CONTROVERSIES IN DERMATOLOGY

Problems in Defining Melanoma Regression and Prognostic Implication

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Abstract. Between 10% and 35% of all melanomas show histological regression. That is, there is an area within the melanoma where the tumor retreats or disappears to be progressively replaced by fibrosis with presence of melanophages and variable degrees of inflammation, and increased vascularity. Such regression is generally considered an indicator of poor prognosis in melanoma, although a number of studies contradict this affirmation.

In this review, we summarize the leading articles about the influence of regression on melanoma prognosis. The results of these studies are very inconsistent, and so the prognostic significance of regression is somewhat controversial. We believe that some of these differences can be explained by differing criteria for regression and so we propose clear histological criteria to define early and sustained regression.

Key words: melanoma, regression, prognosis, sentinel lymph node, metastasis.

REGRESIÓN EN EL MELANOMA: PROBLEMAS EN SU DEFINICIÓN E IMPLICACIÓN PRONÓSTICA

Resumen. Entre un 10 y un 35% de todos los melanomas presentan regresión histológica, es decir, un área en el seno del melanoma en el que el tumor disminuye o desaparece y es sustituido progresivamente por fibrosis, con cantidades variables de melanófagos, inflamación y neovascularización. Aunque mayoritariamente se considera la presencia de regresión como un factor de mal pronóstico en el melanoma, existen varios trabajos que contradicen esta idea. En esta revisión resumimos los principales artículos publicados sobre la influencia de la regresión en el pronóstico del melanoma y encontramos resultados muy dispares, de modo que el significado pronóstico de la regresión en el melanoma es, a la vista de los trabajos publicados, cuando menos controvertido. Pensamos que parte de las diferencias encontradas se pueden deber a la disparidad en cuanto a los criterios utilizados para definir la regresión, y por ello proponemos unos criterios histológicos que aclaren los conceptos de regresión temprana y establecida.

Palabras clave: melanoma, regresión, pronóstico, ganglio centinela, metástasis.

Introduction

From 10% to 35% of all primary cutaneous melanomas show histologic regression,[1] meaning that a fibrous stroma progressively replaces the dermal portion at the center of the tumor. As this portion diminishes or disappears, tumor melanocytes become scarce or absent and melanophages, lymphocytes, and newly formed vessels appear. Inflammation predominates in the initial phases of regression as irregularly distributed lymphocytes and sometimes plasma cells infiltrate the tumor. Fibrosis has not yet started, but melanophages may already be present and vacuoles can usually be seen in the basal layer of the epidermis. There may be fissures at the dermal-epidermal junction and it is not unusual to find necrotic keratinocytes or melanocytes that appear as small, round eosinophilic structures (Civatte bodies) at the base of epidermal ridges. In later phases of regression, an atrophied epidermis will overlie the melanoma. Rete ridges will have been lost, some nonatypical melanocytes may have survived, and melanocytic hyperplasia may be observed. A few atypical melanocytes might also still be observed at the

junction. On rare occasions, epidermal hyperplasia, with hyperkeratosis and hypergranulosis, might be present. The papillary dermis is replaced by evident fibrosis in these late phases, and varying degrees of edema, neovascularization or vessel dilation may be found along with accompanying melanophages and a few lymphocytes.

Clinical signs of regression include areas of depigmentation within or around the melanoma. The color may be white, red, blue, or gray. Melanoma regression tends to occur in adult or elderly patients and is extremely rare in young people.

The prognostic significance of a histopathologic finding of regression in melanoma is much debated. Regression has traditionally been considered to augur a poor prognosis, as it cannot be ruled out that the initial thickness of the melanoma in the area of regression might have been superior to that suggested by the Breslow depth of the remaining tumor.[2] Nonetheless, in practice we have seen that regression only affects thin melanomas.[3-5] We might speculate that regression is responsible for thinning, but this seems unlikely given that regression is an unusual finding in a nodular melanoma.[5]

It may also be that regression is an immune response against the primary tumor, in which case it might have a certain protective effect.[6] In practice, however, the most widely held notion is that histologic regression predicts a poor outcome. Thus, although most hospitals practice sentinel node biopsy in melanomas with a Breslow depth of 1 mm or more, many also carry out this procedure when there is evident histologic regression, even if the Breslow depth is less than 1 mm. Debate continues, however, regarding the extension and characteristics of regression that should be present for it to be considered important: some authors require full regression of 50% of the dermal component or even two-thirds of the surface extension of the tumor.

Prognostic Implications of Regression

It has now been demonstrated that the status of the sentinel lymph node draining a melanoma is the most important prognostic factor in localized disease.[7,8] When our department studied the relationship between the presence or absence of spread to sentinel nodes and the clinical and pathologic characteristics of primary melanomas,[9] we were surprised to find that regression and a dense lymphocytic infiltrate were most often found in melanomas that had not spread to the sentinel node. Those 2 variables seemed to have a "protective" effect. However, differences that were statistically significant in the univariate analysis lost significance on multivariate analysis, in which only the Breslow depth and the mitotic index continued to be predictors. We must admit, however, that confounders may

have affected the results, given that more negative sentinel lymph nodes may have been included in the group with regression partly because sentinel node biopsy is ordered when the Breslow depth is less than 1 mm provided there is regression. In other words, a sentinel node biopsy would not otherwise have been ordered for a thin tumor. However, our results led us to question the criteria we used to define regression on the one hand and on the other to wonder about the truth of the assumption of poor prognosis associated with regression. We proceeded to review the literature in an attempt to discover reliable histopathologic criteria of regression in melanoma and also to determine the prognostic implications of the presence of regression according to real evidence rather than intuition or speculation. We selected the following studies because each included a clear histologic definition of regression and a large patient series in which the prognostic relevance could be assessed.

The most important study we retrieved was that of Morriset and coworkers,[10] who reviewed 1349 localized cutaneous melanomas, in 931 of which the status of the sentinel lymph node was established. These authors defined regression by the presence of a highly vascularized fibrous or edematous stroma with various degrees of inflammation replacing the primary tumor. Cases of partial regression, in which less than 50% of the total extension of the melanoma is occupied, were included along with cases of extensive regression in which more than half was replaced. They found that the sentinel lymph node was more often positive when there was no regression (18%) than when the tumor had regressed (10%). Even when cases were stratified by Breslow depth, the risk of finding a positive sentinel node was not greater for melanomas with regression than for those with no regression. They also observed that recurrences were more frequent in thin melanomas (Breslow depth less than 1 mm) without regression (6%) than in those with regression (1%). The only limitation affecting the interpretation of these results is the small number of patients (only 13) with extensive regression (on more than 50% of the surface extension of the melanoma tumor). In an earlier study similar to the previous one, but with fewer patients, Fontaine and coworkers[11] looked at the histologic characteristics of 97 melanomas in which the sentinel lymph node status was known. These authors likewise found no evidence of greater risk of metastasis to the node for patients with regression (observing positive nodes in 29% of both groups, with and without regression). A more recent study along the same lines is that of Kaur and coworkers,[12] who applied a much more detailed definition of histologic features of regression than that used in the previous 2 studies. They identified 3 phases of regression: first, reduction of the dermal melanoma; second, disappearance of the dermal melanoma but persistence of the tumor at the dermal-

epidermal junction; and third, disappearance of both the dermal and epidermal tumor. These authors then studied 146 melanomas with known sentinel lymph node status, including those with a Breslow depth greater than 1 mm, Clark level IV criteria, or regression. They found 17 positive sentinel lymph nodes, 13 of them in cases without regression and 4 in cases with regression, and concluded that regression is probably a predictor of good prognosis in melanoma. However, when Oláh et al[2] studied 134 patients with melanomas of a Breslow depth of 2 mm or less and known sentinel node biopsy status, they found that risk of metastasis was much greater for patients with melanomas with regression (64%) than for those without regression (15%). This is to say, they found that regression was associated with a much higher risk of metastasis to the sentinel node, concluding that thin melanomas with histologic regression should be considered candidates for sentinel node sampling, thus contradicting the findings of the 3 previously mentioned articles.

Before sentinel lymph node sampling came to be performed widely, a different approach was used to investigate the possible association between histologic regression and risk for metastasis in general and the effect on survival. Studies of this type included case series of thin melanomas in which a certain proportion had metastasized or ended in death. Authors usually looked at clinical or histopathologic factors, or both, that might be associated with a poor prognosis and that, therefore, would identify a subgroup of high-risk patients with thin melanomas. Gromet et al[13] observed that 22% of thin melanomas—with a Breslow depth of less than 0.76 mm or Clark level II—and regression (5 out of 23) metastasized, whereas only 2% of the tumors without regression (2 out of 98) did so. The differences were statistically significant. Guitar et al[14] reported similar findings in a more recent study comparing 43 thin melanomas with metastasis to 42 without metastasis. The patients were similar in age, sex, tumor location, and Breslow thickness. Forty-two of the metastatic melanomas displayed extensive regression (>50%) whereas only 7% showed partial regression (<50%). They observed extensive regression in only 5% of the melanomas that had not metastasized. Slingluff and coworkers[15] reviewed a series of 681 melanomas with a Breslow thickness less than 0.76 mm in search of clinical and histopathologic indicators of poor prognosis. They found that 40% of cases with metastasis also had "severe" histologic regression (defined as the presence of marked fibrosis and nearly complete absence of melanocytes), whereas regression was evident in only 17% of the melanomas that had not metastasized. Furthermore, in the subgroup of patients without metastasis (always with a Breslow thickness less than 0.76 mm) the percentage of disease-free survival at 5 years was 72% in the group with extensive tumor regression, compared with 94% in the

group without regression or with only slight or moderate regression (defined as isolated inflammation without fibrosis or with slight fibrosis in the papillary dermis, respectively). Ronan and coworkers[16] likewise found that regression was associated with a poor prognosis in a series of 103 melanomas with a Breslow thickness less than 0.76 mm. As only 7 of the patients in this series of 30 had regression affecting over 77% of the melanoma, and 6 of those patients died, the authors underline the importance of the percentage of tumor extension in regression. They also included areas of inflammation and scarring in the category of regression, only excluding cases with lymphocytic infiltrates but no evidence of destruction of melanocytes. Clark and coworkers[17] constructed a model to predict survival in stage I melanoma, finding that the presence of regression is a predictor of poor prognosis. Among the 90 patients with melanomas showing regression, the 8-year survival rate was 60%, in comparison with 77% survival in the 174 patients with melanomas without regression. Finally, Blessing and coworkers[18] studied thin melanomas (<1.5 mm) that had metastasized or led to death in comparison to tumors in patients who remained disease-free at 6 years (controls). These authors found that in 13 of 26 cases in which there was metastasis or the patient had died, tumor regression had been present, whereas this was the case in only 1 of the 40 control cases. They therefore concluded that regression is a factor of poor prognosis in this disease.

Other authors, however, have failed to find a statistically significant association between regression and prognosis in melanoma. Kelly et al[19] studied survival in a total of 844 patients with melanoma stratified in 3 groups according to Breslow thickness (<0.76 mm, between 0.76 and 1.5 mm, or >1.5 mm). Although 5-year survival tended to be slightly lower in all 3 strata if tumor regression was present, the differences were not significant. Moreover, the authors noted that differences might be attributable to sex and tumor location given that statistically significant associations were found between regression and male sex and a tumor location on the trunk. This study also called into question the earlier one by Gromet and coworkers,[13] given that the same patients at the Melanoma Clinic of the University of California at San Francisco, in the United States, were being reassessed 7 years later. The later study included more patients and the follow-up period was longer. The rate of metastasis fell to 7.2% among cases of thin melanoma with regression (vs 21.7% in the earlier study of Gromet et al) and rose to 3.8% in the group without regression (vs 2% in the earlier study). Similar results were reported by McGovern and coworkers,[20] who reviewed the cases of 353 patients with thin melanomas (up to 0.7 mm thick) to study the prognostic value of the presence or absence of regression. Unlike Kelly and coworkers, who only studied late-phase regression, these authors

included regression in early (inflammation) and later (scarring) phases, finding slightly more metastases from melanomas without regression (8% vs 5% for regressing and nonregressing tumors, respectively). Ten-year survival was practically the same in the 2 groups, however. This study extended and contradicted the results of a previous one at the same center in which regression was associated with a poor prognosis, particularly in men.[21] Brogelli and coworkers[3] also looked at the possible influence of the presence or absence of histologic regression, studying a group of 201 stage I melanomas. Like McGovern et al, they included cases of early- and late-phase regression. The differences in disease-free survival and overall survival in this series of melanomas with a Breslow depth of less than 0.76 mm did not reach statistical significance, although there was a trend toward better prognosis for tumors with regression. They were unable to assess melanomas with a Breslow thickness greater than 0.76 mm because there were too few tumors with regression in that category.

We did not attempt a systematic review of all the literature on melanoma and regression, although we did retrieve 2755 titles from the MEDLINE database using the search terms *melanoma* and *regression* using the PubMed portal in January 2009. We selected those we considered most interesting on the basis of the number of cases and a focus on histologic regression and its correlation with prognosis. We deliberately excluded studies with small series,[22,23] which are relatively unreliable for assessing prognosis, as well as those in which regression was only assessed clinically[24,25] and a study in which it was unclear whether or not histologic regression was investigated.[26]

In any case, the prognostic importance of regression in melanoma is clearly uncertain, at least based on the literature available to date. Even when only selecting the largest series, those including the largest number of patients, to analyze the significance of the presence or absence of regression,[10,19,20] we saw that this factor cannot be considered be predictive of poor prognosis in melanoma. Like many previous authors, we also pose the question of whether the marked differences in prognostic significance of regression found from one study to another might be due to differences in the definition of histologic regression. We refer not only to the minimum histologic criteria proposed for defining regression—which as we know is a dynamic process and therefore subject to changes in histologic findings depending on which phase is studied (see discussion of this below)—but also to the percentage of the diameter of the melanoma that is affected by regression. Cooper and coworkers[23] emphasized the importance of a lack of congruence in the definition of regression in different studies and criticized this, as they considered there is a group of melanomas in which it is possible to talk about probable regression or even doubtful regression that have not been included in any study. They

carried out a study in which cases were only categorized as regression if they observed 1 or more well-defined segments with marked reduction or complete absence of malignant melanocytes, replaced by varying degrees of fibrosis and inflammation inside the tumor. Incontinentia pigmenti, degenerated tumor cells, and telangiectasis might also appear, and there might sometimes be marked reduction or absence of changes at the juncture of the epidermis overlying the area of regression in comparison with the surrounding epidermis. These were not essential criteria, however. Although the authors only studied 48 melanomas with a Breslow thickness of 1 mm or less—for which reason we did not include this study in Table 1—they concluded that regression has no prognostic significance in most cases of thin melanoma.

The Concept of Regression and Its Definition

Kang and coworkers[27] described 3 successive phases of regression, each with distinct histologic features. In the early phase an area of the tumor can still be discerned in the papillary dermis and in the epidermis, with dense lymphocytic infiltrates erasing or replacing some nests of melanocytes. A few necrotic melanocytes may be present but fibrosis has not yet appeared. In the intermediate phase of regression, the melanoma is still recognizable but there is tumor reduction or disappearance in the papillary dermis and, sometimes, in the overlying epidermis, as malignant tissue is replaced by lymphocytes and fibrosis. Some telangiectases and melanophages will still be seen in this phase. Finally, late-phase regression would be characterized by an area of marked regression in a tumor that remains recognizable, or by complete disappearance of the tumor in this portion as it is replaced by dense fibrotic tissue and telangiectases and melanophages in varying numbers, with few or no lymphocytes under a thinned epidermis. The only histologic feature these authors consider to be absolutely necessary for a diagnosis of third-phase regression is fibrosis. When 2 dermatopathologists reviewed 50 melanoma cases, 44 of them with regression, in order to detect regression in a 2-mm circumscribed area on each slide and in the rest of the lesion, there was 96% agreement on whether regression was or was not present for the circumscribed area and 90% agreement for the remaining lesion. However, agreement fell to 86% (circumscribed area) and 66% (rest of the lesion) when the they were asked to assign cases to the 3 successive subgroups described. It therefore seems to be fairly impractical to subdivide regression into so many phases. To avoid controversy, many authors only take into consideration the last phase of regression, ignoring the earlier inflammatory phases. It may be most sensible to divide regression into only 2 phases, as discussed by Massi

Table 1. Summary of Studies on the Prognostic Implications of Melanoma Regression

Study	Regression = Poor Prognosis	Definition of Regression
Kaur et al[12]; 146 cases (all with known SLN status)	No, with respect to SLN positivity	3 phases of regression (partial dermal, total dermal, and dermal-epidermal; any extension)
Morris et al[10]; 1349 cases (931 with known SLN status)	No, with respect to either SLN positivity or recurrence	Late-phase regression (extension > or < 50%)
Fontaine et al[11]; 97 cases (all with known SLN status)	No, with respect to SLN positivity	Late-phase regression (not quantified)
Oláh et al[2]; 134 cases (SLN) MM < 2 mm	Yes, with respect to SLN positivity	Late-phase regression (percentage not specified)
Guitar et al[14]; 85 cases MM < 1 mm	Yes, with respect to ability to metastasize	Late-phase regression (poor prognosis for extensive regression, > 50%)
Brogelli et al[3]; 201 cases. MM, stage I	No, with respect to disease-free survival and overall survival	Early- or late-phase regression (not quantified)
Blessing et al[18]; 66 cases. MM < 1.5 mm	Yes, with respect to ability to metastasize and survival	Early- or late-phase regression (according to the definition of McGovern et al)
Clark et al[17]; 386 cases. MM, stage I	Yes, with respect to survival	Late-phase regression
Slingluff et al[15]; 681 cases. MM < 0.76 mm	Yes, with respect to ability to metastasize and disease-free survival	Early-, advanced-, and late-phase regression (poor prognosis associated with the last)
Ronan et al[16]; 103 cases. MM < 0.76 mm	Yes, with respect to ability to metastasize and overall survival	Early-, intermediate-, and late-phase regression (associated with a poor prognosis if regression in >77% of the tumor)
Kelly et al[19]; 844 cases. MM < 0.76 mm; 0.76-1.5 mm; > 1.5 mm	No, with respect to survival	Late-phase regression (percentage not specified)
Gromet et al[13]; 121 cases. MM < 0.76 mm	Yes, with respect to rate of metastasis	Late-phase regression
McGovern et al[20]; 353 cases. MM < 0.7 mm	No, with respect to survival	Early-phase regression (74% of cases) or late-phase (26%) regression (extension not specified)

Abbreviations: MM, malignant melanoma; SLN, sentinel lymph node.

and LeBoit[28] in their book on the histologic diagnosis of nevi and melanoma. These authors recognize an initial, or inflammatory, phase which they label "regressing melanoma" and a later, or scarring, phase they call "regressed melanoma." In this way they are able to study melanomas in early stages of regression but avoid too many subdivisions that might make interobserver agreement difficult to attain. Our proposal for the definition of regression is presented in Table 2.

Classifying the inflammatory phase as genuine regression might be a confounding factor in some studies, particularly given that the isolated inflammation (with no other histologic features present) seen in many melanomas has been shown to augur a good prognosis, especially if the lymphocytic infiltrate is dense.[17] Alongside the debate over the definition of regression, there is similar uncertainty as to what percentage

of the lesion should demonstrate regression in order to be considered meaningful. Some authors claim melanomas in regression must have 75% or more of the surface extension affected.[28] Others, however, include all cases with any degree of regression and simply subdivide the series into tumors with partial regression if less than 50% is affected or extensive regression if 50% or more is affected.[10]
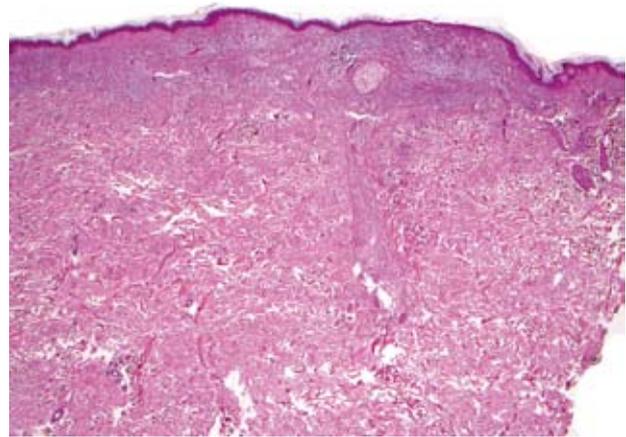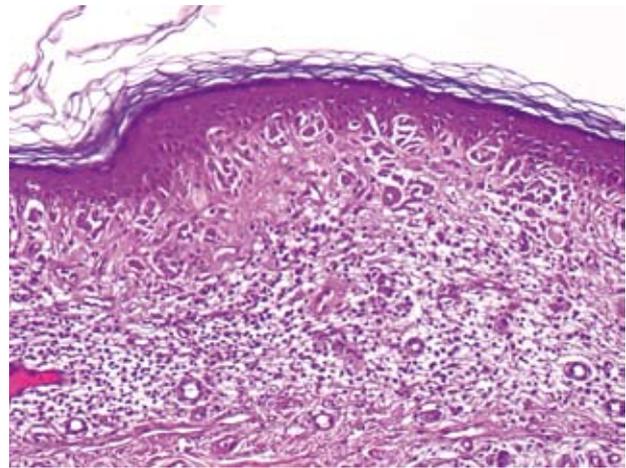
Conclusion

Many aspects of melanoma regression remain obscure. Regression clearly must begin with an accompanying inflammatory infiltrate, but the mere presence of inflammation within a melanoma is insufficient reason, according to our present knowledge, to consider that

Table 2. Proposal for Histologic Criteria for Defining Melanoma Tumor Regression

Reduction or disappearance of the melanoma within a circumscribed area of the tumor
Inflammatory infiltrate
Fibrosis
Melanophages
Increased vascularity
Epidermal thinning
Necrotic or apoptotic keratinocytes or melanocytes
Early-phase regression (Figures 1 and 2)
Focal reduction of the melanoma with an inflammatory infiltrate, with or without necrotic or apoptotic keratinocytes or melanocytes, and possibly other histologic criteria but excluding fibrosis
Established regression (Figures 3 and 4)
Frank focal disappearance of the melanoma or area of evident fibrosis, with or without melanophages, increased vascularity, or epidermal thinning

Figure 1. Low-magnification view of an early-regressing melanoma (hematoxylin-eosin, original magnification ×40).

Figure 2. Detail of Figure 1 showing small necrotic melanocytes nesting at the dermal-epidermal junction, with lymphocytic infiltration and increased dermal vascularity (hematoxylin-eosin, original magnification ×200).

a process of regression has started. An inflammatory infiltrate only indicates that an immune response to the tumor has occurred within the host. This response may or may not be effective in stopping the tumor from growing or achieving partial or complete regression. Many studies have found that dense inflammatory infiltrates, without other signs of melanoma regression, are clearly associated with a better prognosis.[29] We have also reported findings corroborating this association between dense infiltrates and an absence of metastasis to the sentinel lymph node.[9] It might be that the nature of inflammation in such cases is different from that in tumors that eventually regress. Alternatively, only the most aggressive melanocyte clones may be selected during the initial destruction associated with melanoma regression induced by the inflammatory infiltrate. In that case advanced regression would indeed imply a worse prognosis and, consequently, this would account for the highly contradictory results we have seen in the different studies reviewed here. In other words, the prognostic significance of regression would be different at the different phases in which it is assessed: regression would be favorable in initial phases and unfavorable in later ones. Nonetheless, we are merely speculating. Studies are needed to determine accurate criteria for regression, and if tumors in both early- and late-phase regression are studied, the prognostic value should be evaluated in each separately. It would also be interesting to characterize phenotypes of lymphocytic tumor infiltrates in both early- and late-phase regression, and to describe the immune microenvironment (cytokine profile, presence of plasmacytoid dendritic cells and their activation state) as the process of regression takes place. Studies have investigated the nature of inflammatory infiltrates inside halo nevi to clarify why these lesions, unlike melanomas, regress without fibrosis.[30] This research has brought forth interesting results, such as that mainly CD8 lymphocytes are found in Sutton nevi whereas melanomas contain CD4 lymphocytes. Different cytokine profiles have also been observed.

Conflict of Interest

The authors declare no conflicts of interest.
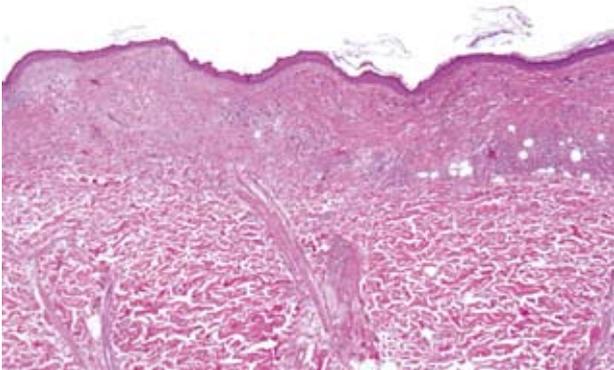
Figure 3. Low-magnification view of a melanoma tumor at an advanced stage of regression (hematoxylin-eosin, original magnification ×40).
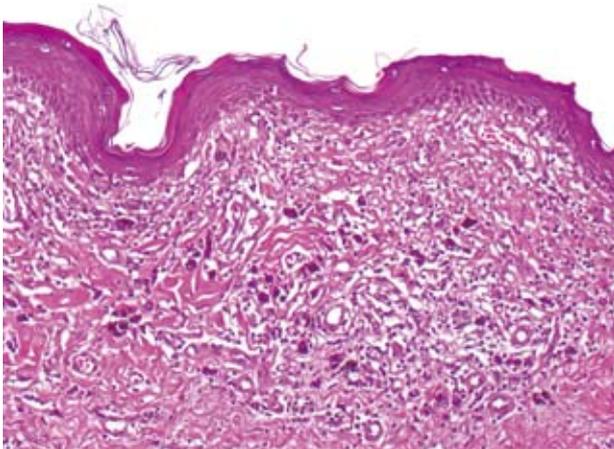
Figure 4. Detail of Figure 3 showing melanophages in abundance, with fibrosis and vascularization. There is scant lymphocytic infiltrate present and nothing remains of the melanoma (hematoxylin-eosin, original magnification ×200).

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