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Commentary

Bistered and Tawny-Malignant Melanotic Nerve Sheath Tumour

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Malignant melanotic nerve sheath tumour is an exceptionally discerned, aggressive peripheral nerve sheath tumour. Malignant melanotic nerve sheath tumour may emerge as a sporadic neoplasm or configure a segment of Carney complex. Previously designated as a benign neoplasm, tumefaction commonly emerges in concurrence with spinal nerves or visceral autonomic nerves.

As per contemporary classification of World Health Organization (WHO), malignant melanotic nerve sheath tumour is associated with malignant biological behaviour. Neoplasm is consistently comprised of Schwann cells demonstrating melanocytic differentiation and exhibits fascicles or sheet-like proliferation of intensely pigmented, uniform, plump, spindle shaped cells. Tumour cells manifest a co-expression of S100 protein and SOX10 along with immune reactivity to melanocytic markers as human melanoma black 45 (HMB45) antigen or MelanA. Absence of PRKAR1A expression suggests a link to Carney complex.

Malignant melanotic nerve sheath tumour is additionally designated as melanotic schwannoma, psammomatous melanotic schwannoma or malignant melanotic Schwannian tumour.

Malignant melanotic nerve sheath tumour is associated with an incompletely understood pathophysiology and configures an estimated < 1% of nerve sheath tumours.

Mean age of disease representation appears at 41 years although neoplasm may be encountered within 11 years to 84 years. A specific age, gender or geographic predilection is absent [1,2].

Malignant melanotic nerve sheath tumour preponderantly arises within spinal nerves, para-spinal sympathetic chain or gastrointestinal tract, especially within locales as oesophagus and gastric region.

Sites such as cerebellum, orbit, heart, trachea, bronchus, cervix, bone, soft tissue or diverse cutaneous regions may be exceptionally implicated [1,2].

Majority of neoplasms appear as sporadic lesions. Characteristically, a complex karyotype with reoccurring monosomy confined to chromosomal band 22q, variable whole chromosomal gains and repetitive genomic losses within chromosomes 1, 21 and 17p may be encountered [1,2].

An estimated 50% of psammomatous malignant melanotic nerve sheath tumours appear concurrent to Carney complex demonstrating genetic mutation within chromosome 17 with involvement of PRKAR1A/17q24 band [1,2].

Malignant melanotic nerve sheath tumour demonstrates loss of expression of PRKAR1A gene, in concurrence with mutations confined to the gene. Neoplasms with aforesaid genomic alterations appear indicative of Carney complex [1,2].

Cytogenetic evaluation exhibits trisomy 6p and ring chromosome 11, thereby indicating the occurrence of genetic aberrations concordant with malignant melanoma. Nevertheless, the neoplasm appears to lack BRAF V600E gene, as encountered within malignant melanoma. Missense DDR2 genetic mutation confined to Q231K locus may be documented [2,3].

Malignant melanotic nerve sheath tumour exemplifies a localized tumefaction associated with pain and neurological symptoms. Aforesaid clinical symptoms may be incidental or appear contingent to incriminated site and proportionate to tumour progression.

Neoplasms abutting nerves (~35.5%) may exhibit motor or sensory anomalies [2,3].

Enlarged tumours may depict pressure symptoms. Cutaneous lesions may manifest clinical features reminiscent of malignant melanoma. Around one third (~29%) of tumefaction may be asymptomatic.

Upon gross examination, majority of neoplasms exceed > 5 centimetre diameter. Tumefaction is well circumscribed and superimposed with an attenuated fibrous membrane. Neoplasm may abut a nerve or erode adjacent bone [2,3].

Superficial tumour surface may exemplify solid cysts. Cut surface enunciates a tar-like consistency and varies from grey brown to pitch black [2,3].

Upon microscopy, a circumscribed, non encapsulated lesion is encountered. Neoplasm is configured of interlacing fascicles or cellular nests wherein tumour cells and melanophages delineate accumulation of melanin. Tumefaction is composed of plump, spindle shaped cells and epithelioid cells imbued with spherical, elliptical or elongated nuclei with delicate, evenly disseminated nuclear chromatin and miniature, distinct nucleoli. Few cellular nuclei may exhibit enlarged and prominent nucleoli. Mitotic figures are exceptionally discerned.

Tumefaction associated with Carney complex may enunciate sheets of adipose-like cells along with psammoma bodies [2,3].

Occasionally, foci of degenerative nuclear atypia, significantly enlarged, hyperchromatic nuclei, smudgy nuclear chromatin or intracytoplasmic nuclear inclusions may be encountered [2,3].

Psammoma bodies may represent as isolated foci or innumerable, calcified articulations. Accompanying, discernible tumour necrosis configures a preponderantly geographic pattern [3,4].

Although meticulous diagnostic criterion of malignant metamorphosis remain undefined, combined histological features as enlarged, vesicular nuclei with macro-nucleoli, significant mitotic activity or tumour associated necrosis appear indicative of malignant transformation and aggressive biological behaviour [3,4].

Upon ultrastructural examination, epithelial Schwann cells and pigmented spindle shaped cells appear as bundle shaped, interleaved or wheel shaped articulations. Tumour cells appear intermingled with spherical to elliptical nuclei and conspicuous nucleoli. Nuclear division is exceptionally encountered [3,4].

Innumerable elongated tumour cell processes, duplication of basement membrane and melanosomes may be enunciated within diverse stages of neoplastic development [3,4].

Malignant melanotic nerve sheath tumour appears immune reactive to S100 protein, SOX 10, melan A, human melanoma black 45 (HMB 45) antigen or tyrosinase. SMARCB1 gene is retained within tumour cells. Ki67 proliferation index appears < 5% in majority (~90%) of instances although figures such as 8% may be variably encountered.

Antigen Ki67 exhibits an average mitotic index of 3% although values ranging from 1% to 20% may be observed [4,5].

Malignant melanotic nerve sheath tumour is immune non reactive to glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA) or cytokeratin AE1/AE3.

Tumefaction depicts absence of PRKAR1A genetic expression [4,5].

Malignant melanotic nerve sheath tumour requires segregation from neoplasms such as malignant melanoma, pigmented neurofibroma, pigmented dermatofibrosarcoma protuberans, pigmented epithelioid melanocytoma and schwannoma with haemorrhage or neuromelanin accumulation [4,5].

Malignant melanotic nerve sheath tumour can be appropriately discerned with cogent clinical history. Tissue sampling can be subjected to precise histological examination [4,5].

Tumour evaluation upon computerized tomography (CT) or magnetic resonance imaging (MRI) is an optimal, recommended diagnostic modality [4,5].

Computerized tomography enunciates an iso-attenuating or hyper-attenuating lesion exhibiting focal calcification along with remodelling and erosion of subjacent bone [4,5].

Fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) can be beneficially employed to categorize the neoplasm and determine malignant biological behaviour contingent to glucose uptake and metabolism, prior to specific morphological alterations [4,5].

Fluorodeoxyglucose positron emission tomography (FDG PET/CT) appears advantageous in differentiating benign from malignant lesions, discerning occult tumour metastases, monitoring response to therapy and assessing prognostic outcomes [4,5].

Upon magnetic resonance imaging (MRI), imaging signal appears variable due to melanin content and distribution within the neoplasm or intra-tumour haemorrhage [4,5].

T1 weighted imaging exhibits hyper-intense signals whereas T2 weighted imaging exemplifies hypo-intense signals on account of paramagnetic effect of melanin. Comprehensive surgical eradication of the neoplasm is an optimal mode of therapy [4,5].

Adoption of adjuvant radiotherapy remains debatable and appears superfluous in the absence of cogent histological evidence of malignant metamorphosis. Therefore, adjuvant therapy requires circumvention and meticulous clinical or radiographic monitoring is necessitated [4,5].

Adjuvant radiotherapy appears beneficial in instances exhibiting histological criteria indicative of malignant metamorphosis, inadequate surgical resection, tumour reoccurrence or distant metastases. However, precise treatment protocol of radiotherapy remains undefined.

Malignant melanotic nerve sheath tumour confined to vertebral column can be optimally subjected to stereotactic spinal radio-surgical intervention [4,5].

Although majority of lesions demonstrate a benign, indolent clinical course, tumefaction frequently exhibits aggressive clinical behaviour. Localized tumour reoccurrence or proportionate distant metastasis varies from 26% to 44% [4,5].

Of unpredictable biological behaviour, distant metastasis may ensue in the absence of morphological confirmation of malignant metamorphosis. Mitotic activity > 2 per 10 high power fields appears concurrent with tumour metastases [4,5].

Tumour reoccurrence and metastases may ensue within a significant duration or may be delayed to > 20 years following disease discernment. Localized tumour reoccurrence appears within an average of 35% instances and distant metastases occur within ~42% subjects. Frequently, distant metastasis may ensue within pulmonary parenchyma or pleural space. Besides, sites such as mediastinum, diaphragm, pericardium, endocardium, bone, hepatic parenchyma or spleen may be incriminated [4,5].

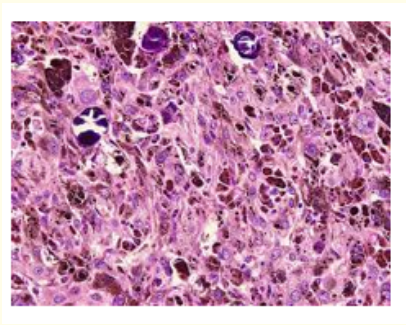

Figure 1: *Malignant melanotic nerve sheath tumour depicting fascicles and nests of uniform spindle shaped to epithelioid cells pervaded with spherical to elongated nuclei, miniature nucleoli and even nuclear chromatin. Tumour cells and melanophages are imbued with melanin. Mitotic activity and focal necrosis are absent [6].*

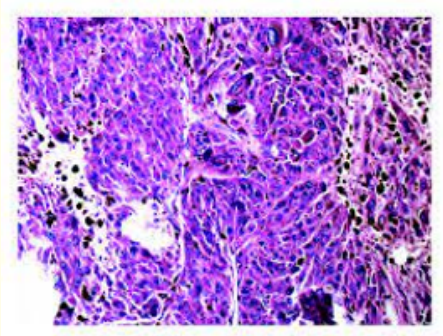

Figure 2: *Malignant melanotic nerve sheath tumour delineating nests and bundles of spindle shaped and epithelioid cells permeated with spherical or elliptical nuclei and conspicuous nucleoli. Tumour cells and melanophages are permeated with melanin [7].*

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6. Image 1 Courtesy: Pathology outlines.

7. Image 2 Courtesy: Hindawi.com.

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