CASE REPORT

Pigmented epithelioid melanocytoma: Report of a case and review of 173 cases in the literature

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ABSTRACT

Pigmented epithelioid melanocytoma (PEM), or animal-type melanoma, is an unusual variant of melanoma which has been reported to have indolent behavior and a relatively good prognosis. We report a 12-year-old girl with PEM on the third finger web of her right hand. Histopathologically, it was composed of heavily pigmented dermal epithelioid and spindled melanocytic tumor cells. A sentinel lymph node biopsy was negative, and no recurrence was noted 1 year later. We reviewed 173 previously published cases of PEM or so-called animal-type melanoma in the literature. Among the 173 cases and our case, extremities were the most common sites of occurrence (52/129, 40.3%), and most of the depth of invasions were Clark level IV and V (76/114 (66.7%) and 33/114 (28.9%), respectively). Lymph nodes metastasis was noted in 39/89 (43.8%) of the cases being investigated. Only two cases died of the disease with visceral metastasis. Thus, a more advanced level of invasion and the presence of lymph node metastasis did not imply a definitely malignant clinical course, because spreading beyond lymph nodes was rare (5/174, 2.9%). However, long-term follow-up with more cases and further research are needed to fully delineate the true biological nature of this pigmented melanocytic tumor.

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Figure 1 (A) A 0.4 × 0.4 cm, brown-black nodule on the third fingerweb of the right hand; (B) the scanning view of the section showed an ulcerated and heavily pigmented lesion (H&E, 40×); (C) the tumor is composed of predominantly heavily pigmented polygonal epithelioid cells with large nuclei and prominent nucleoli. Heavily pigmented spindle cells constitute the minor component (H&E, 400×); (D) the neoplastic cells demonstrate round nuclei with prominent nucleoli. Mitosis is rare, but could be found in the section (arrow) (melanin bleached H&E, 400×); (E) focal vascular invasion (arrow) at the junction of deep dermis and subcutis (melanin bleached H&E, 200×); (F) the tumor cells were positive for S-100 protein (200×); (G) the tumor cells were negative for HMB-45 (200×); (H) the tumor cells were negative for Melan-A (200×); (I) immunohistochemical stain of the specimen with Ki-67 revealed some positive immunoreactivity of the tumor cells with low proliferative index (6%; 400×); (J) One year after wide excision with full-thickness skin graft, there was no local recurrence. However, due to the disfigured lesion, the patient wore a glove at all times, and a dividing line of fair-colored and tan-colored skin on the forearm was noted (arrow).
Discussion

PEM is a distinctive clinicopathological variant of melanocytic tumor of unknown malignant potential. It is characterized by its unique feature of indolent behavior compared to conventional melanoma. While Zembowicz et al. reported an equal sex predilection for younger individuals without ethnic predominance, Antony et al. reported that middle-aged to old adults have a predilection for the disease. Extremities were the most common sites of occurrence, followed by trunk and head and neck. Histopathologically, these lesions often have a wedge-shaped configuration and are composed of heavily pigmented dermal melanocytic tumor cells with a mixture of epithelioid and spindled cells. Mitosis can be seen, but is rare. The histopathological differential diagnoses of PEM include cellular blue nevus, malignant blue nevus, Spitz nevus, deep penetrating nevus and epithelioid blue nevus. The most specific differentiating feature between PEM and cellular blue nevus is the presence of abundant epithelioid cells in PEM. However, it is challenging to differentiate between PEM and malignant blue nevus, since they both have atypical epithelioid cells. The presence of significant nuclear pleomorphism, hyperchromatism, prominent eosinophilic nuclei, brisk mitotic activity, atypical mitoses and tumor necrosis are important features for malignant blue nevus. Besides, malignant blue nevus is classically defined as malignant melanoma arising within a preexisting blue nevus or the site of prior biopsy/excision of a blue nevus. Spitz nevus usually presents with maturation and prominent demarcation, which can be distinguished from PEM. Deep penetrating nevus is a distinctive deeply pigmented lesion showing overlapping features with blue nevus and Spitz nevus. Histologically, deep penetrating nevus shows a typical wedge-shaped, deeply pigmented dermal tumor with a junctional component. Tumor cells are arranged in nests or bundles and have a short spindle-shaped or, less commonly, round morphology. In addition, a thin rim of sustentacular cells is present around the edges of many nests. One characteristic feature of deep penetrating nevus is the extension of sustentacular cells is present around the edges of many nests. One characteristic feature of deep penetrating nevus is the extension of sustentacular cells. The extension of sustentacular cells is present around the edges of many nests. One characteristic feature of deep penetrating nevus is the extension of sustentacular cells. The presence of prominent lymphatic invasion, and the relation-ship between these two entities is still not entirely clear. Zembowicz et al. proposed the term PEM to compose of animal-type melanoma and epithelioid blue nevus as malignant and benign end of this histological spectrum. Murali et al. suggested that a subset of epithelioid blue nevus remained and was distinct from PEM by less cell density and less pigmentation. Zembowicz et al. mentioned that ulceration was the only feature more common in PEM than epithelioid blue nevus of Carney complex. In our case, the tumor was highly cellular, heavily pigmented and showed cellular atypia with ulceration, and, in our opinion, was best considered as PEM.

Molecular testing of histologically ambiguous primary cutaneous melanocytic tumors by using techniques such as comparative genomic hybridization or fluorescence in situ hybridization (FISH) may assist in establishing a diagnosis of melanoma if multiple chromosomal aberrations are identified. However, there was still a limited result in the field of PEM. There were only two cases of congenital PEM being studied by FISH, and one had focal FISH positivity. This study revealed that there were still limits in the technique for the diagnosis of PEM. Thus, a definitive diagnosis for puzzling lesions such as PEM should not rely on molecular data alone. The associations between clinical, histopathological and FISH data are needed. Another molecular study showed a loss of expression of protein kinase A regulatory subunit 1α (R1α) coded by the PRKAR1A gene in 28 of 34 (82%) PEMs and in 8 of 8 Carney complex-associated epithelioid blue nevus, whereas R1α was expressed in 29 of 292 various benign and malignant non-PEM melanocytic lesions and in 5 of 5 equine melanomas. The results of these studies suggested that PEM and Carney complex-associated epithelioid blue nevus are closely related neoplasms. Although being a morphological mimic, PEM is a distinct melanocytic lesion. The controversy in its cellular pathogenesis from cellular blue nevi, malignant blue nevi, Spitz nevi, deep penetrating nevus, melanomas of various types and equine melanocams. We reviewed 17 literature publications from the year 1999 to 2010 and identified 173 previously reported cases (Table 1). Among the cases with detailed data (including our case), there were 72 (55.8%) females and 57 (44.2%) males. There were four cases of congenital PEM. The most common sites of occurrence were the extremities (52/129; 40.3%), followed by trunk (36/129; 27.9%) and head and neck (36/129; 27.9%). Most of the tumors at the time of diagnosis involved Clark’s level IV (76/114; 66.7%) or Clark’s level V (33/114; 28.9%). Among the 174 cases, 39 cases (22.4%) had lymph node metastases; only 5 cases (2.9%) had spread beyond lymph nodes. The most common site of visceral metastasis was liver (4/5, 80%). Two cases (1.1%) died of the disease due to visceral metastasis during follow-up (Table 2). Although presenting at deep levels, PEM has better prognosis than conventional melanoma.

The true nature of PEM remains controversial. Many consider it a tumor of uncertain malignant potential or possibly a low-grade malignancy. Although it has a tendency to have deep invasion and even spread to regional lymph nodes, distant metastasis is rare. Even if it recurs or metastasizes, it has a better prognosis compared to conventional malignant melanoma with the same depth of invasion. Ludgate et al. and Zembowicz et al. reported SLNB positive rates of 47% (8/17) and 46% (11/24), respectively. However, in contrast to these two studies, Orlandi et al. and Scolyer et al. reported no positive SLNB in 7 and 5 patients with PEM, respectively (Table 1). Among the 174 cases we reviewed, the positive rate of lymph node metastasis either confirmed by SLNB or complete lymph node dissection (CLND) was 43.8% (39/89), accounting for 22.4% of the total number of cases. The variation in these results may be due to the small number of cases in previous reports, and the criteria for performing a SLNB/CLND not being clearly established. Thus, the positive rate in cases undergoing lymph nodes sampling or dissection may be over-estimated due to deeper tumor cell invasion or a more progressive clinical course. Regardless of the relatively high rate of lymph node metastasis, there were only 2.5% of cases whose disease had spread beyond the lymph nodes (Table 2). Thus, whether SLNB or CLND is needed for all cases of PEM is still controversial. Some suggested that PEM may not need to be managed as aggressively as conventional melanoma, due to its indolent behavior; while others recommended SLNB as a "diagnostic procedure" in an attempt to better recognize the biological
potential of these tumors. Ludgate et al. recommended performing a SLNB in PEM that is greater than 1 mm in Breslow depth or 0.75–1 mm with other adverse features such as ulceration or a high mitotic rate. The longest follow-up to date was reported after a median follow-up period of 67 months (range from 39 to 216 months) of 26 patients by Mandal et al. All of these patients were alive and free of disease during the follow-up period. These results showed that the presence of lymph node metastases in PEM does not necessarily imply a malignant clinical course. Examination of sentinel lymph nodes by lymphoscintigraphy and assessment by sentinel lymph node biopsy.* Two 21-day cycles of chemotherapy and three cycles of interleukin-2 and interferon-alfa every 6 weeks.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of cases</th>
<th>Sex</th>
<th>Location</th>
<th>Clark level</th>
<th>Outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludgate et al.11</td>
<td>2010</td>
<td>22</td>
<td>M: 13 F: 9</td>
<td>Head &amp; neck: 6 Trunk: 6 Extremities: 9 Genitalia: 1</td>
<td>I: 1 III: 2 IV: 16 V: 3</td>
<td>SLNB (+): 8/17 (47%) Recurrence: 4 cases (18%) (2 had distant metastasis, and 1 died of visceral metastasis 2.5 y following the initial diagnosis.)</td>
<td>Median: 17.6 mo</td>
</tr>
<tr>
<td>Battistella et al.22</td>
<td>2010</td>
<td>2</td>
<td>M: 1 F: 1</td>
<td>Head &amp; neck: 1 Extremity: 1</td>
<td>V: 1 Another N/A</td>
<td>SLNB was not performed in both cases.</td>
<td>26 mo and 15 mo, respectively</td>
</tr>
<tr>
<td>Yun et al.16</td>
<td>2010</td>
<td>1</td>
<td>F: 1</td>
<td>Head &amp; neck: 1 Extremity: 1</td>
<td>V: 1</td>
<td>Congenital PEM. Excision was performed at 5 mo, regional LN metastasis at 7 mo and the patient underwent 8 courses of CVD-BIO biochemotherapy. Tumor-free for 20 mo after excision.</td>
<td>20 mo</td>
</tr>
<tr>
<td>Orlandi et al.12</td>
<td>2009</td>
<td>7</td>
<td>M: 2 F: 5</td>
<td>Head &amp; neck: 3 Trunk: 3 Extremities: 1</td>
<td>IV: 1 V: 6</td>
<td>SLNB (+): 0.7/0.5% One died of cardiac failure without evidence of disease progression.</td>
<td>3 y (4/7) and 5 y (3/7)</td>
</tr>
<tr>
<td>Ito et al.17</td>
<td>2009</td>
<td>2</td>
<td>F: 2</td>
<td>Head &amp; neck: 2</td>
<td>V: 2</td>
<td>SLNB was not performed in both cases. Alive and free of disease during follow-up.</td>
<td>22 mo and 16 mo, respectively</td>
</tr>
<tr>
<td>Vezzoni et al.18</td>
<td>2008</td>
<td>1</td>
<td>F: 1</td>
<td>Trunk: 1</td>
<td>IV: 1</td>
<td>SLNB (+). Alive and free of disease during follow-up.</td>
<td>N/A</td>
</tr>
<tr>
<td>Sabah et al.19</td>
<td>2007</td>
<td>1</td>
<td>F: 1</td>
<td>Extremity: 1</td>
<td>V: 1</td>
<td>Local recurrence occurred 9 y after previous simple excision. SLNB (-) Alive and free of disease during follow-up.</td>
<td>46 mo</td>
</tr>
<tr>
<td>Antony et al.4</td>
<td>2006</td>
<td>14</td>
<td>M: 8 F: 6</td>
<td>Head &amp; neck: 5 Trunk: 3 Extremities: 6</td>
<td>Only mentioned the Breslow level, no Clark level.</td>
<td>SLNB or CLND (+): 5 Distant metastasis (liver): 1 Local recurrence: 3 No recurrence or metastasis: 6</td>
<td>Median 5 y (range 1–17 y)</td>
</tr>
<tr>
<td>Lu et al.20</td>
<td>2006</td>
<td>1</td>
<td>F: 1</td>
<td>Head &amp; neck: 1</td>
<td>IV: 1</td>
<td>SLNB was not performed. Alive and free of disease during follow-up.</td>
<td>3 mo</td>
</tr>
<tr>
<td>Ward et al.21</td>
<td>2006</td>
<td>1</td>
<td>M: 1</td>
<td>Trunk: 1</td>
<td>IV: 1</td>
<td>SLNB (+). Alive and free of disease during follow-up. The first case was followed up for 60 mo; another one was N/A.</td>
<td>6 mo</td>
</tr>
<tr>
<td>Howard et al.22</td>
<td>2005</td>
<td>2</td>
<td>M: 1 F: 1</td>
<td>Head &amp; neck: 1 Extremity: 1</td>
<td>IV: 2</td>
<td>CLND (+): 1, with radiation therapy and intravenous alfa-interferon therapy. Alive and free of disease during follow-up.</td>
<td>N/A</td>
</tr>
<tr>
<td>Zemboiczic et al.3</td>
<td>2004</td>
<td>40 (with 41 lesions)</td>
<td>M: 18 F: 22</td>
<td>Head &amp; neck: 10 Trunk: 11 Extremities: 18 Genitalia: 2</td>
<td>IV: 30 V: 11</td>
<td>SLNB (+): 11/24 (46%) 1 case: congenital PEM with hepatic metastasis discovered at presentation, is well during the 3-y follow-up. No death during follow-up.</td>
<td>Mean: 32 mo</td>
</tr>
<tr>
<td>Scolyer et al.13</td>
<td>2004</td>
<td>45</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>SLNB (+): 0/5 (0%). CLND (+): 1/1</td>
<td>N/A</td>
</tr>
<tr>
<td>Kazakov et al.23</td>
<td>2004</td>
<td>1</td>
<td>F: 1</td>
<td>Extremity: 1</td>
<td>IV: 1</td>
<td>SLNB (+). Alive and free of disease during follow-up.</td>
<td>24 mo</td>
</tr>
<tr>
<td>Requena et al.24</td>
<td>2001</td>
<td>1</td>
<td>M: 1</td>
<td>Trunk: 1</td>
<td>V: 1</td>
<td>SLNB (+), had chemotherapy with interferon alfa-2b. Alive and free of disease during follow-up.</td>
<td>4 mo</td>
</tr>
<tr>
<td>Crowson et al.25</td>
<td>1999</td>
<td>6</td>
<td>M: 3 F: 3</td>
<td>Head &amp; neck: 1 Trunk: 2 Extremity: 1 Genitalia: 1 (another one: unknown)</td>
<td>IV: 4 V: 1 (another one: unknown)</td>
<td>1 died of the disease with metastasis to regional LN, liver, and lungs. 1 had regional LN metastasis, but was alive and well. 1 had local recurrence, but was lost to follow-up. 1 had chest mass, but had not yet been investigated. 2 were alive and free of disease during follow-up.</td>
<td>From 5 mo to 4 y</td>
</tr>
<tr>
<td>Our patient</td>
<td>2011</td>
<td>1</td>
<td>F: 1</td>
<td>Extremity: 1</td>
<td>V: 1</td>
<td>Alive and free of disease during follow-up.</td>
<td>12 mo</td>
</tr>
</tbody>
</table>

CLND = complete lymph node dissection; F = female; LN = lymph nodes; M = male; N/A = not available; SLNB = sentinel lymph node biopsy.
can be categorized as a borderline melanocytic tumor or a low-grade melanoma. PEM is characterized by a predominantly intraepidermal deeply pigmented melanocytic lesion, composed mainly of epithelioid and spindled cells. Some cytologic atypia can be found, but mitotic activity is low. PEM may involve regional lymph nodes, but it has a limited ability to spread beyond the lymph nodes. Although it showed indolent behavior and an overall good prognosis in the 174 cases we reviewed, its potential for aggressive behavior should not be ignored. Whether SLNB should be performed as a staging procedure in every case of PEM remains controversial. Longer periods of follow-up with more cases and further molecular studies for PEM are needed to fully delineate the true biological nature of this disease.

References