

Tumoral PD-L1 expression in desmoplastic melanoma is associated with depth of invasion, tumor-infiltrating CD8 cytotoxic lymphocytes and the mixed cytomorphological variant

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Recently, patients with metastatic desmoplastic melanoma (DM) have been shown to respond more favorably to anti-PD1/PD-L1 therapy than other melanoma subtypes. Given this, we evaluated PD-L1/2 expression in primary DM samples and correlated these with subtype, CD8+ lymphocyte status, histopathological prognosticators, and select genetic alterations. Eighty-six (36 mixed DM, 50 pure DM) archival annotated samples met inclusion criteria and were immunohistochemically semiquantitatively evaluated. Per established criteria, for PD-L1/L2, cases with $\geq 5\%$ tumoral expression, and for CD8, cases with a predominantly peri/intratumoral CD8+ infiltrate were scored positive. Univariate analysis (chi-square and Wilcoxon) identified potential confounders and a nested case–control study was accomplished using multiple logistic regression. For PD-L1, 49% of cases were positive and 71% of cases with thickness > 4 mm were positive; PD-L1 expression differed by median depth (3.29 mm, interquartile range = 3.58 mm for PD-L1 positives vs 1.75 mm, interquartile range = 2.04 mm for PD-L1 negatives, $P = 0.0002$) and was linearly associated with increasing depth of invasion ($P = 0.0003$). PD-L1-positive cases were more likely to display CD8+ lymphocytes (60 vs 28% $P = 0.0047$). The presence of CD8+ lymphocytes correlated significantly with depth of invasion > 1 mm ($P = 0.022$). On multivariate analysis, PD-L1 was 6.14 \times more likely to be expressed in mixed DM than pure DM ($P = 0.0131$), CD8+ staining was 6.22 \times more likely in PD-L1 positive cases than in PD-L1 negative ($P = 0.0118$), and tumor depth was associated with greater odds of PD-L1 expression (OR = 1.61, $P = 0.0181$). PD-L2 expression was observed in 48% of cases but did not correlate with any variables. Correlation of tumoral PD-L1 with increased depth and CD8+ lymphocytes implicates the tumoral immune microenvironment with advancing disease in DM. Enhanced tumoral PD-L1 expression in the mixed cytomorphological variant provides an insight into the differential pathogenesis of the subtypes and suggests that these patients are likely better candidates for anti-PD/PD-L1 therapy.

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Desmoplastic melanoma (DM), an uncommon morphological variant of melanoma, is associated with old age, chronic sun exposure, and location on the head and neck.^{1,2} Although relatively rare, the incidence of DM appears to be on the rise with a 4.6% annual increase noted from 1992 to 2007.²