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Carcinoembryonic Antigen in the CSF of Cancer Patients – the value of intrathecal synthesis and correlation with IgA-diffusion dynamics

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Abstract

Objective: the diagnostic impact of carcinoembryonic antigen (CEA) was evaluated in serum and CSF of cancer and control patients.

Methods: 97 analyses of CEA in CSF and serum from 83 cancer patients were compared with 41 cases without malignancy. CEA diffusion dynamics were evaluated with IgA CSF/serum quotients (Q IgA). Intrathecal synthesis of CEA was analysed both by calculating an index Q CEA/Q IgA and within the IgA-diagram.

Results: in 73 samples without synthesis of IgA or CEA, both quotients correlated well with a mean Q CEA/Q IgA of 1.1 (95% CI 0.97-1.2). The Q CEA/Q IgA was significantly higher in metastasizing adenocarcinomas than in controls or other malignancies. In leptomeningeal disease from adenocarcinoma, Q CEA/Q IgA was significantly higher than in controls, while patients with CNS and/or bone metastases had intermediate values. The sensitivity to detect leptomeningeal disease was 91% and 69% for brain metastases. Q CEA/Q IgA and CEA synthesis assessed with the IgA diagram were equally sensitive.

Conclusions: evaluation of CEA in the IgA diagram is feasible and of clinical value. The consideration of intrathecal CEA synthesis correlates better with the clinical status than absolute CSF-CEA or the correlation with albumin.

Key words: Carcinoembryonic Antigen; CEA; CSF; meningeal carcinomatosis.

Introduction

CEA is a glycoprotein first described in 1965 (1). It has a molecular weight of 180 kD (2) and is constitutively expressed in intestinal mucosa and other epithelia (3, 4). Overexpression of CEA is found in the tissue of colorectal cancer and, to a lesser extent, in stomach, breast or lung cancer (5). CEA can be found in low concentration in the serum of healthy individuals. Moderately elevated levels of serum CEA are known in benign liver disease or pancreatitis. Highly elevated levels are caused by malignant diseases, predominantly in colorectal cancer, but also in stomach, breast or lung cancer, and associated with activity and dissemination of the disease (6).

While solid metastases into bone and central nervous system structures can be shown with radiologic methods, the diagnostic sensitivity and specificity of radiology or CSF cytology for the detection of meningeal involvement are limited. Therefore, a marker of solid CNS or meningeal involvement would be valuable to supplement cytologic and radiologic methods.

The clinical impact of CSF-CEA concentrations has been examined in numerous studies (7-13). Usually, the detection of malignant disease was based on the assessment of absolute values of CSF-CEA and limits of normal values set to 1-4 ng/mL (14, 15). With 4 ng/mL, a sensitivity for the detection of leptomeningeal involvement of 31% with a specificity of 90% was achieved (15). With 1 ng/mL, the sensitivities ranged from 73% (14) to 82% (11) for leptomeningeal disease and achieved a sensitivity of 27% for brain metastases (11).

In a previous study, our group intended to achieve a better sensitivity and specificity for the detection of leptomeningeal involvement by calculating a quotient of CEA in CSF and serum (Q CEA) and correlating it with the CSF/serum albumin quotient (Q A). With this strategy, misinterpretations of CSF-CEA levels that were elevated by high serum concentrations or by disturbance of the blood brain barrier should be avoided. By such, a sensitivity of 89% for leptomeningeal disease and of 47% for brain metastases was achieved (16). The molecular weights of albumin (66kD) and CEA (180kD), however, differ considerably, which may cause different diffusion kinetics especially in patients with slow CSF flow. Therefore, in the last years, the Q CEA

was evaluated with the IgA diagram (17) in our laboratory to detect intrathecal CEA-synthesis. Alternatively, in patients without IgA synthesis, a quotient Q CEA / Q CEA may be valuable to detect intrathecal CEA synthesis.

In the study presented here, we reviewed retrospectively analyses of patients with neoplastic and non-neoplastic disease for the results of CEA in CSF and serum. The aim of the study was to evaluate if the diffusion kinetics of CEA are comparable to those of IgA, as it has to be expected from the molecular weights, and if the analysis of the Q CEA synthesis with the IgA diagram or the coefficient Q CEA / Q IgA are reliable indicators of neoplastic involvement of the CNS.

Materials and methods

We evaluated retrospectively 138 analyses of CSF / serum pairs from 83 patients with and 41 patients without malignant disease which had been performed between 1990 and 2004 as routine diagnostic in our laboratory because of known or suspected malignant disease.

CEA measurement in CSF and serum

CEA concentrations in CSF and serum were measured with the COBAS CORE CEA-EIA II Kit (Roche Diagnostics Mannheim, Germany). CEA-EIA II is a one-step, solid phase sandwich bead-ELISA for automated analyses. Up to 3 mL CSF (depending on the amount of CSF available) and 200 μl serum were incubated overnight with a polystyrene bead coated with anti-CEA (clone C 19), for antigen trapping, and with monoclonal mouse clone T 84 conjugated with horseradish peroxidase. After a washing procedure, the enzyme reaction was started with COBAS CORE substrate. The resulting fluid was pipetted into a microtitre plate and measured separately. Signal intensities were compared with a dilution standard.

Correlation of IgA and CEA and clinical impact

To assess if CEA and IgA follow similar kinetics for the diffusion from the serum into the CSF, samples from both control and tumor patients without synthesis of IgA or CEA – as evaluated in the IgA diagram – were selected. Analyses in which the CSF-CEA concentration could not be determined were excluded.

At first, we analyzed the correlation between Q CEA and Q IgA by linear regression. Additionally, the correlation between the CSF/ serum coefficients of IgA and CEA was calculated and an index Q CEA / Q IgA assessed for samples without IgA synthesis. For this index, 95, 98 and 99% confidence intervals were calculated to assess variability and limits of normal values. This index was compared with the evaluation of CEA synthesis within the IgA diagram. To evaluate the clinical impact of both Q CEA / IgA index and CEA synthesis, we compared patients without and with malignant disease, grouped for patients with adenocarcinomas or other histology, with different stages of metastases or with leptomeningeal involvement.

Statistical analyses

To evaluate the correlation between CEA and IgA, CSF/ serum coefficients were compared with linear regression. The importance of CEA-synthesis in the CSF was analyzed by calculation of an index Q CEA/ IgA for each analysis and comparison of the indices with the Kruskal Wallis Test. Specificity and sensitivity of indices and calculation of CEA synthesis were calculated with the 2 × 2 table.

Results

In total, 138 analyses of CSF/ serum pairs could be included into this retrospective study: 97 analyses from 83 patients with neoplastic diseases and 41 analyses from patients without active neoplasms. Malignancies of the samples analysed were: adenocarcinoma (56), small cell carcinoma (5), lung cancer, non-small cell, non-adeno (6), haematological malignancy (5), glioblastoma (3), melanoma (2), carcinoma of unknown primary with unknown histology (3), malignant fibrous histiocytoma, renal cell carcinoma and hepatocellular carcinoma (1 each). Adenocarcinomas included breast carcinoma (29), lung cancer (5), gastrointestinal (11), urinary tract (6), and unknown primary (5). Diseases of the patients in which a malignant disease had been excluded in the further course of treatment were: inflammatory CNS-disease (n = 11), CNS infections (15), neurodegenerative disease (5), vascular disease (4), epileptic fit (3), vertebral spine degeneration (2), headache (1). Five of these patients had a history of previous malignant disease. The specimens were sent by the departments of Neurology, Neurosurgery, Psychiatry and Hematology / Oncology.

In 2 control patients and 1 cancer patient, no exact CSF-CEA value could be measured due to an insufficient amount of CSF available for the analysis.

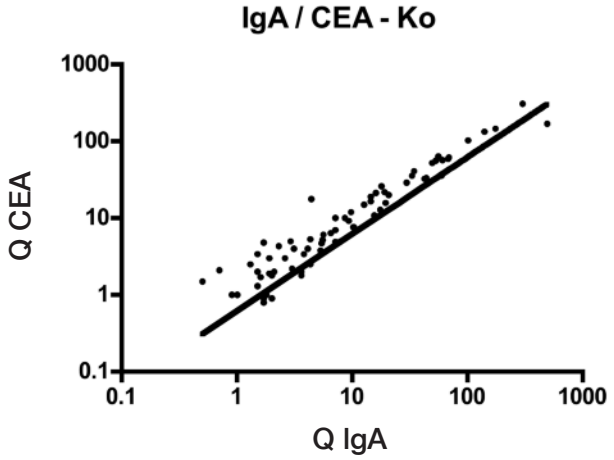

FIG. 1. — The correlation between the CSF/ serum coefficients show that Q CEA tends to be slightly higher than Q IgA.

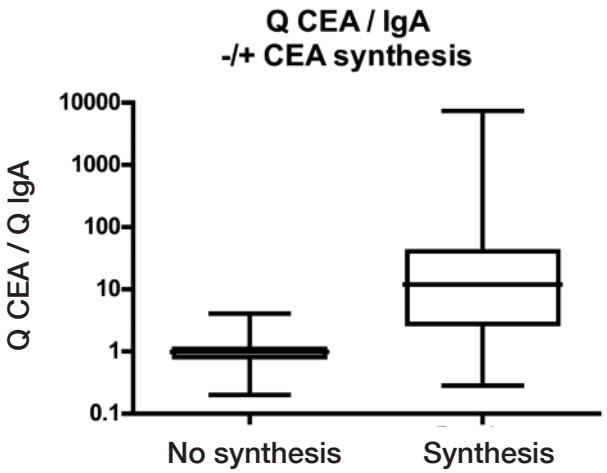

FIG. 2. — Q CEA/ Q IgA is significantly higher in cases with CEA synthesis, indicating the validity of both methods.

Correlation of IgA and CEA coefficients

First we analyzed if the coefficients of IgA and CEA correlate as well as could be expected from the molecular weight. To this end, we pooled all analyses that showed no synthesis of CEA or IgA in the control and the tumor group and compared the values with linear regression. In those 73 analyses, the IgA CSF/ serum coefficients correlated significantly with the CEA coefficient ($P < 0.0001$, Fig. 1). The mean CEA coefficient was 1.11 (SD ± 0.62) of the IgA coefficient. The 95% confidence intervals (CI) were 0.97-1.2, the 98% CI 0.94-1.29 and the 99% CI was 0.92-1.31.

Correlation with the clinical course

To evaluate the clinical impact of the CEA analyses, we evaluated the index Q CEA / Q IgA and the CEA synthesis as assessed with the IgA diagram and compared both methods (Fig. 2). In the controls without history of systemic malignancy and in malignancies other than adeno- or small cell carcinomas, the median and mean Q CEA / Q IgA were within the 98% CI (Table I). In samples of patients with adenocarcinomas, the Q CEA / Q IgA was significantly elevated as compared with control patients ($p < 0.01$, Fig. 3). In patients with small cell carcinomas, a non-significant trend towards elevation of the Q CEA / Q IgA was observed. In one patient with malignant melanoma, the Q CEA / Q IgA was elevated to 4.0. In one of five cases of lymphoma, synthesis of CEA in the CSF was found. In all other neoplasms, the median and mean Q CEA / Q IgA were within the 98% CI. No elevation of the Q CEA / Q IgA index was seen in 3 patients with glioblastomas and in one patient each with malignant fibrous histiocytoma, hepatocellular or renal cell carcinoma. *CEA synthesis was found in seven of 83 patients (8%) with negative conventional cytology but elevated cell counts. Of these, six patients also had elevated CSF lactate levels. Occult leptomeningeal disease, as observed in adherent types of neoplastic meningitis, can not be absolutely excluded in these cases.*

The more detailed analysis of the adenocarcinomas showed that the Q CEA / Q IgA of patients with positive CSF cytology was significantly higher than in the control group ($P < 0.001$) and in patients without known metastases ($p < 0.05$; Fig. 4). In patients with bone or CNS metastases, the Q CEA / Q IgA tended to be higher than in controls or patients without known metastases and lower than in patients with meningeal disease ($p > 0.05$). The sensitivity for CSF disease was 91% both for a Q CEA / Q IgA index over 1.5 and for CEA synthesis. The sensitivity for the detection of brain metastases was 69% for both methods. The specificity calculated for the control group was higher with CEA synthesis (94%) than with the index (81%; Table II), but 67% for the index and 56% for the synthesis in the group without known metastases.

Discussion

In the retrospective study presented here, we evaluated the correlation of 138 analyses of CEA in CSF/ serum pairs of patients with neoplastic and non-neoplastic disease for the correlation with IgA values and the involvement of the central nervous system (CNS).

Table I

Medians and means ± standard deviation (SD) of the index Q CEA/ Q IgA in different groups. The positivity of the index ≥ 1.5 is compared with the CEA synthesis as calculated in the IgA diagram in patients with exact values of CSF-CEA and IgA. Patients with previous history of cancer (5 pts.), or with IgA synthesis (2 pts.) were excluded. In the analysis of the adenocarcinoma group, only patients with known extent of their disease were included

	n	Q CEA / Q IgA Median	Q CEA / Q IgA Mean ± SD	Q CEA/IgA ≥ 1.5 (%)	CEA Synthesis % of samples
No CEA Synthesis	73	1.0	1.1 ± 0.62	12	0
CEA Synthesis	42	13.5	315 ± 1191	93	100
Controls	31	1.1	1.35 ± 0.8	19	6
Adeno	64	2.7	223.4 ± 974.4	69	65
SCC	8	1.3	5.6 ± 10.8	38	50
Other	9	1.0	1.2 ± 1.1	11	11
Adeno no mets.	9	1.0	3.4 ± 4.8	33	44
Adeno bone mets.	8	2.4	89.5 ± 235.1	63	50
Adeno CNS mets.	13	2.5	13.5 ± 16.2	69	69
Adeno CSF Involv.	19	19.4	590.5 ± 1615	91	91

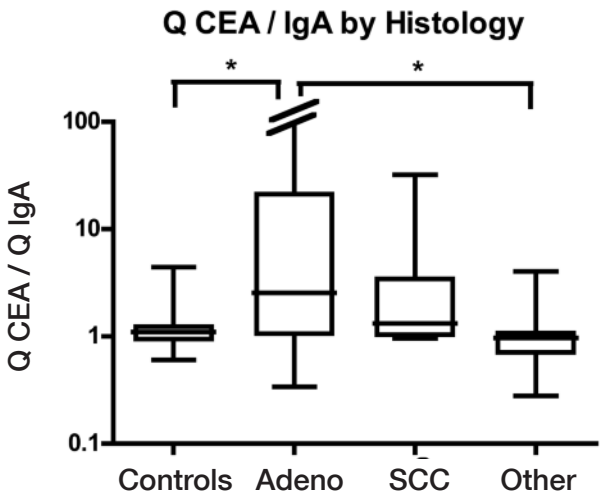

FIG. 3. — Levels of Q CEA/ Q IgA in controls and different malignancies. SCC = small cell lung cancer.

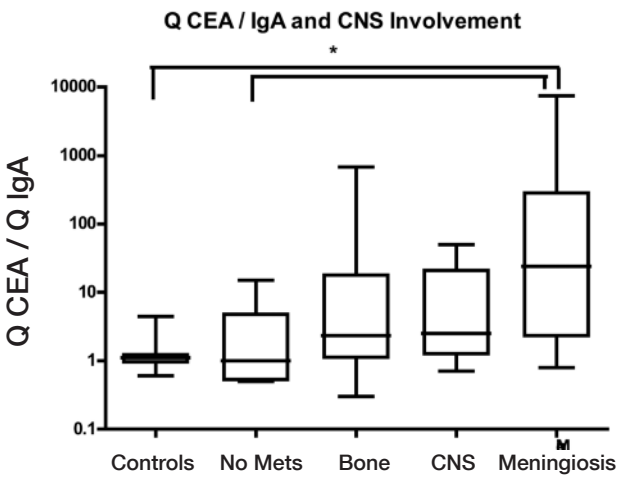

FIG. 4. — Levels of Q CEA/ Q IgA in patients with adenocarcinoma or scc grouped by extent of metastases.

In cases of unknown origin of symptoms, the analysis of CEA in CSF and serum can contribute to the diagnosis of neoplastic disease affecting the central nervous system. With a molecular weight of 180 kD, CEA can enter the CSF by diffusion. In cases of high serum CEA concentrations or of blood-brain-barrier disturbance, absolute CSF-CEA levels will be elevated even without neoplastic CNS disease. Our group therefore proposed in previous studies the correlation of the Q CEA with the Q albumin to exclude CSF-CEA concentrations that were elevated by disturbance of the blood-brain-barrier. With this strategy, a good sensitivity for the detection of CSF involvement of the neoplasma and moderate sensitivity for CNS metastases was achieved (16). The molecular weight of albumin (66 kD), however, is only about one third of CEA (180 kD). Therefore, different dynamics of diffusion of both proteins have to be expected. In the last years, we evaluated the Q CEA within the diagram of IgA, whose molecular weight of 160 kD is comparable to CEA. In the study presented here we reviewed retrospectively the data and asked if this method is suitable and reliable.

With the bead ELISA, exact CSF-CEA values could be determined in almost all cases. We found a good correlation between the CSF/ serum coefficients of CEA and IgA. This indicates that the diffusion of CEA from the serum into the CSF can be well described by diffusion dynamics of proteins (17) and that the diffusion of CEA from serum into the CSF is comparable to that of IgA. Q CEA values were

Table II

Sensitivity and specificity of the index Q CEA / Q IgA and of CEA synthesis for the detection of leptomeningeal disease

		Q CEA / Q IgA > 1,5	CEA Synthesis
Control / Meningeosis	Sensitivity	91	91
	Specificity	81	94
No metastasis / Meningeosis	Sensitivity	91	91
	Specificity	67	56
Control / CNS metastasis	Sensitivity	69	69
	Specificity	81	94
No met. / CNS metastasis	Sensitivity	69	69
	Specificity	67	56

slightly higher than the Q IgA with a mean Q CEA / Q IgA of 1.1. Following the concept of diffusion dynamics, the CSF fraction of the smaller IgA would be expected to be higher than that of CEA. Differences of lipophilia and conformation of the two molecules may account for this deviation from the expected result. The upper 98% confidence interval of the index Q CEA / Q IgA was 1.31. We therefore assume an index of 1.5 as a suitable cutoff for pathological CEA analyses.

The clinical relevance of CEA in the CSF has been evaluated repeatedly (7-9, 11-15, 15, 18-23). Moreover, CEA was considered a prognostic marker for the outcome of breast cancer patients with leptomeningeal disease (24). Most of the studies evaluated absolute values of CSF-CEA and considered this marker to be helpful for the diagnosis of CNS involvement of carcinomas.

With absolute values, sensitivities of 31-82% were achieved for the detection of leptomeningeal metastases and of 27% for CNS metastases, depending from the study and the cutoff for pathological CSF values (11, 14, 15). In a previous study, our group achieved a sensitivity of 89% for the detection of leptomeningeal metastases and of 47% for brain metastases by correlating the Q CEA with the Q albumin (16). In our current work, the sensitivities were 91% for carcinomatous CSF disease and 69% for brain metastases with acceptable specificities. This is in line with the results of Corsini *et al*. who also assessed the intrathecal CEA-synthesis (25). In our hands, neither the calculation of CEA synthesis nor the index Q CEA / Q IgA were superior to the other method with respect to sensitivity or specificity. This indicates that the correlation of CSF-CEA with the serum levels and with the Q IgA is feasible and of clinical importance. The correlation of the Q CEA with the Q IgA is superior to the measurement of absolute CSF concentrations or the correlation with the Q albumin for the detection of CNS metastases or CSF involvement.

The correlation with the clinical data showed significantly higher Q CEA / Q IgA indices in the samples of patients with adenocarcinomas than in the control group or in malignancies other than adeno- or lung carcinoma. Patients with CSF involvement had significantly higher CEA/ IgA indices than patients without known parenchymal metastases, while both patients with bone and solid CNS metastases had a similar, non-significant trend towards higher values. Similar results have been observed by other groups (8, 9) and may be explained by the high rate of bone metastases to the vertebral spine with close vicinity to the spinal CSF. Because no clear diagnostic cutoff was observed between the clinical groups, we conclude that the assessment of intrathecal CEA synthesis is still of limited specificity and will remain to be a complementary method to CSF cytology and radiology.

Although CEA is most often elevated in patients with adenocarcinoma, we also observed intrathecal synthesis or elevated Q CEA / Q IgA frequently in patients with small cell lung cancer and in one case of Non-Hodgkin-Lymphoma and of melanoma each. This can be explained by the limited specificity of CEA for adenocarcinomas. Serum levels can be elevated in about half of patients with small cell lung cancer (26) and in single cases of hematological malignancies (6) or lymphoma (27) and reactivity can be found in the tissue of malignant melanomas (28). Also two patients in the control group had intrathecal CEA synthesis, one with suspected, but not proven tuberculous meningitis. In studies on CEA concentrations in pleural effusions, elevated CEA was found in 40% of pleural empyema and in 7% of tuberculosis (29). In one patient, elevated CEA serum levels decreased markedly after successful treatment of multivisceral tuberculosis (30).

Obviously, inflammatory reactions can cause elevations of soluble CEA. However, only one of our four patients with false positive results had both CEA synthesis and elevated Q CEA/Q IgA, which indicates that the combination of both methods may further improve the specificity.

In this study, we identified seven of 83 patients (8%) who had both intrathecal CEA synthesis and elevated Q CEA/ Q IgA but negative conventional cytology in spite of elevated CSF cell counts. In these patients, leptomeningeal involvement can not completely ruled out. Such a constellation could especially occur in adherent types of neoplastic meningitis without malignant cells floating in the CSF (31). Such cases can be identified when high resolution contrast-enhanced MRI is compared with cytology, as we could demonstrate in a more recent series of patients (32). Unfortunately, in the series reported here, several older cases had to be included where the clinical course was unequivocal, but the radiological documentation was not good enough to allow for a robust analysis. The results obtained here need therefore to be validated in a prospective study comparing the value of MRI, conventional cytology and intrathecal CEA synthesis to detect leptomeningeal and solid CNS metastases.

We conclude that the analysis of CEA in the CSF is helpful for the diagnosis of CNS- and CSF- involvement especially by adenocarcinomas and has an acceptable sensitivity and specificity. CEA concentrations in CSF and serum should be correlated by calculating the Q CEA. The correlation with the Q IgA and calculation both of the index Q CEA/Q IgA and the CEA synthesis within the IgA diagram may yield the best specificity with a good sensitivity. The data collected are not yet sufficient to establish a specific CEA diagram. The value of the index Q CEA / Q IgA with the proposed cutoff of 1.5 as compared with cytology and MRI should be evaluated in a prospective study.

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