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ORIGINAL PAPER

Seropositivity for MIA and S100 in patients with gastrointestinal carcinomas

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Serum levels of melanoma inhibiting activity (MIA) and S100, both markers in malignant melanoma, are increased only in few patients with non-melanocytic tumors. We examined a series of serum samples from patients with colorectal (CRC) (*N*=56), gastric (GC) (*N*=43), pancreatic (PC) (*N*=29), hepatocellular (HCC) (*N*=30), cholangiocellular and gallbladder carcinoma (CCC) (*N*=18). MIA and S100 were measured by commercially available assays. Positive serum levels for MIA and S100 were found in 16.1% and 5.4% of the patients with CRC, 11.6% and 9.3% with GC, 34.5% and 13.8% with PC, 0% and 30% with HCC and 16.7% with CCC, respectively. All patients with sera positive for either MIA or S100 suffered from advanced tumors and received palliative treatment. Elevated serum levels of MIA and S100 are frequent in patients with gastrointestinal cancer. Further investigation is warranted to define the role of MIA or S100 seropositivity in gastrointestinal cancer with regard to follow-up.
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Keywords: melanoma inhibiting activity; S100; tumor marker; ELISA; gastrointestinal carcinomas

Introduction

MIA and S100 are regarded as the most sensitive serum markers in malignant melanoma. Enhanced serum levels especially are measured in stage III and IV disease.[1,2] Both proteins are an important aid for staging, detection of tumor progression or recurrence and monitoring therapy.[3,4] Their biological function is still barely understood. While previous studies have seldom found significant MIA or S100 serum levels in non-melanocytic tumors, we more often observed this in patients with gastrointestinal carcinomas. To further confirm these observations we examined a series of serum samples from patients with colorectal (CRC), gastric (GC), pancreatic (PC), hepatocellular (HCC), cholangiocellular and gallbladder carcinoma (CCC) in this study.

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Materials and methods

Patients

Serum samples were randomly collected from patients with gastrointestinal carcinomas referred to our oncology unit. Samples were analyzed from 56 patients with colorectal carcinoma, 43 patients with gastric carcinoma, 29 patients with pancreatic carcinoma, 30

patients with hepatocellular carcinoma and 18 patients with cholangiocellular or gallbladder carcinoma. Most of the patients suffered from advanced tumors. The diagnoses were based on histological examination. Patients' data are summarized in Table 1.

Detection of MIA and S100 in serum

MIA and S100 were measured by commercially available assays: a one-step ELISA (MIA ELISA, Boehringer Mannheim, Mannheim, Germany) and a monoclonal two-site immunoluminometric assay (LIA-mat Sangtec 100 and LIA-mat Starter-Kit, Byk-Sangtec Diagnostica, Dietzenbach, Germany). Using the provided internal standard reagents the manufacturer's instructions were precisely followed. All sera were coded and stored at $-80^{\circ}C$ until analysis. The technician who performed the assays was unaware of clinical information and patients' data. In another study by our group concerning malignant melanoma we measured MIA and S100 in healthy volunteers to define appropriate cutoff values.[5] Evaluating 38 serum samples, 95th percentiles were found with MIA 7.9 ng/ml and S100 0.11 µg/l. In none of the controls were MIA or S100 elevated above upper limits determined in larger reference groups examined elsewhere and recommended by the manufacturers.[2] Since the cutoff values we found were similar to those, namely MIA 6.5 ng/ml and S100 0.12 µg/l, we decided to use the latter in our analysis. Reproducibility of test results was confirmed by measuring repeatedly eight standard sera using different ELISA lots.

Results

MIA serum levels in patients with gastrointestinal carcinomas varied between 0.0 and 64.9 ng/ml. All sera from patients with hepatocellular carcinoma were negative, whereas 5 (11.6%) of 43 sera from patients with gastric carcinoma, 9 (16.1%) of 56 sera from patients with colorectal carcinoma, 3 (16.7%) of 18 sera from patients with cholangiocellular carcinoma and 10 (34.5%) of 29 sera from patients with pancreatic carcinoma were positive (Figure 1, Table 2).

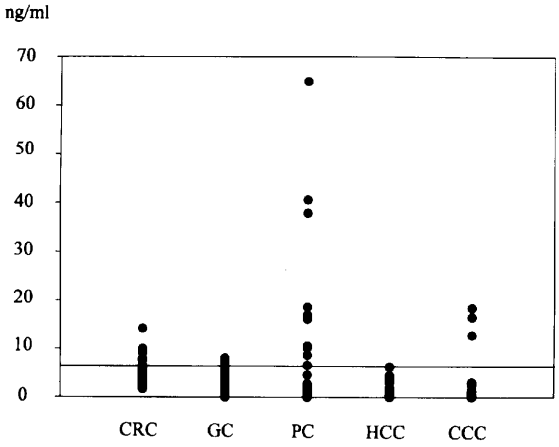

Figure 1 *MIA serum levels in gastrointestinal cancer. (Cutoff 6.5 ng/ml; CRC, colorectal cancer; GC, gastric cancer; PC, pancreatic cancer; HCC, hepatocellular cancer; CCC, cholangiocellular cancer).*

Table 1 Patients' characteristics

	Colon cancer	*Rectum cancer*	*Colorectal cancer*	*Gastric cancer*	*Pancreatic cancer*	*HCC*	*CCC*
N	46	10	56	43	29	30	18
Male/female	20/26	9/1	29/27	26/17	17/12	23/7	9/9
Age (yr) (mean ± s.d.)	63.4 ± 8.4	60.1 ± 12.3	62.8 ± 9.1	57.0 ± 11.4	57.0 ± 7.2	57.5 ± 13.5	55.6 ± 10.8

Table 2 MIA and S100 seropositivity

	Colon cancer	*Rectum cancer*	*Colorectal cancer*	*Gastric cancer*	*Pancreatic cancer*	*HCC*	*CCC*
N	46	10	56	43	29	30	18
MIA (%)	7 (15.2)	2 (20)	9 (16.1)	5 (11.6)	10 (34.5)	0	3 (16.7)
S100 (%)	3 (6.5)	0	3 (5.4)	4 (9.3)	4 (13.8)	9 (30)	3 (16.7)
Both positive (%)	2 (4.3)	0	2 (3.6)	1 (2.3)	2 (6.9)	0	0

The corresponding S100 serum levels ranged from 0.0 to 1.065 µg/l. 3 (5.4%) of 56 sera from patients with colorectal carcinoma, 4 (9.3%) of 43 sera from patients with gastric carcinoma, 4 (13.8%) of 29 sera from patients with pancreatic carcinoma, 3 (16.7%) of 18 sera from patients with cholangiocellular carcinoma and 9 (30%) of 30 sera from patients with hepatocellular carcinoma scored positive. Only in the subgroup of patients with rectal carcinoma were all sera negative (Figure 2, Table 2).

All patients with sera positive for either MIA or S100 suffered from advanced tumors and received palliative treatment.

Discussion

In the present study elevated serum levels of MIA or S100 were observed in up to more than 30% of patients with gastrointestinal carcinomas.

Pathological MIA concentrations were especially found in sera of patients with pancreatic carcinoma. In these patients the highest values could also be detected. MIA serum levels did not exceed normal range in patients with hepatocellular carcinoma. In non-neoplastic tissue MIA is expressed in developing and mature cartilage.[2,6] In addition to malignant melanoma elevated serum levels were observed in some patients with sepsis and advanced epithelial tumors, e.g. in 17% of patients with pancreatic carcinoma and 7.3% of patients with colon carcinoma. By reverse PCR analyses MIA mRNA expression was detected in breast and colon cancer specimens, so that unspecific binding can be ruled out.[2]

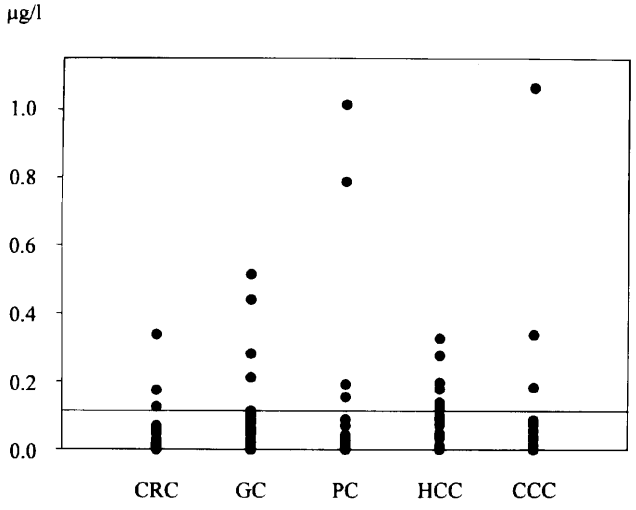

Figure 2 *S100 serum levels in gastrointestinal cancer. (Cutoff 0.12 µg/l; CRC, colorectal cancer; GC, gastric cancer; PC, pancreatic cancer; HCC, hepatocellular cancer; CCC, cholangiocellular cancer)*

Elevation of S100 was most often observed in patients with hepatocellular carcinoma. The maximum concentration of S100 was measured in sera of patients with cholangiocellular or gallbladder carcinoma. In all patients with rectal carcinoma S100 serum levels were normal. S100 is found in a variety of cells and tissues, e.g. in melanocytes, adipocytes, striated muscles, heart, kidney and especially the nervous system.[7–13] So it has been suggested to be not only a sensitive marker of malignant melanoma but also of brain damage in patients with cerebral lesions, after minor head injury or extracorporal circulation.[14–21] However, there was no evidence for cerebral metastases in the 23 S100 positive patients and only one of them had a history of seizures. Six of these patients suffered from cholestasis with serum bilirubin ≥ 2 mg/dl, which suggests a possible influence of liver function on S100 serum levels. Previous immunohistochemical studies regarding S100 in epithelial tumors have shown inconsistent results. While some could not detect this marker in gastrointestinal carcinomas, others found S100 positivity in up to 50%.[22–24] In a serologic study using the same test assay as in the present examination only 5% of sera from patients with advanced carcinomas including pancreatic and colon cancer scored positive.[2] We speculate that this may be put down to an influence of differences in tumor grading on S100 expression.

In summary this study confirms the observation of elevated serum levels of MIA and S100 in patients with gastrointestinal carcinomas. Depending on still unknown influence factors the percentage of positive sera in a sample collective may be higher than previously expected. So one should not only think of malignant melanoma if patients appear with pathological MIA or S100 serum levels. Further investigation is necessary to define the role of MIA or S100 seropositivity in gastrointestinal carcinomas with regard to follow-up.

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