LETTER TO THE EDITOR

Melanoma extravascular migratory metastasis: an important underrecognized phenomenon

Editor,

Extravascular migratory metastasis (EVMM) is the spread of metastases on the external surfaces of microvascular channels, a phenomenon noted by Recamier in 1829, and by Borst (cited by Handley in 1907).[1]

We present a case of an 83-year-old male with a pathology-confirmed invasive melanoma on the anterior aspect of his shoulder, Breslow thickness 1.4 mm and dermal mitotic rate of 6/mm. There was EVMM but no intravascular invasion (Fig. 1), confirmed with a combined CD34/SOX10 immunohistochemical stain (Fig. 2).

The presence of EVMM identifies an alternate means of metastatic spread when identified within the primary tumour. This may be an important mechanism in the development of melanoma satellites and in-transit metastases. EVMM has been reported in various tumours, including melanoma, cutaneous squamous cell carcinoma, prostatic adenocarcinoma, pancreatic adenocarcinoma, carcinosarcomas of the ovaries and endometrium, glioma, glioblastoma and liposarcoma.[2]

The underlying mechanism of EVMM is thought to be pericyte mimicry (PM) by melanoma cells.[3] Pericytes are modified smooth muscle cells which surround and send out processes along normal microvasculature channels. They are separated from endothelial cells and the parenchyma by a thin layer of basal lamina. Their functions include angiogenesis, vessel stabilization, vascular permeability, localized blood pressure control, haemostasis and tissue homeostasis. They exhibit macrophage-like activity and are also progenitors of mesenchymal cells.[4]

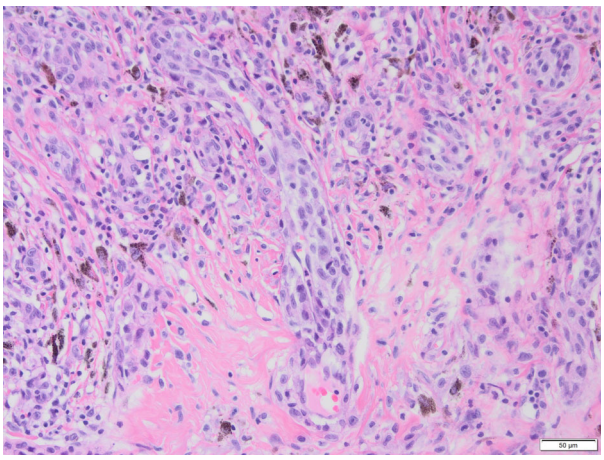

Figure 1 High-power H&E section showing spread of melanoma along vessels.

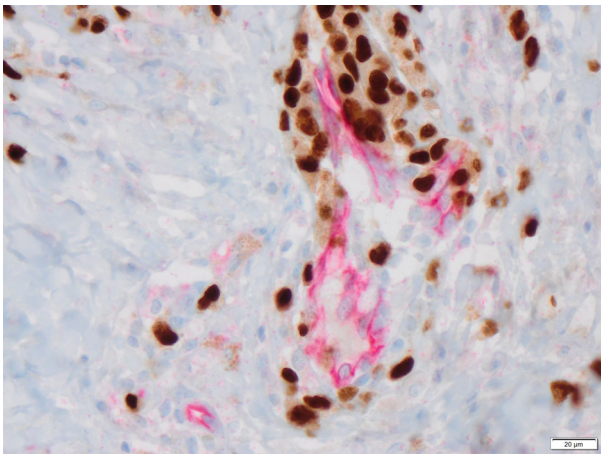

Figure 2 Combined SOX10 (brown) and CD31 (red) immunohistochemical staining showing the spread of melanoma cells on the abluminal surface of vessels.

In PM, melanoma or other neoplastic cells express antigens that occur on pericytes, allowing them to interact with endothelial cell surface receptors. This may induce differential expression of malignancy-associated genes linked to metastasis, disease progression, epithelial to mesenchymal transition, embryonic/stem cell properties and pericyte recruitment. PM allows tumour cells to adhere to and spread along the external surfaces of microvessels, a process which largely occurs at the leading edges of tumours.[3]

Intermittent intense ultraviolet (UV) light exposure with an associated neutrophilic response increases melanoma motility, angiotropism, pericyte mimicry and metastasis, and in mouse models causes accelerated melanoma growth and enhanced metastases and angiogenesis[5].

UVB radiation induces IL8, a neutrophilic chemoattractant.[6] This together with increased secretion of CXCL chemokines attracts neutrophils to the site of tumour. Neutrophil granules contain vascular endothelial growth factor (VEGF) which activates endothelial cells and promotes endothelial growth, which

is enhanced by TNF alpha and CXCL chemokines. Direct neutrophil to endothelial cell interaction followed by binding of the adhesion molecule ICAM-1 on the endothelium with integrin on the neutrophils allows the neutrophil to activate the endothelial cell and promote angiogenesis.[7]

The adhesion of malignant melanocytes to endothelial cells followed by tumour spread is facilitated by laminins located within the amorphous matrix. The role of laminins includes cell adhesion, migration, signalling, outgrowth and metastasis. In vitro experiments showed that the C16 peptide γ1 laminin chain has angiotropic, extravascular migration promoting activity in melanoma. Angiotropic melanoma cells over-express some laminins and laminin receptors.[8]

The mechanism is similar to that occurring in embryogenesis, in which melanoblasts derived from Schwann cell precursors in the neural tube migrate along the dorsolateral pathway to the skin by travelling alongside microvascular channels.[9]

Extravascular migratory metastasis is associated with regional and distant metastases in primary cutaneous melanoma. In a retrospective study, the presence of EVMM was associated with distant metastases and disease progression; however, overall survival was not affected.[10]

Extravascular migratory metastasis is probably more common than reported. A recent study suggested that up to 37% of cases of melanoma exhibit EVMM when immunohistochemical stains for melanocytic and vascular markers were employed.[10] The larger medical community should be made aware of this feature.

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