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REVIEW

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Follicular colonization in melanocytic nevi and melanoma: A literature review

Martina Lambertini[1,2] | Costantino Ricci[3,4] | Barbara Corti[5] | Giulia Veronesi[1,2] | Pietro Quaglino[6] | Simone Ribero[6] | Giovanni Pellacani[7] | Bor Hrvatin Stancic[8,9] | Elena Campione[10] | Emi Dika[1,2]

[1]Melanoma Centre, Dermatology, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy

[2]Dermatology, Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna, Italy

[3]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy

[4]Pathology Unit, Maggiore Hospital, AUSL Bologna, Bologna, Italy

[5]Pathology Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy

[6]Dermatology Clinic, Department of medical sciences, University of Turin, Turin, Italy

[7]Dermatology Clinic, Department of Clinical Internal, Anesthesiologic and Cardiovascular Sciences, Sapienza Medical School, Sapienza University of Rome, Rome, Italy

[8]Dermatovenerology Department, University Medical Centre Ljubljana, Ljubljana, Slovenia

[9]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[10]Dermatology Unit, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Correspondence
Bor Hrvatin Stancic, Dermatovenerology Department, University Medical Centre Ljubljana, Slovenia.
Email: bor.hrvatin.stancic@kclj.si

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Abstract

The lentiginous spread of melanocytes into the hair follicle can be observed in a number of benign melanocytic neoplasms such as in nevi but also in sun-induced melanocytic hyperplasia and melanoma. The follicular colonization by melanocytes in melanoma is classified into three distinct patterns: primary follicular melanoma, melanoma with folliculotropism, and invasive melanoma arising from melanoma in situ with folliculotropism. The role of follicular colonization in melanoma pathologic staging is still a matter of debate though the description of the latter has been recommended by the *International Collaboration on Cancer Reporting*. In this review, we will discuss the role of follicular colonization in melanoma and melanocytic nevi as well as the facts and controversies regarding this topic.

KEYWORDS
follicular colonization, hair follicle, histopathology, melanoma, nevi

1 | INTRODUCTION

An estimated 5 million hair follicles (HF) cover the body skin, generating hairs cyclically.[1] A great amount of literature has been recently written about the unexpected biological properties of HF, including cooperation with the neuroendocrine and immune system in the immune-surveillance against pathogens.[1] Particular attention has been given to the multipotent stem cells within the hair bulge, a specific compartment of the HF.[2] Epithelial stem cells, which express and produce cytokeratins, adhesion molecules, cytokines, and growth factor

Martina Lambertini and Costantino Ricci contributed equally to this study.

receptors play a central role in the renewal of the hair cycle and wound regeneration.[3–7] The outer root sheath contains melanocytic stem cells, thought to be a reservoir for mature and differentiated melanocytes.[8–10] Mesenchymal stem cells, recently discovered in the connective tissue of the sheath and dermal papillae of the HF, have been suggested to exert hematopoietic properties.[11] Epidermal healing and repair functions are supported by both epithelial and mesenchymal stem cells.[12,13] Finally, a recently discovered subtype of stem cells resident in the hair bulge, the neural crest-like stem cells, express embryonic stem cell markers with the potential to differentiate into multiple lineages.[14] Much remains to be discovered regarding the real function of HF in the neoplastic cells diffusion during the initiation and progression of skin cancer. It has been hypothesized that HF may be involved in host immune-surveillance.[1] However, the exact role of HF is still unclear and contradictory results have been reported on its ability to limit and prevent the spread of neoplastic cells.[15] Some authors suggested that HF attenuates tumor diffusion, representing a physical and immunologic "barrier".[16] On the contrary, other authors supported the so-called "direct spread" theory, suggesting that HF may contribute to the neoplastic cell diffusion.[17–19]

2 | INVOLVEMENT OF THE FOLLICULAR UNIT IN MELANOCYTIC NEVI

The lentiginous spread of melanocytes into the HF is not a pathognomonic criterion of malignancy as it is observed in several subtypes of benign melanocytic neoplasms such as dysplastic nevus, special-site nevus, sun-induced melanocytic hyperplasia, but mostly congenital nevus (present at birth or appearing in the first year of life) and congenital nevus-like acquired nevus/"early-onset" acquired nevus (appearing between the first and the second year of life).[20–23] This evidence is connected with the genesis of these nevi, which arise from melanocyte precursor cells around and inside nerves and follicular structures and ascend to colonize the dermis, the epidermis, and the HFs after birth.[20] Some authors proposed that the degree and extent of HF involvement could represent an additional diagnostic criterion, as melanocytes in nevi are usually confined within the infundibulum and are restricted to a small portion of non-contiguous HFs, on the other hand in melanoma they spread down to the isthmus and the bulge involving most of the HF in a contiguous manner.[20–22]

3 | INVOLVEMENT OF THE FOLLICULAR UNIT IN MELANOMA: FACTS AND CONTROVERSIES

Follicular spreading of atypical melanocytes into the HF is a common finding in melanoma and it is considered a defining feature of specific subtypes, including lentigo maligna melanoma and superficial spreading melanoma.[19–21] In dermatopathology the term "folliculotropism" had been coined for inflammatory/lymphomatous pathology to indicate inflammatory cells that colonize the epidermis.[15–21] Indeed, although there are differences between these two phenomena, both refer to a cell population colonizing an epidermal structure driven by mechanical, chemotactic, hormonal and paracrine stimuli.[15–21] Follicular colonization by melanocytes in melanoma could be histopathologically classified into three distinct patterns (Figure 1): *primary follicular melanoma*, *melanoma with folliculotropism*, and *invasive melanoma arising from melanoma* in situ *with folliculotropism*.[24,25] *Primary follicular melanoma* primarily involves the HF with a subsequent extension of atypical melanocytes into the epidermis; *melanoma with folliculotropism* is an in situ and/or invasive melanoma that primarily occurs on the epidermis of the interpapillary plate showing a subsequent extension of atypical melanocytes to the HF, on the other hand *invasive melanoma arising from melanoma* in situ *with folliculotropism* is a melanoma in situ with an extension into the HF and a subsequent infiltration of the peripapillary dermis. The role of HF involvement in melanoma and HF biology are still a matter of debate with numerous studies reporting conflicting results, and no difference in terms of biologic behavior was reported among the described patterns.[1,8–11]

3.1 | Prognostic aspects

Perifollicular and follicular destructive invasion by atypical melanocytes was reported as a potential contributing factor to melanoma metastasis in five out of eight cases of thin, low-risk melanomas that failed to show other potential risk factors for progression, such as vertical growth phase, ulceration, regression, or numerous mitoses.[17] Moreover, it was hypothesized that an extensive HF involvement could have the same biological meaning as vertical growth phase.[17] Speculations about this topic have been largely intensified and a great amount of literature data has been acquired, also including different and/or partially conflicting results.[17–19,26–30] HF involvement by atypical melanocytes was analyzed in a series of 62 invasive head and neck melanomas, with a Breslow depth ranging from 0.2 to 8 mm.[31] Histopathological subtypes consisted of 22 cases of lentigo maligna melanoma (35.5%), 27 cases of superficial spreading melanoma (43.5%), and 13 cases of nodular melanoma (21.0%). A novel quantitative parameter for the classification of HF involvement by neoplastic cells was proposed. A "diffuse type" of follicular colonization when atypical melanocytes were present in more than three contiguous HFs for every six observed in each specimen, "a focal type" when less than three contiguous HFs were involved, and "absence of follicular colonization" in case of lack of HF diffusion. Globally, 55 cases (87.7%) showed diffuse and/or focal follicular colonization. The diffuse type was observed in 28 cases and correlated with scalp localization, the nodular histopathological subtype, higher Breslow depth, and disease recurrence. The occurrence of malignant melanocytes in the bulb region was uncommon and the "follicular Breslow depth" compared to Breslow depth did not change significantly.

Contrarily to previous reports, in a series of 100 cases of primary melanomas (61 in situ and 39 invasive melanomas with a significant in situ component) it was found that 82 cases showed tumor cells within

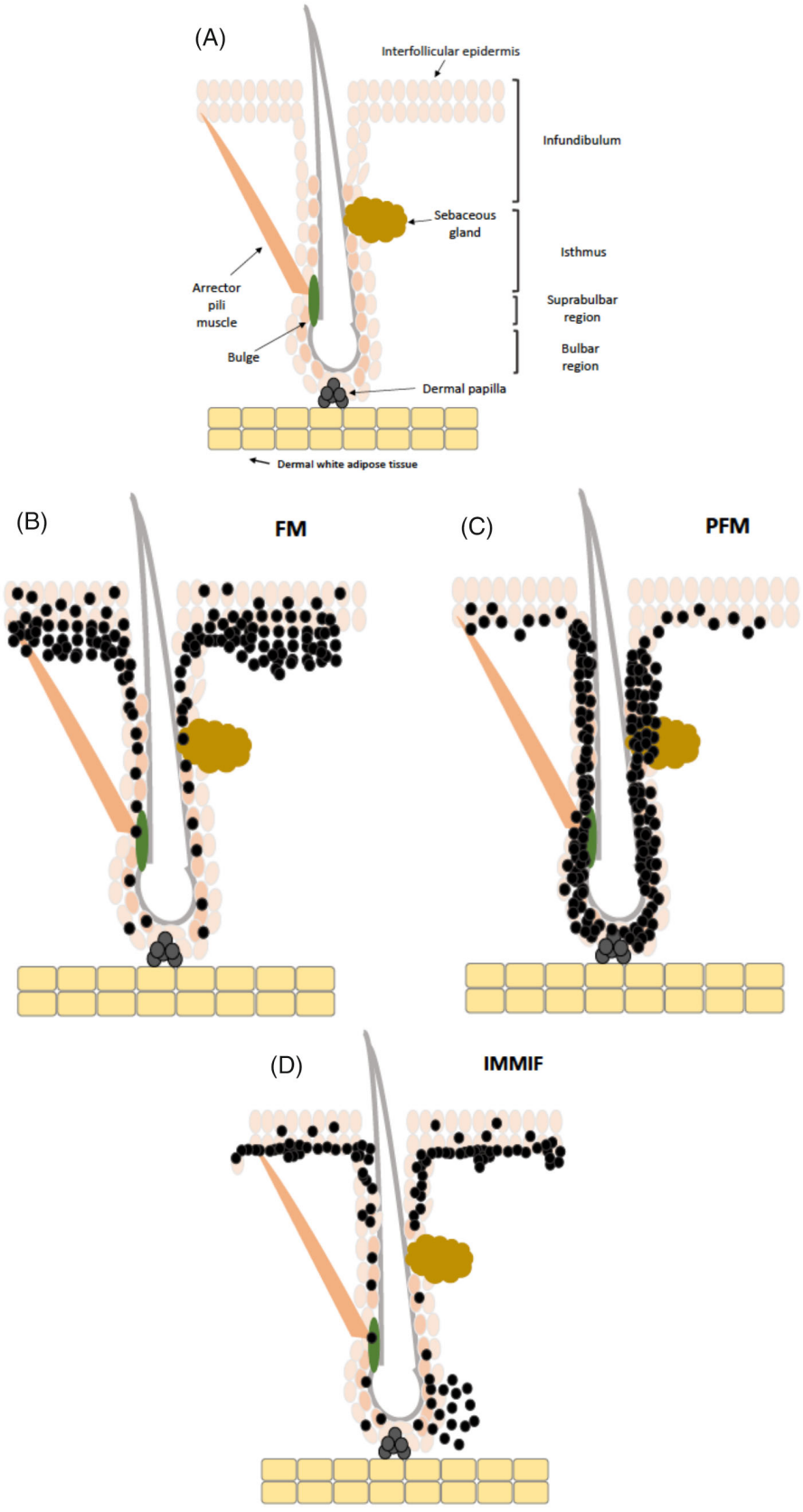

FIGURE 1 Graphic illustration of the hair follicle structures (A), melanoma with folliculotropism (B) primary follicular melanoma (C) and invasive melanoma arising from melanoma in situ with folliculotropism (D).

at least one HF. Of those, 57 cases (69.5%) showed atypical melanocytes within the infundibulum; the extension to the isthmus was present in 24 cases (29.3%) and in only one (1.2%) case the tumor cells were detected beneath the level of the bulge.[16] The authors hypothesized the existence of physiological barrier limiting the intraepithelial spread of melanoma cells beyond the level of the stem cell niche in the

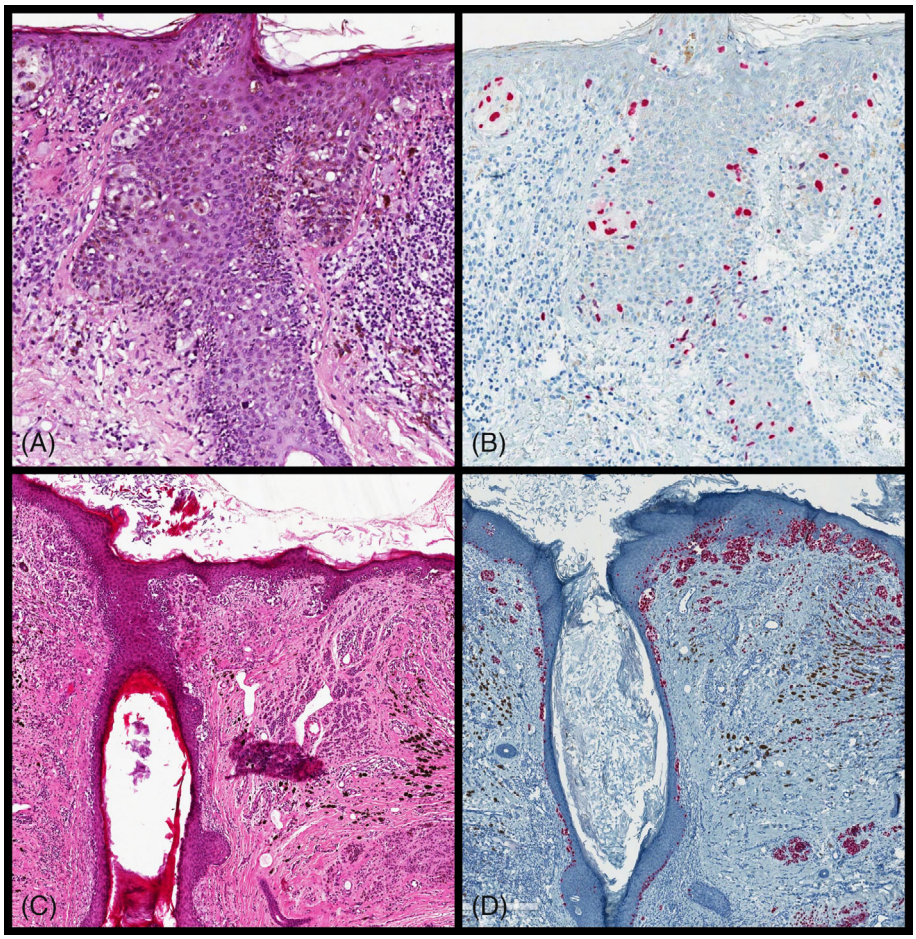

FIGURE 2 Melanoma with folliculotropism-superficial spreading histotype (A: H&E, original magnification ×200) with malignant melanocytes arranged in single cells and small nests (B: SRY-related HMG-box 10 [SOX10], original magnification ×200) clearly spreading into the pilosebaceous unit. Melanoma with folliculotropism–nevoid histotype (C: H&E, original magnification ×80) showing an extension of malignant melanocytes into a dilated/distorted follicular unit (D: SOX10, original magnification ×80). In both cases, SOX10 stain (red) the nuclei of malignant melanocytic cells.

bulge.[16] The "immunologic" barrier theory originates from the observation that human bulge outer root sheath cells overexpress CD200R, a type 1 transmembrane glycoprotein that codifies for a repressor signal expressed on the myeloid lineage cells and T CD cells.[16,26,27] The "physical" barrier hypothesis is supported by the undetermined cell mediators produced in the deeper portion of the HF with the function to limit the spread of neoplastic cells. One of the possible mediators is tenascin-C, a glycoprotein implicated in the epithelial microenvironment interaction during the tumor progression.[16,28] It has also been proposed that peptide fragments of hair lysates may provide natural protection, inhibiting the proliferation of melanoma cells in vitro.[15]

3.2 | Primary follicular melanoma

A separate mention deserves *primary follicular melanoma*, which shows atypical clinical findings, such as small pigmented papules resembling macrocomedones or cysts. Neoplastic cells primarily invade the pilosebaceous unit, with a secondary epidermal localization (Figure 2).[25] In a case series of *primary follicular melanomas*, contrarily to lentigo maligna melanoma, the depth of follicular involvement was greater than the length of interfollicular epidermal involvement.[25] All the lesions occurred on sun-exposed skin and mostly in the elderly.[25] A second case series was reported with three *primary follicular melanomas* occurring in young patients with no chronic sun damage.[24] The authors distinguished the histologic features of *primary follicular melanoma* from folliculotropic melanoma metastases and follicular involvement melanocytes observed in nevi.[24]

3.3 | Periadnexal extension in primary cutaneous melanoma

An additional hot topic is the evaluation and the prognostic relevance of periadnexal extension in primary cutaneous melanoma, defined as the extension or "tongue" of tumor extending beyond the depth of the main tumor mass within adventitial or extra-adventitial tissue immediately adjacent to skin appendageal structures.[20–22,29] It should be measured from the granular layer of the overlapping epidermis to the deepest point of extension (and not from the epithelium of the nearest follicular structure), and eventually reported in the histopathological report as "extension beyond the Breslow thickness", but not considered as the real Breslow thickness. In our experience, the phenomenon of infiltrative components represented only by rare melanocytic cells with periadnexal growth is uncommon. In this exceptionally rare case (invasive melanoma component represented only by isolated melanoma cells in the perifollicular adventitial dermis) an alternative

option could be the measurement of Breslow thickness from the center of the follicular epithelium rather than the overlying granular layer; however, in the absence of clear-cut guidelines, we suggest a descriptive report followed by a patient-based approach with the discussion of the case at a multidisciplinary meeting with dermatologists to evaluate the best therapeutic/follow-up approach.[29,30,32,33] In a case–control study the incidence of periadnexal extension was reported to be around 1.5% in melanoma (257/16692 cases between 2005 and 2015) with improved rates of melanoma-specific survival, overall survival, and disease-specific survival, although none with statistical significance. However, a higher rate of sentinel lymph node metastasis in the periadnexal group versus the control group in tumors >1-mm thick (24/100 = 24% vs. 23/187 = 12.3%) was described. These results were not easily explained and needed further studies to be validated and clarified.[29]

3.4 | Histopathology report

Based on the growing findings highlighting that follicular colonization could be an unfavorable prognostic factor in primary cutaneous melanoma, the evaluation and the reporting of HF involvement by atypical melanocytes in melanoma diagnosis has been recommended by the *International Collaboration on Cancer Reporting*.[30] Nevertheless, these guidelines have not been extensively accepted and adopted worldwide, and other ones do not recommend a standard report.[32,33] It was reported that "follicular Breslow depth", measured from the granular cell layer to the deep follicular involvement (as the deepest atypical melanocyte extending into the follicular epithelium) could allow clinicians to select appropriate surgical management and follow-up. However, "follicular Breslow depth" could lead to an overestimation of the risk of progression, as it may not reflect the real "tumor volume and/or tumor extension". For this reason, it is recommended not to replace the conventional Breslow depth.[18,34]

3.5 | Dermoscopic features

Very recently, the dermoscopic features associated with HF involvement in lentigo maligna and lentigo maligna melanoma have been described. The detection of gray circles in lentigo maligna has been correlated with an isthmic or bulb follicular extension of malignant melanocytes, while the presence of gray circles, light/dark brown pseudo-networks, and light brown structureless areas in lentigo maligna melanoma has been associated with focal/diffuse distribution of malignant melanocytes in the HF.[35]

4 | CONCLUSIONS

In conclusion, the role of HF involvement by melanoma neoplastic cells is still controversial. As for other criteria used in the differential diagnosis between nevi and melanoma, the presence of follicular colonization, the degree of HF involvement by benign or malignant-looking melanocytes and periadnexal involvement or extension need to be integrated with other features (cytological atypia, pleomorphism, mitosis, maturation, pagetoid spreading, etc.) in a holistic interpretation that takes into account also dermatological, dermatoscopic, immunohistochemical, and genetic features. Further investigations and a greater focus on the role of HF cells in melanoma may offer interesting results regarding the pathogenesis and biological behavior of this aggressive tumor.

We believe that only the presence/absence of follicular colonization should be specified in the histopathology report, without mentioning the type, the level of invasion or the "follicular Breslow depth". In our experience, the presence/absence of follicular colonization has a prognostic relevance, mainly in terms of local recurrences and especially for lentigo malignant melanoma of the face, which to date is "difficult or premature" to prognostically split into the different types of folliculotropsim, the extension to the infundibulum and/or the "follicular Breslow depth".[31,35,36] In that way, the histopathology report is not overloaded with information that could be redundant and useless for the clinician (dermatologist or oncologist) who reads the report.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Review article.

ORCID

Costantino Ricci https://orcid.org/0000-0001-7254-4195
Giulia Veronesi https://orcid.org/0000-0001-6595-7776
Bor Hrvatin Stancic https://orcid.org/0000-0001-5294-2225
Emi Dika https://orcid.org/0000-0003-3186-2861

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