Dermoscopic patterns of cutaneous melanoma metastases

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Although the long experience acquired with the widespread use of dermoscopy has allowed the establishment of criteria for the recognition of benign and malignant skin lesions, very few data are available on cutaneous melanoma metastases. As the characteristic clinical aspects are multiform and even histological evaluation may sometimes be difficult, we have studied and characterized the patterns of cutaneous melanoma metastases in dermoscopy. In this paper, we report dermoscopic data on 130 histologically confirmed metastases observed in 32 patients affected by melanoma, with particular emphasis on dermoscopic features. Nine dermoscopic elements (homogeneous, saccular, amelanotic, polymorphic and vascular patterns, colour, perilesional erythema, pigmentary halo, peripheral grey spots) were studied in 130 cutaneous melanoma metastases and compared with those of 350 melanomas, 150 common naevi, 40 blue naevi, 40 haemangiomas and 50 basal cell carcinomas. The saccular and vascular patterns (especially polymorphic atypical vessels and winding vessels), as well as pigmentary halo and peripheral grey spots, seem to be the most significant elements suggestive of cutaneous melanoma metastases. The interest in and importance of the dermoscopic aspects of cutaneous melanoma metastases cannot be neglected if the American Joint Committee has determined that microsatellitosis and micrometastases are fundamental in the new TNM staging classification for cutaneous melanoma. *Melanoma Res* 14:367–373 © 2004 Lippincott Williams & Wilkins.

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Introduction

The reported frequency of melanoma metastases to different organs is as follows: skin/dermis and lymph nodes, 42–57% (skin involvement and lymph node metastases are always considered together); lungs, 18–36%; liver, 14–20%; brain, 12–20%; bone, 11–17%; small intestines, 1–7% [1].

The risk of metastatic spread depends on the tumour thickness, presence or absence of ulceration, anatomical location and clinical presentation. However, advanced or recurrent melanoma may also depend on inadequate radical surgery [2], as well as on local aspects of the disease, such as neovascularization, which represents a crucial factor in melanoma progression during which the newly formed vessels substitute the extracellular matrix. The newly formed vascular beds facilitate the escape of tumour cells from the primary lesion, while the deposits of extracellular matrix associated with these new vascular channels provide a scaffold for the tumour, favouring melanoma growth and metastatic spread [3]. The fatty acid synthase (FAS), variably expressed in primary melanoma, is abundantly expressed in cutaneous (local recurrences or in-transit) and lymph node metastases [4], as demonstrated by immunochemistry.

Characteristic histological aspects of cutaneous malignant melanoma metastases (CMMMs) are the prevalent dermal involvement, with respect to the lesser epidermal involvement, of the atypical melanocytes (subcutaneous fat or dermis up to the overlying epidermis: dermis $\geq$ epidermis) [5,6], the presence of atypical melanocytes within vascular and lymphatic vessels, the thinning of the epidermis by the atypical melanocyte aggregates, together with the widening of dermal papillae and the absence of junctional activity [7].

In reality, the distribution of atypical melanocytes may fall anywhere along a spectrum of histological possibilities, including that of an exclusive epidermal involvement, rendering differential diagnosis from epidermotropic metastatic malignant melanoma and *in situ* melanoma quite difficult [8]. Moreover, patients with a previous history of melanoma are those at highest risk of developing multiple primary melanomas [9], with a prevalence ranging from 1.28 to 5.3% [10].

Together, these considerations sometimes make a precise histological diagnosis difficult. Other aspects that influence and cannot be ignored in CMMM diagnosis are the small size, large number, symmetric distribution and the

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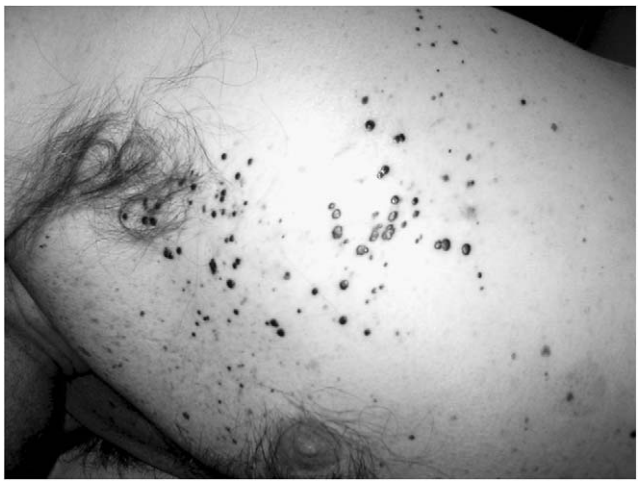
Fig. 1



Satellitosis and in-transit metastasis.

variable time delay from primary melanoma diagnosis. In contrast with the literature, in which CMMMs have been reported to be observed even after 20 years from initial melanoma diagnosis, we report an average time of 1 year and 7 months after initial diagnosis. Undoubtedly, the importance of distinguishing between CMMMs and primary melanoma [11] is related to their different prognosis and therapy. CMMMs may present in various clinical forms, and differential diagnosis includes common naevi, haemangiomas, blue naevi and primary melanoma. In satellite-type, in-transit or distant metastases, CMMMs may present as single or multiple (up to 20 or more), homogeneous or non-homogeneous lesions (Fig. 1).

Dermoscopy, a non-invasive technique, allows the visualization of particular morphological features, not visible to the naked eye, in melanocytic and non-melanocytic skin lesions. This 'submacroscopic' technique, in combination with the clinical and dermopathological aspects, may contribute to the diagnosis. In particular, pattern analysis, the ABCD rule method, a seven-point checklist [12] and, as proposed recently, a three-point checklist [13] are relevant criteria in dermoscopic melanoma diagnosis. In contrast, for CMMMs, there is, as yet, no precise definition by epiluminescence microscopy.

The aim of this study was to identify possible characteristic dermoscopic patterns of CMMMs.

Patients and methods

We studied 130 CMMMs in 32 patients (17 women, 15 men) with a median age of 57 years (range, 31–83 years) at the time of melanoma diagnosis. In these 32 patients, the sites of cutaneous malignant melanoma involvement were the trunk (13 patients), lower limbs (nine patients), acral sites (five patients), upper limbs (three patients) and scalp (two patients). Patient distribution according to Clark's level of invasion was as follows: three cases of level III, 22 cases of level IV and five cases of level V, with two unclassified cases. Patient distribution according to Breslow's tumour thickness was as follows: T1 (up to 1 mm) in one case, T2 (1–2 mm) in seven cases, T3 (2–4 mm) in 16 cases and T4 (more than 4 mm) in six cases, with two unappreciable cases. The median thickness calculated was 2.9 mm (range, 0.85–6.2 mm). On average, the time delay between melanoma diagnosis and CMMM onset was 1 year and 7 months.

At least five histologically confirmed metastases were excised from each of the 32 patients. The observed frequency of specific metastases was as follows: 41% satellite-type metastases (13 patients), 28% in-transit metastases (nine patients), 19% satellitosis with concomitant in-transit metastases (six patients) and 12% distant metastases (four patients).

The control group included 350 primary melanomas, 150 common naevi, 40 blue naevi, 40 haemangiomas and 50 basal cell carcinomas (BCCs) (Table 1), all histologically confirmed.

All lesions were analysed with a surface microscope, and photographed with a Leica Wild M-650 microscope (Leica AG, Heerbrugg, Switzerland), a Sony 3CCD DXC-930P colour video camera and DBDERMO MIPS software (Dell'Eva/Burroni Studio, Florence/Siena, Italy) at variable magnifications (16/25/40 ×). This system offers high-quality, real-time images, allowing the acquisition of many features in epiluminescence microscopy (ELM).

Statistical data

For each of the nine ELM features examined, the pairwise differences of the ratios between CMMMs and melanomas, common naevi, blue naevi, haemangiomas and BCCs were tested using either the chi-squared test or Fisher's exact test, as appropriate. Forty-five comparisons were made and, after the Bonferroni adjustment procedure, the level of significance was set at $P = 0.001$. The sensitivity of CMMM diagnosis was calculated as the number of scored positive metastases divided by the total number of CMMMs. The specificity was calculated as the number of scored negative lesions in the control group divided by the total number of lesions. The positive likelihood ratio (LR +) was calculated as follows: LR + = (true positive rate)/(false positive rate) = (sensitivity)/(1 – specificity). LR + expresses how much the odds of the disease increases with a positive test.

Table 1 Statistical data

	CMMMs *n* 130 Sens (%)	Melanomas *n* 350 Spec (%)	Common naevi *n* 150 Spec (%)	Blue naevi *n* 40 Spec (%)	Haemangiomas *n* 40 Spec (%)	BCCs *n* 50 Spec (%)
Homogeneous pattern	39.2	98.0*	86.7*	7.5*	92.5*	96.0*
Saccular pattern	25.4	96.9*	96.0*	100.0*	87.5†	100.0*
Amelanotic pattern	32.3	96.0*	86.7*	100.0*	25.0*	54.0‡
Polymorphic pattern	3.8	48.9*	80.0*	100.0‡	95.0‡	50.0*
Colour						
Red–pink	32.3	90.0*	84.7†	100.0*	5.0*	36.0*
Brown–grey	39.2	30.9*	14.7*	70.0‡	100.0*	82.0†
Black	16.2	84.0‡	92.0‡	100.0†	97.5†	82.0‡
Blue	12.3	96.0†	96.7†	30.0*	97.5‡	100.0†
Vascular pattern	53.1	90.0*	88.0*	100.0*	92.5*	16.0*
Polymorphic atypical vessels	19.2	96.9*	100.0*	100.0†	100.0†	94.0†
Winding vessels	26.2	96.0*	100.0*	100.0†	100.0*	94.0†
Perilesional erythema	12.3	94.0†	92.7‡	100.0†	90.0‡	92.0‡
Pigmentary halo	40.8	98.9*	98.7*	87.5†	90.0*	100.0*
Peripheral grey spots	25.4	96.0*	96.0*	100.0*	97.5†	54.0†

Positive likelihood ratio	Melanomas *n* 350	Common naevi *n* 150	Blue naevi *n* 40	Haemangiomas *n* 40	BCCs *n* 50
Homogeneous pattern	19.6	2.9	0.4	5.2	9.8
Saccular pattern	8.2	6.4	8	2.0	8
Amelanotic pattern	8.1	2.4	8	0.4	0.7
Polymorphic pattern	0.1	0.2	8	0.8	0.1
Colour					
Red–pink	3.2	2.1	8	0.3	0.5
Brown–grey	0.6	0.5	1.3	8	2.2
Black	1.0	2.0	8	6.5	0.9
Blue	3.1	3.7	0.2	4.9	8
Vascular pattern	5.3	4.4	8	7.1	0.6
Polymorphic atypical vessels	6.2	8	8	8	3.2
Winding vessels	6.6	8	8	8	4.4
Perilesional erythema	2.1	1.7	8	1.2	1.5
Pigmentary halo	37.1	31.4	3.3	4.1	8
Peripheral grey spots	6.4	6.4	8	10.2	0.6

BCCs, basal cell carcinomas; CMMMs, cutaneous malignant melanoma metastases; Sens, sensitivity; Spec, specificity. *$P<0.001$. †$P>0.001$, $P<0.05$. ‡$P>0.05$.

Results

ELM findings

The following dermoscopic features were analysed by ELM: homogeneous, saccular, amelanotic, polymorphic and vascular patterns, colour (pink–red, brown–grey, dark, blue), perilesional erythema, pigmentary halo and peripheral grey spots.

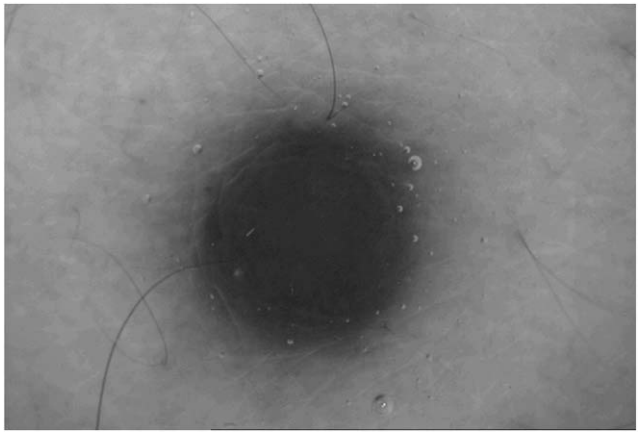
A homogeneous pattern (Fig. 2) was present in 39.2% of CMMMs and the prevalence differed in a statistically significant manner when compared with each control group ($P < 0.001$). The LR+ was 19.6, 9.8 and 5.2 for melanomas, BCCs and haemangiomas, respectively. The presence of this feature increased the odds of CMMMs, except in blue naevi.

In 25.4% of CMMMs, a saccular pattern (Fig. 3) was observed, with high specificity and high LR+ in every control group, except for haemangiomas where LR+ = 2.

An amelanotic pattern (Fig. 4) was found in 32.3% of CMMMs. The prevalence ranged from 86.7% to 100.0% in common naevi, blue naevi and melanomas. It was 25.0% ($P < 0.001$) for haemangiomas and 54.0% ($P > 0.05$) for BCCs, with an LR+ of 0.4 and 0.7, respectively.

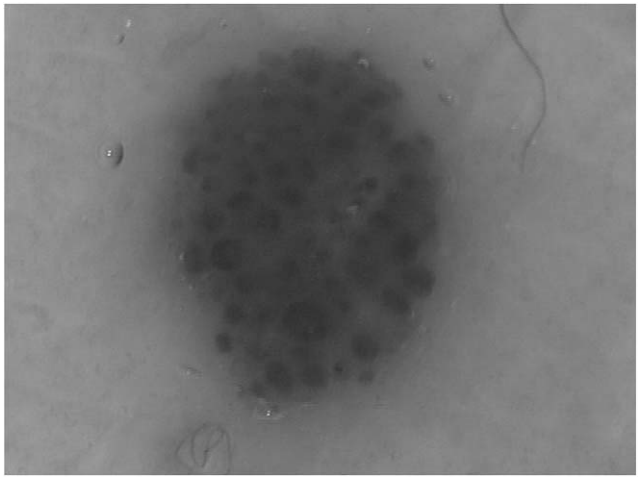
The prevalence of a polymorphic pattern (Fig. 5) was low in CMMMs (3.8%) when compared with melanomas (48.9%) and BCCs (50.0%).

Fig. 2



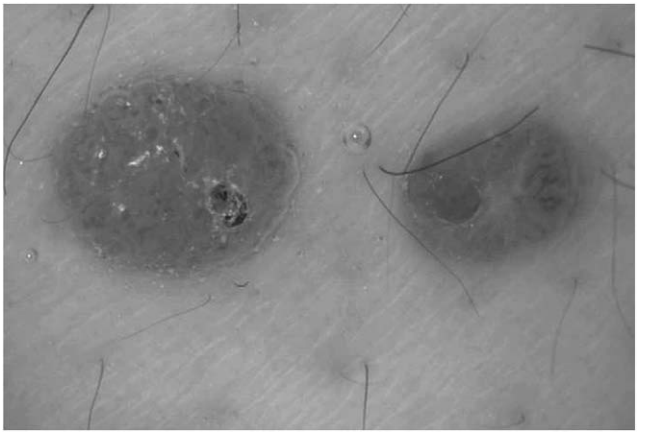
Homogeneous pattern.

Fig. 3



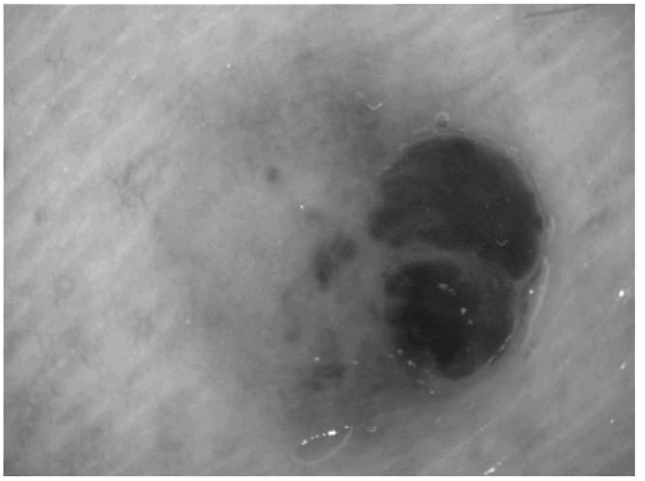
Saccular pattern.

Fig. 4



Amelanotic pattern.

Fig. 5



Polymorphic pattern.

The colour of CMMMs was brown–grey in 39.2%, red–pink in 32.3%, black in 16.2% and blue in 12.3%.

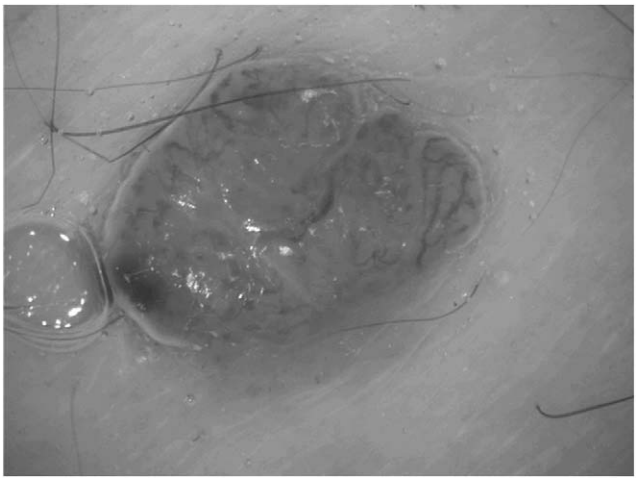
The presence of a vascular pattern was observed in 53.1% of CMMMs, with a high specificity in all control groups except for BCCs (16.0%); LR + increased the odds of the disease except in BCCs. As far as the vascular pattern was concerned, polymorphic atypical vessels (Fig. 6) and winding vessels (Fig. 7) were present in 19.2 and 26.2% of CMMMs, respectively, with a very high specificity in every group; LR + was infinite with respect to common naevi, blue naevi and haemangiomas, and was 6.2 and 3.2 in melanomas and BCCs, respectively.

Perilesional erythema (Fig. 8) was observed in 12.3% of CMMMs, with high specificity in melanomas and blue naevi, and with no significant differences with respect to the other groups.

A pigmentary halo was present in 40.8% of CMMMs (Fig. 9), with an LR + of 37.1 for melanomas, 31.4 for common naevi and an infinite LR + for BCCs.

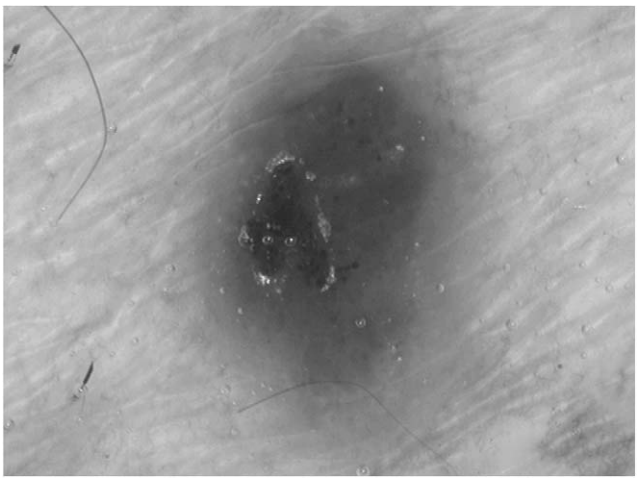
Peripheral grey spots were observed in 25.4% of CMMMs, with high specificity in every group except for BCCs, in which the specificity decreased to 54%. LR + was infinite with respect to blue naevi and was 10.2 and

Fig. 6



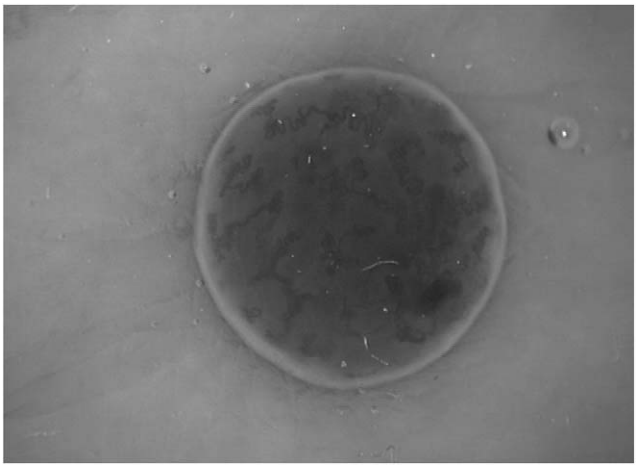
Polymorphic atypical vessels.

Fig. 8



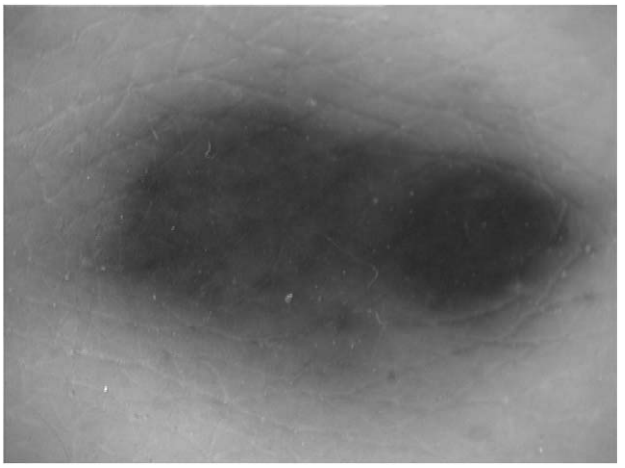
Perilesional erythema.

Fig. 7



Winding vessels.

Fig. 9



Pigmentary halo.

0.6 when compared with haemangiomas and BCCs, respectively.

Therefore, according to our observations, homogeneous, saccular and vascular patterns (showing aneurysms and winding vessels), together with pigmentary halo and peripheral grey spots, may suggest the presence of CMMMs.

Discussion

In comparison with internal organ metastases, CMMMs should theoretically be identified earlier as they are visible to the naked eye. Nonetheless, this is not always true, especially at onset, when the lesions are small and diagnosis may be difficult [10]. For this reason, we have attempted to identify characteristics peculiar to CMMMs in dermoscopy, controversially considered to be feasible according to different authors [11].

Indeed, a similar study has previously been carried out comparing a case group of 30 histologically confirmed CMMMs in seven patients affected by melanoma with a control group of 100 primary melanomas, 50 dysplastic naevi, 50 common naevi, 30 blue naevi and 20 haemangiomas, using ELM. The prevalence of four of

the 24 features studied (vascular and saccular patterns, light-brown halo and peripheral erythema) was different in the case and control groups, whereas only two (polymorphic and/or horizontally dilated capillaries and saccular pattern) were common to CMMMs and primary melanomas, being depicted as malignant features of the lesions. Peripheral grey spots, lesions surrounded by grey streaks (melanoma cell infarcts of the vessels) and microscopic ovoid lakes of blood (spontaneous micro-haemorrhages) were not observed in the benign lesions [10].

According to our data, ELM features are useful in distinguishing between primary melanoma and CMMMs as polymorphism and homogeneity are characteristic of each lesion, respectively. In addition, a homogeneous pattern is also peculiar to blue naevi but, in this case, the blue colour predominates whilst the presence of a vascular pattern is referable to CMMMs. A blue colour is present even in BCCs, particularly in pigmented forms as grey–blue ovoid nests, globules or dots and where maple leaf-like areas are very typical.

Even though a saccular pattern is common to both haemangiomas and CMMMs, blood stores and fibrous shoots are characteristic of the former, whilst nests of melanocytes in the absence of fibrous shoots are peculiar to the latter.

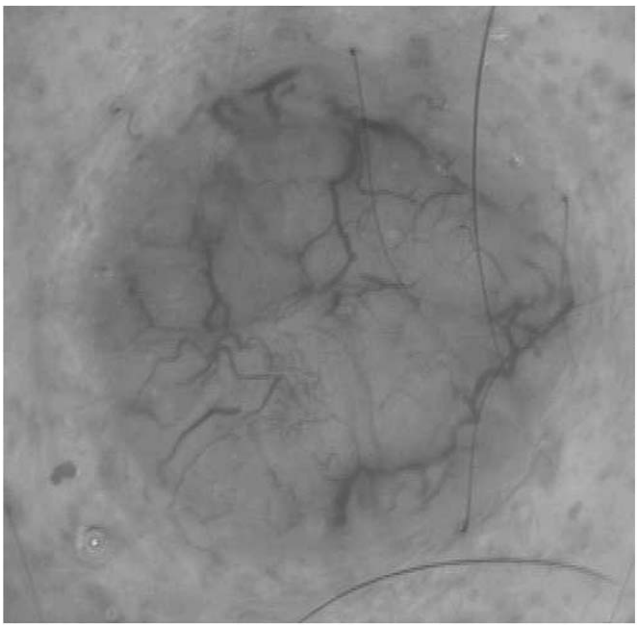
In CMMMs, the vascular pattern is very important. CMMMs have a much more monomorphic aspect of aneurysms and winding vessels, differing from that of BCCs where it is polymorphic (Fig. 10).

The presence of both a vascular pattern and pigmentary halo is a strong indicator of CMMMs.

In addition, in the topography of melanoma, we have shown the importance of acral sites in five of the 32 cases.

We carried out this study due to the lack of data on the dermoscopic aspects of CMMMs. This information may contribute to the staging of melanoma, even though the histopathology is fundamental. This can be seen in the light of the final version of the staging system for cutaneous melanoma, according to the American Joint Committee on Cancer, in which the number of positive lymph nodes and the type of metastasis (micro-, macro-, intralymphatic metastasis) are considered. The presence of satellite metastases around a primary melanoma or in-transit metastases between a primary lesion and regional lymph nodes is considered as an intralymphatic metastasis, leading to a poor prognosis in stage II melanoma [14]. Moreover, in patients affected by melanoma and showing metastases, about two-thirds present with local or regional metastases (intralymphatic or nodal metastases) and only one-third present with distant metastases [1].

Fig. 10



Vascular pattern in basal cell carcinoma.

Even though histological evaluation is fundamental in melanoma staging, a knowledge of the possible dermoscopic patterns of CMMMs may provide an aid to this process.

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