



Analysis of the vascular patterns of 52 amelanotic cutaneous melanoma metastases: a prospective descriptive study

Analiza vaskularnih obrazaca 52 amelanotične kutane metastaze melanoma: prospektivno deskriptivna studija

Danijela Popović*, Željko Mijušković†‡, Andrija Jović*, Sladjana Cekić*,
Nataša Vidović§, Danica Todorović*||

University Clinical Center Niš, *Clinic for Dermatovenereology, §Center for Pathology and Pathological Anatomy, Niš, Serbia; †Military Medical Academy, Department for Dermatology and Venereology, Belgrade, Serbia; ‡University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; ||University of Niš, Faculty of Medicine, Niš, Serbia

Abstract

Background/Aim. Early diagnosis of amelanotic cutaneous melanoma metastases (ACMM) represents a great challenge and is essential for determining the stage, treatment, and prognosis of the disease. The aim of the study was to evaluate the vascular structures and their arrangement and frequency in ACMM. **Methods.** The study was conducted as a prospective, descriptive, multicenter study of pathohistologically confirmed ACMM. **Results.** The study included a total of 52 ACMM from 17 patients (8 men and 9 women, with an age range of 32–91 years, median 63.12 years) with a previous history of primary melanoma. The most prevalent were elevated ACMM – 39 (75.0%) lesions, while 13 (25.0%) ACMM were flat. Linear irregular blood vessels were statistically significantly more often associated with elevated ACMM, compared to flat ACMM (92.3% vs. 50.0%, $p < 0.001$). Dotted blood vessels were statistically

significantly more frequent in flat ACMM, compared to elevated ACMM (76.9% vs. 28.2%, $p = 0.003$). Diffuse distribution of blood vessels was the most prevalent, with 92.3% of flat ACMM and 76.9% of elevated ACMM ($p = 0.416$). Peripheral arrangement of blood vessels was detected in 15.4% of elevated ACMM and 7.7% of flat ACMM ($p = 0.815$). The central arrangement of blood vessels was seen in 2.6%, while the cluster (segmental) schedule was present in 5.1% of elevated ACMM. The monomorphic vascular pattern was the predominant pattern in 84.6% of flat ACMM and 61.5% of elevated ACMM ($p = 0.232$). **Conclusion.** Our study supports the finding that linear irregular blood vessels are more commonly associated with elevated ACMM, while the dotted ones are dominant in flat ACMM.

Key words:

blood vessels; dermoscopy; diagnosis; melanoma, amelanotic; neoplasm metastasis; skin.

Apstrakt

Uvod/Cilj. Rana dijagnoza amelanotičnih kutanih metastaza melanoma (AKMM) predstavlja veliki izazov i od izuzetnog je značaja za određivanje stadijuma, lečenje i prognozu bolesti. Cilj rada bio je da se procene vaskularne strukture i njihov raspored i učestalost u AKMM. **Metode.** Studija je sprovedena kao prospektivna, deskriptivna, multicentrična studija patohistološki potvrđenih AKMM. **Rezultati.** Istraživanje je uključilo ukupno 52 AKMM kod 17 bolesnika (8 muškaraca i 9 žena, starosti 32–91 godina, prosečno 63,12 godina) sa prethodnom istorijom primarnog melanoma. Najzastupljenije su bile uzdignute AKMM – 39 (75,0%) lezija, dok je 13 (25,0%) AKMM

bilo u nivou kože, ravnih. Linearni iregularni krvni sudovi bili su statistički značajno češće povezani sa uzdignutim AKMM u odnosu na ravne AKMM (92,3% vs. 50,0%, $p < 0,001$). Tačkasti krvni sudovi bili su statistički značajno češći kod ravnih AKMM u odnosu na uzdignute AKMM (76,9% vs. 28,2%, $p = 0,003$). Difuzna distribucija krvnih sudova bila je najzastupljenija, u 92,3% ravnih AKMM i 76,9% uzdignutih AKMM ($p = 0,416$). Periferni raspored krvnih sudova utvrđen je u 15,4% uzdignutih AKMM i u 7,7% ravnih AKMM ($p = 0,815$). Centralni raspored krvnih sudova uočen je u 2,6%, a klaster (segmentni) raspored u 5,1% uzdignutih AKMM. Monomorfni vaskularni obrazac bio je prisutan kod 84,6% ravnih AKMM i 61,5% uzdignutih AKMM ($p = 0,232$). **Zaključak.** Naša studija podržava nalaz da

su linearni iregularni krvni sudovi češće povezani sa uzdignutim AKMM, dok su tačkasti krvni sudovi dominantni kod AKMM u nivou kože.

Ključne reči:
krvni sudovi; dermoskopija; dijagnoza; melanom, amelanotičan; neoplazme, metastaze; koža.

Introduction

Dermatoscopic evaluation of amelanotic or hypomelanotic melanomas (AHM) and amelanotic cutaneous melanoma metastases (CMM) – ACMM is still challenging. Prompt diagnosis of such lesions is crucial due to the potential implications for prognosis and management. As ACMM has no specific dermatoscopic features, diagnosis is still based on evaluating vascular structures¹.

The clinical appearance of ACMM varies widely and may mimic other benign and malignant tumors, including hemangiomas, intradermal nevi, sebaceous hyperplasia, basal cell carcinoma, Bowen's disease, and primary amelanotic melanomas²⁻⁶. Both AHM and ACMM have a poor prognosis, most probably due to a delay in diagnosis and subsequent treatment⁷.

The aim of the study was to analyze vascular morphology and distribution patterns in ACMM.

Methods

Our research was a prospective, descriptive, multi-center study of pathohistologically confirmed ACMM carried out in two centers: the Clinic for Dermatovenerology of the University Clinical Center Niš, Serbia, and the Clinic for Dermatovenerology of the Military Medical Academy in Belgrade, Serbia, from July 2019 to July 2023. The Medical Ethics Committees of the University Clinical Center Niš (No. 16297/6, from May 2019) and the Faculty of Medicine, University of Niš (No. 12-74-76-2/4, from July 2019) approved the study design. Informed consent was previously obtained from all study participants.

The study recorded general data such as gender, age, Breslow index of primary melanoma, the interval time to metastasis (defined as the time in months between the diagnosis of the primary melanoma and the appearance of the first cutaneous metastasis), and anatomical location of primary melanoma and ACMM (head, arms, legs, trunk).

ACMM were divided into flat (macules) and elevated (papules/nodules) and categorized into regional (satellites or in-transit metastases) or distant skin metastases.

Clinical and contact polarized dermatoscopic photographs were taken for each lesion using a Nikon Coolpix 4300® camera attached to a DermLite Foto II Pro®. High-resolution dermatoscopic images of ACMM were evaluated independently by three dermatologists with more than ten years of experience in the field of dermatoscopy. Dermatoscopic images with insufficient resolution or image quality, including cases without histopathological confirmation of ACMM, were excluded from the study.

Dermatoscopic evaluation of ACMM included vascular pattern assessment and arrangement, predominant morphological pattern (monomorphic or polymorphic), and evaluation of additional dermatoscopic features.

The following vascular structures were evaluated: linear irregular, dotted, glomerular, arborizing, and hairpin-like vessels. Predominant morphologic patterns included a monomorphic pattern (one morphological type of vessel within the lesion) and a polymorphic one (two or more morphological types of vessels).

Statistical analysis

Continuous variables are reported as mean \pm standard deviation (SD). Further, *t*-tests or Mann-Whitney *U* tests were used to compare continuous variables, and Chi-square tests or the Fisher exact test were used for proportions. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the R software, Version 3.0⁸.

Results

General data

The study included data on 52 ACMM from 17 patients, including 8 (47.1%) men and 9 (52.9%) women. Demographic and clinical characteristics of patients with ACMM are shown in Table 1.

The mean age of patients was 63.12 years (SD: 17.01 years). The mean time to ACMM onset after primary melanoma surgery was 22.59 months (SD: 12.64 months). Clinical evaluation revealed 11 (64.7%) patients with elevated ACMM, flat ACMM in 4 (23.5%), and there were 2 (11.8%) patients with both types of lesions. Location-wise, the lower extremities were the most frequently affected (64.7%), followed by the trunk (17.6%), head (11.8%), and arms (5.9%). As for the number of ACMM, most patients (82.4%) had less than 10 lesions, 11.8% had 11 to 50 lesions, and 5.9% had more than 50 ACMM.

Dermatoscopic findings

We analyzed 52 ACMM in 17 patients with a previous history of primary melanoma. All 52 (100.0%) ACMM showed the presence of vascular structures.

Generally speaking, as far as the vascular patterns observed in ACMM are concerned, the results (Table 2) indicate that the linear irregular vessels are the most common (78.8%), while dotted vessels account for 40.4% of all cases. Moreover, the diffuse distribution pattern is the most prevalent (80.8%). The research also revealed that the

Table 1**Demographic and clinical features of patients with amelanotic cutaneous melanoma metastases (ACMM) (n = 17)**

Parameter	Values
Gender	
male	8 (47.1)
female	9 (52.9)
Age, years	63.12 ± 17.01 (32–91)
Tumor thickness according to Breslow	4.70 ± 3.42 (0.75–12.00)
Time to ACMM onset after surgical excision of primary melanoma	22.59 ± 12.64 (12–48)
Morphological type of cutaneous metastases	
flat lesions (macules)	4 (23.5)
elevated lesions (papules, nodules)	11 (64.7)
flat and elevated lesions	2 (11.8)
Localization	
head	2 (11.8)
trunk	3 (17.6)
arms	1 (5.9)
legs	11 (64.7)

All values are given as mean ± standard deviation (minimum-maximum) or numbers (percentages).

Table 2**Dermatoscopic characteristics of the vascular pattern in amelanotic cutaneous melanoma metastases (ACMM) (n = 52)**

Parameters	Values
Vessels	
dotted	21 (40.4)
glomerular	4 (7.7)
linear irregular	41 (78.8)
arborizing	1 (1.9)
hairpin-like	7 (13.5)
Distribution pattern	
diffuse	42 (80.8)
peripheral	7 (13.5)
central	1 (1.9)
cluster	2 (3.8)
Morphologic pattern	
monomorphic	35 (67.3)
polymorphic	17 (32.7)
Additional features	
ulceration	11 (21.1)
white lines	16 (30.8)

All values are given as numbers (percentages).

dominant morphologic pattern is the monomorphic one (67.3%). Regarding the additional features of the ACMM, it was noticed that 21.1% developed ulceration, whereas white lines were found in 30.8% of the analyzed cases.

Clinical and dermatoscopic presentations of ACMM are shown in Figure 1.

Linear irregular vessels were statistically more associated with elevated ACMM compared to flat lesions (92.3% vs. 50.0%, $p < 0.001$), while dotted blood vessels were more associated with flat ACMM (76.9% vs. 28.2%, $p = 0.003$). Glomerular vessels were detected in 10.3% of ACMM ($p = 0.563$). Arborizing and hairpin-like vessels were equally detected in ACMM ($p = 1.000$ and $p = 0.171$, respectively) (Table 3).

Diffuse vessel distribution was the most prevalent, with 92.3% in flat ACMM and 76.9% in elevated ACMM ($p = 0.416$). Peripheral distribution was found in 15.4% of elevated and 7.7% of flat ACMM ($p = 0.815$). The central and cluster distributions were seen in 2.6% and 5.1% of elevated ACMM, respectively (Table 3).

Regarding patterns, a monomorphic pattern was present in 84.6% of flat ACMM and in 61.5% of the elevated ones ($p = 0.232$) (Table 3) (Figure 1D).

Concerning additional dermatoscopic features, white lines were statistically more often present in patients with elevated ACMM (38.5% vs. 7.7%, $p = 0.044$) (Figure 1F). Additionally, ulcerations and erosions were found in 25.6% of elevated ACMM and 7.7% of the flat ones (Table 3).

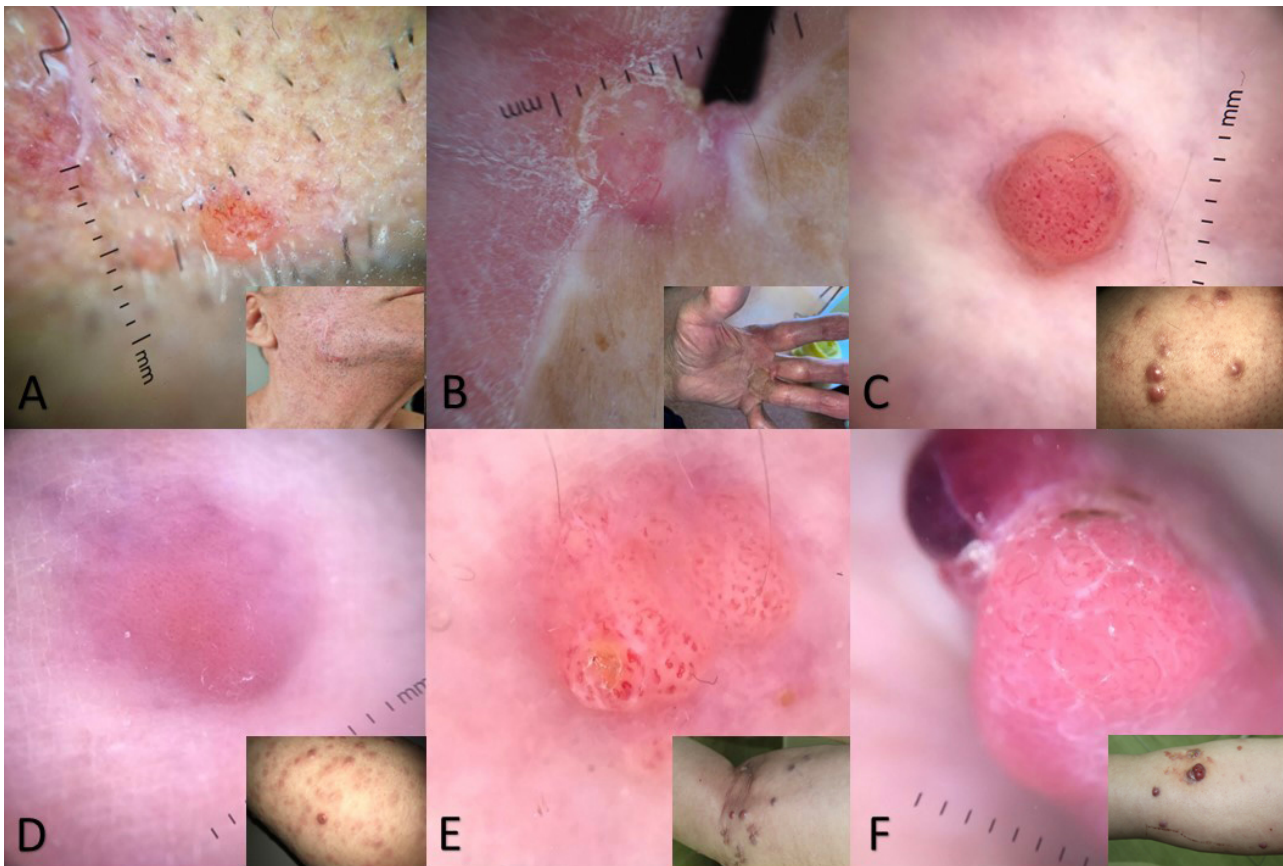


Fig. 1 – Clinical and dermatoscopic presentations of amelanotic cutaneous melanoma metastases (ACMM): pinkish papule 3 mm in diameter, located 5 mm from the surgical scar showing linear irregular vessels (A); pinkish papule 5 mm in diameter on the scar showing arborizing vessels (B); numerous flat and elevated in-transit ACMM on the leg, dermatoscopy revealed dotted, glomerular, and linear irregular vessels (C); monomorphic pattern of dotted vessels in a flat lesion (D); vascular pattern with linear irregular and corkscrew-like vessels (E); elevated ACMM with linear irregular vessels and white lines (F).

Table 3

Dermatoscopic characteristics of vascular pattern according to the morphologic type of 52 amelanotic cutaneous melanoma metastases (ACMM)

Parameter	Lesions		p-values ¹
	flat (n = 13)	elevated (n = 39)	
Vessels			
dotted	10 (76.9)	11 (28.2)	0.003
glomerular	0 (0.0)	4 (10.3)	0.563
linear irregular	5 (38.5)	36 (92.6)	0.001
arborizing	0 (0.0)	1 (2.6)	1.000 ²
hairpin-like	0 (0.0)	7 (17.9)	0.171 ¹
Distribution pattern			
diffuse	12 (92.3)	30 (76.9)	0.416
peripheral	1 (7.7)	6 (15.4)	0.815
central	0 (0.0)	1 (2.6)	1.000 ²
cluster	0 (0.0)	2 (5.1)	1.000 ²
Morphologic pattern			
monomorphic	11 (84.6)	24 (61.5)	
polymorphic	2 (15.4)	15 (38.5)	0.232
Additional features			
ulceration	1 (7.7)	10 (25.6)	0.252 ²
white lines	1 (7.7)	15 (38.5)	0.044 ²

¹ Chi-square test; ² Fisher test.

All values are given as numbers (percentages).

Discussion

Early diagnosis of ACMM is essential for determining the stage, treatment, and prognosis of the disease. Unfortunately, ACMM are still challenging due to their ambiguous clinical and dermatoscopic appearance. Misdiagnosing due to a number of benign and malignant lesions resembling ACMM is a common occurrence¹⁻⁶. So far, a rare small series of ACMM and individual cases have been described in the literature⁹⁻¹².

The most common anatomical localization of CMM in the study of Plaza et al.² were the lower extremities and the scalp, followed by the upper extremities, face, and feet. Kostaki et al.¹³ reported that 45.24% of CMM cases were located on the lower limbs, with the trunk being the second most common site at 23.08%, followed by the head (21.43%) and upper limbs (4.76%). Our findings are consistent with those of Kostaki et al.¹³, showing the lower extremities as the most common site of ACMM (64.7%), followed by the trunk (17.6%), head (11.8%), and upper extremities (5.9%). A recent study by Todorovic et al.¹⁴ also reported the lower extremities as the most common localization at 28.1%, followed by the trunk (19.3%), head and neck (17.5%), and upper extremities (12.3%). The notable differences in ACMM localization observed in our study could be attributed to the primary melanoma site and the locoregional distribution of ACMM.

From the clinical perspective, the most common clinical manifestations of CMM are erythematous papules with a linear arrangement¹⁰. In our study, papular appearances were also the dominant clinical finding (64.7%) (Figure 1A, B).

In a study by Savoia et al.¹⁵, the average time from the diagnosis of primary melanoma to the appearance of locoregional metastases is 1.3 years, while for distant metastases on the skin was 2.9 years. In Bono et al.⁵, the average time of occurrence of CMM was 1.7 years after the diagnosis of primary melanoma. In the study by Reed et al.¹⁶, the average time of occurrence of locoregional CMM was 15.6 months. In a series of 47 ACMM in 18 patients, Jaimes et al.¹⁰ found that the average onset time of CMM was 17 months from the diagnosis of primary melanoma. In our study, the average time from diagnosis of primary melanoma to onset of CMM was 22.59 months.

All (100%) ACMM in our study were locoregional (satellites and in transit). In the study by Jaimes et al.¹⁰, 89.0% of ACMM were regional.

Zalaudek et al.¹⁷ emphasized the importance of dermatoscopic observation of vascular structures in their series of seven AHM in six patients, indicating that atypical blood vessels with a central pink or white veil represent dermatoscopic hallmarks of AHM. Due to neoangiogenesis, vascular structures are more common in CMM than in primary cutaneous melanomas^{6, 18, 19}. Rubegni et al.¹⁹ point out that punctate blood vessels predominate in thin lesions, while corkscrew-like vessels are the most common in the thick ones²⁰. Mendes et al.¹¹ also highlight the finding of punctate blood vessels in thin melanomas, while in melanomas with a Breslow index greater than 1 mm, the vascular structure is a mixture of irregular linear, hairpin-

like, corkscrew-like, and punctate blood vessels. Melanoma metastases follow this pattern of appearance with a high prevalence of irregular linear blood vessels to thicker lesions. Our results were in line with this finding, indicating that dotted vessels are statistically more associated with flat ACMM (76.9%), while linear irregular vessels were statistically more associated with elevated ones (92.3%).

In a 2012 study by Jaimes et al.¹⁰, the predominant dermatoscopic finding in patients with ACMM was a vascular pattern with serpentine, glomerular, hairpin-like, and corkscrew-like blood vessels. Our study also revealed linear irregular blood vessels were the most prevalent (92.3% of elevated and 50.0% of flat lesions), then come the dotted blood vessels (76.9% of flat and 28.8% of elevated lesions), hairpin-like vessels (17.9% of elevated lesions), glomerular (10.3% of elevated lesions), and finally, arborizing vessels (2.6% of elevated lesions) (Figure 1B, C).

The arrangement of vascular structures can be a valid diagnostic indicator and contribute to the possible differentiation of metastatic from primary melanoma. While vascular structures in CMM are closer to the edge of the tumor (peripheral arrangement), they are centrally located in primary tumors^{9, 19, 21}. In our study, diffuse distribution of vascular structures was dominant (80.8%), while peripheral distribution was found in 13.5%.

Our results regarding an additional dermatoscopy feature – ulcerations, are in line with the literature^{9, 10, 22}, appearing in 25.6% of elevated lesions and 7.7% of the flat ones.

Like the prognosis of patients with AHM, the prognosis of patients with ACMM is worse than that of those with pigmented lesions, probably due to delayed treatment⁷. Even though early detection of CMM does not necessarily mean longer survival, some studies show that it does result in a better survival rate of patients compared to those where CMM were detected at a late stage^{14, 23-25}.

Limitations of the study

Although this study is limited by a low number of patients, it emphasizes the importance of dermatoscopic recognition of vascular structures and patterns for a more accurate diagnosis of ACMM. However, further research is needed on a larger number of patients to achieve a more precise identification of vascular findings.

Conclusion

When using dermatoscopy to assess amelanotic lesions, examining the blood vessel patterns is crucial. Recognizing and observing specific vascular patterns is important to diagnose ACMM early. The absence of pigment in ACMM makes detecting the vessels within the lesion easier. Our study supports the finding that linear irregular blood vessels are more commonly associated with elevated ACMM, while the dotted ones are dominant in flat ACMM. However, while specific vascular patterns strongly indicate a malignant condition, in the case of an apigmented single lesion, no differentiation can be made between primary amelanotic melanoma or ACMM.

R E F E R E N C E S

- Zalaudek I, Kreusch J, Giacomel J, Ferrara G, Caticala C, Argenziano G. How to diagnose nonpigmented skin tumors: a review of vascular structures seen with dermoscopy: part I. Melanocytic skin tumors. *J Am Acad Dermatol* 2010; 63(3): 361–74; quiz 375–6.
- Plaza JA, Torres-Cabala C, Evans H, Diwan H A, Suster S, Prieto VG. Cutaneous metastases of malignant melanoma: a clinicopathologic study of 192 cases with emphasis on the morphologic spectrum. *Am J Dermatopathol* 2010; 32(2): 129–36.
- Abernethy JL, Soyer HP, Kerl H, White WL. Epidermotropic metastatic malignant melanoma simulating melanoma in situ. A report of 10 examples from two patients. *Am J Surg Pathol* 1994; 18(11): 1140–9.
- Heenan PJ, Clay CD. Epidermotropic metastatic melanoma simulating multiple primary melanomas. *Am J Dermatopathol* 1991; 13(4): 396–402.
- Bono R, Giampetruzzi AR, Concolino F, Puddu P, Scoppola A, Sera F, et al. Dermoscopic patterns of cutaneous melanoma metastases. *Melanoma Research* 2004; 14(5): 367–73.
- Chernoff KA, Marghoob AA, Lacouture MA, Deng L, Busam KJ, Myskowski PL. Dermoscopic Findings in Cutaneous Metastases. *JAMA Dermatol* 2014; 150(4): 429–33.
- Koch SE, Lange JR. Amelanotic melanoma: the great masquerader. *J Am Acad Dermatol* 2000; 42(5 Pt 1): 731–4.
- R Development Core Team. R: A Language and Environment for Statistical Computing [Internet]. R Foundation for Statistical Computing, Vienna, Austria; 2014 [accessed on: 2024 Aug 13]. Available from: <http://www.R-project.org/>
- Pizzichetta MA, Canzonieri V, Massarut S, Baresic T, Borsatti E, Menzies SW. Pitfalls in the dermoscopic diagnosis of amelanotic melanoma. *J Am Acad Dermatol* 2010; 62(5): 893–4.
- Jaimes N, Halpern JA, Puig S, Malvehy J, Myskowski PL, Braun RP, Marghoob AA. Dermoscopy: an aid to the detection of amelanotic cutaneous melanoma metastases. *Dermatol Surg* 2012; 38(9): 1437–44.
- Mendes MS, Costa MC, Gomes CM, de Araiho LC, Takano GH. Amelanotic metastatic cutaneous melanoma. *An Bras Dermatol* 2013; 88(6): 989–91.
- Kuonen F, Gaido O. Residents' corner February 2015. Clues in Dermoscopy: Dermoscopy of amelanotic cutaneous melanoma metastases. *Eur J Dermatol* 2015; 25(1): 97–8.
- Kostaki M, Plaka M, Moustaki M, Befon A, Champsas G, Kypreou K, et al. Cutaneous melanoma metastases: Clinical and dermoscopic findings. *J Eur Acad Dermatol Venereol* 2023; 37(5): 941–4.
- Todorovic D, Stojkovic-Filipovic J, Marghoob A, Argenziano G, Puig S, Malvehy J, et al. Dermoscopic patterns of cutaneous metastases: A multicentre cross-sectional study of the International Dermoscopy Society. *J Eur Acad Dermatol Venereol* 2024; 38(7): 1432–8.
- Savoia P, Fava P, Nardò T, Osella-Abate S, Quaglino P, Bernengo MG. Skin metastases of malignant melanoma: a clinical and prognostic survey. *Melanoma Res* 2009; 19(5): 321–6.
- Reed KB, Cook-Norris RH, Brewer JD. The cutaneous manifestation of metastatic malignant melanoma. *Internat J Dermatol* 2012; 51(3): 243–9.
- Zalaudek I, Argenziano G, Kerl H, Soyer HP, Hofmann-Wellenhof R. Amelanotic/Hypomelanotic melanoma--Is dermoscopy useful for diagnosis? *J Dtsch Dermatol Ges* 2003; 1(5): 369–73.
- Al-Ostoot FH, Salma Salab S, Khamees HA, Khanum SA. Tumor angiogenesis: Current challenges and therapeutic opportunities. *Cancer Treat Res Commun* 2021; 28: 100422.
- Rubegni P, Lamberti A, Mandato F, Perotti R, Fimiani M. Dermoscopic patterns of cutaneous melanoma metastases. *Int J Dermatol* 2014; 53(4): 404–12.
- Martin JM, Bella-Navarro R, Jordá E. Vascular patterns in dermoscopy. *Actas Dermosifiliogr* 2012; 103(5): 357–75. (Spanish)
- Moloney FJ, Menzies SW. Key points in the dermoscopic diagnosis of hypomelanotic melanoma and nodular melanoma. *J Dermatol* 2011; 38: 10–5.
- Stojkovic-Filipovic J, Kittler H. Dermoscopy of amelanotic and hypomelanotic melanoma. *J Dtsch Dermatol Ges* 2014; 12(6): 467–72.
- Leiter U, Buettner PG, Eigentler TK, Forschner A, Meier F, Garbe C. Is detection of melanoma metastasis during surveillance in an early phase of development associated with a survival benefit? *Melanoma Res* 2010; 20(3): 240–6.
- Niebling MG, Haydu LE, Lo SN, Rawson RV, Lamboo LGE, Stollman JT, et al. The prognostic significance of microsatellites in cutaneous melanoma. *Mod Pathol* 2020; 33(7): 1369–79.
- Mrazek AA, Chao C. Surviving cutaneous melanoma: a clinical review of follow-up practices, surveillance, and management of recurrence. *Surg Clin North Am* 2014; 94(5): 989–1002; vii–viii.

Received on May 28, 2024

Revised on July 31, 2024

Accepted on August 13, 2024

Online First October 2024