Completely regressed primary cutaneous melanoma – difficulties in diagnosis and classification

IRINA MĂRGĂRITESCU¹, AUREL DORU CHIRIȚĂ², FLORINA VASILESCU³

¹Laboratory of Anatomic Pathology, "Onco Team Diagnostic", Bucharest, Romania  
²Department of Dermatology, “Carol Davila” Emergency Central Clinical Military Hospital, Bucharest, Romania  
³Department of Pathology, “Carol Davila” Emergency Central Clinical Military Hospital, Bucharest, Romania

Abstract
Complete regression of primary cutaneous melanoma is a very rare phenomenon. Only 49 cases of well-documented completely regressed primary cutaneous melanoma have been reported to date. The clinical picture and histological findings may vary considerably. The presence of regional lymphadenopathy represents a necessary requisite for the diagnosis of completely regressed primary cutaneous melanoma. However, some cases lie outside these criteria and are difficult to diagnose and classify. Moreover, completely regressed melanoma is not specifically referred to in the current AJCC (American Joint Commission on Cancer) melanoma staging system. We report three cases of completely regressed primary cutaneous melanoma. One of the cases presented with unquestionable clinical and histopathological findings of completely regressed primary cutaneous melanoma, but without concomitant regional lymph node metastasis. As expected, this patient eventually developed nodal metastatic disease. An extraordinary case of a completely regressed melanoma that appeared in association with a congenital melanocytic nevus is also documented. This case revealed a unique type of regression that affected only the melanoma. The nevus was left undisturbed by the immunological response.

Keywords: melanoma, regression, metastasis.

Introduction
Spontaneous regression of cancer was initially defined by Everson and Cole in 1968 [1, 2], as the partial or complete disappearance of a malignant tumor in the absence of therapy that is capable of inducing anti-neoplastic effects or in the presence of therapy without significant impact on the disease [3, 4]. Spontaneous remission has been confirmed in many tumor types including renal cell carcinoma, head and neck cancer, neuroblastoma, lymphomas/leukemias, and melanoma. It is well known that melanoma is a highly immunogenic tumor as proved by the higher number of confirmed cases of spontaneous regression compared to other types of tumors. Melanoma demonstrates regression six times more often than other malignant neoplasms [5].

Although partial regression in primary cutaneous malignant melanoma occurs in 10–35% of cases [6] documentation of complete histological regression is rare, with an estimated incidence of 0.22–0.27% [7]. Almost all of the completely regressed melanoma cases reported in the literature presented with lymph node metastases in the area of drainage of the primary melanoma. Some cases presented with both nodal and visceral metastases. Also, there are patients with documented regressed primary melanoma which present with distant visceral metastases without regional lymph node involvement. These patients do not fulfill the current criteria of regressed melanoma, which allow for inclusion of only those patients with regional lymphatic involvement. Therefore, there are authors [8] who are questioning the actuality of the original criteria for defining completely regressed primary melanoma, which were set forth by Smith and Stehlin in 1965 [9]. These criteria are as follows: clinical or anamnestic evidence of a pigmented lesion situated in an area drained by the tumor-involved lymph nodes; the absence of any other possible primary cutaneous melanoma; the presence of the typical histological features of regression (attenuated epidermis, dermal melanophages, lymphocytic or chronic inflammatory infiltrate, reactive vascular proliferation, and fibrosis) at the site of the untreated presumed primary melanoma; and the absence of malignant melanoma cells confirmed by step-serial sections throughout the entire site of the presumed primary lesion.

There are only 49 cases of well-documented completely regressed primary cutaneous melanoma reported in the literature to date [4, 8–27].

We report three more additional cases of completely regressed primary cutaneous melanoma. One of the cases is a “classical” completely regressed melanoma, which presented with regional metastases. Other case presented with unquestionable clinical and histopathological findings of completely regressed primary cutaneous melanoma, but without concomitant regional lymph node metastasis. As expected, this patient eventually developed nodal metastatic disease. The last case is an extraordinary case of a completely regressed melanoma, which appeared in association with a congenital melanocytic nevus. Only the melanoma regressed, leaving the nevus unchanged. After a careful Medline/PubMed search, the authors were unable to find a well-documented report of a similar finding. Only two brief descriptions on this phenomenon were found by the authors in two book chapters devoted to the subject of regression of melanoma. Only one description
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is accompanied by photographic documentation and shows a partially but not completely regressed melanoma in association with a nevus [28, 29].

Materials and Methods

We searched our dermatopathology database for cases of completely regressed primary cutaneous melanoma over a period of six years (November 2007–December 2013). We used the clinical and histological criteria for completely regressed melanoma as established by Smith and Stehlin [9]. Cases lacking histological documentation or those that had only partial regression were excluded.

For all cases, paraffin blocks of routinely fixed and processed tissue were available for review and immunohistochemical study. Four-μm-thick serial sections were stained with Hematoxylin–Eosin (HE).

The immunohistochemical analysis was accomplished on 5-μm-thick sections, on poly-L-Lysine coated slides. The immunohistochemical technique used was an indirect biotin-avidin technique, based on polymerized Dextran conjugated with secondary antibody and horseradish peroxidase (DAKO, EnVision), using overnight primary antibodies incubation and DAB saline solution with 0.03% hydrogen peroxide as substrate. Both positive and negative controls were used. The following antibodies were used: S100 (polyclonal, 1:500 dilution, Dako), Melan A (A103 clone, 1:50 dilution, Leica) and HMB45 (HMB45 clone, 1:60 dilution, Leica). Previous immunohistochemical staining for pan melanoma cocktail (HMB45 + MART-1 + Tyrosinase) was available for the evaluation of the lymph node in Case No. 2.

Histopathological and immunohistochemical evaluation was performed with Leica DM2500 microscope and images were acquired using Leica DFC490 camera.

We were able to find five cases of completely regressed primary cutaneous melanoma. However, two cases were excluded from the study. One case of regressed plantar melanoma with ipsilateral inguinal metastatic lymphadenopathy was excluded due to lack of clinical follow-up. The other case was a metastatic melanoma to the right submandibular lymph nodes and parotid gland. The patient recalled having a pigmented lesion in the skin overlying the right submandibular region that faded away. However, we were unable to identify a cutaneous lesion that could have represented a primary regressed melanoma since the surgeon submitted only the lymph node and parotid gland tissue for histological evaluation. Hence, this case was interpreted as metastatic melanoma of unknown primary origin.

Results

Case No. 1

A 45-year-old woman presented with left-sided axillary lymphadenopathy of several months’ duration. Lymph node biopsy revealed a metastatic melanoma which was confirmed using S100 (Figure 1D), HMB45, and MART-1 immunohistochemical stains. Subsequently, complete left axillary nodal dissection was performed, which confirmed that there was no melanoma metastasis in any of the remaining nodes. Brain, thoracic, and abdominal computed tomography (CT) scans were unremarkable. The patient was referred to the dermatologist. A careful examination of the entire skin and mucosal surfaces with special focus on the lymphatic drainage area of the affected axillary nodes revealed a discrete “vitiligo-like” macule measuring 2 cm in diameter, confined to the left suprascapular region (Figure 1A). Upon detailed questioning, the patient recalled having had a pigmented lesion on that site for two or three years. The lesion spontaneously faded away few months before lymphadenopathy developed. The lesion was completely excised and the histological examination revealed an atrophic hypopigmented epidermis, loose fibroplasia of the papillary dermis, a sparse superficial perivascular lymphocytic infiltrate with a few dermal melanophages, and increased vascularity (Figure 1, B and C). Step sections throughout the entire lesion did not reveal any evidence of atypical melanocytic proliferation. The final diagnosis was completely regressed primary cutaneous melanoma on the left suprascapular region with left axillary lymphadenopathy (AJCC stage III disease). The patient was finally referred to the oncologist and interferon therapy was initiated. She died of metastatic disease 20 months after the diagnosis.

Figure 1 – (A) Case No. 1 presented with a “vitiligo-like” macule on the left suprascapular region. (B) Low-power view reveals subtle changes of regression in the papillary and superficial part of the reticular dermis, HE staining, ×12.5.
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Figure 1 (continued) – (C) High-power view shows loose, delicate fibroplasia and a sparse superficial perivascular infiltrate. Normal melanocytes repopulate the dermo-epidermal junction, HE staining, ×100. (D) S100 stains neoplastic melanocytes in the regional lymph node, ×200.

Case No. 2

A 45-year-old man presented with a 2.5/2 cm asymmetrical, variegated pigmented flat lesion with irregular borders on the left upper back that appeared four years previously (Figure 2A). Six months before surgery the patient has started to notice some change in the color of the lesion that was accompanied by pruritus. At the time of presentation, regional lymphadenopathy was not observed. Also, radiographic and ultrasound studies did not reveal any pathological findings. The lesion was completely excised and submitted for histological evaluation. The biopsy showed a large asymmetrical lesion with a flat epidermis, a thickened papillary dermis distended by marked fibrosis, increased vascularity, and a band-like infiltrate of lymphocytes and plasma cells, accompanied by numerous melanin-containing macrophages. No atypical melanocytic proliferation was observed, in spite of careful scrutiny of serial sections (Figure 2, B and C). Also, the immunohistochemical studies for S100, Melan-A, and HMB45 confirmed the absence of an atypical melanocytic proliferation. Six months later the patient developed an ipsilateral axillary lymphadenopathy. The patient underwent complete left axillary lymphadenectomy. The largest lymph nodes measured 3.6/1.6 cm and 3.4/1 cm, respectively. HE-stained sections revealed only a few dispersed faintly pigmented cells, which were difficult to interpret. However, pan melanoma cocktail (HMB45 + MART-1 + Tyrosinase) identified subcapsular microdeposits of melanoma (Figure 2D). A whole body CT-scan yielded negative results. The final diagnosis of completely regressed primary cutaneous melanoma on the left upper back with left axillary lymphadenopathy (AJCC stage III disease) was established. Adjuvant interferon therapy was initiated. He has remained disease free 15 months after the diagnosis.

Case No. 3

A 40-year-old man presented with recent onset of left fronto-temporal headache, dizziness and loss of equilibrium. A magnetic resonance imaging (MRI) study of the brain revealed a 2 cm space-occupying lesion in the left Sylvian fissure. The lesion was excised and the histopathological examination raised the suspicion of metastatic melanoma, which was confirmed by S100, Melan-A, and HMB45 immunohistochemical stains (Figure 3, D and E). The patient was referred to the dermatologist for the identification of the primary melanoma. A careful clinical examination of the patient revealed a right axillary lymphadenopathy and a suspicious melanocytic lesion situated on the periumbilical region of the ipsilateral flank. The lesion was well delimited and slightly unevenly pigmented with somehow irregular borders, measuring 1.2/0.6 cm. Part of the pigmented lesion seemed to have been disappeared, as it ended abruptly at its lateral margin. The pigmented lesion was in continuity with an irregularly contoured slightly erythematous macule, measuring 2/1.2 cm (Figure 3A). The patient easily recalled the lesion being present since childhood. He also noticed significant changes in size, shape and color in the last few years, with complete disappearance of the modified part in the last few months. History and clinical examination did not reveal any other primary lesion that could have represented the original lesion of melanoma. The patient underwent a complete right axillary lymph node dissection. The cutaneous lesion was excised in toto. Histopathological examination of the enlarged node revealed nodular aggregates of large atypical cells, which stained positive for S100, Melan-A, and HMB45 (Figure 3F). Nodal metastatic melanoma was diagnosed. Serial sections through the pigmented cutaneous lesion revealed a melanocytic proliferation located in both the dermis and the epidermis. The dermal component consisted of typical melanocytes with round to oval, small, monomorphous nuclei and scant cytoplasm. The cells were disposed in nests, strands and large aggregates at the level of the papillary and reticular dermis, with evidence of maturation and stromal response, typical for a congenital melanocytic nevus (Figure 3C). These findings were consonant with the history of melanocytic lesion presence since birth. The epidermal component consisted of a proliferation of relatively small melanocytes with slightly pleomorphic and hyperchromatic nuclei, disposed as solitary units and in small nests, predominantly at the dermal–epidermal junction. Few melanocytes were disposed as solitary units above the junction in the epidermis overlying the center part of the lesion. To some extent, these changes
are accepted and expected in the epidermis overlying a congenital melanocytic nevus. Step sections through the erythematous part of the lesion revealed a hypopigmented epidermis with loss of the rete ridges, and a scar-like fibroplasia over a broad zone in the papillary and superficial part of the reticular dermis. There was increased vascularity and a relatively abundant band-like lympho-plasmocytic infiltrate with only a few dermal melanophages. No atypical melanocytic proliferation was present in this part of the lesion (Figure 3B). The final diagnosis was completely regressed primary cutaneous melanoma in association with a congenital melanocytic nevus, with nodal and cerebral metastasis (AJCC stage IV disease). The patient was referred to the oncologist and chemotherapy was initiated. He is still alive five months after diagnosis.

The clinical features and histopathological findings are summarized in Tables 1 and 2.

Figure 2 – (A) Case No. 2 presented with an asymmetrical, variegated pigmented flat lesion with irregular borders on the left upper back. (B) Low-power view shows a large asymmetrical lesion with impressive changes of regression, HE staining, ×12.5. (C) High-power view reveals an abundant inflammatory infiltrate accompanied by numerous melanophages. No atypical melanocytic proliferation can be seen, HE staining, ×100. (D) Pan melanoma cocktail (HMB45 + MART-1 + Tyrosinase) identifies subcapsular microdeposits of melanoma, ×400.

Figure 3 – (A) Case No. 3 presented with a completely regressed melanoma in association with a nevus. (B) The regressed part of the lesion showed scar-like fibroplasia and increased vascularity, HE staining, ×50.
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Figure 3 (continued) – (C) The pigmented part revealed a typical congenital melanocytic nevus, HE staining, ×100. (D) This patient presented with brain metastasis. HE staining shows masses of very atypical and pleomorphic epithelioid cells, ×400. (E) These cells stained with Melan-A, ×200. (F) S100 stained metastatic deposits in the regional lymph node, ×200.

Table 1 – Summary of clinical information pertaining to three cases of completely regressed primary cutaneous melanoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Gender</th>
<th>Age [years]</th>
<th>Site</th>
<th>Size [cm]</th>
<th>Clinical aspects</th>
<th>Site of metastases</th>
<th>Therapy and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>45</td>
<td>Suprascapular region</td>
<td>2</td>
<td>“Vitiligo-like” macule</td>
<td>Axillary lymph nodes</td>
<td>Interferon therapy, DOD 20 months after diagnosis</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>45</td>
<td>Upper back</td>
<td>2.5</td>
<td>Variegated pigmented flat lesion</td>
<td>Axillary lymph nodes (developed after six months)</td>
<td>Interferon therapy, NED at 15 months</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>40</td>
<td>Periumbilical region</td>
<td>1.2/0.6</td>
<td>Erythematous macule</td>
<td>Axillary lymph nodes, brain</td>
<td>Chemotherapy, still alive five months after diagnosis</td>
</tr>
</tbody>
</table>

F – Female; M – Male; DOD – Died of disease; NED – No evidence of disease.

Table 2 – Microscopic features in three cases of completely regressed primary cutaneous melanoma

<table>
<thead>
<tr>
<th>Histological features</th>
<th>Case No. 1</th>
<th>Case No. 2</th>
<th>Case No. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal changes</td>
<td>Atrophic epidermis, hypopigmentation, normal melanocytic regrowth at the dermo-epidermal junction</td>
<td>Flat epidermis</td>
<td>Loss of rete ridges</td>
</tr>
<tr>
<td>Fibroplasia</td>
<td>Loose</td>
<td>Marked</td>
<td>Scar-like fibroplasia</td>
</tr>
<tr>
<td>Inflammatory infiltrate</td>
<td>Sparse superficial perivascular</td>
<td>Heavy, band-like</td>
<td>Relatively abundant, band-like</td>
</tr>
<tr>
<td>Melanophages</td>
<td>Very few</td>
<td>Abundant</td>
<td>Few</td>
</tr>
<tr>
<td>Vascularity</td>
<td>Increased</td>
<td>Marked increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Presence of atypical melanocytic proliferation</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Association with a preexisting lesion</td>
<td>No</td>
<td>No</td>
<td>Congenital melanocytic nevus</td>
</tr>
</tbody>
</table>
Discussion

The largest review devoted to the subject of completely regressed melanoma was published in 2005 by High et al. [8]. They found 34 well-documented cases of completely regressed primary cutaneous melanoma, which fulfilled the criteria established by Smith and Stehlin [9], and detailed four additional cases. Since this study was published, the literature has expended to include another 11 cases [10, 27, 30, 31]. Of the 49 cases published to date, 19 were female and 34 were male. The mean age at presentation was 49 years (range, 21–72 years). Lesions ranged from 0.2 to 3 cm in size. The back, especially the scapular region, was the most affected site, followed by the lower leg. Other reported sites were the head and neck region, the upper extremity, and the abdomen. Our cases also showed a similar male predominance, but a younger age at presentation (mean age 43 years). Scapula was also the preferred location in our cases.

In the great majority of cases, the lesions present as irregularly contoured macules or patches, but they can also present as papules. They can be hyperpigmented (black, shades of brown, blue), variegated, erithematous, angiomatoid, or hypopigmented (depigmented scar-like and vitiligo-like lesions) [8–27].

Histopathologically, completely regressed primary cutaneous melanoma is an exceedingly difficult lesion to diagnose, especially in the absence of metastatic disease and/or a history of regression of an atypical melanocytic lesion. The histological findings may be very impressive, with an abundant infiltrate of lymphocytes and plasma cells, accompanied by numerous melanophages arranged in a broad band in a thickened papillary dermis distended by marked fibrosis (Figure 2C). However, the findings can be very discrete, with a sparse superficial perivascular lymphocytic infiltrate with few if any dermal melanophages, and a loose, delicate fibroplasia of the papillary dermis (Figure 1C). There is an increase in vascularity, which gives the lesion the appearance of a scar (Figure 3B). An atrophic hypopigmented epidermis overlies the dermal changes. There is no evidence of an atypical melanocytic proliferation, either in the dermis or the epidermis. However, non-atypical melanocytes can be found at the dermo–epidermal junction and might represent melanocytic regrowth (Figure 1C) [32].

The presence of regional lymphadenopathy represents a necessary requisite for the diagnosis of completely regressed primary cutaneous melanoma, in accordance to the currently accepted criteria [9]. Indeed, almost all of the reported cases presented with lymph node metastasis in the area of drainage of the primary melanoma.

There are several reasons why a patient with a regressing/regressed melanoma does not seek medical attention. Location of the lesion is one of them. As many of these lesions are located on the back, they are difficult to be observed and followed by the patient. Moreover, regression is usually asymptomatic or accompanied by minor symptoms, which are not worrisome for the patient. In addition, some patients are quite relieved by the fact that the lesion disappeared and do not address the problem until signs and symptoms of metastatic disease appear [33, 34].

Another diagnostic difficulty arises with patients that present with indubitable historical, clinical and histological features of completely regressed melanoma but without concomitant regional lymphadenopathy or visceral metastases at the time of diagnosis. Our Case No. 2 stands proof to this. There is no clinical diagnosis other than melanoma in this particular case. Moreover, the histopathological aspects are quite characteristic for a completely regressed melanoma. Even in the absence of an atypical melanocytic proliferation, the large size of the lesion and the presence of a heavy band-like infiltrate of melanophages are strong indicators of a completely regressed melanoma.

The following question arises: which stage these patients should be classified as until lymphadenopathy or other signs of metastatic disease appear? According to the literature [8, 10, 29], some cases of completely regressed melanoma have no evidence of metastatic disease years after the diagnosis is made. One solution to solve this problem could be provided by the sentinel lymph node biopsy procedure. As regression has not been demonstrated to be strong independent predictor of melanoma outcome, there are no current recommendations for performing this procedure in cases of regressing/regressed melanoma [35, 36]. Moreover, completely regressed melanoma is not specifically referred to in the current AJCC melanoma staging system.

Cases of completely regressed primary cutaneous melanoma with anamnestic, clinical, and/or histological evidence of regression, which present with distant metastasis of melanoma without preceding nodal disease and cases of “occult” primary melanoma [10] are other controversial topics. Current criteria for complete regressed primary cutaneous melanoma allow for inclusion of only of those patients with regional lymphatic involvement. Therefore, High et al. propose modification of the current criteria to allow for cases of metastatic melanoma without regional nodal involvement, but with a clinical or anamnestic evidence of a regressed pigmented lesion with unambiguous histological evidence of regression [8].

Our Case No. 3 revealed an extraordinary finding regarding the phenomenon of melanoma regression. In this case, melanoma appeared in association with a congenital melanocytic nevus and only the melanoma underwent regression. The nevus was not affected by the regression. This phenomenon is hardly mentioned in the literature. The authors were unable to find a well-documented report of a similar finding, except for only two brief descriptions in two book chapters devoted to the subject of regression in melanoma [28, 29]. However, only one description is accompanied by photographic documentation. The histological pictures provided do not show a completely regressed melanoma but “a regressing and partially regressed melanoma that developed in the upper part of a previous nevus” [29].

We can only speculate on the mechanisms behind this phenomenon. It is well known that melanoma is a highly immunogenic tumor and the immune mechanism is most consistently associated with melanoma regression. Melanocytic nevi can also undergo complete regression and this phenomenon is seen even more often than in melanoma [37]. The histopathology of regressing mela-
noma differs in some respect from the histopathology of regressing nevus. The infiltrate accompanying regressing melanomas has a predominance of CD4+ T-cells, while the infiltrate of a regressing nevus has a predominance of CD8+ T-cells [38]. Also, fibrosis in regressing nevi is usually lesser than the one replacing a regressed melanoma [39]. These different histopathological and immunological features may reflect different pathological mechanisms involved in regression of nevi and melanomas. The type of regression in our Case No. 3 probably originated in an immune response to antigens expressed only by the malignant melanocytes and not by the benign ones. Certainly, the mechanisms are more complex, and further insight into this fascinating area is warranted.

Conclusions

Cases of indubitable completely regressed primary cutaneous melanoma that present without concomitant regional lymphadenopathy, like our Case No. 2, can pose difficulties in diagnosis and classification. Such cases defy current criteria for inclusion as completely regressed melanoma. Moreover, completely regressed primary cutaneous melanoma is not specifically referred to in the current AJCC melanoma staging system. Our Case No. 3 revealed a unique type of regression that affected only the melanoma developed in association with a congenital melanocytic nevus. The nevus was left undisturbed by the immunological response. Elucidation of the mechanisms behind this phenomenon could provide more insight into the fascinating area of tumor regression.

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**Corresponding author**

Irina Mărgăritescu, MD, DipRCPath, Laboratory of Anatomic Pathology, “Onco Team Diagnostic”, 27 Tony Bulandra Street, Sector 2, 021967 Bucharest, Romania; Phone +40721–671 649, Fax +4031–266 20 20, e-mail: irina.margaritescu@gmail.com

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