Desmoplastic melanoma

Melanoma desmoplástico

ABSTRACT

First described in 1971 by Conley and colleagues, desmoplastic melanomas represent less than 4% of cutaneous melanomas. It is a distinctive and uncommon variant characterized by a spindle cell fibrous tumor of collagen-forming cells, isolated by dense fibrous matrix. Desmoplastic melanomas are frequently misdiagnosed, mainly due to their similarity to other fibrous neoplasms. A review of about 600 reported cases unexpectedly revealed the pigmented clinical presentation of a deep and fibrous nodule that is classically associated with a precursor lesion. The ability to recognise this lesion's characteristics is very important, due to its recurrent behaviour and subsequent need for a specialized surgical approach.

Keywords: melanoma; neoplasm recurrence, local; gp100 melanoma antigen; melanoma-specific antigens.

RESUMO

Descrito pela primeira vez em 1971 por Conley et al., o melanoma desmoplásico (MD) representa menos de 4% dos melanomas cutâneos. Trata-se de variante distinta e incomum, que se caracteriza por tumor fibroso de células fusiformes liberadoras de colágeno em matriz fibrosa. Seu diagnóstico é propenso a erro, principalmente por sua semelhança com outras neoplasias fibrosas. Em cerca de 600 casos descritos na literatura, observou-se apresentação clínica não pigmentada, profunda e de aspecto fibroso, associada à lesão precursora. Seu reconhecimento é de grande importância devido ao comportamento de caráter recidivante e à consequente necessidade de abordagem cirúrgica distinta.

Palavras-chave: *melanoma; recidiva local de neoplasia; antígeno gp100 de melanoma; antígenos específicos de melanoma.*

First described in 1971 by Conley and colleagues, desmoplastic melanoma (DM) represents less than 4% of cutaneous melanomas.[1,2,3] It is an uncommon and distinct variant, which is characterized by a collagen-forming fibrous tumor of fusiform cells, isolated in a dense fibrous matrix. DM often presents neurotropism, a growth pattern similar to that of neuroma, and neural differentiation, which is also a neural transformation phenomenon.[1,4,5]

More than 600 cases have been reported to date.[1] Mainly due to their similarity to other fibrous neoplasms, DMs can be easily misdiagnosed.[1,6] However, it is of paramount importance that it is correctly diagnosed, due to its particular development and the need for a specialized surgical approach.[1,7]

Since it was first described, evidence has accumulated that DM behaves differently from other forms of melanoma; it recurs and is frequently associated with a precursor lesion.[1-3,8]

The condition's pathogenic mechanism is still unknown. However, ultrastructural studies greatly increased the understanding of its histogenesis. In 1983, premelanosomes were observed

Continuing Medical Education

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by From and colleagues in fibroblast-like cells, in addition to a predominant positivity for protein S-100, among other melanocyte differentiation antigens such as Tyrosinase, Melan-A, "Microphtalmia transcription factor" and gp100. Those finding provided the basis of the theory of melanocyte differentiation in fibroblastic phenotypes, known as "adaptive fibroplasia." [1]

Desmoplasia is believed to develop from the induction of collagen synthesis by fibroblast proliferation, which results from the interaction between the tumor and the extracellular matrix, through the action of tumor cytokines. Nonetheless, it is known that the melanoma cells synthesize collagen, and therefore contribute to the formation of desmoplastic stroma.[1]

An experimental study of the growth of melanoma cells with desmoplasia induced by the injection of human melanoma cell lineages (UCT-Mel7) in mice displayed five successive stages: initial limited growth, stasis, regression, quiescence, and rapid final progression with fast and lethal tumor growth. An inverse correlation between desmoplasia and the growth rate was also observed in the study.[5,8]

Using electron microscopy, it was possible to observe features similar to those of DM's fusiform melanocytes' fibroblasts. Otherwise, there are no specific ultrastructural characteristics of DM.[1,8]

From an analysis of about 600 cases described in the literature, it could be inferred that DM is prevalent in males (64-67%) with chronic photo-damage aged 11-92.[1,6,9] The mean age group described in the literature ranges from 59-62.8.[1,5,9] and the condition occurs more often in the cephalic segment (41.5-75%),[1,6,8,9] yet it can also affect the mucosal and acral regions.

DM is clinically characterized by a nodule, papule, or firm plaque, apparently fibrous, which can reach up to the dermis or subcutaneous tissue. (1) In most cases (44.3-73%), there is no pigmentation but there is a precursor lesion – which in 42% of cases is lentigo maligna.[1,6,8,9]

Delayed diagnosis, or even misdiagnosis, of DM is not uncommon, given that it presents characteristics similar to those of other fibrous lesions. Among malignant conditions, carcinoma, fibrosarcoma, and amelanotic melanoma are the most frequent misdiagnoses of DM. Of benign lesions, fibromatosis, dermatofibroma, and melanocytic nevus represent the most misdiagnoses.[1,6]

This malignant melanoma variant most often develops in association with a precursor lesion – which in some studies was linked to an increased survival rate (86%). [8] A higher incidence of DM can be observed in lentiginous-type melanomas, with a high frequency of melanomas in situ that follow a lentiginous intraepidermal growth pattern, such as lentigo maligna, which occurs in 42-56% of cases , compared to 4% of all cutaneous melanomas.[1,2,6,8] Likewise, an association with superficial spreading melanomas was observed: acral lentiginous melanomas occurred in 2.7% of cases,[3] and in 15-20% of the reported cases, no associated precursor was found entailing the phenomenon was regarded as being "new." [6,8] Explaining this finding requires questioning the occurrence of ulceration, regression, or even inadequate collection of material for examination, all of which could hide such a lesion.[8] Another hypothesis is that the histopathogenesis occurs from a dermal melanocyte, a cell derived from the neural crest, or even from a hair follicle.[10]

Although dermoscopic aspects have not yet been established, Debarbieux and others have recently described characteristics found in six DM cases. 11 Criteria for melanocytic lesions were observed in only 50% of the sample, multiple coloring was observed in 5 (out of 6) lesions, signs of regression similar to scarring in 100%, and "peppering" appearance in 50%. Vascular structure abnormalities (an indication of melanoma) were observed in 5 lesions, linear-irregular vessels in 5, and milky-red areas in 3 lesions. Moreover, the presence of a pigmented network was noticed only when there was association with conventional melanoma, in addition to the absence of globules and striae, possibly due to the non-pigmentary appearance of the lesions assessed. The authors called attention to signs of regression, such as scarring and "peppering" areas, and vascular patterns such as milky-red areas and linear-irregular vessels, as main features of DM.

The most commonly observed anatomic-pathologic features of DMs were atypical fusiform cells' fascicles that penetrated the dermis and subcutaneous tissue, arranged in varying patterns of desmoplasia, neurotropism, and neural differentiation.[8] There was a predominantly pink hue, collagenous stroma, and a fusiform cells tumor of diffuse infiltrative pattern, with expansion into the subcutaneous fibrous septa. (1) Dense intratumoral lymphocytic aggregates and in situ superficial melanoma can be frequently observed.[1]

Nonetheless, the DM cases described in the literature present a wide range of histological features, which vary from a predominantly fibrous appearance to displaying schwannian characteristics. A variable degree of density and cellular atypia was observed, ranging from a scar-like paucicellular appearance to that of the sarcomatous pattern of a fusiform pleomorphic melanoma. There is also a significant heterogeneity in the tumor's phenotype regarding its fusiform and epithelioid cellularity proportions, in addition to a variable fibrous component.[1]

Although many authors have described this specific form of melanoma, there is no consensus regarding the diagnostic criteria yet. DM can be classified in grades according to its fibrocellular components (Grade 1: > 50% fibrous, Grade 2: fibrous = cellular, Grade 3: cellular > fibrous). (10) In the literature there are diagnosed lesions with a minimum of 1/3 fibrous compromise;[9] or with a 50% of desmoplasia;[7] or even any degree of dysplasia.[3,7,9] Desmoplastic compromises greater than 90% were categorized as "pure histology" and correlated to a better prognosis.[9]

The classification of the lesion into pure and combined DMs – the latter defined as lesions with a desmoplasia component less than 90% that present a densely cellular tumoral focus and an absence of fibrosis. In addition, the nucleus of combined DMs tends to be widened, hyperchromatic, irregular, and have higher mitosis rates – and survival rates are lower.[6,12] More recent studies have established differences regarding the greater involvement of the lymph nodes in combined DMs (22% X 0%).[13]

The myxoid DM variant has also been described, which is characterized by the presence of myxoid material in the fibrous stroma.[14] The deposition of mucin in those cases was associated with a worse prognosis.[1,10] Likewise, the neurotropic variant of DM – which presents a growth pattern similar to that of the neuroma and tends to involve prominent infiltration of peripheral nerves (called neurotropic desmoplastic melanoma, or NDM) – displayed a more aggressive behavior.[4,10,14]

It is of paramount importance, however, to note that not all neurotropic melanoma are necessarily desmoplastic,[1] a fact that calls into question the true aggressiveness of NDMs, since they can be diagnosed with or without the desmoplastic component and cause different patterns of neural damage. Also, they might be limited to a single focus of perineural invasion, present schwannian differentiation and extend into neural transformation.[3,5]

Regarding the associated histological parameters, in most cases DM presents a thickness of more than 1 mm at diagnosis, reaching up to, on average, 2.5-6.5 mm.[2,6,8,9,15] DMs generally penetrate to the reticular dermis and are classified as 89-98%, Clark levels IV-V.[2,6,8,9] Ulceration is present in 18-20% of cases and in general there is a presence of lymphocytic infiltration with a tabby pattern.[2,4,8,9] The presence of both criteria was associated with a worse prognosis.[8] Endo or perineural involvement was found in 30-40% of patients.[6,9] Regression, determined by fibrosis of the papillary dermis, blood vessels ectasia, and epidermal thickening, was detected in 15% of cases.[8] Regarding the number of mitoses found, more than half of participants in the study carried out by Carlson and colleagues had more than one mitosis per field; this level was suggested as a criterion for a worse prognosis.[8]

DM presents a positive immunohistochemical profile for various antibodies, including the S100 protein, which, although not specific to DMs, is present in 100% of the studies. Another high sensitivity antigen studied more recently – the great molecular weight melanoma-associated antigen (HMW-MMA) – figured as a reagent in over 85% of DM cases.[13] In general DMs are negative for other melanocytic differentiation antigens, such as HMB45, Gp100, Melan-A/Mart-1, Tyrosinase and microphthalmia transcription factor., reacting less frequently to SMA, Desminin, XIII A factor, laminin, and type IV collagen.[1] Particularly in the neurotropic variant of DM, reactivity with vimentin, neuron-specific enolase, and EMA are verified, illustrating the neural differentiation suggested by the histology.[8] The antigen associated with HMW melanoma presents greater sensitivity than HMB-45 and Mart-1, and also allows the detection of hidden metastases.[13]

Treatment for DMs consists mainly of surgical excision of the lesion as early as possible. Due to their more invasive behavior, particularly in the neurotropic subtype, it is advisable to perform resection with a minimum margin of 1.0 cm, ideally reaching 2.0cm.[2]

Radiotherapy has been studied as an adjuvant treatment to the surgical approach in order to reduce local recurrence.[16] Due to the low incidence of lymph node involvement in this particular entity, clinical follow-up and a selective biopsy of sentinel lymph node (LNB) seems appropriate. Notwithstanding, it has been proposed that mapping and LNB should be carried out in all patients with a Breslow thickness greater than 1 mm, Clark level greater than IV, or with ulcerated presentation – even when there is no clinical evidence of lymph node involvement.[2,3]

There is controversy about the prognosis of DM, due to both the variability in the degree of desmoplasia at diagnosis and the need for a better comparative studies methodology. Initially, it was seen as a disease with a more aggressive behavior and lower survival rates than those of other types of melanoma.[3,17] In 1988, three studies demonstrated a better prognosis of melanomas associated with desmoplasia, based on a comparison to other melanoma types with a similar thickness.[8,10,18] Nonetheless, the analysis of an extensive series of 280 patients did not yield a statistically significant difference in the 5-year survival rate between melanomas (68-79%) and associated desmoplasias (75.2-90,0%).[6] Apparently, the advanced Breslow DM cases present the best prognosis, as demonstrated in a study by Spatz and others, who analyzed DMs larger than 5 mm.[18]

Some histological characteristics, such as the lesion's thickness ($p = 0.012$), the presence of ulceration, mitotic rate greater than HPF 6 ($p < 0.001$), occurrence of regression, and presence of lymphocytic infiltrate, have been associated with a worse prognosis.[19] It was observed that lesions thicker than 6.98 mm were correlated with a higher incidence of visceral metastases, while those larger than 5.42 mm were frequently associated with recurrences, and those smaller than 3.37 mm were free of the condition.[20]

In general, a higher rate of local recurrence is reported in DMs. Notwithstanding, many of the series analyzed do not make a distinction between persistent tumors and cutaneous metastasis, which is a recurrence of the tumor in the dermis or subcutaneous tissue after the excision of the primary lesion without compromising the margins.[18] In any case, the rate of local recurrence described in the current literature ranges from 11-49% – a level considerably higher than other melanomas (3.2%).[1,6] In addition, higher incidences of recurrence were observed among the neurotropic subtypes (20%) compared to DMs (6.8%). This finding could be justified by the frequent neural invasion of DM, which makes the complete resection of those tumors difficult. 3,21

Histologically, local recurrence corresponds to a dermal or subcutaneous tumor, which can be mistaken for a scar lesion or even a sarcoma, often with neural compromise and angiotropism. 22 Its cytology may present a recurrence similar to that of the primary tumor, but it often appears more pleomorphic and with a sarcomatous pattern.[1] An earlier incidence of recurrence can be observed in DM cases: before 24 months in 78.2% of cases.[6,23]

There is consensus regarding the lower rates of involvement of the lymph nodes in DMs (9-42%) compared to other types of melanoma (47%).[1,2,4,5,6,8,15] It affects 4% of the DM in stage III, whereas in other types it affects 20% of cases.[6] It seems

that distant metastases comprise about 26% of DM cases, with the lung as the most frequently affected organ (4-57%).[1,2,8]

Although there are still many controversies about DM, there are noticeable differences in the behavior of this uncommon and difficult-to-diagnose melanoma variant. This finding implies that a therapeutic approach that is different from that recommended for other types of melanoma is necessary. ●

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Questions for continuing medical education (CME)

1) As a rule, desmoplastic melanoma (DM) presents the following, except:
a) fibrous tumor
b) spindle cells that produce or liberate collagen
c) neurotropism, with a growth pattern similar to that of neuroma
d) hyperpigmentation
e) neural transformation

2) DM usually develops in:
a) areas with chronic photodamage
b) palmoplantar regions
c) genital or anal mucosa
d) lower limbs
e) scalp

3) DM's pathogenic mechanism is based on the following observations, with the exception of:
a) presence of premelanosomes in fibroblasts
b) positivity for S-100 protein and other melanocytic differentiation antigens
c) differentiation of melanocytes by fibroblastic phenotype
d) induction of collagen synthesis by fibroblastic proliferation
e) collagen synthesis by melanoma cells

4) What precursor lesion is most frequently associated with DM?
a) superficial extensive melanoma
b) lentigo maligna
c) acral lentiginous melanoma
d) atypical melanocytic nevi
e) acquired primary melanosis

5) Which of the following is not commonly observed in DM's histopathology?
a) atypical spindle cells' fascicles
b) standard variable of desmoplasia, neurotropism, and neural differentiation
c) collagenous stroma
d) invasion of the dermis and subcutaneous tissue
e) isolated and scattered inflammatory cells

6) Which antigen presents the greatest sensitivity in DM's immunohistochemical profile?
a) S-100 protein
b) HMB45
c) HMW-MMA
d) tyrosinase
e) melan-A/mart-1

7) Which of the following aspects is the least important for surgical planning in DM?
a) more invasive behavior, particularly of the neurotrophic subtypes
b) lower rates of lymph node involvement
c) usual location in the head and neck
d) tumor thickness
e) increased rate of local recurrence

8) The most frequently affected organ in the event of distant metastases in DM is:
a) liver
b) lungs
c) bones
d) central nervous system
e) kidneys

9) Which are less frequent dermoscopic characteristics of DMs?
a) regression signs similar to scars
b) "peppering" appearance
c) irregular linear vessels
d) milky-red areas
e) atypical pigment network

10) The following entities can be cited in the differential diagnosis of DM, except:
a) fibrosarcoma
b) Kaposi's sarcoma
c) amelanotic melanoma
d) fibromatosis
e) dermatofibroma

Key
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1d, 2c, 3b, 4b, 5c, 6d, 7b, 8c, 9d, 10c

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