

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,800

Open access books available

142,000

International authors and editors

180M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Combined Nevi

Jelena Stojkovic-Filipovic and Miljan Vlahovic

Abstract

Combined nevi (CN) are clinically defined as melanocytic lesions comprising two or more distinct melanocytic nevus components, and from the cytological point of view, CN are determined by the presence of two or more different nevus cell types in one biopsy specimen. They are very uncommon and represent less than 1% of all biopsied melanocytic nevi. CN comprise any melanocytic nevi, but the most prevalent combination is CN that consist of blue nevus associated with common melanocytic nevus. CN owe their diversity to combination of different nevi, that are variously combined. Consequently, they can have variable clinical aspects and dermatoscopic features. Because of the presence of at least two distinct subtypes of nevomelanocytes, dermatoscopically CN can show multicomponent, unspecific, and peculiar patterns. Therefore, CN can mimic melanomas, their most important differential clinical, dermatoscopic and histopathological diagnosis.

Keywords: combined nevi, combined blue nevi, melanoma, dermatoscopy, dermoscopy

1. Introduction

Combined nevi (CN) are specific, uncommon type of melanocytic nevi, and they represent less than 1% of all biopsied melanocytic nevi [1, 2]. Clinically, they are defined as melanocytic lesions comprising two or more distinct melanocytic nevus components [3]. From a histopathologic point of view, combined nevi are determined by the presence of two or more different nevus cell types in one biopsy specimen [4]. Based on their clinical and histopathological features, CN represent a subcategory of so-called collision or compound tumors, which are defined by the occurrence of two distinctive neoplastic skin lesions, that collide concurrently within the same specimen [5].

Combined nevi can be comprised by any melanocytic nevi. Although any collision is possible, it is most likely that CN present a combined variant of blue nevus, acquired nevus (Clark nevus), superficial congenital nevus, Spitz nevus or deep penetrating nevus [1]. The most frequent combination that is seen in practice is that of blue nevus associated with common melanocytic nevus and Spitz nevus [4].

2. Clinical features

Combined nevi are mainly congenital, although they are not always visible at birth, but later in life [6]. Although CN could be seen in childhood, as well as at an old age, they are most frequent in young adults (median age reported from 29 to 47) [1, 4, 7, 8]. In early studies of CN, a slight predominance in females was reported



Figure 1.
Combined nevus clinical presentation: Slightly raised, round lesion; small black spot in the center, surrounded by brown area (Targetoid combined blue nevus type).

[1, 4, 8], with the female: male ratio 1.1:1 [1]. Newer study with larger number of observed CN, has shifted that ratio towards male predominance 0.6:1 [7].

In the view of distribution, the predilection site has not been officially established, but literature data show that this nevus type does most frequently appear on the trunk [1, 4, 7–9] and head and neck region [7], and it is less common on the extremities [7].

Since CN are composed of distinct nevi, their clinical appearance could be very diverse. In practice, CN are usually small, flat, or minimally raised lesions [1, 7], often characterized by a small blue or black spot (corresponding to the blue nevus component) in the context of a larger area of brown color (corresponding to the common nevus) surrounding the blue nevus part [10] (**Figure 1**). The latter is known as the targetoid combined blue nevus type [11].

3. Dermatoscopic features

Since CN are composed of at least two different nevus types in various combinations, their dermatoscopic features are characterized by mostly multicomponent, unspecific, and random patterns. Typically, multicomponent structure of CN exhibit reasonably symmetrical appearance [3, 7] (**Figure 2**), which is consistent with already established findings that benign nevi tend to exhibit symmetry [12]. This is one of the most distinguishing features when differentiating CN from melanomas, as chaos (asymmetry of structure or colors) is principally imperative of a malignant neoplasm [6, 13].

Looking at the color, simultaneous occurrence of different colors (primarily brown and blue, rarely black, and white) is common appearance in CN, where the pigmentation originates from both junctional and dermal portion of the skin [6]. Since blue nevus is the most common component of CN, structureless blue part of the lesion is frequently presented [7], usually covering about 30% of the lesion (**Figure 2A and B**). Being such a regular finding, structureless blue area is an important element in the dermatoscopic analysis of this nevus type [7], even

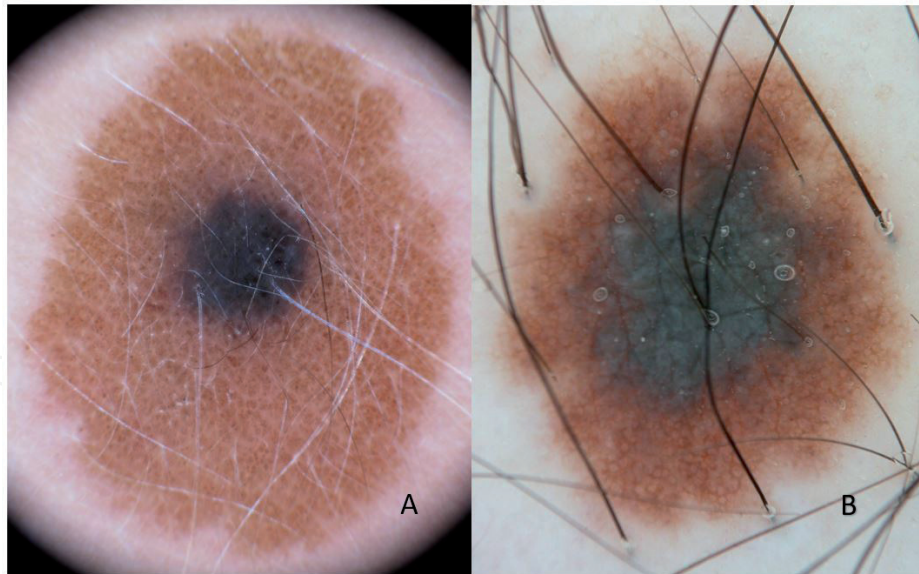


Figure 2.
Combined nevus dermatoscopy: A. well defined structureless blue area in the center of the lesion, pigmented globules at the periphery; B. ill-defined structureless blue area in the center of the lesion, brown reticular lines at the periphery.

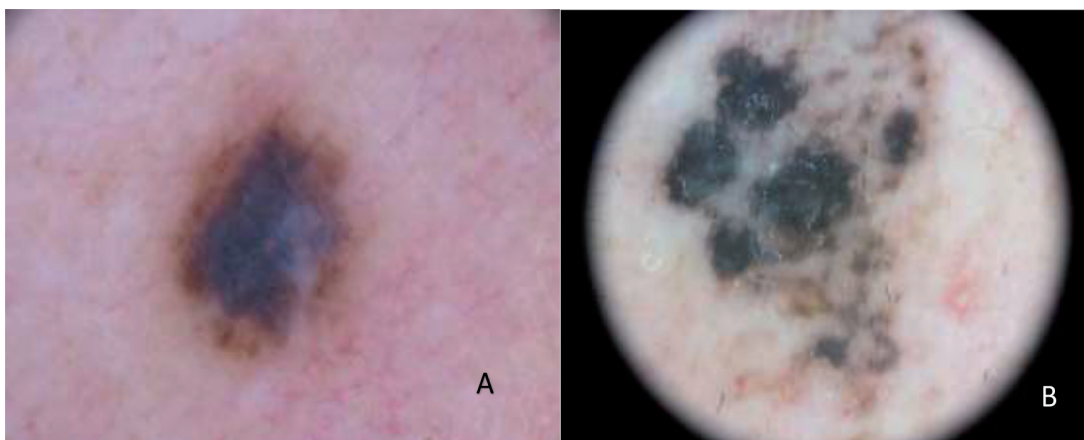


Figure 3.
Combined nevus dermatoscopy: A. diffuse distribution of structureless blue area, structureless brown at the periphery; B. patchy distribution of structureless blue area.

reported as a hallmark of CN [14]. Both well and ill-defined structureless blue areas (**Figure 2A** and **B**) are presented in CN. It is important to remember that the presence of ill-defined structureless blue area in any lesion must always raise suspicion, since it may resemble the “blue veil”, common characteristic of melanomas with the blue part [7].

Regarding the position of the structureless blue areas and their proximity to the edge of the lesion, in the majority of observed cases, these areas do not touch the edge of the lesions (**Figure 2A** and **B**) [7]. Diffuse and patchy type of structureless blue areas distribution appears in only less than 10% CN and cannot be considered as a specific feature for this nevus type (**Figure 3A** and **B**). Structureless blue area could be presented either eccentrically (**Figure 4**) or in the central part of CN, whereas central distribution is more common (**Figure 2A** and **B**) [7, 9], distinctive for benign lesions and reflects benign nature of these nevi. If located centrally, blue structureless area is surrounded by another pattern, mostly brown clods (**Figure 2A**), or reticular pattern (**Figure 2B**), which was previously stated as the stereotypical appearance of CN [15]. Within and around the structureless blue area of CN brown



Figure 4.
Combined nevus dermatoscopy: Eccentric structureless blue area, at the edge of the lesion.

dots may be present [14, 16]. Yet, this cannot be considered as a dermoscopic clue specific for CN, since it could be found in melanomas as well.

Curved lines at the periphery of the lesion can be contemplated as additional specific dermoscopic features of CN [9, 14]. The other dermoscopic features like radial circumferential or segmental lines, branched lines, as well as blue and gray clods and dots are not specific for CN [7, 17]. In some cases, when blue nevus is associated with a dermal nevus, gray-blue pigmentation could be distributed irregularly [9].

In cases where CN exhibit chaotic appearance, featuring eccentric structureless, particularly blue area (**Figure 4**), CN lack clues such as white lines, gray structures, pseudopods/radial lines, thick reticular lines, ulcerations, and polygons which are typical for melanomas [7]. Lesions with multicomponent pattern and eccentric, particularly structureless blue area, lacking specific dermoscopic features of melanoma do not require excision.

4. Differential diagnosis

Due to their variable nature and different nevus types combined in variety of patterns, clinical and dermoscopic determination of CN could be challenging. For that reason, differential diagnoses may include several benign or malignant neoplasms. Combined nevus may resemble blue nevus, common nevus, Spitz nevus (pigmented type), pigmented spindle cell nevus, plexiform spindle cell nevus, benign vascular tumors, hemosiderotic variant of dermatofibroma, pigmented basal cell carcinoma, cutaneous metastases [6, 9, 18, 19]. Despite this broad similarity to the various skin lesions, CN usually simulate melanoma, which is the most common differential diagnosis. Due to their inconsistent, atypical and irregular clinical and dermoscopic appearance, CN are frequently misdiagnosed as melanomas [1] and careful histologic examination to exclude melanoma is occasionally required.

5. Histopathology

The term “combined” can be both used in cytological and dermoscopic context. Histopathological features of CN depend on nevi that are combined within the lesion, and vary depending on the nevi types present.

Histopathologically, there are several types of CN, characterized by the combination of any morphological expression of congenital and/or acquired nevi. Superficial congenital nevus combined with blue nevus, either common or cellular type are most common combination seen in practice. Less frequent are Spitz nevus combined with Clark nevus (“SPARK”), superficial congenital nevi combined with deep penetrating nevus, and blue nevus combined with Spitz nevus (“BLITZ”) [7].

The most common histopathological finding in diagnosis of CN is a compound or dermal nevus with a dermal population of enlarged nevus cells (**Figure 5A**), either admixed with or overlie pigmented epithelioid and/or spindled melanocytes component in association with melanophages [19] (**Figure 5B and C**).

In the case of blue nevus, dendritic, cellular blue or deep penetrating nevus are present, with melanin in the deeper dermal portions [1]. Common blue nevus is characterized by elongated, often slightly wavy melanocytes with long, branching dendrites, either grouped together or in bundles in the upper and mid dermis, parallel to the epidermis, with variable numbers of macrophages and increase amount of collagen [1]. Melanocytes could extend into the subcutaneous tissue or approach the epidermis, but they never alter the epidermis structure [1, 19]. In case of cellular

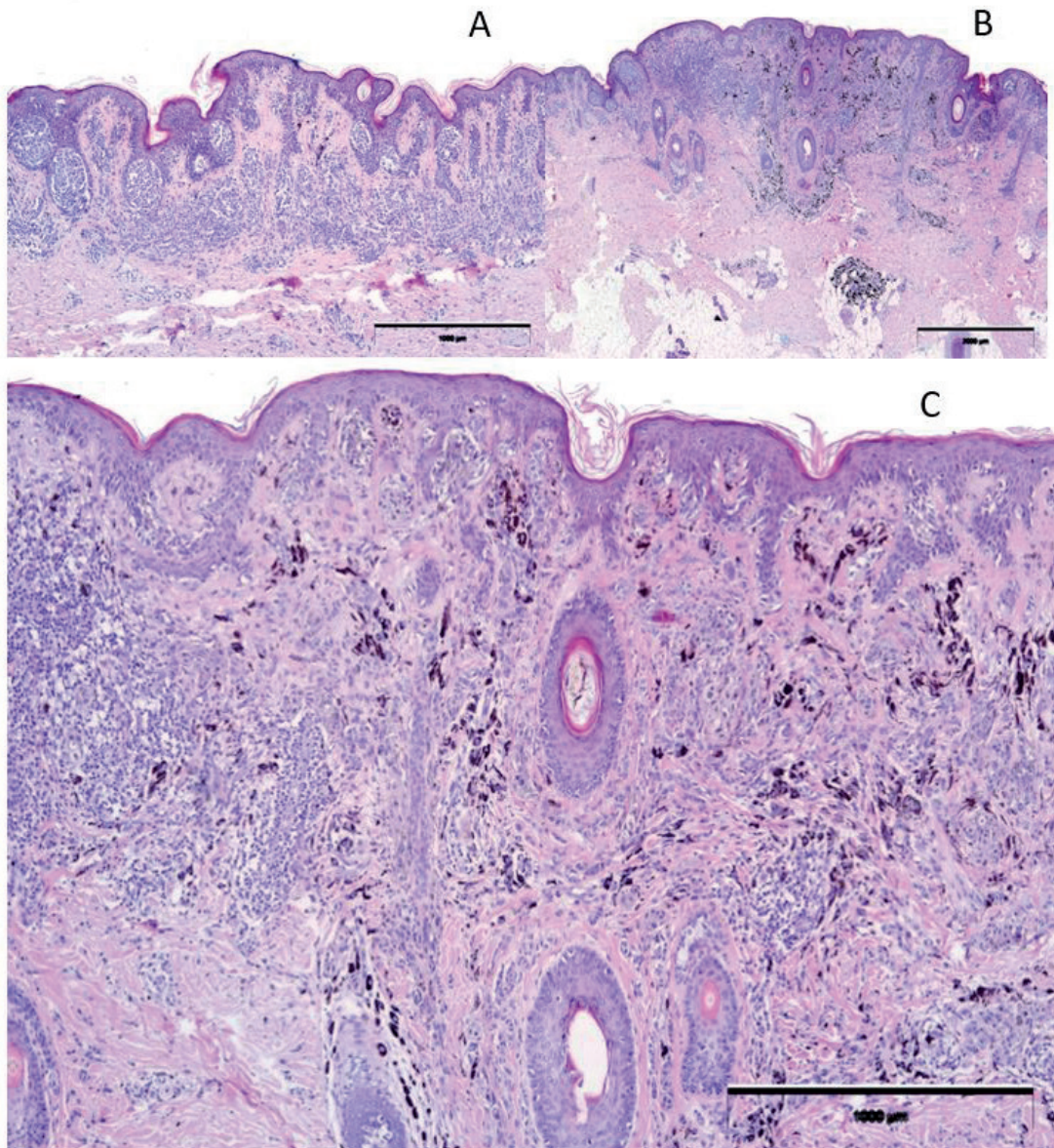


Figure 5. Combined nevus histopathological findings: A. epidermal and dermal nests of common melanocytic nevus, no signs of atypia or mitotic activity; B, C. slender spindle cells and melanophages in the center of the lesion.

blue nevus, deeply pigmented dendritic melanocytes are visible in addition to nests and fascicles of spindle-shaped cells with abundant pale cytoplasm containing little or no melanin. These melanocytes also frequently penetrate the subcutaneous tissue. Some of the cells may appear atypical, with nuclear pleomorphism accompanied by multinucleated giant cells, rare mitoses, and inflammatory infiltrates. In addition to this, overlapping features of common and cellular blue nevi could be seen in some lesions [19].

If Spitz nevus is present, nests of large epithelioid cells, spindle cells or both can be seen, usually extending from the epidermis into the reticular dermis, within hyperplastic epidermis and mononuclear and multinucleate giant epithelioid cells infiltrating dermal collagen. In some observed cases, necrotic cells, mitotic figures and intraepidermal eosinophilic globules were found [19].

6. Management

Better and more uniformed description of clinical and dermatoscopic features of CN, together with improvement in routine differentiation between CN and melanomas can significantly reduce the number of excisions and biopsies performed. Biopsy should still be considered for any suspicious lesion. If distinction from melanoma cannot be clearly made, complete surgical excision is recommended.

Author details

Jelena Stojkovic-Filipovic^{1,2*} and Miljan Vlahovic^{3,4}

1 Clinic of Dermatovnerology, University Clinical Center of Serbia, Belgrade, Serbia

2 Faculty of Medicine, University of Belgrade, Belgrade, Serbia

3 Department of Health NSW, Sydney, NSW, Australia

4 Monash University, Melbourne, VIC, Australia

*Address all correspondence to: sf.jelena@gmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Scolyer RA, Zhuang L, Palmer AA, Thompson JF, McCarthy SW. Combined naevus: a benign lesion frequently misdiagnosed both clinically and pathologically as melanoma. *Pathology*. 2004;36(5):419-27
- [2] Strungs I. Common and uncommon variants of melanocytic naevi. *Pathology*. 2004;36(5):396-403
- [3] Barnhill RL. Combined naevus. In: LeBoit PE, Burg G, Weedon D, Sarasin A, eds. *World Health Organization Classification of Tumours Pathology & Genetics Skin Tumours*. Lyon: IARC Press, 2006; 100-102
- [4] Baran JL, Duncan LM. Combined melanocytic nevi: histologic variants and melanoma mimics. *Am J Surg Pathol*. 2011;35:1540-8.
- [5] Cosme Alvarez Cuesta C, Vazquez Lopez F, Perez Oliva N. Dermatoscopy in the diagnosis of cutaneous collision. *Clin Exp Dermatol* 2004;29:199-200.
- [6] Kittler H, editor. *Dermatoscopy. Pattern analysis of pigmented and non-pigmented lesions*. Vienna: Facultas Universitätsverlag, 2nd edition. 2016.
- [7] J. Stojkovic-Filipovic, D. Todorovic, A. Lallas, et al. Dermatoscopy of combined blue nevi: a multicentre study of the International Dermoscopy Society. *J EADV* 2020;.....: 900-905
- [8] Schweizer A, Fink C, Bertlich I et al. Differentiation of combined nevi and melanomas: Case-control study with comparative analysis of dermoscopic features. *J Dtsch Dermatol Ges*. 2020;18:111-118.).
- [9] de Giorgi V, Massi D, Salvini C et al. Dermoscopic features of combined melanocytic nevi. *J Cutan Pathol*. 2004;31:600-4.
- [10] Dermoscopy of melanocytic neoplasms: combined blue nevi. *Arch Dermatol*. 2004;140:902.
- [11] Argenziano G. Dermoscopy of melanocytic neoplasms: Targetoid combined blue nevi. *Arch Dermatol*. 2004;140:1576.
- [12] Kim JK, Nelson KC. Dermoscopic features of common nevi: a review. *G Ital Dermatol Venereol*. 2012;147(2):141-8.
- [13] Rosendahl C, Cameron A, McColl I, Wilkinson D. Dermatoscopy in routine practice – ‘chaos and clues’. *Aust Fam Physician*. 2012;41:482-7.
- [14] Ferrari A, Lozzi GP, Fargnoli MC, Peris K. Dermoscopic evolution of a congenital combined nevus in childhood. *Dermatol Surg*. 2005;31 (11 Pt 1):1448-50.
- [15] Zalaudek I, Manzo M, Savarese I et al. The morphologic universe of melanocytic nevi. *Semin Cutan Med Surg*. 2009;28:149-56.
- [16] Piccolo D, Altamura D, Lozzi GP, Peris K. Blue-whitish veil-like structure as the primary dermoscopic feature of combined nevus. *Dermatol Surg*. 2006;32:1176-8.
- [17] Yaginuma A, Nobeyama Y, Miyake-Nakano S et al. Case of combined nevus showing a speckled distribution pattern. *J Dermatol*. 2018;45:e232-e233
- [18] Cabo H. Combined nevi. In H. P. Soyer, G. Argenziano, R. Hofmann-Wellenhof, R. H. Johr (Eds.). *Color Atlas of Melanocytic Lesions of the Skin*. Springer. 2007; 97-101.
- [19] Bologna J, Scaffer JV, Cerroni L. *Dermatology*. St Louis: Mosby Elsevier; 2018.