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• *RAPID COMMUNICATION* •

New tumor-associated antigen SC6 in pancreatic cancer

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Abstract

AIM: To examine the concentration of a new antigen SC6 (SC6-Ag) recognized by monoclonal antibody (MAb) in patients with pancreatic cancer and other malignant or benign diseases and to understand whether SC6-Ag has any clinical significance in distinguishing pancreatic cancer from other gastrointestinal diseases.

METHODS: Six hundred and ninety-five serum specimens obtained from 115 patients with pancreatic cancer, 154 patients with digestive cancer and 95 patients with non-digestive cancer were used and classified in this study. Serum specimens obtained from 140 patients with benign digestive disease and 89 patients with non-benign digestive disease served as controls. Ascites was tapped from 16 pancreatic cancer patients, 19 hepatic cancer patients, 16 colonic cancer patients, 10 gastric cancer and 6 severe necrotic pancreatitis patients. The samples were quantitated by solid-phase radioimmunoassay. The cut-off values (CV) of 41, 80, and 118 U/mL were used.

RESULTS: The average intra- and interassay CV detected by immunoradiometric assay of SC6-Ag was 5.4% and 8.7%, respectively. The sensitivity and specificity were 73.0% and 90.9% respectively. The levels in most malignant and benign cases were within the normal upper limit. Among the 16 pancreatic cancer cases, the concentration of SC6-Ag in ascites was over the normal range in 93.8% patients. There was no significant difference in the concentration of SC6-Ag. Decreased expression of SC6-Ag in sera was significantly related to tumor differentiation. The concentration of SC6-Ag was higher in patients before surgery than after surgery. The specificity of SC6-Ag and CA19-9 was significantly higher than that of ultrasound and computer tomography (CT) in pancreatic cancer patients. Higher positive predictive values were indicated in 92.3% SC6-Ag and 88.5% CA19-9, but lower in 73.8% ultrasound and 76.2% CT.

CONCLUSION: The combined test of SC6-Ag and CA19-9 may improve the diagnostic rate of primary cancer. The detection of SC6-Ag is valuable in the diagnosis of pancreatic cancer before and after surgery.

Key words: Tumor antigen SC6; Pancreatic neoplasm; Immunoradiometric assay

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INTRODUCTION

Pancreatic cancer is the fourth or the fifth leading cause of cancer-related deaths in the Western world[1,2]. Approximately 50% of pancreatic cancer patients have metastatic disease at the time of diagnosis with a median survival of 3-6 mo[2,3]. However, even 70-80% of patients, whose tumor could be completely removed, suffer from an incurable local relapse, distant metastases, or peritoneal carcinosis[4,5]. The overall 5-year survival rate of pancreatic cancer patients is only 1%[6,7]. Ultrasound, computer tomography (CT), magnetic resonance imaging and other methods have made it easier to define the late-stage disease and to establish its diagnosis. Unfortunately, these imaging and diagnostic methods cannot detect the early-stage disease[8-11].

In recent years, there has been an increasing clinical attention to the role of tumor markers in the pathogenesis of pancreatic cancer[12-14]. The most widely used marker for pancreatic cancer is CA19-9[15-18]. CA19-9 has a mean sensitivity of 81% and a mean specificity of 90% for pancreatic cancer[19-23]. Other mucin-type markers such as CA50, CA242, DU-PAN2, CA195 and CAM17.1/WGA have also been described for pancreatic cancer[24-28]. These markers have been investigated less widely than CA19-9 but available evidence appears to provide similar data[29-33]. CA19-9 remains as the "gold standard marker"[10] against which tumor markers for pancreatic cancer are evaluated.

Antigen SC6 (SC6-Ag) recognized by monoclonal antibody SC6 (MAb SC6) against human colonic cancer is a relatively new marker compared with CA19-9, CA242, CEA, AFP, DU-PAN-2 and β_2-MG[34-36]. The antigen was purified by immunoaffinity chromatography using the MAb SC6 at our laboratory. The results of SDS-

PAGE, Western blotting and amino acid analysis indicate that SC6-Ag is a glycoprotein with a molecular weight of 67 kμ and contains 18 amino acids. An immunoradiometric sandwich assay of SC6-Ag has been established by us[37]. The diagnostic value of SC6-Ag was evaluated in patients with pancreatic cancer. The sensitivity and specificity of SC6Ag for patients with pancreatic cancer are similar to those of CA 19-9 detected by radioimmunodetection[38]. Therefore, in the present study, we analyzed and compared the pattern of SC6Ag expression in pancreatic cancer and other gastrointestinal cancers to evaluate whether it might be also of high biological strategy in the diagnosis of pancreatic cancer.

MATERIALS AND METHODS

Patients

Serum specimens were obtained from 115 patients with pancreatic cancer (41 females and 74 males, mean age 61 years, with a range of 39-80 years). Among them, 39 had well-and moderately-differentiated tumor, 55 had poorly-differentiated tumor and 21 had differentiated tumor with unknown reason. According to International Union Against Cancer criteria, 9 patients had stage I disease, 33 stage II, 46 stage III and 6 stage IV. Fifteen primary esophageal cancer specimens, 43 gastric cancers specimens, 11 specimens of cancer of papilla of Vater, 39 hepatocellular carcinoma specimens and 46 colonic cancer specimens were classified. Fifteen esophagitis patients (5 females and 10 males; mean age 41 years), 27 gastritis patients (11 females and 16 males; mean age 38 years), 16 papilla of Vater cancer patients (7 females and 9 males; mean age 43 years), 28 pancreatitis patients (15 females and 13 males; mean age 35 years), 23 cirrhosis patients (10 females and 13 males; mean age 44 years) and 31 colitis patients (17 females and 14 males; mean age 35 years) were obtained. The diagnosis of pancreatic cancer was made based on histology and clinical and radiological findings. We noted weight loss, duration of symptoms and tumor position. Other cancers were diagnosed by abdominal ultrasound and CT scan, surgery and pathology. Ninety-five cancers involving lung and bladder were determined. Fifteen out of 42 suspicious patients before surgery were diagnosed having pancreatic cancer after surgery. CA 19-9 was examined in the same samples. Ascites was tapped from 16 pancreatic cancer patients, 19 hepatic cancer patients, 16 colonic cancer patients, 10 gastric cancer and 6 severe necrotic pancreatitis patients.

Sample collection

Blood samples were obtained from all the subjects after an overnight fast. The plasma was immediately separated by centrifugation. The samples were frozen and stored at -20 °C until assay.

Radiolabeling of MAb SC6

MAb SC6 is a murine MAb of the IgG1 isotype against purified antigen SC6 from human colonic cancer tissues as described previously[34-36]. MAb SC6 was isolated from the ascitic fluid of BALB/C mice in which hybridoma cell line SC6 was injected intraperitoneally and purified by protein A-Sepharose 4B columns (Bioinstitute, Shanghai, China). Normal murine immunoglobulin (IgG1, Bioinstitute, Beijing, China) was used as nonspecific control antibody. The MAb was labeled with $Na^{125}I$ by the iodogen method. The average intra- and interassay CV of the method was 5.4% and 8.7% respectively. The recovery rate was 96.5-108.0%, average 102.3%.

Sandwich measurement by radioimmunoassay

After the MAb SC6 was labeled, ^{125}I uncombined with MAb SC6 was separated from bound iodine by gel filtration on a Sephadex G-25 column. Microtiterplates (96-well) were coated with MAb SC6 (20 ng/mL, 100 μL/well) overnight and then incubated with 100 μL/well of 3% bovine albumin in phosphate-buffered saline at 37 °C for 2.5 h. Standard SC6-Ag, various sera, quantity control sera and nonspecific control were incubated at 37 °C for 1 h. ^{125}I-MAb SC6 (25 ng/mL, 100 μL/well) was coated at 37 °C for 3 h and the radioactivity of each well was determined with a Gamma counter (Instrument Factory, Xian, China). After each step, the wells were washed four times with phosphate-buffered saline.

The cut-off values (CV) of SC6-Ag were determined and expressed as mean±SD. The SC6-Ag concentration in sera of controls was lower than CV. The CV of 41 U was mean±2SD, 80 U was mean±3SD, 118 U was mean±4SD. CA 19-9 kit (Abbott Diagnostics, USA) was quantitated by solid-phase radioimmunoassay, CV of 37 U/mL were used.

Statistical analysis

Analysis was performed using SPSS 10.0 software package. For the comparison of various tumor markers, CV representing 90% and 95% specificity levels in patients with relevant benign diseases were determined. The correlation between SC6-Ag and CA 19-9 concentrations was calculated by linear regression using the logarithms of the serum levels. The statistical comparison of multifactors was made and results were significant ($P<0.05$).

RESULTS

SC6-Ag levels in pancreatic cancer and other diseases

The characteristics of the 695 patients are presented in Table 1. Low concentration SC6-Ag was found in the sera from 102 healthy individuals and the cut-off of its normal upper limit was 41 U/mL (20.7±9.8). Among the 115 patients with pancreatic cancer, the cut-off was over the normal range in 73.3% patients, more than 118 U/mL in 48.7% patients and over 41 U/mL in 29.9% patients. The SC6-Ag level was mainly elevated in colonic cancer, hepatic carcinoma and gall bladder tract/bile duct cancers. Non-digestive cancers were mainly non-small cell lung cancer and renal carcinoma. Lower levels of SC6-Ag were observed in benign digestive and non-digestive diseases

Table 1 SC6-Ag levels in patients with malignant and benign disease

Groups	Cases	>41 U/mL	>80 U/mL	>118 U/mL
		n (%)	*n* (%)	*n* (%)
Control	102	7 (6.9)	2 (2.0)	0 (0.0)
Pancreatic Ca	115	84 (73.0)	68 (59.1)	56 (48.7)
Digestive Ca	154	46 (29.9)	24 (15.6)	11 (7.1)
Non-digestive Ca	95	11 (11.6)	8 (8.4)	4 (4.2)
Benign digestive Diseases	140	13 (9.3)	9 (6.4)	2 (1.4)
Non-benign digestive Diseases	89	8 (9.0)	4 (4.5)	0 (0.0)

Table 2 SC6-Ag concentration in ascites from patients with different digestive diseases (mean±SD)

Groups	Cases	SC6-Ag (U/mL) Concentration	>41	>80	>118
			n (%)	*n* (%)	*n* (%)
Pancreatic Ca	16	120.9±109.1	15 (93.8)	11 (68.8)	7 (43.8)
Hepatic Ca	19	55.7±33.4	10 (52.6)	3 (15.8)	1 (5.3)
Colonic Ca	16	54.9±36.7	9 (56.3)	4 (25.0)	1 (6.3)
Gastric Ca	10	38.1±23.4	3 (30.0)	1 (10.0)	0 (0.0)
Several pancreatitis	6	30.9±26.3	2 (33.3)	0 (0.0)	0 (0.0)

mainly including acute pancreatitis and obstruction of gall bladder/bile duct and acute renal impairment.

Relationship between SC6-Ag and clinicopathological factors

SC6-Ag was not significantly related with clinicopathological factors in patients with pancreatic cancer. Decrease of SC6-Ag in the pancreatic head was compared with that in its body and tail. However, the difference failed to reach statistical significance ($P>0.05$).

SC6-Ag concentration in ascites from patients with different digestive diseases

Among the 16 patients with pancreatic cancer, the concentration of SC6-Ag in ascites was over the normal range in 93.8% patients, over 41 U/mL in 33.3-52.6% patients and more than 118 U/mL in 43.8% patients (Table 2).

Parameters for SC6-Ag, CA19-9, ultrasound and CT in patients with pancreatic cancer

The sensitivity of SC6-Ag and CA19-9 was similar to that of ultrasound and CT, while the specificity of SC6-Ag and CA19-9 was significantly higher than that of ultrasound and CT in patients with pancreatic cancer. Higher positive predictive values were found in 92.3% SC6-Ag and 88.5% CA19-9, but lower positive predictive values were found in 73.8% ultrasound and 76.2% CT (Table 3).

Table 3 Comparison of parameters for SC6-Ag, CA19-9, ultrasound and CT in patients with pancreatic cancer

	SC6-Ag (%)	CA19-9 (%)	Ultrasound (%)	CT (%)
Sensitivity	73.0 (84/115)	84.3 (97/115)	82.6 (95/115)	83.5 (96/115)
Specificity	90.9 (70/77)	84.4 (65/77)	55.8 (43/77)	59.7 (46/77)
Positive predictive value	92.3 (84/91)	88.5 (92/104)	73.8 (96/130)	76.2 (99/130)
Negative predictive value	69.3 (70/101)	73.9 (65/88)	69.4 (43/62)	74.2 (46/62)

DISCUSSION

It is obvious that early diagnosis has the greatest impact on the survival of patients with pancreatic cancer. Clinically, fast spiral CT using dynamic intravenous contrast and the potential for improved MRI can provide high-resolution images of small masses[9-13]. Endoscopic retrograde cholangiopancreatography with improved cytology, brushes, and biopsy forceps should enhance preoperative diagnosis of this malignancy. Endoscopic ultrasound also may help detect small lesions and determine the depth of invasion and vascular involvement. Tumor markers are normally produced in low quantities by cells in the body. Detection of a higher serum level of tumor markers by radioimmunoassay or immunohistochemical techniques usually indicates the presence of a certain type of cancer. In some types of cancer, tumor marker levels may reflect the extent or stage of the disease and can be useful in its diagnosis. Recently, the most widely used marker for pancreatic carcinoma is CA19-9, but SC6-Ag has also been found in China[34-38].

In the present study, high levels of SC6-Ag over the normal upper limit (41 U/mL) were found in 73.0% patients with pancreatic cancer, and in 29.8% patients with other digestive tumors. Using a cut-off point of 80 U/mL, the proportion of patients with elevated levels was 59.2%. But over 118 U/mL SC6-Ag was detected in 48.7% patients with pancreatic cancer, in 5.8% patients with digestive cancers, in 4.2% patients with non-digestive carcinoma and in 2% patients with benign digestive diseases. Furthermore, patients with certain benign diseases such as jaundice and pancreatitis, may present with elevated levels of CA19-9[12-14], suggesting that SC6-Ag and CA19-9 may have similar value in the diagnosis of pancreatic cancer.

Increased SC6-Ag concentrations in ascites are not specific for adenocarcinoma of the pancreas when the CV is 41 U/mL, which was evaluated in other digestive tumors and pancreatitis in our study (Table 2). With a cut-off point of 118 U/mL, the respective specificities for patients with pancreatic cancer were high compared to patients with gastric cancer or pancreatitis, indicating that high SC6-Ag level can be used to distinguish pancreatic cancer from benign disorders. However, decreased level of SC-Ag in pancreatic head compared to that in its body and tail failed to reach statistical significance, and there was no relationship between SC-Ag and tumor stage, size and duration ($P>0.05$).

Up to now, it is difficult to diagnose pancreatic cancer using one of the tumor markers because tumor marker levels can be elevated in patients with benign conditions.

In the recent study, the sensitivity, specificity and positive predictive value of SC6-Ag were found to be 73.0%, 90.9% and 92.3%, respectively. By analyzing the four factors, we found that the sensitivity of SC6 and CA19-9 was lower than that of ultrasound and CT, but their specificity was significantly higher (Table 3). Positive predictive values in SC6-Ag and CA19-9 were 92.3% and 88.5%, which were distinctly higher than those of ultrasound (73.8%) and CT (76.2%). The lack of sensitivity and specificity also limits the diagnosis of pancreatic cancer although CA19-9 and SC6-Ag may be useful in differentiating benign from malignant pancreatic disease in non-jaundiced patients. However, combined measures are more useful in the diagnosis of pancreatic cancer.

In conclusion, detection of SC6-Ag is valuable in the diagnosis of pancreatic cancer before and after surgery. The combined test of SC6-Ag and CA19-9 may improve the diagnostic rate of primary cancer.

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