Proposal of a Quantitative Method to Describe Melasma Distribution in Women

Humberto Antônio Ponzio, MD, PhD; Ana Lenise Favaretto, MD; Evandro Ararigboia Rivitti, MD, PhD

The lack of an objective method to histopathologically classify melasma as epidermal, mixed, or dermal led the authors to develop an empirical formula that would allow the melanin existing in the dermis in melasma cases to be quantified. Thus, from histology slides of a historic series of melasmas in women, a cross-sectional study was designed with the goal of classifying melasma cases according to the quantity of dermal melanin deposits. Through this study, a quantitative classification method was proposed. Data from 50 women with clinically and histopathologically confirmed melasma were analyzed for the following variables: age, skin color, melasma progression time, age at menarche, irregularity of menstrual cycles, total pregnancies, full-term pregnancies, oral contraceptive use, attributable cause, and topographic classification according to the histopathologic classification and the quantity of melanin in the dermis as expressed by the dermal melanin concentration index (DMCI). According to the histopathologic classification, 58% of melasma cases were epidermal, 24% were mixed, and 18% were dermal; according to the topographic classification, 82% were central. The distribution of cases by the DMCI was one tailed, with a discrete bimodal tendency. When comparing melasma types classified by histopathology, the only differences noted were with the use of oral contraceptives, which was more frequent among women with dermal melasmas. A moderate correlation between age and the DMCI and between the number of pregnancies and the DMCI was identified. There was a strong positive correlation between DMCI and histopathologic classification ($r_{Spearman}=0.571$; $P<.001$). We concluded that, in melasmas in women, it is possible to determine an index that would translate the quantity and size of melanin deposits in the dermis and classify them as epidermal, mixed, or dermal. In this study, this index was the DMCI. Because this distribution is quantitative, it shows favorable performance in distributing and correlating melasma types.

Dr. Ponzio is Associate Professor of Dermatology, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil. Dr. Favaretto is a Dermatologist, Private Practice, Porto Alegre, RS, Brazil. Dr. Rivitti is Professor, Departamento de Dermatologia, Universidade de São Paulo, São Paulo, SP, Brazil.

The authors report no conflict of interest in relation to this article.

The merely unaesthetic nature that is attributed to melasmas, as well as their easy clinical identification, has contributed to the lack of biopsies performed during routine visits, particularly when cost-effectiveness is considered. In addition, low value is given to the histopathologic findings of melasma, partly because of the lack of criteria needed to classify the condition. Thus,

studies involving the histopathologic aspects of melasma are uncommon. According to Sánchez et al,[1] 2 distinct melasma patterns, epidermal and dermal, can be identified at histopathology. In the epidermal pattern, a higher melanin concentration can be seen in the basal and suprabasal layers, which extend through keratinocytes up to the corneal layer. Dermal involvement is modest, being restricted to the presence of some perivenular melanosome-laden melanophages in the superficial dermis.[1] The dermal pattern exhibits the findings seen in the epidermal pattern, but without the same profusion and adding a discrete perivascular inflammatory reaction and more focal melanophages that occur in the reticular dermis as well. The criteria for histopathologic classification of melasma take into consideration the degree of dermal impairment and melanic pigment location. In another study,[2] however, cases were identified in which melanic deposits in the dermis were moderate; such cases were then classified as mixed melasma. In all cases, the epidermis showed a higher quantity of melanin, but it is in the epidermal cases that the highest concentration of melanin is observed.[2] This classification, in practice, depends on subjective observations and the expertise of the examiner.

The importance of differentiating dermal from epidermal melasmas lies in the variation in therapeutic response that they present. Epidermal melasmas are more sensitive to therapeutics, whereas dermal melasmas require a distinctive approach that is not always successful.[3]

With the purpose of contributing to a better understanding of this little-studied skin disease and establishing more objective criteria to differentiate epidermal from dermal melasmas, thereby increasing the accuracy of their histopathologic diagnosis, we retrospectively analyzed, diagnosed, and biopsied melasma in women. These cases had been filed at the dermatopathology unit of the Santa Casa de Misericórdia de Porto Alegre Hospital complex, which is associated with the Federal University of Rio Grande do Sul, Brazil. Because of the need to establish a cut-off point that could histopathologically distinguish dermal melasmas from epidermal melasmas, we tried to quantify and describe the distribution of dermal melanin deposits, group the various melasma types according to the characteristics of this distribution, and correlate these newly obtained groupings with the results from routine histopathologic examinations taken from the patients' medical records.

MATERIALS AND METHODS

Once the patients' files were reviewed and the cases of diagnosed melasma were identified, new histologic sections were performed whenever the quantity of material contained in the paraffin blocks available at our dermatopathology unit allowed. The slides were stained following the routine histologic technique. The blocks were assembled and cut using a hand microtome; attention was given to keeping the section thickness within 3 µm to 5 µm. The obtained sections were mounted on slides for subsequent staining using the Schmorl technique.[4]

Sites with higher melasma intensity were chosen for biopsy using a Wood lamp. All the remaining data relative to the selected patients were obtained from their respective medical records, especially age, skin color, melasma progression time, age at menarche, irregularity of menstrual cycles, total pregnancies, full-term pregnancies, as well as information on the use of oral contraceptives (OCs). For the attributable cause, we used what was deemed to be the melasma trigger at the time the original samples were taken. Clinically, all cases were classified topographically as central or peripheral and histopathologically as epidermal, mixed, or dermal according to the criteria previously specified.[2] In every new slide stained using the Schmorl technique, we identified, in small magnification, the 3 best histologic sections. The best sections had to meet the following criteria: no artifacts (eg, folds or failures left by the scalpel) could be present; the epidermis, superficial dermis, and middle dermis had to be clearly represented on the slide; and the staining had to be uniform. For such an observation, a Zeiss binocular microscope with ×10 eyepieces and ×10 objective lens was used. Once the sections to be studied were chosen, melanin in the dermis was identified and quantified using the same microscope and the same eyepieces, but with the ×40 objective lens, which produces visual fields of 0.4 mm.

To quantify the melanin in the dermis in each case, an index—the dermal melanin concentration index (DMCI)—was arbitrated based on the melanic agglomeration concentration in the superficial and reticular dermis and on the size of the granules contained therein. The quantity of melanosomes found in the dermis was referred to as the density index (DI). To determine the DI, the same 3 best histologic sections were examined using a high magnification (×40). The DI was obtained by the average of the values of the 3 examined sections. The DI value was 0 when there was no melanin in the dermis; 1 when there were 10 or fewer melanosomes per melanic agglomeration; 2 when there were between 11 and 20 melanosomes; and 3 when there were more than 20 melanosomes. The superficial dermal index (SDI) reflected the number of melanic agglomerations existing in the high papillary and reticular dermis and corresponded to the average value of the examined microscopic fields under the same conditions as the DI evaluation. The data from 3 consecutive microscopic visual fields in each of the 3 best sections selected

$$DMCI = \frac{(DR \times Md_{DI}) + (SDI \times Md_{SDI}) + (RDI \times Md_{RDI})}{Md_{DI} + Md_{SDI} + Md_{RDI}}$$

Figure 1. Empirical formula used to obtain the dermal melanin concentration index (DMCI). DR indicates density rate; Md_{DI}, median of density indexes; SDI, melanin index in the superficial dermis; Md_{SDI}, median of melanin indexes in the superficial dermis; RDI, melanin index in the reticular dermis; Md_{RDI}, median of melanin indexes in the reticular dermis.

were computed. The reticular dermal index (RDI) was obtained through the average of the examined microscopic fields in the reticular dermis, just as was done for the DI and the SDI. The value was 0 for the absence of melanic agglomerations in the dermis, 1 for 1 through 5 agglomerations, 2 for 6 through 10 agglomerations, and 3 for 11 or more agglomerations per examined field. Using fewer fields did not lead to the exclusion of the case, since the indexes were calculated by the average of the fields that were examined. The SDI and RDI values reflected the concentration of melanic agglomerations in the superficial and reticular dermis, respectively, and the DI values reflected the total size of these agglomerations.

The DMCI calculation was obtained by the weighted average of the original indexes (the DI, the SDI, and the RDI). The weight attributed to each portion was its respective median. The median was selected to determine the DMCI because it is the most appropriate measure when data distribution is skewed. The formula used for determining the DMCI is illustrated in Figure 1.

Once this empirical formula was defined, we proceeded with classifying melasmas as epidermal or dermal based on melanin concentration in the dermis. To do so, we determined the cut-off point that best expressed this dichotomization.

Because there are no defined reference values, the cut-off point in this study was determined arbitrarily. We opted for adopting the percentile that best differentiated epidermal melasma from dermal melasma and, especially, furthered the classification of mixed melasmas into 1 of these categories.

In an earlier study,[2] a sample of melasma cases was classified through routine histopathologic examination as epidermal (42 [57%]), mixed (13 [18%]), or dermal (18 [25%]). When mixed melasmas were excluded, epidermal melasmas accounted for 76% of the cases. It was decided that the cut-off point for melasma classification by the DMCI corresponded to the percentage of epidermal melasmas in this series (76%).

Once the DMCI quantification method was established, the cases comprising the sample were classified using the cut-off point, with cases that had an index lower than the cut-off point (DMCI) being designated as epidermal and the rest, dermal.

To evaluate a difference in melanin quantity in the dermis of patients with epidermal versus dermal melasma with an effect size of 1.5 or higher considering sampling proportions of 3:1 (epidermal:dermal)(α=.05, 90% power [β=.10]), we calculated a sample of 7 or more patients with dermal and 21 patients with epidermal melasmas. Patients with mixed melasma were also included for comparison.

Quantitative data were described by mean and standard deviation and, in the presence of skewness, by median and interquartile range. For categorical variables, the absolute frequency and the percentage were used. Comparisons among patient groups were conducted by analysis of variance and χ^2 test. For assessing associations between melasma histopathologic classifications and DMCI, we used Spearman correlation coefficient, with significance determined through Student *t* test. When evaluating relationships, the box plot graph was used for assessing data distribution and the respective comparisons between patient groups (significance level, α=.05%).[5] Data were processed and analyzed with the aid of Microsoft Office Excel and SPSS version 12.0.

RESULTS

Of the 17,843 biopsies available in the dermatopathology unit of the Federal University of Rio Grande do Sul at the Santa Casa de Misericórdia de Porto Alegre Hospital complex, 50 melasma cases were identified that contained enough material in paraffin blocks to allow new slides to be prepared and submitted for Schmorl staining.[4]

We evaluated the distribution of cases according to routine histopathologic classification and the quantity of melanin identified in the dermis by age, skin color, melasma progression time, age at menarche, irregularity of menstrual cycles, total pregnancies, full-term pregnancies, the use of OCs, attributable causes, and topographic classification.

By routine histopathologic examination using H&E staining, the sample cases were classified as epidermal (58%), mixed (24%), or dermal (18%).

Figure 2 shows the distribution of frequencies according to the DMCI value obtained. Case distribution by the DMCI showed a higher frequency of lower values, exhibiting a descending curve outlining 2 peaks (modes) corresponding to the DMCI values 0.6 and 2.2. Therefore, we found a one-tailed distribution with

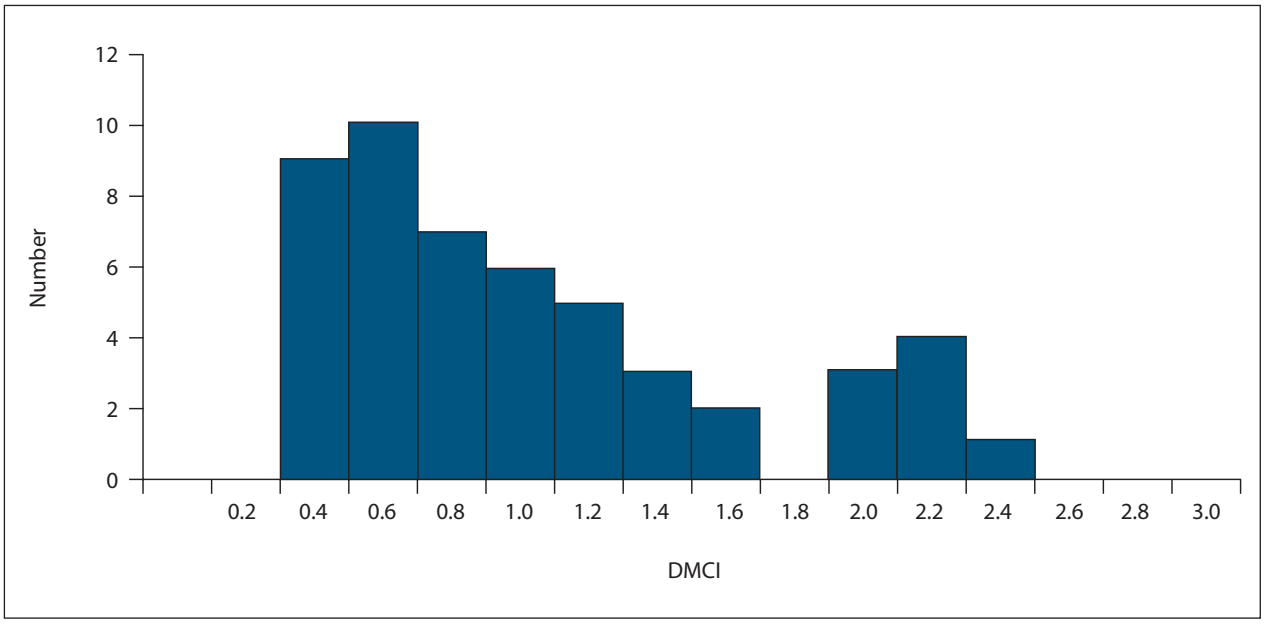

Figure 2. Distribution of dermal melanin concentration index (DMCI) values in a sample of 50 women with epidermal, mixed, and dermal melasmas.

a slight bimodal trend that allowed us to dichotomize the sample.

Table 1 outlines the values for the studied variables according to the 3 melasma types identified through routine histopathologic examinations. The studied sample was composed of women aged 19 to 54 years. Mean age was highest in the mixed melasma group, followed by the dermal malasma group. This finding, however, was not significant. Most of the studied cases were of white women (72.9%), and no preponderance of melasma type was observed.

No differences were found in melasma progression time among the melasma types, as classified by routine histopathologic examination. Despite the higher mean age at menarche among patients with epidermal melasma, there was no significant difference among the studied groups. There were more cases of menstrual irregularity in the epidermal and the mixed melasma groups; however, the difference was not significant. The median number of total pregnancies and full-term pregnancies was higher in the dermal and mixed melasma groups and much lower in the epidermal group, although not significantly. Proportionately, the use of OCs was significantly higher among patients with dermal melasma.

Regarding the melasma-triggering causes, unknown factors prevailed, but without differences among the patient groups. Central melasmas were more prevalent among patients with epidermal or mixed types, although it was not possible to determine whether there were differences among the groups. These same variables were studied by comparing them with the DMCI values obtained. These results are shown in Table 2.

There was a moderate correlation between age and the DMCI values; older patients had higher rates. Black patients had higher DMCI values; however, this characteristic did not allow us to differentiate this group from the others (white patients and patients of mixed black and white ancestry). No correlation between the DMCI values and melasma progression time or age at menarche was demonstrated.

Lower but nonsignificant DMCI values were observed in patients with irregular menstrual cycles and those taking OCs. The total pregnancies showed moderate correlation with the DMCI values, but with the total full-term pregnancies, the correlation was only regular and nonsignificant. No differences between attributable causes and the DMCI values were demonstrated. Peripheral melasmas showed higher DMCI values without statistical significance.

Figure 3 demonstrates that the DMCI values, when evaluated in the epidermal, mixed, and dermal melasma types, showed a clear growth, indicating a strong positive correlation between DMCI and melasma type ($r_{Spearman}=0.571$; $P<.001$).

An occasional finding was the scarceness of melanin in lower parts of hair follicles, below the level of the infundibular region. Hair follicles were observed in the histologic sections of 41 of the 50 examined cases; there was always a near absence of melanin in that region.

COMMENT

Sánchez et al[1] were the first to propose a classification for melasmas on the grounds of clinical and histopathologic

TABLE 1

Distribution and Comparison of Several Studied Variables in Melasma Types, Classified Through Routine Histopathologic Examinations

Characteristics	Epidermal (n=29)	Mixed (n=12)	Dermal (n=9)	*P*
Age, y*	30.6±7.1	35.5±6.6	33.0±9.4	.17
Skin color, no. (%)				.77
White	20 (71.4)	9 (75.0)	6 (75.0)	
Brown	6 (21.4)	1 (8.3)	1 (12.5)	
Black	2 (7.1)	2 (16.7)	1 (12.5)	
Progression time, y†	7.0 (1.7–10.0)	4.0 (2.0–5.0)	6.5 (3.5–9.0)	.51
Age at menarche, y*	13.4±2.2	12.8±0.9	12.0±2.0	.30
Irregular cycles, no. (%)	11 (47.8)	4 (44.4)	0 (0.0)	.10
Total pregnancies, no.†	1.0 (0.0–3.0)	2.5 (0.0–3.3)	2.5 (1.8–5.3)	.16
Total full-term pregnancies, no.†	0.0 (0.0–2.0)	2.0 (0.0–3.0)	2.0 (1.0–3.0)	.10
OC use, no. (%)	12 (48.0)	1 (12.5)	5 (71.4)	.05
Attributable cause, no. (%)				.24
Not identified	17 (58.6)	9 (75.0)	4 (44.4)	
Pregnancy	8 (27.6)	2 (16.7)	5 (55.6)	
OC use	4 (13.8)	1 (8.3)	0 (0.0)	
Topographic classification, no. (%)				.10
Central	26 (89.7)	10 (83.3)	5 (55.6)	
Peripheral	3 (10.3)	2 (16.7)	4 (44.4)	

*Data are presented as mean ± SD.
†Median (interquartile range).
OC indicates oral contraceptive.

findings. More recently, Kang et al[6] described the major histopathologic changes found in melasma, although without proposing a classification.

In the present study, all selected cases were reexamined microscopically, and the medical records were reviewed. Special attention was given to the differential diagnosis with Riehl melanosis, which histopathologically shows an inflammatory stage, with the presence of perivascular lymphocyte infiltration and basilar liquefaction, which results in increased melanophages in the superficial dermis. Melasmas do not have this inflammatory stage, but show an accumulation of melanosomes, primarily in the cytoplasm of keratinocytes.[7] This differentiation is especially important in extrafacial melasma, which is uncommon and often mistaken for Riehl melanosis or other postinflammatory hypermelanoses.

The sample was composed of all the melasma cases in women that existed in the files of the dermatopathology unit and that met the inclusion criteria. These cases were submitted for biopsy because of a previous study that was conducted at the same institution.[2] When this first study was conducted, all patients who had been clinically diagnosed with melasma and who agreed to undergo the procedure were biopsied.

Schmorl stain was chosen for the new histologic sections. This technique is little known by the medical community of Brazil but is routine in the Netherlands and unites convenience, effectiveness, and low cost. Histologic preparations of all selected cases for the sample were reexamined. H&E–stained and Schmorl-stained slides were reviewed. All observed cases showed increased melanin in the epidermis. Dermal deposits, not always identified in the routine examination, should not be overlooked on careful observation. The decision to classify melasmas as epidermal, mixed, or dermal using these criteria is empirical and not always trustworthy. Sánchez et al[1] classified melasmas as epidermal or dermal; however, they did not make appropriately clear the limits for

TABLE 2

Comparison of Several Characteristics Among Melasma Types Classified Through the Dermal Melanin Concentration Index (DMCI)

Characteristics	DMCI (N=50)	*P*
Age, y*	r=0.32	.03
Skin color†		.13
White	1.12±0.52	
Brown	0.89±0.51	
Black	1.56±0.90	
Melasma progression time, y*	r=0.08	.59
Age at menarche, y*	r=–0.10	.54
Menstrual cycles†		.60
Regular	1.20±0.58	
Irregular	0.99±0.59	
Total pregnancies*	r=0.36	.02
Total full-term pregnancies*	r=0.21	.17
OC use†		.44
Yes	1.13±0.52	
No	1.24±0.62	
Attributable cause†		.61
Unidentified	1.18±0.60	
Pregnancy	1.16±0.64	
OC use	0.90±0.37	
Topographic classification†		.54
Central	1.08±0.56	
Peripheral	1.47±0.61	

*Data are presented as correlation coefficient.
†Data are presented as mean ± SD.
OC indicates oral contraceptive.

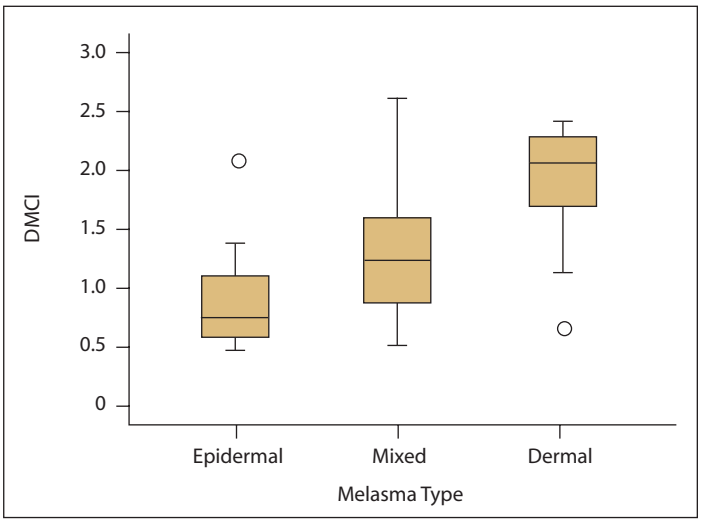

Figure 3. Correlation of dermal melanin concentration index (DMCI) with melasma types, classified by regular histopathologic examination.

each melasma type and the proportion of each melasma type present in the patient sample they studied.

The frequency of the different types of melasma found in this study (58% epidermal, 24% mixed, and 18% dermal) seems to be consistent with those found in clinical practice when considering the behavior and, mainly, the therapeutic response observed in daily practice. This obviously needs to be validated.

As for topographic classification, we chose the one adapted by Ponzio and Cruz.[2] Thus, 82% of melasmas were central—a close value to the sum of midfacial and malar melasmas reported by Sánchez et al.[1]

By histopathologic classification, the mean ages found in the different melasma groups corresponded to potentially childbearing ages. It is during these years that estrogen and progesterone levels are highest, which meets the findings in the literature.[8] When distributing melasma cases by their quantity of melanin in the dermis, expressed by the DMCI values, we observed a moderate and significant correlation—that is, the older the patient, the higher the quantity of melanin in this site.

The majority (72.9%) of the sample was composed of white women; black women and women of mixed black and white ancestry accounted for the rest. These data do not differ from the greater population of patients seen by this dermatology department that had already been evaluated in a previous study.[9] No racial differences among melasma groups, as classified through histopathologic examination, were observed, even when distributed by the quantity of melanin (DMCI), perhaps

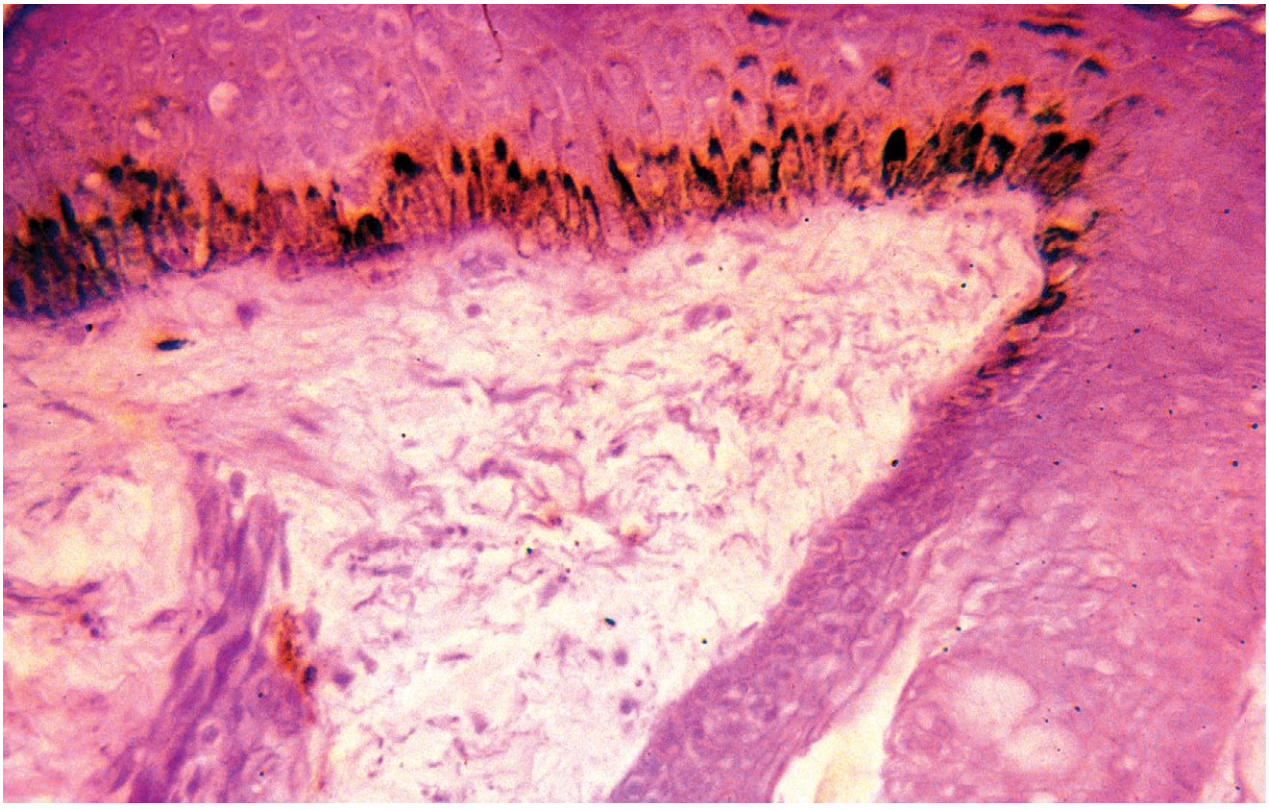

Figure 4. Interruption of the sequence of melanin-laden cells in the basal layer of the infundibulum of a hair follicle (Schmorl ×400).

because the racial composition of the population from Rio Grande do Sul is mostly white.

The hypothesis that precocious menarche, caused by higher exposure to gonadal hormones, could contribute to the increased incidence of dermal melasmas was not confirmed. Although mean ages in the melasma groups might suggest this tendency, this may have occurred by chance.

The total number of pregnancies was higher among patients with mixed and dermal melasmas, although not significantly higher among groups; however, the quantity of melanin in the dermis and the total number of pregnancies showed a moderate and significant correlation. When considering only full-term pregnancies, the findings were similar, although not significant.

Irregularity of menstrual cycles among the melasma groups was similar and not correlated with melanin deposits in the dermis. Patients who most commonly took OCs were those with dermal melasmas, although this difference, when compared with the DMCI values, was not significant. This finding may result from the manner in which patients were questioned.

The only possibly attributable causes that were determined in the study sample were pregnancy and OC use, even though associations were found in only 40% of cases—pregnancy was considered to be causative in 30% of the cases, OC use in 10%. Behrman[10] observed melasma in only 0.5% of OC users, an apparently low percentage and contrary to the findings of other authors who state that melasma is incident in a third of OC users.[11-13] However, it should be noted that, at the time when these papers were published, OCs contained a higher concentration of estrogen than those used today. In our patient sample, OC use was significantly higher among those with dermal melasmas.

The role of pregnancy in melasma genesis is reported by several authors.[1,2,14-16] Pregnancy is implicated in a third of cases as a trigger. Our patient sample was not different, suggesting that dermal melasmas are incident in women with a higher number of pregnancies.

The DMCI values were shown to be strongly correlated with the routine histopathologic classification. Because this was a continuous variable and indirectly translated to the quantity of melanin in the dermis, this index allowed us to describe the distribution of melasma types, demonstrating that lower quantities of melanin in the dermis were present in epidermal melasmas and higher quantities were present in dermal melasmas. Mixed melasmas had intermediary values. Thus, it was possible to correlate age and total pregnancies with a higher quantity of melanin in the dermis in our sample.

A consistent observation in our study, not reported in the reviewed literature, was the scarceness of melanosomes in the basal layer of hair follicles, beyond the infundibular region (Figure 4). The interruption of the sequence of melanin-laden cells occurred at the level of the junction of the papillary and reticular dermis. Hair follicles were observed in 41 of the 50 cases studied in this sample, and all exhibited similar aspects.

CONCLUSION

In melasma cases in women, it is possible to determine an index that translates the quantity and size of melanin deposits in the dermis. In this study, this index was the DMCI.

The correlation of epidermal, mixed, and dermal melasmas in women, classified through routine histopathologic examination, with age, skin color, melasma progression time, age at menarche, irregularity of menstrual cycles, total pregnancies and full-term pregnancies, attributable causes of melasma, and topographic classification showed that this examination did not allow the identification of significant differences among these variables in the 3 melasma types. Proportionally, OC use was significantly higher among patients with dermal melasmas when the histopathologic classification was used. When distributed by quantity of melanin in the dermis, expressed by the DMCI values, there was a moderate correlation between this distribution and age; the same occurred with the total pregnancies. Regarding the other variables, there was no significant correlation with the DMCI values.

The correlation with DMCI values increased across the different types of melasma as defined by the histopathologic classification, indicating a strong positive correlation between the DMCI and the histopathologic classification. Because the DMCI is a quantitative variable, it is better correlated with melasma types and clearly expressed the spectrum of the disease, suggesting that melasmas in women do not present distinctive clinical categories and that the DMCI may be a good quantitative method to classify melasma.

The scarceness of pigment on the follicular walls of infundibular regions may be included in the histopathologic criteria for the diagnosis of melasmas.

REFERENCES

1. Sánchez NP, Pathak MA, Sato SS, et al. Melasma: a clinical, light microscopic, ultrastrutural, and immunofluorescence study. *J Am Acad Dermatol.* 1981;4:698-710.
2. Ponzio HA, Cruz MF. Acurácia do exame sob a lâmpada de Wood na classificação dos cloasmas. *An Bras Dermatol.* 1993;68:325-328.
3. Ponzio HA. *Contribuição à classificação clínica e histopatológica dos melasmas*. Dissertação (Mestrado). Universidade Federal of Rio Grande do Sul. Brasil. Faculdade de Medicina. Curso de Post-Graduação em Medicina: Clínica Médica, Porto Alegre, Brazil; 2000.
4. Schmorl G. *Die Pathologisch-Histologichen Untersuchurgsmethoden*. Leipzig, Germany: Vogel; 1922.

5. Lang TA, Secic M. *How to Report Statistics in Medicine: Annotated Guidelines for Authors, Editors, and Reviewers.* Philadelphia, Pa: American College of Physicians; 1997.
6. Kang WH, Yoon KH, Lee ES, et al. Melasma: histopathological characteristics in 56 Korean patients. *Br J Dermatol.* 2002;146: 228-237.
7. Mishima Y. Histopathology of functional pigmentary disorders. *Cutis.* 1978;21:225-230.
8. Snell RS, Bischitz PG. The effect of large doses of estrogen and estrogen and progesterone on melanin pigmentation. *J Invest Dermatol.* 1960;35:73-82.
9. Bopp C, Bernardi CD, Müller R, et al. Análise interpretativa das dermatoses mais freqüentes em Porto Alegre—Rio Grande do Sul, Brasil. *An Bras Dermatol.* 1973;48:117-132.
10. Behrman SJ. Norethindrone, 2 mg: an evaluation. *Obstet Gynecol.* 1964;24:101-105.
11. McKenzie AW. Skin disorders in pregnancy. *Practitioner.* 1971;206:773-780.
12. Thiers H, Villedieu P, Moulin G. Chloasma during treatments with synthetic estroprogestagens [in French]. *G Ital Dermatol Minerva Dermatol.* 1966;107:1335-1338.
13. Resnik S. Melasma induced by oral contraceptive drugs. *JAMA.* 1967;199:601-605.
14. Hellreich PD. The skin changes of pregnancy. *Cutis.* 1974;13:82-86.
15. Winton GB, Lewis CW. Dermatoses of pregnancy. *J Am Acad Dermatol.* 1982;6:977-998.
16. Pathak MA, Fitzpatrick TB, Kraus EW. Usefulness of retinoic acid in the treatment of melasma. *J Am Acad Dermatol.* 1986;15:894-899. ■