Dermoscopic features of mammary Paget's disease: a retrospective case-control study by the International Dermoscopy Society

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Abstract

Background Mammary Paget's disease (MPD) is a rare intraepidermal adenocarcinoma of the nipple-areola complex, associated with an underlying breast cancer in approximately 90% of cases. Delayed diagnosis of MPD is common. Its dermoscopic features have been ill defined in the literature.

Objectives To determine the clinical and dermoscopic features of MPD versus other dermatologic entities that involve nipple and areola.

Methods Members of the IDS were invited to submit any case of histologically confirmed MPD, as well as other benign and malignant dermatoses that involve the nipple and areola complex. A standardized evaluation of the dermoscopic images was performed and the results were statistically analyzed.

Results Sixty-five lesions were included in the study, 22 (33.8%) of them MPD and 43 (66.2%) controls. The most frequent dermoscopic criteria of MPD were white scales (86.4%) and pink structureless areas (81.8%), followed by dotted vessels (72.7%), erosion/ulceration (68.2%) and white shiny lines (63.6%). The multivariate analysis showed that white scales and pink structureless areas were significant predictors of MPD, posing a 68-fold and a 31-fold probability of MPD, respectively. Split of the population into pigmented and non-pigmented lesions showed that in pigmented MPD, pink structureless areas, white lines and grey granules and dots are positive predictors of the disease. Among non-pigmented lesions, pink structureless areas, white lines, erosion/ulceration and white scales served as predictors of MPD.

Conclusions The most frequent profile of an individual with MPD is an elderly female with unilateral, asymptomatic, erythematous plaque of the nipple, dermoscopically displaying pink structureless areas, fine white scales, dotted and a few short linear vessels. In case of pigmentation we may also observe brown structureless areas and pigmented granules.

Limitations Small sample size, retrospective design.

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Conflicts of interest

None declared.

Funding sources
None declared.

Introduction
Mammary Paget's disease (MPD) is a rare intraepidermal adenocarcinoma of the nipple-areola complex, accounting for about 1% of all breast cancers. An underlying breast adenocarcinoma is diagnosed in approximately 90% of patients with MPD.[1,2] Recent studies suggest that the development of MPD in breast cancer patients represents an independent negative prognostic indicator of survival.[3,4]

On clinical grounds, MPD displays an unspecific morphologic pattern, usually manifesting as an ulcerated, crusted or scaly patch or plaque on the nipple that may extend to the areolar region.[1] The clinical recognition of MPD is challenging, since it may closely simulate a variety of benign and malignant skin conditions.[5–11] Early diagnosis is crucial to initiate detailed work-up for the detection and management of the very probable underlying breast malignancy. Mammography and B-mode ultrasonography are considered the diagnostic methods of choice for all the other forms of breast cancer, but they have limited value for diagnosing MPD, since no specific findings have been identified.[12,13] Therefore, the application of other diagnostic tools that could enhance the clinical recognition of MPD and help to minimize diagnostic delays is definitely welcome.

Dermoscopy is extensively used in daily practice for early recognition of malignant and benign skin diseases.[14,15] Given the rarity of MPD, its dermoscopic features have been ill defined in the literature.[16–19] The current case-control study was designed to investigate the dermoscopic features seen in MPD, and identify potential clinical and dermoscopic predictors that might aid in the differential diagnosis of MPD vs. other benign and malignant dermatologic entities that involve the nipple and areola complex.

Methods
This was a retrospective morphological study launched by the IDS via an online call for contributions published on the IDS website (www.dermoscopy-ids.org). Members of the IDS were invited to submit cases of histopathologically confirmed MPD, as well as any other benign or malignant dermatoses affecting the nipple and areola that could serve as a control group. For all tumours (e.g. melanoma, Bowen's disease, seborrhoeic keratosis) a histopathologic confirmation of the diagnosis was necessary, whilst for inflammatory diseases (e.g. dermatitis, psoriasis), cases diagnosed on a clinical basis only were also deemed eligible. High quality clinical and dermoscopic images of the lesions were mandatory. Information on the patients' and lesions' characteristics, including age, gender and lesion size was also mandatory.

Table 1 Epidemiological and lesional characteristics of the studied population

	Paget (n = 22)	Controls (n = 43)
Sex		
Males	0	15 (34.9%)
Females	22 (100%)	28 (65.1%)
Mean age (years)	62.4 ± 12.38	46.8 ± 19.59
Clinically pigmented		
Yes	4 (18.2%)	20 (46.5%)
No	18 (81.8%)	23 (53.5%)
Anatomic distribution		
Nipple	10 (45.5%)	10 (23.25%)
Areola	1 (4.5%)	23 (53.5%)
Nipple and areola	11 (50.0%)	10 (23.25%)
Clinical morphology		
Patch	4 (18.2%)	12 (27.9%)
Plaque	18 (81.8%)	25 (58.1%)
Papule/nodule	0	6 (14.0%)
Mean diameter (cm)	1.62 ± 1.14	1.19 ± 0.92

Table 2 Frequency of dermoscopic criteria in mammary Paget's disease (MPD, n = 22) and other diagnoses (controls, n = 43)

Dermoscopic criteria	MPD (n, %)	Controls (n, %)
Pigmentation quantity†		
0	10 (45.4%)	22 (51.1 %)
1–50%	8 (36.3%)	2 (4.6%)
>50%	4 (18.1%)	19 (44.1%)
Structureless brown areas	3 (13.6%)	3 (7.0%)
Structureless blue/grey areas	2 (9.1%)	6 (14.0%)
Structureless pink areas	**18 (81.8%)**	**4 (9.3%)**
Structureless white areas	8 (36.4%)	7 (16.3%)
Granules/dots/globules brown	7 (31.8%)	6 (14.0%)
Granules/dots/globules blue/grey	2 (9.1%)	2 (4.7%)
Pigment network	1 (4.5%)	9 (20.9%)
Dotted vessels	16 (72.7%)	12 (27.9%)
Linear vessels	11 (50.0%)	8 (18.6%)
Erosion/ulceration	15 (68.2%)	8 (18.6%)
White scales	**19 (86.4%)**	**7 (16.3%)**
Yellow scales	3 (13.6%)	10 (23.3%)
White shiny lines	14 (63.6%)	2 (4.7%)

Values in bold represent multivariate predictors of MPD.
†Pigmentation quantity values are explained as below.
0: no pigmentation. 1–50%: pigmentation was present but covering not more than half of the lesion's surface. >50%: pigmentation was present and covered more than half of the lesion's surface.

Three independent investigators (ZA, AL, EL), who were blinded for the histopathologic diagnosis, evaluated images for the presence of predefined dermoscopic criteria. The selection of

Table 3 Dermoscopic criteria of diseases included in the control group

Criterion	Dermatitis (*n* = 10)	Psoriasis (*n* = 3)	Melanosis (*n* = 4)	Naevus (*n* = 9)	Melanoma (*n* = 1)	BCC (*n* = 3)	SCC (*n* = 2)	Breast Ca (*n* = 1)	Breast Ca met (*n* = 1)	Seborrhoeic keratosis (*n* = 3)	Melanoma metastasis (*n* = 1)	Haemorrhage (*n* = 1)	Epidermal cyst (*n* = 1)	Apocrine hidrocystoma (*n* = 1)	Skin tag (*n* = 2)
Pigmentation quantity															
0	10 (100)	3 (100)	0	0	0	3 (100)	2 (100)	1 (100)	0	0	0	0	1 (100)	0	2 (100)
1–50%	0	0	1 (25)	0	0	0	0	0	0	1 (33)	0	0	0	1 (100)	0
>50%	0	0	3 (75)	9 (100)	1 (100)	0	0	0	1 (100)	2 (67)	1 (100)	1 (100)	0	0	0
Structureless brown areas	0	0	1 (25)	0	0	0	0	0	1 (100)	1 (33)	0	0	0	0	0
Structureless blue/grey areas	0	0	1 (25)	1 (11)	0	0	0	0	0	1 (33)	1 (100)	1 (100)	0	1 (100)	0
Structureless pink areas	2 (20)	0	0	0	0	1 (33)	0	0	0	0	0	1 (100)	0	0	0
Structureless white areas	0	0	0	1 (11)	0	2 (66)	1 (50)	0	0	0	0	0	1 (100)	1 (100)	1 (50)
Granules/dots/ globules brown	0	0	0	4 (44)	1 (100)	0	0	0	0	1 (33)	0	0	0	0	0
Granules/dots/ globules blue/grey	0	0	0	1 (11)	0	0	0	0	1(100)	0	0	0	0	0	0
Pigment network	0	0	2 (50)	5 (56)	1 (100)	0	0	0	0	1 (33)	0	0	0	0	0
Dotted vessels	6 (60)	3 (100)	0	0	0	0	1 (50)	0	0	0	0	0	0	0	2 (100)
Linear vessels	3 (30)	1 (33)	0	0	0	2 (67)	1 (50)	0	0	0	0	1 (100)	0	0	0
Erosion/ulceration	3 (30)	0	0	0	0	3 (100)	1 (50)	1 (100)	0	0	0	0	0	0	0
White scales	2 (20)	3 (100)	0	0	0	2 (67)	0	0	0	0	0	0	0	0	0
Yellow scales	9 (90)	0	0	0	0	0	1 (50)	0	0	0	0	0	0	0	0
White shiny lines	1 (10)	0	0	0	0	0	0	0	0	0	0	1 (100)	0	0	0

Numbers in parenthesis represent percentages (%).

dermoscopic variables that were included in the evaluation was based on available previous literature and preliminary observations of the authors in clinical practice.

A case-control analysis was held to compare the dermoscopic characteristics of MPD to other benign and malignant dermatoses of the nipple area. A subgroup analysis of pigmented and non-pigmented lesions was also performed.

Absolute and relative frequencies were obtained for the dermoscopic characteristics. Non-parametric (Pearson's χ^2, Mann–Whitney, Kruskal–Wallis) or parametric (Student's *t*-test, ANOVA) tests were used following normality explorations. For logistic regression analysis, dichotomous outcome variables were set to MPD or other dermatoses separately. Relative risks were calculated for these dichotomous variables. Adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated by conditional multivariate logistic regression (backward elimination according to likelihood criteria). The α level was set at 0.05 whilst an α level of 0.10 was used as the cut-off point for variable removal in the automated model selection for multivariate logistic regression. Statistical analyses were performed using IBM SPSS v.23 (Armonk, NY, USA).

Results

After the initial online call, 23 MPD cases from 13 different centres were collected. One case was excluded from analysis because of inadequate image quality. Resulting, the final study-set included 65 lesions, 22 (33.8%) MPD and 43 (66.2%) controls. The control group consisted of lesions with the following diagnoses: dermatitis (10), naevus (9), melanosis (4), psoriasis (3), basal cell carcinoma (3), seborrhoeic keratosis (3), skin tag (2), squamous cell carcinoma (2), epidermal cyst (1), apocrine hidrocystoma (1), primary breast carcinoma (1), haemorrhage (1), breast cancer metastasis (1), melanoma (1) and melanoma metastasis (1).

Table 1 illustrates epidemiological data of the study population and clinical characteristics of the lesions. The mean age of the studied population was 52 years (SD: 18.9, range: 7.0–84.0) and, as shown in the table, higher in MPD group. In univariate analysis, age was found to be a risk factor for MPD. The mean size in centimetres of all the studied lesions was 1.3 (range: 0.2–4.2, SD: 1.0). After splitting cases into clinically pigmented and non-pigmented lesions, we found that the mean size at diagnosis was 0.95 cm, and 1.77 cm for pigmented, and non-pigmented MPD, accordingly (Mann–Whitney *U*-test, $P = 0.044$).

The analytic results of dermoscopic evaluations are shown in Tables 2 and 3. The most frequent dermoscopic criteria of MPD were white scales (86.4%) and pink structureless areas (81.8%), followed by dotted vessels (72.7%), erosion/ulceration (68.2%) and white shiny lines (63.6%).

Concerning the differential diagnosis between MPD and the other diagnoses, multivariate analysis revealed white scales and pink structureless areas as potent predictors of MPD, posing a 68-fold and a 31-fold probability, respectively, if present in a lesion.

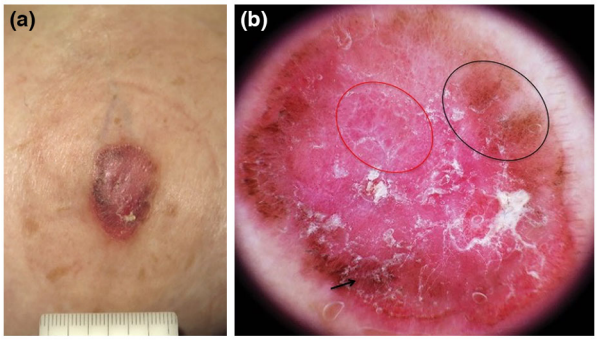

Figure 1 An example of mammary Paget's disease (MPD) clinically manifesting as a slightly pigmented plaque (a) and dermoscopically displaying white scales, pink structureless areas, white lines (white circle), brown and grey dots/globules (black circle) and erosions (arrow) (b).

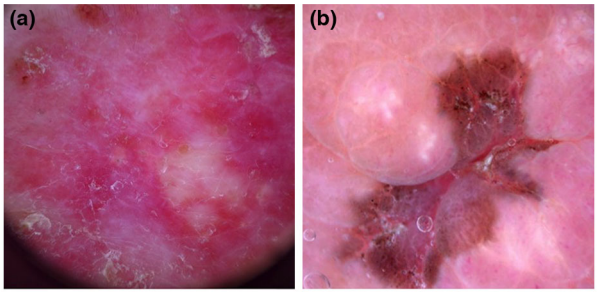

Figure 2 Dermoscopy of a non-pigmented mammary Paget's disease (MPD) revealing pink structureless areas, white structureless areas, white scales and a few dotted vessels (a). A pigmented MPD dermoscopically characterized by brown structureless areas, pink structureless areas, white lines and brown and grey dots/globules (b).

Statistical analysis was repeated after the split of the population into pigmented and non-pigmented lesions, but the small sample size prohibited a multivariate analysis. Therefore, only univariate predictors were calculated. The group of pigmented lesions included MPD, naevus, melanosis, seborrhoeic keratosis, apocrine hidrocystoma, haemorrhage, breast carcinoma metastasis, melanoma and melanoma metastasis. The group of non-pigmented lesions included MPD, psoriasis, dermatitis, basal cell carcinoma, skin tag, squamous cell carcinoma, primary breast carcinoma and epidermal cyst. The latter analysis found pink structureless areas, white lines and grey granules/dots as positive predictors of MPD amongst pigmented lesions only. In regard to non-pigmented lesions, pink structureless areas, white lines, erosion/ulceration and white scales served as univariate predictors of MPD.

Notably, seven lesions were assessed as clinically non-pigmented but displayed dermoscopic pigmentation. Interestingly, in all of these cases, pigmentation corresponded to grey or brown granules. Of these seven lesions, six were MPD and one was melanoma.

Discussion

Our study investigated the dermoscopic morphology of MPD and identified potent dermoscopic predictors for the discrimination of the disease from other tumours or inflammatory diseases involving the nipple and areola region.

Patients with MPD in our sample were significantly older than those with other diagnoses. This is not surprising, since MPD is known to affect mainly an elderly population, whereas frequent benign tumours such as naevi and melanosis of the nipple usually appear earlier in life. Concerning inflammatory diseases, psoriasis also appears earlier in life and dermatitis may occur in any age group.

From a macroscopic aspect, all MPD lesions manifested as patches, or plaques and none as papule, or nodule, suggesting that a papular, or nodular clinical morphology is indicative of a different diagnosis. Another noteworthy finding was that the nipple was involved in all but one cases of MPD, in contrast to other dermatoses that were frequently restricted to the areola without affecting the nipple. The latter finding suggests that the diagnosis of MPD is very unlikely if a lesion develops on the areola without involving the nipple. An additional interesting result was that pigmented MPD lesions were significantly smaller in diameter than non-pigmented ones. This finding indicates that patients and physicians are more alert when dealing with pigmented lesions in the nipple area. In contrast, in cases of erythematous patches or plaques, dermatitis and psoriasis are the most common diagnoses. These benign entities are often diagnosed on a clinical basis without the need of a diagnostic biopsy. This may lead to significant delays in the diagnosis of non-pigmented MPD, which is reasonably larger in size at the time of diagnosis.

The results of our main analysis indicate that dermoscopy might contribute in the early recognition of MPD by revealing clinically invisible morphologic criteria (Fig. 1). The most frequent dermoscopic criteria of non-pigmented MPD are pink structureless areas, white lines, dotted vessels, erosion/ulceration and white scales (Fig. 2a). Amongst non-pigmented lesions, dermatitis is the most common differential of MPD and dermoscopy might enhance the discrimination between these two entities. Analytically, dermatitis is dermoscopically typified by the combination of yellow scales and scattered dotted vessels,[15] whilst in MPD yellow scales were absent. In a recent study evaluating nipple lesions with the use of dermoscopy and reflectance

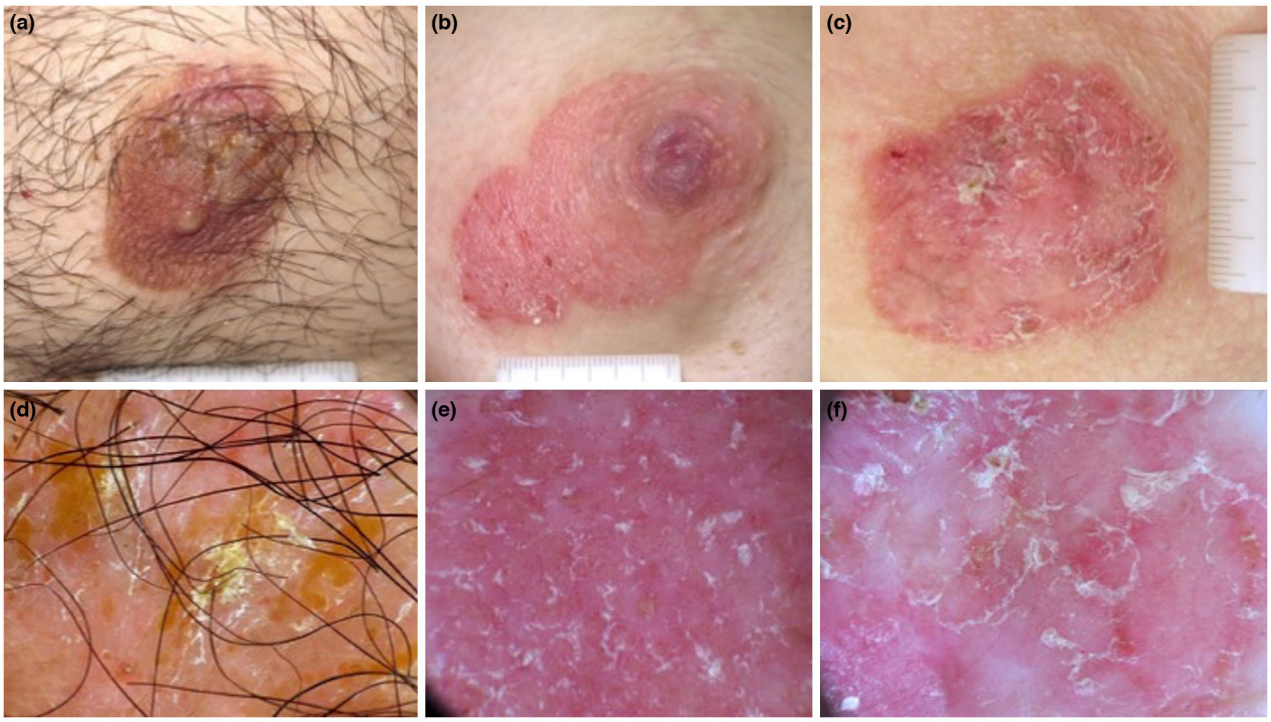

Figure 3 Eczema (a), dermoscopically typified by yellow crusts (d), psoriasis (b) by uniformly distributed dotted vessels and white scales (e) and non-pigmented mammary Paget's disease (MPD) (c) displaying white scales, pink structureless areas and focally distributed dotted vessels (f).

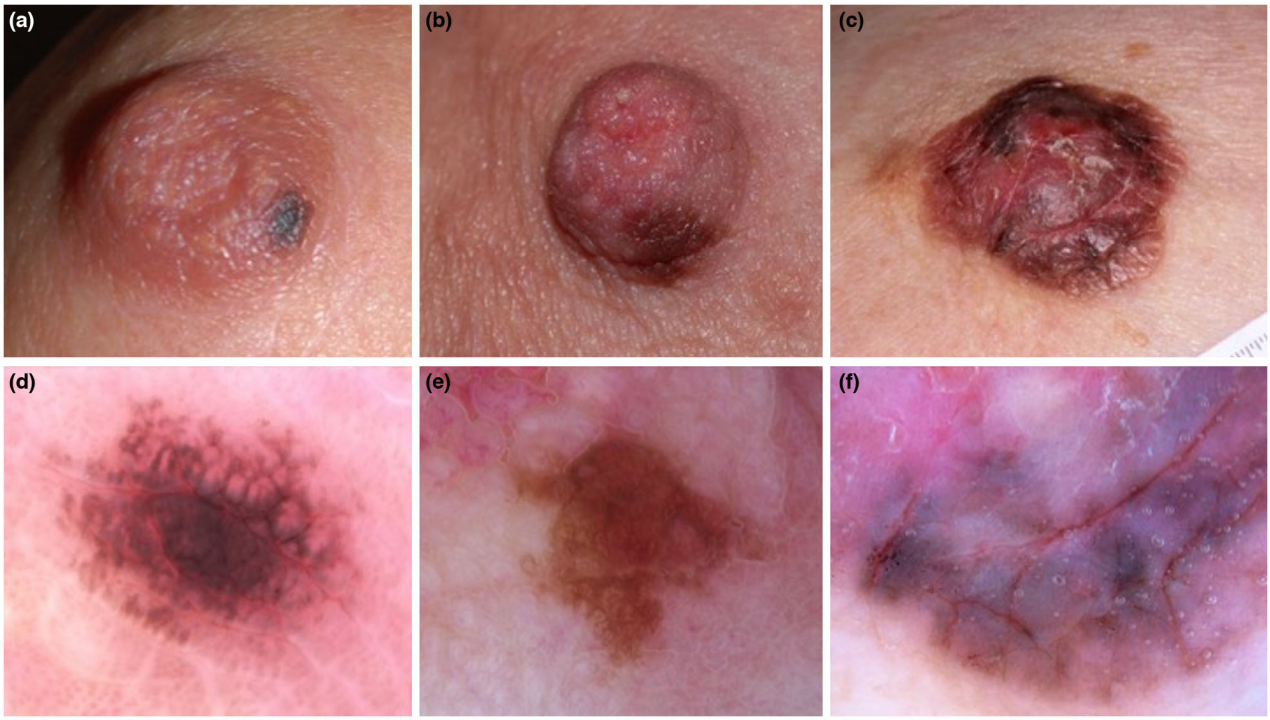

Figure 4 A naevus (a) dermoscopically characterized by a homogeneous pattern in the centre and reticular at the periphery (d), a melanosis (b) typified by a reticular dermoscopic pattern (e) and a pigmented mammary Paget's disease (MPD) (c) showing brown structureless areas, pink structureless areas, white lines brown and grey dots (f).

confocal microscopy, it was suggested that a more irregular vascular pattern in MPD might enhance its differentiation from eczema. However, the latter study did not include an evaluation of the quantitative and qualitative characteristics of scales. Considering that yellow scales/crusts represent the dermoscopic 'hallmark' of dermatitis it can be concluded that the assessment of the overall dermoscopic profile of dermatitis vs. MPD was not complete.[16] Another frequent inflammatory dermatosis that may affect the nipple and areola complex and might mimic MPD is psoriasis. Psoriasis is well-known to display a characteristic dermoscopic pattern consisting of regularly distributed dotted vessels and white scales.[15] Although dotted vessels might also be seen in MPD, they are not so numerous and not uniformly distributed as they are in psoriasis. Another neoplastic entity that falls into the spectrum of differential diagnosis of MPD is definitely Bowen's disease. However, given the rarity of Bowen's disease affecting the nipple and the fact that this entity was not found in our databases, we are not able to comment on similarities or differences between them. Figure 3 illustrates typical examples of non-pigmented MPD, psoriasis and dermatitis of the nipple, highlighting the different dermoscopic patterns of the three entities.

Our study suggests that dermoscopy might also be helpful in the clinical scenario of a pigmented patch or plaque of the nipple/areola, since pigmented MPD seems to display different features from the ones seen in the tumours included in the differential diagnosis. Analytically, the most frequent dermoscopic criteria of pigmented MPD are grey granules/dots, pink structureless areas and white lines (Fig. 2b). In contrast, lentigo and melanosis of the nipple-areola, which represent the most common differential diagnoses, are dermoscopically characterized by a regular pigment network, or cobblestone pattern, features that are almost never present in pigmented MPD.[9,20] Classic pigment network was recorded in only 1 out of 23 (4.5%) cases of MPD. Melanocytic

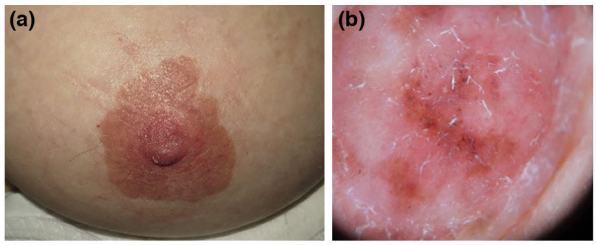

Figure 5 A mammary Paget's disease (MPD) that does not display clinically detectable pigmentation (a) but dermoscopically shows brown and grey dots (b).

naevi, depending on their type (congenital, or acquired), may display either a classic pigment network, or a globular or structureless pattern of pigmentation, or combined patterns. Figure 4 illustrates the clinical and dermoscopic pictures of a naevus and a melanosis of the nipple, vs. a pigmented MPD. Melanoma of the nipple is exceedingly rare, with less than twenty cases reported in the literature.[21–24] The dermoscopic descriptions of melanomas arising on the nipple and areola complex are scarce.[24] Literature data suggest that discrimination of pigmented MPD from melanoma on the clinical, dermoscopic, or even RCM grounds is not easy.[16,24–26] In our control group, there was 1 case of a primary melanoma and 1 case of melanoma metastasis. In the former, dermoscopy revealed an atypical pigment network and areas of regression, whilst in the latter, structureless blue-black coloration and white veil were the most striking dermoscopic features. Taking into consideration, the rarity of these tumours and the heterogenous dermoscopic findings, safe conclusions are not attainable. In this context, our recommendation is that suspicious pigmented lesions should be biopsied.

Finally, our results suggest that special attention should be paid to lesions that are clinically non-pigmented but dermoscopically display granular pigmentation, since the latter finding was strongly suggestive of MPD (Fig. 5). The granular pigmentation was described in a recent study evaluating MPD vs. other benign and malignant dermatoses, as 'regression features'.[16] However, this finding is more probable to correspond histologically to aggregations of large pigmented MPD in the epidermis, rather than regression phenomena, since the latter are not described amongst the common histologic findings of the disease.

Our study has several limitations, including the small sample size, retrospective design and a highly heterogenous control group. Another possible limitation is the lack of histopathologic confirmation in some of the inflammatory dermatoses. The impact of this limitation is minimized by the availability of follow-up information. Overall, our results can only be considered as indications and require further confirmation.

In summary, the most frequent profile of an individual with MPD is an elderly female with unilateral, asymptomatic, erythematous patch or plaque involving the nipple, dermoscopically displaying pink structureless areas, fine white scales, dotted and a few short linear vessels. In case of pigmentation, brown structureless areas and pigmented dots/granules might also be observed.

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