

Complete regression of primary melanoma associated with nevi involution under BRAF inhibitors: A case report and review of the literature

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Abstract. Melanoma is one of the most immunogenic tumors among human neoplasms, with numerous clinical observations of partial or completely regressed tumors. It is an aggressive tumor, with the greatest reported number of somatic mutations, BRAF mutation being the most common one. BRAF mutation is also present in a higher percentage in benign nevi. Complete regression of primary tumor and involution of nevi are, however, rare phenomenon in melanoma that can appear in relation with UV exposure, surgical trauma, target therapy in melanoma, pregnancy or host immune response to an evolving melanoma tumor. We present the case of a 58-year-old man with a completely regressed metastatic melanoma who developed a second melanoma with concomitant involution of papillomatous nevi under BRAF inhibitors treatment. In reviewed literature we have found 53 cases of completely regressed primary melanomas, neither of them reporting nevi involution. Complete regression of primary tumor can occur as an immune response to tumor progression. Nevi can involute under BRAF inhibitor therapy, but development of new malignant lesions under BRAF inhibitors is linked to BRAF wild-type. Documentation of primary tumor and dynamic changes in nevi highlight the need of a good clinical skin examination and increase the utility of baseline and sequential dermoscopy in melanoma.

Introduction

The regression of cutaneous pigmented lesions, benign or malignant, is a well-known phenomenon. The underlying mechanism is not completely understood, but factors like host immune system, UV radiation and trauma have been suggested. Melanoma is a multifactorial disease which demonstrates a very complex interplay between identifiable risk factors such as UV exposure, phenotype and genotype (1-3). According to Bastian (4) melanoma risk increase with the presence of multiple enlarged acquired nevi. Melanomas can be epithelium-associated or not and can show different age distribution and different relationships to UV exposure.

Melanoma is the tumor with the highest number of reported somatic mutations across human cancer types (5). The most common one, that occurs in ~50% of melanomas is BRAF mutation. His variant V600E is the most prevalent one and has been associated with younger age at diagnosis and location of primary tumor often on the trunk. BRAF V600E mutation is also present in 70% of benign nevi (6).

After the discovery of BRAF mutations, new targeted therapies like BRAF inhibitors have been introduced for the treatment of melanoma. Although well tolerated when used in clinical practice, they present some adverse events, cutaneous adverse events being the most common ones. Under BRAF therapy dynamic changes in melanocytic lesions like involution of nevi, changes in pigmentation and size and appearance of new melanomas have been described (7,8).

Although partial regression is relatively frequent and occurs in 10-35% of cases, spontaneous complete regression with documented histology is very rare and occurs only in 0.22-0.27% of all melanoma cases (9).

Case report

A 58-year-old man presented in the Department of Surgical in 2014 with a 6/4.5 cm subcutaneous tumor on the left lateral chest wall of several months duration. Excision of the lesion revealed a nodular, solid, dermo-hypodermic proliferation

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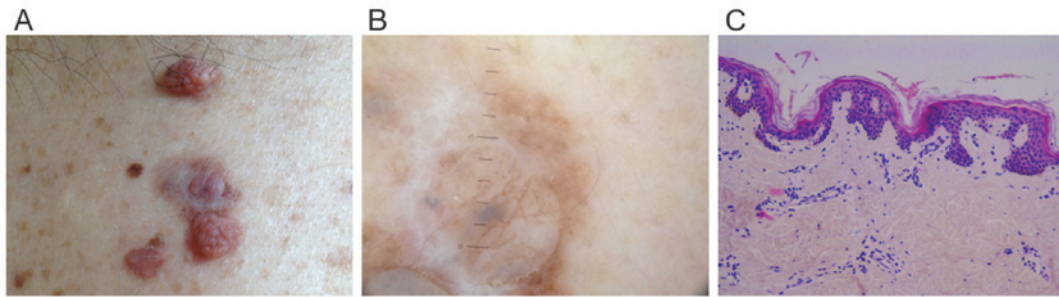


Figure 1. Clinical, dermoscopic and pathological presentation of a completely regressed melanoma. (A) Clinical presentation of the regressed melanoma showing a suspicious elevated lesion with grayish appearance. (B) Polarized dermoscopy of the regressed melanoma showing scar like depigmentation, pigmented globules and white transverse lighter bands. (C) Histologic analysis of the regressed melanoma showing flat rete ridges, lamellar fibrosis, increased vascularity, focal lymphocytic infiltrate with no melanocytic proliferation. Hematoxylin and eosin; magnification, x50.

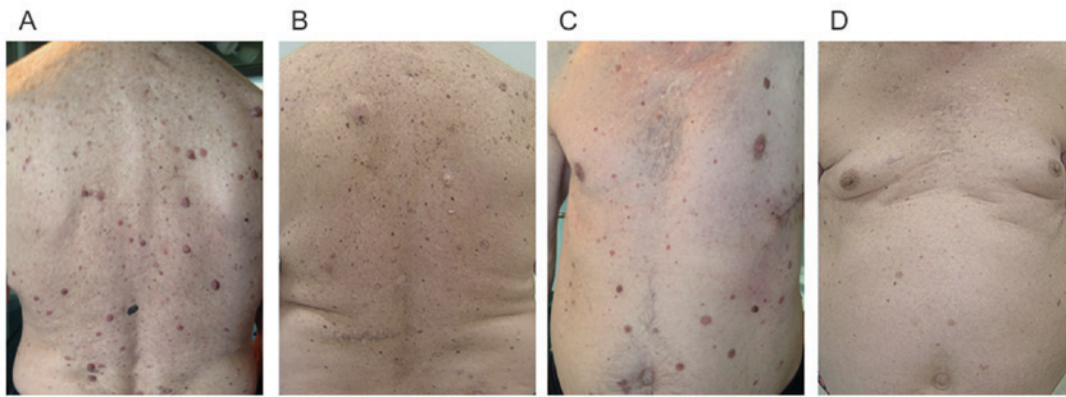


Figure 2. Clinical image of the patient before and after three years of BRAF therapy. (A) Baseline clinical evaluation of the back and (C) front before treatment. (B) Clinical evaluation of the back and (D) front after three years of BRAF inhibitors.

with large atypical round, polygonal cells, high number of mitosis (12/10 HPF) at pathological examination. It showed HMB45 and S100 positivity on immunohistochemical staining, concluding to an in-transit metastasis of unknown primary melanoma.

The clinical examination showed in the left lumbar region a suspicious elevated lesion, unknown to the patient, with grayish appearance (Fig. 1A) and multiple enlarged papillomatous nevi on the trunk (Fig. 2A). Polarized dermoscopy revealed scar like depigmentation, pigmented globules and white transverse lighter bands between two papillomatous lesions (Fig. 1B). The clinical and dermoscopic aspect of the lesion, the ipsilateral location indicated a regressed tumor, most likely the primary melanoma. He also presented left-sided axillary lymphadenopathy on clinical examination, confirmed by the CT scan. Surgery was performed on the suspicious lesion and axillary lymph nodes. Pathological examination of the regressed lesion showed flat rete ridges, lamellar fibrosis, increased vascularity, focal lymphocytic infiltrate with rare melanophages and no signs of melanocytic proliferation (Fig. 1C). Four of the 26 axillary lymph nodes removed showed tumoral cells with positivity for the HMB45 staining concluding to a lymph node melanoma metastasis. After surgery the patient showed rapid progression with detection of pleural metastasis on the CT scan. The patient was diagnosed with a stage IV melanoma with pleural metastasis and a completely regressed primary tumor. BRAF V600E mutation was detected in the subcutaneous lesion.

The patient started Vemurafenib treatment and showed partial response on the pulmonary CT scan after 3 months of therapy, but with numerous cutaneous adverse events: Multiple keratoachantomas, warts and changes in nevi color. One month later an atypical pigmented lesion (Fig. 3A and B) at the base of a papillomatous nevus that changed from baseline evaluation was excised. It turned out to be a 0.7-mm Breslow index superficial spreading melanoma with less than 1 mitosis/mm², a brisk lymphocytic infiltrate and no regression present (Fig. 3C). In the same time involution of some papillomatous nevi was observed, by diminished size and lighter color. After other three months Vemurafenib treatment was stopped because of insurance issues and another BRAF inhibitor was started, Dabrafenib, which became available for BRAF mutated melanoma patients in Romania at that time.

After three years of BRAF inhibitor monotherapy all his papillomatous lesions involuted (Fig. 2B and D). The patient had excellent systemic response with stable disease and no cutaneous or systemic side effects from BRAF inhibitor therapy. He is still under surveillance.

The present case is interesting because the association of completely regressed melanoma with metastases, and development of a new lesion under BRAF treatment.

Methods

We performed a search on PubMed using the terms 'primary melanoma', 'spontaneous regression', 'complete regression' to

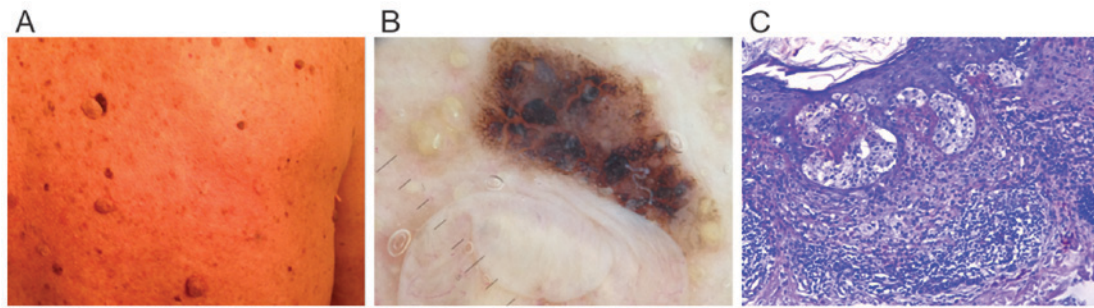


Figure 3. Clinical, dermoscopic and pathological presentation of the second melanoma under BRAF therapy. (A) Clinical presentation showing an atypical pigmented lesion at the base of a nonpigmented papillomatous nevus. (B) Polarized dermoscopy of the new melanoma showing flat eccentric pigmentation at the base of a nonpigmented papillomatous nevus. (C) Histologic presentation of the new melanoma showing nests of melanocytes with variable size and shape, pagetoid spreading, large cells with abundant eosinophilic cytoplasm with prominent nuclei. Hematoxylin and eosin; magnification, x100.

identify similar cases, restricting the papers to those published in English or French. Additional articles using the reference lists of the identified papers were noted. We found 50 cases of fully regressed melanomas which developed metastasis and three cases of initially confirmed melanomas with complete regression after partial incisional biopsy. Two cases of completely regressed melanomas with no confirmed distant metastasis in spite of extensive work up for two year follow-up were excluded from this study (10,11). Age, sex, location of the tumor and site of metastasis were noted for each case. We also recorded information about the diagnosis of the primary tumor, if it was retrospective or initial and pathologically confirmed. Dermoscopy of complete regressed melanomas was reported only in 10 cases (10-12).

We did not find in the literature any association between completely regressed melanomas and BRAF mutational status. Demographic and clinical information on the patients are summarized in Table I.

Discussion

Complete regression in melanoma is a rare event, being reported only in 0.22-0.27% of all melanoma cases (9). Clinical and pathological presentation of complete regressed melanomas have been extensively described through the literature. Dermoscopic evaluation of completely regressed melanoma is based only on a few case reports in the last 10 years (10-12). We did not find in the literature any association between completely regressed melanomas and BRAF mutational status. Nevi involution associated with melanoma was reported in the literature as a result of melanoma development followed by spontaneous regression of nevi or as a result of targeted therapy with BRAF inhibitors (35,36).

Clinical presentation of completely regressed melanoma. Completely regressed melanoma usually presents as a hypopigmented macule with pink or scar-like appearance. In rare cases, they can also appear as either hyperpigmented macules, or with remnants of pigmentation as blue-gray discolorations (11). Our review showed that all melanomas were epithelium associated (4), with a male predominance representing 62.26% of all cases and a median age of 48.5 years. Eighty-three percent of cases presented in relation with low UV exposure in non-chronic sun damaged skin (39,62%

involving the trunk and 43.39% involving arms and legs) and only 16.98% were located on chronic sun damaged skin (cervical), in relation with high UV exposure. The diagnosis of regressed melanoma was consistent with criteria of Smith and Stehlin and was retrospective in all cases except one (14). Three pathologically confirmed melanomas (two superficial spreading and one nodular melanoma) completely regressed after incisional partial biopsy of primary tumor (32-34).

Dermoscopic presentation of completely regressed melanoma. There are no established dermoscopic criteria for the diagnosis of complete regressed melanomas. In the literature we found only 10 reported cases of completely regressed melanoma with pathological confirmation and dermoscopic evaluation. Seven cases are reported by Bories *et al* (12) who showed that the most frequent dermoscopic features present in all cases were scar-like depigmentation and pink background. Eighty-six percent of patients in his serie had linear irregular vessels as defined by Argenziano *et al* (37) and remnants of pigmentation on dermoscopic evaluation. Forty-three percent of patients in Bories *et al* (12) serie had 'peppering' as defined by Zalaudek *et al* (38), white transverse lighter bands in polarized dermoscopy and globular vessels. High *et al* (11) recorded just 'peppering' and dusty blue-gray coloration on dermoscopic evaluation, performed in only two of his 38 melanoma cases reported. Pozzobon *et al* (39) found that 'peppering' is a dermoscopic feature frequently associated with regression in BRAF mutated melanoma. They stated that this can be considered a morphological consequence of BRAF mutated melanoma biological behavior.

Our case presented on polarized dermoscopy: Scar-like depigmentation, pigmented globules and white transverse lighter bands, features associated with regression (Fig. 1B).

Scar-like depigmentation and white transverse lighter bands on a pink background were observed in our patient also at the level of some regressed papillomatous nevi.

Pathological analysis of completely regressed melanoma. To confirm the diagnosis of a completely regressed melanoma is often very difficult. The diagnostic approach is almost always retrospective, with primary lesion being detected in metastatic stage (11). There is only one reported case of complete primary regressed melanoma detected before metastatic stage (30). According to Massi and LeBoit (40) the important issue is

Table I. Demographic and clinical information on the patients.

Author (year)	Ref.	No. of patients	Age (years)	Sex	Location of primary tumor	Sites of metastasis	Diagnosis of primary tumor
Dasgupta <i>et al</i> , 1963	(13)	2	35	M	Trunk	Ipsilateral cervical and axillary lymph nodes	Retrospective/skin examination/excisional biopsy
			49	M	Trunk	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
Smith <i>et al</i> , 1965	(14)	7	40	M	Trunk	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
			45	M	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
			29	F	Arm	Ipsilateral epitrochlear & axillary lymph nodes	Retrospective/skin examination/excisional biopsy
			27	M	Arm	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
			33	M	Cervical	Ipsilateral cervical lymph nodes	Retrospective/skin examination/excisional biopsy
			31	F	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
			44	M	Trunk	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
Todd <i>et al</i> , 1966	(15)	1	31	M	Cervical	Ipsilateral cervical lymph nodes	Retrospective/skin examination/excisional biopsy
Milton <i>et al</i> , 1967	(16)	1	53	M	Cervical	Contralateral cervical lymph nodes	Retrospective/skin examination/excisional biopsy
Cochran <i>et al</i> , 1970	(17)	2	41	M	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
			50	M	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
McGovern, 1975	(18)	1	57	M	Trunk	Supraclavicular and. cervical lymph nodes	Retrospective/skin examination/excisional biopsy
McDougal <i>et al</i> , 1976	(19)	1	72	F	Cervical	Ipsilateral cervical lymph nodes	Retrospective/skin examination/excisional biopsy
Whicker <i>et al</i> , 1980	(20)	1	53	F	Cervical	Ipsilateral cervical lymph nodes	Retrospective/skin examination/excisional biopsy
Pelligrini, 1980	(21)	1	50	F	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
Landthaler and Braun-Falco, 1981	(22)	2	41	M	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
			63	F	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
Kessler <i>et al</i> , 1984	(23)	1	40	F	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
Rampen and Meijer, 1985	(24)	1	37	M	Cervical	Brain	Retrospective/skin examination/excisional biopsy
Paul and Müllhofer, 1990	(25)	1	60	M	Trunk	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
Bottger <i>et al</i> , 1992	(26)	2	41	M	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
			63	F	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
Avril <i>et al</i> , 1992	(27)	7	40	F	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
			57	M	Trunk	Contralateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
			42	M	Trunk	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
			68	M	Arm	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
			52	M	Arm	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
			33	F	Trunk	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy

Table I. Continued.

Author (year)	Ref.	No. of patients	Age (years)	Sex	Location of primary tumor	Sites of metastasis	Diagnosis of primary tumor
			63	M	Trunk	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
Shai <i>et al</i> , 1994	(9)	1	53	F	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
Sais <i>et al</i> , 1994	(28)	1	57	F	Cervical	Ipsilateral parotid gland, brain	Retrospective/skin examination/excisional biopsy
High <i>et al</i> , 2005	(11)	4	68	M	Trunk	Ipsilateral axillary lymph nodes, brain	Retrospective/skin examination/excisional biopsy
			48	M	Trunk	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
			55	M	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
			21	F	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
Emanuel <i>et al</i> , 2008	(29)	2	40	F	Trunk	Regional lymph nodes NOS	skin examination/excisional biopsy first
			53	M	Cervical	Soft tissue NOS	Retrospective/skin examination/excisional biopsy
Bories <i>et al</i> , 2008	(12)	1	63	M	Trunk	Bilateral axillary lymph nodes	Retrospective/skin examination/Excisional biopsy
		2	38	F	Trunk	Ipsilateral sus-clavicular lymph nodes	Retrospective/skin examination/Excisional biopsy
		3	48	M	Foot	Ipsilateral inguinal lymph nodes and lung	Retrospective/skin examination/Excisional biopsy
		4	36	F	Cervical	Ipsilateral cervical lymph nodes	Retrospective/skin examination/Excisional biopsy
		5	63	M	Trunk	Ipsilateral axillary lymph nodes	Retrospective/skin examination/Excisional biopsy
		6	68	F	Leg	Ipsilateral inguinal lymph nodes, iliac nodes and bone	Retrospective/skin examination/Excisional biopsy
		7	78	F	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/Excisional biopsy
Margaritescu <i>et al</i> , 2014	(30)	3	45	F	Trunk	Ipsilateral axillary lymph nodes	Retrospective/skin examination/excisional biopsy
			45	M	Trunk	Ipsilateral axillary lymph nodes	skin examination/Biopsy first
			40	M	Trunk	Brain	Retrospective/skin examination/excisional biopsy
						Ipsilateral axillary lymph nodes	
Yamada <i>et al</i> , 2016	(31)	1	65	M	Leg	Ipsilateral inguinal lymph nodes	Retrospective/skin examination/excisional biopsy
Complete regression of primary tumor after incisional biopsy							
Dunn <i>et al</i> , 2008	(32)	1	39	F	Trunk	No distant metastasis	Initial partial biopsy (SSM 1.8 mm growth Breslow thickness, vertical fase) complete regression in 12 weeks (excision)
Menzies and McCarthy, 2015	(33)	1	62	M	Leg		Initial partial biopsy (SSM 0.7 mm Breslow thickness) complete regression in 18 months on punch biopsy
Khosravi <i>et al</i> , 2016	(34)	1	49	M	Trunk	Multiple metastasis	Initial partial biopsy (ulcerated NM 8 mm Breslow thickness) complete regression in 4 weeks (excision)

to differentiate between a completely regressed nevus and a completely regressed melanoma, and they proposed some criteria. In a regressed nevus the epidermis is normal, with preserved rete ridges, no tumor melanosis and a lymphocytic infiltrate that leaves the nevus undisturbed. In completely regressed melanoma the epidermis is rarely normal; it can be atrophic or irregularly hyperplastic. There is dermal fibrosis, sometimes with foci of tumor melanosis and a rich lymphocytic infiltrate. We can also note the presence of an ectatic superficial vasculature (Fig. 1C). A challenging situation is when, like in our case, regression involves a melanoma developed in a nevus (Fig. 1A and B).

Mutational status in completely regressed melanomas. Across human cancer type, melanoma is the tumor with the highest prevalence of somatic mutations (5). Bastian (4) found that BRAF mutational status was highly present in melanoma arising in non-chronic sun damaged skin, but it can be present in a small percentage in melanomas arising on chronic sun damaged skin or glabrous skin. The most common somatic mutation in melanoma is BRAF V600E, present in up to 90% of BRAF mutated melanomas (41,42). It is associated with younger age at diagnosis and primary lesion located often on the trunk (6). Partial regression, found in 10-35% of primary melanoma cases, is a common dermoscopic criteria associated with BRAF mutation (39). We present for the first time to our knowledge a case of completely regressed primary melanoma which harbors BRAF V600E mutation in the metastatic lesion and develops a second primary BRAF wild-type melanoma under BRAF inhibitors.

BRAF mutation is present in nevi in a higher percentage than in melanoma (70-82% in nevi vs. 50-60% in melanomas) (43). The introduction of BRAF inhibitor therapy in the treatment of melanoma improved response rates and overall survival in patients with melanoma but with nevi dynamic change as a common side effect. Nevi involution, especially for the papillomatous compound type, increasing in size and pigmentation for the flat lesions but also appearance of new BRAF wild-type melanoma were reported (36,44). This is due to paradoxical activation of MAPK pathway, especially with BRAF inhibitor monotherapy, also associated with resistance to therapy (45).

Spontaneous complete regression - possible mechanisms. A lot of factors leading to complete regression in melanoma were mentioned in the literature. There are exogenous factors like surgical trauma, vaccines (BCG, rabies), UV exposure, medication (BRAF inhibitors) and endogenous factors like pregnancy (32,33,46-49). The host immune system has an important role in tumor regression in melanoma. The occurrence of regression in primary tumor after lymph node or visceral metastases is highly related to an effective immune response against tumor cells (46,49).

In conclusion, we present for the first time to our knowledge a case of completely regressed BRAF V600E mutated melanoma which showed nevi involution and developed a new BRAF wild-type melanoma after therapy with BRAF inhibitors. On one hand, this case favors the role of BRAF mutation in melanoma immune pathogenesis, and on the other hand, shows the importance of clinical and dermoscopic follow-up

in melanoma patients. Our review shows that the diagnosis of completely regressed melanoma is very difficult, especially because there are no unifying concepts in assessing complete regression dermoscopically and pathologically.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GLE, AV, LU, RC were responsible for conception of the manuscript, data analysis and contributed to writing the manuscript. NB, CS, SS, EC, OF contributed to data acquisition and the critical revision of the manuscript for important intellectual content. All authors read and approved the final version of manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the 'Iuliu Hatieganu' University of Medicine and Pharmacy (no. 170/12.05.2014; Cluj-Napoca, Romania). All the participants gave their consent to be included in the study.

Patient consent for publication

The patient gave his written consent for image and data publication.

Competing interests

Rodica Cosgarea has received speaker fees from Roche Pharma and Novartis Pharma. Grigore Lavinia Elena has received a speaker fee from Novartis Pharma.

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