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Conceptual Paper

The Myxoid Sensatory - Nerve Sheath Myxoma

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Preface

Nerve sheath myxoma is an infrequently discerned, benign neoplasm engendered from the nerve sheath. Harkin and Reed initially described and appropriately nomenclated the term nerve sheath myxoma in 1969. Traditionally, nerve sheath myxoma is cogitated as a benign, cutaneous neoplasm derived from Schwann cells of peripheral nerve sheath, although the neoplasm is devoid of characteristic features of a conventional schwannoma. Albeit, the neoplasm can be contemplated as a myxoid variant of schwannoma [1].

The neoplasm was previously considered to be clinically and morphologically akin to classic or myxoid variant of neurothekeoma. However, aforesaid neoplasia are recently considered to enunciate disparate, distinctive origins. The benign, myxoid tumefaction of neural origin predominantly arises from Schwann cells [1,2].

Disease characteristics

Of obscure aetiology, nerve sheath myxoma is a neoplasm preponderantly situated within the dermis and subcutaneous tissue. Extremities (85%) are commonly implicated, especially the fingers, whereas the neoplasm is exceptional upon head and trunk. The neoplasm predominantly arises in young and middle aged adults although no age of tumour emergence is exempt. A gender predilection is absent and males are implicated with equal frequency as the females [1,2].

Neurothekeoma demonstrates a five times greater incidence than nerve sheath myxoma. Considerable controversy exists regarding cellular differentiation of nerve sheath myxoma and concurrence with neurothekeoma. However, aforesaid entities are distinct and can be segregated with appropriate histological, immune histochemical, ultrastructural, molecular and genetic evaluation [2,3].

Clinical elucidation

Nerve sheath myxoma demonstrates a solitary, miniature, painless, gradually progressive, mobile, flesh coloured to translucent nodule. Duration of neoplastic occurrence is extensive and usually exceeds > 20 years. Typically, a superficial, soft, painless, mobile, asymptomatic, gradually evolving tumour nodule of varying magnitude is discerned, principally confined to the dermis and subcutaneous tissue. Frequently incriminated sites are extremities, fingers, hands, knees, lower limbs, ankle, feet or head and neck [3,4].

Histological elucidation

On macroscopic examination, a partially skin covered nodule with unremarkable cutaneous surface and variable dimensions is observed. The cut surface is greyish-white to yellow. Macroscopically, majority of nerve sheath myxomas are beneath < 2.5 centimetres along the greatest diameter and vary from 0.4 centimetre to 4.5 centimetre in magnitude. Of rubbery to firm consistency, the neoplasm emerges as a well- demarcated, translucent to whitish nodule with a mucoid or glistening cut surface [3,4].

The benign tumefaction with Schwannian differentiation is a multi-lobulated and myxoid neoplasm.

On fine needle aspiration cytology, nerve sheath myxoma provides a greyish, jelly- like substance intermingled with singly dispersed, spheroidal to stellate cells with bland nuclei. The commingled myxoid stroma is metachromatic and fibrillary, appears pink on a Diff-Quik stain and pale blue on Papanicolaou stain. A proportion of cells can configure cords and loosely adhered clusters. Multiple, elongated cytoplasmic processes can be discernible. Bi- nucleated and multi nucleated cells are encountered [3,4].

Upon cogent aspiration cytology, nerve sheath myxoma requires a differentiation from myxoid neurofibroma, myxoid schwannoma, myxoid neurothekeoma or cutaneous mucinosis. It can be challenging to demarcate nerve sheath myxoma from cutaneous mucinosis upon cytology [4].

On microscopic examination, multiple myxoid nodules of varying magnitude are exemplified along with circumscribing fibrous tissue septa. Tumour cells are spheroid to elliptical to spindle- shaped, depict cytoplasmic projections and are enveloped in a myxoid stromal backdrop [4,5].

Morphological assessment of nerve sheath myxoma demonstrates a well- defined, multinodular neoplasm constituted of myxoid lobules subdivided by fibrous tissue septa. Tumour lobules depict loosely aggregated benign, spindle -shaped or stellate cells and epithelioid cells admixed within a myxoid stroma.

An un-encapsulated, multi-lobulated neoplasm, nerve sheath myxoma is predominantly confined to the dermis or subcutaneous tissue. Well- circumscribed, myxoid lobules are encompassed by mature fibrous tissue. Neoplastic cells are miniature and can be spindle-shaped, stellate, epithelioid or ring- shaped with frequent cytoplasmic invaginations into the nucleus. Mild nuclear atypia is cogitated although mitotic figures are exceptional or absent [4,5].

Dermal nerve sheath myxoma displays a characteristic, lobulated neoplasm composed of sharply demarcated neoplastic lobules with intervening fibrous tissue septa. Tumour lobules are comprised of an abundant myxoid matrix with commingled neoplastic cells which are spindle-shaped, epithelioid, ring- like or stellate cells and configure cellular cords, nests or syncytium-like cellular aggregates. Mitotic figures are infrequent [4,5].

Tumour cells demonstrate a scanty, eosinophilic cytoplasm which circumscribes the miniature, spheroidal nuclei delineating thin, bipolar or multipolar, spider-like nuclear processes. Intercellular connectivity is frequent, thus cord- like, nesting or syncytial cellular arrangements can ensue. Hyperplasia and hyperpigmentation of superimposed epidermis is exemplified, akin to epidermal reactions discerned in benign fibrous histiocytoma [4,5].

Myxoid ground substance can be stained with alcian blue although the substance may not be highlighted by a periodic acid Schiff's stain [5].

Immune histochemical elucidation

Nerve sheath myxoma is immune reactive to S100 protein whereas epithelial membrane antigen (EMA) and CD34 are immune non-reactive. The neoplasm is diffusely immune reactive to S100 protein, a feature which distinguishes it from neurothekeoma. Also, tumour cells are immune reactive to glial fibrillary acidic protein (GFAP), vimentin and collagen type IV [6].

Apart from S100 protein and glial fibrillary acidic protein (GFAP), nerve sheath myxoma depicts a diffuse immune reactivity CD57 (Leu-7), neuron specific enolase (NSE) and p75 (neurotrophin receptor). Immune reactive collagen IV depicts an intense pericellular staining. Epithelial membrane antigen (EMA) is immune reactive in certain perineurial cells in an estimated > 50% instances. CD34 is immune reactive in pertinent intra-neural fibroblasts. Infrequently, neoplastic cells are immune reactive to concomitant AE1/AE3 cytokeratin. Perineurial cells, immure reactive S100 protein, glial fibrillary acidic protein (GFAP) and epithelial membrane antigen (EMA), are often discerned upon the perimeter of tumour lobules [6].

Nerve sheath myxoma is immune non-reactive to CD10, human melanoma black (HMB-45) antigen 45, CD63 (NKI-C3) and smooth muscle actin (SMA). Exceptionally, neurofilament can highlight certain axons.

Nerve sheath myxoma is identical to dermal schwannoma upon cogent molecular analysis, in contrast to neurothekeoma, which resembles a cellular fibrous histiocytoma [6].

Differential diagnosis

Dermal nerve sheath myxoma requires a segregation from neoplasia such as acral fibromyxoma, superficial angiomyxoma, soft tissue myoepithelioma and cellular neurothekeoma. Nerve sheath myxoma requiring separation from myxoid and mixed variants of neurothekeoma can be subjected to gene expression profiling which demonstrates the origin of nerve sheath myxoma as arising from peripheral nerve sheath cells whereas neurothekeoma morphologically resembles a cellular fibrous histiocytoma and the neoplasm originates from fibroblastic cells. In contrast, neurothekeoma is immune reactive to epithelial membrane antigen (EMA) and immune non-reactive to S100 protein and glial fibrillary acidic protein (GFAP). Commonly, neurothekeoma emerges upon the head and neck as a solitary nodule. Distinction of a nerve sheath myxoma from neurothekeoma is crucial as nerve sheath myxoma demonstrates a higher propensity for localized tumour reoccurrence [6,7].

Neurothekeoma frequently implicates female subjects and particularly appears upon the head and neck region. The multi-lobulated or micro-nodular neoplasm demonstrates a spindle-shaped or epithelioid cell component. Neurothekeoma is immune reactive to neuron specific enolase (NSE) in around 89% instances, CD63 and focally immune reactive to smooth muscle actin (SMA) in nearly 34% to 60% subjects. The neoplasm is immune non-reactive to S100 protein and glial fibrillary acidic protein (GFAP). Neurothekeoma is consistently immune reactive to CD10. Cellular neurothekeoma is composed of plump, fleshy spindle- shaped and epithelioid cells, in contrast to a dermal nerve sheath myxoma [6,7].

Nerve sheath myxoma mandates a histological differentiation from diverse myxoid neoplasia such as plexiform neurofibroma, myxoid neurofibroma, myxoid schwannoma, extra-neural perineurioma and cutaneous, juxta- articular or intramuscular myxoma. Myxoid neurofibroma is a poorly circumscribed, un-encapsulated neoplasm devoid of lobular architecture with a patchy immune reactivity to S100 protein [6,7].

Myxoid schwannoma demonstrates distinct foci of Antoni A areas intermingled with Verocay bodies. Although a multinodular tumour configuration is absent, immune reactivity to S100 protein is discerned. Myxoid schwannoma is generally an encapsulated neoplasm although distinctive, individual tumour lobules are absent. Pertinent morphological features are comprised of alternating Antoni A and Antoni B areas, configuration of Verocay bodies with peripheral nuclear palisading and hyalinised blood vessels [7,8].

Extra-neural perineurioma is constituted by cellular whorls and fascicles intermixed with a myxoid or collagenous stroma. In contrast to nerve sheath myxoma, extra-neural perineurioma is intensely immune reactive to epithelial membrane antigen (EMA) and immune non-reactive to S100 protein, CD34 or glial fibrillary acidic protein (GFAP) [7,8].

Cutaneous myxoma preponderantly appears within the dermis and subcutaneous tissue. Multiple, myxoid aggregates comprised of spindle-shaped or stellate tumour cells are observed. Cutaneous myxoma is immune reactive to CD34 and immune non-reactive to S100 protein. Cutaneous myxoma or superficial angiomyxoma is associated with Carney's complex in an estimated 50% instances. The neoplasm is commonly discerned upon the trunk or head and neck and is exemplified as a well circumscribed, mildly lobulated tumour with a preponderant mucinous matrix and enhanced vascularity. Of diminished cellularity, the neoplasm is constituted by variably shaped fibroblasts. Accompanying inflammatory infiltrate is comprised of neutrophils. Around 25% tumours demonstrate entrapped, endothelial configurations. The neoplasm is immune reactive to CD34 although S100 protein is immune non-reactive [7,8].

Nerve sheath myxoma necessitates a demarcation from plexiform neurofibroma which is a disorder frequently associated with neurofibromatosis type 1. Tumour nodules are expansive. Intervening stroma is comprised of collagen fibres with a typical "shredded carrot" appearance. Few fibroblastic cells are immune reactive to CD34 and Schwann cells are immune reactive to S100 protein [7].

Cutaneous myoepithelioma can depict a lobular, reticular or syncytial pattern of tumour evolution with an intermingled myxoid stroma. The neoplasm is poorly circumscribed and frequently demonstrates a hyperplastic superimposed epidermis. The tumefaction is immune reactive to S100 protein, glial fibrillary acidic protein (GFAP), cytokeratin AE1/AE3 or epithelial membrane antigen (EMA). Soft tissue myoepithelioma is devoid of sharply demarcated tumour lobules, characteristic of dermal nerve sheath myxoma [7,8].

Superficial acral fibromyxoma or digital fibromyxoma is a well circumscribed neoplasm delineating minimal quantities of myxoid matrix and essentially emerging adjacent to the nailbed or fingers and toes. The tumefaction is consistently immune reactive to CD34 with variable immune reactivity to CD10, CD99 and smooth muscle actin (SMA). The tumour is associated with decimation of retinoblastoma protein 1 (RB1) and is immune non-reactive to S100 protein and desmin.

Dermal mucinosis is a coterie of predominantly disparate, non-neoplastic disorders (excluding cutaneous myxoma) which exemplify dermal deposition of mucin. Neoplastic cellularity can be decimated with the occurrence of few, stellate- like cells as encountered in disorders such as pretibial myxoedema or scleroderma. Sharply demarcated tumour lobules are absent. The neoplasm can demonstrate a certain proportion of fibroblastic proliferation as with sclero-myxoedema. Perivascular lymphocytic infiltrate is prominent [7,8].

Intramuscular and juxta -articular myxoma depicts an identical histology although a clinical demarcation from dermal nerve sheath myxoma is possible.

Superficial angiomyxoma lacks a peripheral circumscription by fibrous tissue and comprises of thin- walled blood vessels along with foci of neutrophilic infiltration.

Plexiform neurofibroma arising in concurrence with neurofibromatosis usually incriminates enlarged neural trunks. The neoplasm is a multinodular, myxoid lesion which is immune reactive to S100 protein [8].

Investigative assay

Non-polarized contact dermoscopy delineates a diffuse, grey to yellow tinted backdrop intermingled with cobble- stone like zones along with greyish, amorphous, structure-less regions with encompassing hairpin, linear or twisted blood vessels [7].

Nevertheless, nerve sheath myxoma is devoid of specific clinical or diagnostic features. Diagnosis of nerve sheath myxoma can be achieved with a detailed histological enunciation of a cogent tissue specimen [8].

Therapeutic options

The completely benign nerve sheath myxoma can be suitably managed with a comprehensive, localized surgical excision along with a tumour- free surgical perimeter. A subsequent, extensive follow up is recommended on account of an elevated tumour reoccurrence at an estimated 47% as accompanied with simple or incomplete surgical extermination [7,8].

Tumour Type	Capsule	Myxoid Stroma	S-100 protein	Epithelial membrane antigen
Nerve sheath myxoma	+	++	+	+/-
Neurothekeoma	-	+/-	-	+/-
Perineurioma	+	+/-	+	++
Schwannoma	+	-	++	+/-
Neurofibroma	-	+/-	+	+/-

Table: *Differential diagnosis of nerve sheath myxoma [8].*

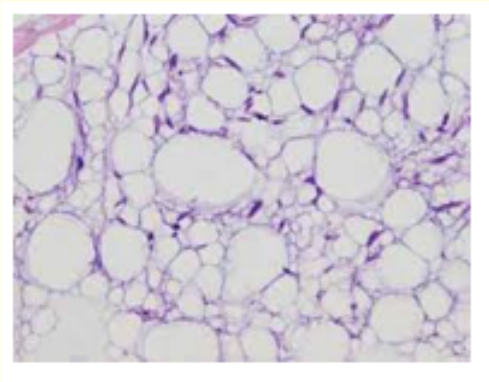

Figure 1: *Nerve sheath myxoma demonstrates lobules of spindle-shaped, epithelioid and ring-like cells with intermingled myxoid stroma [9].*

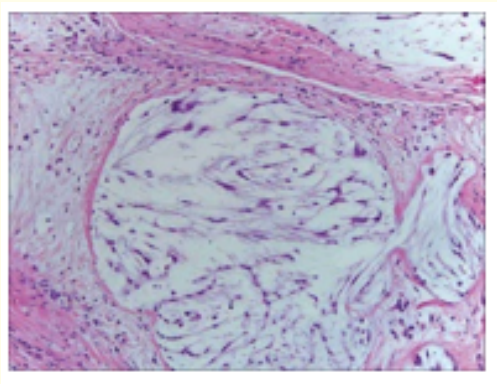

Figure 2: *Nerve sheath myxoma demonstrating a multi-lobulated tumour composed of abundant myxoid matrix and thin populated cellular component comprised of spindle-shaped and epithelioid cells [10].*

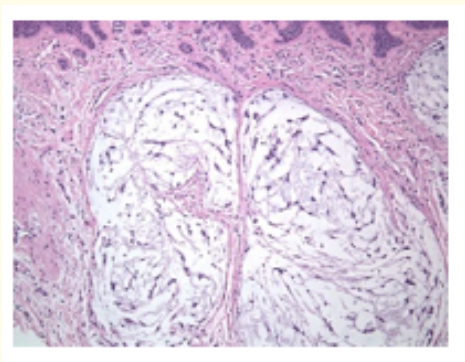

Figure 3: *Nerve sheath myxoma depicting lobules of dermal and subcutaneous tumour with ample myxoid stroma and a populace of spindle-shaped and epithelioid cells with superimposed epidermal hyperplasia [11].*

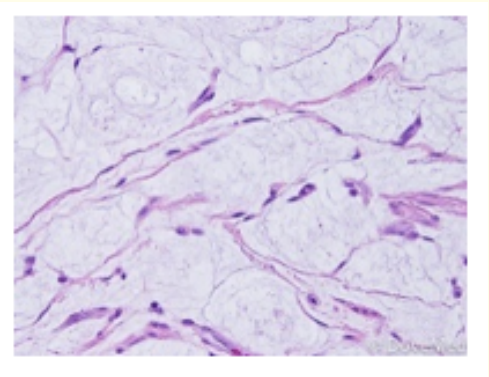

Figure 4: *Nerve sheath myxoma delineating lobules of myxoid stroma with a scanty, spindle-shaped cellular component [12].*

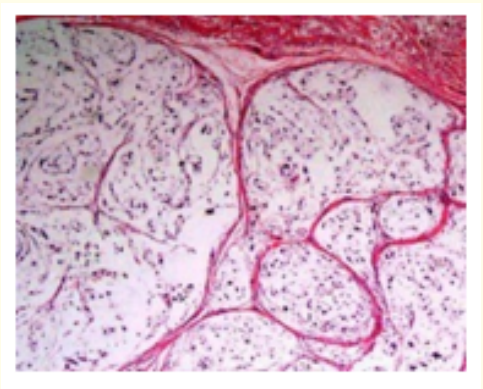

Figure 5: *Nerve sheath myxoma enunciating lobules of tumour cells composed of abundant myxoid stroma and a perimeter of spindle-shaped and epithelioid cells [13].*

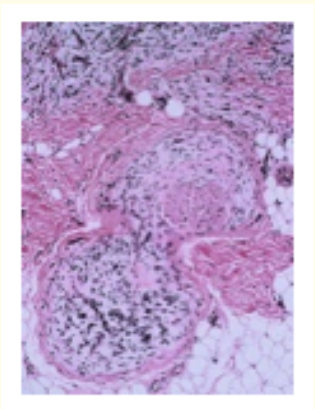

Figure 6: *Nerve sheath myxoma exemplifying lobules of a preponderantly myxoid neoplasm with abundant matrix and a spindle cell component with intervening fibrous tissue septa [14].*

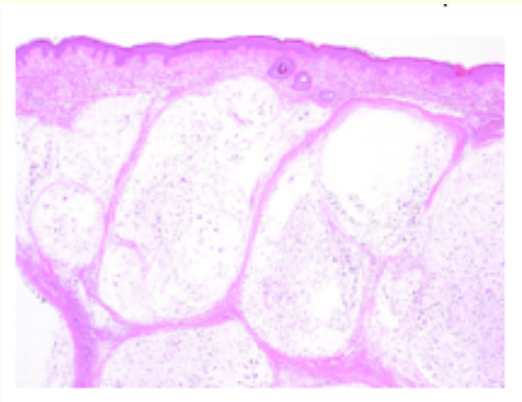

Figure 7: *Nerve sheath myxoma with lobules of myxoid ground substance, fibrous tissue septa, spindle-shaped tumour cells and superficial epidermal hyperplasia [15].*

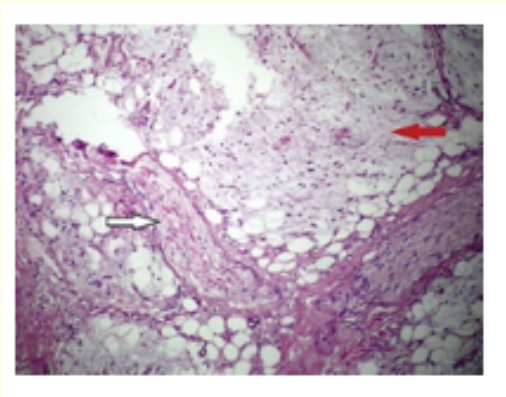

Figure 8: *Nerve sheath myxoma displaying lobules of myxoid material, epithelioid or spindle-shaped tumour cells and intermingled fibrous tissue septa [15].*

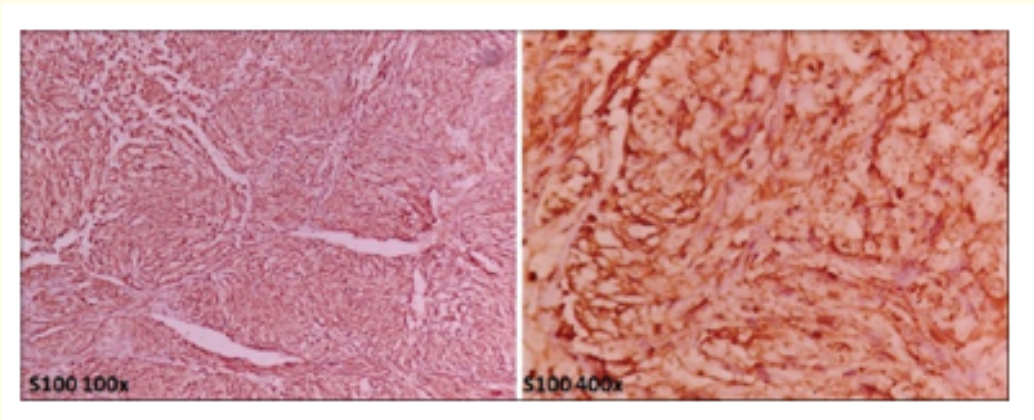

Figure 9: *Nerve sheath myxoma immune reactive to S100 protein [16].*

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9. Image 1 Courtesy: cesko-slovenskapatologie.com.

10. Image 2 Courtesy: IDOJ.com.

11. Image 3 Courtesy: Twitter.com.

12. Image 4 Courtesy: Dovemed.

13. Image 5 Courtesy: Internet Scientific Publications.

14. Image 6 Courtesy: Science Direct.

15. Image 7 and 8 Courtesy: Research Gate.

16. Image 9 Courtesy: Int J Trichology.

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