Two congenital cases of pigmented epithelioid melanocytoma with unique clinical and genetic features

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Abstract

Pigmented epithelioid melanocytomas (PEM) are intermediate-grade melanocytic lesions with frequent lymph node involvement and rare metastases that tend to follow an indolent course with a favorable outcome. We report two unique cases of congenital PEM with *PRKCA* fusion transcripts: a multifocal PEM with an aggressive incompletely resectable scalp tumor and a solitary palmar PEM with newly reported *ITGB5-PRKCA* fusion. Through these case reports and a summary of previously reported cases, we outline the spectrum of disease of PEM and highlight the key clinical and histopathologic features associated with PEM with *PRKCA* fusion transcripts. We also discuss the treatment options and suggest that surgical excision without further adjuvant systemic treatment is reasonable first-line therapy given the favorable prognosis.

Keywords: epithelioid, melanocytoma, pigmented. PRKCA

Introduction

Pigmented epithelioid melanocytomas (PEM) are melanocytic neoplasms that typically follow an indolent course with favorable outcome. Amongst reported cases, lymph node involvement is common, whereas distant metastases are rare. Pigmented epithelioid melanocytomas was first defined in 2004 as an umbrella term for borderline melanocytic lesions encompassing animal-type melanomas, Carney complex's epithelioid blue nevus (EBN), and pigment synthesizing melanoma [1]. Historically, all these terms have all been lumped, but a PEM-like pigmented fatal melanoma that was categorized as pigment synthesizing menlanoma has been reported [2]. Since then, further research has defined the variable genetic drivers of PEM, including a subset with *PRKCA* fusion transcripts [3]. We present two cases of congenital PEM with *PRKCA* fusion transcripts and review existing reported cases to illustrate the spectrum of presentation.

Case Synopsis

Case 1

A term healthy 3-month-old male presented with a large ulcerated pigmented plaque of the scalp with an associated firm subcutaneous occipital mass and multiple blue-black papules on the trunk and extremities (**Figure 1A**, **B**). There was no history of Carney-complex-associated clinical findings in the patient or family members. The lesions were present from birth, but the ulceration was acute. Significant palpable cervical lymphadenopathy was noted.

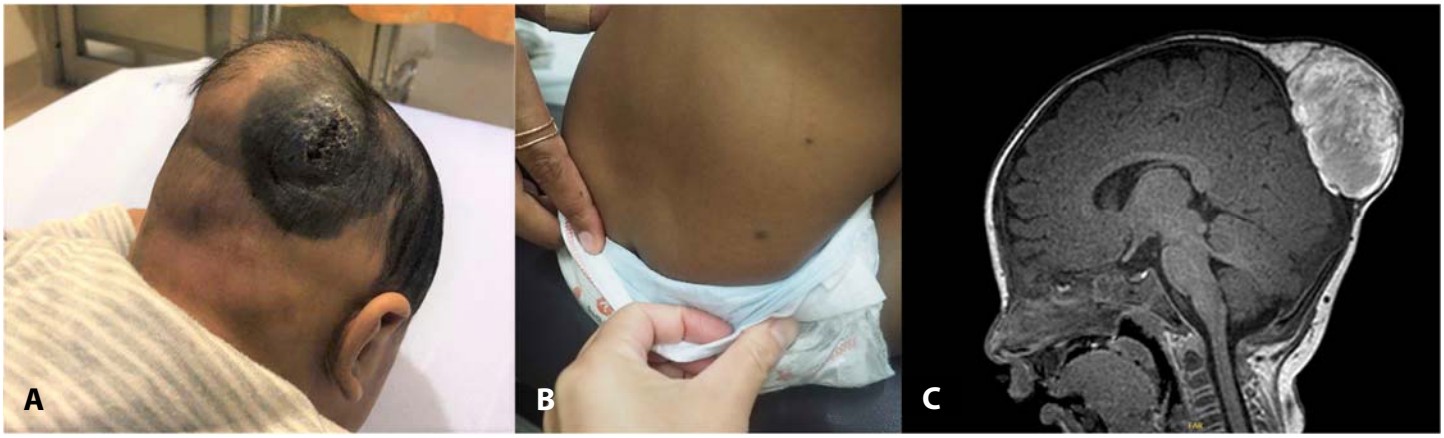

Figure 1. *Clinical and MRI Findings of the pigmented epithelioid melanocytomas in Patient 1.* ***A)*** *Posterior scalp mass with overlying ulcerated blue-black plaque, as well as visible lymphadenopathy on the right posterolateral neck.* ***B)*** *Multiple blue-black papules on the trunk.* ***C)*** *T1-weighted MRI of the brain demonstrating a intrinsic T1 hyperintense mass, with invasion of the bilateral parieto-occipital bones. There is mass effect with mild narrowing of the superior sagittal sinus and intracranial extension into the extra-axial space with mass effect on the underlying brain parenchymal without evidence of intra-parenchymal invasion.*

Neurologic examination was normal. MRI revealed a heterogeneous tumor with areas of melanosis, hemorrhage, calcification, and invasion of the calvaria (**Figure 1C**) with prominent right cervical lymph nodes. CT scans of the chest, abdomen, and pelvis were unremarkable. Incisional biopsy of the scalp identified a nodular proliferation of heavily pigmented melanocytes with a monomorphic epithelioid and focally spindle cell morphology, with mild pleomorphism and mitotic activity (3/mm^2). Tumor cells had moderate amounts of cytoplasm with finely granular melanin pigment and nuclei were round-to-oval with finely dispersed-to-vesicular chromatin and prominent nucleoli. The tumor edge extended into deep soft tissue and was characterized by melanocytes extending between collagen bundles. Clusters of peripheral melanophages were present. No evidence of a pre-existing or co-existing melanocytic nevus was seen. The overlying epidermis was thinned and ulcerated (**Figure 2**). Tumor cells were S100+, HMB45+, Melan A+, with partial loss of HK27M. A lymph node biopsy demonstrated several subcapsular and parenchymal deposits of similar cells. TruSight RNA Pan-Cancer panel assay (slightly modified for pediatric use) revealed a *SCARB1-PRKCA* fusion transcript. The fusion breakpoints were consistent with previously reported cases of PEM with *SCARB1-PRKCA* fusions [3]. Expanded genetic analysis using an 864 gene cancer panel on paired tumor/normal (blood) through the SickKids Cancer Sequencing (KiCS) program revealed no additional oncogenic variants in the tumor (including variants in *PRKAR1A*, *RAS* pathway genes, *TERT*, cell cycle genes), and no whole

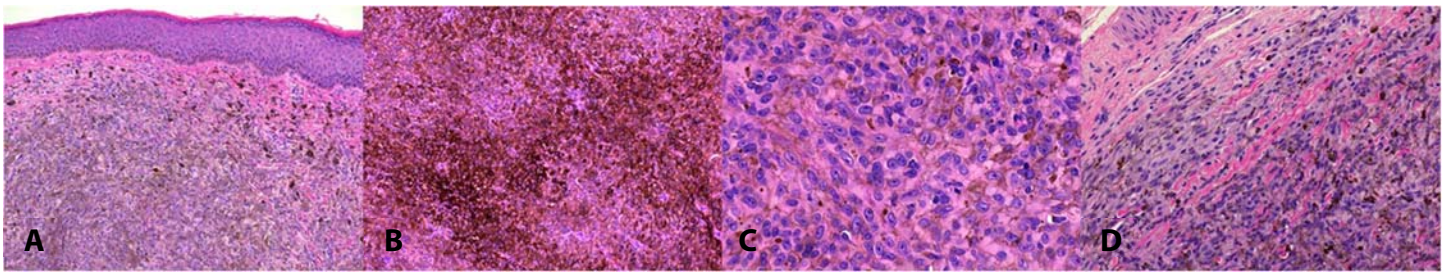

Figure 2. *H&E histopathologic findings of the pigmented epithelioid melanocytomas in Patient 1.* ***A)*** *Medium power view of the lesion showing epidermal atrophy overlying a lesion comprising sheets of heavily pigmented melanocytes, 100×.* ***B)*** *Medium power view showing sheets of heavily pigmented predominantly monomorphic epithelioid melanocytes, 100×.* ***C)*** *High power view of the lesion showing cytological detail, with epithelioid melanocytes, finely dispersed melanin, and round to oval nuclei with mild pleomorphism and even chromatin and prominent nucleoli. A mitotic figure is present upper right of photo, 400×.* ***D)*** *Deep part of the lesion showing infiltration and wrapping of individual collagen bundles by tumor cells, 200×.*

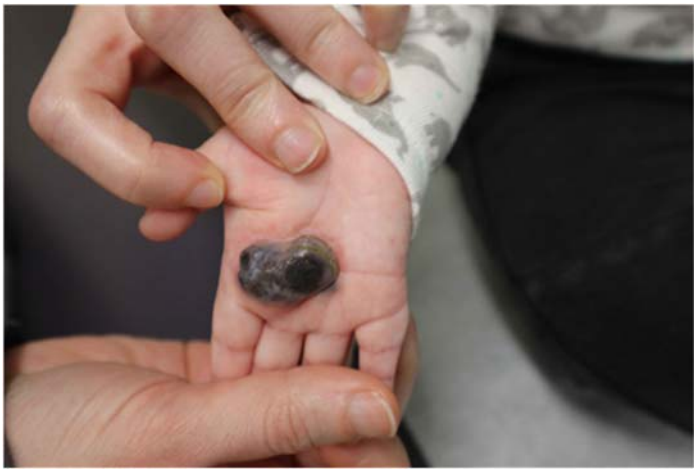

Figure 3. *Clinical findings of the pigmented epithelioid melanocytomas in Patient 2. Black, soft, and lobulated tumor on the right palm.*

chromosomal, segmental, or focal copy number changes. There were no pathogenic or likely pathogenic germline variants. Skin biopsy of a truncal papule showed similar histopathological findings with the same fusion transcript. Based on these findings, the patient was diagnosed with multifocal PEM. Surgical excision of the large scalp lesion was attempted, but complete resection proved impossible due to infiltration of the dura. Instead, the carpet of melanocytic material infiltrating the dura was radically cauterized and scraped, as appropriate. Right lateral (levels 2-5) and bilateral occipital neck dissection revealed multiple involved lymph nodes (41 lymph nodes were sampled with 9 positive). No further interventions were performed. At two years follow-up, the patient continues to grow and develop appropriately, with no regrowth or progression on clinical examinations and serial imaging.

Case 2

A full-term healthy 3-month-old male presented with an asymptomatic blue-black, soft, and lobulated tumor on his right palm present from birth (**Figure 3**). There was no history of Carney-complex-associated clinical findings in the patient or family members. The lesion remained stable in size over several months, although it was complicated by superficial ulceration. There was no lymphadenopathy. Histopathologic examination from incisional biopsy revealed sheets of heavily pigmented epithelioid melanocytes with mild atypia. Cells were epithelioid and contained moderate amounts of cytoplasm with finely granular melanin pigment in many cells. Nuclei were round-to-oval with finely dispersed to vesicular chromatin and prominent nucleoli. Mitotic activity was present (up to 2.5/mm^2). At the deep margin, the border was infiltrative and clusters of melanophages were seen. There was no evidence of a co-existing or pre-existing nevus (**Figure 4**). Molecular analysis was positive for an *ITGB5-PRKCA* fusion transcript. Histologic and genetic findings were consistent with PEM. Management involved surgical excision of the tumor (depth 1.3cm) with acceptance of microscopically-positive margins to avoid damage to

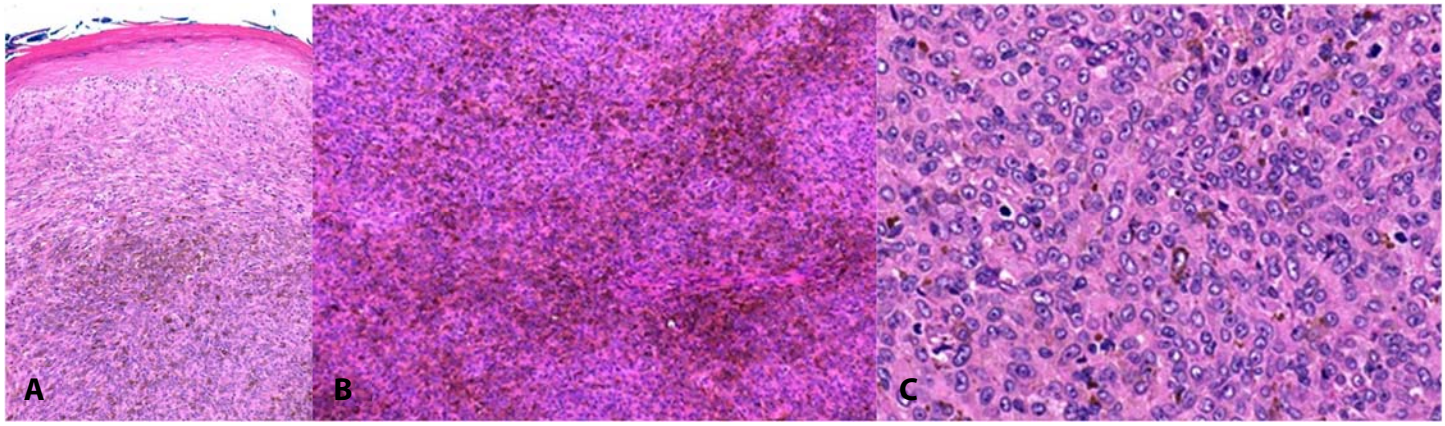

Figure 4. *H&E histopathological findings of the PEM in Patient 2.* ***A)*** *Medium power view of the lesion showing epidermal atrophy overlying sheets of variably pigmented melanocytes, some with epithelioid and some with a spindle morphology, 100×.* ***B)*** *Medium power view showing sheets of heavily pigmented predominantly monomorphic epithelioid melanocytes with mild pleomorphism, 100×.* ***C)*** *High power view of the lesion showing epithelioid melanocytes, finely dispersed melanin, and round to oval nuclei with mild pleomorphism and even chromatin and prominent nucleoli, 400×.*

surrounding tissues. The post-resection skin defect was reconstructed with Integra and a full thickness skin graft. Lymph node biopsy was deferred due to lack of clinical lymphadenopathy, relative stability of the tumor over time, and potential for secondary morbidity. At two years follow up, the patient has remained stable with no evidence of regrowth.

Case Discussion

Pigmented epithelioid melanocytomas is an umbrella term currently used to refer to the histologically-similar epithelioid blue nevus (EBN) associated with the Carney complex [1] animal-type melanoma, and pigment-synthesizing melanoma [4]. Although these were previously described as unique entities, they may, however, represent a spectrum of discrete lesions. With more comprehensive molecular characterization, distinct clinical behaviours may become more apparent.

Pigmented epithelioid melanocytomas can develop at any age, but congenital cases are rarely reported [4,5]. To our knowledge, there have been only 18 cases of congenital PEM previously reported in the literature, none demonstrating features or genetic changes associated with Carney complex [4-8]. No congenital cases were reported to be fatal. More broadly, PEM typically follows an indolent course. Limited ability to spread beyond local lymph nodes has been described, with only rare distant or visceral metastases and a low risk of local recurrence [1]. As demonstrated in **Table 1**, reported patients with *PRKCA* fusion transcripts presented with both congenital and acquired disease. Pigmented epithelioid melanocytomas was overwhelmingly focal, except for our case with multifocal disease.

The diagnosis of PEM can be challenging and requires clinical, pathological, and molecular correlation. Several publications have described PEMs as having features of both nevus (epithelioid blue nevus) and melanoma (animal-type melanoma), [1,9]. In both our cases, the histopathological features were very similar to those previously described in PEM: epithelioid melanocytes arranged in sheets and nodules with pigmented cytoplasm, vesicular nuclei, and prominent nucleoli. Overlying ulceration as well as deep infiltration was also described [9]. Further, specifically for tumors harboring *PRKCA* rearrangements, overlying epidermal atrophy and deep infiltration by insinuating cells between collagen bundles were described [9], as in both current tumors.

The optimal management of PEM has not yet been established. Current limited evidence suggests local excision with clear surgical margins is sufficient [6]. However, management is further complicated by the presence of multifocal cutaneous and lymph node involvement; the role of systemic therapy remains unclear [10]. Interferon is reported in the management of sentinel lymph node metastases in one case series [10]. Another case report describes the use of nivolumab for multiple distant metastases [8]. Two other congenital cases were treated with traditional chemotherapy. One achieved no appreciable effect on the size of the mass and then underwent wide local excision with no recurrence [4]; the other was treated with chemotherapy after excision of the primary scalp lesion due to the presence of positive lymph nodes, with no subsequent recurrence of disease [7]. Conversely, an additional two cases of congenital multifocal PEM underwent excision of the largest lesion with no active therapy for other foci; absence of disease progression was reported for these cases, as well [11,12].

In our first case, extensive involvement of the pericranium and dura made complete excision impossible. Radical excision was also avoided with case two to balance the suspected favorable prognosis of PEM with unwanted iatrogenic morbidity. Our experience supports the paradigm that despite the local invasiveness of these lesions, even subtotal resection may yield favorable outcomes, although ongoing longitudinal follow-up is needed and caution is warranted given the challenge in differentiating PEM from malignant melanoma. Herein, molecular studies may play a key role.

Pigmented epithelioid melanocytomas represents a genetically heterogeneous entity, including a subset with reported inactivating mutations in the protein kinase, cAMP-dependent, regulatory, type I, alpha

(*PRKAR1A)* gene [9], found as a heterozygous germline mutation in 40% of individuals with Carney complex [13]. Therefore, patients presenting with PEM should undergo genetic testing if possible, with ongoing monitoring for development of additional associated features when indicated. Pigmented epithelioid melanocytomas have also been related to mutations in *GNAQ, MAP2K1, BRAF, NRAS*, and *PRKCA* fusions, among others [3,9]. *PRKCA* fusions with *RNF13, SCARB1, CD63, ATP2B4*, and *MAP3K3* have been reported [3,9,14] and likely represent the most common molecular subset of PEM unrelated to Carney complex. Although the *PRKCA* chromosomal locus lies in proximity to *PRKAR1A*, *PRKCA* has yet to be implicated as a constitutional driver in *PRKAR1A*-negative patients with clinically-diagnosed Carney complex and mutations in *PRKCA* and *PRKAR1A* in PEM appear to be mutually exclusive [3]. The *PRKCA* product has a variety of cellular functions, including proliferation, apoptosis, differentiation, and motility [15]. The conserved *PRKCA* kinase domain induces the phosphorylation of RAF-1, which activates the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) cascade, a key signaling pathway in melanocyte growth and survival [16]. Therefore, activation of the kinase domain likely leads to dysregulated melanocyte proliferation [14]. Importantly, *PRKCA* fusions have not been reported in databases of sequenced cutaneous melanomas [17].

In this report, we present a case of PEM resulting from a novel *ITGB5-PRKCA* fusion transcript. *ITGB5* is part of the integrin family of cell adhesion receptors, which regulate a diverse array of cellular functions crucial to the initiation, progression, and metastasis of solid tumors [18]. Its specific role in the pathogenesis of PEM remains unknown.

Conclusion

Our cases highlight the key clinical and histopathologic features of PEM while providing insight into the molecular underpinnings, including a novel *ITGB5-PRKCA* fusion gene. Further research is needed to explore the associations between genetics and clinical phenotypes and ultimately inform management and prognosis.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Summary of reported cases of pigmented epithelioid melanocytomas with PRKCA fusion transcripts.*

Reference	N	Patient	*PRKCA* Fusions	Age, Congenital/ Acquired	Clinical Appearance	Focal/ Multifocal	Site(s)	Histopathologic features	Treatment	Outcome	Follow-up
Bahrami et al. [13]	1	1	*ATP2B4–PRKCA*	5 mo Congenital	6-cm protuberant mass	Focal	Vertical - occipital scalp	Heavily pigmented intradermal proliferation of large, epithelioid melanocytes with mild cytologic atypia, low mitotic activity, focal necrosis, and ulceration	Complete Surgical excision of the mass	No Recurrence	1 y
Cohen et al. [8]	2	2	*ATP2B4-PRKCA*	9 y Acquired	None provided	Focal	Cheek	Nodular appearance with a box-like silhouette and an infiltrative leading edge	None provided	None provided	None provided
		3	*RNF13-PRKCA*	44 y Acquired	None provided	Focal	Wrist	Plaque-like shape with a wedge-shaped silhouette and bulbous base	None provided	None provided	None provided
Isales et al. [2]	5	4	*SCARB1-PRKCA*	10 y Acquired	None provided	Focal	Back, upper	Sheets of epithelioid melanocytes (wedge pattern), nuclear atypia(moderate), mitoses (3/mm2)	None provided	No Recurrence	1 y
		5	*CD63-PRKCA*	21 y Acquired	Nevus, vascular	Focal	Parietal Scalp	Sheets of epithelioid melanocytes (wedge pattern), nuclear atypia(moderate), mitoses (2/mm2)	None provided	No Recurrence	4 y
		6	*SCARB1-PRKCA*	5 y Acquired	None provided	Focal	Upper lip	Sheets of epithelioid melanocytes (nodular pattern), nuclear atypia(moderate), mitoses (2/mm2)	None provided	No Recurrence	1 y
		7	*ATP2B4-PRKCA*	6 y Acquired	None provided	Focal	Chest wall	Sheets of epithelioid melanocytes (plexiform pattern), nuclear atypia(moderate), mitoses (1/mm2)	None provided	No Recurrence	4 y
		8	*MAP3K3-PRKCA*	12 y Acquired	Hyperpigmented papule	Focal	Earlobe	Sheets of epithelioid melanocytes (nodular pattern), nuclear atypia (focal high Grade), mitoses (<1/mm2)	None provided	No Recurrence	8mo
This study	2	9	*SCARB1-PRKCA*	3 mo Congenital	Posterior scalp mass with an overlying blue-black ulcerated plaque, multiple	Multifocal	Scalp and body	Nodular proliferation of heavily pigmented melanocytes with a predominant epithelioid morphology, with mild	Partial resection of scalp mass	No Recurrence	11 mo

					blue papules scattered on the body			pleomorphism and mitotic activity (3/mm2).			
		10	*ITGB5 (exon 14)-PRKCA* (exon 9)	6 mo Congenital	Black, soft, lobulated tumor on the right palm	Focal	Palm	Nodular proliferation of heavily pigmented melanocytes with epithelioid morphology, mild atypia and mitotic activity (2.5/mm2).	Subtotal resection of tumor	No recurrence	11 mo

mo-moths, y-years.