Guidelines: Should primary desmoplastic neurotropic melanomas be treated differently?

Desmoplastic melanoma

Desmoplastic melanoma (DM) is a rare sub-type of melanoma (1-4% of primary cutaneous melanoma) that may be difficult to recognise, both clinically and pathologically, and behave differently compared to non-desmoplastic melanoma (non-DM).\cite{1,2,3,4,5} As a consequence, the guidelines for the management of non-DM may not be directly applicable to DM and special consideration of this sub-type is warranted.

Conley et al first described desmoplastic melanoma in 1971.\cite{6} It has been characterised histologically by variably pleomorphic, spindle-shaped cells with associated collagen production/stromal desmoplasia. The cells resemble fibroblasts as would be found in scar tissue.\cite{1}

DM usually present as a firm plaque, nodule or thickening that is often not pigmented.\cite{7} There may be little or no change in the appearance of the overlying epidermis. The often unremarkable appearance leads to delayed diagnosis in many cases.\cite{8,9} As a result of the later presentation, the mean and median thickness of DM is close to 4.0mm (2.0 mm- 6.5mm) in many reported series.\cite{1,2,3,4,8,10,11,12,13,14,15,16} The vast majority of DM are Clark level IV or V.

DM are strongly associated with sun-exposure and most frequently arise in the head and neck region.\cite{1,11,12,3,17,15,16} In a large study of scalp melanomas, 29% were desmoplastic.\cite{18} DM have been shown in all published series to be more common in males (M:F 2:1). Patients with DM are generally older at presentation than patients with non-DM. The DM median age is 60-70 years whereas non-DM is 50 years.\cite{1,19,11,12,2,3,4,13,15,16,14,20}

In 2005, it was proposed that DM should be further sub-classified into pure DM (pDM) and mixed DM (mDM) on the basis that the subclasses have differing clinical behaviour.\cite{21,22,23} Pure DM have been defined as those with 90% or more desmoplastic component while mixed DM were defined as those with greater than 10% and less than 90% desmoplastic component. pDM account for close to 50% of all DM.\cite{12,2,3,4,13,16,14} In a review of 252 DM, Murali et al showed pDM to differ significantly from mDM in location, Clark level, Breslow thickness, mitotic rate, perineural invasion and locoregional recurrence rate (4% vs 12%).\cite{14} A lower rate of distant metastasis with pDM and better survival\cite{21,23,12,4} has been demonstrated in some series while not in others.\cite{11,14}
Reflecting the role of sunlight exposure in the aetiology of melanoma, cutaneous melanoma is known to have the highest number of mutations of any cancer. Recent evidence indicates that desmoplastic melanoma has the highest mutation burden of any melanoma. Similarly the driver mutations events associated with desmoplastic melanoma differ from those more commonly seen in other types of cutaneous melanoma. Common mutations in desmoplastic melanoma include: NF1, ERBB2, MAP2K1, MAP3K1, BRAF, EGFR, MET, TERT, NFKBIE, NRAS PIK3CA PTPN11.

An important histological feature of DM is a propensity for neurotropism. This subtype is referred to as desmoplastic neurotropic melanoma (DNM). Neurotropism was first described by Reed and Leonard in 1979 and further defined by Chen et al and Varey et al with the following characteristics 1) tumour extension along nerves perineurally or endoneurally; 2) formation within the tumour of structures resembling nerves; 3) a change in the morphology of the tumour cells to resemble neural tissue. This is seen in 30–60% of DM and may be more frequently found in pDM. Occasionally named nerves can be involved, an issue that can be particularly troublesome with cranial nerves and their branches due to extension towards the base of the skull.

Neurotropic melanoma

Importantly, up to 30% of neurotropic melanomas arise in non-desmoplastic melanomas. However, neurotropic melanoma has rarely been discussed in the literature outside the setting of DNM. Varey et al (2017) reported 191 such cases (28%), with the remaining 480 cases of neurotropic melanoma being DNM (72%).

The overall incidence of non-DM neurotropic melanoma is unknown, but likely to be less than 1% of all melanomas. There is some evidence to suggest that there may be also be a higher incidence of neurotropism in acral lentiginous melanoma (ALM), possibly up to 8% cases. A study by Scanlon et al (2014) of 32 NM cases found that only 34% were DNM, with 22% ALM (acral lentiginous melanoma) and 41% superficial spreading or nodular. A study of ALM by Nagore et al (2008) found neurotropism to be present in 2 of 25 cases (8%), compared to 8 of 549 (1.5%, p=0.014) other melanoma subtypes (superficial spreading, nodular and lentigo maligna, but excluding DNM).

See:
- What is the optimal management for primary desmoplastic and neurotropic melanomas?
- What is the role of sentinel node biopsy for desmoplastic melanoma?

References


