# Pigmented Epithelioid Melanocytoma: Favorable Outcome After 5-year Follow-up

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**Abstract:** Pigmented epithelioid melanocytoma (PEM) is a recently described entity encompassing epithelioid blue nevus (of Carney complex) and most tumors earlier considered as so-called "animal-type melanoma". Loss of expression of a Carney complex gene, cyclic adenosine 3′,5′ monophosphate-dependent protein kinase regulatory subunit 1α, is observed in the majority of PEMs. Initial reports with short-term follow-up have suggested that although PEMs frequently metastasize to lymph nodes, they have a more favorable outcome than conventional melanomas. In this report, we present the results of long-term follow-up in 26 patients with PEMs from North America and Australia. There were 9 males and 17 females, with a median age of 20 years. The tumors involved the trunk (6 cases), extremities (12 cases), genitalia (1 case), and the head and neck region (7 cases) had a median Breslow thickness of 2.2 mm (range 0.80 to 10.0 mm) and a median Clark level of 4. Eight of the patients developed lymph node metastases. After a median follow-up period of 67 months (range 39 to 216 mo), all patients are alive and free of disease. These findings provide further evidence that PEM is a unique low-grade melanocytic tumor with limited metastatic potential (to lymph nodes), but a favorable long-term clinical course.

**Key Words:** pigmented epithelioid melanocytoma, nevus, melanoma, equine melanotic disease, epithelioid blue nevus, Carney complex, protein kinase A regulatory subunit 1α, pathology, diagnosis

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Pigmented epithelioid melanocytoma (PEM) is a recently described entity[22] which subsumes lesions earlier considered to be so-called "animal-type melanomas",[5,6] and epithelioid blue nevi (EBN)[3] occurring in patients with Carney complex (CNC), a familial lentiginosis and neoplasia syndrome.[4]

Most CNC-associated PEMs and sporadic PEMs share loss of expression of cyclic adenosine 3′,5′ mono phosphate (AMP)-dependent protein kinase A regulatory subunit 1α (R1α), a CNC complex-associated gene product.[23] This finding provides a molecular basis supporting the common phenotype of CNC-associated and sporadic cases of PEM. Importantly, no loss of R1α was observed in blue nevi which frequently harbor somatic mutations in GNAQ, a member of the q class of G-protein α-subunits involved in mediating signals between G-protein-coupled receptors.[21]

Initial[22] and subsequent reported series[1,9,17] showed that deposits of PEM were frequently found in sentinel lymph nodes (SLNs), but short-term follow-up suggested a better prognosis for PEM than for conventional metastatic melanoma. In view of these apparently paradoxical findings, we proposed that PEM be considered to be a unique low-grade melanoma or a borderline melanocytic tumor with capacity to metastasize to lymph nodes but with less frequent systemic spread.[22]

In this study, we report clinical outcomes in 26 sporadic PEMs with a long-term follow-up.

## METHODS

### Materials

All the patients included in this study had sporadically occurring PEMs with confirmed follow-up of at least 3 years from the date of the initial biopsy of the primary tumor. They included second opinion consultation (M.C.M, A.Z) cases from outside institutions (including 15 previously reported cases from the original series describing PEM),[22,23] and new cases from the Melanoma Institute Australia/Sydney Melanoma Unit and Department of Anatomical Pathology, Royal Prince Alfred Hospital, Sydney, Australia), Central Coast Dermatology, Inc, San Louis Obispo, CA, and Cutaneous Pathology Laboratory, Nedlands, Western Australia. Histologic slides from the primary tumor in all cases were

reviewed by at least 3 of the authors (A.Z in all cases and at least 2 other authors) confirming a diagnosis of PEM in each case. In some cases, expression of cyclic AMP-dependent protein kinase A R1α was studied by immunohistochemistry, exactly as described earlier.[23] Lymph node specimens were reviewed by the authors in all but 1 case. Patient demographics, primary tumor characteristics, and follow-up data were recorded. Follow-up information was confirmed by contacting primary physicians or patients directly. The study was approved by the Institutional Review Boards of the Massachusetts General Hospital, Boston, MA, and Royal Prince Alfred Hospital, Sydney, Australia.

## RESULTS

There were 9 male and 17 female patients, with a median age of 20 years (range 3 to 70 y). The sites of the tumors included the trunk (6 cases), extremities (12 cases), genitalia (1 case), and the head and neck region (7 cases). All patients underwent complete local excision. All tumors were dermal proliferations with a median depth of invasion of 2.2 mm (range 0.80 to 10.00 mm). The histologic features of PEMs were described in detail in previous reports.[9,17,22] All cases were essentially indistinguishable from EBN of CNC.[3] The Clark level of invasion was level 3 in 2 cases, level 4 in 19 cases, and level 5 in 5 cases. Satellite lesions were not identified in any of the cases. Ulceration was present in 2 lesions. SLN biopsy was performed in 18 patients, and 2 patients (cases 15 and 19) underwent a complete lymphadenectomy without SLN biopsy. Eight of these patients had nodal metastases. In 1 case (case 22), capsular deposits were identified and interpreted in an outside laboratory as most likely representing capsular nevus deposits. The slides from this case were not available for re-review. The extent of nodal involvement (such as size of lymph node deposits) was not recorded, but ranged from large tumor deposits resulting in clinically palpable lymph nodes to small clusters of cells. Complete lymphadenectomies were performed in all cases with positive SLNs. Five of the patients with SLN metastasis (cases 13, 14, 16 to 18) received interferon treatment. After a median follow-up period of 67 months (range 39 to 216 mo), all patients are alive and free of disease.

The clinical and pathologic information is summarized in Table 1. A representative case, with the longest clinical follow-up in the present series is illustrated in Figure 1.

## DISCUSSION

PEM is a recently described entity encompassing EBN of CNC and most lesions earlier considered to be so-called "animal-type melanoma".[22,23] The morphologic observations that suggested that PEM is a distinct tumor occurring in the context of the CNC syndrome and, more frequently, in a sporadic setting were further confirmed by a recent study showing that PEM frequently shows loss of expression of cyclic AMP-dependent protein kinase 1 R1α, a product of a gene mutated in families with CNC.[23] Cyclic AMP signaling is critically involved in regulation of melanocyte proliferation and pigment synthesis.[15] Therefore, loss of R1α expression is consistent with its pathogenic role in PEM and helps explain dark pigmentation of this tumor.

Upon its introduction, the concept of PEM as an entity encompassing EBN and so-called "animal-type melanoma" seemed controversial due to conflicting data regarding the biologic behavior of these lesions. There was no evidence at the time of metastatic behavior of EBN occurring in the context of CNC. In contrast, morphologically indistinguishable lesions with documented metastasis were termed "animal-type" melanoma because of their resemblance to melanomas in animals, especially gray horses.[6] As a consequence, such heavily pigmented melanocytic lesions were a source of considerable diagnostic difficulty. On the basis of the then prevailing and, in retrospect, likely flawed assumptions that the presence of lymph node metastases indicates malignancy and that all metastasizing melanocytic tumors are equally malignant, SLN biopsy was used as a "diagnostic adjunct" in an attempt to establish the biologic potential of diagnostically difficult melanocytic proliferations. Initial studies with relatively short follow-up periods indicated that PEM patients with positive SLNs did better than would be expected in patients with melanoma of a similar stage.[22] This observation, together with the lack of documented metastases in any patient with an EBN of CNC (despite this entity being recognized for more than 25 y), suggested that SLN involvement in at least the majority of PEMs does not have the same adverse prognostic significance as in conventional melanoma.

Longer follow-up data reported in this study support this notion. After a median follow-up period of 67 months in this study, no adverse outcomes were seen in patients with PEM, including in those with SLN metastases. The results illustrate that spread of PEM beyond local lymph nodes is rare and that the prognosis is significantly more favorable than that of conventional melanoma. Importantly, the findings indicate that the presence of lymph node metastases in PEM does not imply a malignant clinical course. Yet, the follow-up period reported in this study is still too short to allow confident categorization of PEM as an entirely benign tumor, as it is well-known that malignant behavior and metastasis in melanoma may occur many years and even decades after excision of the primary tumor.[2]

So, what is PEM? Given its unique clinicopathologic features and, most importantly, favorable long-term outcome demonstrated in this study (even in the presence of lymph node involvement), PEM seems to behave differently to conventional melanoma. However, the limited ability of PEM to spread to regional lymph nodes and to even present clinically as lymph node metastases, argues that it may not be merely a conventional nevus. We believe that this entity is best understood if the traditional dichotomous "nevus versus melanoma"

**TABLE 1.** Clinical and Pathologic Features of Cases of Pigmented Epithelioid Melanocytoma

| No. | Age (y) | Sex | Site | Breslow (mm) | Clark Level | Ulceration | Sentinel Node Status | Follow-up (mo) |
|---|---|---|---|---|---|---|---|---|
| 1 | 13 | Female | Leg | 4.10 | 4 | Absent | Negative | 50 |
| 2 | 51 | Female | Arm | 0.89 | 4 | Absent | Negative | 59 |
| 3 | 70 | Female | Buttock | 2.10 | 4 | Absent | Negative | 61 |
| 4 | 12 | Female | Arm | 2.40 | 5 | Absent | Negative | 66 |
| 5 | 20 | Female | Cheek | 1.80 | 4 | Absent | Negative | 67 |
| 6 | 9 | Male | Hip | 4.40 | 4 | Absent | Negative | 72 |
| 7 | 7 | Female | Eyelid | 3.00 | 4 | Absent | Negative | 72 |
| 8 | 40 | Male | Hand | 4.00 | 4 | Absent | Negative | 74 |
| 9 | 31 | Female | Arm | 1.80 | 4 | Absent | Negative | 74 |
| 10 | 40 | Female | Nipple | 1.50 | 4 | Absent | Negative | 84 |
| 11 | 23 | Female | Back | 1.90 | 4 | Absent | Negative | 94 |
| 12 | 40 | Male | Back | 1.80 | 4 | Absent | Positive | 49 |
| 13 | 38 | Female | Calf | 2.50 | 5 | Absent | Positive | 61 |
| 14 | 32 | Male | Arm | 3.00 | 5 | Absent | Positive | 62 |
| 15 | 9 | Female | Face | 2.30 | 4 | Absent | Positive* | 77 |
| 16 | 21 | Female | Thigh | 10.00 | 4 | Present | Positive | 81 |
| 17 | 27 | Male | Scalp | 2.20 | 4 | Absent | Positive | 95 |
| 18 | 9 | Male | Scalp | 3.50 | 5 | Absent | Positive | 116 |
| 19 | 3 | Female | Scalp | 10.00 | 5 | Absent | Positive* | 216 |
| 20 | 16 | Female | Shoulder | 0.80 | 3 | Absent | Unknown | 39 |
| 21 | 45 | Male | Neck | 1.50 | 4 | Absent | Unknown | 47 |
| 22 | 26 | Female | Thigh | 0.90 | 3 | Absent | Equivocal | 53 |
| 23 | 16 | Male | Chest | 0.95 | 4 | Absent | Unknown | 56 |
| 24 | 3 | Male | Arm | 2.00 | 4 | Present | Unknown | 67 |
| 25 | 20 | Female | Back | 1.50 | 4 | Absent | Unknown | 72 |
| 26 | 13 | Female | Labia | 2.90 | 4 | Absent | Unknown | 67 |

*Positive lymph node in complete lymphadenectomy; no sentinel lymph node biopsy was performed.

paradigm is modified to include a third, intermediate category of melanocytic proliferations, capable of regional lymph node metastasis but rare systemic spread with a generally indolent clinical course. We propose that the term ''melanocytoma'' could be applied as a general category for these lesions.

Adoption of a nevus/melanocytoma/melanoma paradigm may offer a new intellectual framework for understanding other diagnostically difficult melanocytic proliferations such as some atypical deep penetrating nevi, metastasizing variants of blue nevus, and most importantly, more common and diagnostically more challenging, atypical Sptiz tumors, which have been reported to be capable of spreading to regional lymph nodes but are associated with a favorable prognosis.[16,18] As in PEM, SLN sampling has been used as an adjunctive test in an attempt to predict the biological potential of diagnostically difficult atypical Spitz tumors. Combined data from published institutional series[7,10,11,13,19,20] reporting outcomes in 145 patients shows that SLN metastases are found in 29% to 50% of atypical Spitz tumors. All the reported patients were well without evidence of residual or recurrent disease with a median follow-up of 35 months. This data indicates that, although being distinct entities, atypical Spitz tumor and PEM have similar biological potential and may be considered as members of the same class of melanocytic lesions.

One remaining question is about the nosological standing of the rare lesions previously included in the category of animal-type melanoma, which do not meet strict criteria of PEM, including those rare cases where PEM is a minor component of an otherwise obvious melanoma. Further research is needed to determine if they represent a distinct entity and still deserve to be recognized under the rubric of animal-type melanoma or are best considered as a heterogenous group of darkly pigmented melanomas, perhaps unusual variants of malignant blue nevus or malignant neurocristic hamartoma.

Our study provides additional useful information to help guide the management of patients with PEM. The primary cutaneous lesion should be removed with clear margins to reduce the risk of local recurrence. It is not clear if completely excising PEMs with margins as wide as those recommended for conventional melanoma of corresponding depth of invasion is necessary. Furthermore, it is questionable whether PEM patients benefit from SLN biopsy. Certainly, it is difficult to justify SLN sampling in patients with PEM arising in the context of CNC, as there are no reports of patients with EBN (in whom SLN biopsy has not, to the best of our knowledge, ever been performed) developing nodal or other metastases. In sporadic PEM in which SLN sampling was performed, the presence or absence of lymph node metastases does not seem to affect prognosis. The only rationale for performing the procedure in these patients would seem to remove the potential tumor burden harbored within the SLNs. Yet, it seems unlikely that removal of any tumor that may be present in SLNs is necessary or beneficial in most cases, as many patients have not had SLN sampling and we are not aware of

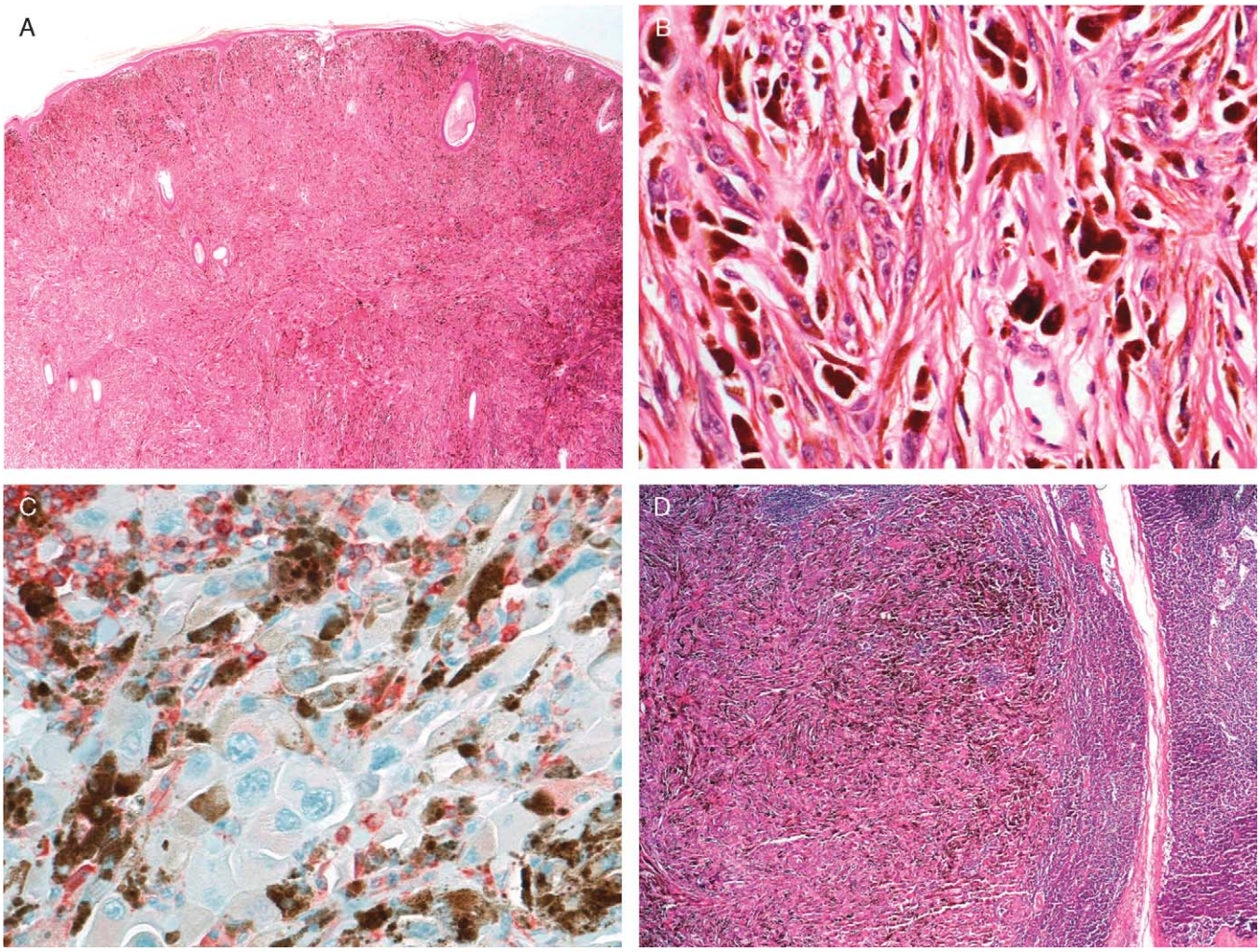


**FIGURE 1.** Pigmented epithelioid melanocytoma (case 19) from the scalp of a 3-year-old girl. Superficial portion of an excision specimen (A) shows pigmented deep dermal tumor composed of blue nevus-like dendritic cells, darkly pigmented polygonal cells, and large epithelioid cells (B) showing loss of cyclic adenosine 3′,5′ monophosphate-dependent protein kinase A regulatory subunit 1α on immunohistochemical stains (C). The tumor metastasized to lymph nodes (D). The patient is well without any evidence of residual disease 20 years later.

nodal recurrence or adverse outcomes in these patients.[1,8,9,12,14,17,22] Moreover, any potential benefit of the SLN biopsy has to be balanced against the morbidity of the procedure and the uncertainty about true long-term biological potential of these tumors because of limited follow-up. However, identifying the SLNs by lymphoscintigraphy for subsequent close monitoring by clinical examination and ultrasound offers a noninvasive strategy that may allow early detection of growing metastases. Certainly, patients with PEM with lymph node deposits should not be re-classified as having melanoma because the behavior of PEM, in most cases, is much more favorable than that of conventional melanoma. PEM is clearly a distinct disease from conventional melanoma. This also implies that there is no rational justification to commence PEM patients found to harbor lymph node deposits on toxic biologic or chemotherapeutic agents, such as interferon, approved for treatment of metastatic melanoma.

In summary, our study indicates that PEM is a low-grade melanocytic tumor that may involve regional lymph nodes but has limited ability to spread beyond lymph nodes, and has a favorable clinical outcome in most cases.

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