Desmoplastic melanoma – challenges in the diagnosis and management of a rare cutaneous tumor

IRINA MĂRGĂRITESCU¹, AUREL DORU CHIRITĂ²

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

Abstract
Desmoplastic melanoma (DM) represents a distinctive rare variant of spindle cell melanoma with a predilection for chronically sun-exposed skin of the elderly. This neoplasm is notoriously difficult to diagnose, both clinically and histopathologically. Therefore, DM is deeply infiltrative at the time of presentation. Histologically, the tumor presents as a proliferation consisting of non-pigmented spindle cells arranged in poorly formed fascicles. The neoplastic cells have a deceptively bland appearance with slightly pleomorphic and hyperchromatic nuclei, inconspicuous nucleoli and low mitotic activity. DM can mimic a whole range of benign and malignant neoplasms with spindle cell and fibrous appearance. Even though S100 remains the first-choice marker for DM, currently, there is no reliable marker with both high sensitivity and specificity for its detection. However, emerging melanoma markers, such as SOX10, have shown promising results in the diagnosis of DM. An accurate diagnosis of DM should always be based on the integration of all the clinical, histological and immunohistochemical features. Once diagnosed, DM should be aggressively excised with at least 2 cm lateral margins and down to the fascia. We present a case of DM that appeared on a non sun-exposed site. The tumor recurred multiple times in spite of repeated surgery involving wide local excisions and histologically reported negative margins. We emphasize the difficulties encountered in the diagnosis and management of both the initial tumor and its recurrence.

Keywords: desmoplastic melanoma, neurotropism, recurrence, S100 protein, SOX10.

Introduction
First described by Conley et al., in 1971 [1], desmoplastic melanoma (DM) represents a distinctive rare variant of spindle cell melanoma with a predilection for chronically sun-damaged skin of the elderly [2–5].

This neoplasm is notoriously difficult to diagnose, both clinically and histopathologically. The correct diagnosis is often delayed by the non-specific clinical presentation and the tumor resemblance with a benign lesion. Therefore, DM is deeply infiltrative at the time of presentation. Histologically, DM presents as a deceptively bland non-pigmented spindle cell proliferation and can be easily mistaken for a scar. Also, DM can mimic a whole range of benign and malignant neoplasms with spindle cell and fibrous appearance [6, 7].

Even though S100 remains the first-choice marker for DM, currently, there is no reliable marker with both high sensitivity and specificity for detection of DM [8, 9]. However, emerging melanoma markers, such as SOX10, have shown promising results in the diagnosis of DM [10]. Nevertheless, an accurate diagnosis of DM should always be based on the integration of all the clinical, histological and immunohistochemical features.

Not only this neoplasm is difficult to diagnose, but it also poses a management challenge. Thus, DM has a high rate of local recurrences that is explained not only by inadequate surgical margins, but also by its propensity for neurotropism [6, 11, 12]. Local recurrence also correlates with an increased risk of systemic metastatic disease [5, 13–15].

We present a case of DM with multiple recurrences in spite of repeated surgery involving wide local excisions and histologically reported negative margins. We emphasize the difficulties encountered in the diagnosis and management of both the initial tumor and its recurrence.

Patient, Methods and Results
A 61-year-old diabetic woman presented with an asymmetrical, irregularly contoured erythematous indurated plaque located on the right lower back, measuring 3.5/2.5 cm. At one of its margins, the lesion demonstrated irregular pigmentation with areas of regression (Figure 1A). The patient started to notice the lesion six months prior to presentation. The lesion was accompanied by pain, numbness, and paresthesia. There were no clinical signs or family history of melanoma. Radiographic and ultrasound findings were unremarkable. The tumor was excised all the way down to the fascial plane and with 1 cm lateral margins. The surgical specimen was submitted for histological evaluation.

The surgical specimens were routinely fixed and paraffin embedded. 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 bistadial one, based on polymerized Dextran conjugated secondary antibody and horseradish peroxidase.
Irina Mărgăritescu, Aurel Doru Chirita

(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, dilution 1:500, Dako), Melan A (A103 clone, dilution 1:50, Leica) and HMB-45 (HMB-45 clone, dilution 1:60, Leica), NGFR (7F10 clone, dilution 1:50, Leica), vimentin (V9 clone, dilution 1:800, Leica), and Ki67 (MM1 clone, dilution 1:100, Leica). Histopathological and immunohistochemical evaluation was performed with Leica DM2500 microscope and images were acquired using Leica DFC490 camera.

Figure 1 – (A) Irregular pigmentation with areas of regression overlying an indurated plaque located on the right lower back in a 61-year-old woman. (B) Proliferative process that occupies the whole reticular dermis and is accompanied by fibrosis and collections of lymphocytes, HE staining, ×12.5. (C) Bland non-pigmented spindle cells arranged in poorly formed fascicles. Inset shows more atypical cells with big hyperchromatic and pleomorphic nuclei, HE staining, ×50, ×200. (D) Features of melanoma undergoing regression in the overlying epidermis and papillary dermis. Inset shows a band-like inflammatory infiltrate, fibrosis and remnants of an intraepidermal atypical melanocytic proliferation, HE staining, ×50, ×100. (E) S100 and (F) p75NGFR highlight the spindle-cell proliferation with better advantage, ×200.

At low power, histological examination revealed a proliferative process that occupied the whole reticular dermis (Breslow depth 5 mm) and was accompanied by fibrosis and collections of lymphocytes (Figure 1B). On
higher magnification, the proliferation consisted of non-pigmented spindle cells arranged in poorly formed fascicles. Overall, the spindle cells had a deceptively bland appearance with slightly pleomorphic and hyperchromatic nuclei, inconspicuous nucleoli and low mitotic activity. However, careful scrutiny revealed more atypical cells with big hyperchromatic and pleomorphic nuclei (Figure 1C). Features of melanoma undergoing regression were present in the overlying epidermis and papillary dermis (Figure 1D). Serial sections did not reveal vascular invasion or perineural involvement.

Immunohistochemically, the spindle cell proliferation expressed S100 (Figure 1E), p75NGFR (nerve growth factor receptor) (Figure 1F) and vimentin. The spindle cells were negative for HMB-45 and MART-1. Based on the clinical, histological, and immunohistochemical findings, a DM was diagnosed.

Even though the surgical margins were found to be clear, we decided to perform a re-excision with 1 cm margin around the scar to achieve the currently recommended margins for DM [16]. A full computed tomography (CT) scan was performed and did not reveal any abnormal changes.

The patient underwent regular follow-up, which consisted of physical examination every three months. Paraclinical examination including CBC (complete blood cells) count, biochemical tests and imaging studies (abdominal and lymph node ultrasons) was performed every six months. Also, determination of serum melanoma markers S100 protein and MIA (melanoma inhibiting activity) was performed every six months. A chest X-ray examination was conducted every year.

One year after the initial surgery, an asymptomatic subcutaneous nodule located under the scar, measuring 1.5/1 cm, was detected during the physical examination. The nodule and the scar were removed in toto with wide margins. Histology revealed a recurrent DM that was confirmed by immunohistochemistry. No perineural involvement was detected on serial sections and the margins were free of tumor involvement. Paraclinical studies did not reveal any signs of metastatic disease.

Two years after the initial surgery, the patient presented with a 3/1.5 cm painful, indurated subcutaneous mass, located adjacent to the scar. Physical examination did not reveal regional lymphadenopathy. All the paraclinical studies, including a full CT scan, failed to reveal any signs of metastatic disease. This time, a 3 cm lateral margin was obtained and dissection was carried down to the muscular fascia. Histological examination revealed a new recurrence (Figure 2A). Distinction of the recurrent DM from a scar proved to be a real challenge. A typical mature scar with a bland proliferation of fibroblasts and myofibroblasts accompanied by horizontally oriented thickened collagen bundles and vertically arranged capillary vessels was present in the reticular dermis (Figure 2B). Below the scar, another “scar”-like spindle cell proliferation was evident and occupied the whole subcutaneous tissue all the way down to the muscle fascia. The spindle cells were arranged in poorly formed fascicles embedded in a myxoid stroma and admixed with the bland scar fibroblasts and myofibroblasts (Figure 2C). The proliferation was punctuated by aggregates of lymphocytes. These findings were very reminiscent of the initial tumor. Compared to the scar fibroblasts, the spindle cells of the “scar”-like proliferation had more pleomorphic and hyperchromatic nuclei. As the proliferation advanced deeper into the tissue, the atypia of the cells became more evident (Figure 2D). Moreover, the proliferation manifested evident neurotropism (Figure 2E). Immunohistochemical examination was also challenging. Although difficult to appreciate because of the background staining, the immunohistochemical reactivity for S100 (Figure 2F) and NGFR of the big hyperchromatic cells confirmed the clinical and histopathological suspicion of recurrent DM.

The patient was alive and well without evidence of local or distant disease at the time of last follow-up (December 2013).

Discussion

DM represents a rare variant of spindle cell melanoma that appears especially on sun-exposed areas of elderly people [4, 5]. DM affects twice as many men as women.

The most common site involved is the head and neck region, representing more than half of cases, followed by the upper limbs, thorax, and lower limbs [1, 4]. Rare reported sites are the lip, palate, nasal vestibule, conjunctiva and the genitalia [17–20].

Figure 2 – (A) Second recurrence in the form of a large subcutaneous nodule, HE staining, ×12.5. (B) Typical mature scar in the reticular dermis, HE staining, ×25.
The clinical presentation is often nonspecific. DM may present as an amelanotic nodule or an ill-defined indurated scar-like plaque, which makes the clinical diagnosis very difficult. Moreover, the tumor may be misinterpreted as a benign lesion, such as a cyst, dermatofibroma, hypertrophic or a keloid scar. Hence, the correct diagnosis is usually delayed and the tumors are deeply infiltrative by the time of diagnosis [21–23]. However, some tumors show areas of irregular pigmentation or regression that represent important clinical clues for the diagnosis (Figure 1).

Histologically, DM can also pose diagnostic problems. It presents as a poorly demarcated neoplasm that usually occupies the whole dermis and may extend into the subcutaneous fat. Advanced lesions may present with skeletal muscle and bone involvement. The neoplasm is composed of a diffusely infiltrative spindle cell proliferation arranged in poorly formed fascicles. Due to the associated marked interstitial fibrosis, the tumor may be easily misinterpreted as a fibrosing process such as a scar or a dermatofibroma, especially in early stages. Moreover, the melanocytes are non-pigmented spindle cells that usually have a bland appearance and may easily be mistaken for fibroblasts, myofibroblasts, smooth muscle cells or Schwann cells. They are typically elongated and have small amounts of eosinophilic or basophilic cytoplasm. The nuclei are slightly pleomorphic and hyperchromatic with inconspicuous nucleoli and usually have a low mitotic activity [24].

However, there are some important clues that point to the real nature of the neoplasm. At scanning magnification, the presence of nodular aggregates of lymphocytes that punctuate the neoplasm is one of the first clues that should alert the pathologist to seek for other signs of DM. Careful scrutiny of the whole specimen will reveal, at least in some foci, cells with big hyperchromatic and pleomorphic nuclei. Also, features of melanoma in situ or regression can be found in the overlying epidermis or in the superficial dermis in approximately half of cases.

Given the clinical and histological diagnostic difficulties, immunohistochemistry is critical in arriving at the correct diagnosis. The great majority of DMs stain with S100. However, the specificity of S100 is low as other cells stain with this marker, such as macrophages, dermal dendrocytes, cells with Schwannian differentiation and fibroblasts/myofibroblasts [8]. This low specificity can create real problems in the diagnosis of both primary and recurrent DM. Moreover, the negativity of DM for the common melanoma markers HMB-45, MART1 and MITF further accentuates the diagnostic dilemma. Besides
S100 protein, DM may expressNSE (neuron-specific enolase), vimentin, NKI/C3 (CD63) and p75NGFR (nerve growth factor receptor). The last antibody stains cells of DM with high sensitivity [8]. Some studies found that p75NGF-R exhibits superior staining characteristics and a greater sensitivity in identifying DMs than S100 [9]. However, the specificity of this marker is not well-established [8]. SOX10, a transcription factor that plays an important role in melanocyte development, has recently been found to be highly expressed in DM [6, 25]. Hence, SOX10 seems to be a promising marker for DM. Nevertheless, an accurate diagnosis of DM should not be based only on immunohistochemical findings, but on the integration of all the clinical, histological and immunohistochemical features.

DM should be differentiated from both benign melanocytic and non-melanocytic lesions, such as sclerotic blue nevus, desmoplastic Spitz nevus, desmoplastic nevoid, neurofibroma, cellular neurothekeoma, schwannoma and dermatofibroma. The following features aid in the differential diagnosis: architectural and cytological characteristics, the presence of an atypical intraepidermal melanocytic proliferation, neurotropism, and lymphocytic aggregates dispersed throughout the lesion [6].

The more cellular variants of DM should be distinguished from a wide array of malignant spindle-cell neoplasms. These include spindle-cell atypical fibroxanthoma, malignant fibrous histiocytoma, dermatofibrosarcoma protuberosan, malignant peripheral nerve sheath tumor, spindle-cell squamous cell carcinoma and leiomyosarcoma. Appropriate immunohistochemistry using a large panel of antibodies coupled with a careful clinicopathological correlation allows for the correct diagnosis in each and every case [10].

As in our case, distinguishing DM, especially recurrent lesions of it, from scar tissue may be very difficult. Accurate evaluation of the architectural and cytological features of the proliferating spindle cells coupled with the immunoreactivity for S100, NGFR and SOX10 of the atypical spindle cells is very helpful in these situations. Unlike S100, SOX10 is not expressed by background fibrocytes and histiocytes within scars [6, 25, 26].

Compared to patients with conventional melanoma, DM patients have a lower frequency of lymph node involvement, a lower loco-regional recurrences rate and better prognosis. The presence of neurotropism is almost always associated with high recurrence rates [27]. Our case stands proof to it. The tumor recurred twice in spite of repeated surgery with histologically negative margins. However, in our case, neurotropism was not obvious until the second recurrence.

There is a direct relationship between previous recurrences and tumor thickness on one hand and systemic metastases on the other hand. Extensive screening did not reveal any signs of metastatic disease in our patient. However, the short follow-up precludes definitive conclusions on this point. The predilection site for systemic metastases is the lung [5, 13, 14].

Early and complete resection of the neoplasm with clear surgical margins is the treatment of choice for DM. Wide excision with margins of 2–3 cm is currently recommended to prevent local recurrences [2].

Lymph node involvement represents a rare event in the evolution of DM. Hence, SLNB may be unnecessary for these patients [5, 15, 28]. However, this procedure should be discussed with the patient in certain circumstances, such as the presence of deep infiltration, neurotropism, ulceration, and high mitotic rate [29].

Adjuvant radiotherapy may be of benefit for patients with locally recurrent DM, residual gross tumor, perineural involvement and narrow/positive excision margins [16]. The efficacy of systemic treatments such as Ipilimumab or Vemurafenib in metastatic DM remains to be determined.

**Conclusions**

We report a case of DM that recurred twice in spite of repeated wide excisions with histologically proven negative margins. The neoplasm appeared on a non-exposed site (lower back) which is unusual for DM that commonly involves sun-exposed areas. As the clinical presentation is often nonspecific and the histological appearance is rather bland, the correct diagnosis is usually delayed and the tumors are usually infiltrative by the time of diagnosis. Distinguishing DM, especially recurrent lesions of it, from scar tissue may be very difficult. Accurate evaluation of the architectural and cytological features coupled with the immunoreactivity for S100, NGFR and SOX10 of the atypical spindle cells is very helpful in these situations. Due to its infiltrative and neurotropic characteristics, DM has a propensity to spread and recur. Hence, management is extremely difficult. Early and complete resection of the neoplasm with surgical margins of at least 2 cm represents the current recommended treatment for DM.

**References**


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

Received: January 26, 2014

Accepted: August 25, 2014