer was 68% and 70%, respectively. There was a higher positivity of CA 19-9 in cancers than in benign masses (23/34; 68% versus 15/50; 30%, $P<0.01$) with cut-off values of 37 U/mL. Higher positivity rates were obtained in cancers using other cut-off values such as 100, 200 and 300 U/mL. Values over 300 U/mL were 100% specific for malignancy, but occurred in only 5 (of whom had distant metastases) of 34 patients.

Conclusion CA 19-9 level in excess of 300 U/mL in mass lesions in chronic pancreatitis was always indicative of malignancy.

Keywords Chronic pancreatitis · Carbohydrate antigen · Inflammatory head masses

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Introduction

Mass lesions in the pancreas occur in 20–30% of cases of chronic pancreatitis.[1] Chronic pancreatitis has a strong association with pancreatic malignancy and may be etiologically associated with it. In parts of Southern India, there exists a form of idiopathic chronic pancreatitis unassociated with alcohol abuse, which has been variously described as tropical calcific pancreatitis, tropical pancreatitis, idiopathic pancreatitis of the tropics, fibrocalculous pancreatitis and others. A high incidence of pancreatic cancer among these patients has been described previously.[2] The presence of a mass in the head of pancreas, which is already afflicted by chronic pancreatitis presents a clinical dilemma – on the one hand, resectional surgery may be too radical for benign disease with resultant problems of pancreatic insufficiency, and on the other hand, drainage operations for malignancy would be ineffective. Despite advances in imaging techniques, it may be difficult to differentiate inflammatory head masses (IHM) from malignant masses.[3] Differentiation between benign (inflammatory) and malignant masses has important therapeutic implications – avoid unnecessary resection in inflammatory masses, and avoid leaving behind a cancer. Many patients with cancer of the pancreas superimposed on chronic pancreatitis may have incurable disease because of multicentricity or advanced stage at presentation.

The carbohydrate antigen CA 19-9 has been a useful marker, both in diagnosis as well as follow-up of pancreatic cancer.[4] However, CA19-9 is also elevated in inflammatory lesions of the pancreas.[5] The published literature has hitherto examined the role of CA 19-9 in differentiating benign versus malignant masses in the pancreas. The critical issue is to differentiate a benign from malignant mass in a patient who has clear-cut evidence of chronic pancreatitis in the form of ductal calculi, and downstream ductal changes. Most studies that have addressed this issue have come from the Western world where alcohol abuse is the commonest etiology for chronic pancreatitis. The value of CA 19-9 in patients with mass lesions in idiopathic (tropical calcific pancreatitis) has not been studied. This study aims to assess the value of CA 19-9 estimation in patients with chronic pancreatitis and a pancreatic mass lesion, in determining its benign versus malignant status.

Methods

The case records of patients with chronic calcifying pancreatitis who had mass lesions in the pancreas were retrieved from the prospectively compiled database. Eighty-four consecutive patients with mass lesions were identified and formed the basis of the study. The inclusion criteria were:

1. Chronic calcifying pancreatitis as evidenced by 2 out of the following 4 criteria: (a) calculi on abdominal X-ray, (b) dilated pancreatic duct on ultrasound, (c) changes of pancreatitis on ERCP and/or MRCP and (d) EUS appearances of pancreatitis.[2] These criteria were used to define a pure cohort of patients. For example, calcification may indicate calcinosis and not necessarily pancreatitis. Similarly, pancreatic duct dilatation may also occur in tumors.
2. Mass lesions on ultrasound or CT scan.

The end-points of the study were (1) histological confirmation of malignancy by biopsy (radiology/endoscopy or surgery) or (2) establishment of benign nature of disease by follow-up of more than 3 years without any evidence of recurrence of mass or metastatic disease.

These 84 patients had been treated during a 10-year period, January 1991–July 2001. All cases had calculi on abdominal X-ray, 71 had dilated ducts on imaging, and all patients had ductal changes of chronic pancreatitis on pre-operative or intra-operative imaging. Of the 84 patients, 43 had biochemical jaundice (30 in the malignant group and 13 in the benign group). Pre-operative estimation of serum CA 19-9 was done in all patients. All patients were treated surgically, by head coring with lateral drainage in 52 and by resection in 32 cases. There was no operative mortality. All cases were subjected to intra-operative biopsy by needle, or shave techniques. Histological examination was undertaken by the same pathologist throughout the study.

Patients were followed up for a minimum period of 3 years before compiling the results.

Statistical methods

Sensitivity, specificity, positive and negative predictive values were calculated using four cut-off values: 37, 100, 200 and 300 U/mL. Receiver operating characteristics (ROC) were studied (SPSS, PC version 10.0).

Results

There were 50 benign cases (established by follow-up and negative histology) and 34 histological-proven cancers. The distribution of CA 19-9 positivity among the benign and malignant masses is shown in Fig. 1. The overall sensitivity of CA 19-9 was 68% and specificity 70% using cut-off values of 37 U/mL.

There was a significantly raised positivity of CA 19-9 among cancers than in benign cases (23/34; 68% versus 15/50; 30%, $P<0.001$). Significantly higher positivity of CA 19-9 was observed with higher cut-off values as well (Table 1).

The sensitivity, specificity, positive and negative predictive values of CA 19-9 at the various cut-off levels is shown in Table 1.

There was no difference in CA 19-9 levels according to age, sex, presence of jaundice, or features of acute inflammation (Table 2).

ROC curves using different cut-off values revealed a trade-off between sensitivity and specificity (Fig. 2).

CA 19-9 levels in patients with cancer: as indicated in Table 1, 23 out of 34 patients with histologically proven cancer had raised CA 19-9 beyond 37 IU/mL. Of these, 17 had head masses, and 6 patients had mass lesions in the body or tail region. Only 12 patients were jaundiced and the bilirubin levels ranged from 3.2 mg/dL to 27.6 mg/dL. There was no correlation between CA 19-9 levels and serum bilirubin (Table 2). Of the 5 patients with values above 300 IU/mL (420, 780, 1150, 1400 and 1780), 2 patients had distant metastases, and underwent supportive therapy only, whereas 3 patients underwent surgical resection followed by chemotherapy with survival period for 23, 14 and 38 months, respectively.

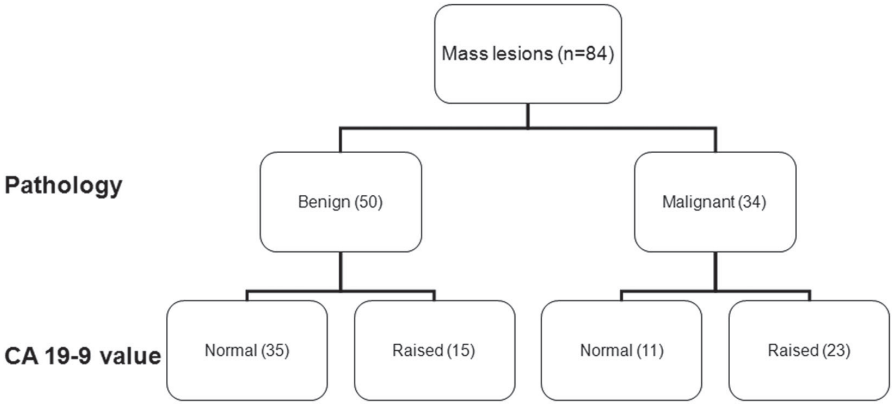

Fig. 1 Distribution of CA 19-9 positivity among the 84 patients

Discussion

The frequency of development of a mass lesion in chronic pancreatitis is reported to be between 20% and 30%.[1] Although imaging techniques have improved, it is still difficult to reliably differentiate an inflammatory mass lesion in the head from a neoplasm in all cases. The sensitivity and specificity of dynamic CT scan is reported to be in the range of 70–90% and 80–100%, respectively in cases of *de novo* malignancy in the head of pancreas.[6] However, the accuracy of CT scan is highly variable in cases of cancer developing on chronic pancreatitis as the inflammatory changes of pancreatitis themselves can render differentiation of true inflammatory mass from superimposed cancer difficult.

Despite great technical and therapeutic advances, the prognosis of pancreatic malignancy is poor.[7] The prognosis is worse in patients with pancreatic malignancy in the setting of chronic pancreatitis.[8] This is because the tumors are often locally advanced at the time of diagnosis due to difficulty in early diagnosis (due to significant overlap of symptomatology) and due to the multicentric nature of the disease. Therefore, serum marker tests that facilitate differential diagnosis are important.

CA 19-9 is still considered to be the best serum marker of pancreatic carcinoma due to its high sensitivity of 70%–90% and specificity of approximately 90%.[4] The diagnostic value of CA 19-9 in patients with carcinoma developing in chronic pancreatitis has not been studied. Other newer tumor markers like tissue polypeptide-specific antigen (TPS)[9] and CAM 17-1[10] are found to have better specificity and sensitivity to differentiate chronic pancreatitis from malignancy. However, the estimation of these markers is not readily available and they are expensive. Hence, we have chosen CA 19-9 as the marker in this study.

As pre-operative diagnosis of malignancy is often unreliable at radiology, fine needle biopsy and/or endoscopic

Table 1 Sensitivity, specificity, positive predictive value and negative predictive value of CA 19-9 at different threshold levels

Cut-off value*	Benign		Malignant		Sensitivity %	Specificity %	PPV	NPV
	Normal	Increased	Normal	Increased				
37	35	15	11	23	68	70	61	76
100	43	7	20	14	41	86	67	68
200	48	2	26	8	24	96	80	65
300	50	0	29	5	15	100	100	63

PPV: positive predictive value; NPV: negative predictive value.
*Value of CA 19-9 in U/mL.

Table 2 CA 19-9 levels in various groups of patients

CA 19-9 values	Benign cases (***n***=50)	Malignant (***n***=34)
Overall	15 (3–224)	76 (7–1780)
Levels in jaundiced patients	17 (3–142)	88 (11–890)
Male:female	12:19	71:82 Values are as median (range)

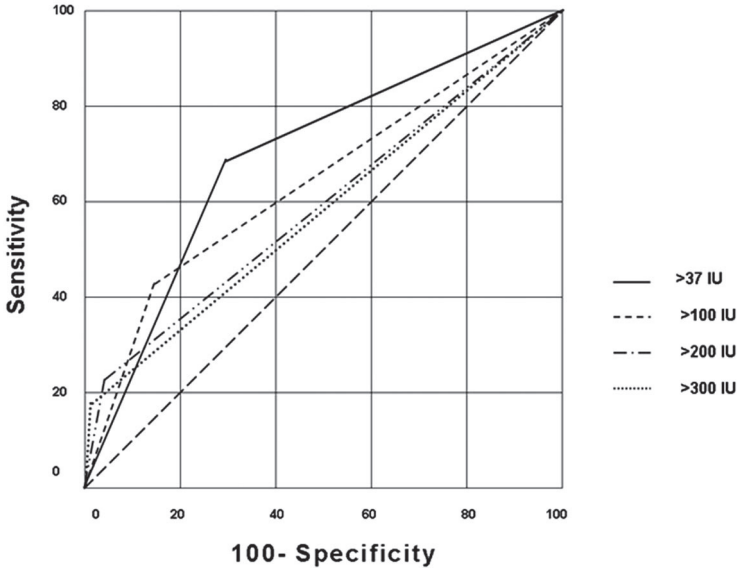

Fig. 2 Receiver operating characteristic (ROC) plot showing the sensitivity and specificity at different cut-off levels

methods, only patients who had undergone surgical therapy were included in the study. Malignancy was proven histological either by *Tru-cut* biopsy, shave technique or in resected specimen. All 84 patients in our study had undergone surgery. The benign nature of the mass could be affirmed by fairly long follow-up for a minimum period of 3 years.

Our study has shown that CA 19-9 has a sensitivity and specificity of 68% and 70%, respectively using cut-off value of 37 U/mL. Previous studies have shown that CA 19-9 has a sensitivity of 70–90% in diagnosing carcinoma pancreas.[3] The specificity of this tumor marker was in the range of 90%.[4] The low specificity of CA 19-9 in our study compared with other studies is probably due to the fact that all the previous studies evaluated the value of this marker in differentiating chronic pancreatitis from *de novo* pancreatic cancer. In contrast, we have exclusively studied patients with chronic pancreatitis who had a mass; similar data have not been published earlier.

When CA 19-9 of 37 U/mL is taken as the cut-off limit, 27% of patients with pure chronic pancreatitis had an elevated CA 19-9, which may account for the low specificity and high rate of false positivity.[5] Further, CA 19-9 levels have been reported to be falsely high among jaundiced patients.[11,12] In our series, however, the range of values in jaundiced and non-jaundiced patients were similar (Table 2).

ROC analysis is a graphic method to determine the optimal threshold for evaluation of sensitivity and specificity profiles of serum tumor markers.[13] Thus, by progressively increasing the threshold level of CA 19-9, the specificity of the test also increased. ROC analysis has shown that at a threshold level of 300 U/mL, CA 19-9 has a 100% specificity in diagnosing carcinoma pancreas patients with idiopathic chronic pancreatitis. Similar cut-off level has been proposed by Nouts *et al.*[14] in a study comparing *de novo* pancreatic cancer and chronic pancreatitis.

Raising the threshold level of CA 19-9 to 300 U/mL increases its predictive value as a positive test to 100%. These operational characters of CA 19-9 suggest a "ruling-in" usage of this marker for diagnosis of carcinoma in patients with chronic pancreatitis.

The coincidence of pancreatic cancer in patients with alcoholic pancreatitis has been reported between 1.8% and 4%.[15] The incidence of carcinoma in tropical pancreatitis is presumably higher; our experience has shown that the majorities of superadded malignancies on tropical pancreatitis are inoperable at diagnosis and has a worse prognosis than *de novo* pancreatic cancer.[2,8]

Thus, an elevated CA 19-9 greater than 300 U/mL in the setting of head mass with chronic pancreatitis strongly suggests malignancy; this has therapeutic and prognostic implications. Further, the absence of a considerable inflammatory response in tropical pancreatitis as opposed to alcoholic pancreatitis may account for the absence of high values in benign disease. Such increase in CA 19-9 levels (above 300 U/mL) was, however, seen only in 5 out of 34 patients with cancer, and that indicates a high false negative rate, which limits its benefit.

If cut-off levels of 37 U/mL are used, the predictive value in differentiating cancer from inflammatory masses in chronic pancreatitis is very poor.

In conclusion, CA-19-9 was not of great value in the diagnosis of cancer in patients with chronic pancreatitis. A value of >300 U/mL helped in discriminating cancer from benign masses in a small number of patients.

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