

PRAME Expression in Two Infantile Melanocytic Neuroectodermal Tumors: Mimicker and Innocent

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ABSTRACT

Objective: Infantile melanocytic neuroectodermal tumor is a rare, locally aggressive, osteolytic neoplasm, most commonly seen in the anterior maxilla of infants. The tumor contains cuboidal and epithelioid cells that contain melanin in alveolar and tubular patterns, and neuroblast-like round cells. Although this tumor usually shows rapid growth, it is generally considered benign.

Case Report: Two patients with unusual localizations at the arm and parietal bone are presented.

Conclusion: PRAME expression in this tumor has not been investigated so far. We present these two cases with PRAME immunoeexpression in the light of the literature.

Keywords: Infantile melanocytic neuroectodermal tumor, Calvarium, Retinal anlage tumor, Melanotic progonoma, PRAME

INTRODUCTION

Infantile melanocytic neuroectodermal tumor (IMNT) is a rare, locally aggressive neoplasm, most commonly seen in infants and often in the anterior maxilla (1,2). Although it grows rapidly, it is generally accepted as having benign biological behavior since it can be controlled by surgical excision (1). We present two patients with parietal bone and arm localization, with their clinical and histological features documented in the context of the literature.

CASE REPORT

Case 1

An 8-month-old girl with swelling on her head that had begun 4 months ago presented to the Neurosurgery Department. Subsequently, a mass was detected in the calvarium using magnetic resonance imaging (MRI). She had no history of nausea, vomiting, or seizures and her neurological examination and laboratory results were normal. At her first admission, a smooth, solid mass lesion (32 x 17 x 22 mm) invading the parietal bone was observed. Both lateral ventricles were enlarged. Four months later, computerized tomography (CT) showed a hyperdense mass lesion (38 x 24 mm) with a calcific hyperdense ossification focus, and with occasional loss of bone cortex integrity. Bilaterally, the frontal lobes and superior sagittal sinus had extended into the posterior region. Calvary mass excision was planned.

In the macroscopy, the excised bone material had dimensions of 6.8 x 6.2 x 2.1 cm. In the concave part of the material, a solid, firm, hemorrhagic, partly off-white mass (4.2 x 3.3 x 2.2 cm) was observed. The tumor that had irregular borders had infiltrated the full thickness of the corticotrabecular bone tissue. The mass was 0.9 cm away from the lateral surgical margin at the closest point on the concave face. On microscopic examination, the tumor was characterized by the presence of cuboidal, epithelial cells featuring alveolar and tubular patterns and containing varying concentrations of melanin in fibrotic stroma. Some of the tumor cells that had narrow cytoplasm and hyperchromatic nuclei were in the alveolar and tubular groups, and some were scattered and infiltrative in the desmoplastic stroma (Figure 1A-C). The tumor exhibited a biphasic growth pattern. Atypia, necrosis, and mitosis were not observed. Two cell groups of tumor cells were positive for synaptophysin, pankeratin, Cam5.2 (Figure 1D), and EMA, and negative for desmin, S100, SOX10 (Figure 1E), HMB45, PRAME (Figure 1F), and BerEP4. There was no proliferative activity based on staining for Ki-67. All antibodies were ready to use. The clones and companies of the antibodies used in the study are presented in Table I. A chemotherapy regimen that included vincristine, doxorubicin, cyclophosphamide, dactinomycin, ifosfamide, and etoposide was planned. No changes or new masses were detected on the MRI examination performed 44 months after the surgery.

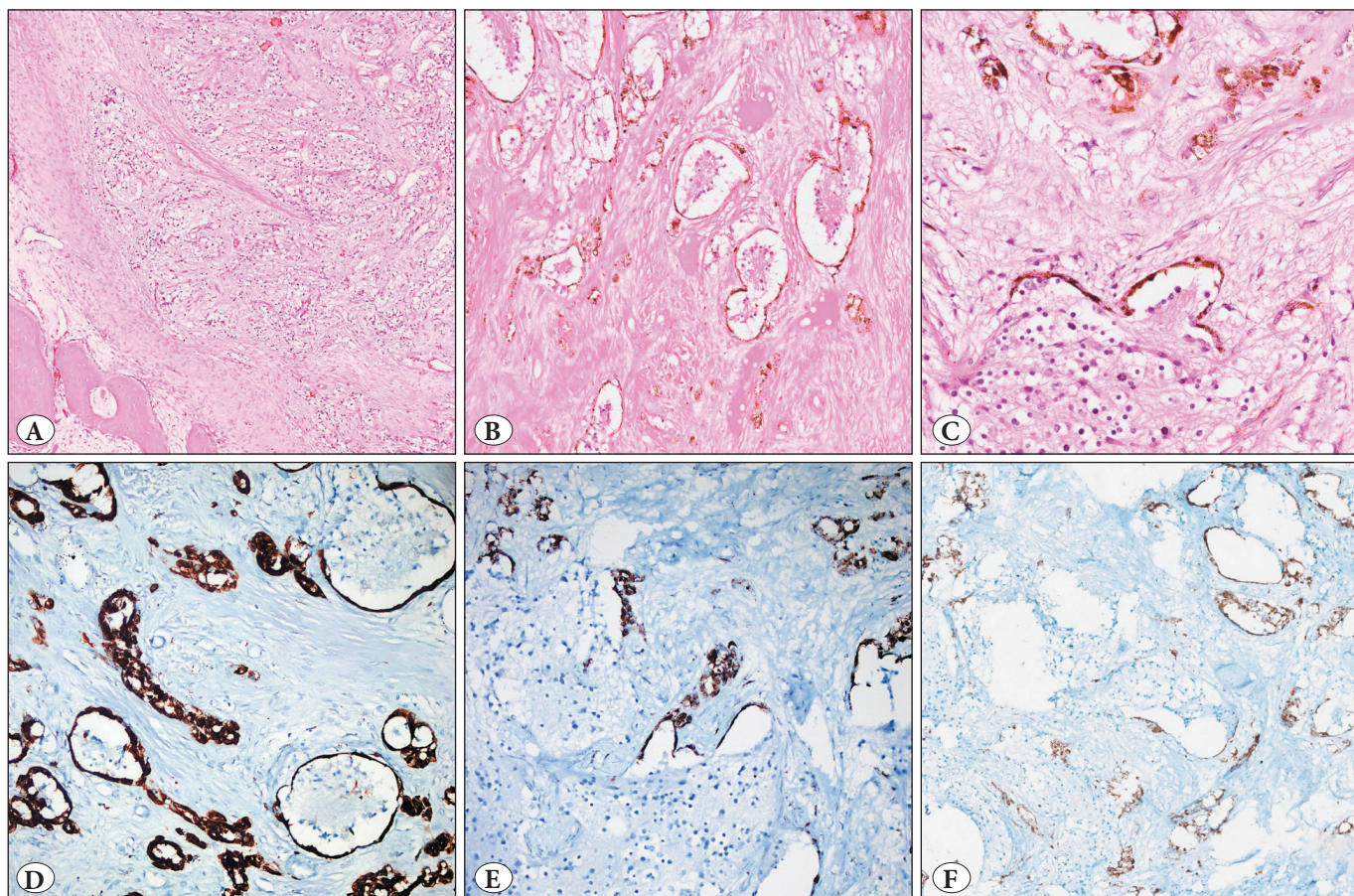


Figure 1: A-C) The first patient's tumor includes melanin-containing cubic cells with a tubular pattern and small, hyperchromatic cells with scanty cytoplasm like neuroblasts (H&E, 50X, 100X, 200x). D) Tumor cells positive with Cam5.2 (DAB, 200x). E) Peripheral melanin-containing cells and SOX10-negative small tumor cells in the center (DAB, 200x). F) Tumor cells negative with PRAME (DAB, 100x); the brown pigment in this figure is melanin pigment.

Table I: Immunohistochemical clones and companies of the antibodies used in the study

Antibody	Species and clone	Company
Cam5.2	Monoclonal mouse, Cam5.2	Roche, Arizona, USA
Pankeratin	Monoclonal mouse, AE1/AE3/PCK26	Roche, Arizona, USA
EMA	Monoclonal mouse, E29	Roche, Arizona, USA
Synaptophysin	Rabbit monoclonal, MRQ-40	Cell Marque, Arizona, USA
SOX10	Rabbit monoclonal, SP267	Roche, California, USA
Desmin	Monoclonal mouse, DE-R-11	Roche, Arizona, USA
HMB45	Monoclonal mouse	Arizona, USA
Ber-Ep4	Monoclonal mouse	Cell Marque, California, USA
S100	Monoclonal mouse, 4C4.9	Roche, Arizona, USA
Ki-67	Rabbit monoclonal, 30-9	Roche, Arizona, USA
PRAME	Rabbit monoclonal, EPR20330	Roche, Arizona, USA

Case 2

A 2-year-old boy was first diagnosed with a hematoma when he was 2 months old after a swelling was noticed in his arm. In the macroscopy, a white and black solid mass measuring 9.5 x 8 x 4 cm under the skin in the section of the excision material was noted. The surgical margins were intact. MRI showed a 45x33x30 mm heterogeneous, hyperintense, and peripherally-enhancing mass with lobulated contours that arched over the biceps and brachialis muscles and extended to the skin.

Microscopy of this tumor was similar to the first one, and it was not related to the skin (Figure 2A,B). Desmin and S100 (Figure 2C) were negative, and synaptophysin (Figure 2D), pankeratin, HMB45, CD99, and SOX10 were positive at both of the tumors' cells. PRAME was diffusely positive in both cell groups of the tumor. The staining was not strong in any of them and was generally moderate (Figure 2E). There was no proliferative activity based on staining with

Ki-67. Some of the immunohistochemical markers differed among the cases. The same chemotherapy regimen was planned for this patient. No changes or new masses were detected in the MRI examination performed 14 months after the surgery.

DISCUSSION

IMNT is a rare, locally aggressive, osteolytic neoplasm, first described by Krompecher in 1918, and is most commonly seen in the anterior maxilla in early infancy (under one year of age) (1,2). The incidence of tumors in males is slightly higher (3). Confusion related to the origin of the tumor has led to different nomenclatures such as congenital melanocarcinoma, retinal sign tumor, pigmented congenital epulis, and melanotic progonoma (2). In 1966, Borello and Gorlin suggested that some of the tumors were derived from neural crest cells, based on the elevated level of vanillylmandelic acid (VMA) (2,4).

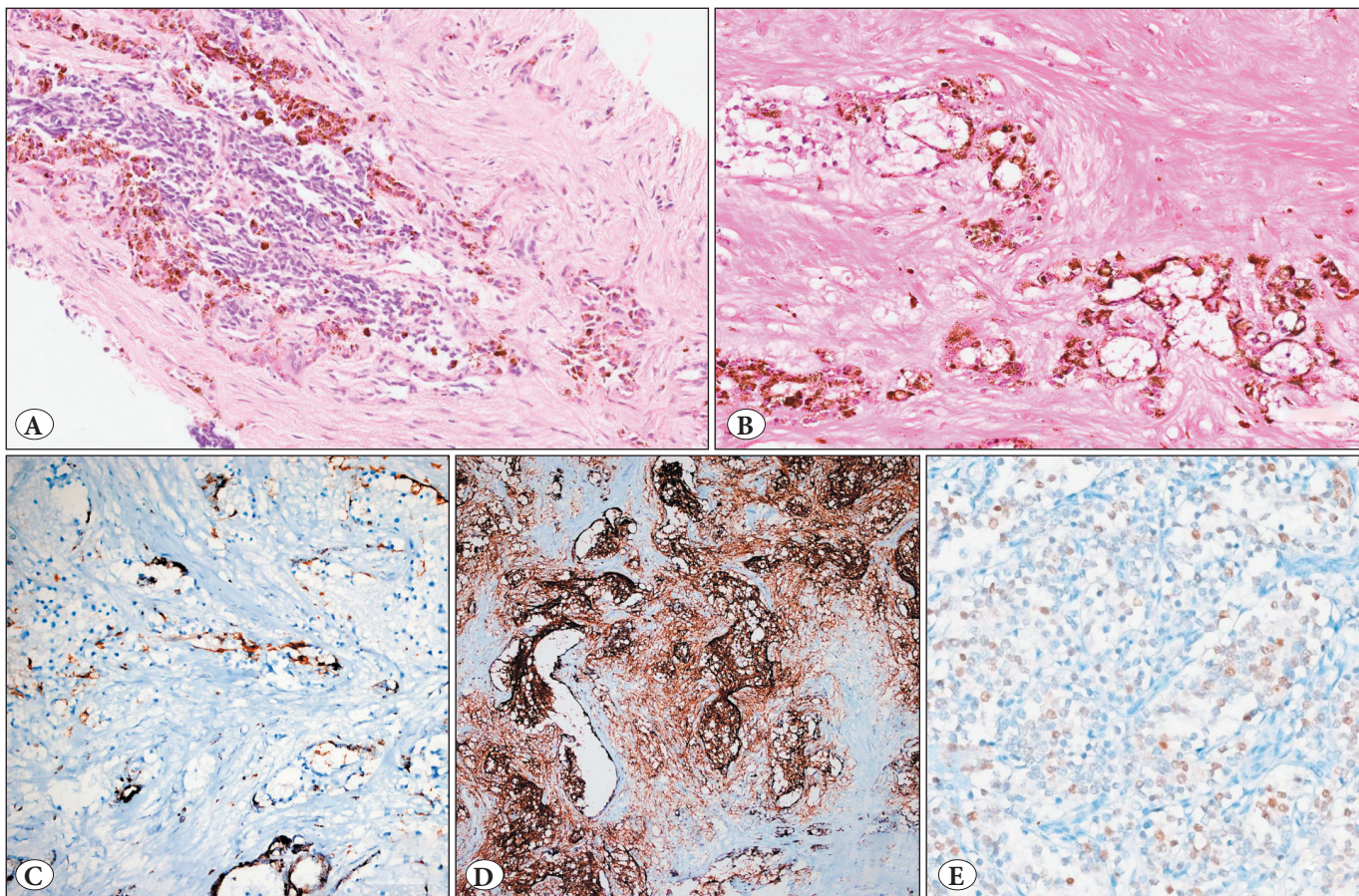


Figure 2: A,B) Higher magnification of the second patient's tumor that includes melanin-containing cubic cells with a tubular pattern and the center contains small, hyperchromatic cells with scanty cytoplasm like neuroblasts (H&E, 150X, 400x). C) Peripheral melanin-containing cells and S100-negative small tumor cells in the center (DAB, 200x). D) Tumor cells positive with synaptophysin (DAB, 200x). E) Tumor cells were diffusely and moderate to weakly positive for PRAME (DAB, 100x).

More than 90% of these tumors are seen in the craniofacial region. The most common place of origin is the maxilla, followed by the skull, mandible, and brain. The mediastinum, testis, epididymis, shoulder, thigh, femur, ovary, and uterus are other locations where the tumor is seen (5,6). Although it grows rapidly, it is generally considered benign because it responds well to local surgical excision. Aggressive histological features like an infiltrative growth pattern that can tend to lead to malignancy may trigger unnecessarily extensive surgical excision (1).

A total of 472 cases were reported between 1918 and 2013, as stated in a comprehensive review by Rachidi et al. (2,3). Radiographic findings are typically in the form of a central, radiolucent area separated from the surrounding bone tissue by sharp margins. CT is helpful for the determination of surgical margins.

This biphasic tumor is comprised of a mixture of small, neuroblast-like round cells and large, polygonal, epithelioid cells that resemble melanocytes containing varying amounts of melanin deposits arranged in an alveolar pattern in fibrocellular stroma. The tumor does not have a microscopic capsule (7). The alveolar spaces have peripheral and central cell populations. The peripheral cells are irregular, larger, cuboidal, and epithelioid and contain melanin (7). The central cells exhibit a small, round, neuroblast-like appearance with hyperchromatic nuclei and narrow cytoplasm, and show dense vesicles under electron microscopy (7). Peripheral cells express HMB45, neuron-specific enolase (NSE), pankeratin, and synaptophysin, while the central cells are positive for NSE, GFAP, and synaptophysin. Both cell populations are negative for chromogranin and neurofilament protein (8). Earlier researchers had concluded that IMNT represented retinal anlage (1,2,4). Keratin 7, 8, 18, and 19 are expressed by cultured retinal pigment epithelial cells, and keratin 7 and 19 (expressed less frequently in IMNT) disappeared directly in cells isolated from the eyes (1,2,4). Keratins are more often observed in large cells but are immunoreactive in both cell populations (4). NB84 is a useful antibody for neuroblastoma and the non-staining of IMNT indicates that the “neuroblastic” cells are different from those seen in this primitive neuroectodermal tumor (4). In a case series of eight patients, one of the cases had an increased mitotic rate, Ki-67 positive fraction (> 25%), and CD99 expression. This case presented with rapid involvement of the entire upper jaw, which occurred within one month after local excision. In the other seven cases, no microscopic changes or recurrence was observed. These characteristics were thought to be predictive of aggressive biological behavior (1,4). A later case reported by

Marschall et al. and a 6-week maxillary lesion reported by Manoclovic showed increased mitotic figure levels (5–10 / 10 HPF), 30% Ki-67 index in neuroblastic cells, and CD99 reactivity in epithelioid cells. However, tumor recurrence was not seen in the 18th postoperative month. These findings indicate that Ki-67 and CD99 expression and increased mitotic activity do not predict biological behavior in IMNT and therefore should not be used to confirm the diagnosis of malignancy (1,6). Necrosis is rare but has been reported in a 13-year-old patient with a calvarial lesion and extensive intracranial metastasis (5).

Neuroblastoma, small round cell tumors (Ewing sarcoma, rhabdomyosarcoma, desmoplastic small round cell tumor, peripheral primitive neuroectodermal tumor, and lymphoma), malignant melanoma, and congenital granular cell tumor are the main tumors to consider in the differential diagnosis because of their rapid growth potential and the location of the tumor in infants (2). The different immunohistochemical phenotypes of these tumors is helpful in the diagnosis (6,9). It differs from melanoma by the difference in patient age, lack of epidermal involvement, small cell component, tubule formation, and cytokeratin expression. PRAME expression has not been reported previously in this tumor and stained only in one of our tumors (10). Similar to IMNT, rhabdomyosarcoma, Ewing’s sarcoma and desmoplastic small round cell tumor may also exhibit an alveolar growth pattern. The histomorphological features that distinguish these tumors from IMNT may be the presence of multinucleated giant cells in alveolar rhabdomyosarcoma, wider necrosis in the foci surrounding blood vessels in Ewing’s sarcoma, and an abundance of desmoplastic stroma in desmoplastic small round cell tumor. Rosettes can be seen in neuroblastoma, Ewing’s sarcoma, and rarely in desmoplastic small round cell tumor. Neuroblastoma may also show some evidence of neural or ganglionic differentiation and have calcification (9). Congenital granular cell tumor is present at birth and no infiltrative pattern is expected (2, 11).

In our second patient, the tumor in the arm was positive for HMB45, SOX10, and PRAME. Although this immunoprofile is similar to melanocytic tumors, the distinction can be easily made with the typical morphology of IMNT and other markers such as synaptophysin and CAM5.2 (Table II).

Although there is no evidence to suggest the appropriate margin size, conservative surgical excision is generally recommended for IMNT. The 5-year recurrence rates have been reported as 22-25% (1). Fully resected tumors require long-term follow-up, although complete remission is achieved after adjuvant therapy. This was demonstrated in

Table II: Immunohistochemical staining of tumors.

	Positive	Negative
Patient 1	Synaptophysin, Pankeratin, Cam5.2, EMA	SOX10, Desmin, HMB45, BerEP4, S100, PRAME
Patient 2	Synaptophysin, Pankeratin, SOX10, HMB45, CD99, PRAME	Desmin, S100

an 11-year-old girl with reported recurrence 12 years after subtotal tumor excision and two sessions of radiosurgery (5,12). In some patients, increased mitotic index and intracranial metastatic masses were observed in the tumor and these features suggest that the tumor has malignant behavior. Only two of eleven malignant IMNTs had intracranial, metastatic lesions. One had subarachnoid metastasis and the other had also subarachnoid metastasis (5,9,12).

Recently, chemotherapy that targets neurobiotic cells observed in neuroblastomas has been proposed as an additional treatment option for IMNT (13-15). When IMNT has a dominant neuroblastic component, chemotherapy has been proposed as the primary treatment. Chemotherapy may be used to stop the progression of IMNT before surgery (14,15). Radiotherapy or chemotherapy may be applied in cases with surgical margin positivity (16). The local recurrence rate and the risk of metastasis were reported as 15-40% and 0-29%, respectively (4,16). Metastatic disease has been reported in the lymph nodes, liver, adrenal gland, and spinal cord (8). The only valid indicator of recurrence and disease-free survival is the age at diagnosis. Survival increases as the age at diagnosis increases. Closer monitoring of patients younger than 2 months of age has been recommended (2). Recurrence is rare in patients who are diagnosed after four and a half months (1,3). Recurrences observed during the first 4 weeks after surgery have been thought to be caused by multicentric tumors, iatrogenic seeding, or tumors that have been removed with an inadequate surgical margin (7). It is very important to implement an aggressive clinical approach in follow-up after surgery because recurrences often occur in the first 4 weeks, and most often within 6 months of the initial treatment (3,6).

Not considering the patient's medical history, in addition to the presence of neuroblast-like cells, the infiltrative nature of the IMNT, and the absence of a capsule may incorrectly lead to the impression of malignancy. Due to its rapid growth and ability to cause deformities in the surrounding tissues, the early diagnosis of IMNT greatly increases the probability of a positive and functional result for the patient. However, better indicators are needed to predict the recurrence and biological behavior of malignant IMNT.

Conflict of Interest

There are no conflicts of interest in connection with this paper.

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Authorship Contributions

Concept: **DB, LY**, Design: **DB**, Data collection or processing: **DB, LY**, Analysis or Interpretation: **DB, LY**, Literature search: **DB**, Writing: **DB**, Approval: **LY**.

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