S100β As a Predictor of Brain Metastases

Brain versus Cerebrovascular Damage

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BACKGROUND. The identification of brain metastases in patients with malignant disease has important implications for determining their treatment and prognosis. Asymptomatic metastatic brain tumors may be detected by surveillance imaging techniques, but longitudinal follow-up of patients who are at risk is sporadic primarily due to cost. Because the development of brain metastases is accompanied and detected by extravasation of contrast agents across the blood-brain barrier (BBB), the authors hypothesized that peripheral analysis of the BBB indicator S100β may be useful as a screening tool for brain metastases in patients who have no neurologic symptoms.

METHODS. Thirty-eight patients were enrolled for the current study. All patients had newly diagnosed lung carcinoma and had no neurologic symptoms or known history of brain metastasis. Patients underwent an initial magnetic resonance imaging (MRI) scans and S100β blood tests. S100β tests were repeated in a subset of patients at the time of routine follow-up MRI scans.

RESULTS. Based on imaging studies and on serum S100β analyses, the patients were divided in 3 categories: 1) patients with normal S100β levels (0.08 ± 0.02 μg/L; n = 22 patients) and normal MRI scans; 2) patients with elevated S100β levels (0.5 ± 0.28 μg/L; n = 8 patients) and pronounced microvascular changes on MRI scans but with no metastases; and 3) patients with elevated S100β levels (0.28 ± 0.19 μg/L; n = 7 patients) and metastatic brain tumor(s) on MRI scans.

CONCLUSIONS. Because of the significant overlap in S100β levels between patients with cerebral microvascular diseases and patients with brain metastases, the authors concluded that the serum S100β level may be used as a surveillance tool to predict or detect brain metastases if appropriate prescreening radiologic tests are obtained and if patients who are candidates for false-positive results are identified and excluded. Cancer 2005;104:817–24. © 2005 American Cancer Society.

KEYWORDS: blood-brain barrier, brain metastases, cerebral microvascular disease, lung carcinoma, S100β, vascular leakage.

The identification of brain metastases in patients with newly diagnosed or established lung carcinoma has important implications for determining their prognosis and treatment options. Estimates of the incidence of brain metastases in these patients vary widely from about 2% to nearly 15%, depending on the stage of disease (ranging from newly diagnosed, limited disease to established, widespread disease).1,2 This feature contrasts with most of the rest of the body, where metastatic spread is much more common. Accordingly, there has been some controversy about the role of surveillance imaging in patients with lung carcinoma who do not have neurologic symptoms.3,4 Because of the high costs associated with a routine schedule of magnetic resonance image (MRI) studies over multiple years of surveillance, most clinicians opt instead only to obtain imaging stud-
ies when indicated according to the presence of neurologic symptoms or as a requirement for entry into an investigational protocol. However, evidence indicates that the overall incidence of brain metastasis is rising in patients with lung carcinoma due to improved therapy for systemic disease. The treatment of brain metastases has improved over the past 3 decades to the point where a patient with a limited number of brain metastases has a prognosis that is more dependent on the status of their extracranial disease than on the presence of brain metastases. Furthermore, brain metastases are treated more effectively when they are detected early; consequently, there is a premium on the discovery of brain metastases before they produce neurologic symptoms.

Loss of blood-brain barrier (BBB) function is a hallmark of many neurologic diseases. Invasion is the process by which a tumor gains access to the local tissue around it and gradually replaces it. This step is the first in the metastatic process by which tumor cells seed to remote sites. Consequent neovascularization produces a tumor vascular system that does not have a fully functional BBB. For diagnosis as well as planning and evaluation of therapy, imaging techniques, such as computed tomography (CT) and contrast-enhanced MRI (CE-MRI), are invaluable tools for detecting lesions that have a disrupted BBB. In CE-MRI, contrast enhancement of tumor tissue is secondary to extravasation and subsequent accumulation in the interstitium of small contrast agents, such as gadolinium diethylenetriaminepenta-acetic acid (Gd-DTPA). Tumor vessels generally are leakier than normal vessels and, thus, will permit faster extravasation. Hence, dynamic CE-MRI measurements allow identification of suspected malignancies by highlighting regions with increased rates of wash-in and wash-out of contrast agents.

An alternative approach for the detection of BBB abnormalities was developed recently that relies on the detection of changes in a serum marker that indicates BBB disruption. This marker, S100β, is a protein that is found in astrocytes and is released into serum only when the BBB is breached. S100β primarily is synthesized in the brain by the endfeet process of the astrocytes and is released quickly from the brain in the blood when the BBB is disrupted. S100β also has been found in other tissues but at lower concentrations. Although the appearance of S100β in plasma correlated well with BBB openings, it has been shown that S100β increases in plasma, cerebrospinal fluid, or both as a consequence of other pathologies that are not limited to the central nervous system (CNS). S100β also may detect brain damage or may indicate advanced metastasis in patients with melanoma. The fact that S100β can increase in serum independent of brain (or neuronal) damage was demonstrated indirectly in a study of the effects of boxing and other high cardiovascular output activities on the levels of S100β in serum. It is noteworthy that, in that study, a significant increase in S100β was observed in the serum of individuals who undertook activities that involved repetitive, jarring movement or contact to the head (such as boxing, sparring, running, and jogging); however, essentially, no increase was observed in individuals who exerted themselves through exercise on a stationary bicycle. Clearly, these activities neither caused nor promoted brain damage, but the rise in S100β protein in running activities may be due to astroglial activation, astroglial destruction, BBB disruption, or a combination of the 3. This finding also indicates that the source of S100β was not influenced greatly by secretion of the protein from extracranial tissue.

We hypothesized that, if BBB leakage is a hallmark of brain metastasis, then peripheral markers of BBB function may be useful, noninvasive, and inexpensive tools to confirm or rule out brain invasion by highly malignant tumors. To test this, we measured S100β in serum from patients who presented with lung carcinoma, a malignancy that is characterized by a relatively high propensity for CNS metastasis. A corollary of this study was to further examine the usefulness of serum markers as an alternative to enhancement-based neuro-imaging.

**MATERIALS AND METHODS**

This prospective study included patients who presented to the Cleveland Clinic with newly diagnosed lung carcinoma. Potential candidates for this study were identified by a pulmonologist (P.M.) or a medical oncologist (T.M.). To be included in the study, patients had to have newly diagnosed nonsmall cell lung carcinoma with no neurologic symptoms or signs and with no known brain metastases. Many patients with newly diagnosed lung carcinoma at the Cleveland Clinic undergo screening MRIs as part of their initial routine evaluation. All patients signed an informed consent according to institutional review protocols at The Cleveland Clinic Foundation. Radiologic examination was performed within 3 weeks of the time of when the blood sample was obtained. These patients underwent diagnostic or volumetric MRI studies at The Cleveland Clinic Foundation in 2003–2004.

S100β was measured with an enzyme-linked immunosorbent assay, as described elsewhere. Routine MRI studies included T1-weighted sequences with and without gadolinium (Gd-DTPA), T2-weighted im-
ages, and fluid-attenuated inversion recovery (FLAIR) images. Contrast-enhanced, 3-dimensional volume acquisition with 1-mm slice interval and supplementary 2-mm spin echo images through the area of interest were obtained. All MRIs were analyzed for contrast enhancement.

Classification of Imaging Studies
Routine MRI studies included T1-weighted sequences with and without gadolinium (Gd-DTPA), T2-weighted sequences, and FLAIR images. Scan results were interpreted by a neuroradiologist, and routine paradigms were used to determine the presence or absence of vascular changes.

Statistical Analysis
Analyses of variance were used to determine statistical significance. A difference with $P < 0.05$ was considered statistically significant.

RESULTS
We obtained blood samples from 38 patients during their visits to the Cleveland Clinic Foundation. No patients underwent more than one blood draw or imaging study. A summary of the clinical characteristics, imaging results, and S100$\beta$ levels are listed in Table 1.

First, we explored the dependency of serum S100$\beta$ on patient age or body weight. The results are shown in Figure 1A,B. No significant correlation was found between S100$\beta$ and body weight or patient age ($P = 0.54$ and $P = 0.86$, respectively). Similarly (Fig. 1C), S100$\beta$ levels were not dependent on gender ($P > 0.3$).

Analysis of the imaging studies revealed that the patient population could be divided in three groups. Approximately 58% of patients (22 of 38 patients) had no sign on initial MRI or CT studies, suggesting the presence of brain metastasis or chronic cerebrovascular disease (“normal”). Approximately 24% of patients (9 of 38 patients) had no metastasis but had significant chronic vascular changes on their initial imaging studies (“cerebral microvascular changes”). The remaining patients (7 of 38 patients; 18%) had at least 1 brain metastasis on their initial imaging study (“metastasis”).

Analysis of serum S100$\beta$ levels showed that patients who had normal imaging studies had lower levels of this serum marker of BBB function compared with patients who had imaging studies that showed cerebral microvascular changes or metastasis (Fig. 1D) (mean normal, 0.07 $\mu$g/mL; mean vascular, 0.49 $\mu$g/mL; mean metastasis, 0.28 $\mu$g/mL). However, no significant difference was observed in the degree of serum S100$\beta$ elevation in the vascular change group and the metastasis group ($P > 0.10$). Figure 1E shows the distribution of S100$\beta$ values for each imaging group. Based on previous experience and published work,$^{10,13}$ we assumed S100$\beta$ levels of 0.12 $\mu$g/mL as the upper limit for normal; this is indicated by the shaded area in Figure 1E.

Figure 2 shows examples of patients’ MRIs and their associated serum S100$\beta$ levels. Figure 2A shows a representative MRI from a patient who was classified with cerebral microvascular changes but who did not have a brain metastasis. This patient’s S100$\beta$ level was 0.21 $\mu$L/L, which is considered elevated. Figure 2B shows a representative MRI from a patient who had no evidence of vascular disease, but this patient also had an elevated S100$\beta$ level (0.46 $\mu$L/L). This scan initially was read as normal, but subsequent examination revealed the presence of a small metastatic lesion (see Fig. 2B, circled area).

Based on these results, we calculated the positive predictive value (PPV) and negative predictive value (NPV) of an S100$\beta$ level $> 0.12$ $\mu$g/mL on the presence of a brain metastasis. The NPV was 1.00; no patient with a “normal” S100$\beta$ level was had either brain metastasis or cerebral microvascular changes. The PPV of an elevated S100$\beta$ level was 0.471 for the entire series or 0.875 if the patients who had a cerebral microvascular pattern were excluded. The fitness of analysis = PPV $\times$ NPV $\times$ 1000) was 471 if patients with vascular disease were grouped together with patients who had metastasis and 875 if the patients with vascular disease were excluded. The sensitivity of the S-100$\beta$ ELISA, as reported by Diasorin, is 0.03 $\mu$L/L ($B_0 + 3$ SD). The intra-assay variation of the assay was calculated by ANOVA to be $< 10\%$, with an inter-assay variation of $< 15\%$ in the range of concentration from 0.18 to 4.0 $\mu$L/L.

The main finding of our study is that the elevated, 100% negative predictive value of serum S100$\beta$ warrants is further evaluation and use as an alternative to contrast-based MRI scans routinely used to evaluate BBB integrity and possible CNS metastases in lung carcinoma patients. This finding, together with previous reports on other patients affected by neurological disorders or brain tumors,$^{9,10,13,26,27}$ suggest that a simple blood test may be used to screen patients prior to more extensive, and expensive, MRI evaluations.

DISCUSSION
Many neurologic disorders and lesions are associated with increased BBB permeability, including primary and metastatic brain tumors, ischemia, hypertension, dementia, epilepsy, infection, multiple sclerosis, and trauma.$^{28}$ The BBB is composed primarily of microvascular endothelial cells linked by tight junctions,
### TABLE 1
Summary of the Clinical Characteristics, Imaging Results and S100β Levels in Patients with Newly Diagnosed Lung Carcinoma

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>S100β (µg/L)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Age (yrs)</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT12702-1130</td>
<td>0.71</td>
<td>M</td>
<td>67.7</td>
<td>72.0</td>
<td>Newly diagnosed, extensive-stage small cell lung CA, left shoulder weakness</td>
</tr>
<tr>
<td>LT12050-1300</td>
<td>0.15</td>
<td>M</td>
<td>85.3</td>
<td>52.9</td>
<td>Malignant neoplasm bronchi/lung; anxiety, numbness, and weakness in right leg</td>
</tr>
<tr>
<td>LT123102-0830</td>
<td>0.29</td>
<td>F</td>
<td>37.1</td>
<td>70.3</td>
<td>Other lung disease, lung mass.; sided chest pain, diverticulitis, hysterecomy; seizures during pregnancy.</td>
</tr>
<tr>
<td>LT203803-1445</td>
<td>0.13</td>
<td>M</td>
<td>81.7</td>
<td>75.2</td>
<td>Nonsmall cell lung CA, hypertension, carotid stenosis, hypothyroidism, abnormal gait</td>
</tr>
<tr>
<td>LT049002-1530</td>
<td>0.22</td>
<td>M</td>
<td>75.0</td>
<td>67.6</td>
<td>Other lung disease, lung mass, hypertension, high lipids, gout, diabetes mellitus, cataracts</td>
</tr>
<tr>
<td>LT041403-1230</td>
<td>0.26</td>
<td>M</td>
<td>85.0</td>
<td>65.1</td>
<td>Other lung disease, osteoarthritis, diabetes mellitus (type 2), hypertension, atrial fibrillation, hyperlipidemia</td>
</tr>
<tr>
<td>LT100203-1430</td>
<td>0.21</td>
<td>F</td>
<td>95.2</td>
<td>65.8</td>
<td>Nonsmall cell CA, lobectomy (adenocarcinoma 6/2002; hysterectomy, 1978), pulmonary nodules, dry cough</td>
</tr>
<tr>
<td>LT120602-1245</td>
<td>1.08</td>
<td>M</td>
<td>67.1</td>
<td>59.3</td>
<td>Primary lung CA with lymphatic spread, upper GI bleed, hiatal hernia, hypertension, tuberculosis</td>
</tr>
<tr>
<td>LT121202-0930</td>
<td>0.52</td>
<td>M</td>
<td>83.9</td>
<td>69.5</td>
<td>Benign hypertension, coronary atherosclerosis, MI, hypothyroidism, malignant neoplasm bronchi/lung</td>
</tr>
<tr>
<td>LT041603-1400</td>
<td>0.32</td>
<td>M</td>
<td>124.0</td>
<td>79.3</td>
<td>Nonsmall cell lung CA, hermia repair, partial thyroidectomy, hypertension, glaucoma, osteoarthritis, hemoptysis</td>
</tr>
<tr>
<td>LT062303-1230</td>
<td>0.35</td>
<td>F</td>
<td>72.0</td>
<td>66.6</td>
<td>Stage IIIA nonsmall cell lung CA, chronic sinusitis, difficulty swallowing, colostomy (25 yrs ago), pneumonia, RU lung lesion.</td>
</tr>
<tr>
<td>LT100603-1130</td>
<td>0.68</td>
<td>F</td>
<td>65.6</td>
<td>66.3</td>
<td>Nonsmall cell lung CA, carotid endarterectomy, asthma, fever with palpitations, cataracts, and hypertension</td>
</tr>
<tr>
<td>LT024003-1630</td>
<td>0.48</td>
<td>F</td>
<td>64.7</td>
<td>68.5</td>
<td>Squamous cell CA (10/2003), pneumonia, SVT ablation, diverticulitis, hematuria, hysterecomy, Legionnaire disease</td>
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<tr>
<td>LT100603-1130</td>
<td>0.47</td>
<td>M</td>
<td>95.3</td>
<td>66.0</td>
<td>Nonsmall cell lung CA, shortness of breath, hypertension, stroke, knee surgery, noninsulin-dependent diabetes</td>
</tr>
<tr>
<td>LT025004-1214</td>
<td>0.14</td>
<td>M</td>
<td>86.9</td>
<td>74.3</td>
<td>Bronchogenic malignancy, coronary artery bypass grafting, hepatitis B, hyperlipidemia, mitral valve disorder, atrial fibrillation, bloody sputum</td>
</tr>
<tr>
<td>LT020604-1345</td>
<td>0.34</td>
<td>M</td>
<td>86.9</td>
<td>72.2</td>
<td>Malignant neoplasm bronchi/lung, heart transplant (1994), congestive heart failure, chronic renal insufficiency, bacterial pneumonia, neoplasm larynx, small vessel disease</td>
</tr>
<tr>
<td>LT111402-1330</td>
<td>&lt; 0.02</td>
<td>M</td>
<td>73.0</td>
<td>80.3</td>
<td>Other lung disease (NEC), aortocoronary bypass, MI, hyperlipidemia</td>
</tr>
<tr>
<td>LT111802-0915</td>
<td>0.02</td>
<td>F</td>
<td>55.8</td>
<td>41.5</td>
<td>Nonsmall cell lung CA (surgery 4/2002), lung CA malignant neoplasm bronchi/lung</td>
</tr>
<tr>
<td>LT111902-1130</td>
<td>0.07</td>
<td>M</td>
<td>99.2</td>
<td>65.7</td>
<td>Malignant neoplasm bronchi/lung; anxiety, numbness, and weakness in right leg</td>
</tr>
<tr>
<td>LT112602-0900</td>
<td>0.10</td>
<td>M</td>
<td>98.4</td>
<td>83.1</td>
<td>Nonsmall-cell lung CA, MI (1998), angiplasty, diabetes mellitus (type 2), hypertension, white lung</td>
</tr>
<tr>
<td>LT120302-1230</td>
<td>0.08</td>
<td>F</td>
<td>58.4</td>
<td>78.6</td>
<td>Other lung disease (NOC), hypertension, chronic hematuria, fibromyalgia, pneumonia, upper lobe lung nodule</td>
</tr>
<tr>
<td>LT120602-1230</td>
<td>&lt; 0.02</td>
<td>F</td>
<td>52.2</td>
<td>49.5</td>
<td>Nonsmall cell lung CA, ovarian cyst removed, arthroscopic knee surgery, appendectomy, joint pain</td>
</tr>
<tr>
<td>LT121602-1440</td>
<td>&lt; 0.02</td>
<td>F</td>
<td>70.1</td>
<td>58.6</td>
<td>Bronchogenic malignancy; left upper lobe lung mass, breast lesion</td>
</tr>
<tr>
<td>LT102003-1420</td>
<td>0.18</td>
<td>M</td>
<td>77.7</td>
<td>75.0</td>
<td>Adenocarcinoma of L upper lobe, hernia, deafness, arthritis, asthma, pulmonary TB</td>
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<tr>
<td>LT102703-1140</td>
<td>0.12</td>
<td>F</td>
<td>67.6</td>
<td>74.8</td>
<td>Chronic airway obstruction, chronic heart failure, asthma, benign hypertension, pulmonary nodules, motor vehicle collision (1995)</td>
</tr>
<tr>
<td>LT021303-1430</td>
<td>0.11</td>
<td>M</td>
<td>103.0</td>
<td>59.5</td>
<td>Newly diagnosed lung CA, CAD, lower GI bleeding, erectile dysfunction, hyperlipidemia</td>
</tr>
<tr>
<td>LT031803-1500</td>
<td>&lt; 0.02</td>
<td>F</td>
<td>68.0</td>
<td>58.5</td>
<td>Other lung disease, partial hysterecomy (1991), knee surgery, tonsillectomy, chest pain, right side chest pain, pleurisy, abnormal chest X-ray.</td>
</tr>
<tr>
<td>LT040203-1230</td>
<td>0.06</td>
<td>M</td>
<td>176.0</td>
<td>61.4</td>
<td>Metastatic nonsmall cell lung CA, Hodgkin disease, neuropahty, endarterectomy, upper lobe lesion, bilateral adrenal nodules</td>
</tr>
<tr>
<td>LT050503-1430</td>
<td>&lt; 0.02</td>
<td>M</td>
<td>82.3</td>
<td>73.2</td>
<td>Other lung disease, peptic ulcer, diabetes mellitus, TB, hemorrhoids, hypertension, cataracts, skin CA, nocturia, weight loss, lung mass</td>
</tr>
<tr>
<td>LT051203-1020</td>
<td>0.03</td>
<td>M</td>
<td>87.0</td>
<td>78.1</td>
<td>Lung CA, gall bladder surgery, chest discomfort, abnormal X-ray</td>
</tr>
<tr>
<td>LT060503-1400</td>
<td>0.03</td>
<td>M</td>
<td>86.0</td>
<td>66.3</td>
<td>Other lung disease, cardiac disease, atrial fibrillation, coronary atherosclerosis, hemoptysis</td>
</tr>
<tr>
<td>LT062503-1200</td>
<td>0.04</td>
<td>F</td>
<td>117.0</td>
<td>56.9</td>
<td>Malignant neoplasm bronchi/lung, hypertension, hyperthyroidism, cholecystectomy, shortness of breath, coughing</td>
</tr>
<tr>
<td>LT062703-1430</td>
<td>0.06</td>
<td>M</td>
<td>72.3</td>
<td>85.4</td>
<td>Other lung disease, prostatectomy (benign), CAD with bypass, abdominal aortic aneurysm, hypertension, hyperthyroidism</td>
</tr>
<tr>
<td>LT070103-1600</td>
<td>0.59</td>
<td>M</td>
<td>95.9</td>
<td>62.1</td>
<td>Squamous cell CA, angioplasty, osteoarthritis, RU lobe lung lesion</td>
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<tr>
<td>LT071703-0530</td>
<td>0.05</td>
<td>M</td>
<td>93.8</td>
<td>61.7</td>
<td>Other lung disease, hypertension, high lipids, kidney trauma and repair, appendectomy, fatigue, lung lesions, liver lesions</td>
</tr>
<tr>
<td>LT072503-1400</td>
<td>&lt; 0.02</td>
<td>F</td>
<td>57</td>
<td>76.5</td>
<td>Malignant neoplasm bronchi/lung, incontinence, partial hysterecomy, vein stripping, foot neuroma, hemoptysis, chest wall pain</td>
</tr>
<tr>
<td>LT082803-1500</td>
<td>0.03</td>
<td>M</td>
<td>96.6</td>
<td>63.3</td>
<td>Chest swelling, mass/lump, hypertension, CAD</td>
</tr>
<tr>
<td>LT082803-1200</td>
<td>0.06</td>
<td>M</td>
<td>80.1</td>
<td>74.5</td>
<td>Other lung disease, hyperplasia of prostate, varicose veins (leg), hyperlipidemia, benign neoplasm of large bowel, osteoporosis, chest pain</td>
</tr>
</tbody>
</table>

**ID:** Identification; **M:** male; **F:** female; **CA:** carcinoma; **GI:** gastrointestinal; **MI:** myocardial infarction; **RU:** right upper; **SVT:** superficial vein thrombosis; **NEC:** necrotizing enterocolitis; **COPD:** chronic obstructive pulmonary disease; **NOC:** not otherwise classified; **TB:** tuberculosis; **CAD:** coronary artery disease.
which largely prevent molecular communication between blood and the brain. Astrocytes and their processes invest >90% of endothelial capillaries, and their endfeet are projected tightly around the endothelial cells. This relation between the astrocytes and endothelial cells is essential for the formation of a fully functional BBB. Astrocytic proteins are synthesized and released next to capillaries; however, due to the negligible transendothelial permeability to proteins, they extravasate into the serum only when the BBB is breached. Under these conditions, S100β is expected to appear in the systemic circulation. 

Although several studies clearly demonstrated that serum S100β is a marker of BBB function, others demonstrated a positive correlation with brain damage. How could these seemingly contrasting two findings be explained? Modeling of these 2 phenomena predicted that high levels of serum S100β would be correlated with brain damage, whereas lesser increases above normal values would be associated with BBB leakage in the absence of parenchymal damage.

The results of this prospective study confirmed the presence of a correlation between imaging evidence of a loss of BBB integrity and elevated levels of serum S100β. Furthermore, these results suggest that serum S100β may be used to screen for brain metastases in a certain group of patients who have a known systemic malignancy. Because no patient with cerebral metastases was missed by the test (NPV, 100%), although nearly 50% of the whole sample had normal values, we propose the use of S100β as a screening test for the presence of asymptomatic cerebral metastases in patients who have a malignancy that has a known predilection for the development of brain metastases.

An elevated S100β level did not always correlate...
with the presence of brain metastasis, however. In the current series of patients, an elevated S100\(\beta\) level was associated either with brain metastasis or with the presence of imaging changes suggestive of chronic, diffuse cerebral microvascular disease. This finding makes the use of S100\(\beta\) as a sole marker for the detection of brain metastasis problematic. Clearly, patients who have an elevated S100\(\beta\) level will need to undergo neuroimaging studies to confirm the diagnosis of brain metastasis. Patients who have evidence of chronic cerebrovascular disease likely will receive no further benefit from routine screening of their serum S100\(\beta\) level and, instead, will need to be followed clinically. Further study of this group of patients may reveal that the onset of a brain metastasis is associated with a further elevation in the absolute level of their S100\(\beta\) level.

**FIGURE 2.** These radiologic imaging studies from typical patients exemplify the criteria used to construct the data illustrated in **FIGURE 1.** Scans from normal participants are not shown. (A–C) These magnetic resonance images (MRI) and computed tomography (CT) scans were obtained from patients with small metastases who had serum S100\(\beta\) levels of 0.21 \(\mu\)g/L (A), 0.46 \(\mu\)g/L (B), and 0.34 \(\mu\)g/L (C) at the time of the imaging studies (Gd: gadolinium). (D) These MRI studies were obtained from a patient with obvious, large metastases who had a serum S100\(\beta\) level of 0.71 \(\mu\)g/L at the time of the imaging studies. (E,F) These MRI studies were obtained from patients who had vascular leakage without metastases and who had serum S100\(\beta\) levels of 0.68 \(\mu\)g/L (E) and 0.35 \(\mu\)g/L (F) at the time of the imaging studies (for details, see text).
serum S100β, although this remains to be determined. Conversely, patients who have normal MRI studies in the face of an elevated serum S100β levels may benefit from closer follow-up imaging studies. We are investigating other serum markers actively that may distinguish between the two groups described here (patients with cerebral microvascular and patients with brain metastasis).

Early identification of brain metastases, before neurologic symptoms or signs develop, provides patients with a wider set of treatment options and likely will enhance their quality of life. Small, asymptomatic brain metastases most often can be treated successfully with stereotactic radiosurgery and, in certain circumstances, without the need for whole-brain irradiation. It has been shown that aggressive treatment of brain metastases improves overall survival to the point where prognosis is more dependent on the status of the extracranial disease.

It has to be underscored that S100β had a 100% negative predictive accuracy. Thus, all patients who presented with brain metastasis had elevated S100β values. In one patient (see Fig. 2A), S100β was increased above normal values, although the MRI scans revealed metastatic lesions only after careful examination. In another patient, a negative scan accompanied by an elevated S100β level was followed by the development of a metastasis, suggesting that blood tests sometimes may be more accurate than radiologic screening. One possible application of the test could be envisioned as follows: After the diagnosis of a systemic tumor with a demonstrated propensity toward CNS metastasis but with no obvious metastases at that time, a first S100β test is performed. A positive result above normal values is interpreted as a sign of cerebrovascular disease consistent with BBB leakage. A negative S100β value, conversely, is an indicator of an intact BBB. Both signals are used as a baseline, and additional, repetitive tests are used to detect a departure from the patient’s “S100β score.” This event is interpreted as a sign of possible metastatic growth that will be confirmed or disproved by a radiologic examination.

This approach may optimize the timing of radiologic examination, increasing the possibility of the early detection of CNS changes consistent with the spread of systemic carcinoma to the brain. Additional prospective studies currently are being designed to evaluate this possibility.

In conclusion, the current results demonstrate that detection in the serum of the astrocytic protein S100β is a potential candidate protein for the nonradiologic, inexpensive screening of brain metastasis in lung carcinoma patients. We propose that S100β be used as a screen to indicate who should receive an MRI scan for brain metastases. This conclusion is based on the fact that S-100β had a negative predictive value of 100% in this study and in our preliminary investigations published elsewhere.10

REFERENCES

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