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Chapter 4

Desmoplastic Melanoma: A Review of Current Management

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Abstract

Desmoplastic Melanoma (DM) is a rare variant of melanoma accounting for less than 5% of melanoma diagnoses. It is more common in males, affects older patients and occurs in sun-exposed areas. It remains a challenging diagnosis due to its often benign clinical appearance. Histologically, there are two distinct subtypes described as pure and mixed, and it is often associated with perineural invasion.

Due to its rarity, consensus regarding the clinical relevance of these histological features, and various aspects of management remain controversial. This review aims to summarise the current literature regarding clinical and pathological diagnosis and to present the evidence regarding the surgical management of DM and the use of adjuvant radiotherapy.

Keywords: Desmoplastic Melanoma; Melanoma; Dermatohistopathology; Radiotherapy; Immunotherapy; Targeted Therapy; Sentinel Lymph Node Biopsy.

1. Introduction

Desmoplastic melanoma (DM) is a rare variant of melanoma, that was first described by Conley et al. in 1971 [1]. It accounts for less than 5% of malignant melanoma (MM) diagnoses [2] and has a reported incidence of 2 per million population, which is steadily increasing [3]. It is more common in males and tends to affect older patients, with a mean age of diagnosis at 66 years [3].

Due to the rarity of this condition, and difficulty in diagnosis, the incidence of DM may be underestimated, and its natural history is poorly understood. It is considered as the 'sarcomatoid variant' of melanoma due to its' differing behaviour [4]. This review of the literature aims to look at the current evidence behind the diagnosis, prognosis and surgical management of this rare but locally aggressive form of malignant melanoma.

2. Diagnosis

DM often poses difficulty in clinical diagnosis, as it usually presents as a non-pigmented plaque or nodule, though it is often associated with a local area of lentigo maligna [5]. It predominantly occurs in sun-exposed areas such as the head and neck [6, 7], making chronic UV exposure one of the suspected risk factors [4]. There is frequent clinical uncertainty around the diagnosis of DM, resembling basal cell carcinoma, dermatofibroma or other benign skin lesions [8]. Dermoscopy and Reflectance Confocal Microscopy (RCM) can aid in the detection of DM. However, the presence of positive dermoscopic features for melanoma has been reported to be absent in approximately half of the cases of DM [9]. In contrast, Chen et al. (2013), report that desmoplastic lesions reveal at least one melanoma-specific structure upon dermoscopic examination based upon their case series of 37 DM cases [4]. The presence of recognised RCM features for melanoma (such as pagetoid cells and cell atypia) are commonly present in DM. However the limited depth of exploration of RCM means that more specific dermal features of DM such as the presence of abundant spindled cells intermingled with collagen fibers may not be observable [10]. The lack of well-defined clinical and dermoscopic criteria may contribute to the diagnosis of DM at a later and more advanced stage [11].

Some of the challenges in the presentation are evident in the (**Figure 1**) below, where we present the case of a 56-year-old male who presented with a 6-month history of a fleshy coloured papule on his right upper arm. While the lesion itself was relatively non-descript, with bland dermoscopy (**Figure 2**), histological analysis demonstrated an 8.5mm Breslow Thickness desmoplastic melanoma (DM).

3. Histological Features

On histological analysis, desmoplastic melanoma is characterised by atypical, spindle shaped melanocytes (**Figure 3a**), intimately mixed with ropy dense collagen fibrils (**Figure 3b**). As with MM, S100 and MelanA (**Figure 3a**) stains may be used to diagnose DM, as well as assessing for markers such as collagen IV, trichrome, CD68 and MDM2. In addition, a BRAF mutation is identified in approximately 5% of cases [12].

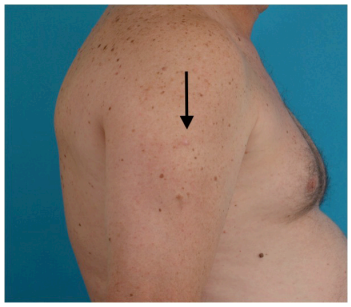

Figure 1: 56-year-old male with a 6-month history of fleshy papule right upper arm, as marked with an arrow.

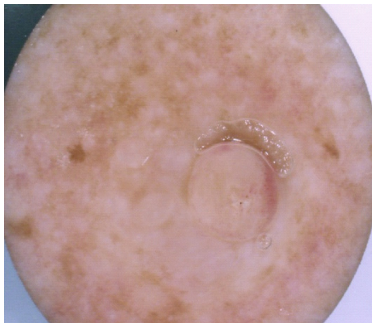

Figure 2: Dermoscopic examination of 8.5mm desmoplastic melanoma.

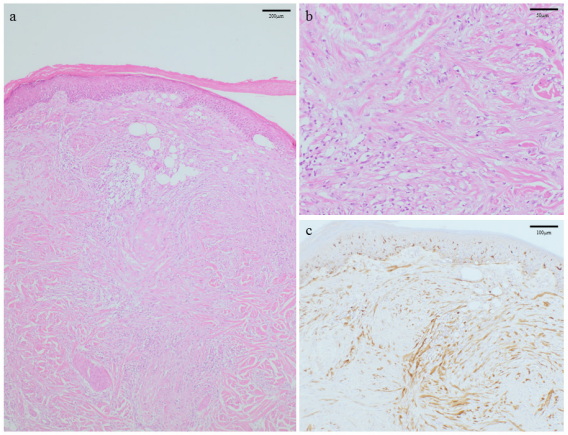

Figure 3: Histological sections of a desmoplastic melanoma (a, x4 magnification) showing atypical spindle melanoma cells (b, x 20 magnification) dissecting between the dermal collagen fibres and (c, x10 magnification) showing diffuse immunostaining positive for melanoma marker S100.

3.1.Tumour Depth

Given the difficulty in diagnosis, DM tends to be thicker than malignant melanoma on initial diagnosis. In their analysis of 1,129 cutaneous cases of DM, Feng et al. (2011) reported that the majority of cases had a Clark's Level of IV-V. However, cases were almost evenly distributed throughout the Breslow thickness categories [3]. Others have also replicated this

finding with the literature reporting a Breslow thickness at presentation ranging from 2.0mm to more than 4mm. [2, 13-15]. This is a stark contrast to MM, where the majority of tumours present at a thickness of less than 1mm [16].

3.2. Subtypes

In 2005 a new framework for subtyping DM was proposed by Busam et al.(2011) , divided into ‘pure DM (pDM) and combined or mixed DM (mDM). The paper described pDMs as those in which the overwhelming majority (90%) of the tumour was associated with prominent stromal fibrosis, with dispersed melanocytes, resulting in a low cellular density. Those that are considered as mixed were described as those in which dense cellular foci contributed to more than 10% but less than 90% of the tumour [17]. Pure DM (pDM), and Mixed DM (mDM) have been largely accepted in the literature; however, not yet fully incorporated into clinical practice. Nevertheless, this difference has recently been reported as a determining factor in certain aspects of management, which will later be discussed herein.

3.3. Neurotropism

DM has been proposed to behave similarly to soft tissue sarcoma, with low regional lymphatic spread but high local recurrence rates, and one of the contributing factors to this is felt to be neurotropism, in other words, the ability to invade nervous tissue. While there are neurotropic melanomas that may arise in non-desmoplastic lesions [18], they are primarily discussed in the setting of DM. The aggressive clinical course of DM lesions with neurotropism was described initially by Reed and Leonard[19] in 1979 and has since widely been reported [4, 20]. The degree of nerve involvement can take many forms, ranging from focal perineural spread to extensive neurotropism [4]. Lens et al. (2005) reported a neurotropism rate of 16.7%-77.8% in their analysis of 856 DM patients [15]. Desmoplastic Melanoma tumours which display features of neurotropism have been shown to have deeper Clark levels and higher mitotic activity than those without [2]. This leads to significant clinical consequences in head and neck cancers with facial nerve neuropathies being reported in the literature [21-23].

Neurotropism has been accepted as a significant challenge when obtaining definitive surgical margins [4], though due to variations in its’ nomenclature [24], its' impact on overall survival is unclear. Historically, studies would suggest that in the case of DM, neurotropism is associated with a significant decrease in survival [25]. In cutaneous MM, neurotropism has been demonstrated to be associated with higher rates of local recurrence. However, neurotropism in cutaneous MM loses its prognostic significance when factored with other variables, and is not thought to be an independent risk factor [26]. This finding appears to be replicated in DM. Livestro et al. (2005) reported a higher local recurrence rate of neurotropic DM (20%) compared to non-neurotropic (6.8%); although, they found no difference in overall survival [27]. Similar findings were reported by Han et al. (2015), though in describing perineural

invasion (PNI) as 'tumour cells in perineurium, or extensively surrounding and distorting cutaneous nerves'. This study reported PNI as a significant predictor of worse recurrence-free survival on both univariable and multivariable analysis, though a predictor of overall survival on univariable analyses only [28]. In summary, evidence to date suggests that neurotropism is associated with an increased rate of local recurrence, though it may not impact on overall survival, as was previously thought. However, the role of neurotropism and PNI in DM needs to be further elucidated and would be aided by standardisation of descriptive terminology.

4. Surgery

Analogous with other types of MM, surgery remains the first-line treatment for DM, and current guidelines recommend wider excision of the primary lesion, with a margin determined by the original Breslow thickness [29, 30]. This aims to decrease the likelihood of local recurrence.

There are no clinical trials that specifically examine the appropriate margins to minimise recurrence in the specific case of DM, though definitive surgical control is associated with decreased local recurrence in both neurotropic and non-neurotropic cases [18, 20, 21, 31]. Surveillance, Epidemiology and End Result Database (SEER) Data also suggests that a wider excision in the setting of DM is associated with improved 5-year survival [20].

In a study assessing the risk of local recurrence in 176 thin melanomas of any subtype after excision, Mackenzie Ross et al. (2016) determined that a desmoplastic subtype itself was an independent predictor of local recurrence. This study demonstrated that in melanomas with a Breslow Thickness <1mm, a desmoplastic subtype was associated with a local recurrence in the event of a surgical margin <1cm (8mm histologically). The authors recommended that in this subtype, as well as in acral and lentigo maligna melanomas, a margin should be greater than 1cm where possible [32]. In addition, data from one review of 280 patients demonstrated that for those with an excision margin <1cm, risk of local recurrence was significantly higher than those with a margin >2cm. However, this does not seem to remain significant when comparing those with an excision margin of 1-2cm and >2cm [2].

Maurichi et al. (2010) further explored this, comparing subtypes of DM, with their retrospective study analysing pDM and mDM specimens under and over 2mm thickness. They demonstrated that under 2mm thick pDM patients who had a 1cm margin had a worse 5-year Overall Survival (60 %), and higher local recurrence, than those with 2cm margins (85.2%) ($p= 0.014$). Interestingly, those with pDM lesions larger than 2mm with 2cm margins had a similar 5-year OS to their under 2mm controls. They recommended that treatment should be with excision of 2cm for all pDM. This did not apply to mDM, as the retrospective study demonstrated 5-year overall survival decreasing with advancing tumour stage, behaving independently of the margin of clearance [33].

There is evidence to suggest that similar to other forms of MM, a wide excision margin, of greater than 1cm, is necessary to decrease the risk of local recurrence. There is no current evidence to suggest this should deviate from the margins usually recommended for MM, though in the setting of pDM, a wider margin could be considered.

5. Sentinel Node & Lymph Node Involvement

Similarly to other aspects of DM care, the prevalence of lymph node metastases and role for sentinel lymph node biopsy (SLNB) remains controversial.

The original description of DM reported lymph node metastases in 3 out of 7 cases [1], though this is now disputed. Rates of 1- 13% [3, 13-15, 18, 20, 27, 34, 35] are reported for sentinel lymph node positivity, or lymph node involvement in DM, which is reassuring in comparison to the rates of approximately 20% usually quoted in MM [36]. The National Comprehensive Cancer Network guidelines 2019 recommend that a sentinel node lymph node biopsy should be considered and offered to any patient for who the probability of sentinel node positivity is 5-10%. In this regard, this is a procedure that should be considered in DM, as it is in other forms of MM, and patients counselled accordingly [29].

Interestingly, this apparent lower rate of lymph node metastases seen in DM does not have a definite impact on survival. Wasif et al. (2011) found that 29% of their 1,735 patients, 3% had a positive SLNB. Overall, four per cent of the entire group, regardless of SLNB status, were found to be nodal positive. However, this was found to be independent of the overall 5-year survival rate [20]. Smith et al. (2012) also found no survival difference in SLNB patients in their analysis of 244 head and neck DM patients [37].

Dunne et al. (2017), recently attempted to clarify the relevance of SLNB with their 2016 systematic review of 1,519 DM patients. This review reported that lymph node metastases are lower than in DM patients in comparison to the rates quoted in the literature for MM, with 6.5% DM patients having a positive SLNB. However, some studies still reported sentinel node positivity impacting upon disease-free and melanoma-specific survival. When DM was further divided into its proposed histological subtypes, pDM and mDM, a more striking difference was noted with positive SLNB in 13.8% (38) mDM cases compared to 5.4% (17) pDM cases. Dunne et al. (2017) also noted mDM is known to have a more aggressive course and worse disease-free survival than pDM. For this reason, the authors recommended SLNB for mDM patients but not for pDM patients due to low-risk stratification, procedural complications and cost [38].

In the setting of an over SLNB positivity rate of 6.5%, we would suggest that SLNB should still be considered in DM patients, as would be the case for other forms of MM, though emphasis should be placed upon its' utilisation in cases of mDM.

6. Radiation & Local Recurrence

In contrast to their decreased propensity for lymph node metastases, DMs are perceived as more likely to recur in comparison to their non-DM counterparts locally. Local recurrence is reported to occur in approximately 27% of patients [15], though recurrence is reduced where surgical control is adequate [21].

As 51% of DMs are found in the head and neck [4], an obvious limitation of treatment in the setting of likely regional recurrence, lies in attaining adequate margins while maintaining an acceptable cosmetic appearance. Whilst it must be clearly state that the ideal treatment in the setting of inadequate margins is further surgery, this may often be challenging and in some cases, not feasible. As such, radiotherapy (RT) is often utilised in an effort to reduce local recurrence rates. However, there are no published randomised controlled trials addressing the potential benefit of adjuvant radiotherapy in this setting, and there is limited understanding of the impact on overall survival.

In 2008, Chen et al.'s analysis of 128 patients demonstrated a preference for using radiotherapy in this cohort with DM of the head & neck with less adequate surgical margins and found it was more likely to be used in those with an advanced stage or older patients. However, they also demonstrated that the recurrence rates, despite these poor prognostic features, were similar to those patients treated only with surgery, and concluded that adjuvant RT aids in decreasing local recurrence where adequate surgical excision is not possible [21].

Several studies have demonstrated a benefit with adjuvant RT. Strom et al. (2014) retrospective review of 277 patients showed a decrease in local recurrence in those with positive surgical margins (89% vs 18%) and those with head and neck primaries with negative margins (95% vs 76%) [31]. Similarly, local control is improved by the receipt of postoperative RT in other smaller sized studies [39-41], or in those known to be high risk for local recurrence [42]. However, the long term survival benefit of this is questionable - Wasif et al.’s (2011) large SEER Registry study found that receipt of RT was associated with a decreased 5-year OS [20]. An ongoing randomised clinical trial (NCT00975520) to assess the role of adjuvant radiotherapy is currently underway, with data collection completed in January 2021. This trial will also evaluate the impact on overall survival as a secondary outcome measure [43]. The results of these studies would suggest that adjuvant RT could be offered to patients who have inadequate surgical margins and considered in those with head and neck primaries or other high-risk features. However, the current impact on overall survival is unclear, and as such, clear definitive guidelines are not currently available.

7. Adjuvant Treatments

Melanoma has been revolutionized in recent times with the advent of adjuvant treat-

ments such as targeted and immune- therapies. However, the evidence surrounding the application of these therapies in the treatment of DM is limited. Whilst DM often displays mutations in BRAF, and other genes associated with the MAPK pathway, reports of the characteristic BRAFV600E mutations seen in MM are varied. Whilst this mutation has been reported as reduced or absent in genomic studies [44, 45], others have reported the incidence this mutation to be up to 30%[46]. Whilst there is limited evidence outlining the role of these BRAF inhibitors specifically, it stands to reason that where the mutation is present, these treatments may be effective.

PD-1 blockade has shown positive results when utilised in the treatment of DM, though in small cohorts only. Eroglu et al. (2018) analysed sixty patients with unresectable metastatic disease retrospectively, who had been treated with either a PD-1 or PD-L1 monoclonal antibody. This study reported objective tumour response in 70% of patients, and a complete response in 32% [47]. As the authors note, DM has a high mutational burden, ranking highly regards to mutational burden among other cancers [44]. It is thought that this mutational burden is immunogenic, and that PD-1 blockade can aid in reactivating a pre-existing adaptive immune response. Most recently, Pembrolizumab has been licensed by the FDA for treatment of tumours with a high mutational burden specifically [48], supporting its' use in advanced presentations of DM.

8. Survival

When first described by Conley et al. (1979), desmoplastic melanoma was reported as 'an aggressive, infiltrating and potentially metastasising tumour' which was 'usually fatal', and this was traditionally thought of as a more aggressive subtype of melanoma. However, further studies have since challenged this view. In 1995, Skelton et al. (1995) reported that even DMs with a thickness >4mm had a survival of 61%; a significantly better prognosis compared to other melanomas of the same depth[49]. Since this, overall 10-year survival rates for DM have been reported at 79.2% [3], which compares favourably to that of MM, as even in thin melanomas <1mm, 10-year survival is reported at 76-86% [50]. Similarly, when compared with case-match controls for tumour thickness, sex, age and year of diagnosis in smaller case series, patients with DM have survival rates similar to those with other melanomas [27].

9. Conclusions

Desmoplastic melanoma (DM) is a rare variant of melanoma, that may often pose difficulty in diagnosis and of which clinicians that check the skin should be aware. In treating DM, every effort should be made to obtain a wide, clear surgical margin to ensure definitive excision as a first treatment. The role of other adjunctive treatments remains controversial in DM.

10. We recommend that:

- Surgical excision, with an adequate excision margin is the current definitive treatment, and should be obtained where possible.

- SLNB should be offered as it would be in non-desmoplastic MM, with particular emphasis placed upon its' value in mDM

- Adjuvant radiation may be offered to patients with inadequate surgical margins, or otherwise concerning features for local recurrence such as neurotropism.

- Limited evidence suggests that adjuvant treatments such as PD-1 blockade may be effective in the treatment of metastatic disease.

Further research into the impact of histological features, such as neurotropism and subtypes, on clinical management is required, and there needs to be an effort to standardise nomenclature within the literature.

11. Conflict of Interest Statement

The authors have no conflict of interest to declare

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