

The calico transmutation-malignant melanoma

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EDITORIAL

Malignant melanoma is a neoplasm emerging from melanocytes present within cutis, mucosa or autochthonous melanocytes manifest within internal viscera as gastrointestinal tract or central nervous system. Malignant melanoma may occur de novo or emerge within pre-existing nevus, designated as melanoma arising in nevus. Previously scripted as melanose or fungoid disease, the cutaneous tumefaction is associated with significant mortality. Five year survival of localized disease is 99% whereas proportionate tumour reoccurrence of advanced grade lesions is 13% within 2 years. Malignant melanoma arises due to concurrence of genomic, environmental and host factors. Initiation with mitogenic driver mutations as encountered with *BRAF* mutation along with circumvented primary senescence and decimated *CDKN2A*, lack of apoptosis with *TP53* mutation and cellular immortalization associated with *TERT*-p mutation engenders the neoplasm. Predominant oncogenic signalling pathways are comprised of Mitogen Activated Protein Kinase (MAPK) pathway with constituent RAS, RAF, MEK or ERK molecules. Additionally, *PI3K*, *AKT* and *mTOR* along with Wnt or β -catenin signalling pathway may be implicated. Cumulative Sun Damage (CSD) with minimal, sunlight-inflicted cutaneous injury may engender superficial spreading melanoma or low cumulative sun damage nodular melanoma. Extensive, actinic induced deterioration generates variants as lentigo maligna melanoma, desmoplastic melanoma or high cumulative sun damage nodular melanoma. Nevertheless, Spitz melanoma, acral melanoma, mucosal melanoma, melanoma arising in congenital nevus, melanoma arising in blue nevus and uveal melanoma appear inconstantly associated with actinic induced cutaneous injury. Factors contributing to neoplastic emergence are fair-skinned individuals of Fitzpatrick scale I and II, excessive moles >50, dysplastic nevus, intense, intermittent exposure to sunlight or ultraviolet radiation, immunosuppression, preceding or familial malignant melanoma or germline mutations of *CDKN2A*, *CDK4*, *MITF*, *TERT*, *ACD*, *TERF2IP*, *POT1*, *MC1R* or *BAP1* genes. A male predominance is observed with a male to female proportion of 1.5:1 [1,2]. Cutaneous malignant melanoma commonly appears upon lower extremities or trunk although no site of tumour emergence is exempt. Subungual lesions maybe delineated. Extra-cutaneous malignant melanoma may be discerned upon uvea, leptomeninges, anorectal region and upper aero-digestive or sino-nasal tract. Generally, nodular, polypoid, verrucous, flattened or mildly elevated, pigmented tumefaction is observed.

Amelanotic melanoma enunciates achromic lesions. Superficial spreading melanoma, lentigo maligna melanoma or acral lentiginous melanoma can be appropriately assessed with features as asymmetry, irregular border, variation in colour, lesion diameter >6 millimetres and tumour evolution. Malignant melanoma can concur with dysplastic nevus syndrome, *BAP1* inactivated tumour syndrome, Xeroderma pigmentosum or Parkinson's disease. Grossly, elliptical or asymmetric cutaneous lesions with variable surface representation and magnitude >6 millimetres are observed [1,2]. Malignant melanoma expounds an extensively variable cytological representation with diverse cluster configuration and may simulate a gamut of malignant tumefaction [1,2]. Tumour is composed of epithelioid cells, spindle-shaped cells or giant cells imbued with finely-granular, dispersed melanin pigment and admixed melanophages. Pigmentation can be diffusely subtle or may obscure cellular features. Significant anisocytosis, enlarged, irregular nuclei with prominent, eosinophilic nucleoli and nuclear pseudo-inclusions are observed. Upon microscopy, melanoma in situ exhibits confluent lesions with 'skip areas' and contiguous tumour progression, tumour cell nests of variable magnitude and configuration, inadequately defined lesion perimeter, pagetoid melanocytes with singular, dis-cohesive, disseminated melanocytes confined to the superficial epidermis, ulcerated epidermal layer and irregularly disseminated junctional melanocytes. Epithelioid or spindle-shaped tumour cells are imbued with dusty, pigmented cytoplasm, nuclei with significant pleomorphism, hyperchromasia, enlargement, anisocytosis and prominent eosinophilic nucleoli. The nuclear chromatin is coarse and irregular with peripheral condensation, designated as "peppered moth" nuclei. Circumscribing stroma exhibits a variable infiltrate of chronic inflammatory cells as lymphocytes, subdivided into brisk or non-brisk exudate. Stroma may be devoid of inflammation. Dermal expansion of tumefaction enunciates radial growth with infiltration of singular cells or miniature tumour cell nests within the papillary dermis. Dermal fibrosis is focal and melanin pigment is irregularly disseminated. Vertical tumour expansion exemplifies predominant tumour cell aggregates within the papillary dermis whereas junctional cell nests appear minimal.

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Complex, asymmetrical tumour evolution delineates irregular nests, fascicles and expansible sheets of neoplastic cells. Tumour cells appear devoid of maturation expounded by decreasing magnitude of melanocyte nests towards the base of the lesion. Focal necrosis and enhanced dermal mitotic activity >1 per mm² may occur [1,2]. Superficial spreading melanoma is a frequent subtype comprised of asymmetrical proliferation of atypical melanocytes, predominant junctional activity with singular melanocytes, significant pagetoid spread > 0.5 mm² and mutation of *BRAF V600E* gene. Lentigo maligna melanoma commonly occurs in elderly subjects with chronic actinic cutaneous injury. Confluent progression of singular melanocytes along dermo-epidermal junction configure miniature nests with evolution of 'lentiginous pattern'. Amalgamated, horizontal cell nests of variable magnitude and outline display a nevoid or dysplastic nevus-like pattern. Tumour cells may extend into hair follicles. Solar elastosis is significant. Dermal infiltration of atypical melanocytes may ensue. Lesion is associated with mutation of *BRAF non-V600E*, *NRAS* or *KIT* genes.

- Acral lentiginous melanoma is commonly discerned in African, Caribbean or Asian population. Tumefaction exhibits an acral location wherein lesions are situated upon palms, soles or subungual region. An asymmetrical, lentiginous proliferation of magnitude >7 millimetres is common. Melanocytes are predominantly accumulated upon tips of cristae profunda intermedia. Tumour cells may extend into eccrine ducts. Mutation of *KIT* gene may occur.
- Desmoplastic melanoma is an infrequent variant occurring in elderly subjects with chronic actinic cutaneous injury. Tumefaction can manifest as a subtle, scar-like, paucicellular, dermal proliferation of spindle-shaped cells or a sarcoma-like, pleomorphic melanoma with spindle-shaped cells and partial desmoplasia. Junctional melanocytic proliferation in an atypical lentiginous pattern may ensue. Perivascular lymphocytic aggregates may appear along with foci of neuro-tropism. Desmoplastic melanoma may arise singularly or may appear admixed with foci of conventional melanoma with >10% of conventional or spindle-shaped cellular subtype (Fig 1,2)
- Pure desmoplastic melanoma exhibits enhanced localized reoccurrence with minimal regional lymph node involvement. Tumefaction in (Table 1) is immune non-reactive to MelanA, tyrosinase or *HMB45*. Mutations within *NF1* or *TP53* genes may ensue [1,2].
- Nevoid melanoma is comprised of verrucous lesions or dome-shaped tumefaction. Lesions are minimally asymmetric, devoid of radial tumour expansion and demonstrate elongated, thinned, rete ridges with stuffed dermal papillae, designated as 'puffy shirt sign'. Focal pseudo-maturation is observed along with elevated mitotic activity.
- Melanoma arising in blue nevus appears upon the periphery of preexisting, blue nevus. Tumefaction is intensely cellular and devoid of intervening stroma. Focal necrosis is observed. Nuclear decimation of *BAP1* ensues. Genomic mutations of *GNAQ*, *GNA11*, *CYSLTR2*, *EIFIAX* genes occur along with mutation of *BAP1* or *SF3B1* genes [1,2].

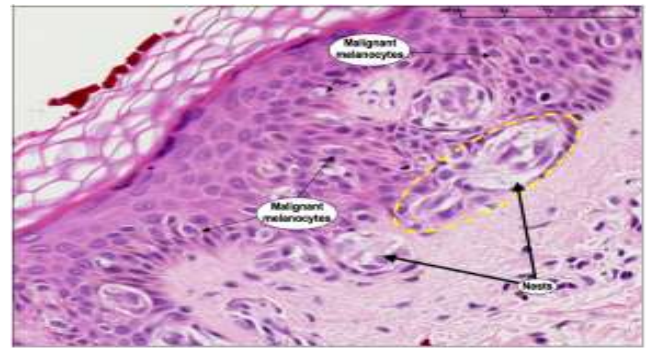


Figure 1) Malignant melanoma depicting intra-epidermal nests of neoplastic melanocytes cells with significant pleomorphism, hyperchromasia and dusty pigmentation.

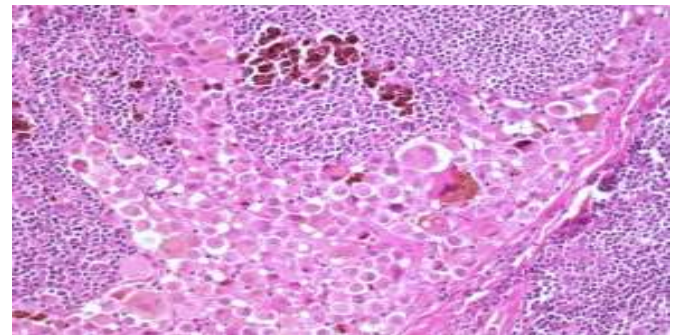


Figure 2) Malignant melanoma with metastasis in lymph node demonstrating melanin laden cells with abundant cytoplasm, vesicular nuclei and anisocytosis surrounded by lymphoid cells

Table 1: TNM classification of Malignant Melanoma

Tumour	Node	Metastasis
T0: Melanoma cells absent at primary site	N0: Regional lymph nodes deposits absent	M0: Distant metastasis absent
T1: Tumour ≤1mm • T1a: Tumour <0.8mm thick, non ulcerated • T1b: Tumour <0.8mm, ulcerated or between 0.8mm to 1cm, ulcerated/non ulcerated	• N1a: Microscopic deposits in ≤3 lymph nodes • N1b: Tumour spread to one adjacent node • N1c: Satellite tumours or spread to cutaneous lymphatic channels	M1: Distant metastasis into lungs, liver, brain with raised lactic hydrogenase
• T2a: Tumour between 1mm to 2mm, non ulcerated • T2b: Tumour between 1mm to 2mm, ulcerated	• N2a: Microscopic deposits in ~3 lymph nodes • N2b: Tumour spread ≤3 lymph nodes • N2c: Satellite tumours or spread to cutaneous lymphatic channels & lymph nodes	

- T3a:Tumour<4mm, non ulcerated •T3b:Tumour between 2mm to 4mm, ulcerated
- T4a:Tumour >4mm, non-ulcerated •T4b: Tumour >4mm, ulcerated
- N3a: Tumour deposits ~ 4 regional nodes •N3b: Tumour spread to≥4 nodes with palpable lymph node •N3c: Tumour deposits in adjacent, matted lymph nodes

Tis: Melanoma in situ

On ultrastructural examination, intracytoplasmic melanosomes and premelanosomes can be detected. Malignant melanoma is immune reactive to S100 protein, *SOX10*, *MelanA/MART1*, *HMB45*, *tyrosinase*, *MiTF*, *PRAME*, *PNL2* or *KBA62*. *Ki67* proliferative index is >10%. Tumour cells are immune non reactive to p16, cytokeratin, *CD34*, *CD45* or *CD68*. Malignant melanoma depicts multiple chromosomal copy number aberrations which can be appropriately discerned with FISH, Comparative Genomic Hybridization (CGH), array CGH and single nucleotide polymorphism array. Genomic gains are observed in chromosomes, 6p, 7q, 17q, 20q, 4q, 8q, 1q or 11q. Genomic losses occur in chromosomes 9p21, 10 or 21q. Genetic driver alterations of *BRAF*, *NRAS*, *NF1*, *KIT*, Telomerase Reverse Transcriptase Promoter (*TERT-p*), *CDKN2A*, *PTEN* or *TP53* genes can be discerned with PCR or next generation sequencing. Generally, tumour mutational burden is elevated and appears at >10 mut/Mb [3,4]. Gene Expression Profile (GEP) and mRNA expression of uveal and cutaneous melanoma related genes depicts immune reactive *PRAME*, *S100A9* component, 8 immune related genes and 9 housekeeping genes. Invasive malignant melanoma may simulate and requires segregation from several undifferentiated malignant neoplasms. Conditions such as benign melanocytic nevus, dysplastic nevus, persistent or recurrent nevus, melanocytic nevi of special sites as scalp, ear, cutaneous folders, breast or genitalia, mitotically active nevi, Spitz tumour, *BAP1* inactivated melanocytic tumour, pigmented epithelioid melanocytoma, deep penetrating nevus, cellular blue nevus, metastatic malignant melanoma, Bowen's disease(squamous cell carcinoma in situ), extra-mammary Paget's disease, Merkel cell carcinoma, atypical fibroxanthoma or pleomorphic dermal sarcoma, poorly differentiated squamous cell carcinoma, cutaneous leiomyosarcoma, epithelioid angiosarcoma or anaplastic lymphoma necessitate demarcation. Comprehensive evaluation of cutaneous surfaces and suspicious lesions is required with cogent histopathological determination. Advanced neoplasms exhibit elevated levels of lactic dehydrogenase. Concurrence with parameters as age, gender, anatomical location and dermoscopic features is beneficial.

Evaluation of *BRAF* genetic mutation is recommended in stage III or stage IV neoplasms. Upon dermoscopy, features such as atypical pigmented network, blue-whitish veil, atypical vascular pattern, abrupt tumour cut-off, atypical dots or globules, pseudopods, radial steaming, milky-red areas, shiny white or regression structures, scar-like depigmentation, multicomponent pattern or neoplastic colour >4 can be observed. Features accompanying superior prognostic outcomes are young, female subjects with lesions of preliminary stage incriminating accessible sites as lower extremities. Histologic subtypes as pure desmoplastic melanoma or Spitz melanoma exhibits favourable outcome. A brisk inflammatory response of tumour infiltrating lymphocytes is advantageous. Factors demonstrating inferior prognosis are incrimination of elderly, male subjects with lesions of enhanced Breslow index situated upon relatively unexposed sites as posterior trunk, upper arm, head and neck or acral region. Tumour deposits within sentinel lymph node, lymphatic invasion, enhanced angiogenesis, discernible micro-satellites, neuro-tropism or localized reoccurrence, ulcerated lesions with elevated dermal mitotic activity, absent or non-brisk inflammatory response with tumour infiltrating lymphocytes are associated with unfavourable outcome. Comprehensive surgical extermination with broad perimeter of uninvolved tissue, contingent to Breslow index, is a recommended therapeutic strategy. In situ lesions require removal of cutaneous margin of 0.5 cm, lesions with Breslow depth of up to 2 mm mandate a safe perimeter of 1 centimetre and tumefaction with Breslow depth >2 millimetres necessitate a 2 cm cutaneous clearance. Sentinel lymph node biopsy can be optimally adopted for tumour staging and assessment of prognostic outcomes. Adjuvant or systemic therapy is employed for treating advanced, stage III malignant melanoma. Targeted therapy with *BRAF*, *MEK* and *KIT* inhibitors can be utilized. Besides, checkpoint inhibitors with *PDI* / *PDL1* inhibitors or blockade of *CTLA4* pathway can be adopted. Chemotherapy and radiotherapy are relevant in certain advanced, inadequately differentiated lesions [3,4].

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