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Editorial

The Afferent Recherche' - Malignant Peripheral Nerve Sheath Tumour

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Preface

Malignant peripheral nerve sheath tumour (MPNST) is an extremely exceptional, aggressive sarcoma of neural crest origin manifesting neural differentiation or appearing in association with a peripheral nerve. World Health Organization (WHO) specifically designates neoplasm arising from malignant transformation of peripheral nerve sheath as malignant peripheral nerve sheath tumour. Thus, contemporary terminology of malignant peripheral nerve sheath tumour (MPNST) is adopted. With archaic nomenclature tumefaction was denominated as neurO.

Fibrosarcoma, malignant schwannoma, neurilemmosarcoma, malignant fibrosarcoma, malignant neurilemmoma or neurogenic sarcoma. Terminology corresponds to malignant proliferation of the nerve sheath, Schwann cells, perineurial fibroblasts or endoneural fibroblasts. Appropriate disease discernment is challenging on account of nonspecific clinical and morphological representation besides lack of standardized diagnostic criterion. Cogent immunohistochemistry is advantageous and confirmatory. Adequate correlation of clinical features, histological findings and immunohistochemistry is necessitated for assessment of Schwannian differentiation and conclusive diagnosis. Neural origin of the neoplasm, especially when engendered from miniature peripheral nerves may be challenging to ascertain. Immune reactivity to S100 protein is universal and comprehensive.

Disease characteristics

An estimated 5% to 10% of soft tissue sarcomas are represented by the malignancy which accounts for nearly 10% to 12% of head and neck lesions [1]. Typically, sarcoma with peripheral nerve sheath differentiation demonstrates an aggressive biological behaviour. Neoplasm appears as a sporadic lesion in around 50% subjects, may be associated with neurofibromatosis type 1 in nearly 40% to 50% individuals and with prior radiation therapy in roughly 10% instances [1,2]. Subjects with neurofibromatosis type 1 (NF1) depict a 10% probability of incurring malignant peripheral nerve sheath tumour whereas approximately 50% of tumefaction arise in individuals with neurofibromatosis type 1 (NF1), especially in concurrence with plexiform neurofibroma [1,2]. Plexiform neurofibroma is a frequently associated precursor lesion in subjects with neurofibromatosis type 1 (NF1). Plexiform neurofibroma emerges in an estimated 50% individuals and roughly 10% to15% of plexiform neurofibromas metamorphose into malignant peripheral nerve sheath tumour [1,2]. Associated nerve sheath tumours such as schwannoma or ganglioneuroma may exceptionally engender secondary malignant peripheral nerve sheath tumour [2]. Diagnostic criterion of malignant peripheral nerve sheath tumour are denominated as • sarcoma arises from a peripheral nerve or •a pre-existing benign nerve sheath tumour as neurofibroma or •neoplasm morphologically demonstrates Schwann cell differentiation. Of obscure histogenesis, emergence of malignant peripheral nerve sheath tumour is a multistep process with incrimination of several genes such as sequential loss of chromosome arm 17q and complete inactivation of NF1 gene. Aforesaid gene encodes a protein designated as neurofibromin which is critical in controlling cellular growth by downregulating RAS genetic products [1,2]. Although precise chromosomal location of NF1 gene upon chromosome 17 is established, neither primary defect of NF1 gene nor the mechanism of malignant metamorphosis is presently recognized. Germline mutations within neurofibromatosis type 1 (NF1) gene predispose to occurrence of peripheral nerve sheath neoplasms with neurofibromatosis type 1(NF1) [1,2]. The sarcoma is cytogeneti-

cally complex and malignant transformation is concomitant with progressive genomic modifications of NF1 or inactivating mutations of CDKN2A, CDKN2B and PRC2 genes. Additional mutations are acquired with progressive malignant metamorphosis of precursor lesions. A subset is associated with point mutations of BRAFV600E gene [1,2]. Radiation therapy predisposes to emergence of secondary sarcoma on account of repetitive denaturation of deoxyribonucleic acid (DNA) and defective genomic regeneration. Around 40% to 50% of neoplasms are associated with family history of neurofibromatosis type 1(NF1). Besides, malignant peripheral nerve sheath tumour may arise de novo or within zones of previous radiation therapy [1,2]. Disease onset is discerned in young individuals between 27 years to 76 years with an average of 50 years. Generally, malignant peripheral nerve sheath tumour commonly arises between 20 years to 50 years. Typically, subjects with neurofibromatosis type1 (NF1) are younger, in contrast to sporadic and radiation -associated neoplasms [1,2]. Tumefaction has an equivalent gender distribution although a female predominance may be observed with female to male proportion of 3:1 with gastrointestinal malignant nerve sheath tumours [1,2]. Commonly, trunk and extremities are incriminated along with head and neck although no anatomic location of tumour distribution is exempt. Frequently implicated sites within the oral cavity are mandible, lips, buccal mucosa, larynx, parapharyngeal or pterygomaxillary space, minor salivary glands besides orbit, cranial nerves, paranasal sinus, nasal cavity and thyroid gland [1,2]. Gastrointestinal malignant peripheral nerve sheath tumours are exceptional. Submucosal malignant nerve sheath tumour can simulate an oesophageal schwannoma, thus may be undiscernible by standardized tissue specimens [3]. Nomenclature of neurofibromatosis type 1 (NF1) associated nerve sheath tumours is exemplified as •atypical neurofibromatous neoplasm of uncertain biological potential (ANNUBP) which demonstrate a minimum of two criterion denominated as cytological atypia, decimated architecture of neurofibroma, hypercellularity and mitotic figures exceeding >1 per 50 high power fields and beneath < 3 per 10 high power fields. •low grade malignant peripheral nerve sheath tumour with aforesaid morphological features of ANNUBP, absence of tumour necrosis and mitotic activity of 3 to 9 per 10 high power fields. •high grade malignant peripheral nerve sheath tumour exhibiting minimal mitotic activity of 10 per 10 high power fields or 3 to 9 per 10 high power fields in combination with tumour necrosis [2,3].

Clinical Elucidation

Clinically, an enlarging nodule associated with pain and neural deficit can be encountered. The neoplasm manifests as an elliptical, well defined, firm, non fluctuant, non tender, non reducible, rapidly progressive swelling of variable magnitude at diverse sites. Superimposed epidermal layer is stretched whereas circumscribing soft tissue is uninvolved. Associated symptoms such as paraesthesia and weakness of sensory or motor branches of incriminated nerve are absent [3,4]. The fleshy malignancy is confluent with adjacent soft tissues and may disseminate through direct extension, haematogenous or perineural spread. Metastasis to regional lymph nodes is exceptional. Cogent histology is mandated although may be non specific and concurrence with clinical and radiologic features is necessitated. Indicative features are proximity to peripheral nerves and associated clinical history of neurofibromatosis type 1 (NF1) or precursor lesions [3,4].

Histological Elucidation

Grossly, the resected tumefaction is a fusiform or globoid, pseudo-encapsulated, greyish/white, hard, bulging lesion with frequent foci of degenerative necrosis. Tumefaction may be adherent to medium-sized or enlarged peripheral nerve with normal, uninvolved mucosa or epidermis superimposed upon foci of tumour elevation. Tumour magnitude varies from 2.5 centimetres to 17 centimetres [3,4]. On fine needle aspiration cytology, tumefaction is extensively cellular and composed of singular or aggregated, uniform, spindle-shaped cells. Morphological simulation with diverse sarcomas is significant and precise [4,5]. On frozen section, high grade neoplasms depict overt features of malignancy such as nuclear pleomorphism, brisk mitotic activity and zones of geographic necrosis. In contrast, discernment of low grade tumefaction can be challenging. Subjects with neurofibromatosis type1 (NF1) displaying enhanced cellularity, mitotic activity or nuclear atypia within a neurofibroma may be indicative of emergent malignant peripheral nerve sheath tumour [4,5]. On microscopy, streaming fascicles of atypical, spindle-shaped cells are interspersed within hypocellular or myxoid stroma. Atypical or uniform spindle-shaped cells are imbued with wavy, comma- shaped, thin, focally buckled, hyperchromatic nuclei and scanty cytoplasm with indistinct cytoplasmic boundaries. Cellular and nuclear pleomorphism or foci of poorly differentiated, malignant tumour cells with extensive incrimination of abutting skeletal muscle may be observed [4,5]. Upon low magnification, the neoplasm depicts a "marbled" appearance denominating alternating areas of hypocellularity and hypercellularity. Perivascular cellular accentuation is observed. Foci

of heterologous differentiation is observed within 10% to 15% instances. Zonal rhabdomyoblastic differentiation is generally associated with adverse clinical behaviour [4,5]. Morphologically, the cellular neoplasm is devoid of a classical, well defined appearance. Majority (80% to 85%) of neoplasms display a fibrosarcoma-like fascicular or a focal storiform configuration with mitotic figures exceeding ≥ 4 per high power field. Tumour cells depict uniform cytological features with indistinct cytoplasmic boundaries and configure bundles or fascicles. Foci of myxoid stroma and hyalinization are discerned. Epithelioid tumour cells may be exemplified [5,6]. A cascade of spindle-shaped cells with nuclei of varying magnitude is disseminated within soft tissue stroma. Foci of nuclear pleomorphism or mitotic figures of around 7 per 10 high power fields is discerned [5,6]. Spindle- shaped tumour cells may infiltrate the enveloping interstitial tissue and basal myoepithelium [6]. Tumefaction may be associated with a precursor lesion such as neurofibroma. Glandular elements or nuclear palisading is uncommonly observed. Nearly 15% neoplasms exhibit divergent differentiation with distinct subclassification. Zones of heterologous differentiation as components of chondrosarcoma, osteosarcoma or rhabdomyosarcoma (malignant triton tumour) can be enunciated [5,6]. Additional morphologic features are proliferation of miniature vascular articulations, accumulation of tumour cells

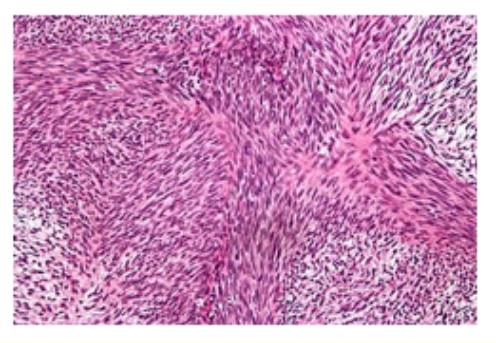

Figure 1: *Malignant Peripheral Nerve Sheath Tumour Depicting Fascicles Of Spindle-Shaped Cells With Thin, Wavy Nuclei Surrounded By Hyalinized Stroma And Minimal Mitosis [9].*

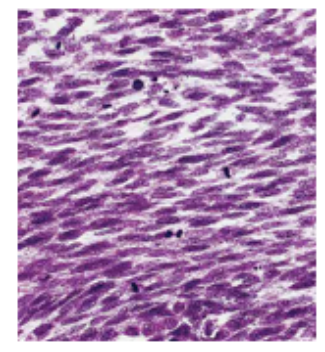

Figure 2: *Malignant Peripheral Nerve Sheath Tumour Demonstrating Bundles Of Spindle-Shaped Cells With Minimal Mitosis And A Focal Storiform Pattern [10].*

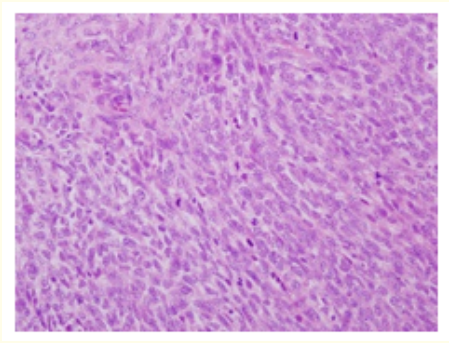

Figure 3: *Malignant Peripheral Nerve Sheath Tumour Delineating Fascicles Of Spindle-Shaped Cells With Admixed Foci Of Hyalinized Stroma [11].*

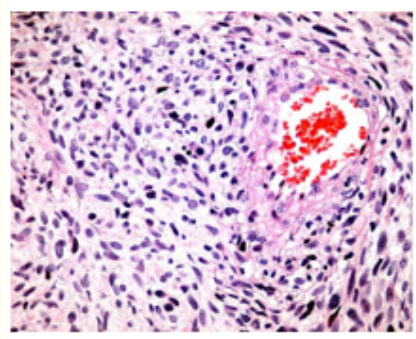

Figure 4: *Malignant Peripheral Nerve Sheath Tumour Enunciating Bundles And Whorls Of Spindle-Shaped Cells With Minimal Mitosis, Focal Haemorrhage And Enveloping Hyalinized Stroma [12].*

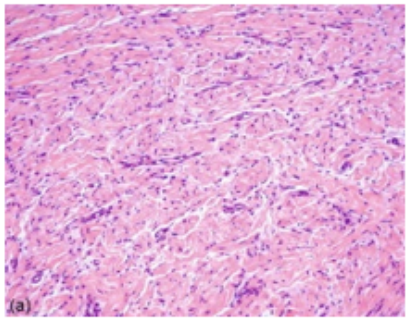

Figure 5: *Malignant Peripheral Nerve Sheath Tumour Exemplifying Strips Of Spindle-Shaped Cells With Thin, Attenuated Nuclei, Eosinophilic Cytoplasm, Minimal Mitosis And Abundant Hyalinized Stroma [13].*

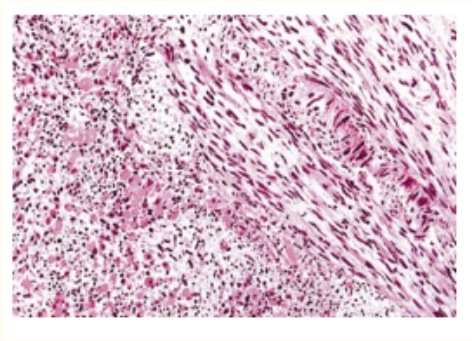

Figure 6: *Malignant Peripheral Nerve Sheath Tumour Exhibiting Fascicles Of Spindle-Shaped Cells With Hyperchromatic, Wavy Nuclei, Abundant Cytoplasm, Minimal Mitosis And Enveloping Hyalinized Stroma [14].*

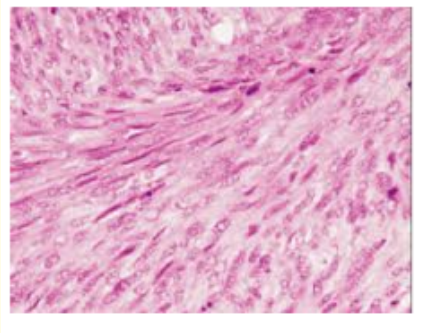

Figure 7: *Malignant Peripheral Nerve Sheath Tumour Depicting Fascicles Of Spindle-Shaped Cells With Hyperchromatic Nuclei, Eosinophilic Cytoplasm And Occasional Mitotic Figures Encompassed Within A Hyalinized Stroma [15].*

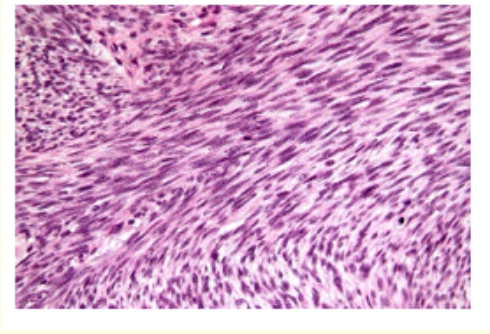

Figure 8: *Malignant Peripheral Nerve Sheath Tumour Enunciating Fascicles Of Spindle-Shaped Cells With Attenuated, Hyperchromatic Nuclei, Eosinophilic Cytoplasm, Absent Mitosis And An Encompassing Fibrotic Stroma [16].*

within the subendothelial vascular zone, occurrence of concomitant neurofibromas (especially with neurofibromatosis type 1, geographic necrosis and pseudo-palisading of tumour cells) [5,6].

Immune histochemical elucidation

Malignant peripheral nerve sheath tumour is immune reactive to S100 protein, vimentin, nestin, SOX-10, high mobility group A2 (HMG-A2) and leukocyte common antigen (LCA). Tumour cells of neural origin are immune reactive to S100 protein, vimentin and B cell lymphoma 2 (Bcl-2) antigen. Immune staining for S100 protein or SOX10 may be patchy, focal and discerned in around 50% neoplasms. Foci of rhabdomyosarcomatous transformation are immune reactive to desmin, myogenin or MyoD1 [1,2]. The neoplasm is immune non reactive to CD99, CD34, epithelial membrane antigen (EMA), cytokeratin (CK-7), desmin, diverse melanocytic markers as human melanoma black 45 (HMB-45) antigen or Melan-A along with antibodies against spinal muscular atrophy which excludes muscle-specific, spindle-shaped cellular malignancies [1,2]. High grade, sporadic and radiation-associated neoplasms depict loss of nuclear reactivity to H3K27me3, an epigenetic modification to histone H3. However, sensitivity of detection is decimated in low grade and neurofibromatosis type 1 (NF1) associated malignant peripheral nerve sheath tumours with complete absence in around 72% instances and mosaic or partial loss in roughly 19% subjects [1,2]. Approximately 50% of epithelioid variant and 67% of malignant peripheral nerve sheath tumours are immune non reactive to nuclear integrase interactor 1(INI-1) [1,2]. MIB-1 proliferative index of malignant peripheral nerve sheath tumour is around 25%, indicative of a malignant neoplasm. MIB-1 index varies from 5% to 65%, a feature which is beneficial in differentiating benign tumours from malignant neoplasia [1,2].

Differential diagnosis

Malignant peripheral nerve sheath tumour requires segregation from diverse neoplasia such as fibrosarcoma, monophasic.

- Synovial sarcoma, leiomyosarcoma, desmoplastic melanoma, solitary fibrous tumour and nodular fasciitis [7,8].
- Fibrosarcoma demonstrates a fascicular configuration with histological features simulating malignant peripheral nerve sheath tumour. However, evidence of nerve sheath differentiation is absent. Tumour cells are uniform and are characteristically arranged in elongated, sweeping fascicles. The neoplasm is immune reactive to smooth muscle actin (SMA) and muscle specific actin (MSA) and is immune non reactive to cytokeratin (CK), epithelial membrane antigen (EMA) or S100 protein [7,8].
- Synovial sarcoma demonstrates a uniform, fascicular, biphasic tumour configuration composed of fibroblast-like, spindle-shaped cells admixed with gland-like epithelial structures and mucin containing glandular lumina. The epithelial component depicts moderate, distinctive amphophilic cytoplasm with round to ovoid nuclei. Majority (90%) of neoplasms are immune reactive to cytokeratin (CK) or epithelial membrane antigen (EMA) and 60% to 70% tumours react to CD99 (MIC-2). The neoplasm is immune non reactive to S100 protein [7,8].
- Monophasic synovial sarcoma exemplifies monotonous cytological features. Immune reactivity to keratin or epithelial membrane antigen (EMA) is patchy. Genomic rearrangements of SYT gene are observed.
- Leiomyosarcoma is classically composed of spindle-shaped tumour cells with intensely eosinophilic cytoplasm and centric, blunt-ended, cigar shaped nuclei with juxta- nuclear vacuoles. Leiomyosarcoma is immune reactive to smooth muscle markers such as myosin, calponin, smooth muscle actin (SMA), desmin and h-caldesmon [7,8].
- Neurofibroma is a minimally cellular neoplasm delineating Schwann cells with wavy, serpentine nuclei, wire-like collagen fibrils, stromal muco-substances, mast cells, Pacinian corpuscles, Wagner-Meissner corpuscles and axons highlighted by silver or acetylcholinesterase stains. The neoplasm is devoid of nuclear atypia or mitotic activity [7,8].

- Atypical neurofibroma can arise in concurrence with neurofibromatosis type 1(NF1). The neoplasm displays preservation of tumour architecture, lack of significant cytological atypia or tumour necrosis and mitotic activity is usually below < 3 per10 high power fields [7,8].

- Spindle cell melanoma depicts atypical, pigmented spindle-shaped cells with significant pleomorphism and mitosis infiltrating the circumscribing stroma. Tumefaction is diffusely immune reactive to S100 protein along with reactivity to diverse mature melanocytic markers [8].

- Metastatic malignant melanoma clinically manifests as a soft tissue neoplasm composed of melanocytes with clear or dusty cytoplasm and fine nuclear chromatin. Mitotic figures, pleomorphism or cellular and nuclear atypia is observed. Tumefaction may be associated with preceding history of primary cutaneous melanoma, incrimination of regional lymph nodes and immune reactive melanocytic markers such as human melanoma black45 (HMB-45) antigen, Melan-A, tyrosinase and micropthalmia transcription factor (MiTF) [7,8].

- Dedifferentiated liposarcoma demonstrates an admixture of well differentiated and poorly differentiated components, enhanced cellularity, cellular and nuclear pleomorphism, mitotic activity exceeding 5 per 10 high power fields and appears as a non lipogenic sarcoma. Amplification of MDM2 gene is observed [7,8].

- Low grade fibromyxoid sarcoma is moderately cellular with bland, fusiform or spindle-shaped cells delineating focal or diffuse whorls interspersed within an extensively collagenized stroma. Epithelioid cell aggregates or enlarged collagen rosettes may be discerned. Mitotic activity, cellular and nuclear pleomorphism, atypia and enhanced cellularity are occasional. The neoplasm is immune reactive to MUC4 and demonstrates FUS-CREB genetic rearrangements [7,8].

- Cellular schwannoma is composed of an element of foamy macrophages and hyalinized vascular articulations. The neoplasm is intensely immune reactive to S100 protein [7,8]. Additionally, segregation is required from diverse mesenchymal malignancies such as fibrosarcoma, leiomyosarcoma, malignant melanoma or synovial sarcoma. Hypocellular and myxoid stromal regions are additionally denominated in leiomyosarcoma, malignant fibrous histiocytoma or fibrosarcoma [7,8]. Benign lesions such as solitary fibrous tumour or nodular fasciitis are associated with restricted tumour progression and precise morphology [8].

Investigative assay

Endoscopic ultrasound fine needle aspiration biopsy (EUS-FNAB) and boring biopsy are beneficially adopted in discerning submucosal malignant peripheral nerve sheath tumour. The neoplasm can display superimposed ulceration of protruding variety. Appropriate quantities of tumour cells may appear accumulated upon floor of the ulcer. Tumour surface is coated with necrotic tissue and aggregates of fibroblasts. Aforesaid procedures are recommended following initial, nondiagnostic tissue specimens [7,8]. Radiographic examination depicts a soft tissue neoplasm with absence of bony incrimination. Nevertheless, an intraosseous tumour confined to the oral cavity delineates comprehensive bone destruction with bone expansion, erosion, tooth mobility, well defined bony radiolucency along with enlargement of mandibular canal or mental foramen [7,8]. Upon barium fluoroscopy, gastrointestinal malignant peripheral nerve sheath tumour depicts a semi-circular, raised lesion. Upper gastrointestinal endoscopy reveals a hard, greyish neoplasm with superficial ulceration [7,8]. Endoscopic ultrasound (EUS) demonstrates an isoechoic mass. Computerized tomography (CT) displays a tumefaction of minimal density and variable magnitude. Adjacent regional lymph nodes may be incriminated [7,8]. Contrast enhanced computerized tomography (CT) scan demonstrates an enlarged, heterogeneous, enhancing, space occupying soft tissue lesion [7,8]. Magnetic resonance imaging (MRI) demonstrates a hyperintense mass on T2 weighted imaging which is accompanied by prolonged contrast enhancement. Tumour invasion into surrounding soft tissue is usually absent. MRI depicts association of the neoplasm with an enlarged peripheral nerve or a neurofibroma [7,8]. Normally, nerve cells manifest abundant glucose transporter type 3 (GLUT-3), a molecule which transports glucose into neural cells and depicts enhanced uptake with fluoro-deoxy glucose positron emission tomography (FDG-PET). Avidity on fluoro-deoxy glucose positron emission tomography (FDG PET) maybe nonspecific although may demarcate malignant peripheral nerve sheath tumour from neurofibroma Adoption of diverse preoperative imaging assays may not adequately distinguish the grade of malignancy [7,8].

Therapeutic options

Optimal treatment strategy is extensive surgical extermination of the neoplasm with adjuvant radiotherapy and/ or chemotherapy. Comprehensive surgical eradication of the neoplasm with broad perimeter of uninvolved, tumour-free tissue is recommended. Preoperative detection of malignant tumefaction is subjected to radical resection which is accompanied by superior prognostic outcomes.

Appropriate localized tumour control is recommended with adoption of radiation therapy following competent surgical excision [7,8]. Postoperative histological evaluation with pertinent immunohistochemistry is beneficial in confirming the diagnosis. Dissection of regional lymph nodes is not warranted as the nodes may be devoid of tumour deposits [7,8]. Localized tumour reoccurrence is documented. Distant metastasis is exceptional and is associated with inferior prognosis. Frequent sites of distant metastasis are pulmonary parenchyma, bones and lymph nodes. Conventional chemotherapy is indicated for enlarged tumefaction and treating distant metastasis [7,8]. Adjuvant chemotherapy with doxorubicin or combination of doxorubicin with ifosfamide is recommended for managing distant tumour metastasis. Adjunctive radiotherapy can be employed. Individual survival, treatment benefits and tumour response to radiotherapy and chemotherapy are unclear and controversial [7,8]. Therapeutic strategies for managing metastatic malignant peripheral nerve sheath tumour are limited. Response to treatment with adoption of vemurafenib is documented in an instance harbouring BRAFV600E genetic mutation [7,8]. Prognostic outcomes are inferior with an overall 5 year survival of 40% to 75%. Prognostic outcomes are contingent to tumour magnitude, tumour localization and incrimination of vital organs. Concurrence of neurofibromatosis type 1 (NF1) is a factor unassociated with prognostic outcomes of malignant peripheral nerve sheath tumour [7,8]. Generally, malignant peripheral nerve sheath tumour delineates an aggressive biological behaviour with frequently observed localized tumour reoccurrence and distant metastasis. Particularly, high grade neoplasms are aggressive. Neoplasms situated upon the trunk or tumours associated with neurofibromatosis type 1(NF1) or radiation-associated tumefaction depict an inferior prognosis. Neoplasia exhibiting foci of rhabdomyoblastic differentiation as encountered with malignant triton tumour demonstrate an aggressive countenance [7,8].

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