ORIGINAL ARTICLE

The Clinical Significance of Elevated Levels of Serum CA 19-9

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Summary

The tumour marker CA19-9 is a sensitive marker for pancreatic, gastric and hepatobiliary malignancies. High CA 19-9 level indicates unresectable lesions and a poor prognosis. The objective of the study was to determine the significance and implications of elevated CA 19-9 levels in the serum. A one-year retrospective review of all patients who had CA19-9 measured in our Medical Centre was undertaken; 69 patients were found to have CA 19-9 level above the cut-off value (37 U/ml). Thirty-six patients had malignant and the remaining 33 had benign lesions. CA 19-9 was found to be elevated in malignancies of pancreas, colorectum, lung, liver and ovary. Benign conditions associated with elevation of CA 19-9 included disease of the hepatobiliary system, pneumonia, pleural effusion, renal failure and SLE. In two individuals, there was no obvious cause for the elevation of this marker. CA 19-9 levels were significantly lower in benign than in malignant conditions. In conclusion, elevated CA 19-9 may be found in patients with benign as well as malignant disease. Therefore, it is important (1) that elevated levels of CA 19-9 are interpreted in the light of the clinical presentation of the patient and (2) to be aware of the benign conditions that can be associated with increased levels of this marker. With these factors in mind, CA 19-9 can be used to assist in the diagnosis of pancreatic cancer and assessment of resection adequacy post-operatively.

Key Words: CA19-9, Benign conditions, Malignant conditions, Pancreatic carcinoma

Introduction

Carbohydrate antigen 19-9 (CA 19-9) was originally isolated from a human colorectal cancer cell line as a mucin like product[1]. The antigen is found in the normal epithelial cells of the gall bladder, biliary ducts, pancreas and stomach[2]. Multiple studies have shown that while elevations in serum CA 19-9 appear to be useful in the diagnosis of adenocarcinoma of the upper gastrointestinal tract and in monitoring of colonic carcinoma, its greatest sensitivity is in the detection of pancreatic adenocarcinoma[3]. Elevations in CA 19-9 level correlate with the degree of tumour differentiation as well as the extent of tumour mass[4]. In his studies, Steinberg found that CA 19-9 has over all specificity of 90% and sensitivity of 80% in detecting adenocarcinoma of the pancreas[5]. High CA 19-9 levels have been associated with unresectable lesions and a poor prognosis for patients presenting with pancreatic carcinoma[6].

Elevated CA 19-9 levels are not pathognomonic of cancer of the pancreas; it may be elevated in other malignancies as well as in benign conditions[7,8]. The objective of the study was to determine the significance and implications of elevated CA 19-9 levels in the serum.

Materials and Methods

A one-year (January 2001 to December 2001) retrospective review of all patients who had CA 19-9

This article was accepted: 16 April 2003

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level measured was undertaken. The results were retrieved from the laboratory information system, Department of Pathology, University Malaya Medical Centre, Kuala Lumpur, and all patients who had CA 19-9 greater than the cut-off value 37U/ml were noted. The full clinical records of these patients were reviewed. Ca 19-9 was measured in the serum using a commercially available immunometric assay kit (Immulite, DPC). The upper limit of normal for CA 19-9 in our study was 37 U/ml.

Results

Of 650 patients, whose sera were analyzed for CA 19-9, 69 had their level above the cut-off value 37 U/ml. Thirty six patients (52.2%) had malignancy and the remaining 33 (47.8%) had benign disease. The mean and range, and the distribution pattern of CA 19-9 in the malignant and benign conditions are shown and in Tables I and II and Figures 1 and 2 respectively. The mean of CA 19-9 in the benign group was 83.81 U/ml whereas that in the malignant group was 1632.06 U/ml; there was a statistically significant difference between the two conditions (p value < 0.005).

The benign conditions in which CA 19-9 were found to be elevated were mostly diseases of the hepatobiliary system (16/33). Other benign conditions associated with elevation of CA 19-9 were pulmonary diseases (11/33), end stage renal failure (3/33) and polymyositis. In 2 patients, the cause of the raised CA 19-9 level was not clear; neither had evidence of any malignancy or other organic diseases. In benign conditions, the tumour marker was rarely elevated more than 200U/ml except in one patient with liver cirrhosis and another with cholecystitis. Overall, the level of this tumour marker was less than 100 U/ml in 69.7% of the benign conditions. Levels higher than this were observed only in patients with liver cirrhosis and cholecystitis.

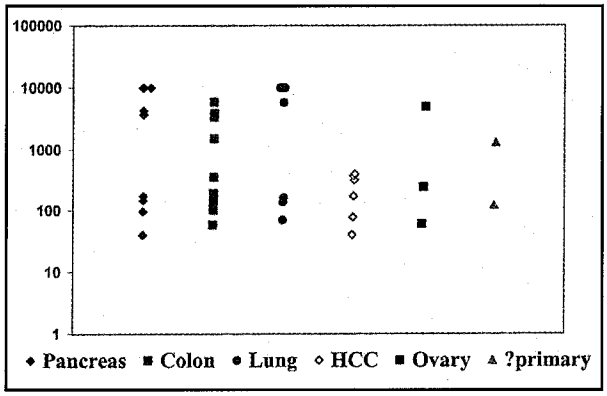
The malignant conditions with elevated CA 19-9 level were colorectal, pancreatic, hepatic, lung and ovarian carcinoma. Two patients with bony metastasis but unknown primary also had high CA 19-9 level in the serum. In the present study, this tumour marker was more than 500 U/ml in 50% of the patients with malignancies. Markedly raised levels of more than 10,000 U/ml were observed in patients with advanced stages of colorectal, pancreatic and lung carcinoma. It is notable that in a sizable proportion (22.2%) of the cases, the CA 19-9 levels were less than 100 U/ml. This included 2 patients with pancreatic cancer; both patients were post-operative cases who had testing done for assessment. With the exclusion of these 2 subjects, the majority of pancreatic cancer patients were found to have significantly elevated CA 19-9.

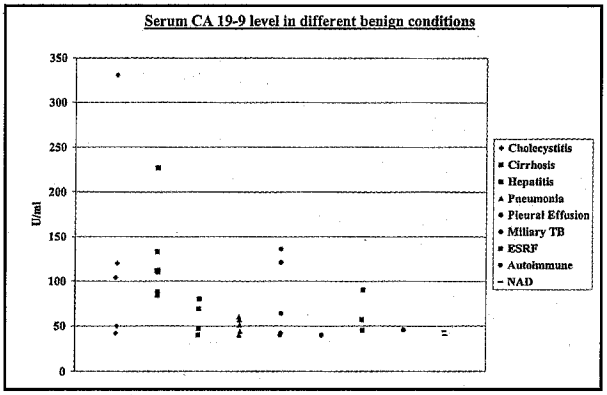
Table I: The mean and range of CA 19-9 in malignant and benign conditions

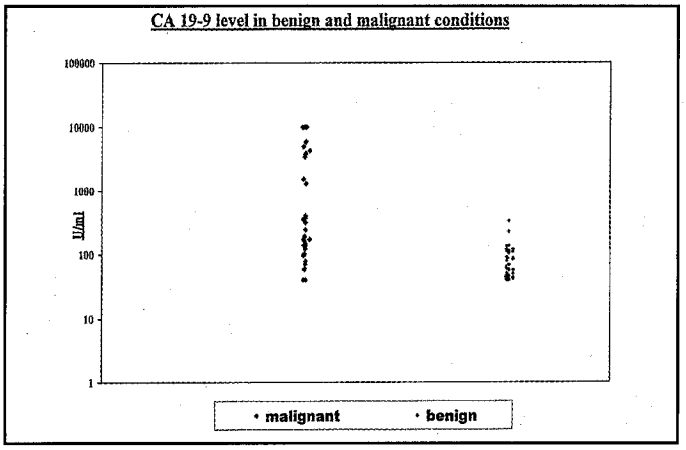
	No: of subjects	Mean	Range
Malignant Conditions			
Colorectal	10	1970.5	40 - 10000
Pancreatic	9	4274	40 - 10000
Hepatic	6	222.9	40 - 400
Lung	6	4361.7	70 - 10000
Ovary	3	1763	60 - 4986
Primary	2	709.5	122 - 1297
Benign Conditions			
Hepatitis	4	59	47 - 80
Cirrhosis	7	123.7	84 - 227
Cholecystitis	5	129.4	50 - 331
Pneumonia	5	49.6	40 - 60
Pleural effusion	5	80.6	40 - 136
Renal failure	3	64	45 - 90
Autoimmune	1	46	
Miliary Tuberculosis	1	42	
No abnormality	2	42	40 - 44

Table II: Distribution of CA19-9 assay values

	No: of subjects	37.0 -100	100.1-200	200.1-500	>500
Malignant Conditions					
Colorectal	10	1	2	1	6
Pancreatic	9	2	2	-	5
Lung	6	1	1	-	4
Hepatic	6	2	1	3	-
Ovary	3	1	1	-	1
Primary	2	1	-	-	1
Benign Conditions					
Hepatitis	4	4	-	-	-
Cirrhosis	7	2	4	1	-
Cholecystitis	5	2	2	1	-
Pneumonia	5	5	-	-	-
Pleural effusion	5	3	2	-	-
Renal failure	3	3	-	-	-
Autoimmune	1	1	-	-	-
Miliary Tuberculosis	1	1	-	-	-
No abnormality	2	2	-	-	-







Discussion

Since its discovery by Koprowski and coworkers, CA 19-9 antigen has been used widely as a tool for the investigation and management of patients with pancreatic carcinoma. CA 19-9 antigen in tissue exists primarily as an epitope present on a glycolipid, sialo-lacto-N fucopentose II ganglioside; in serum, the CA 19-9 antigen is associated with a mucin[9]. The oligosaccharide on which the CA 19-9 epitope was found is a sialylated Lewis A blood group antigen[10]. Patients who are genotypically Lewis a-b cannot synthesize the CA 19-9 antigen and thus it had been said that the maximum achievable sensitivity of this investigation in serum would be 95%[11].

The CA 19-9 is a tumour associated, but not a tumour specific antigen. It is synthesized by normal human pancreatic and biliary ductular cells, as well as by gastric, colonic, endometrial and salivary epithelia[12] and has been found in normal seminal fluid. This explains the elevated level of CA 19-9 in many malignancies.

Although CA 19-9 was found to be elevated in many different malignancies in our study, very high values were observed only in patients with advanced stages of colorectal carcinoma and in pancreatic adenocarcinoma. This finding is similar to what other workers had found in their studies[6, 13]. CA 19-9 level has been suggested as a prognostic indicator of patient survival[5]. However, we are unable to verify this in the present study, as there was no further follow up of the study subjects in most instances. We also observed markedly increased level of CA 19-9 in carcinoma of lung with metastasis. CA 19-9 had been found in epithelial tumours of the lung[14] explaining the presence of elevated levels of this antigen in lung cancer. High levels CA 19-9 were reported to be related to advanced stage adenocarcinoma of the lung[15]. Elevation of this tumour marker in hepatocellular carcinoma had been reported by other workers[16]; however, similar degrees of elevation had also been observed in patients with cirrhosis. Therefore, CA 19-9 is not considered an informative marker in the diagnosis of hepatocellular carcinoma[17]. This observation is also substantiated in our study.

In patients with primary epithelial ovarian carcinoma, CA 19-9 had been stated to have sensitivity of 55.9%[18]. However, unlike the carbohydrate antigen 125 (CA - 125), CA 19-9 shows no correlation with clinical stage[18]. In our series of patients, there was only one case of ovarian carcinoma; this patient had metastasis to the lung and a high serum CA 19-9. In the two cases of unknown primary cancer with secondaries in the bone, histopathological examination showed that the lesions were metastatic adenocarcinoma. Our observation support a previous report stating that increased levels of CA 19-9 is related to metastatic adenocarcinoma and to advanced stages of cancer of unknown primary [19].

CA 19-9 is elevated not only in hepatobiliary malignancies, but also in benign hepatobiliary disorders[20]. Of the 33 patients with benign diseases who had elevated level of CA 19-9, 16 of them had hepatobiliary disorders (48%). Cholestasis is believed to play an important role in causing raised CA 19-9 level in these patients[21]. Hence, caution is needed in interpreting elevated CA 19-9 in patients with jaundice. In fact, extraordinarily elevated CA 19-9 had been reported in patients with acute cholangitis causing diagnostic dilemma in those patients[22]. In all our cases of hepatitis, the tumour marker was less than 100 U/ml; however, we noted higher levels in patients with liver cirrhosis and cholecystitis with gallstones.

Other non-malignant conditions in which we found raised CA 19-9 included benign pulmonary diseases and end stage renal failure. In all but 2 of our cases, both of whom had benign pulmonary disease, CA 19-9 was elevated to less than 100U/ml. CA 19-9, had been shown to be expressed in mucous cells of the bronchial gland and surface of the bronchiolar surface epithelium cells in benign pulmonary disease by immunohistochemical staining[23]. This may explain the elevated level of CA 19-9 in pulmonary diseases. Increased evidence of malignancy had been reported in end stage renal failure patients. Tumours of kidney and corpus uteri are the most common forms of neoplasia seen in renal failure[24]. In our three cases of renal failure the tumour marker was above the cut-off value but less than 100 U/ml; none of them had any sign of malignancy. Tumour markers have been reported to be higher in uraemic patients compared to the normal controls[25], which may be related to the metabolic aberrations in this condition[26]. Therefore, care should also be exercised in interpreting the tumour marker level in renal failure patients.

The tumour marker was elevated in one patient with polymyositis; Shimomura et al had also reported the same findings[27]. CA 19-9 elevation may indicate severe disease or involvement of lungs due to the underlying disease process[27]. In two individuals in whom the tumour marker had been requested as a screening

procedure, CA 19-9 was found to be elevated, albeit only mildly. In these two individuals, there was no evidence of malignancy or any benign diseases. This emphasizes the fallacy of using tumour markers as a routine screen in patients in whom there are no indications.

Our data shows that CA 19-9 is elevated in both benign and malignant conditions, although the level in malignancy is significantly higher. The marker is useful as an adjunct in diagnosis of pancreatic carcinoma and in the assessment of surgical adequacy post-operatively. However, its interpretation must be made in conjunction with clinical findings and other ancillary investigations. It should not be used as a screening test for malignancies. Patients with a variety of benign conditions such as hepatobiliary diseases, pulmonary diseases and renal failure have levels above the cut-off value.

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