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A Misdiagnosed Desmoplastic Neurotropic Melanoma of the Scalp: A Challenging Case for the Pathologist and Surgeon

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ABSTRACT Desmoplastic neurotropic melanoma (DNM) is a rare melanoma subtype that shows tropism for the nerves, perineural invasion correlates to higher rate of local recurrence, poorer prognosis and worse morbidity. Given the paucity of typical melanoma features, both clinical and pathological, this confusing skin cancer may act as a pretender, thus leading clinician to misdiagnosis and subsequent inappropriate conservative treatment. Sarcomatoid-like cells rearrangement and absence of pigmentation can lead towards sarcoma diagnosis, so specific skills are required to pathologist to properly recognize this melanoma subtype. In this case report, we present an example of how challenging can be the diagnosis, and how it can affect clinical outcome.

KEY WORDS: desmoplastic, neurotropic, melanoma, skin tumor, sarcomatoid, dermatosurgery

INTRODUCTION

Desmoplastic neurotropic melanoma (DNM) is a rare variant of spindle-cell melanoma composed of strands of neoplastic cells surrounded by thick fibrous collagen matrix and a tendency to adopt a circumferential arrangement around small nerves in the deep dermis (this feature is known as "neurotropism"). Due to the rarity of this form of melanoma, its biological features and clinical behavior are still unclear. It is estimated that its frequency is approximately 1-4% of all new melanomas. The male to female ratio has been reported around 2:1, and patients with DNM tend to be older compared with patients without DNM, with a mean age 66 years at time of diagnosis. DNM frequently occurs on sun-exposed areas and mostly in head and neck regions (1-6).

DNM often presents as a firm nodule or plaque or an ill-defined scar-like skin lesion, and it is frequently not pigmented (1-6).

This kind of skin cancer can be mistaken for a benign lesion (e.g. dermatofibroma or intradermal benign nevus), which may result in a delayed diagnosis. There may sometimes be an area of *lentigo maligna* close or superficial to DNM that can hide the thicker component, causing under staging (5-7).

Epiluminescence microscopy (ELM), the gold standard in early melanoma detection, seems to fail in leading to correct diagnosis due to absence of typical dermatoscopic features such as an atypical pigment network, irregular dots/globules, and regression area.

It is always advisable to palpate every lesion under evaluation for early subcutaneous nodule detection or to evocate mild pain due to nerve involvement.

From a histological perspective, DNM is defined as a pauci-cellular proliferation of malignant spindle

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cells within an abundant desmoplastic stroma. Main differential diagnosis of a desmoplastic lesion include both benign lesions (e.g. neurofibroma, sclerosing melanocytic nevus, and dermatofibroma) and malignant ones (e.g. myxofibrosarcoma, leiomyosarcoma, clear cell sarcoma, and sclerosing-spindle cell squamous carcinoma). Important histopathological features that are often identified close to or in continuity with DNM are a melanoma *in situ* component (up to 80% of all DNM) and infiltrating lymphocytes, sometimes even arranged in aggregates at the neoplastic infiltrative edge. Pathologist findings can include cells spreading along perineural spaces (perineural invasion) or invading the endoneurium sheath directly (intraneural invasion). It is also not unusual for melanocytic cells to rearrange themselves into nerve-like structures (neural transformation) (8-11). Perineural invasion correlates to a higher rate of local recurrence, poorer prognosis, and greater morbidity compared with DNM without nerve involvement (8-10). Desmoplastic neurotropic melanoma tends to be thick when identified, which may be due to delayed diagnosis.

Prognosis is controversial, even when considering the tumor thickness (11,12). It has a high local recurrence rate (mostly when it is associated with neurotropism) (11) and it is less likely to metastasize to local lymph-nodes. In this case report, we offer an example of how challenging the diagnosis can be and how it can affect the clinical outcome.

PATIENT HISTORY

At the beginning of 2020, a 87-year-old male patient presented to our outpatient clinic, affected by a soft tissue mass of about 10×3 cm located on the left parietal region of the scalp (Figure 1).

The nodule had developed in proximity of the lateral-posterior border of a skin graft due to reconstruction after tangential wide excisions, performed in a secondary hospital.

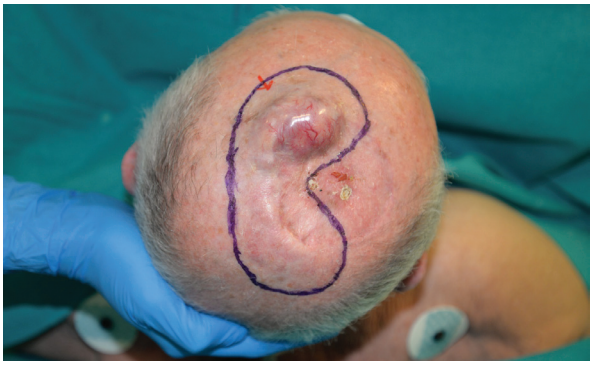

Figure 1. Patient scalp at first surgery; the skin graft is on the right side of the image, while the second tumor recurrence is visible on the left side. The subcutaneous mass was palpable along all the left border of the skin graft.

The lesion did not present any pigmentation or ulceration on its surface, the skin color was whitish, and consistency seemed elastic based on finger palpation.

No clinical evidence of pathological growth of cervical lymph nodes was found.

The patient suffered from arterial hypertension, benign prostatic hypertrophy, and glaucoma, and he also had a cardiac pacemaker, without any further clinical documentation.

Home therapy consisted in terazosin, quinazide, aspirin and tafluprost eye drops daily.

During the previous year, the patient had undergone surgery twice for the same lesion: the first operation was a day surgery because the limited size of the new skin lesion on the scalp, after which a diagnosis of dermatofibrosarcoma protuberans was established and excision margins were evaluated as cancer-free.

Immediate reconstruction with skin graft was performed, and the post-op course was uneventful.

After 8 months, a local recurrence developed on the anterior border of the previous graft and brought the patient back to the operative room for a wide excision and a larger skin graft.

The recurrence specimen was analysed by a different pathologist, who established a diagnosis of malignant melanoma (Breslow thickness of 16 mm, V level of Clark, mitotic index of 10 mitoses/mm^2, without vascular or lymphatic invasion, no microsatellites or necrosis, with ulceration and isolated lymphocytic infiltration not brisk, pT4b AJCC 2018).

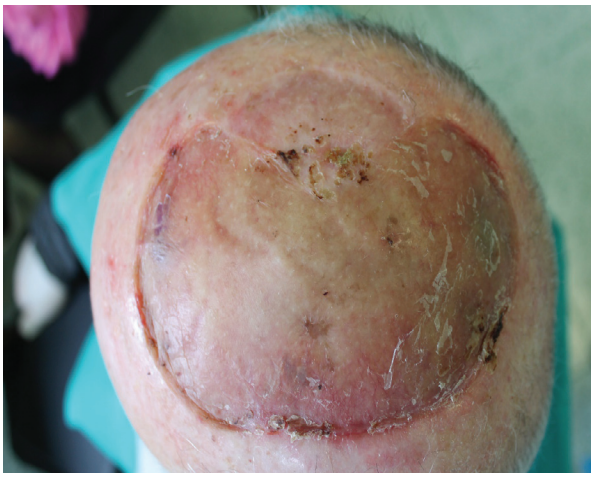

Figure 2. Patient's scalp two weeks after the second surgery, which revealed radical. Healing of the skin graft is complete.

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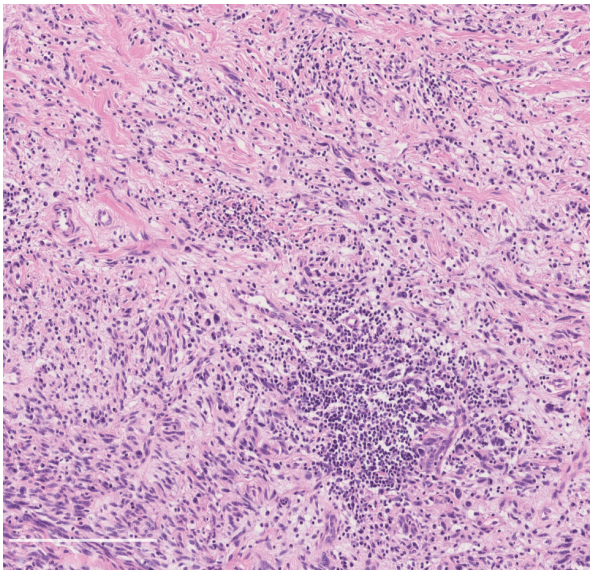

Figure 3. A poorly circumscribed intradermal lesion with a fascicular pattern composed of spindle cells with prominent desmoplastic stroma. A diffuse inflammatory lymphocytic infiltrate is associated with neoplastic cells.

To our knowledge, sentinel lymph node biopsy (SLNB) was not performed.

A second massive relapse of melanoma then developed on the patient's scalp.

Total body CT scan and cervical and abdominal ultrasound (US) failed to reveal any distant metastasis, and no pathological lymph nodes were clinically detectable.

Cranial diploe resulted in being free of cancer invasion on CT scan, so it was feasible to spare the periosteum sheath from resection and to proceed to a new skin graft, avoiding major reconstruction with local flap.

SLNB was not deemed reliable due to the vast scalp area involved in the melanoma, which would have meant performing multiple lymph node biopsies in different Robbin's levels at both neck sides.

BRAF, NRAS, and CKIT genes analysis was performed, and the results were negative for mutation.

Surgery was scheduled and the cancer was excised; no skull bone or periosteum infiltration was found, so a skin graft harvested with dermatome from the lateral thigh was used to cover the left parietal region.

The patient stayed overnight for monitoring and was discharged the following day without any early sign of complication.

The skin graft was fully successful, and complete healing was achieved in about 15 days with weekly dressing changes (Figure 2).

Histopathological analysis, performed by a skilled pathologist at our tertiary hospital, revealed a desmoplastic neurotropic melanoma with widespread desmoplastic areas (Figure 3). Excision margins resulted were cancer-free but less than 1 cm from the lesion in most parts of the tissue sample, with focal aspects of perineural invasion and diffuse positivity for S100, Sox10, Vimentin, and WT1 (Figure 4).

After a multidisciplinary team evaluation of the case, a wider excision was proposed and accepted, in order to obtain larger margins from the cancer to reduce the chance of new local and regional recurrence.

Even if the diagnosis of melanoma was confirmed, lymph node biopsy was excluded for the abovementioned reasons.

No further cancer cells were detected in the last specimen, and the patient healed without complications.

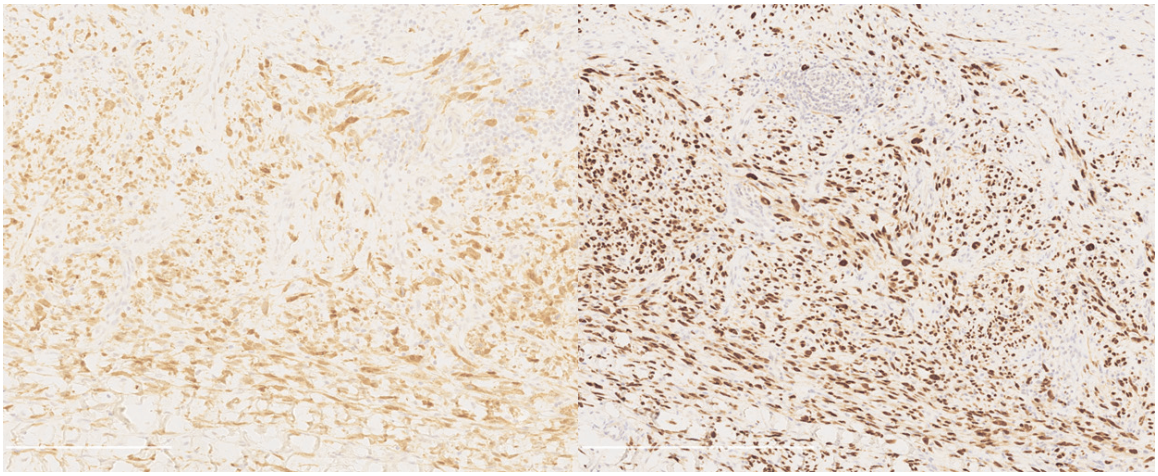

Figure 4. S-100 (left) and SOX10 (right) immunoreactivity in the dermal spindle cells shows a melanocytic origin of the neoplastic cells and highlights the plexiform growth-pattern of malignant cells.

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DISCUSSION

This case shows how challenging the diagnosis of DNM can be, which can mislead even expert clinicians and pathologists.

Desmoplastic clinical features are quite different from the usual melanoma because of the absence of the pigmentation and pattern alterations at dermoscopy. Its progressive growth and elastic texture make it look like a neoplasm from mesodermal origin more than one of neuroectodermal origin.

Sarcomatoid-like cell rearrangement and absence of pigmentation can lead towards a soft-tissue sarcoma-like diagnosis; therefore, specific skills and significant experience are required for the pathologist to properly recognize this rare spindle-cell subtype of melanoma.

Sox10 shows an increased specificity for the characterization of neural crest origin because its expression is retained in Schwann cells and melanocytes. Therefore, Sox10 should be used in combination with S100 immunohistochemistry to establish the correct diagnosis of DNM in the differential diagnosis with soft-tissue neoplastic lesions such as dermatofibrosarcoma protuberans and clear cell sarcoma (13).

Several case series in the literature have reported an initial incorrect diagnosis followed revision by a senior pathologist and subsequent diagnosis of DNM.

Two different histologic subtypes have been reported for distinguishing the clinically relevant outcome according to the degree of desmoplasia within DNM: "pure" DNM and "mixed" DNM. "Pure" DNM is defined as being composed of more than 90% of stromal fibrosis, with malignant melanocytes typically dispersed throughout fibrous tissue. On the other hand, "mixed" DNM is composed of 10-90% cellular non-fibrotic areas intermixed with collagenous stroma. A melanocytic lesion which contains less than 10% fibrosis should not be considered as desmoplastic. In different retrospective studies, significant differences in clinical behavior between "pure" and "mixed" DNMs have been reported: specifically, "mixed" DNM is associated with a worse prognosis (5 year-melanoma mortality of 31% in "mixed" DNMs versus 11% in "pure" DNMs; $P<0.01$) (14). In our case, the tumor presented both components, i.e. neoplastic and fibrous tissue in almost equal parts, so it falls under the "mixed" kind of DNM.

An interesting finding was the high Breslow thickness (16 mm, V level of Clark) at the time of patient presentation to our clinic: rapid growth in only 3 months (from October 2019 – the date of second surgery – to January 2020 – the date of third surgery) correlates with sarcomatoid features and suggests aggressive biologic behavior.

Thus, wide surgical excision, providing large free margins, is mandatory to minimize the risk of local recurrence (15).

Resection at minimum distance from lesion invariably leads to local recurrence and to ineffective several operations, and such an inappropriate approach increases the operative risk as well, given the senior mean age of patients at time of surgery.

In the present case, sentinel lymph node biopsy (SLNB) was not performed initially because of the incorrect diagnosis, and later due to the elapse time it was considered excessive to provide adequate prognostic value.

In the literature, the indication of SLNB in melanoma treatment is controversial; while its predictive value is clear in thin melanoma (Breslow <4 mm), its role in thicker melanoma is still under discussion, especially in desmoplastic melanoma, which has showed a significantly lower SLNB positivity rate (16,17).

DNM with perineural invasion is associated with a low rate of distant metastases, so it is not unreasonable to exclude SLNB in this case, after multidisciplinary discussion and after also considering negative staging exams.

Indicating SLNB has been debated, and it has been demonstrated that SLNB positivity has no impact upon survival in desmoplastic melanoma, although other studies consider neurotropism a risk factor for SLNB positivity (1,5,18-20).

Neurotropism is widely considered a negative prognostic factor, despite the paucity of evidence (15).

Some studies showed no significant influence of neurotropism on local recurrence, but nevertheless an aggressive surgical approach is always suggested for a successful prime site disease management (8,9,15).

DNM is radiosensitive, and Varey *et al.* reported that it is advisable to complete the treatment with adjuvant radiotherapy in patients with sub-optimal surgical margins, but no significant benefit was evident when an aggressive surgical treatment was successful in obtaining wide free margins (16).

Other authors reported similar results, but there is still no common agreement on the role of adjuvant radiotherapy (1,21).

Bearing clinical features that are far from usual, desmoplastic neurotropic melanoma (DNM) can undermine the well-defined diagnostic and therapeutic process for melanoma, causing hazardous late

diagnosis and subjecting patients to reiterated suboptimal treatments.

Both clinicians (dermatologists, plastic surgeons, general surgeons) and pathologists have to keep in mind this insidious differential diagnosis in the presence of a rapidly growing soft tissue mass.

Given the paucity of typical melanoma features, DNM represents a diagnostic challenge and thereby a therapeutic challenge as well.

A deep knowledge of this rare malignant melanocytic entity is required for proper surgical treatment and satisfactory clinical outcomes.

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