

Educational Case: Invasive Melanoma



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Introduction

Diagnosing invasive melanoma can be challenging with the various subtypes and benign mimics. Many pitfalls in obtaining biopsies and pathology evaluation can occur that may obscure the definitive answer. Melanoma progression is on a spectrum from superficial spreading types to vertical growth phase seen in nodular melanoma. To address these concerns, we developed a continuing medical education piece for medical students and pathology residents describing the clinical presentations of melanoma and common benign conditions (such as lentiginosis, seborrheic keratosis, keloid scars, etc) and the benign and malignant pathologic differential diagnosis (spritz nevis, atypical melanocytic nevus, irritated nevus, superficial spreading melanoma, and lentigo maligna melanoma, etc) that should be considered with a possible case of invasive melanoma.

Methods

Articles for the continuing medical education piece were found using Google Scholar and PubMed. These papers were inspected for relevant research studies relating to the clinical presentation, clinical differential diagnosis, pathologic diagnosis, pathologic differential and various diagnostic tools used to confirm a melanoma diagnosis. 145 articles and texts related to melanoma diagnosis and differential were reviewed and incorporated into this work. Four malignant melanoma subtypes and six benign lesions that were pathologically similar to invasive melanoma are described. Additionally, common pitfalls are discussed and explored.

Conclusion

Determining benign versus malignant melanoma can be challenging. Careful sampling of patient samples and using molecular alternations can assist with determining the specific subtype of melanoma. Careful analysis of the histologic features of prognosis and the use of molecular alterations can help clinicians to provide accurate care for patients.

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Results

Diagnosis	Epidemiology and body location	Clinical Features	Histological Features
<i>Spritz Nevis</i>	Normally children to adolescent, rarely in adults; ¹³⁵ Face and lower extremities ¹³⁶	Scaly pink round nodule ¹³⁶	Circumscribed, symmetrical large maturing spindle and epithelioid melanocytic nests ³⁶
<i>Atypical Melanocytic Nevus</i>	Usually >30 years of age ¹³⁷ , trunk and upper back ¹³⁸	Borders are fuzzy irregular and multicolored brownish, pinkish, tan patch ¹	Mild asymmetry, lentiginous growth of individual melanocytes along rete ridges, nuclei are enlarged, hyperchromatic with prominent nucleoli ⁴⁰
<i>Acquired Melanocytic Nevus</i>	Develop around 6-12 months of age, peak occurrence in 30s, women more likely on limbs, men more likely on trunk ¹³⁹	Compound: light brown to tan macule, regular borders ⁴ Dermal: minimal pigmentation and appear colored pink to fleshy as a nodule or papule with regular borders ⁴ Junctional: brown to black macules, with regular borders ⁴	Separated nests at the dermal-epidermal junction with dermal melanocyte proliferation ³ Nests of melanocytes are restricted to the dermis; possible junctional melanocytic hyperplasia ³ Nests of bland melanocytes are witnessed at the rete ridge tips; no pagetoid or lentiginous spread ³
<i>Irritated Nevus</i>	Similar to acquired nevi, in first 20 years of life; ¹⁴⁰ commonly found in areas such as the beard-area or axilla or men and women respectively ¹⁴¹	Nodular, lesions, with color varying from pink to dark brown, symmetric and circumscribed borders, possibly erythematous border ¹⁴²	Spongiosis, erosion superficially, some small melanocytic cells with benign nuclear features invading the epidermis, pagetoid spread is rare ⁴²
<i>Recurrent/persistent Nevus</i>	Melanocytic cells growth at removal site of a benign lesion, ⁴³ women 20-30 years old back, face, extremities ¹⁴³	Development from original biopsy site, macular sized irregular streaky hypo and hyperpigmentation ¹⁴⁴	Epidermal effacement with melanocytic growth in junctional or compound pattern, possibly with pagetoid spread ⁴³
<i>Acral Nevus</i>	Common in ages under 50, palms and soles ¹⁴⁵	Macular to mildly elevated, with color variations of homogenous light brown to dark brown ¹⁴⁵	Scattered melanin pigmentation in stratum corneum, pagetoid spread of nesting small melanocytes of into the upper epidermis ⁴⁴

Table 1. Summary of Benign Differential for Melanoma. Epidemiology, clinical features and histological diagnosis are provided for the six most common histologic mimics of melanoma: spitz nevus, atypical melanocytic nevus, acquired melanocytic nevus, irritated nevus, recurrent nevus, and acral nevus

Melanoma Subtypes	Risk Factors, epidemiology, body location	Clinical Features	Histological Features	Molecular Alterations ⁹³
Superficial Spreading Melanoma ² (SSM)	Lightly pigmented skin, over 50 years of age, trunk and extremities ¹⁷	Brown to blackish non-homogeneous macule with irregular borders ¹⁷	Intraepidermal pagetoid spread of atypical melanocytes, possibly with junctional melanocytic nests ²¹	BRAF V600E
Nodular Melanoma (NM)	Men over 50 years, trunk and extremities ¹⁸	Nodular blueish black to reddish pink ^{19,20}	Confluent cohesive nests of atypical melanocytes in the dermis, with vertical growth pattern and no radial growth phase; no intraepidermal atypical melanocytes past three epidermal rete ridges on either side of tumor, ulceration is common ¹⁹	Share variations from other melanoma types; BRAF and NRAS
Lentigo Maligna Melanoma (LMM)	Sun exposure, >60 years of age, men more likely than women, head and neck ^{21,22}	non-homogenous brownish black patch or plaque with irregular borders ²²	Atypical melanocytes along the basal layer with prominent solar elastosis in the dermis; pagetoid spread not common in early lesions only older patches ¹⁹	NF1, BRAF V600K. non-V600E BRAF mutations, NRAS
Acral Lentiginous Melanoma (ALM)	Average of 63 years of age; occurs more often in African Americans and Asians; palm, soles, and nail beds ²³	Asymmetric, non-homogenous brownish black patch or plaque with irregular borders ²⁴	Atypical large melanocytes with spindle shaped elongated dendrites in the epidermal basal layer, nests of melanocytes frequently seen at tips of rete ridges ⁸⁴	KIT, CCND1 (increased copy number variation and amplifications)

Table 2. Summary Table of Melanoma Subtypes. Histologic features are provided for the four subtypes of invasive melanoma: Superficial spreading melanoma (SSM), Nodular Melanoma (NM), Lentigo Maligna Melanoma (LMM), and Acral Lentiginous Melanoma (ALM)