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ORIGINAL ARTICLE

Descriptive Dermoscopic Study of Depigmentation in Melanocytic Nevi Without a Visible Halo

J.M. Martín,^{a,*} J. Núñez,^a V. López,^a M. Rubio,^a C. Monteagudo,^{a,b} E. Jordá^a

^aServicio de Dermatología, Hospital Clínico Universitario, Valencia, Spain

^bServicio de Anatomía Patológica, Hospital Clínico Universitario, Universidad de Valencia, Valencia, Spain

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KEYWORDS

Depigmentation;
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Regression

Abstract

Background and objectives: There are few cases described in the literature in which depigmentation of melanocytic nevi occurs without the appearance of halos. The aim of this study was to analyze the correlation between clinical and dermoscopic findings and to assess the usefulness of dermoscopy to identify possible markers of complete regression in melanocytic lesions.

Materials and methods: A prospective, observational, descriptive study of 77 melanocytic lesions in 52 patients was undertaken over a 5-year period. Melanocytic lesions from patients who underwent periodic follow-up in the digital dermoscopy unit were analyzed if they had exhibited partial or total, permanent depigmentation without a clinically apparent halo.

Results: We observed substantial variation in the time taken for pigmentation to disappear and the morphological characteristics of the nevi during the depigmentation process. Female sex and dermoscopic evidence of melanophage activity or of a halo were all associated with more rapid involution of pigmented lesions. The only variable which displayed a statistically significant association with complete depigmentation of melanocytic nevi was the presence of vascular proliferation. Fibrosis was the only variable that displayed a statistically significant association with heterogeneous depigmentation of melanocytic nevi.

Conclusions: In this study, we have identified patterns of depigmentation in melanocytic lesions that differ from the classic halo nevus.

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*Corresponding author.

E-mail address: Martin.josemaria@gmail.com (J.M. Martín).

PALABRAS CLAVE

Depigmentación;
Halo nevus;
Nevo melanocítico;
Regresión

Estudio descriptivo dermatoscópico de los nevos melanocíticos con despigmentación sin halo clínico

Introducción: La despigmentación de nevos melanocíticos sin halo perilesional se ha descrito de forma excepcional en la literatura.

Material y métodos: Estudio observacional, descriptivo y prospectivo de 77 lesiones melanocíticas correspondientes a 52 pacientes, llevado a cabo durante un período de 5 años. Se han analizado las lesiones melanocíticas de pacientes revisados periódicamente en la unidad de dermatoscopia digital que habían sufrido una despigmentación permanente, ya fuera total o parcial, pero sin presentar clínicamente un halo blanquecino alrededor de los mismos.

El objetivo fue estudiar la correlación entre los hallazgos clínicos y dermatoscópicos a estudio, y establecer el valor de la dermatoscopia para identificar posibles marcadores de regresión completa de lesiones melanocíticas.

Resultados: Hemos observado mecanismos de despigmentación sin halo muy dispares, tanto en lo referente al tiempo que tardaban las lesiones en perder la pigmentación, como en las características morfológicas de los nevos durante el proceso de involución. La presencia de melanofagia, halo dermatoscópico y el sexo femenino fueron las variables que demostraron una asociación estadísticamente significativa, con un menor tiempo de involución de las lesiones pigmentadas. La existencia de proliferación vascular fue la única variable que demostró una asociación estadísticamente significativa con la despigmentación completa de los nevos melanocíticos. La existencia de fibrosis fue la única variable que ha demostrado una asociación estadísticamente significativa con la despigmentación heterogénea de los nevos melanocíticos.

Conclusiones: El presente estudio ha permitido identificar la existencia de patrones de despigmentación de lesiones melanocíticas diferentes al halo nevo clásico.

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Introduction

Spontaneous regression of tumors, one of the most fascinating and intriguing phenomena that can be observed in medicine, has been described in almost all types of cancer. Although it is a rare occurrence, it is often reported for both benign and malignant cutaneous melanocytic tumors, since the loss of pigment makes it easier to detect.¹⁻³ A number of mechanisms may be implicated in the induction of regression, including the immune response, apoptosis, inhibition of angiogenesis, terminal differentiation of cells, and genomic instability.^{4,6}

Most descriptions of depigmentation in melanocytic lesions involve the presence of a whitish halo around the lesion. In recent years, however, depigmentation has been reported to occur without the formation of a visible halo, especially in giant congenital nevi and melanomas.⁷⁻¹¹ Depigmentation of melanocytic nevi without the occurrence of a halo has rarely been described in the literature.^{12,13} The widespread introduction of digital dermatoscopy into clinical practice in dermatology, however, has facilitated detailed monitoring of patients with multiple melanocytic nevi, and this has helped to improve our understanding of the morphology of pigmented lesions, particularly in relation to changes occurring over time.^{14,15} Thanks to this technique, it is now possible to monitor the course of these lesions and identify both transient and permanent morphological changes, including depigmentation processes that do not involve the formation of a halo.

The aim of this study was to analyze the correlation between clinical and dermoscopic findings and to assess the value of dermatoscopy for identifying markers of complete involution in melanocytic lesions.

Materials and Methods

A prospective, observational, descriptive study was carried out between 2005 and 2009 to analyze melanocytic lesions in patients undergoing follow-up in the digital dermatoscopy unit of the Department of Dermatology at Hospital Clínico Universitario in Valencia, Spain. Patients with multiple or atypical nevi were seen every 3 to 6 months. Lesions were included in the study if a permanent loss of pigmentation, either total or partial, had been observed and follow-up data were available. Lesions were excluded if the patient reported prior trauma, if a halo had been clinically visible during the process of depigmentation, or if areas of regression were observed during the initial examination, since these lesions were immediately excised. The lesions were examined by 3 dermatologists with experience in the use of dermatoscopy (JMM, MR, and VL).

Data were collected on the following variables: sex and age of the patients, site of the lesion, time taken for depigmentation to occur (months), and various dermoscopic characteristics of the lesions. The dermoscopic data used in the analysis were obtained using the video camera attached to the Fotofinder digital

dermoscopy apparatus (FotoFinder Systems GMBH, Bad Birnbach, Germany).

The dermoscopic variables assessed in each lesion corresponded to the predominant structural pattern of the nevus (globular, reticular, homogeneous, parallel furrow, or a combination of those patterns) and the characteristics of the depigmentation process (total or partial, homogeneous or heterogeneous, loss of structure and pigmentation [fibrosis], appearance of vascular structures [vascular proliferation], blue-gray dots [melanophages], or dermoscopic halo).

In nevi with partial regression, the process was considered to have terminated if further changes were not observed after 6 months. All lesions with clinical or dermoscopic signs of atypia were excised. Lesions were only left without excision when the process of depigmentation occurred gradually and homogeneously, and in all cases the patients were carefully monitored.

Statistical Analysis

Quantitative variables were expressed as means (SD) and medians (interquartile range [IQR]) and were compared using the Mann-Whitney test. Qualitative variables were expressed as percentages and compared using the χ^2 test or the Fisher exact test when the expected value of 1 or more cells was less than 5.

To identify variables that were independently associated with the length of the regression process, multiple linear regression was performed to obtain a parsimonious model with a high discriminative capacity. The variables

Table 1 Frequencies of Morphological Variables Observed by Dermoscopy

Morphological Pattern	%
Reticular	44.2
Globular	27.3
Reticular and globular	28.6
Complete depigmentation	37.6
Partial depigmentation	62.4
Homogeneous depigmentation	62.3
Heterogeneous depigmentation	37.7
Vascular proliferation	16.9
Melanophages	50.6
Dermoscopic halo	12.9
Fibrosis	59.7

included in the final model were selected according to the magnitude of the change in R^2 (coefficient of determination). A cutoff of $P < .05$ was set for statistical significance. Statistical analyses were performed using SPSS for Windows version 11.

Results

Descriptive Analysis

We studied 77 lesions in 52 patients (42.9% men and 57.1% women). The mean age of the patients was 27.6 (12.1)



Figure 1 The principal dermoscopic characteristic associated with very rapid regression of melanocytic nevi was the presence of dense melanophages along with the disappearance of the existing dermoscopic structural pattern.

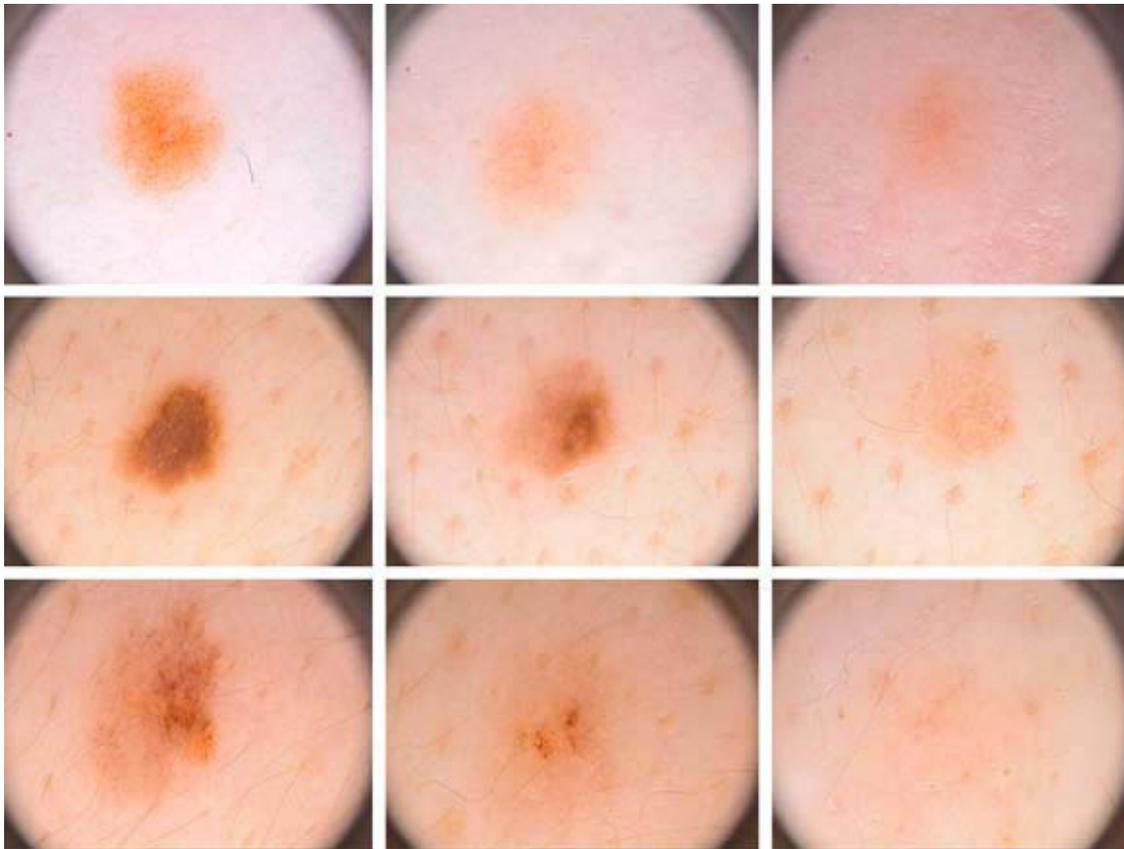


Figure 2 Examples are shown of gradual depigmentation without halo formation in melanocytic nevi.

years and the median was 25 years (range, 8-67 years). Most patients were between 20 and 33 years of age (50% of the group).

Lesions were most often found on the trunk, predominantly the back (59.7% of cases) and chest (21% of cases). The remaining cases comprised 9.7% on the abdomen, 4.8% on the arms, and 4.8% on the legs.

The mean length of time for depigmentation of melanocytic nevi (months elapsed from onset to completion of depigmentation) was 29 (14.4) months (range, 5-59 months) and the median was 32 months (IQR, 15-41 months). Depigmentation occurred during the first year of follow-up in 20% of nevi. Follow-up lasted for a minimum of 3 months and a maximum 5 years. The frequency of the morphological characteristics visible by dermoscopy is shown in Table 1.

None of the excised lesions corresponded to a melanoma. Most were junctional or compound dysplastic melanocytic nevi (70%). Areas of regression were observed in 60% of excised lesions (20% of cases corresponded to complete regression).

Statistical Analysis

Assessment of the relationship between time and all other variables analyzed was used to identify those variables that

were predictive of rapid depigmentation of melanocytic lesions. Based on multiple linear regression analysis, the following variables were independently associated with the time taken for depigmentation to occur: presence of melanophages (β , -8.75; standard error [SE], 3.17; $P=$.007), dermoscopic halo (β , -11.18; SE, 4.50; $P=$.015), and female sex (β , -5.97; SE, 3.20; $P=$.066).

The presence of melanophages was the most important variable in the model (responsible for 53.8% of the total R^2), followed by dermoscopic halo (28.1% of the total R^2) and female sex (18.1% of the total R^2).

A multiple logistic regression analysis was also performed to identify variables that were predictive of complete depigmentation of melanocytic lesions. In the multivariate analysis, which included all of the study variables, the only variable that was independently associated with complete depigmentation of nevi was the presence of vascular proliferation (odds ratio, 7.89; 95% confidence interval, 1.95-31.92; $P=$.004).

Finally, multiple logistic regression was used to identify variables that were predictive of heterogeneous depigmentation of melanocytic lesions. In the multivariate analysis, the only variable that was independently associated with heterogeneous depigmentation was the presence of fibrosis (odds ratio, 4.16; 95% confidence interval, 1.44-12.05; $P=$.008).



Figure 3 In a small number of cases, a subtle, clinically unrecognizable halo was visible by dermoscopy during involution.

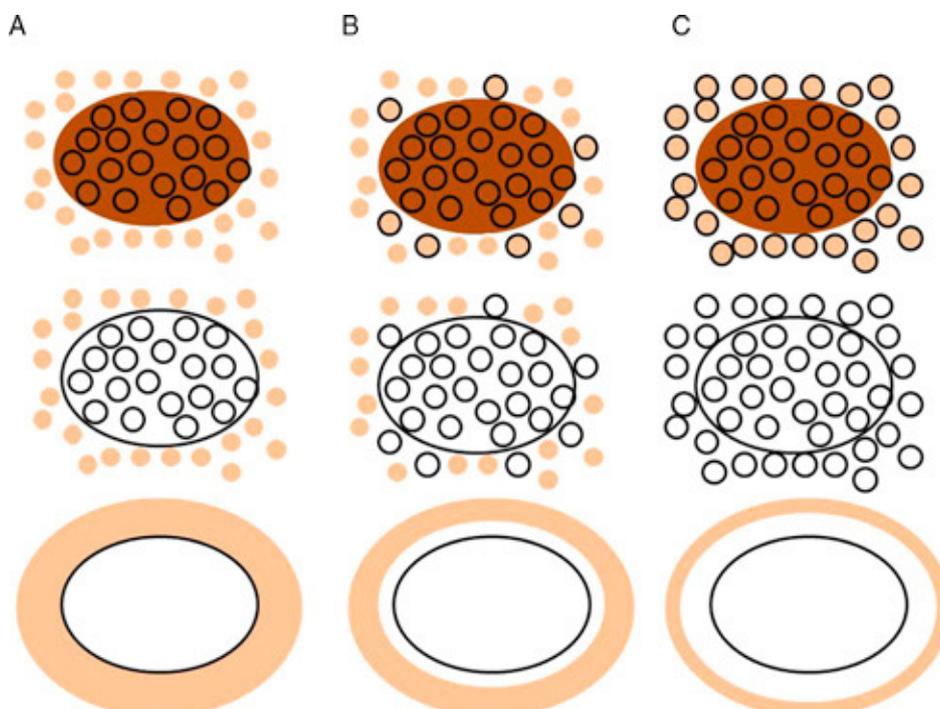


Figure 4 A, Example of a halo nevus with no clinically visible or dermoscopic halo in which there would be no involvement of melanocytes in the skin surrounding the tumor. B, The presence of a dermoscopic halo would be explained by the involvement of a small number of melanocytes in the region around the tumor. C, In conventional halo nevi, a large number of melanocytes in the skin around the nevus would be destroyed. Small black circles indicate cells attacked by the immune system.

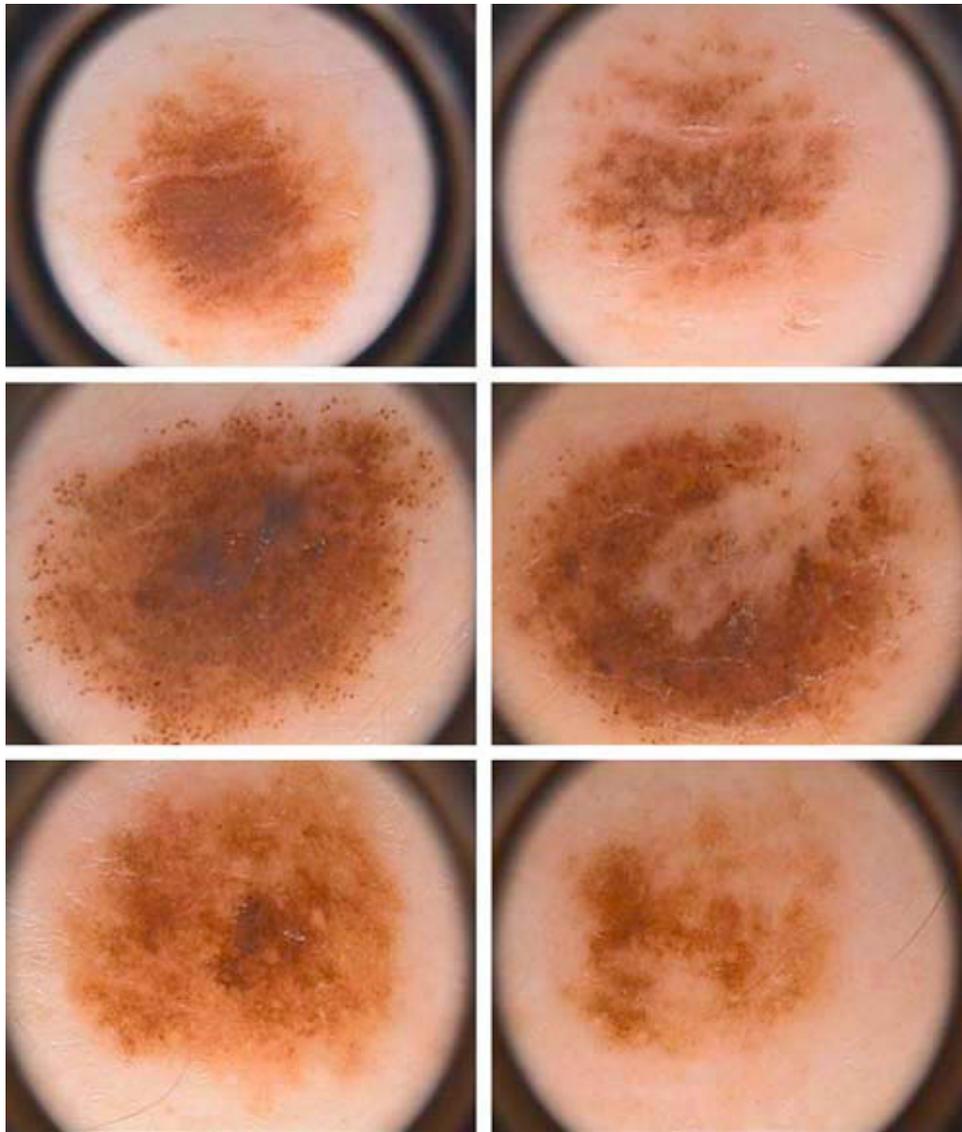


Figure 5 Examples of partial heterogeneous depigmentation.

Discussion

Complete regression of melanocytic nevi and melanomas has been described in the literature.^{7-11,16} Classically, the loss of pigmentation of melanocytic lesions has been associated with the presence of a whitish halo in the surrounding skin. Only on rare occasions have cases been described in which complete involution of melanocytic nevi and melanomas occurred without a visible halo.¹³ In contrast, partial regression of melanocytic lesions has frequently been described, especially in melanomas, in which it has been thought to occur in up to 35% of cases, particularly in the radial growth phase.^{16,17} In our patients, complete regression occurred in approximately a third of the nevi analyzed, whereas depigmentation was only partial in the remaining lesions.

Dermoscopy has been shown to improve the accuracy of diagnosis of melanocytic lesions. Its use can facilitate the identification of patterns of depigmentation that differ from those identified to date.

In this study, we succeeded in identifying various patterns of depigmentation in melanocytic nevi. This substantial variation in morphology and time required for depigmentation may suggest the involvement of different mechanisms in the regression of the lesions. In fact, various mechanisms have been described to explain tumor regression, including autoimmune mechanisms,¹⁷⁻²⁰ apoptosis,^{21,22} senescence,^{23,24} and inhibition of angiogenesis.²⁵

We observed a peculiar pattern of involution of melanocytic nevi characterized by their rapid disappearance. In all cases, dermoscopy revealed complete involution of the nevus within a very short period of time (generally less than



Figure 6 Examples of partial homogeneous depigmentation, in which the process of depigmentation is initiated in cells lying at the periphery.

7 months) compared with the process observed in halo nevi. The main dermoscopic characteristic was the presence of large numbers of melanophages throughout the lesion, alongside the disappearance of the existing dermoscopic structural pattern (Figure 1). In most cases, the residual lesion adopted a very similar morphology to that seen in lichenoid keratosis. The presence of a dermoscopic halo and female sex also displayed statistically significant associations with the rapid disappearance of nevi, and vascular proliferation was associated with complete disappearance of the nevi. In these cases, histology confirmed the complete absence of nevus cells following excision of the residual lesions. In addition, large numbers of melanophages and a particular variety of fibrosis in the subepidermal tissue involving very fine bundles of collagen were observed.

The most plausible pathogenic mechanism to explain this type of regression would be autoimmunity against certain antigens that are expressed only on melanocytes of the affected nevi and not in the adjacent skin or in other nevi, leading to massive and rapid destruction of the corresponding nevi. An alternative pathogenic mechanism could involve massive apoptosis mediated by the immune system through the recognition of abnormal antigens expressed on the cells of the nevus.¹⁹ This theory would be supported by the observation that none of our patients had multiple nevi undergoing depigmentation of this type, unlike the situation with halo nevi, in which it is common to observe multiple similar lesions in the same patient.

This type of regression can be likened to an explosion in which there is a massive and extremely rapid destruction

of tumor cells. The process is therefore suggestive of a cytotoxic mechanism that would be initiated by inflammation acting very rapidly and also disappearing early. This would explain the complete absence of nevus cells upon histological analysis and the presence of numerous melanophages (collecting the debris); the very discrete fibrosis is probably explained by the selectivity and speed of the process.

The statistically significant association between female sex and the time taken for depigmentation to occur could be suggestive of antigenic modification that is specifically related to female sex hormones. In this case, the modified antigens would only be present in involuting nevi in women and not men. Hormonal changes such as those occurring during pregnancy are known to induce changes in melanocytic nevi. Recent immunohistochemical findings have also revealed an increase in the expression of the estrogen receptor β in nevi excised from pregnant women, suggesting an increased response of melanocytes to estrogens during pregnancy.^{26,27}

We also observed another type of depigmentation with dermoscopic characteristics similar to those found in halo nevi, but without the presence of a clinically visible halo (Figure 2). Despite the absence of a clinically visible halo, in a small number of cases (12.9% of nevi) we observed a subtle halo by dermoscopy (Figure 3). Since the structures observed by dermoscopy during regression of these lesions were similar to those described for halo nevi,¹² and also given that the time taken for regression to occur was similar (gradual, homogeneous depigmentation), the mechanism of involution is likely to be similar to that observed in classic halo nevi. The fundamental difference

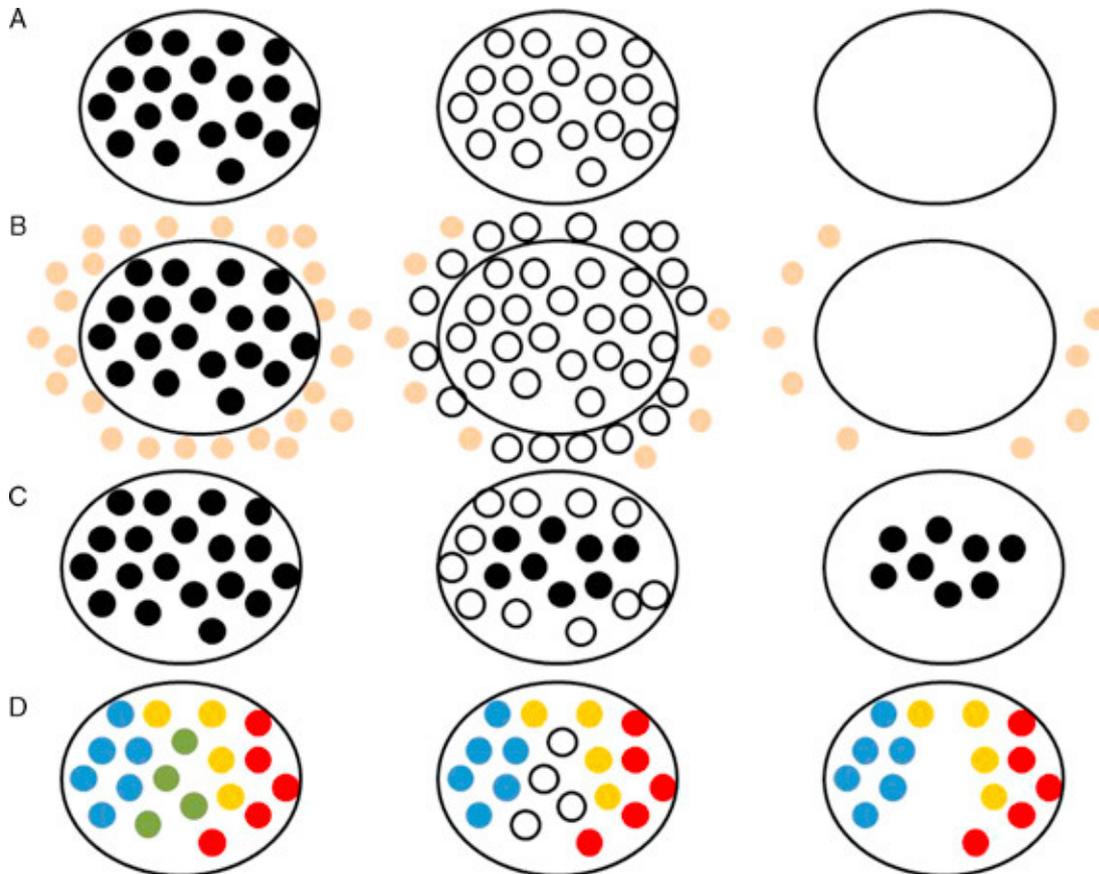


Figure 6 A, In this type of involution, specific melanocyte antigens would act as a target for the immune system, leading to massive, rapid destruction of the melanocytes. B, In halo nevi, the immune system will target modified antigens present on the melanocytes of the tumor, with variable involvement of melanocytes in the skin surrounding the nevus. C, Partial homogeneous depigmentation is probably initiated in cells lying at the periphery. D, Partial heterogeneous depigmentation is likely to be explained by modified antigens that only affect specific clones of melanocytes, which would be destroyed by the immune system.

would lie in the extent of involvement of melanocytes adjacent to the tumor cells.

Halo nevi lacking a visible halo have rarely been described in the literature. To date they appear only to have been diagnosed by histology. Our study shows that dermoscopy is also a useful diagnostic tool, since it allows identification of this variety of melanocytic nevi, which are probably underdiagnosed. Histologically, this type of nevus contains a dense band-like infiltrate in the dermis, with nests of nevus cells located in the central portion, characteristics that are similar to those of conventional halo nevi.¹³

Although the etiology and pathogenesis of halo nevi have yet to be clearly determined, inflammation appears to be a precursor for regression, which probably occurs through a mechanism involving CD8⁺ T-cell-mediated cytotoxicity. Activated T lymphocytes and antibodies against the cytoplasmic components of the melanocytes would be responsible for progressive destruction of the nevus cells, and this immune response would be maintained until the antigenic element that induced it was completely eliminated. As occurs in vitiligo, the halo would form due to the destruction of normal epidermal melanocytes.^{28,29}

Unlike in halo nevi, in which depigmentation occurs in the nevus and the surrounding skin, there is no effect on the surrounding skin of halo nevi that lack a halo. It is therefore to be expected that the antigens which induce the process of regression would only be found on the tumor cells. As in the case of halo nevi, cell-mediated and humoral immunity appear to be strongly implicated in the pathogenesis of the process.¹³ The time required for regression of halo nevi lacking halos also appears to be similar to that of conventional halo nevi.

Cases in which halos are only observed by dermoscopy would represent an intermediate situation in which the epidermal melanocytes surrounding the nevus would be affected but to a lesser extent than in conventional halo nevi.

Taken together, our results extend the current concept of halo nevi and suggest the existence of a spectrum of benign melanocytic lesions in which regression would occur via an immune response directed against antigenic modifications present in the melanocytes of the tumor, with varying involvement of melanocytes in the healthy skin surrounding the nevus. The main differences would lie in the degree of involvement of melanocytes in the surrounding skin

Table 2 Summary of the Main Characteristics of the Depigmentation Mechanisms Observed

Type of Depigmentation	Clinical Characteristics	Dermoscopic Characteristics	Possible Explanation
Complete rapid depigmentation	Complete involution Very rapid	Numerous melanophages Loss of previous pattern	Immune mechanism, cytotoxicity
Gradual complete depigmentation with no halo	Isolated lesions Complete involution Gradual and homogeneous Similar to halo nevus One or more lesions	Gradual homogeneous loss of pigmentation Absence of halo	Massive apoptosis Immune mechanism, cell-mediated and humoral Only cells of the nevus are affected, not melanocytes in the surrounding skin
Gradual total depigmentation with dermoscopic halo	Complete involution Gradual and homogeneous Similar to halo nevus One or more lesions	Gradual homogeneous loss of pigmentation. Subtle whitish halo	Immune mechanism, cell-mediated and humoral Affects melanocytes of the nevus and some in the periphery
Partial homogeneous depigmentation	Partial involution Homogeneous	Partial loss of pigmentation Homogeneous Begins at the edges of the nevus	Immune mechanism Process probably initiated in cells at the periphery
Partial heterogeneous depigmentation	Partial involution Heterogeneous	Partial loss of pigmentation Heterogeneous Presence of fibrosis	Immune mechanism Only certain clones of cells in the nevus are recognized as foreign

(Figure 4). Molecular studies will be required to identify the antigenic differences found both in the melanocytes of the tumor and in those present in the skin surrounding these types of nevi. Hypothetically, when the antigenic stimulus in the skin surrounding the lesion corresponds to the stimulus that initiates the immune response, its magnitude should determine the size of the halo. Nevertheless, individual differences in stromal reaction could dampen the immune response in some cases.^{6,19,30}

Finally, we also observed a group of lesions in which only partial regression occurred, either homogeneously or heterogeneously. In those cases in which heterogeneous depigmentation occurred, the phenomenon could be explained by the presence of antigenic modifications in specific clones of melanocytes, which would be destroyed by the immune system while leaving other cells in the lesion intact (Figure 5).^{6,19} Unquestionably, heterogeneous regression would be an indication for excision of the lesion.

In those cases in which partial homogeneous depigmentation occurs, the process was probably initiated in cells lying at the periphery (as shown by dermoscopy in most of our cases) (Figure 6). It is possible that melanocytes located in the central portion are able to develop escape mechanisms that protect against the immune response,^{6,19} or simply that the process of regression is much slower than in other cases.

Figure 7 summarizes the types of regression described. Table 2 also summarizes their main characteristics.

When interpreting the results of this study, it should be remembered that morphological variables were analyzed in isolation to identify associations with spontaneous

involution of melanocytic nevi without taking into account epidemiological characteristics of the patients (such as sun exposure, skin phototype, number of lesions, or medical history) that could also play a role in the mechanisms of depigmentation described.

Conclusions

Technical improvements in the monitoring of pigmented lesions allow previously unreported patterns of depigmentation to be described in melanocytic lesions.

The range of results obtained, both in terms of the time taken for depigmentation to occur and the morphological structures observed, suggests that multiple mechanisms may be involved in the regression of melanocytic nevi.

Female sex and the presence of melanophages and dermoscopic halos exhibited statistically significant associations with more rapid involution of pigmented lesions.

Vascular proliferation was the only variable that exhibited a statistically significant association with complete depigmentation of melanocytic nevi.

The presence of fibrosis was the only variable that displayed a statistically significant association with heterogeneous depigmentation of melanocytic nevi.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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