# Giant benign intradermal melanocytic nevus of rapid onset

Sarah J Coates, Andrew Avarbock, Garrett T Desman

Affiliations: Weill Cornell Medical College, New York, New York

*Corresponding Author: Garrett Desman, Weill Cornell Medical College, New York, New York, Email:garrett.desman@mountsinai.org*

## Abstract

Benign melanocytic nevi are slowly growing acquired or congenital tumors with varied morphology, commonly encountered in dermatology clinics. Any tumor with rapid clinical growth must be assessed carefully in order to exclude malignancy. We report a woman with a histopathologically benign intradermal nevus that presented as a rapidly evolving large cutaneous mass on the ear. Owing to the discrepancy between the clinical and histopathological findings, an extensive histopathological work-up involving many deeper sections, immunohistochemical stains, and fluorescent in situ hybridization (FISH) analysis was conducted in order to rule out malignancy.

*Keywords: giant melanocytic nevus, melanoma, fluorescent in situ hybridization, FISH, melanoma, proliferative nodule*

## Introduction

Benign melanocytic nevi are frequently encountered in routine dermatology practice. Clinically, these tumors may present as macules, papules, pedunculated, or even lobulated lesions with varying degrees of pigmentation [1]. Among the clinical features most alarming for malignant transformation is the onset on rapid growth, characterized by change in size, shape, or coloration. Any lesion that exhibits these features must be biopsied to rule out malignant melanoma.

## Case Synopsis

A 57-year-old woman presented with a pink multi-lobulated exophytic nodule above her left ear (**Figure 1**). For years the lesion consisted of a small papule measuring approximately 0.5cm. However, recent trauma precipitated rapid growth over a period of one week to the pictured size of 3.5cm. The lesion was mildly tender, but no associated palpable lymphadenopathy was appreciated and physical examination was otherwise unremarkable. She had no relevant past medical history and denied fever, weight loss, or medication changes. No previous therapies had been performed on the lesion. A shave biopsy was performed.

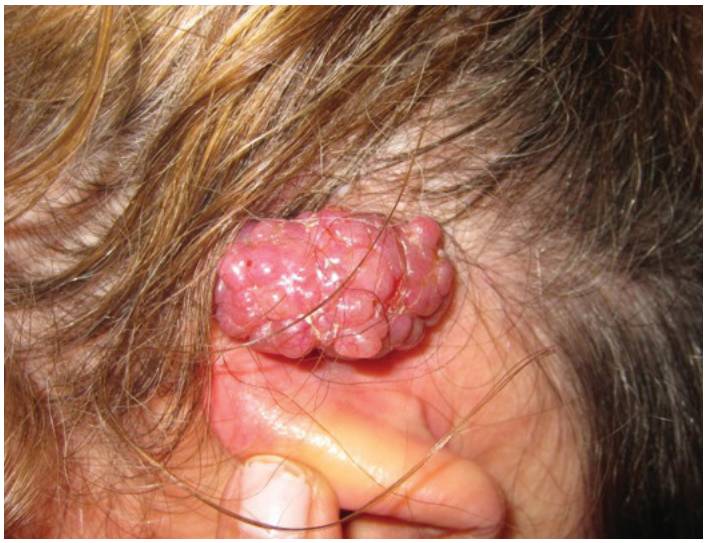

**Figure 1.** *The patient presented with a rapidly growing,* **3.***5cm pink multi-lobulated exophytic nodule above her left ear.*

Histopathological examination revealed hypermelanosis of basal keratinocytes and a low-density lentiginous melanocytic hyperplasia without junctional nests (**Figure 2**). In the superficial dermis, melanocytic nests exhibited a plump epithelioid morphology with variable cytoplasmic pigment deposition. At the lesion's base, cells dissipated into smaller nests and solitary units, which partially tracked along adnexal structures. The epidermis appeared irritated, with foci of sebaceous glands connecting to the epidermal surface. No significant cytologic atypia or dermal mitoses were appreciated. Combined Melan-A/Ki-67 stain confirmed no junctional component or dermal mitotic activity. D2-40 stain of lymphatic vessels failed to reveal intralymphatic

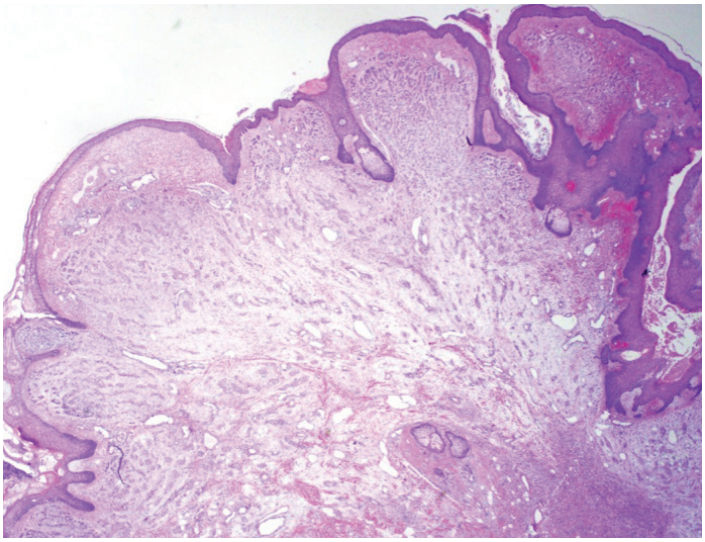

**Figure 2***A. The epidermis is papillomatous with subjacent connective tissue stalk composed of well vascularized, edematous, loosely arranged collagen and nests and cords of basophilic cells. H&E, 2X.*

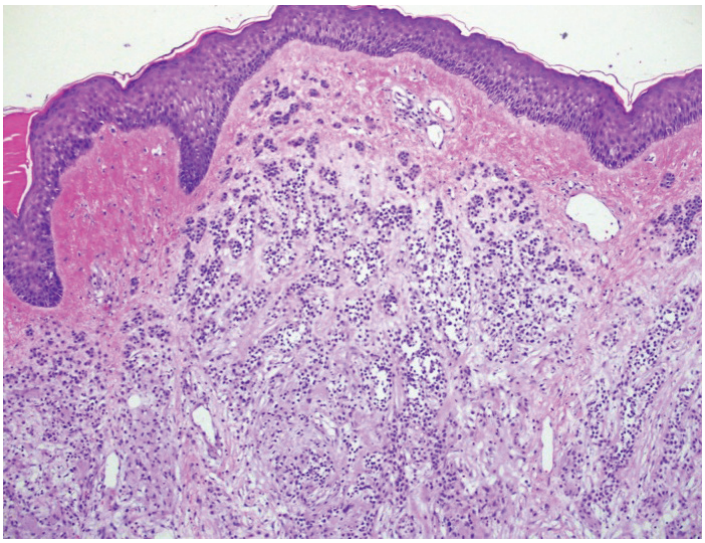

**Figure 2***B. The nests in the superficial dermis are composed of plump epithelioid cells with lightly eosinophilic cytoplasm and uniform round to oval small nuclei (Type A melanocyte). The cells at the deeper aspects of the lesion are much smaller with less cytoplasm and have dense, more darkly staining nuclei resembling lymphocytes (Type B melanocyte). H&E, 4X*

tumor deposits. The R21 (soluble adenylyl cyclase) immunohistochemical stain revealed a perinuclear dot-like staining pattern, commonly seen in benign melanocytic proliferations [2].

The specimen was submitted for cytogenetic analysis based on the abnormal clinical presentation. Using probes to loci on 6p, 6q, 6cent, 9p and 11q, no copy number gains/losses were identified and therefore the tumor did not meet FISH melanoma criteria. The

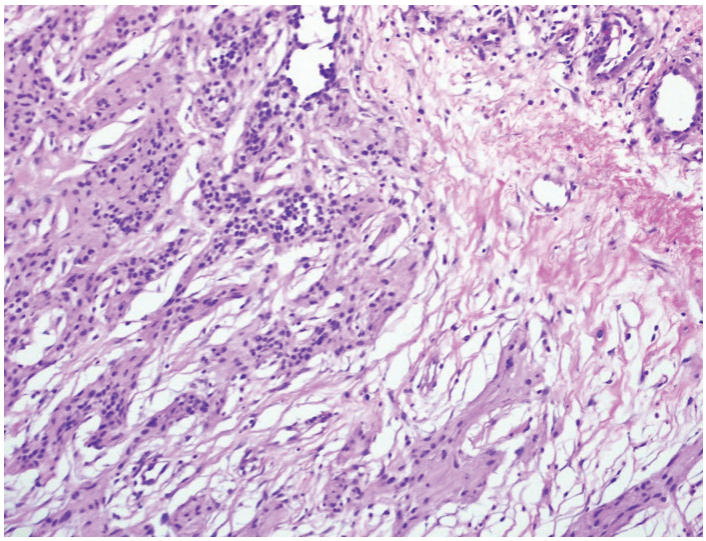

**Figure 2***C. The cells at the deepest component of the lesion exhibit a spindled morphology with Schwann cell-like characteristics (neurotization), such wavy nuclei and a fibrillar appearance with pale eosinophilic cytoplasm (Type C melanocytes). H&E, 10X*

final impression, based on the histopathologic and cytogenetic findings, was that of a benign intradermal nevus, despite the alarming clinical presentation. As a precautionary measure the tumor was completely excised with no regrowth or sequela over a period of 32 months.

## Case Discussion

Benign intradermal nevi may be acquired or congenital and are ubiquitous among the general population. These tumors typically do not warrant the extensive work-up illustrated in this case. Melanocytic nevi may exhibit various clinical morphologies over time, and therefore correlation with the histopathological features provides critical insight into the pathogenesis and behavior of these lesions.

Specific histopathologic features of acquired melanocytic nevi are believed to reflect various stages of melanocyte biology and differentiation. Nests of pigmented epithelioid (type A) nevus cells are typically located at the tips of rete ridges forming junctional nevi [3]. These rounded and polygonal cells have eosinophilic cytoplasm and slightly larger nuclei compared to basilar dendritic melanocytes [3]. The proliferation of these melanocytes is driven by oncogenic mutations. However, gradual upregulation of tumor suppressor mechanisms eventually locks these cells into a non-dividing state, known as

senescence. Intradermal nevi form when all of the nests have become senescent and migrate into the dermis [4]. This migration of melanocytes mirrors the clinical evolution of pigmented macules (junctional nevi) to flesh-colored papules (intradermal nevi), [4]. As the melanocytes migrate deeper into the dermis they undergo an important series of morphologic and biological changes, referred to as maturation with descent. The pigmented epithelioid melanocytes in the superficial dermis are referred to as Type A nevus cells. Type B (lymphocytoid) nevus cells are located deeper in the dermis and contain less cytoplasm and smaller nuclei [3]. The deepest cells are Type C (spindled) nevus cells and represent the final maturation stage characterized by Schwannian (neural) differentiation [3,5]. Their cytomorphology consists of bland, small, wavy nuclei surrounded by pale, loose stroma that may form nerve sheath-like structures [3,5]. This so-called maturation with dermal descent reflects intact cellular senescence and supports the diagnosis of a benign melanocytic nevus when identified. Dermal mitotic activity should be rare or absent in benign melanocytic tumors. In contrast to acquired melanocytic nevi, the natural history of congenital nevi is not as clear since most lesions initially present as intradermal nevi, even in infancy. Their histopathology is essentially identical to acquired nevi with the exception of adnexotropism. Although this feature is commonly associated with congenital onset, it is relatively nonspecific and may also be seen in acquired nevi arising on the head and neck. The biological behavior of congenital nevi is believed to be most closely associated with clinical size: small (< 2cm), medium (2-20 cm), or giant (>20 cm), [6].

The primary significance of benign nevi resides in their relationship to malignant melanoma, which may develop within both acquired and congenital nevi. If tumor suppressor function is compromised, uncontrolled cellular division with subsequent telomere loss may lead to chromosomal instability, resulting in a cascade of chromosomal aberrations and potential transformation into malignant melanoma. Histopathologic features of melanoma in situ include confluent intraepidermal melanocyte growth with scattered pagetoid ascent into the upper epidermal layers. Invasive melanoma is characterized by the downward invasion of these cells into the dermis with mitotic activity, cytologic atypia, and absence of maturation with downward dermal descent [7]. Whereas the vast majority of melanomas initially arise within the epidermis (in situ melanoma) and invade downward into the dermis, a rare form of melanoma, referred to as "nevoid melanoma," may originate within the dermis without an overlying in situ component. Sheets of atypical dermal melanocytes with mitoses and impaired maturation with dermal descent characterize these tumors histopathologically [8]. Interestingly, nevoid melanomas are most strongly associated with pre-existing congenital nevi. Giant congenital nevi pose the highest risk for melanoma, which typically occurs before puberty and is occasionally of dermal origin (nevoid melanoma). The risk of melanoma arising in association with small and medium-sized congenital nevi is low (approximately <1% lifetime risk), typically occurs after puberty, and tends to be exclusively of epidermal origin [6].

Proliferative nodules (PN) are another form of secondary melanocytic neoplasm that can develop in congenital nevi and are thought to be distinct from melanomas. These nodules may present with alarming clinical features, such as rapid growth and even ulceration. However, these lesions tend to stabilize and regress. They arise almost exclusively in giant congenital nevi during infancy [9]. Histopathologically, these lesions are characterized by a nodular proliferation of melanocytes with banal appearance similar to conventional nevi but with increased dermal mitotic activity. Our literature search uncovered only one case of a proliferative nodule arising in a small congenital nevus in a 3-month-old infant [10]. To our knowledge, proliferative nodules have yet to be reported in small congenital nevi after childhood.

Fluorescent in situ hybridization (FISH), performed with probes against 6p, 6q, 6cent and 11q, has been used to distinguish benign nevi from malignant melanoma. FISH reportedly has a sensitivity and specificity of 85% and 95%, respectively, for histopathologically obvious benign and malignant lesions [11]. In lesions with more ambiguous histopathologic features, sensitivity and specificity for malignant melanoma are reportedly only 60% and 50%, respectively [11].

This case illustrates an unusual clinical presentation of a common benign melanocytic tumor. Based upon its large size and rapid growth rate, the clinical differential diagnosis included malignant melanoma, Merkel cell carcinoma, and a malignant adnexal tumor. Large lobulated benign nevi have been previously reported in the literature. However, these lesions exhibited a slow gradual evolution, which the authors attributed to advanced tumor age [1]. An adult-onset proliferative nodule arising within a small congenital nevus was considered in our differential diagnosis, but no dermal melanocyte mitotic activity was appreciated. Additionally, the patient could not confirm that the tumor was present at birth. The most likely explanation for the rapid growth was trauma-induced changes within the lymphatic network, since the dermis was markedly edematous with vascular ectasia and hyperplasia. This case highlights the heterogeneous nature of melanocytic proliferations and the reassuring aspects of adjunct immunohistochemical and molecular diagnostic modalities.

## References

1. Kim DH, Park HS, Paik SH, Jeon HC, Cho KH. Four cases of lobulated intradermal nevus: a sign of aging melanocytic nevus. Ann Dermatol. 2011;23(1):115–8. [PMID: 21738380]
2. Magro CM, Crowson a N, Desman G, Zippin JH. Soluble adenylyl cyclase antibody profile as a diagnostic adjunct in the assessment of pigmented lesions. Arch Dermatol. 2012;148(3):335–44. [PMID: 22105816]
3. Barnhill RL, Vernon S, Rabinovitz HS. Benign Melanocytic Neoplasms. In: Grant-Kels JM, ed. Color Atlas of Dermatopathology. New York, NY: Informa Healthcare USA, Inc.; 2007:264–265.
4. Lim HJ, Kim YT, Choo O-S, Park K, Park HY, Choung Y-H. Clinical and histological characteristics of melanocytic nevus in external auditory canals and auricles. Eur Arch Otorhinolaryngol. 2013;270(12):3035–42. [PMID: 23371542]
5. Sade S, Al Habeeb A, Ghazarian D. Spindle cell melanocytic lesions--part I: an approach to compound naevoidal pattern lesions with spindle cell morphology and Spitzoid pattern lesions. J Clin Pathol. 2010;63(4):296–321. [PMID: 23371542]
6. Price HN, Schaffer JV. Congenital melanocytic nevi-when to worry and how to treat: Facts and controversies. Clin Dermatol. 2010 May-Jun;28(3):293-302. [PMID: 20541682]
7. Strungs I. Common and uncommon variants of melanocytic naevi. Pathology. 2004;36(5):396–403. [PMID: 15370108]
8. Hashiro M, Miyamoto T, Sonoda S, Okumura M. Malignant melanoma developing from an intradermal nevus. Dermatology. 1998;196(4):425–6. [PMID: 9669120]
9. Illig L, Weidner F, Hundeiker M, Gartmenn H, Biess B, Leyh F, et al. Congenital nevi 10cm as precursors to melanoma. Arch Dermatol 1985; 121: 1274–1281. [PMID: 4037820]
10. Murphy MJ, Jen M, Chang MW, Grant-Kels JM, Makkar H. Molecular diagnosis of a benign proliferative nodule developing in a congenital melanocytic nevus in a 3-month-old infant. J Am Acad Dermatol 2008; 59: 518–523. [PMID: 18640742]
11. Busam KJ. Molecular pathology of melanocytic tumors. Semin Diagn Pathol. 2013;30(4):362–74. [PMID: 24342290]