Solitary Melanoma Confined to the Dermal and/or Subcutaneous Tissue

Evidence for Revisiting the Staging Classification

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Background: Several patients presented with a single focus of presumed cutaneous metastatic melanoma with an unknown primary tumor based on clinical and histologic staging criteria of the American Joint Committee on Cancer (AJCC). This population is classified as having stage IV disease by the current AJCC staging system, which carries a dismal prognosis (5%-18% 5-year survival). Our clinical observation was that these patients had a higher survival rate than would be expected for stage IV disease. We believe this population represents a subgroup of primary dermal- and/or subcutaneously-derived melanoma that simulates cutaneous metastatic melanoma in histologic and clinical presentation but may differ in behavior.

Observations: The database records of 1800 patients from the University of Michigan Melanoma Clinic, Ann Arbor, were retrospectively reviewed to identify the prevalence and survival for patients diagnosed with a single focus of presumed metastatic melanoma to the skin based on accepted histologic and clinical parameters. The prevalence of this population was 0.61% (11 of 1800 patients). The Kaplan-Meier 8-year survival estimate was 83% (95% confidence interval, 58%-100%).

Conclusions: By AJCC convention, these cases are classified as stage IV metastatic disease. Our data suggest that these presumed metastatic tumors do not behave like stage IV metastatic disease to the skin via lymphatic or hematogenous spread from an unknown primary site; rather, they are behaving like primary tumors originating in the dermal and/or subcutaneous tissue.

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Estimates of the incidence of metastatic melanoma with an unknown primary tumor generally range from 2% to 5%.1-9 By American Joint Committee on Cancer (AJCC) convention, patients are classified as having metastatic melanoma with an unknown primary tumor if there is a histologic confirmation of metastatic melanoma to the skin, lymph node, or visceras yet the results of a vigorous search for a primary tumor are negative. Approximately two thirds of patients present with melanoma in the lymph nodes while the remaining one third present with melanoma as "distant" or "hematogenous" metastases in various tissues such as the skin and soft tissue, lung, brain, or other organs.

Solitary lesions of melanoma confined to the dermal and/or subcutaneous tissue (presumed metastatic with an unknown primary tumor by AJCC convention) have been reported in 38 patients2,5 (MEDLINE search performed November 1999). The prevalence of this population with solitary lesions of melanoma presenting solely in the dermal and/or subcutaneous tissue ranges from 0.51% to 0.92% in 2 series.2,5 The 5-year survival rate for this subgroup of patients was 80% in one series2 and 83% in the other.2 Additionally, a 4-year survival rate of 100% in 3 patients occurred in 1 series.8 These are uncharacteristically high disease-free survival rates for patients presenting with a single focus of melanoma solely in the dermal and/or subcutaneous tissue without histologic features of regression or an epidermal component (presumed stage IV disease by AJCC convention). We retrospectively reviewed the database from the Multidisciplinary Melanoma Clinic at the University of Michigan, Ann Arbor, to further characterize this patient population.

RESULTS

The database review of 1800 patients resulted in 14 (0.78%) who met our strict criteria for a solitary melanoma confined to the dermal and/or subcutaneous tissue that simulates presumed cutaneous metastatic
PATIENTS AND METHODS

Through the melanoma database at the University of Michigan, we identified 1800 patients treated for solitary dermal and/or subcutaneous melanoma from 1991 to 1998. Although we believe these lesions represent primary dermal and/or subcutaneous melanoma, by AJCC convention they would be classified and staged in the database as solitary metastatic melanoma of the skin with an unknown primary tumor. Therefore, we searched for cases of solitary nodule of presumed metastatic melanoma of the skin with no identifiable primary lesion. Again, for the purpose of an accurate data search for cases that simulate stage IV disease by AJCC convention, we defined inclusion criteria as follows: (1) a histologically confirmed diagnosis of a solitary lesion of presumed metastatic melanoma to the skin as interpreted by a dermatopathologist with expertise in melanoma; (2) the absence of evidence for a primary melanoma after a thorough history and physical examination; and (3) biopsy and histopathologic examination results from any atypical pigmented lesions that exclude a possible primary source. Exclusion criteria for this population of presumed metastatic melanoma to the skin included (1) a history of melanoma; (2) a history of the surgical removal or destruction of skin or an ocular lesion suggestive of melanoma but not submitted for histologic review; (3) a history of a regressed pigmented skin lesion; and (4) the unavailability of histologic material of the study lesion for review by our dermatopathologist.

All biopsy specimens were retrospectively reviewed by 1 dermatopathologist (L.L.). A lesion was presumed metastatic melanoma by convention based on the following criteria: (1) relatively well-circumscribed dermal or subcutaneous tumor nodule; (2) a tumor composed of atypical melanocytes; (3) absence of any junctional activity or epidermal component; and (4) absence of features of regression that would favor a primary lesion. When necessary, immunohistochemical staining with S100 protein, HMB-45, and/or melan A was performed to confirm a melanocytic origin of the neoplasm. For the purpose of this study, Breslow depth measurements were obtained retrospectively in the conventional manner.

Observational follow-up times and outcomes (alive vs dead) were analyzed by the Kaplan-Meier method for survival data. The analysis was performed with SAS statistical software (SAS Institute Inc, Cary, NC). The confidence intervals were computed using the Greenwood method.

Population Characteristics of Patients Presenting With a Single Focus of Presumed Cutaneous Metastatic Melanoma With Unknown Primary Tumor*

<table>
<thead>
<tr>
<th>Case/Sex/Age, y</th>
<th>Anatomic Site</th>
<th>Origin</th>
<th>Breslow Depth, mm</th>
<th>Follow-up Interval, mo</th>
<th>Recurrence</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/89</td>
<td>Back</td>
<td>D</td>
<td>2.05</td>
<td>60</td>
<td>No</td>
<td>AFOD</td>
</tr>
<tr>
<td>2/F/57</td>
<td>Arm</td>
<td>SQ</td>
<td>23.00</td>
<td>44</td>
<td>No</td>
<td>AFOD</td>
</tr>
<tr>
<td>3/M/90</td>
<td>Hand</td>
<td>D</td>
<td>5.50</td>
<td>46</td>
<td>Lung</td>
<td>DOD</td>
</tr>
<tr>
<td>4/M/40</td>
<td>Scalp</td>
<td>D</td>
<td>Not measurable, fragmented</td>
<td>66</td>
<td>No</td>
<td>AFOD</td>
</tr>
<tr>
<td>5/F/28</td>
<td>Back</td>
<td>D</td>
<td>15.00</td>
<td>51</td>
<td>No</td>
<td>AFOD</td>
</tr>
<tr>
<td>6/M/46</td>
<td>Neck</td>
<td>D</td>
<td>1.35</td>
<td>56</td>
<td>No</td>
<td>AFOD</td>
</tr>
<tr>
<td>7/F/55</td>
<td>Arm</td>
<td>D</td>
<td>2.00</td>
<td>104</td>
<td>No</td>
<td>AFOD</td>
</tr>
<tr>
<td>8/M/55</td>
<td>Arm</td>
<td>D</td>
<td>4.80</td>
<td>17</td>
<td>No</td>
<td>AFOD</td>
</tr>
<tr>
<td>9/M/57</td>
<td>Back</td>
<td>D</td>
<td>7.10</td>
<td>36</td>
<td>No</td>
<td>AFOD</td>
</tr>
<tr>
<td>10/F/55</td>
<td>Nose</td>
<td>D</td>
<td>1.00</td>
<td>32</td>
<td>No</td>
<td>AFOD</td>
</tr>
<tr>
<td>11/F/81</td>
<td>Leg</td>
<td>D</td>
<td>6.00</td>
<td>29</td>
<td>Local</td>
<td>AFOD</td>
</tr>
</tbody>
</table>

* D indicates dermal; SQ, subcutaneous; AFOD, alive and free of disease; and DOD, died of disease.

melanoma with an unknown primary tumor. Three patients were excluded because histologic slides or tissue specimens were not available; therefore, only 11 patients (0.61%) were included for retrospective analysis (Table). The man-woman ratio was 2:1:1, and the mean age was 55.7 years with a range from 28 to 90 years. Sites included head and neck (3 sites), upper extremity (4 sites), lower extremity (1 site), and trunk (3 sites). The mean estimated Breslow depth was 6.98 mm with a range from 1.00 to 23.00 mm. Ten lesions were situated primarily in the dermis, and 1 was primarily in the subcutaneous adipose tissue (Figure 1). All had sparse to absent inflammatory host response, which is more typical of a primary lesion.

Of the 11 patients used for analysis, the lengths of follow-up ranged from 17 to 104 months (median, 46 months). The Kaplan-Meier 8-year survival estimate was 83% (95% confidence interval, 58%-100%) (Figure 2).

The only patient in this group to die had pulmonary metastases after 46 months of observation. All patients were treated with wide local excision with 1- to 2-cm margins to fascia. One received adjuvant therapy with interferon alfa. No patients had elective or sentinel lymph node dissection.

Although rare, it occasionally happens that a solitary melanoma confined to the dermal and/or subcutaneous tissue simulates presumed metastatic melanoma to the skin with an unknown primary tumor. Our observed prevalence of 0.61% is similar to reported rates of 0.51% to 0.92% in 2 series.2,3 Giuliano et al2 described 5 patients with surgically resected presumed solitary subcutaneous metastatic melanoma with no known primary tumor. Four pa-
tients (80%) were alive more than 5 years after diagnosis. Schlagenhaufl et al.\(^2\) reported the largest series with 30 similar patients presenting with presumed solitary skin or subcutaneous metastases with no known primary tumor. These lesions were surgically excised with 1- to 2-cm margins, and no elective lymph node dissections were performed. No adjuvant therapy was reported for this population. The 5-year survival rate was 83%. Anbari et al.\(^3\) described 3 patients with a solitary subcutaneous melanoma nodule (presumed metastatic with an unknown primary tumor) treated with surgical excision. All 3 patients were alive at the completion of the study with a reported 4-year survival. All of these 38 cases were similar to our 11 cases, and all groups of patients seemed to have a higher survival rate than would be expected for metastatic (stage IV) disease, which they were classified as having by the AJCC classification staging system.

Survival for stage IV disease is 5% to 17.9% at 5 years, with a median survival of only 6 months.\(^1,3\) Survival for stage III nodal or in-transit disease ranges from 13% to 50%, depending on the number of nodes involved and the presence or absence of extracapsular extension.\(^1,10\) Our 8-year survival estimate of 83% (95% confidence interval, 58%-100%) is consistent with those in the 3 previous reports.

It is acknowledged and recognized that our survival results and those previously reported for this patient population may represent an overestimate of the actual survival for this group. The introduction of a selection bias may skew results in this form of a retrospective analysis. In addition, the numbers are very small. Nonetheless, it is unlikely that the natural history for this population correlates with stage IV disease as presently staged by AJCC criteria. Prospective series are necessary to definitively determine prognosis in this rare population and prevent potential selection bias. Still, it appears that the prognosis for this group is not as grim as previously thought.

The relatively favorable prognosis for this subset of patients also raises some interesting questions as to the origin of these lesions that may have biological significance. The melanoma might actually originate in the dermal and/or subcutaneous tissue, possibly from nonepidermal melanocytes, embryologic-melanocytic migration remnants or aberrations, or melanocytes associated with deeper appendageal structures.

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REFERENCES