# An update on cutaneous melanocytic lesions

Maria C Isales

Victor Li Quan

Erin Garfield

Pedram Gerami

## Abstract

Significant advances in our understanding of melanocytic neoplasms at the genomic level have occurred in the last decade. This includes identifying initiating genomic events which correlate highly to morphology for benign intermediate and malignant melanocytic neoplasms. Among spitzoid melanocytic neoplasms, mRNA sequencing has revealed specific genomic fusions correlating to morphologic features. Additionally a number of biomarkers for intermediate and malignant grade lesions have been identified. This includes molecular studies looking for copy number aberrations or specific mutations in spitzoid neoplasms, deep penetrating nevi, and blue nevi. mRNA expression profiling has become an important test for prognostication of melanoma. In this review, we provide an overview of the molecular landscape and summarize the histomorphology of a subset of melanocytic neoplasms, including blue nevi, deep penetrating nevi, pigmented epithelioid melanocytomas, Spitz nevi, and BAPomas. We further discuss novel biomarkers for prognostication and the recent updates to melanoma staging.

**Keywords** BAPoma; blue nevus; cutaneous melanoma; deep penetrating nevus; pigmented epithelioid melanocytoma; Spitz nevus; staging

## Introduction

Over the past two decades, the incidence of melanoma has been increasing dramatically. In 2016, an estimated 76,380 Americans were diagnosed with invasive melanoma and the lifetime risk of developing in situ or invasive melanoma is 1 in 28.[1] With the significant rise in the number of melanomas and melanoma-related biopsies, there also results a significant number of intermediate grade lesions. Given the dramatic increase in intermediate and malignant melanocytic neoplasms, it is more important than ever to accurately classify melanocytic neoplasms. The many advances in molecular techniques has resulted in molecular tests and biomarkers that assist in the more accurate classification of melanocytic neoplasms and prediction of behavior. These include but are not limited to fluorescent in situ hybridization (FISH), comparative genomic hybridization (CGH), and next generation sequencing (NGS). One example of how molecular diagnostics may play a significant role in interpretation is in the case of *BAP1* loss. For example, *BAP1* (BRCA-1 Associated Protein) loss has been associated with progression from blue nevus (BN) to malignant blue nevus (MBN); however, *BAP1* inactivated melanocytic lesions (BIMT) or BAPomas, comprised predominantly of intradermal proliferations of atypical epithelioid melanocytes, exhibit indolent behavior overall. The contributions of this genomic data to our understanding of melanocytic neoplasia is critical given that diagnostic errors contribute to 10% of patient deaths and are the primary reason for medical malpractice payouts.[2] In this review, we summarize the recent literature on cutaneous melanocytic lesions including advances in the genomic landscape, useful diagnostic adjuncts, and the recent changes and additions to the 8th edition of the American Joint Committee on Cancer (AJCC) melanoma staging system.

***Maria C Isales*** *M.D Resident in Anatomic and Clinical Pathology, Department of Pathology, Northwestern University, Chicago, IL, USA. Conflicts of interest: none.*

***Victor Li Quan*** *B.A Medical Student, Department of Dermatology, Northwestern University, Chicago, IL, USA. Conflicts of interest: none.*

***Erin Garfield*** *B.A Medical Student, Department of Dermatology, Northwestern University, Chicago, IL, USA. Conflicts of interest: none.*

***Pedram Gerami*** *MD Professor of Dermatology, Pathology, and Pediatrics, Department of Dermatology, Northwestern University, Chicago, IL, USA. Conflicts of interest: Dr. Gerami has served as a consultant for DermTech Int. and Castle Biosciences and has received honoraria for this.*

## Benign and intermediate melanocytic neoplasms

### Blue nevi

Blue nevi (BN), first described by Tièche in 1906, are benign dermal proliferations of pigmented dendritic melanocytes often having a wedge-shaped architecture. In the clinical setting, BN typically present as small (<5 mm), well-demarcated, solitary, blue-black papules located on the head and neck, sacral area, and extremities.[3] A number of BN histologic variants have been described in the literature, including cellular blue nevi (CBN), sclerosing or desmoplastic BN, epithelioid BN, amelanotic BN, and malignant BN (MBN). Unlike epidermal-derived nevi and melanoma that commonly harbor *BRAF* and *NRAS* mutations, only 5–15% of BN and CBN contain mutations in the MAPK signaling pathway genes.[4] In contrast, up to 90% of BN and CBN demonstrate activating *GNAQ*, *GNA11*, and *CYSLTR2* mutations.[5] Diagnosing common and cellular BN does not frequently pose a diagnostic dilemma; however, atypical CBN lack consensus criteria. This intermediate diagnostic category of atypical CBN comprises those lesions with insufficient cytologic atypia for MBN but demonstrate concerning features, including areas of nuclear pleomorphism, increased cellularity often with expansile nodules, increased mitotic activity (up to 2–3/mm$^2$), and infiltrating margins.[4] In addition to *GNAQ* mutations found in 60% of atypical CBN, *CLYSTR2*, *PLCB4*, *BRAF* V600E, and *EIF1AX* mutations have recently been described.[6] The term MBN has been used to describe various entities, including melanoma arising at the site of a previously excised blue nevus, melanoma with blue nevus-like features, and melanoma with malignant change within a blue nevus. Most recently, Chan et al. found that MBN were more likely to harbor copy number aberrations involving multiple chromosomes than atypical CBN.[6] Specifically, recurrent gains of 1q, 4p, 6p, and 8q and recurrent losses of 1q and 4q have been described in MBN demonstrating overlap with uveal melanomas.[6] Given the *GNAQ* mutation, the molecular link





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between uveal melanoma and blue nevi has been explored resulting in the detection of *SF3B1* R625 and inactivating *BAP1* mutations in MBN.[7] While the occurrence of atypical BN and MBN is rare, identifying a mutation in *SF3B1* or *BAP1* may aid in distinguishing those cases with an increased likelihood of aggressive clinical behavior.

### Deep penetrating nevi

The deep penetrating nevus (DPN), a term first coined by Seab et al. in 1989, is considered a benign combined pattern melanocytic neoplasm with features of both Spitz and blue nevi (BN) (Figure 1a,b).[8] From a clinical perspective, these lesions are most frequently small (<1 cm), dome-shaped papules with a black, blue or gray color.[9] DPN most commonly occur in the first 3 decades of life with an approximately equal male: female ratio. The head and neck (35%), trunk (25%), and upper extremities (20%) are the most frequent locations while distal extremities have rarely been reported.[10] Histopathologic examination of DPN demonstrates a component of conventional nevus with a secondary proliferation of large oval to epithelioid melanocytes with more notable cytoplasmic pigmentation and admixed melanophages. Recently it has been shown that at the genomic level, DPN are the result of mutations in the mitogen-activated protein kinase (MAPK) pathway followed by mutations in *CTNNB1* which give rise to a subclone of larger more pigmented melanocytes. Yeh and colleagues performed next generation sequencing (NGS) on five cases of DPN-like melanoma demonstrating the acquisition of *CDKN2A*, *TERT*, *TP53*, *ARID1A*, *TET2*, and genomic copy number aberrations showing that at least in some cases these may progress to melanoma.[11]

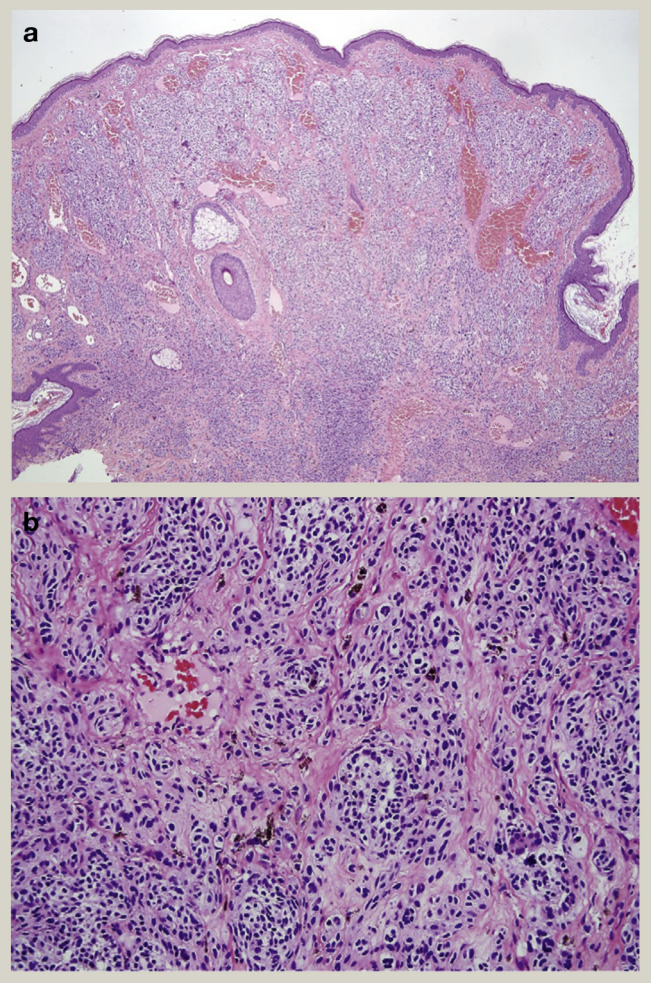


**Figure 1** (**a**): Deep penetrating nevus. Scanning magnification reveals a dermal based biphenotypic melanocytic neoplasm proliferating in close association with adnexal structures. (**b**): Higher magnification reveals nests of melanocytes with variable cytomorphology including some small conventional melanocytes as well as some larger epithelioid melanocytes with lightly pigmented cytoplasm and many intervening melanophages.

### Pigmented epithelioid melanocytomas

Previously known as "animal-type melanoma," pigmented epithelioid melanocytoma (PEM) was originally described as the sporadic counterpart to the epithelioid blue nevus in Carney's complex. However, the clinical, histologic, and prognostic features significantly differ between PEM and other pigmented dermal melanocytic proliferations. PEM are small to large (4–30 mm) pigmented papules commonly located on the head and neck or lower extremities occurring at a mean age of 20 years in both genders.[12] Histologically, PEM are wedge-shaped, intradermal lesions composed of large, pigmented epithelioid, spindled, and dendritic melanocytes and abundant heavily pigmented melanophages (Figure 2a,b).[13] PEM is an intermediate grade melanocytic lesion with a rate of lymph node involvement of approximately 46%; however, extranodal and distant metastases are extremely rare.[13] Previous studies documented loss of PrkaR1α expression and loss of heterozygosity at the *PRKAR1A* locus.[14] Recently, Cohen et al. subclassified PEM into 6 categories based on genetic alterations and morphological features. In the first subset, PEM with *PRKAR1A* and *BRAF* p.V600E genetic alterations demonstrated both a conventional compound nevus and a PEM component. The second subset of PEM demonstrated the classic PEM histologic characteristics, lacking a conventional nevus component, and harbored somatic in-frame deletions of *MAP2K1*. The third subset of PEM also demonstrated classic PEM histology and showed loss of PrkaR1α expression by immunohistochemistry, however, genetic alterations were not detected by NGS. The fourth subset harbored *PRKCA* fusions and were composed of intradermal proliferations of large monomorphic melanocytes with a moderate amount of cytoplasm and finely dispersed melanin. The fifth subset was comprised of tumors with *GNAQ* p.Q209p mutations and composed of an intradermal proliferation of medium-sized melanocytes with small nucleoli, and a moderate amount of dusty cytoplasm. The last subset of PEM lacked a genomic alteration and were histologically characterized by intradermal proliferations of monomorphic, medium-sized melanocytes with prominent nucleoli, abundant dusty cytoplasm, and admixed melanophages.[12] This data and our personal experience suggest that the term PEM is used in a highly heterogeneous manner as indicated by the genetics. Some cases could be classified as a variant of a combined nevus, epithelioid blue nevus or in the family of pigmented Spitz with fusions as the initiating genomic event.

### Spitz nevi and spitzoid melanoma

Spitzoid neoplasms, which include Spitz nevi, Spitz tumors, atypical Spitz tumors (AST), and Spitzoid melanoma, are variably




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