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Prepubertal melanoma arising within a medium-sized congenital melanocytic nevus

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Abstract

We report a case of an 8-year old child who developed a 9.4mm-depth melanoma within a medium-sized congenital melanocytic nevus on the scalp. Genetic analysis revealed an activating NRAS Q61R mutation within the melanoma, which is more commonly associated with large or giant congenital melanocytic nevi. This case demonstrates that even a “low risk” congenital melanocytic nevus at a “low risk” age must be monitored regularly for the development of malignancy.

Keywords

melanoma; congenital melanocytic nevus

CASE REPORT

An 8-year old Caucasian female with a medium-sized congenital melanocytic nevus (CMN) on the scalp (9 cm × 8 cm, predicted adult size of approximately 10 cm according to the categorization schema of Krengel, *et al*) (1) presented for evaluation of a single, 2 cm, heterogeneously pigmented nodule within the CMN that was noticed by her mother several months prior to presentation. Clinical monitoring had not been performed because her parents were previously told that there was no risk for the development of melanoma and that periodic examination was not necessary. The CMN was described as dark brown at birth, but had lightened significantly over time to the point where it was very faint and light brown in color.

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Due to concern for malignant degeneration, urgent excision was performed. Histopathology revealed an expansile nodular dermal proliferation of undifferentiated round cells without maturation (Figure 2); no lymphatic or perineural invasion or epidermal involvement were identified. The adjacent congenital nevus was composed of a predominantly intradermal epithelioid melanocytic proliferation with maturation with depth, wrapping around adnexal structures and extending into the subcutis; no mitoses were seen in the precursor nevus (Figure 3). Single nucleotide polymorphism (SNP) microarray revealed numerous chromosomal aberrations, including mosaic monosomy involving multiple chromosomes, deletion of 1p36, and duplication of 1q23, 8q24 and 6p25. These results were felt to be consistent with a diagnosis of a nodular melanoma arising within a CMN. Tumor thickness was 9.4mm, Clark level 5, without ulceration, with a mitotic rate of 8/mm², and without perineural or vascular invasion. Re-excision with split thickness skin grafting and sentinel lymph node biopsy was performed. All surgical margins were negative, and 2/2 sentinel lymph nodes excised from the left preauricular and posterior cervical chains were negative. All imaging performed, including PET, brain MRI, abdominal and pelvic MRI, and chest CT, was negative for evidence of metastatic disease. Genomic profiling by next-generation sequencing identified NRAS Q61R mutation, MYC amplification, and MLL2 rearrangement at exon 51. Neither a BRAF nor a KIT mutation was identified. No adjuvant therapy was recommended by Oncology. She is currently doing well 12 months after diagnosis with no signs of recurrence, though the period of follow-up is too short to draw any conclusions regarding long-term prognosis.

DISCUSSION

Activating NRAS mutations, often involving codon 61, are commonly seen in large or giant CMN with a prevalence of up to 95% depending on the sensitivity of the assay, while the prevalence of BRAF mutation is significantly lower (~ 5–10%) (2–6). Small and medium CMN less frequently manifest NRAS mutations, which are seen in about 30%, but more commonly demonstrate BRAF mutations, with a prevalence of about 70% (2–4, 6, 7). Activated NRAS signaling occurs through the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/AKT pathways. The PI3K/AKT pathway increases cell proliferation, promotes melanocyte survival, and stimulates directional migration; along with activation of NRAS, activation of this pathway is common in melanoma (8). Aberrant signaling through the PI3K/AKT pathway may predispose CMN with an activating NRAS mutation to malignant degeneration. We are aware of one published report of a melanoma arising within a medium-sized CMN with a documented activating NRAS mutation in a 29-year old male (9).

Although the true lifetime risk of melanoma developing within a small- or medium-sized CMN is unknown due to the inherent limitations on conducting an informative prospective study, the risk is estimated to be less than 1% over a lifetime (10, 11). Although most commonly developing after puberty, melanoma arising within a small- or medium-sized CMN has been reported in younger children (12, 13). Differentiation from a proliferative nodule may be challenging. Proliferative nodules arising within large or giant CMN may develop at any age but most commonly arise in the first year of life. In proliferative nodules, evaluation for the presence of copy number alterations by array-CGH (comparative genomic

hybridization) or SNP array generally results in either a normal genomic profile or the presence of whole chromosomal copy number aberrations, as opposed to the complex partial chromosomal aberrations typical of melanoma (14, 15). In addition, the histopathological characterization of a proliferative nodule is most commonly of a melanocytic proliferation composed of large spindled, nevoid, or epithelioid cells without atypia (5, 14).

This case is a sobering reminder of the need for continued vigilance in monitoring congenital melanocytic nevi of all sizes. While the overall risk for malignant degeneration in small- and medium-sized CMN is quite low, and while spontaneous lightening of CMN may be noted, particularly on the scalp, melanoma may develop at any age, including prepubertal children. Clinicians and caregivers should be aware of this risk in order to allow for informed decision-making regarding management.

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Figure 1.
Clinical photograph from day of presentation showing a tumor within a faint congenital melanocytic nevus.

Figure 2.
High power photomicrograph of round cells with vesiculated nuclei, prominent nucleoli, scant cytoplasm, overall paucity of pigment, and many abnormal mitotic figures (original magnification $\times 40$).

Figure 3.
Low power photomicrograph demonstrating sheets of tumor cells abutting a banal congenital melanocytic nevus component with sharp demarcation between malignant tumor and benign nevus (original magnification $\times 2$).