American Journal of Ophthalmology Case Reports 34 (2024) 102059

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Melanocytoma of the eyelid: Case report and introduction of new nomenclature

Natalie A. Homer [a,*], Kerri E. Rieger [b]

[a] Byers Eye Institute, Stanford University, Palo Alto, CA, USA
[b] Departments of Dermatology and Pathology, Stanford University, Palo Alto, CA, USA

ARTICLE INFO

Keywords:
Melanocytoma
Melanoma
Nevus
Pigmented lesion

ABSTRACT

Purpose: The term melanocytoma was recently proposed for intermediate-stage melanocytic lesions with specific histopathologic and molecular genetic features. Prior studies have demonstrated a heightened potential for these intermediate lesions to spread to regional lymph nodes, with decreased likelihood for distant spread, when compared to melanomas.

Observations: Herein we present a case of a 28-year-old male who presented with a recurrent right lower eyelid margin combined cutaneous and palpebral conjunctival pigmented lesion, ultimately classified as a melanocytoma, to highlight this new nomenclature, characteristic histopathologic and genetic findings, and prognostic implications.

Conclusions: Ophthalmologists should be aware of this new cutaneous histopathologic classification system and apply to the periorbital region to improve melanocytic lesion management and surveillance.

1. Introduction

Cutaneous melanocytic lesions have historically been stratified into two categories: benign nevus and malignant melanoma. Intermediate lesions with less clear biologic potential, such as deep penetrating nevi and rapidly-expanding atypical spitz nevi, have been without a unifying classification. The term melanocytoma was proposed in 2011 for intermediate-stage melanocytic lesions harboring greater malignant potential than simple nevi, but with lower likelihood for systemic spread than malignant melanomas.[1] This novel nomenclature may allow for improved management guidance, surveillance protocols and prognostic counseling for patients with these lesion types.

Although the term melanocytoma, or magnocellular nevus, has been used in ophthalmology to describe a specific category of benign, heavily pigmented tumors arising from the optic nerve head, which show a characteristic magnocellular cytomorphology and abundant cytoplasm, this nomenclature has not yet been widely adopted for periorbital pigmented cutaneous and conjunctival lesions.[2] Herein is presented a case of a young patient with a recurrent right lower eyelid pigmented lesion, deemed upon histopathological examination to be consistent with the melanocytoma classification. Permission was obtained from the patient for publishing this report and accompanying photographs. The collection and evaluation of protected patient health information was HIPAA compliant and adhered to the ethical principles outlined in the Declaration of Helsinki.

2. Case presentation

A 28-year-old male presented for evaluation of a recurrent right lower eyelid margin lesion. He had previously undergone biopsy of a lightly pigmented cutaneous lesion in this location 10 years prior in the United Kingdom, with pathology consistent with a benign nevus. He noted a subsequent increase in size of the anterior non-pigmented lesion segment with darkening of the adjacent conjunctiva pigmentation. He was found to have a 2.5 mm × 3.5 mm non-pigmented elevated lesion less than 1 mm lateral to the inferior punctum (Fig. 1A), with contiguous flat palpebral conjunctival pigmentation (Fig. 1B). Surgical resection was performed. Histopathology demonstrated a combined compound melanocytic nevus and deep penetrating nevus (DPN), with nevocellular and deep penetrating nevus components and positive nuclear beta catenin staining in deeper melanocytes, consistent with melanocytoma classification (Fig. 2A–D). Additional margin excision was recommended, along with full-body dermatologic surveillance. Clinical lymph node evaluation was unremarkable. Upon 13-month follow-up there

* Corresponding author. Byers Eye Institute, Stanford Medicine 2452 Watson Ct, Palo Alto, CA, 94303, USA.
E-mail address: natalie.a.homer@gmail.com (N.A. Homer).

https://doi.org/10.1016/j.ajoc.2024.102059
Received 13 November 2023; Received in revised form 17 February 2024; Accepted 5 April 2024
Available online 16 April 2024
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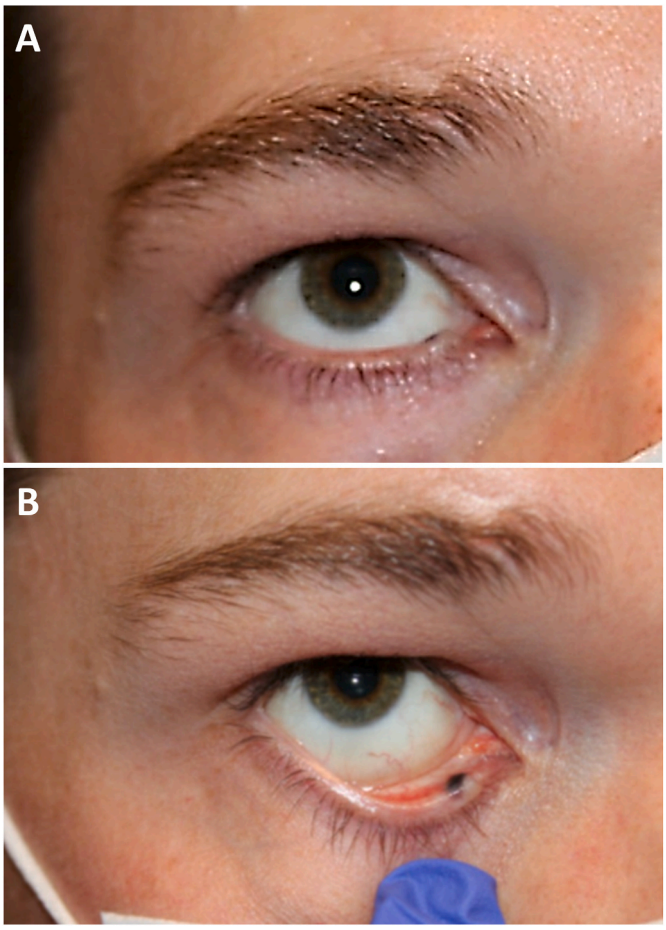

Fig. 1. Patient clinical images demonstrating the (A) anterior non-pigmented and (B) posterior pigmented components of a right lower eyelid lesion.

were no signs of recurrence or systemic involvement (Fig. 3).

3. Discussion

While potentially malignant melanocytic lesions are uncommon on the eyelid, their presence carries serious systemic risk. Thus, improved classification with tailored management guidance is critical. A subset of melanocytic proliferations are historically challenging to characterize, as lesions of varying prognostic potential share overlapping histologic features (Table 1). Previous nomenclature of "melanocytic tumors of uncertain malignant potential" (MELTUMP) was utilized for highly atypical melanocytic proliferations without specific genetic abnormalities that fall just short of diagnostic features of melanoma. These included atypical Spitz tumors, atypical blue nevi and deep penetrating nevi.[3] The 2018 World Health Organization (WHO) skin classification system has recognized a new intermediate melanocytic tumor classification, termed melanocytoma, which instead corresponds to distinctive histopathology with genetically-defined subtypes.[4] Herein was presented a case of a combined melanocytic nevus and deep penetrating nevus (DPN) involving both the eyelid anterior lamella and conjunctiva, consistent with this designation.

The melanocytoma tumor classification serves as a histopathologic and genetic intermediate between benign nevi and malignant melanoma. Isolated nevi most commonly arise from a BRAF V600E mutation, or less commonly an NRAS mutation, which ultimately activates the MAPK pathway.[5] Melanocytic tumors that harbor additional mutations, and thus carry a higher risk of malignant transformation, now fall into this new intermediate classification category.[4,6] A large study assessing for unique clinical identifying features did not find tumor thickness or ulceration to be specific predictive features.[3] Thus histopathologic analysis is mandatory for establishing this diagnosis.

Deep penetrating nevi are histopathologically characterized by a symmetrical proliferation of melanocytes, often with abundant melanophages and a wedge-shaped extension into the deep reticular dermis and subcutis.[7] DPN are known to originate from combined activation of MAP kinase pathway and WNT pathway via B-catenin activation, thus falling under the 2023 WHO designation "WNT-activated deep penetrating nevus/plexiform melanocytoma".[8] DPN involving the conjunctiva with dual genetic alteration are becoming more widely recognized.[9,10] The patient reported herein was found to have a DPN component on histopathology (Fig. 2C).

Atypical Spitz tumors also fall into the category of melanocytomas. Spitz nevi are characterized by dome-shaped, plaque-like morphology with melanocyte maturation in the dermis with a population of enlarged melanocytes.[11–18] Spitz tumors have been demonstrated to harbor *HRAS* mutations, inactivation of *BAP1,* or alternative genomic kinase rearrangements, often in conjunction with *BRAF* mutations.[19] ROS1, ALK, and nTRK mutations may also be seen. This tumor type, though rare, has been reported in the cutaneous eyelid and conjunctival regions.[20]

Blue nevi are classically characterized as congenital lesions, though also may be acquired in early childhood, arising from neural crest-derived melanocytes that become arrested during their migration to the epithelium.[21] The blue appearance of these cutaneous lesions is attributed to the localization of melanin deep within the dermis, whereas conjunctival blue nevi often share the same "brown" appearance as other nevi types. Genetically blue nevi typically harbor dual *BRAF* and *GNAQ* mutations.[22] There have been few reports of atypical blue nevi in the periorbital area with atypical designation and increased potential for metastasis, two initially arising on the cutaneous eyelid and one on the forniceal conjunctiva.[23,24]

Melanocytomas are believed to originate within a preexisting nevus after acquisition of additional mutations, often seen clinically as new dark pigmentation arising within a known nevus.[25] This was likely the case in our patient who observed increased lesion growth and pigmentation after initial biopsy 10 years prior to his presentation.

This diagnostic designation carries prognostic implications, as metastases have been reported.[3] Preliminary evidence has suggested a potential for these intermediate melanocytoma lesions to spread to regional lymph nodes, while maintaining decreased likelihood for distant spread compared to melanomas.[1] A review of 46 these melanocytoma-type lesions revealed not infrequent sentinel lymph node metastases but without distant spread during a median 32-month follow-up.[1] These authors thus questioned whether invasive sentinel lymph node biopsy provided useful prognostic value in determining risk for systemic disease metastasis and instead suggested consideration of non-invasive clinical lymph node palpation and lymphoscintigraphy, with or without ultrasonography, for disease surveillance. A separate review of 46 cases of conjunctival lesions consistent with melanocytomas did not find lesion recurrence or metastasis during a follow up period spanning 0.2–16.3 years.[9] A review of 160 patients with non-periorbital atypical Spitz tumors demonstrated sentinel lymph node metastases in 29–50 % of patients, without evidence of metastasis at median 37-month follow-up.[11–17] The patient herein was recommended to complete surgical excision and maintain close follow-up following diagnosis confirmation, rather than the less frequent surveillance that is typically accepted for benign nevi. Clinical lymph node evaluation has fortunately remained negative.

4. Conclusions

Melanocytoma is a novel histopathologic designation for melanocytic cutaneous and conjunctival lesions that should prompt closer follow-up and non-invasive lymph node evaluation, at a minimum. With continued study, this new classification system will likely continue to be further stratified into lower and higher-risk lesions subcategories to

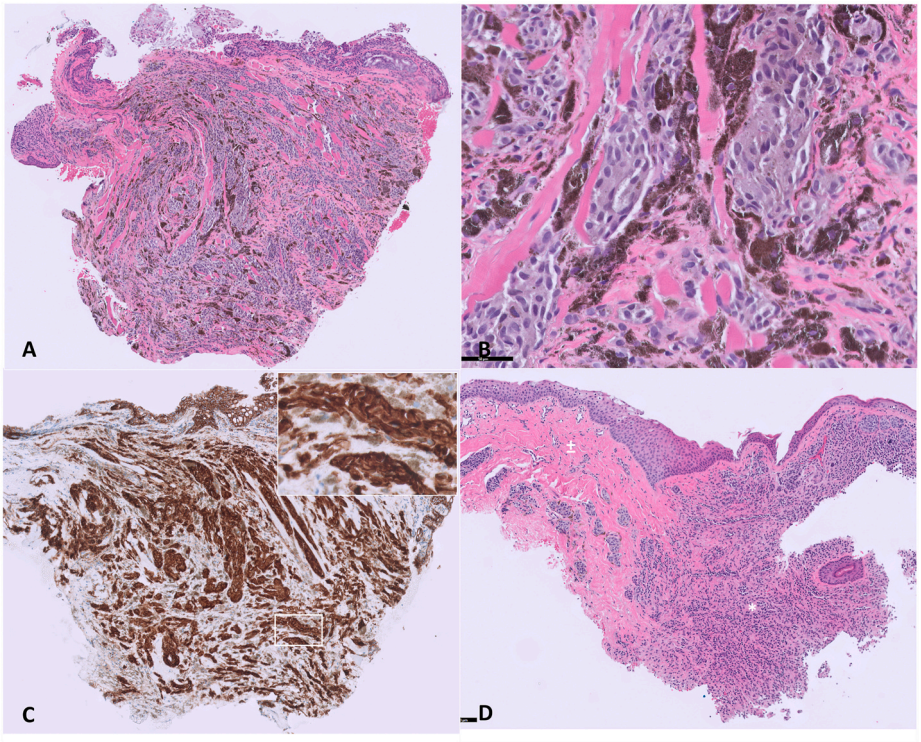

Fig. 2. Histopathologic images demonstrating the melanocytic lesion on (A) low-magnification and (B) high-magnification view, demonstrating nests and cords of fusiform melanocytes interspersed between thickened collagen bundles within the dermis. (C) There is notable retained nuclear beta catenin staining in the deep aspect of the deep-penetrating nevus component apparent on low and (inset) high-magnification. (D) Small, bland appearing background nevus (cross), consistent with pre-existing intradermal nevus, and deep penetrating nevus component (D, asterisk) can be seen.

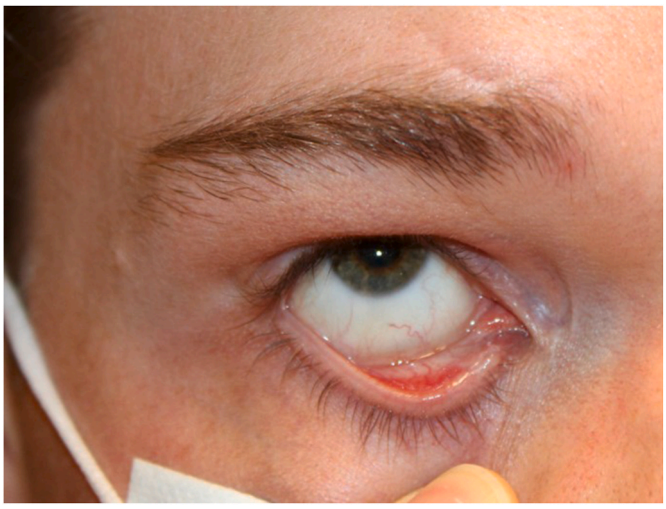

Fig. 3. Patient photograph 13-months post-excision demonstrating well-healed conjunctiva and eyelid without clinically-apparent lesion recurrence.

Table 1
Cutaneous and conjunctival melanocytic lesion classification.

	Clinical Presentation	Histopathology	Genetic Mutation
Simple nevus	Light-to-darkly pigmented macule or papule	Nests of melanocytes in upper dermis without atypia	Isolated *BRAF* mutation (most common) or *NRAS* mutation
Melanocytoma			
Deep penetrating nevus	Darkly-pigmented papule or nodule	Wedge-shaped configuration of melanocytes extending into deep reticular dermis	*BRAF* mutation and B-catenin mutation
Atypical Spitz tumors	Pink or flesh-colored dome-shaped papule or plaque	Deep melanocytic growth with cytologic atypia, aberrant or sheet-like dermal growth pattern with high cellular density	*BRAF* mutation and *HRAS* mutation or inactivation of *BAP1*
Atypical cellular blue nevus	"Blue" hue (cutaneous) or darkly pigmented (conjunctiva) patch	Pigmented dermal melanocytes, grouped spindle cells containing little or no melanin, frequently penetrate subcutaneous layer in well-defined islands with asymmetry or hypercellularity	*BRAF* mutation and *GNAQ* or *GNA11* gene
Melanoma	Poorly demarcated pigmented macule or plaque with or without ulceration	Asymmetric proliferation of atypical melanocytes, cytologic atypia, ± pagetoid involvement of the epidermis, dermal invasion and mitoses	*BRAF* mutation, *NRAS* mutation, *NF1* mutation, *KIT* protein mutation – Often multiple mutations present

provide improved management guidance. Ophthalmologists should be aware of this new cutaneous histopathologic classification system and apply to the periorbital region to improve melanocytic lesion management and surveillance.

Patient consent

The patient provided written consent for publication of the case and corresponding figures.

Funding

No funding or grant support

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

CRediT authorship contribution statement

Natalie A. Homer: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Kerri E. Rieger:** Formal analysis, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

References

1. Zembowicz A, Scolyer RA. Nevus/melanocytoma/Melanoma: an emerging paradigm for classification of melanocytic neoplasms? *Arch Pathol Lab Med*. 2011;135(3):300–306.
2. Reidy JJ, Apple DJ, Steinmetz RL, et al. Melanocytoma: nomenclature, pathogenesis, natural history and treatment. *Surv Ophthalmol*. 1985 Mar-Apr;29(5):319–327.
3. Cerroni L, Barnhill R, Elder D, et al. Melanocytic tumors of uncertain malignant potential: results of a tutorial held at the XXIX Symposium of the International Society of Dermatopathology in Graz. *Am J Surg Pathol*. 2010:314–326.
4. Elder DE, Massi D, Scolyer R, et al. *WHO Classification of Skin Tumours*. fourth ed. Lyon, France: IARC Press; 2018.
5. Roh MR, Eliades P, Gupta S, Tsao H. Genetics of melanocytic nevi. *Pigment Cell Melanoma Res*. 2015;28:661–672.
6. Davis EJ, Johnson DB, Sosman JA, Chandra S. Melanoma: what do all the mutations mean? *Cancer*. 2018 Sep 1;124(17):3490–3499.
7. Gill P, Aung PP. Conventional and atypical deep penetrating nevus, deep penetrating nevus like melanoma, and related variants. *Biology*. 2022 Mar 17;11(3):460.
8. Yeh I, Lang UE, Durieux E, et al. Combined activation of MAP kinase pathway and β-catenin signaling cause deep penetrating nevi. *Nat Commun*. 2017;8.
9. Sekoranja D, Vergot K, Hawlina G, Pizem J. Combined deep penetrating nevi of the conjunctiva are relatively common lesions characterized by BRAFV600E mutation and activation of the beta catenin pathway: a clinicopathological analysis of 34 lesions. *Br J Ophthalmol*. 2020;104:1016–1021.
10. Eder A, Milman T, Singh Mudhar H, et al. Unusual conjunctival melanocytic proliferations. Report of five cases and review of the literature. *Surv Ophthalmol*. 2023 Oct;27(23):S0039–S6257, 00141-8.
11. Gamblin TC, Edington H, Kirkwood JM, Rao UN. Sentinel lymph node biopsy for atypical melanocytic lesions with spitzoid features. *Ann Surg Oncol*. 2006;13(12):1664–1670.
12. Lohmann CM, Coit DG, Brady MS, Berwick M, Busam KJ. Sentinel lymph node biopsy in patients with diagnostically controversial spitzoid melanocytic tumors. *Am J Surg Pathol*. 2002;26(1):47–55.
13. Murali R, Sharma RN, Thompson JF, et al. Sentinel lymph node biopsy in histologically ambiguous melanocytic tumors with spitzoid features (so-called atypical spitzoid tumors). *Ann Surg Oncol*. 2008;15(1):302–309.
14. Su LD, Fullen DR, Sondak VK, Johnson TM, Lowe L. Sentinel lymph node biopsy for patients with problematic spitzoid melanocytic lesions: a report on 18 patients. *Cancer*. 2003;97(2):499–507.
15. Urso C, Borgognoni L, Saieva C, et al. Sentinel lymph node biopsy in patients with "atypical Spitz tumors": a report on 12 cases. *Hum Pathol*. 2006;37(7):779–780.
16. Ludgate MW, Fullen DR, Lee J, et al. The atypical Spitz tumor of uncertain biologic potential: a series of 67 patients from a single institution. *Cancer*. 2009;115(3):631–641.
17. Scolyer RAM, Muramatsu R, McCarthy SW. Atypical deep penetrating nevus forming a component of a combined nevus. In: Zembowicz A, Mihm CMJ, Murphy GF, Tahan SR, eds. *Pigmented Skin Lesions*. Brisbane, Australia: Knowledge Books and Software; 2009:105–124.
18. Harms KL, Lowe L, Fullen DR, Harms PW. Atypical spitz tumors: a diagnostic challenge. *Arch Pathol Lab Med*. 2015;139(10):1263–1270.

19. Wiesner T, Kutzner H, Cerroni L, Mihm Jr MC, Busam KJ, Murali R. Genomic aberrations in spitzoid melanocytic tumours and their implications for diagnosis, prognosis and therapy. *Pathology*. 2016 Feb;48(2):113–131.
20. Shields PW, Jakobiec FA, Stagner AM, Yoon MK. Spitz nevus arising in the eyelid of a teenager. *Surv Ophthalmol*. 2016 Mar-Apr;61(2):228–235.
21. Sayed-Ahmed I, Murillo JC, Monsalve P, et al. Blue nevi of the ocular surface: clinical characteristics, pathologic features, and clinical course. *Ophthalmology*. 2018 Aug;125(8):1189–1198.
22. Gupta M, Gupta R, Jhorar P. Atypical presentation of a late-onset blue nevus. *JAAD Case Rep*. 2022 Oct 27;30:102–104. https://doi.org/10.1016/j.jdcr.2022.10.014.
23. Gündüz K, Shields JA, Shields CL, Eagle Jr RC. Periorbital cellular blue nevus leading to orbitopalpebral and intracranial melanoma. *Ophthalmology*. 1998 Nov;105(11):2046–2050.
24. Demirci H, Shields CL, Shields JA, Eagle RC. Malignant melanoma arising from unusual conjunctival blue nevus. *Arch Ophthalmol*. 2000;118(11):1581–1584.
25. Yeh I. New and evolving concepts of melanocytic nevi and melanocytomas. *Mod Pathol*. 2020;33(1-14).