A rare case of a non-neural granular cell tumor presenting as an enlarging right chest wall nodule in a 4-year-old male and review of the literature

Ali Shahabi1, Hope Hastings1, Harry Winfield2 and Amer Khiyami1

Abstract
Non-neural granular cell tumor was first described in 1991 as an unusual primitive, polypoid variant of the conventional granular cell tumor. To date, this neoplasm remains a rare entity and the cell of origin is uncertain. While the histological features are similar to the conventional granular cell tumor, it represents a distinct entity that is negative for S100 and lacks true nerve sheath differentiation. Here, we describe a case of a 4-year-old male who presented with a painless, soft nodule on his right chest wall that was slowly increasing in size. The mass was excised and sent for pathologic analysis. Microscopic examination reveals spindle and epithelioid cells with vesicular nuclei and prominent granular eosinophilic cytoplasm. Immunohistochemical analysis shows negative staining for S100 and AE1/AE3/PCK26 but is positive for CD68. A diagnosis of a non-neural granular cell tumor was made. We report a rare and diagnostically challenging case in a pediatric patient.

Keywords
Skin, non-neural granular cell tumor, S100

Date received: 19 May 2019; accepted: 3 June 2020

Introduction
Primitive non-neural granular cell tumor (PNGCT) is a rare tumor that was first described by LeBoit et al.1 in 1991. He described four patients with tumors that showed a polypoid, expansile configuration. The histologic features were distinct from the conventional granular cell tumor and included numerous mitotic figures and cytologic atypia. He defined these entities as a “primitive polypoid granular-cell tumor.” Since his original discovery of this neoplasm, it has been reported only rarely in the literature. PNGCT most frequently occurs in young adults and adolescents, with few cases in patients younger than 5 years of age. The tumor typically presents as a smooth, soft nodule arising in the dermis occurring most frequently on the trunk, extremities, or head and neck regions.2,3

Although PNGCT shares similar histologic features with the conventional granular cell tumor, as LeBoit demonstrated, it can be distinguished histologically by increased mitotic activity, nuclear pleomorphism, vesicular nuclei, and prominent nucleoli. In addition, PNGCT is S100 negative due to the absence of nerve sheath differentiation.2

Case report
A 4-year-old male presented with a painless, soft polypoid small nodule on his right chest wall.

The nodule had a red to tan surface and, for the last 3 months, had grown rapidly from a pinpoint lesion to a 0.9 cm × 0.8 cm × 0.7 cm nodule. Ultrasound imaging showed a heterogeneous hypoechoic lesion with no definitive internal vascularity, most suggestive of a hematoma. The mass was excised and sent for pathologic analysis. Microscopic examination reveals spindle and epithelioid cells with vesicular nuclei and prominent granular eosinophilic cytoplasm. Immunohistochemical analysis shows negative staining for S100 and AE1/AE3/PCK26 but is positive for CD68. A diagnosis of a non-neural granular cell tumor was made. We report a rare and diagnostically challenging case in a pediatric patient.

1 Department of Pathology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, USA
2 Department of Dermatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, USA

Corresponding Author:
Ali Shahabi, Department of Pathology, MetroHealth Medical Center, Case Western Reserve University, 2500 MetroHealth Drive, Cleveland, OH 44109, USA.
Emails: ashahabi@metrohealth.org; shahpath55@gmail.com
Histological examination reveals a well-circumscribed lesion consisting of spindle and epithelioid cells that show prominent granular eosinophilic cytoplasm and vesicular nuclei (Figures 1–3). Cytologic atypia is not identified. The tumor extends to the subcutaneous adipose tissue, but the margins of resection are negative. Immunohistochemical staining shows tumor cells staining positive for CD68 and negative for S100 and AE1/AE3/PCK26 (Figures 4 and 5). The SOX10 and NSE are negative (Figures 6 and 7). Postoperative follow-up of our patient at 44 months showed no evidence of lymphadenopathy or reoccurrence of the tumor.

Discussion

Since first reported by LeBoit in the 1990s, non-neural granular cell tumors have been described in patients between 5 and 83 years. In addition to our patient’s young age, our case is unusual as PNGCT shows a female predominance. Another unique clinical feature in our patient was the rapid growth of the lesion. PNGCTs are typically small in size and have a reported range of 0.2 to 2.8 cm (median: 0.5–0.8 cm). While often seen on the trunk, Rawal et al. presented two cases that were in the buccal mucosa and hard palate. Like the skin
lesions, the oral lesions have been reported in a wide age range. The tongue, vermillion of the lower lip, hard palate, alveolar ridge over tooth extraction site, and buccal mucosa are the most commonly affected anatomic areas.6

The tumor typically arises within the dermis, and despite the atypia and frequent mitotic figures, most articles show excision is curative.3 Further complicating this rare entity is that lymph node metastasis has been reported, but follow-up of these patients showed no residual disease.5,7,8 Although the tumor is usually superficially located, extension beyond the dermis with infiltration into adjacent eccrine coils has been seen.9 Even with invasive tumor and lymph node metastasis, the role of lymph node dissection or sentinel biopsy in PNGCT is not currently clear.

Histologically, there is no distinction between a PNGCT that will metastasize versus those that will not.9 Postoperative follow-up of our patient at 44 months showed no evidence of lymphadenopathy or reoccurrence of the tumor. The clinical features and follow-up of the 13 pediatric patients are summarized in Table 1.

In addition to the atypia typically present in PNGCT, these tumors lack the pseudoepitheliomatous hyperplasia that is so common to conventional granular cell tumors.5

Furthermore, non-neural granular cell tumors are usually well-circumscribed lesions with vesicular nuclei, pleomorphism, and averaging 5-6/10 HPF (high-power field) mitosis, while conventional granular cell tumors typically have poorly circumscribed margins and no mitotic figures.11 In addition, the location of the tumor varies, with conventional granular cell tumors most often found in the tongue and gastrointestinal sites, while PNGCT is typically found on the trunk in the superficial dermis.

Ultrastructurally, PNGCTs, like conventional granular cell tumors, show primitive cells with secondary lysosomes of varying sizes. The lysosomal granules in electron microscopy are indistinguishable from those seen in the conventional variant.5 The tumors do not show clear evidence of neural differentiation with absent S100 protein and NSE.5 Congenital (gingival) granular cell tumor, which occurs exclusively on the alveolar ridge of the mandible and maxilla of infants, is S100 negative as well. Little is currently known of these rare oral tumors or their relationship to PNGCT. At the date of this review, there is no clear cell of origin for PNGCT; however, a recent paper has suggested that this tumor may arise from the hair follicle and represent a granular cell dermal root sheath fibroma.10 The granular cells are usually positive for NKI-C3 and CD68, both stains reflecting a non-specific reaction to lysosomes.11

There are some tumors that have granular changes due to lysosome accumulation and remain important considerations in patients with PNGCT. These include conventional granular cell tumor, smooth muscle neoplasms, dermatofibromas, epithelioid cell histiocytes, dermatofibrosarcoma protuberans, fibrous papules, atypical fibroxanthomas, perineuromas, basal cell carcinomas, and metastatic carcinomas.9 PNGCT is negative for desmin, cytokeratin, Smooth muscle actin SMA, and CD34, effectively ruling out most of the differential diagnosis.4 Another diagnostic consideration includes melanoma or a benign melanocytic lesion showing granular cell change. Once again, immunohistochemistry separates these lesions from PNGCT as melanocytic lesions are positive for S100 protein and additional melanocytic markers such as HMB-45, MART-1, or MITF.5

**Conclusion**

PNGCT is a rare tumor with indolent behavior despite its potential to metastasize. Recognition of this tumor in pediatric patients is essential to avoid overtreatment and incorrect interpretation of the atypia and mitotic activity often present. While metastasis to lymph nodes has been reported in some cases, the indication of sentinel lymph node biopsy is not clear. This unique tumor needs additional studies to further understand the etiology.
Table 1. Characteristics of cutaneous non-neural granular cell tumors in children.

| Case          | Age (years) | Sex | Site          | Size (cm) | Duration (months) | Recurrence | Metastases | Follow-up (months) |
|---------------|-------------|-----|---------------|-----------|------------------|------------|------------|-------------------|
| Our case      | 4           | Male| Chest wall    | 0.9       | 3                | No         | No         | 44                |
| LeBoit et al.1 | 6           | Male| Shoulder      | 0.5       | N/A              | No         | No         | 48                |
| Chaudhry and Calonje4 | 6 | Female| Back         | 0.5       | N/A              | No         | No         | 16                |
| Chaudhry and Calonje4 | 8 | Male| Shoulder      | 1.2       | N/A              | No         | No         | 8                 |
| Chaudhry and Calonje4 | 16 | Male| Left wrist    | 0.6       | 12               | No         | No         | 32                |
| Lazar and Fletcher5 | 5 | Male| Back         | 0.8       | 24               | No         | No         | 126               |
| Lazar and Fletcher5 | 7 | Male| Back         | 1.7       | N/A              | N/A        | No         | Lost follow-up    |
| Lazar and Fletcher5 | 10 | Male| Shoulder     | 0.8       | N/A              | No         | No         | 35                |
| Lazar et al.5  | 11          | Male| Back         | 0.6       | No               | No         | No         | 41                |
| Lazar et al.5  | 15          | Female| Back       | 0.9       | N/A              | No         | No         | 96                |
| Fernandez-Flores et al.10 | 15 | Female| Perineal | 1         | N/A              | No         | No         | 120               |
| Fernandez-Flores et al.10 | 15 | Female| Left scapula | 0.4    | N/A              | No         | No         | 60                |
| Fernandez-Flores et al.10 | 16 | Male| Left axilla  | 0.8       | N/A              | No         | No         | 120               |

N/A indicates that result was not available.

Authors’ note
This study was presented as a poster at the College of American Pathologists 2017 Annual Meeting (CAP17), National Harbor, Maryland.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval
Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent
Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ORCID iD
Ali Shahabi https://orcid.org/0000-0001-9720-9131

References
1. LeBoit PE, Barr RJ, Burall S, et al. Primitive polypoid granular-cell tumor and other cutaneous granular-cell neoplasms of apparent nonneural origin. *Am J Surg Pathol* 1991; 15: 48–58.
2. Brenn T. Pleomorphic dermal neoplasms: a review. *Adv Anat Pathol* 2014; 21: 108–130.
3. Feci L, Miracco C, Fimiani M, et al. A case of primitive non-neural granular cell tumor presenting as a single painless bleeding nodule. *Dermatol Pract Concept* 2014; 4: 59–61.
4. Chaudhry I and Calonje E. Dermal non-neural granular cell tumor (so-called primitive polypoid granular cell tumor): a distinctive entity further delineated in a clinicopathological study of 11 cases. *Histopathology* 2005; 47: 179–185.
5. Lazar AJ and Fletcher CD. Primitive nonneural granular cell tumors of skin: clinicopathologic analysis of 13 cases. *Am J Surg Pathol* 2005; 29: 927–934.
6. Rawal YB and Dodson TB. S-100 negative granular cell tumor (so-called primitive polypoid non-neural granular cell tumor) of the oral cavity. *Head Neck Pathol* 2017; 11: 404–412.
7. Al Habeeb A, Weinreb I and Ghazarian D. Primitive non-neural granular cell tumor with lymph node metastasis. *J Clin Pathol* 2009; 62: 847–849.
8. Newton P, Schenker M, Wadehra V, et al. A case of metastatic non-neural granular cell tumor in a 13-year-old girl. *J Cutan Pathol* 2014; 41: 536–538.
9. Yeh I, Tran DT, Davis TL, et al. An infiltrative variant of non-neural granular cell tumor: a case report. *J Cutan Pathol* 2009; 36: 46–51.
10. Fernandez-Flores A, Cassarino DS, Riveiro-Falkenbach E, et al. Cutaneous dermal non-neural granular cell tumor is a granular cell dermal root sheath fibroma. *J Cutan Pathol* 2017; 44(6): 582–587.
11. Al Habeeb A and Salama S. Primitive nonneural granular cell tumor (so-called atypical polypoid granular cell tumor). Report of 2 cases with immunohistochemical and ultrastructural correlation. *Am J Dermatopathol* 2008; 30: 156–159.