Baseline staging of melanoma with unknown primary site: the value of serum s100 protein and positron emission tomography

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Abstract

BACKGROUND: Baseline staging is important in all melanoma types, including melanoma with unknown primary site (MUP). Staging includes different examination strategies, each with different accuracy. OBJECTIVE: To determine the value of serum S100 protein levels and positron emission tomography (PET) in the baseline staging of MUP. METHODS: Twenty patients with MUP were evaluable for the analysis between 1996 and 2007 with both S100 assessment and PET performed for baseline staging. RESULTS: Serum S100 was elevated in 7 patients (35%). The PET scan detected the metastases in 6 of 7 patients with elevated serum S100 protein showing a strong correlation (p = 0.005). Patients with metastases had significantly higher serum S100 levels (p = 0.01) than the ones without. Serum S100 protein was shown to be discriminative between patients with and without metastases (receiver-operating characteristic, p = 0.012) with 75% sensitivity and 92% specificity. CONCLUSION: Serum S100 protein appears to be a sensitive as well as specific marker to detect metastases. We therefore might recommend serum S100 assessment to be included in the baseline staging of MUP.
Baseline Staging of Melanoma with Unknown Primary Site: The Value of Serum S100 Protein and Positron Emission Tomography

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Key Words
Cancer staging · Melanoma of unknown primary site · S100 protein · Positron emission tomography

Abstract
Background: Baseline staging is important in all melanoma types, including melanoma with unknown primary site (MUP). Staging includes different examination strategies, each with different accuracy. Objective: To determine the value of serum S100 protein levels and positron emission tomography (PET) in the baseline staging of MUP. Methods: Twenty patients with MUP were evaluable for the analysis between 1996 and 2007 with both S100 assessment and PET performed for baseline staging. Results: Serum S100 was elevated in 7 patients (35%). The PET scan detected the metastases in 6 of 7 patients with elevated serum S100 protein showing a strong correlation (p = 0.005). Patients with metastases had significantly higher serum S100 levels (p = 0.01) than the ones without. Serum S100 protein was shown to be discriminative between patients with and without metastases (receiver-operating characteristic, p = 0.012) with 75% sensitivity and 92% specificity. Conclusion: Serum S100 protein appears to be a sensitive as well as specific marker to detect metastases. We therefore might recommend serum S100 assessment to be included in the baseline staging of MUP.
more, measuring S100 protein is useful in monitoring success of chemotherapy in stage IV disease [15, 16]. However, the significance of serum S100 protein detection in the diagnosis of MUP has not been specifically investigated.

Positron emission tomography (PET) is widely used in oncology for lesion detection and characterization as well as for accurate lesion localization [17]. The importance of PET in melanoma staging has been extensively studied and its usefulness confirmed [18–20]. Melanoma cells usually demonstrate a high uptake of the glucose analog 18F-fluorodeoxyglucose (FDG), which was the finding that set the rationale for the use of FDG in melanoma [21, 22].

The aim of this study was to determine the value of serum S100 measurement and PET in the baseline staging of patients with MUP.

**Patients and Methods**

**Patients**

We retrospectively reviewed the medical histories of melanoma patients with MUP diagnosed between 1996 and 2007 at our Department. The dates corresponding to S100 evaluation and PET together with respective findings were collected. All patients were assessed according to the guidelines of the Swiss Cancer League for stage III or high-risk melanoma [23]. The assessment was performed as follows: complete examination of the skin including dermoscopy (if available, with computer-assisted systems) of atypical moles, palpation of all lymph node regions and the abdomen, a partial- (without lower legs’ scan) or full-body (with lower legs’ scan) PET scan and the assessment of the serum S100 level. We did not perform any additional examinations to specifically seek for tumors in urogenital, otorhinolaryngological or ophthalmological (noncutaneous) sites. Patient details are shown in table 1.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Site of first metastasis</td>
<td>Skin and subcutaneous</td>
<td>Lymph node</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>PET/CT</td>
<td>Partial-body</td>
<td>Whole-body</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age at first diagnosis, years</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>51.69</td>
<td>24–80</td>
</tr>
</tbody>
</table>

**S100 Protein ELISA**

Serum S100 levels were measured by an enzyme immunoassay at the Department of Clinical Immunology, University Hospital Zurich. The two-site, one-step Sangtec® 100 ELISA was used (DiaSorin, Saluggia, Italy; obtained from Sodiac SA, Losone, Switzerland). Serum S100 protein was considered normal for values < 0.2 µg/l.

**Positron Emission Tomography**

PET scans were performed at the Department of Nuclear Medicine, University Hospital Zurich. PET studies were performed on a GE Advance PET scanner (GE Medical Systems, Waukesha, Wis., USA), which acquires 35 two-dimensional sections of 4.25 mm thickness per increment with an axial field of view of 14.6 cm and a maximum of 13 consecutive cradle positions. After fasting for at least 4 h, the patients were injected 300–400 MBq of FDG intravenously 45–60 min before scanning. PET studies were performed in a partial-body or whole-body mode. Attenuation correction was performed using the built-in rotating 68Ge sources. To improve the image quality and to reduce the computation, a multiplicative iterative reconstruction algorithm for improvement of time was employed.

**Statistical Analysis**

Statistical analysis was performed with the SPSS software package, version 12.0 (SPSS, Chicago, Ill., USA). Receiver–operating characteristic (ROC) curves were used to evaluate the discriminative strength of S100 protein to differentiate between patients with and without metastases as seen by PET. p values of less than 0.05 were considered statistically significant. Box plots and ROC curve graphs were generated using SPSS.

**Results**

The average interval between PET and S100 evaluation was 10 days (range 0–41 days). Twenty patients were evaluable for the analysis. Serum S100 was elevated in 7 out of 20 patients (35%) at the time of diagnosis. There were no differences in S100 levels with respect to different tumor stages (data not shown). Patients with metastases visualized by PET had significantly higher serum S100 levels as compared to the ones without (Mann-Whitney U test, p = 0.01), as shown in figure 1a. Interestingly, 3 out of 7 patients with elevated S100 levels had symptoms (e.g. pain) or findings in the clinical examination suggestive of a tumor, while 4 patients were completely asymptomatic.

The PET scan detected metastases in 6 out of 7 patients with elevated S100 values showing a strong correlation between PET positivity and elevated S100 protein (Spearman’s ρ = 0.606, p = 0.005). Furthermore, serum S100 could be shown to have a discriminative value between patients with and without metastases (ROC, p = 0.012; fig. 1b). Serum S100 levels were indicative of metastases.
with 75% sensitivity and 92% specificity. Furthermore, measurement of S100 had a positive predictive value of 78% (to detect the presence of metastases when S100 was ≥0.2 µg/l) and a negative predictive value of 100% (to exclude the presence of metastases when S100 was <0.2 µg/l).

During the subsequent follow-up, 7 out of 11 patients, who initially had normal S100 levels, demonstrated a pathological increase in serum S100, indicating progression of the disease. The median time between first diagnosis of MUP and the first elevated S100 value was 529 days (range 120–1,911 days). At this time point, 6 out of these 7 patients had imaging-confirmed metastatic disease. The last patient had an unspecified, non-metastasis-associated S100 elevation (0.3 µg/l).

Conclusions

Our current study shows that the use of S100 protein in conjunction with PET is useful in the baseline staging of MUP. Early detection of metastases in melanoma patients, including the ones with MUP, is important to establish an adequate treatment scheme as early as possible. To our knowledge, no standardized international guidelines for staging procedures and follow-up are currently available for MUP. Recommendations for baseline staging for patients with metastatic MUP include chest X-ray/CT, abdominal ultrasound/CT and ultrasound of the regional lymph nodes and brain CT/magnetic resonance imaging [24]. At the University Hospital of Zurich, where our Department is located, staging and follow-up of MUP are performed according to the guidelines of the Swiss Cancer League (Skin Cancer Group) as for stage III or high-risk melanoma patients with tumor thickness >4 mm [23]. Those patients are initially assessed using PET and measurement of serum S100, which is then followed by S100 measurement with either ultrasound examination of lymph nodes + chest X-ray or PET every 6 months together with clinical assessment every 3 months for the first 3 years. Afterwards, ultrasound and S100 assessment or PET or CT scan as well as clinical checks are performed twice a year for 2 years. Five years after the initial diagnosis, annual clinical follow-ups with monitoring serum S100 levels are recommended.

S100 protein is a well-established marker for the detection of new melanoma metastases [13]. Elevation of S100 protein may even present as a first sign of the progressing disease [10]. False-negative results may occur, however, especially in MUP patients and in those with amelanotic melanoma metastases. False-positive findings, on the other hand, are associated with the damage of the central nervous system and increased sun exposure (ultraviolet radiation) [25]. Nevertheless, S100 protein was shown to be more frequently positive in cases with MUP than melanoma antigen E1, another marker employed in the diagnosis of melanoma [26]. Our results demonstrate an unexpectedly higher sensitivity and specificity of S100 measurement in our study group than in previous reports, where sensitivity ranged between 30 and 60% and specificity between 93 and 100% depending on the disease stage [27, 28]. In contrast to other studies, we performed analysis on a rather homogenous collective of patients with MUP, which is probably the reason for the observed high sensitivity and specificity of S100 protein to detect metastases.

Recently, Strobel et al. [29] have shown that PET accurately identifies lymph node or distant metastases in melanoma patients with elevated serum S100 levels. Our
results support these general findings in the special clinical situation of MUP. On the other hand, various other imaging procedures such as ultrasound mapping of lymph nodes, chest X-ray and CT are used for the early detection of progressive disease. For lung metastasis (especially pulmonary lymphatic carcinomatosis) and brain metastases, high-resolution CT and magnetic resonance imaging may be more accurate. Although high-resolution CT is the diagnostic modality of choice, Acikgoz et al. [30] suggested that the recognition of various PET patterns may also allow an accurate diagnosis of melanoma lung metastases. However, in detecting brain metastases of melanoma, magnetic resonance imaging is still more sensitive than fusion PET-CT [31]. These imaging techniques are however rather expensive. Facey et al. [32] have recently shown for the UK that PET scans are used inconsistently in cancer patients throughout the country and that costs vary from 635 to 1,300 GBP per scan. Further studies are required to show the impact of FDG-PET on patient management or the added value in the diagnostic pathway. Furthermore, these imaging techniques may unnecessarily expose patients to ionizing radiation and are not directly associated with tumor biology as S100 (tumor marker) and PET (metabolic activity of the tumor cells). The importance of additional examinations to identify primary melanoma of less frequent origin in the presence of overt metastatic disease (i.e. urogenital, otorhinological or ophthalmological sites) remains unclear. We therefore suggest a broad assessment of serum S100 levels in the clinics in patients suspected of having MUP to allow data collection on a larger group of patients. If serum S100 levels turn out to be reliable in predicting the presence of metastases in MUP, this marker can be used in the future as an indicator for further PET assessment.

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References


20 Rinne D, Baum RP, Hor G, Kaufmann R: Primary staging and follow-up of high risk melanoma patients with whole-body 18F-fluorodeoxyglucose positron emission tomography: results of a prospective study of 100 patients. Cancer 1998;82:1664–1671.


