The utility of serum receptor-binding cancer antigen expressed on SiSo cells in gastrointestinal tract cancers

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BACKGROUND: Receptor-binding cancer antigen expressed on SiSo cells (RCAS1) is a novel tumour marker that has been described in various kinds of cancer. The majority of observations include immunohistochemical studies; however, there are not enough data about the utility of this antigen as a serum tumour marker and its tumour specificity.

AIM: To measure the serum levels of RCAS1 in patients with gastrointestinal (GI) tract cancers and compare them with other GI tract tumour markers.

PATIENTS AND METHODS: Sera collected from patients with GI cancers (14 esophagus, 32 gastric and 36 colon) and from healthy volunteers (30 individuals) were analyzed for RCAS1 and compared with carcinoembryonic antigen (CEA) and cancer antigen 19-9. The relationship between serum RCAS1, tumour stage and tumour grade was also evaluated.

RESULTS: Mean serum RCAS1 level was higher in patients with GI tract cancers compared with the control group (P=0.001). Among GI tract cancers, RCAS1 had lowest and highest sensitivity for esophagus and colon cancer diagnosis, respectively. Serum RCAS1 had a higher sensitivity for malignancy, except in the colon, and lower specificity in all groups compared with CEA. In comparison with cancer antigen 19-9, serum RCAS1 was more sensitive but less specific for all GI cancer groups. Mean serum RCAS1 levels were not statistically significant among histopathological tumour types (P>0.05). Although serum RCAS1 levels were significantly higher in cases with lymph node involvement compared with lymph node-negative cases (P=0.009), there was no difference between cases with and without serosal involvement, vascular invasion and distant metastasis; no correlation was found between tumour size and RCAS1 levels.

CONCLUSIONS: RCAS1 may be used and combined with CEA as a tumour marker in GI tract cancers.

Key Words: *Cancer; Gastrointestinal tract; RCAS1*

L'utilité d'un antigène cancéreux sérique lié aux récepteurs exprimé sur les cellules SiSo en cas de cancers gastro-intestinaux

HISTORIQUE : L'antigène cancéreux lié aux récepteurs exprimé sur les cellules SiSo (ACRS1) est un nouveau marqueur tumoral qui a été décrit dans divers types de cancers. La majorité des observations portent sur des études immunohistochimiques. Cependant, on ne possède pas assez de données sur l'utilité de cet antigène comme marqueur tumorale sérique et sur la spécificité de la tumeur.

OBJECTIF : Mesurer les taux sériques d'ACRSI chez des patients atteints d'un cancer gastro-intestinal (GI) et les comparer à d'autres marqueurs tumoraux GI.

PATIENTS ET MÉTHODOLOGIE : Du sérum prélevé sur des patients atteints d'un cancer GI (14 cancers de l'œsophage, 32 cancers gastriques et 36 cancers du côlon) et sur des volontaires en santé (30 personnes) a été analysé pour relever l'ACRS1, puis comparé à l'antigène carcinoembryonnaire (ACE) et à l'antigène cancéreux 19-9. Le lien entre l'ACRS1 sérique ainsi que la phase et le grade de la tumeur a également été évalué.

RÉSULTATS : Les taux sériques moyens d'ACRS1 étaient plus élevés chez les patients atteints d'un cancer GI qu'au sein du groupe témoin (P=0,001). Parmi les cancers GI, l'ACRS1 s'associait à la sensibilité la plus basse en cas de cancer de l'œsophage, et la plus élevée en cas de cancer du côlon. L'ACRS1 sérique était plus sensible à une malignité, sauf dans le côlon, et moins spécifique que l'ACE dans tous les groupes. Comparativement à l'antigène cancéreux 19-9, l'ACRS1 sérique était plus sensible mais moins spécifique dans tous les groupes de cancer GI. Les taux sériques moyens d'ACRS1 n'étaient pas statistiquement significatifs parmi les types de tumeur histopathologique (P>0,05). Bien que les taux sériques d'ACRS1 aient été considérablement plus élevés en cas d'atteinte que de non-atteinte du nœud lymphatique (P=0,009), on ne cons-tatait aucune différence entre les cas avec et sans atteinte séreuse, invasion vasculaire et métastase distante et aucune corrélation entre la dimension de la tumeur et les taux d'ACRS1.

CONCLUSIONS : L'ACRS1 peut être utilisé et combiné à l'ACE à titre de marqueur tumoral en cas de cancer GI.

Cancer antigen (CA) 19-9, carcinoembryonic antigen (CEA) and other tumour markers have been recognized over the past 20 years to be elevated in various kinds of cancers. Receptor-binding CA expressed on SiSo cells (RCAS1) is a novel tumour marker that was first described in human uterine and ovarian carcinoma (1), but the antigen has been demonstrated in other tumours (1-16). It is thought to play a protective role in tumour cells against the immune system by inhibiting clonal expansion and inducting cell death in immunocytes (6,17). Thus, there seems to be a correlation between RCAS1 expression and tumour prognosis (3,18,19).

RCAS1 expression has been detected in various digestive organs (6,7,9,12,19,20) including the gastrointestinal (GI) tract, through immunohistochemical analysis (6,21,22). However, there have not been enough data regarding its usage as a serum tumour marker in GI tumours. Hence, in the present study we aim to determine the utility of RCAS1 as a GI tumour marker in clinical practice. We also analyzed its

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TABLE 1
Serum concentrations of receptor-binding cancer antigen expressed on SiSo cells (U/mL ± SD) in relation to tumour invasion

Tumour invasion	Negative (n)	Positive (n)	P
Serosa involvement	54.27±82.42 (17)	91.62±106.11 (65)	>0.05
Lymph node involvement	29.82±16.44 (11)	92.25±107.46 (71)	<0.05
Vascular invasion	82.44±96.77 (61)	88.05±119.54 (21)	>0.05
Distant metastasis	83.47±100.1 (71)	86.50±121.09 (11)	>0.05

correlation with general tumour characteristics and compared its sensitivity and specificity with other GI tract tumour markers.

PATIENTS AND METHODS

Eighty-two patients (53 men and 29 women; aged 56.12±8.72 years) with primary GI tract cancers (14 esophagus, 32 gastric and 36 colon) underwent surgery between 2003 and 2005 in the Ankara Oncology Education and Research Hospital (Ankara, Turkey) and Ankara University Medical School (Ankara, Turkey). No distant metastases were detected in any patient at the preoperative examinations. Patients who had adjuvant therapies were excluded. A reference pathologist performed histopathological examinations. The control group included 30 healthy individuals from the hospital staff aged 52.93±20.24 years.

Sera from patients with malignancies were collected before surgery. Sera were from venous blood and were frozen immediately and stored at –25°C until the measuring time. A commercial ELISA kit (Medical and Biological Laboratories Co Ltd, Japan) was used for RCAS1 assays. The same sera was also used for CEA and CA19-9 measurements. Cut-off values for RCAS1, CEA and CA19-9 were 17.5 U/mL, 4.6 ng/mL and 37.0 U/mL, respectively.

Serum RCAS1 concentrations of 17.5 U/mL or greater were defined as positive and those less than 17.5 U/mL were defined as negative. Similarly, serum CEA and CA19-9 concentrations of 4.6 ng/mL or greater and 37 U/mL or greater, respectively, were defined as positive and those less than 4.6 ng/mL and less than 37 U/mL respectively, were defined as negative. Sensitivity was defined as the number of patients diagnosed with GI tract cancers and expressing positive RCAS1, CEA or CA19-9, divided by the total number of patients diagnosed with GI tract cancers. Specificity was defined as the number of controls with negative RCAS1, CEA or CA19-9, divided by the total number of control patients.

SPSS version 10.0 (SPSS Inc, USA) was used to analyze the data. Nonparametric Kruskal-Wallis test was used to analyze the variance among groups. Statistically significant differences obtained from Kruskal-Wallis analysis were further tested by Mann-Whitney U test for post hoc pairwise comparisons between groups. Pearson test was used for correlation analysis. P<0.05 was considered to be statistically significant.

TABLE 2
Sensitivity, specificity, positive and negative predictivity of tumour markers in gastrointestinal tract cancers

Tumour markers	Sensitivity (%)	Specificity (%)	Positive predictivity (%)	Negative predictivity (%)
Esophagus				
RCAS1	78.6	73.3	57.9	88.0
CA19-9	42.9	85.7	60.0	75.0
CEA	71.4	96.4	90.9	87.1
Stomach				
RCAS1	90.6	73.3	78.4	88.0
CA19-9	53.1	85.7	81.0	61.5
CEA	87.5	96.4	96.6	87.1
Colon				
RCAS1	91.7	73.3	80.5	88.0
CA19-9	62.9	85.7	84.6	64.9
CEA	97.1	96.4	97.1	96.4

CA Cancer antigen; CEA Carcinoembryonic antigen, RCAS1 Receptor-binding cancer antigen expressed on SiSo cells

RESULTS

Mean serum RCAS1 level (83.9±102.3 U/mL) was higher in patients with GI tract cancer compared with the control group (16.4±10.1 U/mL) (P=0.001). Patients with gastric cancer had higher RCAS1 levels than patients with esophagus and colon cancer; however, the difference was insignificant (esophagus cancer 80.7±95.7 U/mL, gastric cancer 115.3±130.4 U/mL and colon cancer 57.2±64.3 U/mL).

Mean serum CA19-9 level (45.4±27.4 U/mL) was higher in patients with GI tract cancer compared with the control group (15.9±19.6 U/mL) (P=0.001). Serum CA19-9 levels were comparable in GI tract cancer subgroups (esophagus cancer 39.1±35.6 U/mL; gastric cancer 44.4±26.5 U/mL and colon cancer 48.8±24.7 U/mL)

Mean serum CEA level (47.1±93.6 ng/mL) was higher in patients with GI tract cancer compared with the control group (1.9±1.3 ng/mL) (P=0.001). Patients with colon cancer had significantly higher CEA levels than patients with esophagus cancer (P<0.05) but lower than gastric cancer patients (P>0.05) (esophagus 16.4±18.9 ng/mL, gastric 64.4±121.6 ng/mL and colon 43.6±79.4 ng/mL).

Histopathological grades of tumours and mean serum RCAS1 levels were as follows: 13 squamous cell carcinoma (85.6±97.7 U/mL), 25 well-differentiated adenocarcinoma (81.5±112.3 U/mL), 20 moderately differentiated adenocarcinoma (96.7±105.5 U/mL) and 24 undifferentiated adenocarcinoma (74.8±96.4 U/mL) cases (P>0.05).

In all patients with GI tract cancer, RCAS1 levels were significantly higher in cases with lymph node involvement compared with lymph node-negative cases (P=0.009). However, there was no difference between cases with and without serosal involvement, vascular invasion and distant metastasis (Table 1). There was no correlation between the tumour size and RCAS1 levels (P=0.648).

Among GI tract cancers, RCAS1 had lowest and highest sensitivity for esophagus and colon cancer diagnosis, respectively (Table 2).

DISCUSSION

In the present study, we demonstrated that patients with GI tract cancer had higher serum RCAS1 levels than healthy controls. RCAS1 had higher sensitivity than CA19-9 in all tumour groups; higher sensitivity than CEA in esophagus and stomach cancers but lower sensitivity in colon cancer. We also found that the ratio of RCAS1 positivity was greater in colon and gastric cancers compared with esophageal malignancy. Serum RCAS1 level increased significantly in GI tract tumours with lymph node involvement; however, it was not correlated with tumour grade, serosal and vascular invasion or distant metastasis.

RCAS1 expression has been demonstrated with immunohistochemical analysis in esophagus, gastric and colorectal cancers (6,21,22). Its expression has been reported to be associated with aggressive tumour behaviour. Therefore, there may be a correlation between RCAS1 expression and tumour prognosis. Despite those studies demonstrating RCAS1 expression on tumour cells of the GI tract, there is only one study in the literature analyzing the serum levels of RCAS1 in GI tract tumours. Leelawat et al (22) investigated the expression of RCAS1 in colorectal cancer and measured the serum levels of the antigen. In contrast to the current study, they found that serum RCAS1 concentrations in patients with colorectal cancer were not significantly higher compared with the normal controls. They claimed that this was due to the differences in the biological features of the tumours and the limited number of serum specimens in their study. Nonetheless, cut-off values were higher in their study (greater than 22.5 U/mL in their study compared with greater than 17.5 U/mL in the present study).

Nakakubo et al (21) investigated the immunoreactivity of RCAS1 and its correlation with clinicopathological features in 95 patients who underwent surgical resection for esophageal squamous cell carcinoma. However, the expression was examined by histochemical staining rather than serum analysis. One-third of the cases were strongly positive and four of the 95 cases were negative for RCAS1 staining. They noted that RCAS1 showed significant correlations with stage grouping (stage I and II compared with stage III and IV). However, similar to our results, there was no significant correlation between RCAS1 positivity and histopathological grading, depth of invasion and distant metastasis. In contrast to our findings, there was no correlation between RCAS1-positivity and lymph node involvement. Overall, expression of RCAS1 was associated with shorter postoperative survival.

In a study performed by Nakamura et al (6), RCAS1 positivity was detected immunohistochemically in 96% of 54 gastric cancer patients. Surgical materials were compared according to staining patterns (diffuse or not). Although staining patterns correlated with size of tumours, depth of tumour invasion, histological type and lymph node metastasis in that study, clinicopathological variables did not significantly differ between RCAS1-positive and -negative cases. Surprisingly, RCAS1 was positive in all of the normal gastric epithelial cells and the majority of benign gastric disorders; this could not be explained adequately. The authors claimed that RCAS1 was also expressed in several other normal tissues (1,2) and the biological functions of RCAS1 secreted by noncancerous tissues remains to be investigated.

CEA may be useful in the preoperative staging and postoperative follow-up of patients especially with colon cancer, but it has a variable predictive value for diagnosis in asymptomatic patients (23). We found that CEA was more specific but less sensitive than RCAS1 for GI tract cancers in the present study. On the other hand, CA19-9 was the least sensitive marker for GI tract tumours in the current study.

CONCLUSION

Serum RCAS1 levels are increased in GI tract cancers. RCAS1 and CEA had comparable sensitivity in GI tract cancers; thus, both agents increased the diagnostic efficiency of each in those tumours. Further studies are needed, including comparative analysis of pre- and postoperative serum levels to determine the prognostic significance of RCAS1.

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