

Metástases Tardias de Melanoma Maligno Cutâneo Primário Fino

Regina Caldas¹, Filipa T. Almeida¹, Teresa Pereira¹, Inês Carvalho², Sofia D. Carvalho³, Celeste Brito¹ 

¹Department of Dermatology and Venereology, Hospital de Braga, Braga, Portugal

²Department of Neurology, Hospital de Braga, Braga, Portugal

³Department of Surgical Pathology, Hospital de Braga, Braga, Portugal

RESUMO – O melanoma maligno cutâneo é o terceiro tipo mais comum de cancro de pele, e a sua incidência tem aumentado. A taxa de mortalidade associada é considerável, devido ao seu fenótipo agressivo e grande capacidade de metastização, principalmente nos primeiros anos de seguimento. As recidivas tardias, mais de 10 anos após o diagnóstico, são raras. O principal fator de prognóstico do melanoma maligno cutâneo é a espessura tumoral, que também determina o tipo de abordagem. Os tumores finos, geralmente, têm bom prognóstico. Reportamos o caso de uma mulher de 66 anos com antecedentes de excisão de um melanoma maligno cutâneo primário fino, localizado no dorso, que se apresentou 16 anos mais tarde com uma inesperada recidiva, rapidamente progressiva e letal.

PALAVRAS-CHAVE – Melanoma; Metastase Neoplásica; Neoplasias da Pele; Recidiva.

Late Metastases from a Thin Primary Cutaneous Malignant Melanoma

ABSTRACT – Cutaneous malignant melanoma is the third most common type of skin cancer, and its incidence has been rising. Its mortality rate is considerable, due to an aggressive phenotype and great ability of dissemination, mainly in the first years of follow-up. Late recurrences, those presenting more than 10 years after diagnosis, are rare. The main prognostic factor of cutaneous malignant melanoma is tumor thickness, which also guides management. Thin tumors often have a good prognosis. We report a case of a 66-year-old woman with a history of excision of a thin primary cutaneous malignant melanoma of the dorsum, presenting 16 years later with an unexpected, rapidly progressing and lethal recurrence.

KEYWORDS – Melanoma; Neoplasm Metastasis; Recurrence; Skin Neoplasms.

INTRODUCTION

Cutaneous malignant melanoma (CMM) is the third most common skin cancer, nevertheless its mortality rates are the highest among cutaneous neoplasms. Despite the increasing prevention campaigns, the incidences rates of CMM continue to raise in the majority of developed countries, especially in older people.¹ Fortunately, the vast majority of cases are detected in an early stage, encouraging the concept of “cure” after adequate treatment. The aggressiveness of CMM is reflected in its capability to metastasize to locoregional or distant sites, particularly within first years of

follow-up. Despite being an unusual event, late recurrence, defined as occurring more than 10 years after diagnosis, has been reported and is mainly characterized by distant disease.²⁻⁵

CASE REPORT

A 66-year-old woman was admitted in 2018 for a progressive cognitive decline and weight loss, in the last two months. Her family described signs of short-term memory loss and less autonomy in daily tasks. They also reported the synchronous development of nodular cutaneous lesions on

Correspondência: Regina Caldas
Department of Dermatology and Venereology
Hospital de Braga
Sete Fontes - São Victor
4710-243 Braga, Portugal
E-mail: regina.mimed@gmail.com
DOI: <https://dx.doi.org/10.29021/spdv.78.1.1157>

Recebido/Received 2020/01/17	Aceite/Accepted 2020/02/24	Publicado/Published 2020/04/--
--	--------------------------------------	--

© Autor (es) (ou seu (s) empregador (es)) e Revista SPDV 2020. Reutilização permitida de acordo com CC BY-NC. Nenhuma reutilização comercial.
© Author(s) (or their employer(s)) and SPDV Journal 2020. Re-use permitted under CC BY-NC. No commercial re-use.

Caso Clínico

the trunk. The patient's cancer screening tests were recent and normal. Her medical history was remarkable for a cutaneous malignant melanoma of the right scapular region, managed through wide excision at an oncology referral center, in 2002. Records of the primary tumor's histopathological examination registered a superficial spreading melanoma, Clark level II, Breslow thickness of 1.00 mm, mitotic index of 3/mm², without ulceration. The patient maintained annual surveillance, with no signs of recurrence up to the last follow-up visit, in 2017.

Physical examination revealed cognitive impairment on mental exam and a slight facial asymmetry, with no other motor or sensitive deficits. Multiple erythematous-purplish nodules ranging in size from one to 2 cm were palpable on the dorsum (Fig. 1A), scalp and arms, some of them with a dome-shaped form and a central crateriform ulceration. Erythematous-yellowish, firm, pearly papules, with a waxy surface were evident in the abdomen and breasts (Fig. 1B). Total-body skin examination did not reveal any suspicious primary cutaneous lesion.



Figure 1 - Erythematous nodules distributed over the dorsum and an ulcerated tumour lesion on the left shoulder (A); erythematous papules, with a waxy surface, in the right hypochondrium (B).

Dermoscopy of papular lesions on the abdomen revealed dotted and linear irregular vessels, homogeneously distributed over a pink-yellowish background without pigment network (Fig. 2). However, regarding the patient's oncologic history and clinical presentation, these dermoscopic

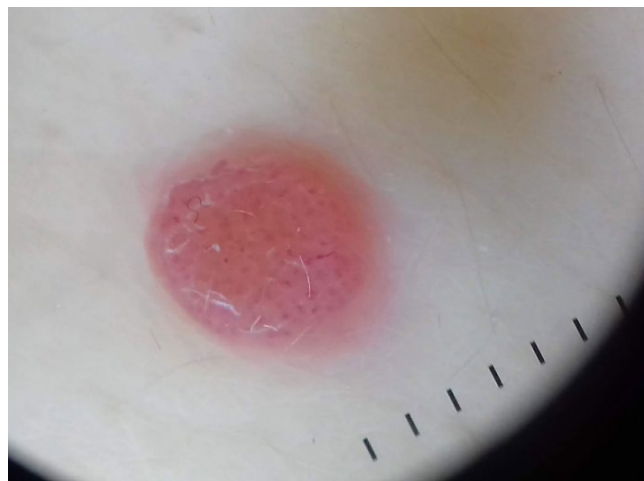


Figure 2 - Dermoscopy revealing dotted and linear irregular vessels, on a background with no pigment network (x10).

findings raised the possibility of a melanoma recurrence. A skin biopsy was performed, and the histologic examination showed a neoplasia with well-defined boundaries limited to the dermis (Fig. 3A), composed of proliferating atypical melanocytes without melanic pigment (Fig. 3B); intraepidermal neoplastic component was not observed, which was compatible with metastasis. The melanocytic origin was confirmed by the diffuse expression of MiTF (Fig. 3C) and Melan-A (Fig. 3D). Imaging studies revealed carcinomatous-like ascites, thoracic adenopathies, cerebral hemorrhages and meningeal tumor dissemination.

The patient was proposed for palliative care. Nevertheless, her neurological status rapidly deteriorated and she died three days after confirmation of the diagnosis.

DISCUSSION

The estimated incidence of late recurrences of CMM is 0.5% - 3.5%, according to the published series.⁶ These cases have been explained by "tumor dormancy", a period in cancer progression in which residual disease is present but remains asymptomatic. The mechanisms regulating this phenomenon are not fully understood, but they might rely on host and tumor factors, respectively immunosurveillance, and cell cycle arrest or preferential hematogenous spread.^{7,8}

One of the most important prognostic factors of CMM is tumor thickness.^{9,10} Our patient had been previously treated for a thin (≤ 1.00 mm) primary tumor, without ulceration. According to the 2002 American Joint Committee on Cancer (AJCC) staging criteria, the patient was classified as stage IA, and underwent wide excision without prior sentinel lymph node biopsy (SLNB).^{11,12} Retrospectively, SLNB was not advocated as a standard of care for CMM patients.¹³ It was actually incorporated for the first time in the AJCC staging manual in its 6th edition (2002), which stated that CMM pathologic stage IA did not require pathologic

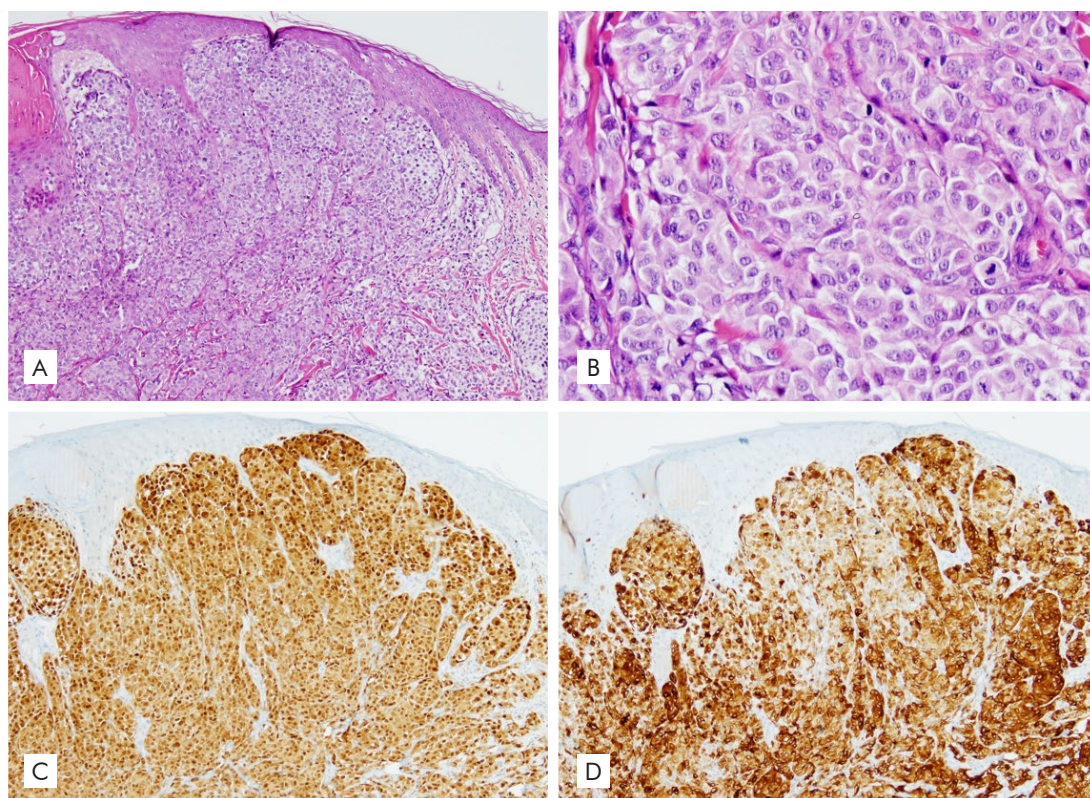


Figure 3 - Microphotograph showing a neoplasm composed of atypical melanocytes, exclusively located in the dermis (A, H&E x100), with abundant mitotic figures (B, H&E x400). Neoplastic cells positively stained for Mitf (C, x100) and Melan-A (D, x100).

evaluation of their lymph nodes.¹¹ The role of SLNB apart from clinical trials was questioned, since no impact on survival had been proved, neither the effectiveness of adjuvant therapy (interferon alfa) had been established.^{13,14} The subsequent approval of targeted therapies and immune checkpoint inhibitors revolutionized the management of CMM, by demonstrating a survival advantage in the adjuvant setting of sentinel lymph node positive patients. Thus, SLNB is now recognized as a standard staging procedure, in appropriate cases.^{9,15} For thin tumors, however, the prognostic value of SLNB results is still unclear, making it difficult to predict those that might progress.^{16,17} There are some reports identifying possible predictive factors for late recurrences from thin primary tumors, namely ulceration, younger age and mitotic rate.^{8,18} The last two predictors were noteworthy in our case.

One could argue that, given the long interval between initial tumor and recurrence, the second disease represented a new malignancy. Since total-body skin examination of the patient showed no evidence of a new primary cutaneous cancer, metastases would have to originate from an unknown second primary tumor. Reported cases of distant disease from an unknown primary are even rarer than late recurrences, with an estimated rate of 0.2%.¹⁹ Nevertheless, this possibility could never be ruled out.

Finally, cutaneous metastases of our patient presented

no melanotic pigment, which may have been a confounding element. Nonetheless, the dermoscopic findings, specifically the vascular pattern of lesions, raised the possibility of an amelanotic recurrence.²⁰ Melanoma metastases can display features different from the primary tumor, at the morphologic and genetic level.⁷ Therefore, besides the particular attention to new pigmented lesions in the wide excision scar and surrounding skin, physicians must also be aware of amelanotic recurrences, in which dermoscopy might be a useful tool for the differential diagnosis.²⁰

We herein report an unusual case of a CMM amelanotic recurrence, sixteen years after surgical resection of a thin primary tumor. This case highlights current recommendations about lifetime surveillance of CMM patients, including those with an expected good prognosis.^{9,10} New predictors and biomarkers are warranted to elucidate which patients with earlier stages might benefit from additional work-up or adjuvant therapy.

Presentations / Apresentações

This case has already been presented as an oral communication in the XVIII National Congress of the Portuguese Society of Dermatology and Venereology (30th November - 2nd December 2018, Lisbon, Portugal), and as a poster in the XXXVII Reunion Anual de Dermatologos Latinoamericanos (4-7th May 2019, Buenos Aires, Argentina).

Caso Clínico

Conflitos de interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do tutor legal para publicação obtido.

Proveniência e revisão por pares: Não comissionado; revisão externa por pares.


Conflicts of interest: The authors have no conflicts of interest to declare.

Financing support: This work has not received any contribution, grant or scholarship.

Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and peer review: Not commissioned; externally peer reviewed

 ORCID

Regina Caldas

<https://orcid.org/0000-0002-6921-7916>

Filipa Tavares Almeida

<https://orcid.org/0000-0001-6561-5338>

REFERENCES

- Whiteman DC, Green AC, Olsen CM. The Growing Burden of Invasive Melanoma: Projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031. *J Invest Dermatol.* 2016;136:1161-71. doi: 10.1016/j.jid.2016.01.035.
- Vukomanovic P, Karanikolic A, Stefanoviic M, Mihajlovic D, Djordjevic B, Kutlesic R. Late recurrence of malignant melanoma mimicking ovarian malignancy. *Eur J Gynaecol Oncol.* 2010;31:590-2.
- Mansour D, Kejarawal D. It is never too late: ultra-late recurrence of melanoma with distant metastases. *BMJ Case Rep.* 2012;bcr0120125474. doi: 10.1136/bcr.01.2012.5474.
- Ruiz-Cuesta P, Hervás-Molina AJ, Villar-Pastor CM, Jurado-García J, Barrera-Baena P. Metastasis gastrica tardia de melanoma cutaneo. *Gastroenterol Hepatol.* 2014;37:564-5. doi: 10.1016/j.gastrohep.2014.01.009.
- Osella-Abate S, Ribero S, Sanlorenzo M, Maule MM, Richiardi L, Merletti F, et al. Risk factors related to late metastases in 1,372 melanoma patients disease free more than 10 years. *Int J Cancer.* 2015;136:2453-7. doi: 10.1002/ijc.29281
- Hansel G, Schönlebe J, Haroske G, Wollina U. Late recurrence (10 years or more) of malignant melanoma in south-east Germany (Saxony). A single-centre analysis of 1881 patients with a follow-up of 10 years or more. *J Eur Acad Dermatol Venereol.* 2010;24:833-6.
- Damsky WE, Theodosakis N, Bosenberg M. Melanoma metastasis: new concepts and evolving paradigms. *Oncogene.* 2014;33:2413-22. doi: 10.1038/onc.2013.194.
- Faries MB, Steen S, Ye X, Sim M, Morton DL. Late recurrence in melanoma: clinical implications of lost dormancy. *J Am Coll Surg.* 2013;217:27-34. doi: 10.1016/j.jamcollsurg.2013.03.007.
- Swetter SM, Tsao H, Bichakjian CK, Curiel-Lewandrowski C, Elder DE, Gershenwald JE, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol.* 2019;80:208-50. doi: 10.1016/j.jaad.2018.08.055.
- Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics - Update 2019. *Eur J Cancer.* 2020;126:141-58. doi: 10.1016/j.ejca.2019.11.014.
- Balch CM, Buzaid AC, Soong SJ, Atkins MB, Cascinelli N, Coit DG, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol.* 2001;19:3635-48.
- Brochez L, Verhaeghe E, Sales F, del Marmol V, Deraemaecker R, Vossaert K, et al. Current guidelines in melanoma treatment. *Melanoma Working Group of Gent and Bordet. Dermatology.* 2000;200:160-6.
- Dunn CL, Zitelli JA. Standards of care for patients with malignant melanoma. *J Am Acad Dermatol.* 2000;43:155-8.
- Kanzler MH, Mraz-Gernhard S. Primary cutaneous malignant melanoma and its precursor lesions: diagnostic and therapeutic overview. *J Am Acad Dermatol.* 2001;45:260-76.
- Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2019. *Eur J Cancer.* 2020;126:159-77. doi: 10.1016/j.ejca.2019.11.015.
- Kyrgidis A, Tzellos T, Mocellin S, Apalla Z, Lallas A, Pilati P, et al. Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma. *Cochrane Database Syst Rev.* 2015;5:CD010307. doi: 10.1002/14651858.CD010307.pub2.
- Stiegel E, Xiong D, Ya J, Funchain P, Isakov R, Gastman B, et al. Prognostic value of sentinel lymph node biopsy according to Breslow thickness for cutaneous melanoma. *J Am Acad Dermatol.* 2018;78:942-8. doi: 10.1016/j.jaad.2018.01.030.
- Gimotty PA, Guerry D, Ming ME, Elenitsas R, Xu X, Czerniecki B, et al. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. *J Clin Oncol.* 2004;22:3668-76.
- Tsao H, Cosimi AB, Sober AJ. Ultra-late recurrence (15 years or longer) of cutaneous melanoma. *Cancer.* 1997;79:2361-70.
- Pizzichetta MA, Talamini R, Stanganelli I, Puddu P, Bono R, Argenziano G, et al. Amelanotic/hypomelanotic melanoma: clinical and dermoscopic features. *Br J Dermatol.* 2004;150:1117-24.