OPEN ACCESS
Freely Available Online

JOURNAL OF CLINICAL AND DIAGNOSTIC PATHOLOGY

ISSN NO: 2689-5773

Research

Doi: 10.14302/issn.2689-5773.jcdp-20-3292

The Neoplastic Whorls-Soft Tissue Perineurioma

Anubha Bajaj[1,*]

[1]Consultant Histopathologist

Abstract

Perineurioma is an exceptional, benign neoplasm entirely composed of neoplastic perineurial cells and arises from the peripheral nerve. Pertaining to location, the neoplasm predominantly demonstrates configurations such as intra-neural or extra-neural, confined to the soft tissue. Perineurioma was initially scripted by Lazarus and Trombetta in 1978 and is additionally nomenclated as localized hypertrophic neuropathy[1]. Extra-neural soft tissue perineurioma and mucosal (intestinal) perineurioma are frequent, in contrast to intra-neural perineurioma or localized hypertrophic neuropathy subtype[1,2].

Corresponding author: Anubha Bajaj, Consultant Histopathologist at A.B, Diagnostics at A-1, Ring Road, Rajouri Garden, New Delhi 110027. Email: anubha.bajaj@yahoo.com

Keywords: Soft tissue perineurioma, mucosal (intestinal) perineurioma

Received: Mar 28, 2020 **Accepted:** Apr 24, 2020 **Published:** Apr 25, 2020

Editor: Jun Wan, Department of Medical and Molecular Genetics, Indiana University School of Medicine, USA.

Disease Characteristics

Intra-neural perineurioma exhibits a proliferation of perineurial cells within the endoneurium. Multiple, concentric layers of perineurial cells circumscribe neural trunks with configuration of typical bulb-like, pseudo-onion articulations. Appearance of pseudo- onion bulbs can be misinterpreted as a reparative or reactive feature on account of organized cellular manifestations. Intra-neural perineurioma can delineate segmental, tubular enlargement of the incriminated nerve. Lesions of intra-neural perineurioma evolve gradually and are accompanied by motor and sensory deficits. Nerve trunks such as the cervical plexus, brachial plexus, intercostal nerves, spinal roots, sciatic nerves and nerves of extremities can be implicated[3].

Extra-neural perineurioma is sub classified into categories such as soft tissue perineurioma, sclerosing perineurioma and reticular perineurioma. Perineurioma arises primarily from the skin or soft tissue and is commonly encountered within the extremities, trunk or head and neck. Middle aged adults are affected and a gender predilection is absent. Tumour magnitude varies from 0.3 centimetres to 20 centimetres with a mean of 4.1 centimetres[1,2].

Soft tissue perineurioma, low-grade fibromyxoid sarcoma and intramuscular / cellular myxoma are neoplasms which demonstrate distinct, identical features such as

a) occurrence in middle aged adults with a preponderance of lesions upon the extremities
b) on cytological examination, aforesaid neoplasia enunciate bland, uniform spindle-shaped cells admixed within a myxoid stroma
c) aforementioned neoplasia depict overlapping immune phenotypes[1,2].

Clinical Elucidation

Clinical assessment demonstrates a median age of disease emergence at 45 years with age of disease occurrence varying betwixt 42 years to 60 years, a slight female predominance with a female to male proportion of 3:2. Preferred sites of tumour incrimination are the thigh, toe and perirectal soft tissue. Mean tumour magnitude is 6.6 centimetres[2,4].

Soft tissue perineurioma is a benign neoplasm which reoccurs exceptionally. A broad anatomic distribution of the lesion is encountered, although a majority of individuals display a painless, subcutaneous nodule confined to the limbs.

Soft tissue perineurioma is preponderantly a sporadic neoplasm wherein exceptional tumours can be delineated in subjects with genomic mutations of neurofibromatosis 1 or 2 (NF1 or NF2) gene[2,4].

Histological Elucidation

On gross examination, a well circumscribed nodule of variable magnitude is discerned which appears distinct from an adjoining peripheral nerve. Cytological smears of soft tissue perineurioma are sparse to moderately cellular and exhibit cogent features such as spindle--shaped to ovoid cells with delicate, elongated cytoplasmic processes and an accompanying lack of tumour necrosis[2,4].

Cytological enunciation of tumour cells as predominantly spindle-shaped to ovoid with scant, delicate, cytoplasmic processes demonstrates several cells which are stripped of cytoplasm and an infrequent delineation of morphologically classical, elongated, bipolar cytoplasmic processes. Nuclear atypia or pleomorphism is absent. Scattered stromal fragments intermixed with miniature, thin- walled blood vessels and the cellular component are exemplified[4,5]. Cogent features enunciated on cytology are myxoid matrix (20%), lack of nuclear and cellular atypia, spindle-shaped nuclei (60%), bipolar cytoplasmic processes(20%) and vascular configurations (20%). On microscopy, elongated, bland cells appear in parallel bundles or fascicles with the configuration of an occasional storiform pattern. The cellular aggregates can simulate a neurofibroma or Pacinian corpsucle. The circumscribing stroma is collagenous with accompanying peri-cellular clefts. Cellular atypia is absent and mitotic figures are exceptional[5,6].

Soft tissue perineurioma can be indicated if a myxoid lesion exhibits a distinctive storiform or fascicular pattern of tumour evolution. Cellular proliferation can be composed of spindle cells, characteristically demonstrating elongated, thin, delicate, bipolar cytoplasmic processes, a pale-staining, eosinophilic cytoplasm with wavy or tapering nuclei and a finely dispersed nuclear chromatin.

The neoplasm can depict perivascular whorls. Mitotic activity can be observed enumerated as 0-13 /30 high power fields, although around 65% tumours are devoid of mitotic activity. Neoplasms of extensive duration can exhibit foci of degenerative atypia with modifications such as nuclear pleomorphism and nuclear hyperchromasia with intracytoplasmic and intra-nuclear inclusions. Tumour necrosis is generally absent[5,6]. Microscopically, a perineurioma composed of bland, ovoid to spindle-shaped cells with elongated, slender nuclei and elongated, bipolar cytoplasmic processes can delineate a storiform, lamellar or a whorled pattern or perivascular aggregates of neoplastic cells are configured, disseminated in a collagenous or focally myxoid stroma. Lesions such as a hybrid schwannoma or perineurioma with features intermediate betwixt a schwannoma and perineurioma can be discerned. Characteristically, bland, ovoid to thinly elliptical, spindle -shaped cells with elongated, delicate, bipolar, cytoplasmic processes are exemplified with a storiform or whorled architectural pattern. Intervening stroma can be myxoid, collagenous or myxo-collagenous[5,6].

Cogent Subtypes Are

Intra-Neural Perineurioma

Intra-neural perineurioma which is a neoplasm delineating proliferation of perineurial cells within the endoneurium. Configuration of concentric, repetitive layers circumscribing the nerve with articulation of characteristic pseudo-onion, bulb-like structures are exhibited. Pseudo- onion bulbs can be misinterpreted as a reparative or reactive process on account of organized cellular arrangements. Intra-neural perineurioma can inculcate segmental, tubular enlargement of the incriminated nerve. Remaining nerve fibres, immune reactive to S100 protein, are enveloped by perineurial cells, immune reactive to epithelial membrane antigen (EMA). Intra neural perineurioma is a grade I tumour as per contemporary classification of World Health Organization (WHO) and is devoid of a malignant metamorphoses. Implicated subjects frequently display muscular weakness in concurrence with or absence of obvious muscular atrophy, although sensory disturbances are exceptional. Intra- neural perineurioma is frequent within the peripheral nerves, upper extremities and young adults[5].

Extra-Neural Soft Tissue Perineurioma

It is a neoplasm which is devoid of gross association with a peripheral nerve. The neoplasm is miniature, solitary, around 10 centimetres in magnitude, well circumscribed and un-encapsulated. Tumour evolution is variable wherein the storiform pattern is a frequent manifestation. Additionally, the neoplasm can demonstrate a lamellar, whorled, pacinian or a fascicular pattern of growth. The stroma is often collagenous and around 20% instances depict foci of myxoid stromal articulations. Extra-neural perineurioma is commonly delineated within superficial soft tissue of trunk and extremities, especially the hands[5,6].

Sclerosing Perineurioma

It is a variant of extra-neural soft tissue perineurioma and is composed of plump, spindle shaped and epitheloid tumour cells encompassed in a hyalinised stroma. Prominent, thin- walled vasculature is discerned with the emergence of peri-vascular and lace- like arrangement of tumour cells surrounding blood vessels. The neoplasm chiefly occurs within fingers of young male subjects. Reticular perineurioma is a variant of extra-neural soft tissue perineurioma with predominant degenerative, myxoid alterations. Configuration of pseudo-cystic spaces can occur. Tumour cells can demonstrate a lace- like reticular pattern[5,6].

Malignant Perineurioma

It is also cogitated as perineurial malignant peripheral nerve sheath tumour. Malignant perineurioma commonly delineates features such as hyper-cellularity, nuclear atypia, hyperchromasia, enhanced mitotic rate, infiltrative growth and necrosis. Concurrent tumour necrosis is indicative of a category of malignant perineurioma as grade 3, classified by World Health Organization. The neoplasm singularly arises from extra-neural soft tissue perineurioma. As an exceptional tumour, it metastasizes infrequently, in contrast to a conventional malignant peripheral nerve sheath tumour[5,6].

Figures(1-11)

Immune Histochemical Elucidation

Soft tissue perineurioma is immune reactive to perineurial markers such as epithelial membrane

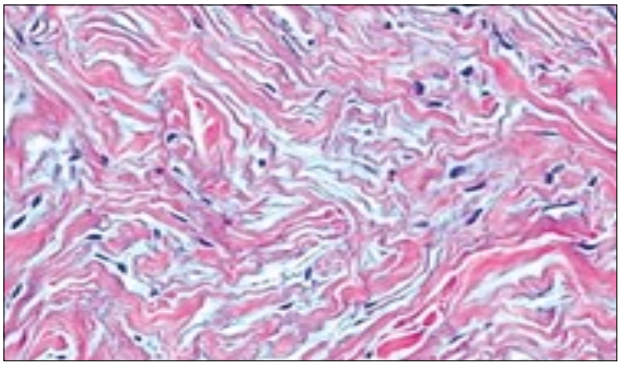

Figure 1. Soft tissue perineurioma with fascicles of bipolar neural cells with elongated cytoplasmic processes, wavy nuclei and an admixture of collagen fibres[11].

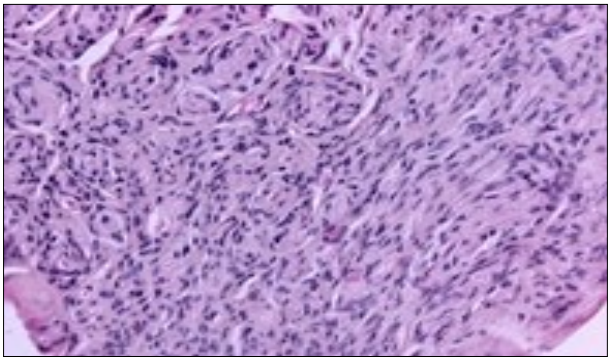

Figure 2. Soft tissue perineurioma with lamellar bundles of neural cells demonstrating elongated cytoplasmic processes, wavy, slender nuclei and admixed collagen fibres[12].

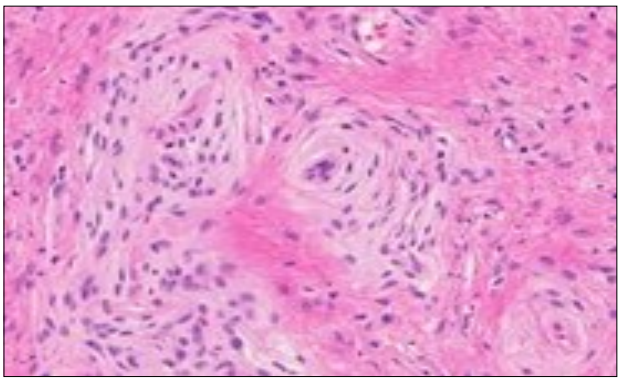

Figure 3. Soft tissue perineurioma with whorls and fascicles of neural cells displaying wavy nuclei, elongated cytoplasmic fibrils and intermingling of collagen fibres[13].

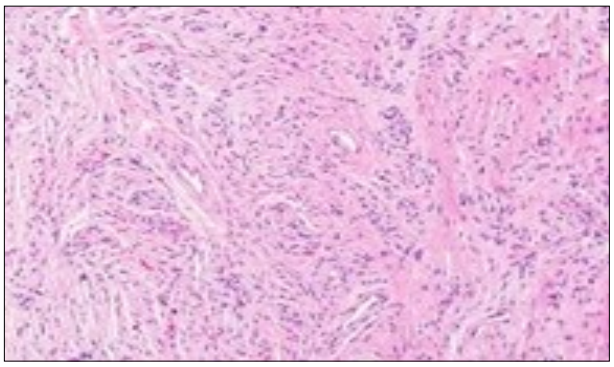

Figure 4. Soft tissue perineurioma composed of whorls and perivascular aggregates of neural cells with bipolar cytoplasmic processes, wavy, slender nuclei and commingled collagen fibres[13].

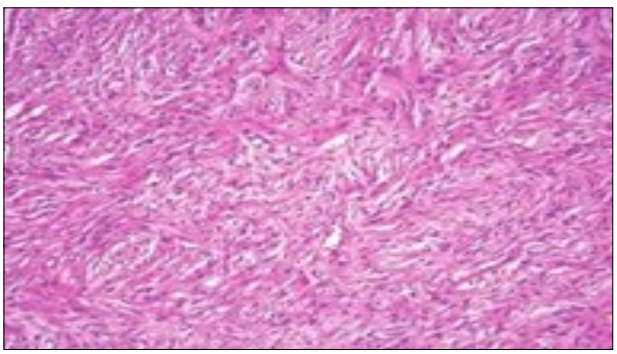

Figure 5. Soft tissue perineurioma /schwannoma with whorls and lamellae of neural cells with bipolar cytoplasmic processes, wavy nuclei and intermingled collagen fibres[14].

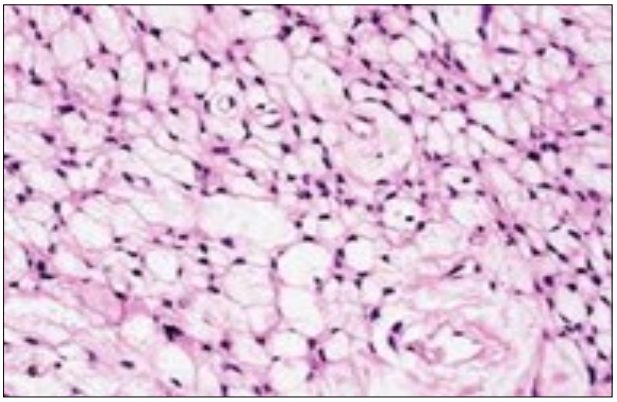

Figure 6. Soft tissue perineurioma with foci of spindle cells with wavy nuclei and an admixture of myxoid and collagenous stroma[15].

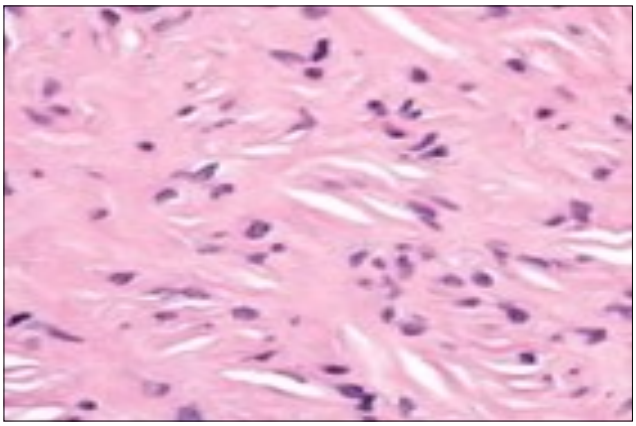

Figure 7. Soft tissue perineurioma with an abundance of collagen fibrils intermixed with a neural element with bipolar cells with elongated cytoplasm and wavy nuclei[16].

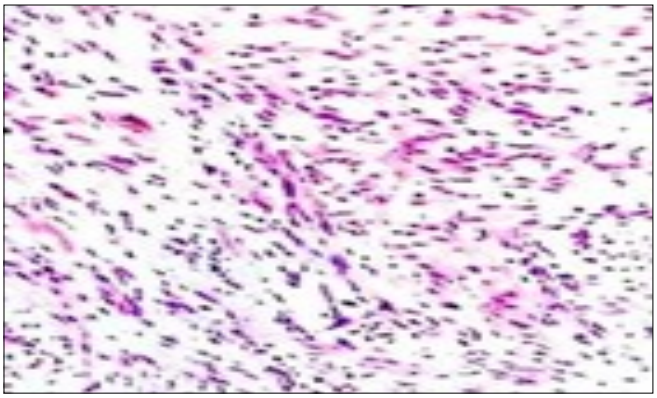

Figure 8. Soft tissue perineurioma with neural cells exemplifying elongated cytoplasmic processes, slender, wavy nuclei and an abundance of collagenous stroma[17].

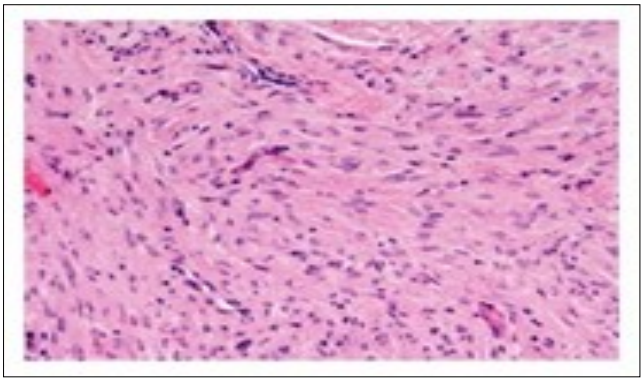

Figure 9. Soft tissue perineurioma with plentiful collagenous fibrils intermixed with lamellar neural tissue with elongated cytoplasmic extensions and wavy, pointed nuclei[18].

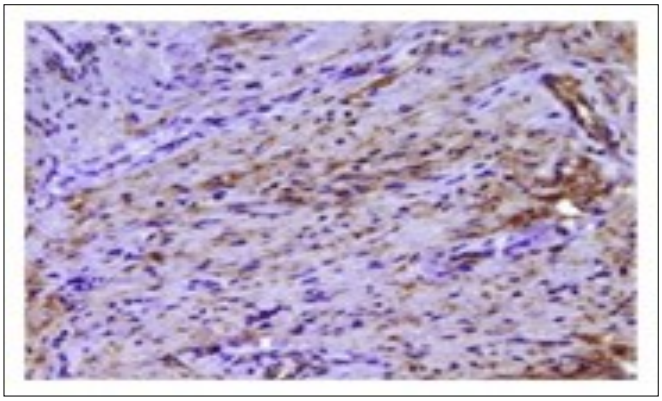

Figure 10. Soft tissue perineurioma demonstrating immune reactivity to epithelial membrane antigen [EMA][18].

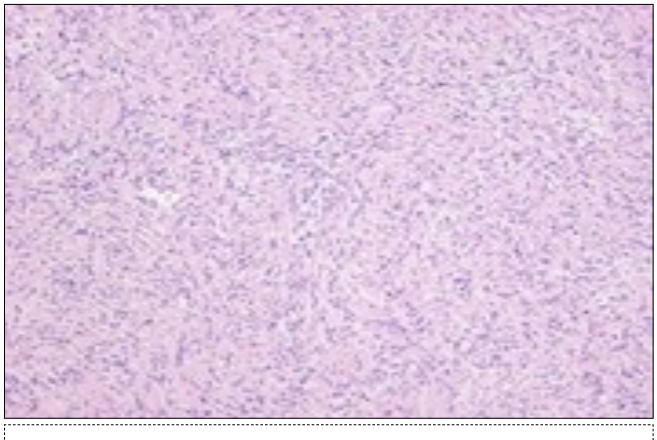

Figure 11. Soft tissue perineurioma with whorls of neural cells delineating spindle cells with bipolar cytoplasm and wavy nuclei and an admixture of collagen bundles[19].

Table 1. Differential Diagnosis of Soft Tissue Perineurioma [7,8,9,10].

Extraneural Perineurioma	**Neurofibroma**	**Low grade fibromyxoid sarcoma**	**Ectopic meningioma**	**Desmoid Fibromatosis**	**Smooth muscle tumour**	**Solitary fibrous tumour**	**Superficial acral fibromyxoma**	**Dermatofi-broma**	**Dermatofibro-sarcoma protuberans**
Collagenous stroma variable architecture, occasional whorls, absent rosettes and staghorn ves-sels	Shredded carrot collagen bun-dles	Occasional giant collagen rosette	Whorled architecture	Ill defined, invasive growth, broad sweeping fascicles	Perpendic-ular inter-secting fascicles	Prominent vascular pattern with staghorn vessels, pattern-less, variable architecture			Classic, storiform architecture
CD34+, EMA+, Claudin-1+ S100-, MUC4-,	CD34+, EMA+, S100+	Claudin-1+, focal, weak EMA, MUC4+	EMA+, Clua-din-1+			Variable EMA, diffuse CD34	EMA (50%),CD34+,Cl audin-1-	EMA focal or weak	Focal, weak EMA, strong, diffuse CD34,
Well circum-scribed, on sub-cutaneous tis-sue		Grossly cir-cumscribed, microscopical-ly infiltrative	Infiltrative growth					Infiltrative growth	
Myxoid areas infrequent with insignificant alternating pat-tern		Myxoid areas definitive with alternating fibrous zones							

Monosomy chromosome 22, STAT6 absent		Typical FUS-CREB3L2 translocation (chromosome 7 and 16)			May express STAT6	NAB2-STAT6 gene fusion, express STAT6			Typical COL1A-PDGFB fusion
Long, thin, spindle cells, absent psammoma bodies or intranuclear incluions, no epidermal induction			Syncitial epitheloid cells, frequent psammoma bodies and intranuclear pseudoinclusions		Blunt ended nuclei, abundant eosinophilic cytoplasm,			Plump, spindled or epitheloid cells, Hyperplastic epidermis	
Nuclear β-catenins absent, infrequent actins				Nuclear β-catenins present, express SMA and MSA	Express actins and desmin				
Usually on extremities or trunk, rarely periungual area							Situated on hands, feet, periungual area		Centred on dermis and often invading subcutaneous region

DOI: 10.14302/issn.2689-5773.jcdp-20-3292

antigen (EMA) and CD34 besides being immune non reactive to S100 protein or mucin 4 (MUC4). Aforesaid immune phenotype simulates normal perineurial cells. Immune reactivity to EMA is variable and appears as focal, mild, intense, membranous or diffuse and is cogent in highlighting the delicate, bipolar, cytoplasmic processes. Immune reactivity to EMA(100%), Claudin- 1 (40%) and CD34 (65%-80%) is demonstrated. Immune reactivity to actins can also be discerned.

Perineurioma is immune reactive to perineurial markers claudin-1 and glucose transporter 1(GLUT1). Perineurial cells and certain soft tissue perineuriomas enunciate the classic tight junction- associated protein claudin-1.7[6,7]'

On electron microscopy, non branching, thin, cytoplasmic processes are observed which are layered by an extraneous lamina and adherent cellular terminals with tight junctions. Organelles are minimal whereas numerous pinocytotic vesicles and filaments of actin and vimentin are discerned. Perineurioma can be detected on cogent ultrastructural examination although can be immune non reactive to EMA.

Molecular studies depict a monosomy of chromosome 22 with genomic deletions at 22q11-13.1[6,7].

Differential Diagnosis

Soft tissue perineurioma requires a segregation from conditions such as intra-neural neurofibroma/ schwannoma, intra-neural malignant peripheral nerve sheath tumour, neural lipofibroma, pacinian neuroma, ectopic meningioma, desmoid fibromatosis, smooth muscle tumour, solitary fibrous tumour, superficial acral myxoma or a dermatofibroma[6,7].

Soft tissue perineurioma necessitates a demarcation from benign tumours such as schwannoma, neurofibroma, intramuscular/ cellular myxoma and nodular fasciitis besides malignant conditions as with low-grade fibromyxoid sarcoma, low- grade myxofibrosarcoma, dermatofibrosarcoma protuberans and low- grade malignant peripheral nerve sheath tumour[6,7].

As perineurioma mandates a distinction from neoplasia such as neurofibroma, dermatofibrosarcoma protuberans, cutaneous meningioma and low-grade fibromyxoid sarcoma, specific manifestations can be discerned within diverse lesions.

Immune reactivity to S100 protein and non reactivity to EMA is discerned in schwannoma and neurofibroma.

Dermatofibrosarcoma protuberans can resemble a perineurioma, especially upon a superficial biopsy and is immune non reactive to epithelial membrane antigen (EMA). Compact cellular clusters and nuclear atypia is observed in dermatofibrosarcoma protuberans and low-grade malignant peripheral nerve sheath tumour[7,8].

Cutaneous meningioma typically emerges upon the scalp of infants and children and is immune non reactive to CD34.

Certain perineuriomas can simulate a low grade fibromyxoid sarcoma which are immune reactive to MUC4.

Differentiation from nodular fasciitis can be obtained upon a cogent history[8,9].

Meticulous examination of cytological and morphological features can aid the distinction as occurrence of pleomorphism and curvilinear vasculature can be delineated in low- grade myxofibrosarcoma. Cogent tissue sampling can display diagnostic morphological manifestations such as classic architectural features as with a whorled or storiform pattern in soft tissue perineurioma, tumour heterogeneity, diverse cellularity and myxoid or a collagenous stroma in low-grade fibromyxoid sarcoma, along with distinctive tumour infiltration appearing as invasion and splaying out of adjacent skeletal muscle fibres discerned in intramuscular/ cellular myxoma[8,9].

Therapeutic Options

Surgical extermination of the neoplasm along with resection of a perimeter of normal, uninvolved soft tissue is usually curative[9,10].

(Table 1)

References

1. Lazarus SS, Trombetta LD" Ultrastructural identification of a benign perineurial cell tumour" Cancer 1978:41; 1823-1829.
2. Antonescu CR, Perry A et al" Perineurioma. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK ed WHO classification of the tumours of the central nervous

system-revised fourth edition" Lyon, France 2016: 222-224.

3. Wang LM, Zhong YF et al " Intraneural perineurioma affecting multiple nerves: a case report and literature review" Int J Clin Exp Pathol 2014:7 (6);3347-3354.
4. Domanski HA, Mertens F et al" Low grade fibromyxoid sarcoma is difficult to diagnose by fine needle aspiration cytology ; a cytomorphological study of eight cases" Cytopathology 2009:20; 304-314.
5. Evans HL" Low grade fibromyxoid sarcoma ; a clinicopathologic study of 33 cases with long term follow up" Am J Surg Pathol 2011: 35;1450-1462.
6. Doyle , Moller E et al" MUC4 is a highly sensitive and a specific marker for low grade fibromyxoidsarcoma" Am J Surg Pathol 2011:35; 733-741.
7. Cates JM, Coffin CM " Neurogenic tumours of the soft tissue" Paediatr Dev Pathol 2012: 15(1Suppl); 62-107.
8. Schaefer IM, Strobel P et al" A soft tissue perineurioma and other unusual tumours in a patient with neurofibromatosis type 1" Int J Clin Exp Pathol 2013: 6(12);3003-3008.
9. Coffin CM, Davis JL et al " Syndrome- associated soft tissue tumours" Histopathology 2014:64(1); 68-87
10. Yang EJ, Hornick JL et al" Fine needle aspiration cytology of soft tissue perineurioma : a comparative analysis of cytomorphology and immunohistochemistry with benign and malignant mimics" Cancer Cytopathology 2016: 124; 651-8.
11. Image 1 Courtesy : Pathology outlines.
12. Image 2 Courtesy : Disease Pictures.
13. Image 3 and 4 Courtesy :Journal of Pathology and Translational Medicine
14. Image 5 Courtesy : Research gate
15. Image 6 Courtesy : Archives of pathology
16. Image 7 Courtesy : Semantic scholar
17. Image 8 Courtesy : Histopathology.india.net
18. Image 9 and 10 Courtesy :Hindawi.com
19. Image 11 Courtesy : USCAP