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Abstract:

Proliferative nodules arising within congenital melanocytic nevi (CMN) often present a diagnostic challenge given a close resemblance to melanoma. Several morphologic variants have been characterized. In difficult cases, ancillary molecular tests can be used to better exclude the possibility of malignant degeneration. Herein, we report a case of an unusual proliferative nodule with overlapping features of angiomatoid Spitz tumor and ancient melanocytic nevus, which demonstrated normal findings on both chromosomal microarray and a gene expression profiling assay.

Introduction:

Benign proliferative nodules (BPNs) arising within large congenital melanocytic nevi (CMN) are a well-described phenomenon that often present considerable diagnostic difficulty for dermatopathologists.1,2 Despite worrisome histology, these lesions, more often than not, prove to demonstrate an indolent clinical phenotype characterized by gradual regression over time.3 However, given a 5-to-15 fold increased risk of melanoma in patients with large CMN,4-11 it is important to accurately classify these lesions. In reality, BPNs comprise a heterogenous category of lesions with varied morphological features including but limited to, expansile nodules of epithelioid cells, small round blue cells, blue-nevus-like cells, nevoid melanoma-like cells, neurocristic and undifferentiated spindled-cell forms.3 In cases with ambiguous morphology, ancillary molecular tests such as array comparative genomic hybridization (aCGH) and gene expression profiling may provide further evidence for or against a malignant phenotype.1,2,12,13 Some BPNs in particular have been shown to demonstrate limited whole numerical chromosomal aberrations distinct from the partial gains and losses that characterize melanoma.[1] In this report, we present a comprehensive clinical, histopathologic, and molecular analysis of a BPN resembling what has been described for an angiomatoid Spitz tumor with degenerative atypia of the so-called ancient melanocytic nevus.

Case Report:

A 10-year-old African American male presented for his annual surveillance examination of a large congenital nevus involving his right lower extremity. There was slight interval enlargement and sensitivity of a firm nodule on his right knee, which had been monitored clinically for over 7 years. Physical examination demonstrated a large congenital nevus extending circumferentially around the right distal thigh through the right proximal leg. The lesion was associated with a 1 cm leg length discrepancy between his right and left lower extremities. On the infra-medial aspect of the patella (Figure 1), there was a firm dome-shaped nodule. An x-ray was negative for any underlying bony growths and showed a soft tissue density at the site of the nodule. An ultrasound revealed a 1.4 x 2.0 x 1.4 cm well circumscribed hyperechoic focus with diffuse internal vascularity.
An incisional 6-mm punch biopsy from within the nodule was obtained (Figure 2). The histology demonstrated a deep dermal and subcutaneous nodular aggregation of enlarged epithelioid melanocytes with amphophilic cytoplasm. Occasional intermixed multinucleated forms were identified. The nuclei of a subset of the tumor cells displayed an open chromatin pattern with prominent nucleoli. There was also a conspicuous population of tumor cells with darker and smudgy appearing chromatin with moderate nuclear pleomorphism. Admixed within the tumor cells, there was a notable peppering of lymphocytes. The intervening stroma was myxoid and highly vascularized with many vessels demonstrating thick hyalinized walls and endothelial cell hobnailing. Fibrosis enveloped the tumoral nodule and was seen extending towards a satellite population of small and monomorphous appearing melanocytes, felt to represent pre-existing congenital nevus. Immunohistochemical analysis revealed positive staining for Sox10, BAP1, and H3K27me3 and an absence of staining for HMB45 and BRAFV600E. Melan-A highlighted the small pre-existing nevocytes but failed to stain the dominant nodular population of large cells (Figure 3). Moreover, the proliferation index was low (<5% staining for MIB1) and the mitotic rate was < 1 per mm2. Subsequent aCGH analysis demonstrated no significant copy number abnormalities (Figure 4a).

Based on the constellation of features, the lesion was diagnosed as a proliferative nodule with features of angiomatoid Spitz tumor and ancient melanocytic nevus and was felt to have a low likelihood of progression. Complete excision of the remainder of the nodule was recommended to further minimize any risk to the patient, given a small degree of diagnostic uncertainty. This was performed 9-months following the initial biopsy, and revealed similar histopathology with clear margins, a low proliferation index, and no discernable mitotic figures (Figures 5 and 6). Within the nodule, there was even more discernable nuclear pleomorphism with many bizarre-appearing melanocytes. Considerable fibrosis was observed throughout much of the specimen with only few small remaining foci of banal appearing congenital nevus (not shown), seen at quite a distance from the actual nodule. Given the unusual architecture and cytology, a clinically validated gene expression profiling test was performed on sections containing the nodule. The sample yielded an exceptionally low (-11.8) score in the "benign" range, further supporting the initial diagnosis (Figure 4b). The patient remains well with no signs of recurrence 1 year following his excision.

Discussion:
Features previously proposed by Xu et al. 2004 to be useful in differentiating BPNs from melanoma include: (1) lack of high-grade consistent cellular atypia, (2) lack of tumoral necrosis, (3) paucity of mitotic figures, (4) maturation in the form of transitional forms between the nevus and cellular nodule, (5) lack of pagetoid scatter within the overlying epidermis, and (6) no destructive expansile growth. Subsequent studies have found that many BPNs may have one or more of these atypical features, complicating the diagnosis in many cases. Moreover, based on
prior literature there is considerable histopathologic diversity between BPNs which makes it difficult to generalize as to what reliably differentiates a BPN from melanoma in a particular case. 14

Our case is noteworthy given its striking resemblance to what has been reported for an angiomatoid Spitz tumor.15 Prior reports indicate that this entity most typically occurs in female patients in their third decade of life.[16] Features described for angiomatoid Spitz tumor include a primarily dermal-based proliferation of enlarged, epithelioid melanocytes containing nuclear pseudo-inclusions and ample amphophilic cytoplasm. Multinucleated melanocytes are a common finding in this subtype of Spitz. Moreover, these lesions have a characteristic (and perhaps defining) interweaving fibrovascular stroma containing large ectatic vessels lined by hobnail endothelial cells. To our knowledge, this particular morphologic subset of Spitz has been described primarily in the context of spontaneous melanocytic tumors arising de novo outside the context of a congenital lesion.15,16 Some authors have postulated that angiomatoid Spitz tumor may represent a form of desmoplastic Spitz nevus which has shown to harbor HRAS mutations and/or 11p copy number gains.15,17 Notably, our case did not demonstrate 11p amplification though an underlying HRAS mutation cannot be entirely excluded.

Importantly, the angiomatoid subtype of Spitz has also been known to simulate regressing melanoma and therefore can cause some diagnostic uncertainty.18 The pronounced cytological atypia and lack of transitional forms certainly raised the possibility of melanoma in this case. However, there were several reassuring features which included the young age of the patient, circumscribed configuration of the nodule, paucity of mitotic figures, low proliferation index, lack of necrosis, lack of expression of PRAME, and preservation of H3K27me3 expression.19 Additionally the lesion demonstrated a benign phenotype on both chromosomal microarray and gene expression analysis.1. Although there are rare melanomas that lack detectable gains or deletions and score in the benign range on gene expression profiling, the false negativity rate of these two molecular tests in the setting of proliferative nodules has yet to be defined.

The bizarre cytological features combined with the unique myxoid and highly vascularized stroma is favored by the authors to represent degenerative atypia characteristic of an "ancient nevus".20,21 It is noteworthy that the lesions described as ancient nevi by Kerl et al. 1998 and Kerl et al. 2011 have some overlapping stromal features with angiomatoid Spitz tumor. A low proliferation index and paucity of mitotic figures is characteristic of these neoplasms. As has been reported in various other contexts in dermatopathology including the ancient schwannoma, symplastic leiomyoma, and symplastic hemangioma these changes may not necessarily represent a pre-malignant state. The authors hypothesize that continued host response to the lesion, as evidenced by the numerous admixed lymphocytes, may be responsible for inducing the observed cytological and stromal derangement. Interestingly, these changes increased further from the time of the original biopsy to the delayed excision specimen. Future studies should aim to better
define the genetic, epigenetic and/or immunologic signature of these lesions as this may help to better predict a benign course in select cases. The relationship between angiomatoid Spitz tumor, ancient change, and regressing congenital nevi also merits further study and discussion.

**Figure 1:** Clinical morphology. Firm hyperpigmented nodule arising on the right knee within a pre-existing congenital nevus.

**Figure 2:** Histopathology of incisional biopsy specimen.  
A) A deep extending nodular aggregation of enlarged epithelioid melanocytes surrounded by fibrosis (H&E, 15x original magnification).  
B) The intervening stroma is edematous and vascular with many of the vessels demonstrating hobnailed endothelial cells (H&E, 50x, original magnification).  
C) Small and monomorphous melanocytes in nests are separated from the atypical proliferation, and felt to represent pre-existing congenital nevus (H&E, 200x original magnification)  
D) The epithelioid melanocytes exhibit amphophilic cytoplasm with a subset exhibiting nuclear hyperchromasias, smudging and pleomorphism (H&E, 300x original magnification).

**Figure 3:** Immunohistochemical analysis revealed positive staining for Sox10, BAP1, and H3K27me3 and an absence of staining for HMB45, PRAME and MIB1 (200x original magnification).

**Figure 4:**  
A) Chromosomal microarray plot. A normal profile was demonstrated with no significant gains or losses.  
B) Gene expression profiling plot demonstrating a score in the benign range.

**Figure 5:** Low power histopathology of excision specimen demonstrating a highly vascularized, circumscribed nodule in the dermis and subcutis enveloped in fibrosis. The fibrosis extends broadly throughout the dermis to both edges of the specimen. (H&E, 15x original magnification).

**Figure 6:** High power histopathology of excision specimen demonstrating enlarged and bizarre appearing melanocytes with significant nuclear pleomorphism (H&E, 300x original magnification).
References


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Myriad myPath® Melanoma Score: -11.8

175x159mm (300 x 300 DPI)
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