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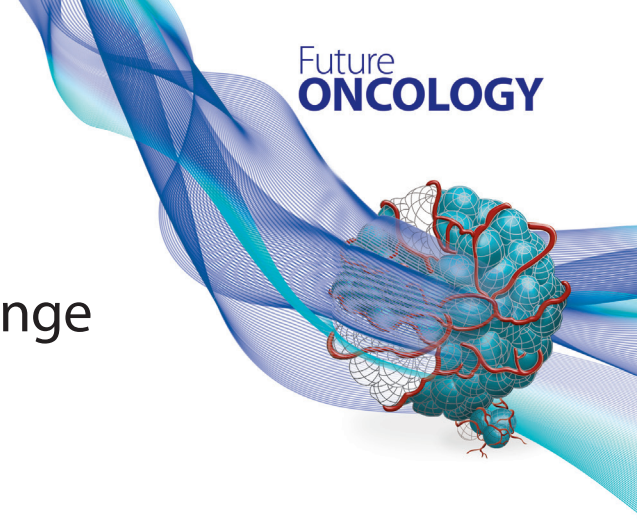

Desmoplastic melanoma: a challenge for the oncologist

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Aim: To evaluate clinical, pathologic and genetic features of desmoplastic melanoma (DM). **Materials & methods:** Analysis of all DM records from 1991 to 2015. **Results:** The most common location of DMs was the head and neck (69%); median age and follow-up were 60.5 and 7.3 years, respectively. A familial predisposition for DMs and others malignancies was analyzed. Thin Breslow thickness (<4.5 mm) was associated with an intraepidermal component or a previous lentigo maligna, whereas high Breslow thickness (>4.5 mm) was observed in 'pure' DM. **Conclusion:** DM could progress from an early phase, characterized by an intraepidermal component, to late phase, characterized by a dermal nodule. This hypothesis correlates with melanoma genetic and *NF1* mutation, which could be an early event in the progression of DM.

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KEYWORDS
• desmoplastic melanoma • lentigo maligna melanoma • mixed desmoplastic melanoma • NF1 • pure desmoplastic melanoma • spindle cell melanoma • stromal collagenization

Desmoplastic melanoma (DM) is a rare subtype of melanoma that shows distinctive clinical and histopathologic characteristics [1]. The first description of DM was made by Conley *et al.* in 1971, defining this tumor as, "an invasive melanoma composed of spindle cells and abundant collagen" [1]. DM is a rare subtype of malignant melanoma (MM); reports suggest that <4% of all primary cutaneous melanomas belong to the desmoplastic type [2–4]. It most frequently occurs in older people on the head, neck and upper trunk areas, and is often associated with significant sun damage. DM is often described as mainly an amelanotic nodule sometimes associated with a flat pigmented component [1,2]. Histologically, Magro *et al.* described DM as, "a form of melanoma in vertical growth phase in which the invasive tumor cells have a spindle morphology and are associated with marked stromal response" [3]. The histopathologic relations between DM and lentigo maligna melanoma (LMM) are still debated, and there appears to be an almost complete correspondence between the morphologic appearance of DM and the vertical growth phase of spindle cell melanoma, as seen in LMM. The histopathological classification then subdivides DM into 'true' DMs, also named 'pure', and 'spindle cell' melanomas, also named 'mixed' [3–6]. The differences between spindle cell DM are often subtle because of somewhat overlapping features and difficulties in collagen content quantification. One possible solution for this diagnostic dilemma was the introduction of an intermediate class (called mixed or combined spindle/DM) [6]. Further pathologic investigations may require the use of immunostains for conventional melanocytic markers (i.e., melan-A and HMB-45) and

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neural crest markers (i.e., S-100 and SOX10), for higher diagnostic accuracy [7–11].

Several DNA mutations have been recognized in MM, including *BRAF, NRAS, GNAQ, KIT* and *NF1* at genetic analysis. Each of these mutated genes has been found to correlate with distinct clinical and histopathologic features, and anatomic sites. Interestingly, activating *BRAF*V600E mutations, which are reported to be present in approximately half of non-DMs, are absent in DM, and provide additional evidence for a different biology of the tumor [12–16]. Recently, some authors reported a high incidence of *NF1* mutations in DM, suggesting a central role for *NF1* in the biology of this MM subtype [17,18]. *NF1* is a GTPase-activating protein whose mutations are correlated to neurofibromatosis type 1 [19,20], but also to the development of several neoplasms, such as: glioma, neurofibroma, peripheral nerve sheath tumors, pheochromocytoma, breast cancer and lymphoma [21–23].

DM diagnosis is usually challenging for the dermatologist. Dermoscopy could be helpful for the identification of melanocytic features and the possible recognition of melanoma-associated patterns [24]. Other imaging techniques could be helpful for the diagnosis and characterization of DM. Reflectance confocal microscopy (RCM) is a versatile imaging technique of established value for accurate diagnosis of many dermatological neoplasms and many other skin diseases [25–29]. The aim of our single-institution study was to examine clinical, pathologic and genetic features of DM patients in order to characterize the role of their family history and report their clinical course.

Materials & methods

Our Unit of Pathology provided the complete register with names and medical records of every patient with a histopathological diagnosis of DM for the period 1991–2015. A retrospective review was completed on 13 patients affected by DM and treated within our Unit of Dermatology. The following information was collected: patient demographics (sex, age, date of diagnosis), family history, pathologic features of the DM, treatment and clinical course. DM data included: tumor site, Breslow thickness, Clark level, mitoses, tumor-infiltrating lymphocytes, perineural involvement, vascular involvement, regression, ulceration, characterization of DM as pure or mixed, American Joint Committee on Cancer stage, date of surgical procedure, margins, clinical lymph node status, lymph node procedure, positive lymph nodes, metastasis, extensive/recurrence, treatment, follow-up, survival and diagnosis of nonmelanoma skin cancer. In addition, the presence and management of the recurrences were detailed. Clinical and dermoscopic images were retrieved from the archives of the Dermatological Unit. Whenever available, RCM images were collected and analyzed. In addition, to decipher the amount of desmoplasia in each sample, an expert pathologist revised the slides present in the archives of the Pathology Unit, classifying them as either pure DM or mixed DM using the Memorial Sloan–Kettering Cancer Center (MSKCC) classification system [3–6,9,11]. Melanomas with desmoplastic structures (paucicellular atypical spindled melanocytes, dermal fibrosis, lymphocytic aggregates) involving at least 90% of the specimen were classified as pure, whereas mixed DM was characterized by desmoplasia involving <90% but >10% of the melanoma. Surgical resection and sentinel lymph node biopsy (SLNB) were performed in all cases. Patients with a positive SLNB were offered complete lymph node dissection (CLND).

Results

Thirteen patients met inclusion criteria and were included in this study **(Table 1 & Figures 1–3)**. Six family trees were drawn in order to define the possible familial associations with other tumors. The analysis revealed a familial clustering of DM with several other neoplasms, in particular with adenocarcinoma of the prostate (two cases among probands and one case among second-degree relatives) and hepatocarcinoma (two cases among first-degree relatives). In addition, there was the sporadic observation of lymphoma (one case among second-degree relatives), laryngeal carcinoma (one case among second-degree relatives), renal cancer (one case among first-degree relatives), lung cancer (one case among one-degree and one case among second-degree relatives), pancreas adenocarcinoma (one case among first-degree relatives), brain tumor (one case among first-degree relatives), one adenocarcinoma of the gastrointestinal system (one among first-degree relatives) and three cancer of unknown site (two among first- and one among second-degree relatives). One of the families showed the clinical criteria for *BRCA1/2* mutations because of multiple breast cancers with early onset and several

Table 1. Clinical and histopathological features of the 13 desmoplastic melanoma patients.

Features	Patient ID												
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Sex	M	M	M	M	M	F	M	F	M	F	M	M	F
Age of onset (years)	78	82	64	43	70	80	52	59	40	67	65	82	85
Location	Scalp	Right shoulder	Head	Scalp	Scalp	Neck	Back	Right arm	Scalp	Head	Head	Left arm	Head
Breslow thickness (mm)	4	4	4.5 mm	6	7	4	5	1.7	6	4.3	4.5	13	8
Clark level	IV	IV	IV	V	V	IV	IV	III	V	V	V	V	V
Mitoses (×10 HPF)	3	0	2	1	4	2	31	2	5	5	3	7	5
Tumor-infiltrating lymphocytes	Absence	Presence	Absence	Absence	Presence	Absence	Presence	Absence	Absence	Presence	Presence	Presence	Presence
Perineural involvement	Presence	Presence	Absence	Presence	Absence	Presence	Presence	Absence	Presence	Absence	Presence	Absence	Presence
Regression	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Presence	Absence	Absence	Absence	Absence	Absence
Vascular involvement	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Absence
Ulceration	Presence	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Absence	Presence	Presence
AJCC stage	IIB	IIA	III	IIB	III	IIA	IIB	IB	IIB	IIB	III	IIC	IIC
SLN	Negative	Negative	1 positive	Negative	1 positive	Negative	Negative	Negative	Negative	Negative	1 positive	Negative	Negative
Lymph node dissection	Not performed	Not performed	No metastasis	Not performed	No metastasis	Not performed	Not performed	Not performed	Not performed	Not performed	No metastasis	Not performed	Not performed
Metastasis	0	0	0	0	0	0	0	0	0	0	0	0	0
Follow-up (years)	1	11	11	9	3	10	7	2	13	9	8	7	4
Survival	Alive	Alive	Deceased	Alive	Alive	Deceased	Alive	Deceased	Alive	Deceased	Alive	Alive	Deceased
Other cancer in the proband	1 BCC	Prostate cancer	3 BCC	0	0	1 BCC	0	Breast cancer	0	0	0	0	0
Cancer in the family	0	0	0	Breast (mother = 61) Uterus (sister = 42)	0	0	0	0	0	0	Breast (sister = 47) Colon (father = 65)	0	0

AJCC: American Joint Committee on Cancer stage; BCC: Basal cell carcinoma; F: Female; HPF: High-power field; M: Male; SLN: Sentinel lymph node.

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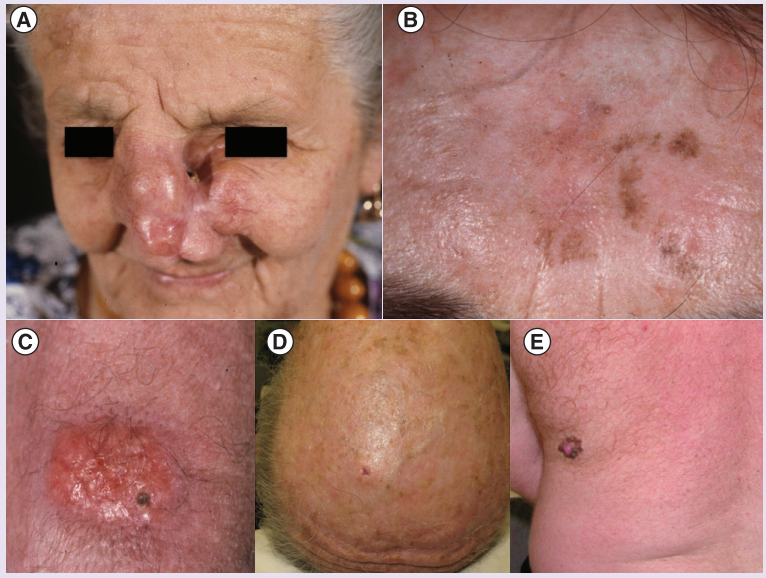

Figure 1. Clinical pictures of desmoplastic melanoma. Nodular lesions with variable morphology and hard consistency. They are mainly located on sun-exposed areas of the body **(A–D)**, but rarely can occur on other body locations **(E)**.

uterine carcinomas among relatives. Median follow-up was 7.3 years. Our demographic data show a male predominance (69%). Median age was 75.6 years, the most common primary site was the head and neck (69%), and the median age of onset was 60.5 years. Median Breslow thickness was 5.5 mm and all lesions were at least a Clark level III. Vascular involvement was absent in all patients; ulceration was present in three patients (23%); and 62% of lesions examined showed perineural invasion. Median mitoses were 5 × 10 high-power fields. Regression and tumor-infiltrating lymphocytes were present in one patient (8%) and in six patients (54%), respectively. Histologic subtype was evaluated in all patients with nine (69%) classified as pure and four (31%) classified as mixed. Some DM presented blue-gray blotches, atypical globules, gray dots, perifollicular brown hyperpigmentation and veil. For one pigmented lesion, RCM images were available and showed the infiltration of pleomorphic and dendritic cells of the infundibular portion of a hair follicle, a typical feature of LMM **(Figure 2)**. Other DMs were amelanotic-ulcerated nodules that showed few dermoscopic patterns, in particular, polymorphous atypical vessels, and milky-red areas and central ulceration **(Figure 3)**. For one amelanotic lesion, RCM images showed the disarrangement of the honeycomb structure, atrophy of the epidermis and limited pagetoid amelanotic infiltrations. A group of hypomelanotic nodular lesions with a peripheral pigmented flat portion presented dermoscopic features that were intermediate with respect to the two previously described prototypes. The rate of regional metastasis was less than expected considering that the patients presented with primary advanced cutaneous melanoma. All patients underwent SLNB. In three patients (23%) a positive SLNB was confirmed. In those three patients a CLND was performed, resulting negative.

Discussion

Our single-institution clinical and pathologic evaluation of DM confirms that DM is an uncommon type of MM, mainly diagnosed in the head and neck regions with distinctive clinical behavior and pathologic features, especially regarding its relationship to LMM and *NF1* gene aberrations. The diagnosis of DM is complex, both from clinical, dermoscopic, RCM and histopathologic perspective. Dermoscopic characterization and RCM analysis could be crucial in the designation of a diagnostic suspect of melanoma, because DM clinically mimics other lesions such as neuroma, neurofibroma, dermal cysts or squamous cell carcinoma. To our knowledge, this is the first description of DM with RCM imaging, focusing on the characterization of the different RCM characteristics between pure and mixed DM.

Previously described neoplasms associated to MM were: renal clear cell carcinoma (associated with *MITF* gene mutations) [30], ovarian cancer and breast cancer (associated with *BRCA2* gene mutations) [31], pancreatic cancer and ocular melanoma (associated with *CDKN2A* gene mutations) [32] or to the wider neoplastic spectrum of the *BAP-1* germline mutation [33]. Although a familial clustering for several tumors was observed in the majority of the DM families analyzed, no significant correlations were defined. This could probably be explained by the small population size, but distinctive familial associations may be uncovered from a larger series in the future.

In the beginning, Conley *et al.* described the DM clinical and histopathologic features, as a variant of melanoma likely to recur and present aggressive behavior [1]. However, DM studies have not confirmed this hypothesis, reporting low incidences of nodal involvement and related

mortality [7–11,34–36]. Recent studies reported that DM rates of nodal metastasis range from 0 to 18.8%; lower rates compared with other types of melanoma [2,6,10,34]. In addition, many authors suggested that survival of DM patients is comparable or better than survival of non-DM patients [8–9,36–39]. Even though many studies support the idea that SLNB is necessary for most variants of MM of 1.0 mm thickness or more, the need to perform SLNB in DM is still debated [17,34–35,38]. In our study, median Breslow thickness was 5.5 mm, and a positive SLNB was observed in three patients (23%), but CLND resulted negative. Such differences in the natural history between DM and other MM may raise many queries about the management of patients with DM. Nevertheless, until there is an agreement on the most effective management of DM patients, SLNB should be performed according to current standards of care for MM.

The histopathologic classification of DM into different subtypes is still a matter of scientific debate [3–6]. In detail, the presence of a predominant spindle cell component with a low collagen content of <10% is characteristic of spindle cell melanoma, a collagen content of 10–90% is indicative of mixed spindle/DM and a collagen content superior to 90% is representative of DM. Recently, a diagnostic algorithm, which does not replace careful histomorphological examination and clinicopathological correlation, has been proposed revealing that two markers, melan-A and trichrome staining, reach the highest diagnostic accuracy [6]. The relationship between LMM and DM is debated and several authors observed that DM usually presents an LMM component in the epidermal portion that overlies the tumor body or in the resection margins [3–4,40]. The significance of dermal elastosis in LMM has been previously analyzed by limited studies [41,42] and it is of crucial importance to define if UV damage is the unique agent responsible for the collagen dermal alterations seen in LMM and DM, or if elastosis and fibrotic dermal grenz zone, observed in these tumors, are the results of a complex interplay between tumor cells and stromal microenvironmental factors. As it was previously demonstrated, fibroblasts play an important role in many tumors, acting as a promoter or a sustainer of epithelial cancerogenesis as for *PTCH1*-mutated fibroblasts in Gorlin–Goltz syndrome, which were able to induce and promote the epithelial basal cell carcinoma development [43]. Similarly the fibroblast component of DM can act in the extracellular matrix production and secretion of protumor growth factors and cytokines. Magro *et al.* proposed an alternative hypothesis regarding the stromal collagenization, in which the DM neoplastic cells are dedifferentiated clonal melanocytes, which act as facultative fibroblast, that is, the tumor population comprised altered or dedifferentiated melanocytes with fibroblastic features [3,44–49]. In our series, approximately a third of DM were associated with the occurrence of an atypical lentiginous intraepidermal melanocytic component. In two additional cases the diagnosis of the DM was preceded by the excision of a recurrent LMM on the same site of

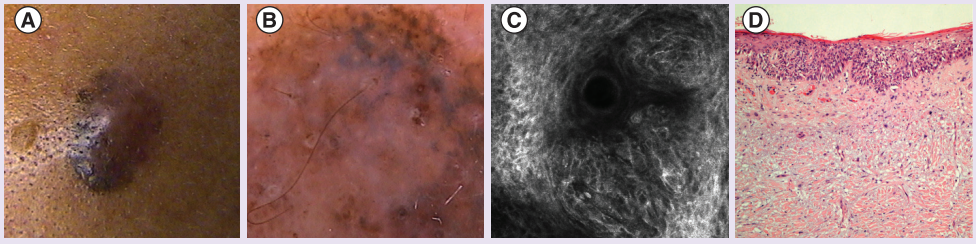

Figure 2. Desmoplastic melanoma associated to an intraepidermal component. Clinical picture of a mixed desmoplastic melanoma. The lesion is located on the scalp, showing a raised and infiltrated portion with a peripheral pigmented flat area. Clinically it is characterized by multiple colors, asymmetry and irregular borders **(A)**. Dermoscopic image shows blue–gray network and blotches, atypical brown globules, gray dots, perifollicular brown hyperpigmentation and veil **(B)**. Reflectance confocal microscopy image acquired at 30 μm depth from the skin surface showing the infiltration of pleomorphic and dendritic cells of the infundibular portion of a hair follicle **(C)**. Histologically, there is a dermal proliferation of spindle cells with nuclear atypia and collagen deposition; an atypical intraepithelial melanocytic proliferation is present **(D)**.

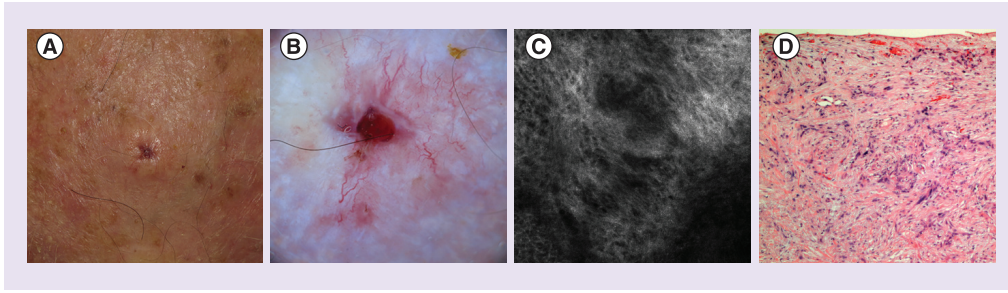

Figure 3. Desmoplastic melanoma not associated to an intraepidermal component. Clinical picture of a pure desmoplastic melanoma. The lesion is an amelanotic-ulcerated nodule located on the scalp **(A)**. Dermoscopic image shows few dermoscopic pattern, in particular, it is possible to identify small telangiectatic vessels, polymorphous atypical vessels, milky-red areas and central ulceration **(B)**. Reflectance confocal microscopy image acquired at 30 μm depth from the skin surface shows the disarrangement of the honeycomb structure, atrophy and disarranged epidermis **(C)**. The invasive tumor cells, have spindle morphology, are devoid of pigment and are associated with a desmoplastic stromal response **(D)**.

the lesion. Our data are intriguing because they strengthen many correlations between DM and LMM. In the past, some authors described the similarities between DM and LMM, suggesting that DM can be categorized into two subtypes: true DMs and spindle cell melanomas, the latter being consistent with the vertical invasive component of LMM [3,40]. These observations were centered largely on the high incidence of tumor on sun-damaged skin, in elderly patients, in the head and neck area, and because the junction aspect of most DM is indistinguishable from the vertical growth phase of LMM [5]. In further studies, it was shown that the magnitude and degree of the intraepidermal melanocytic component decreased in thicker tumors and that the group of DM, which exhibited a connection between dermal and epidermal parts, was considerably thinner than the melanomas that had a collagen-free zone between the two portions [4,38]. Our data, in accordance with the previous analysis by Carlson *et al.* [4,50], show that a low Breslow thickness of the DMs (<4.5 mm) is associated with the presence of an intraepidermal component or a history of previous LMM excision, whereas a high Breslow thickness (>4.5 mm) is mainly seen in 'pure' DM. In our opinion, this observation is of fundamental value and could lead to a unifying concept of DM, suggesting that the biological behavior of these neoplasms could progress from an early phase, that is characterized by the presence of an increased intraepidermal component and a thin/inconsistent dermal component, to a late phase, that is characterized by the absence of the intraepidermal proliferation, probably because of advanced regression, and a thick dermal desmoplastic component. In accordance with this hypothesis, in the first type of lesions ('early' DM), dermoscopy and RCM analysis showed the presence of lentigo maligna-like features. In detail, dermoscopic images showed rhomboid structures, brown circles around hair follicles, gray dots and blue-white regression; RCM showed the presence of atypical dendritic cells in the epidermis and infiltrating the hair follicle, disarrangement of the architecture and atypical cells at the dermal epidermal junction. In the second type of lesions ('late' DM), mainly ulceration and amelanotic melanoma features were observed. In detail, dermoscopic images showed polymorphic vessels, milky-red areas, erosion and ulceration, while RCM showed limited pagetoid hyporefractive cells, epidermal atrophy and compact collagen bundles at the dermal epidermal junction. Our morphological/biological hypothesis correlates well with the recent understandings in the field of melanoma genetics, which have not identified main genetic differences among DM patients, whether they are considered pure DMs or mixed melanomas, according to the classification suggested by Magro *et al.* [3]. From a genetic point of view, DMs do not harbor *BRAF, NRAS, GNAQ, GNA11* and *KIT* mutations. Instead, in >90% of cases, they are characterized by *NF1* gene mutations, as was previously demonstrated by Wiesner *et al.* [18]. *NF1* is a GTPase-activating protein considered to be a suppressed tumor that causes the neurofibromatosis syndrome, an increase in collagen production by fibroblast and the development of neurofibroma, peripheral

nerve sheath tumors, glioma, lymphoma, breast cancer, pheochromocytoma, melanoma, lentiginous melanocytic nevi, melanocytic hyperplasia and lentigo simplex [19–20,51–53]. The important roles of *NF1* in the development of melanocytic lentiginous proliferations, melanomagenesis and collagen production, are important tiles in the understanding of the DM mosaic. Altered melanocytic activity, in terms of metabolism, proliferation or differentiation, are evident because the presence of multiple café-au-lait macules and iris hamartomas of melanocytic origin (Lish nodules) is a major feature of the neurofibromatosis type 1 syndrome. Additionally, there are evidence and reports of a possible association between NF1 mutations and conjunctival melanoma or DM [54–57].

In our view, the loss of *NF1* could be an early event that may explain the natural evolution of DM: from an early melanocytic intraepidermal tumor with a lentiginous-pigmented component, to a deep tumor core that invades the dermis, increases the stromal collagenous matrix and destroys the superficial intraepidermal component by regressive phenomena. The weakness of our study is the relatively small size of the sample.

Conclusion

The results of our study can be summarized as follows: first, several relationships exist between DM and LMM, in particular, a subset of LMM can constitute the early phase of DM, which are characterized by a conspicuous intraepidermal component and a thin dermal component. In our view, the early phase can evolve into a late phase, characterized by a thick dermal desmoplastic component, in the absence of the intraepidermal proliferation. On the basis of this evidence, we suggest a unifying concept of DM that overcomes the histopathologic subclassification into 'true' and 'spindle cell' DM. As a second key point we highlight the crucial role of tumoral stroma in order to define a DM definition: the fibroblastic component is crucial in order to define the desmoplastic behavior of DM. Additionally, the etiopathogenesis of DM-associated stromal collagenization can share the same genetic background of malignant melanocytic neoplastic progression. Further clinical evaluation based on more wide DM series will be able to shed light on the potential familial predisposition associated with the pathogenesis of this rare tumor.

A potential actor of these phenomena could be the *NF1* aberrations, which have been identified in both DM and LMM. At present, in addition to *NF1* sequencing, the adoption of trichromic staining procedures specific for fibroblastic components and immunohistochemical analysis of the samples could be useful. The third point of our conclusion regards the application of modern imaging techniques such as dermoscopy and reflectance confocal microscopy. They represent important tools for the preliminary diagnosis of DM: in detail the recognition of LMM-like features, such as the presence of dendritic atypical infundibular invasion of pagetoid cells, allows the differentiation of 'early-phase' DM, from 'late-phase' DM.

EXECUTIVE SUMMARY

- Desmoplastic melanoma (DM) is a rare subtype of melanoma that shows distinctive clinical, histopathologic and genetic characteristics.
- The relationships between DM and lentigo maligna melanoma (LMM) is of key value, because approximately a third of DM are associated with an atypical lentiginous intraepidermal melanocytic component and the diagnosis of the DM is rarely preceded by the excision of an LMM.
- A subset of LMM, which is characterized by a conspicuous intraepidermal component and a thin dermal component, should be considered in the early phase of DM.
- Late-phase DM is characterized by a thick dermal desmoplastic component, in the absence of the intraepidermal proliferation.
- A familial clustering of several different tumors is described, but no specific correlations were identified.
- The fibroblastic component is crucial for the potential of the DM, and a potential cause of these phenomena could be *NF1* aberrations, which were identified in both DM and LMM.
- Modern imaging techniques such as dermoscopy and reflectance confocal microscopy represent important tools for the preliminary diagnosis of DM: in detail the recognition of LMM-like feature, like the presence of dendritic atypical infundibular invasion of pagetoid cells, allows the differentiation of 'early-phase' DM, from 'late-phase' DM.

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