S-100β and MIA in Advanced Melanoma in Relation to Prognostic Factors


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Abstract. We compared the sensitivity and specificity of S-100 and MIA in advanced melanoma, in 96 patients with no evidence of disease (NED) and 86 patients with metastatic melanoma. Abnormal S100 (>0.2 µg/l) and MIA (>14 ng/ml) results were found in 1.1% and 3.2% of NED patients and in 59.3% and 54.6% of the patients with active melanoma (p<0.001). Using both tumor markers simultaneously, the sensitivity increased up to 69.8% with the same specificity 96.8%. S100 serum levels were not related to growth patterns. By contrast, MIA levels seemed to be related to the growth pattern, with higher levels in nodular melanoma (60.6±87.1 ng/ml) compared with acral-lentigous melanoma (11.9±5.4 ng/ml) (p=0.02). Likewise, S100 was related to the metastases site with significantly higher sensitivity and mean concentrations in patients with brain metastases (p=0.01) with the lowest in those with lung M1. MIA was related to the same metastases locations but without statistical significance. In summary, both S100 and MIA are useful markers related to prognostic factors, being more effective when used in combination.

Malignant melanoma is the most aggressive skin cancer and its incidence is increasing (1). If the current trend continues, it is estimated that 1 out of 75 individuals born in the year 2000 will develop melanoma. In the United States in 1973, the incidence of melanoma was 5.7 cases per 100,000 increasing up to 12.5 cases per 100,000 in 1994 and the mortality per 100,000 increased from 1.6 to 2.2 (2). Unfortunately, a rapid development of metastases is frequent in this malignancy and in advanced cases markers would be useful for monitoring disease progression and detecting distant metastases.

S100β is the marker of choice in malignant melanoma and several authors have reported a correlation between serum S100 levels and disease relapse/progression (3-6) and survival (3, 6-8). Moreover, low sensitivity, mainly in patients in early stage of the disease, makes it necessary to find new tumor markers for this malignancy.

Melanoma inhibiting activity (MIA) has also been suggested as a serum marker for malignant melanoma (9-11). It is an 11 kd protein, identified as a protein that functions as melanoma growth inhibitory factor in the culture supernatant of a metastatic melanoma cell line (12). Recent studies have revealed that MIA leads a reduction of melanoma cell attachment to the extracellular matrix (13), and may, therefore, be related to invasion and metastases in vivo. In normal tissues, MIA is expressed by chondrocytes suggesting that it is fundamental to the cartilage cell phenotype (14, 15) and some authors have described high concentrations of MIA in rheumatic diseases, mainly in rheumatoid arthritis patients (16). In addition, some studies have suggested that MIA levels may predict the presence of clinically undetectable occult metastases in post-surgical melanoma patients (17) and may provide important prognostic information early in the course of stage III melanoma (18). Moreover, there are few studies comparing MIA and S100 (3, 10, 11, 19), thus further studies are required to determine their utility alone or in combination.

The aim of this study was to evaluate the sensitivity and specificity of S100 and MIA alone or in combination, as well as their relationship with well-known prognostic factors such as melanoma growth patterns and the site of metastases.

Patients and Methods

S100 and MIA were prospectively evaluated in 182 patients with malignant melanoma; including 96 patients (46±15 years) with no evidence of disease (NED), and 86 patients (47±12 years) with advanced melanoma (Stage III, IV) (20). The sites of recurrences...
in the latter patients were as follows: 24 patients had cutaneous or lymph node metastases, 9 brain metastases, 3 bone metastases, 13 lung metastases, 5 liver metastases, 5 multiple metastases including the liver, 24 patients with multiple metastases excluding the liver, and finally, 3 patients with other sites of metastases. The growth pattern was known in 45 cases, with the following distribution: 2 lentigo maligna melanoma (LMM), 13 superficial spreading melanoma (SSM), 10 acral lentigous melanoma (ALM), and 20 nodular melanoma (NM). It is important to point out that were excluded from the study samples of patients with renal failure (21).

We considered the upper limit of normality 0.20 μg/l for S100 (8, 22) and 14 ng/ml for MIA. S100 serum specimens were obtained by venous puncture, centrifuged and immediately analyzed. MIA samples were stored at –70°C until assays were performed. Protein S100 was analyzed using a commercially automated (Liaison® Diasorin® Italy) immunoluminometric assay based on a two-site sandwich method using two different monoclonal antibodies directed against different epitopes of the β-subunit of S100 (7). MIA levels were measured using a manual commercial enzymelinked immunosorbent assay (9) (Roche® Germany). The assay is based on a two-site sandwich method, making use of two monoclonal antibodies directed against two different epitopes of MIA.

All data were computerized and statistical analyses were performed using the SPSS software (release 11.0, SPSS Inc.).

Results

Table I shows the S100 and MIA concentrations in NED patients and in patients with advanced melanoma. Significantly higher concentrations of both tumor markers were found in patients with active cancer than in NED patients (p<0.001). Slightly high levels of S100 (<0.24 μg/l) and MIA (<16.4 ng/ml) were found in 1.2% and 3.2% of NED patients, respectively. The sensitivity and specificity of S100 and MIA were similar (Table I). It is interesting to point out that the use of both tumor markers increased the sensitivity of S100 to 69.8% with a similar specificity. Table I also shows the relationship between tumor marker serum levels and the site of metastases. We observed that S100 was clearly related to the site of recurrence with the highest concentrations being found in patients with brain or multiple metastases and the lowest in patients with lung metastases (p=0.01). Likewise, MIA showed a similar pattern, but the differences were not significant.

We also evaluated the possible relationship between the tumor markers and the most frequent growth patterns (SSM, ALM, NM), and observed similar sensitivities between the two tumor markers (Table II). However, MIA serum concentrations were significantly higher in patients with NM than in patients with ALM (p=0.02). No differences were observed in S100.

Discussion

S100 has been studied in advanced melanoma patients as a prognostic factor of early diagnosis of recurrences. Many authors have suggested that it may be useful in detecting metastases in these patients and its levels were found to correlate with the extent of metastases (6, 23). Moreover the low S100 sensitivity in early stages and the false-positive results found in some benign diseases (21, 24-26) justified the search for new markers.

MIA is another marker that could be useful in evaluating progression in patients with malignant melanoma but it has not been adequately studied (9, 3). As EGTM recommends when we introduce a new tumor marker (MIA), it is mandatory to compare it with the marker of choice (27) (S100) in malignant melanoma. Our results with S100 are similar to those reported by other authors, in similar stages (9, 28). Both tumor markers had a similar sensitivity and specificity. Scarcely abnormal tumor marker levels may be found in some benign diseases (21, 24-26) justified the search for new markers.

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Table II. Serum levels and sensitivity in patients with advanced melanoma in relation to growth patterns.

<table>
<thead>
<tr>
<th></th>
<th>S 100 (µg/L)</th>
<th>MIA (ng/mL)</th>
<th>S100 - MIA</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>%&gt;0.2</td>
</tr>
<tr>
<td>SSM</td>
<td>1.98±2.93</td>
<td>0.57</td>
<td>53.8%</td>
</tr>
<tr>
<td>ALM</td>
<td>1.42±2.88</td>
<td>0.11</td>
<td>40%</td>
</tr>
<tr>
<td>NM</td>
<td>1.31±1.91</td>
<td>0.73</td>
<td>75%</td>
</tr>
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SSM: Superficial Spreading Melanoma
ALM: Acral Lentigous Melanoma
NM: Nodular Melanoma

We didn’t find reasons to explain the low proportion of patients with values slightly higher than the cut-off values, but the specificity of both tumor markers was high. We compared MIA and S100 concentrations in relation to well-known prognostic factors. S100 was related to the site of metastases. The highest levels of S100 in brain metastases could be related with the presence of this marker in the central nervous system tissue. On the other hand MIA levels are also high in brain metastases. The cause of the low S100 concentrations in lung metastases cannot be explained (29). MIA serum levels follow a similar profile, but differences were not statistically significant. Further studies including large populations are needed to study this point.

A convenient way to categorize melanomas is by their growth patterns. These growth patterns represent distinct pathological entities and have unique clinical features that should be identifiable by an experienced clinician. There were no differences of sensitivity in evaluating both markers in relation to the most common growth patterns. But it should be important to note that MIA concentrations were related to the growth patterns with significantly higher values in patients with NM, in the present study. This could be related to the fact that nodular melanoma is the sole subtype with a pure vertical growth phase, in other words the more aggressive subtype (30). These observations should be confirmed in further studies with large number of patients.

References


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