Original Article

CA 19-9 as a serum marker in urothelial carcinoma

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Abstract

Introduction: CA 19-9 is a carbohydrate antigen related to Lewis A blood group antigen. It is well-known marker for pancreatic carcinoma and is being investigated for other malignancies including carcinoma bladder. We evaluated the role of serum CA 19-9 as a tumor marker and correlated its level with tumor stage and grade.

Materials and Methods: Seventy-five patients with histologically proven urothelial carcinoma were included in this study as case and 25 healthy volunteers as control. Preoperative 5 ml blood sample was collected. Serum level of CA 19-9 was measured using solid-phase enzyme-linked immunosorbent assay kit. The value of CA19-9 was expressed in U/ml and 37 U/ml was taken as cut-off upper value of normal.

Results: The range of CA19-9 in patients of urothelial carcinoma was 2 to 122 U/ml with a mean of 26.33±29.28, while in control, it was 8.48±5.01 U/ml ($P<0.001$). The sensitivity of CA19-9 was 29%. Serum CA19-9 was significantly elevated in invasive disease in comparison with superficial disease (47.17±34.43 *vs* 16.53±20.13) ($P<0.001$). Significantly high proportion of patients with invasive disease had value ≥37 U/ml (14/24 [58.3%] *vs* 8/51 [15.7%]) with *P* value <0.001. High proportion of high-grade tumor had raised value, 14/34 (41.25%); all patients with metastatic disease had value more than 37 U/ml.

Conclusions: Serum CA19-9 is a marker of aggressiveness of urothelial carcinoma and is almost invariably raised in patients with metastatic disease. Thus, it may be used as a prognostic marker but not as a screening tool due to its low sensitivity.

Key Words: CA19-9, screening, tumor marker, urothelial carcinoma

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INTRODUCTION

Bladder cancer accounts for 2.9% and 1.5% of all cancer deaths in men and women, respectively, with greater than 90% of bladder cancers being transitional cell carcinoma in USA.[1] High rate of recurrence and inability to define population at risk, monitoring measures such as periodic cystoscopic examination and urine-based diagnostic tests have been studied extensively for bladder cancers by various investigative groups.[2,3] Urine cytology has been the gold standard for bladder cancer screening and surveillance in the past,[4,5] but it is subjective and requires adequate number of exfoliated cells in the urine and cellular alterations are likely resulting from changes in collection conditions and therapeutic interventions. Several tumor markers including the bladder tumor antigen (BTA) series of markers, nuclear matrix proteins (NMP22), and fibrinogen degradation products have been approved for clinical use. However, these markers have limited sensitivities and higher false-positive rates.[6,7] The development of hybridoma technology for the preparation of monoclonal antibodies of precisely defined specificity has dramatically improved the chances of identifying new tumor marker antigens. Carbohydrate antigen (CA19-9) is one of such antigen. CA19-9 is a carbohydrate antigen recognized by 1116 NS 19-9 (signet laboratories, Dedham,

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MA), a monoclonal antibody produced by a hybridoma raised against the human colon carcinoma cell lines SW 1116.[8,9] CA19-9 is now a well-known marker for pancreatic carcinoma and has also been reported to be positive in gastrointestinal cancers, papillary carcinoma of thyroid, and endometrial adenocarcinomas.[10-14] In the recent years, cases of urothelial carcinoma displaying high serum CA19-9 level have been reported and investigators have begun studying the diagnostic significance of CA19-9 in the domain of urology as well. CA 19-9 has been studied alone as well as with other markers, but the results have not been consistent. On one hand, serum CA 19-9 has been found to serve as a significant marker for advanced cancer and for tumors with highly malignant potential and is useful for predicting the prognosis of the disease.[15] There are very limited data on the use of CA19-9 as a tumor marker is bladder carcinoma. Thus, it appears that the role of CA19-9 as a serum marker in urothelial cancers has not yet been defined. The present study was undertaken to evaluate serum level of CA19-9 in patients of urothelial carcinoma and to find out whether CA19-9 level was related to tumor stage or grade.

MATERIALS AND METHODS

Patients with complaints of hematuria and suspected to have urothelial carcinoma undergoing treatment in the department of urology, at tertiary health centre, were prospectively enrolled in this study. After obtaining written informed consent, all patients were evaluated clinically and investigated as per standard protocol which includes hemogram, renal function test, urine culture sensitivity, urine cytology, and imaging studies like ultrasound, CT scan/MRI as and when required. Patients diagnosed to have other malignancies and urinary tract infections were excluded from the study. Patients underwent treatment as per routine protocol. Diagnosis was confirmed by histopathological examination of the resected tumor. Staging and grading were done according to tumor, node, metastases (TNM) classification system and WHO/International Society of Urological Pathology consensus classification of urothelial neoplasms of the urinary bladder (Bladder Consensus Conference Committee 1998). G1 and G2 were taken as low grade and G3 and G4 as high grade tumors.[16] Twenty-five healthy volunteers served as controls. Blood sample was collected in a plain vial (5 ml) from each patient during the routine biochemical investigations by peripheral venous sampling and then allowed to clot at room temperature. Serum separation was carried out by centrifugation at 5 000 rpm for 10 minutes and then stored at –20°C till the analysis. CA 19-9 was analyzed using a solid-phase enzyme-linked immunosorbent assay kit (DRG CA 19-9 ELISA EIA 3940 test kit, Marburg Germany), an assay based on sandwich principle. The value of CA 19-9 was expressed in U/ml and the value up to 37 U/ml was taken as cut-off upper value for the normal.

Statistical analysis

Statistical tests were done using the program statistical package for the social sciences (SPSS) version 15 Chicago. Data were expressed as mean±standard deviation. The information collected was transferred to a personal computer. For nonparametric values, '*t*' test was used and for qualitative results, Chi square test was used for statistical analysis. Cross tabulation was done. ANOVA and Mann-Whitney test were also employed. A *P* value of <0.05 was considered significant.

RESULTS

Eighty-five patients suspected to have urothelial carcinoma undergoing treatment were investigated after taking informed consent. Ten patients having no urothelial carcinoma on histopathology were excluded from study. Data of 75 histologically proven cases of urothelial carcinoma were analyzed. There were 68 males and seven females in the age group of 20 to 90 years, with mean age of 54.34 ± 13.38 years. Hematuria was the commonest complaint (*n*=74) followed by dysuria (*n*=33) and urinary frequency (*n*=28). Seventy-four patients underwent transurethral resection of bladder tumors (TURBT). Subsequently, 22 patients underwent radical cystectomy and urinary diversion. In one patient with pelviureteric junction tumor, left nephroureterectomy was done. One patient with locally advanced disease expired due to intestinal obstruction during the treatment. Two patients with locally advanced (T4) disease and one young male patient of 25 years with T2 disease underwent chemoradiation. Fifty-one patients (68%) had superficial tumor (PTa, T1, and TIS) and muscle invasive tumor was diagnosed (T2–T4) in 24 patients (32%) [Table 1]. Six patients had metastatic disease (three lymph nodal, one each had lung, subcutaneous, and penile metastasis). There were 41 patients with low-grade tumor and 34 patients with high-grade tumor. The range of serum CA 19-9 in patients of urothelial carcinoma was 2 to 122 U/ml, with mean of 26.33±29.28 U/ml, whereas in controls, it ranged from 2 to 20 U/ml, with mean of 8.48±5.01 U/ml. The difference of CA 19-9 values between cases and controls was statistically significant with *P* value <0.001. When reference value 37 U/ml was taken as cut-off value of serum CA 19-9, the sensitivity of CA 19-9 for urothelial carcinoma was found to be 29.3%. Twenty-nine (36.8%) patients had serum CA 19-9 more than mean±2SD of control, i.e., 18.5 U/ml. The cases with invasive tumor has significantly higher CA 19-9 in comparison with cases with superficial tumor (*P*<0.001). Significantly more number of patients with invasive tumor had serum CA 19-9 more than 37 U/ml (*P*<0.001) [Table 2]. CA19-9 values were found to be increased in 22 (29.3%) patients. In case of superficial tumors, it was increased in 8 (15.7%) patients, whereas it was increased in 14 (58.3%) patients of muscle invasive disease. The difference in value

Table 1: CA 19-9 level in different T stages, grades, depth of invasion, and in metastatic urothelial tumors

	Number of patients	CA19-9 level in U/ml (mean±SD)	*P* value
T stages			
Ta	12	16.08 ± 16.75	0.001
T1	39	16.67 ± 21.26	<0.001
T2	12	35.92 ± 41.56	0.930
T3	5	41.60 ± 21.42	0.656
T4	7	70.43 ± 16.30	0.002
Cases/controls			
Cases	75	26.33 ± 29.28	<0.001
Controls	25	8.48 ± 5.01	
Tumor grades			
Low grade	41	20.34 ± 23.22	0.308
High grade	34	33.56 ± 34.23	
Tumor invasion			
Superficial tumors	51	16.53 ± 20.13	<0.001
Muscle invasive tumors	24	47.17 ± 34.83	
Tumor spread			
Metastatic disease	6	68.67 ± 29.68	0.002
Non-metastatic disease	69	22.65 ± 26.39	

P value <0.05 was considered significant

Table 2: Patients with CA 19-9 > 37 U/ml in different tumor grades, depth of invasion and in metastatic urothelial tumors

	Number of patients with CA19-9 > 37 U/ml	Percentage	*P* value
Tumor grades			
Low grade	8	19.5	0.040
High grade	14	41.2	
Tumor invasion			
Superficial tumors	8	15.7	<0.001
Muscle invasive tumors	14	58.3	
Tumor spread			
Metastatic disease	5	83.3	0.007
Non-metastatic disease	17	24.6	

P value <0.05 was considered significant

between the groups with respect to staging was statistically significant ($P<0.001$). Higher the T stage, higher was the value. Serum CA 19-9 level was found to be increased (more than 37 U/ml) in 41.18% of high-grade tumors ($n=34$) and 19.51% cases of low-grade tumors ($n=41$), but its value was not statistically significant. Patients with metastatic disease had significantly higher level of CA 19-9 as compared with patients without metastasis. Only 17 of 69 patients (24.6%) had value of serum CA 19-9 more than 37 U/ml, whereas five of six patients (83.3%) with metastatic tumor had value more than 37 U/ml ($P=0.007$).

DISCUSSION

Transitional cell carcinoma is the second commonest malignancy of the genitourinary tract. It has been considered a field change disease with tumors arising at different times and sites in the urothelium.[17] The majority of urothelial tumors are superficial but recurrence rate is particularly high despite adequate resection of the primary lesion. In some patients, the tumor is primarily invasive or can subsequently progress, leading to a grave prognosis.[18] Successful management of transitional cell carcinoma of urinary bladder is largely dependent upon regular surveillance and early detection of persistent or recurrent carcinoma. The greatest challenge in the management of superficial bladder cancer is to prevent progression to invasive disease. On the other hand, 5-year survival patient with invasive bladder carcinoma is only 36 to 48% even after radical cystectomy.[19,20] Patients with invasive cancer are also at significant risk of tumor progression to either regional (lymph nodes) or distant metastasis. The standard follow-up of patients with a history of bladder cancer is based on cystoscopic examination, an invasive procedure that causes discomfort to the patients. Urine cytology has an excellent specificity with few false-positive cases, but its overall sensitivity is poor, especially for those patients with well-differentiated low-grade transitional cell carcinoma.[21] The ideal assay for bladder cancer should be noninvasive, sensitive, specific, easy, and cost effective. Several tumor markers have been developed for the diagnosis and follow up of urothelial cancers including beta human chorionic gonadotropin, CEA, NMP22, and tissue polypeptide antigen. Some of these markers are suggested to correlate with the clinical course of the disease and the response to treatment, but few of them have been routinely available for diagnosis and follow-up evaluation of urothelial carcinoma.[3,22] Therefore, an ideal tumor marker or combination of markers for patients with TCC is urgently needed. In recent years, cases of urothelial carcinoma displaying high serum level of CA 19-9 have been reported sporadically and investigators have begun studying the diagnostic significance of CA19-9 in the domain of urology as well.[14,23] CA 19-9 is a cancer-related carbohydrate antigen and is recognized by using a monoclonal antibody against colorectal cancer. Structurally, it is a Sialyl-Lewis—with sialic acid combined with lea antigen, a blood group carbohydrate. It has been shown to be useful as a tumor marker mainly for cancers of the digestive system.[10,11] The clinical usefulness of monitoring CA19-9 in urothelial carcinoma is less commonly described. The reports so far published have provided different opinions about serum CA 19-9 level in urothelial carcinoma. Some authors found no significant difference in the mean value of CA 19-9 levels between the benign disease, control and tumors, and the cases with abnormally high value were observed in 13.7% of the control group, 13.8% of the bladder cancer, and 57.1% of the upper urinary tract cancer.[15] They stated that the serum level significantly correlated with the concentration in the tumor tissue but displayed no correlation with tumor size, depth of invasion, and degree of differentiation.[15] It has also been suggested that serum levels increased significantly in urinary tract cancer patients and found that the depth of invasion of the tumor

correlated with the serum CA 19-9 level and that the serum CA 19-9 level was significantly higher in the high stage group.[22] Hegele *et al*. also reported that if CEA and CA19-9 levels are raised due to transitional cell carcinoma of urinary bladder and not due to gastrointestinal malignancies, serum levels of CEA and CA19-9 correlate well with tumor invasion and grade of malignancy.[23] However, Lynch and Cohen reported that serum CA19-9 level was not associated with the depth of invasion in their study.[24] In our study, we found that CA 19-9 level is significantly increased in higher stage group and also in the metastatic disease. There can be significant differences in the serum CA 19-9 level with regard to the following parameters: The presence or absence of metastases, presence or absence of infiltration, clinical stage, depth of invasion, and degree of differentiation. In comparison with the survival rate, prognosis is significantly poor in positive group. CA 19-9 might be useful for the prediction of prognosis and follow-up evaluation.[18] These divergent opinions may be due to the difference in the number and composition of diseases. Common to these opinions is that CA19-9 is of low value as a screening test for urothelial cancers but is useful for judging the effects of treatment and detecting the recurrence or metastasis. In this study, we observed that serum CA 19-9 level was increased in patients with urothelial carcinoma, the sensitivity of CA 19-9 for urothelial carcinoma was found to be 29.3%. Cases with invasive tumor had significantly higher CA 19-9 level in comparison to cases with superficial tumors. Patients with metastatic disease had significantly higher level of CA 19-9 than patients without metastasis. CA 19-9 level was also found to be increased in high-grade tumors as compared with low-grade tumors.

CONCLUSION

The level of serum CA 19-9 is a marker of aggressiveness of urothelial cancer and is almost invariably raised in patients with metastatic disease. Therefore, it may be used as a prognostic marker but not as a screening tool due to low sensitivity.

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