Review Article

An update on oral peripheral nerve sheath tumors

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Abstract

Peripheral nerve sheath tumors (PNSTs) are defined as type of sarcomas that develops in cells which forms a protective sheath (covering) around the peripheral nerve, i.e., the cells of myelin sheath. Nerve tumors are of neuroectodermal in origin as it was composed of small rounded ectodermal cells that affect exclusively soft tissues. PNSTs are most common neoplasm with classic clinicopathological features, but they are diagnostically challenging. They consist of wide spectrum of tumors ranging from benign tumors to malignant nerve sheath tumors and its prevalent in oral tissues. Diagnosis of PNSTs are quite hectic but made possible by histopathology and immunohistological markers.

Keywords: Benign to malignant nerve sheath tumors, cells of myelin sheath, neuroectodermal

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INTRODUCTION

Nervous system neoplasm is any tumor affecting both central and peripheral nervous systems.[1] Central tumors are brain tumors, arachnoid cyst, medulloblastoma and optic nerve glioma whereas neurofibroma, schwannomas, granular cell tumors and malignant nerve tumors fall under peripheral variant.[2,3,4] Peripheral nerve sheath tumors (PNSTs) are defined as type of sarcomas that develops in cells which forms a protective sheath (covering) around the peripheral nerve. i.e., the cells of myelin sheath (NCI definition). The nerve sheath is a layer of myelin and connective tissue that surrounds and insulates nerve fibers.[4,5,6] Nerve tumors are of neuroectodermal in origin[5,7,8,9,10] as it composed of small rounded ectodermal cells that mostly affect soft tissues.[11,12,13] PNSTs are most common neoplasm with classic clinicopathological features, but they are diagnostically challenging.[4,7] They consist of wide spectrum of tumors ranging from benign tumors to malignant nerve sheath tumors and its prevalence in oral are rare (20%–40%). More than 90%–95% of tumors are benign and malignant transmission of tumors are rarer (10%).[3,4] However, malignant PNSTs (MPNST) are more aggressive and often associated with neurofibromatosis type 1, Carey- carney complex and schwannomatosis.[4,7]

Oral PNSTs occur due to reactive or neoplastic proliferation of nerve itself or their limiting sheaths as said before.[4] The tumor cells always are found at the outside zone of the nerve, but the tumor itself may either push the nerve aside. Neuromas can arise from different types of nervous tissue that includes the major and minor nerve fibers. The most common oral neural tumors are neurilemomas and neurofibromatosis (56%) and traumatic neuromas (30%).[2,14] The tumor develops most commonly in mental foramen, lower lip and tongue in second to fifth decade of life.[14] Oral malignant peripheral nerve tumors are infrequent through highly hostile arising from Schwann cells and they are seen commonly occurring in tongue.[2,4] The aim of this

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paper is to improving our understanding on oral peripheral nerve tumor and their transmission into malignancy besides highlighting their basic clinicopathological features to aid astute diagnosis of them.

NORMAL ANATOMY OF NERVE

Central nervous system consists of brain and spinal cord, whereas the nerves migrating from the spinal cord comes under peripheral nervous system [Figure 1]. A nerve is the primary structure of the peripheral nervous system that encloses the axons of peripheral neurons and provides the support for electrochemical nerve impulses which transmitted along each of the axons.[4]

The major functional elements of peripheral nerves are axonal process and their myelin sheaths which are made by Schwann cells. Schwann cells are the primary neoplastic component present in the myelin sheath. Each nerve contains many axons which referred as fibers. Within a nerve, each axon is covered by a layer of connective tissue called the endoneurium.[4,7]

Each endoneurium consists of an inner sleeve of material called the glycocalyx which contain fluid as insulating power called glycocalyx fluid or endoneuria fluid and has a mesh of collagen. Axons which is present inside the endoneurium are bundled along with blood vessels, which provide essential nutrients and energy to the metabolically demanding, neurons. The endoneurium has properties analogous to the blood–brain barrier. The axons are bundled together into groups forms fascicles. Each fascicle is wrapped in a layer of connective tissue called the perineurium. These compartments of endoneurium and perineurium are covered by outer layer called epineurium.[4,7]

Peripheral nerve tumors arise from different compartment of nerves namely:

- Myelin sheath surrounding the axons are formed by Schwann cells which comprises of myelin barriers
- Endoneurium forms the inner sleeve of material (glycocalyx) and comprises of fibroblast, capillaries, macrophages and mast cells
- Perineurium consists of a specialized epithelium like structure encompassing the endoneurium.
- Epineurium is the external layer composes of fibro-adipose tissues.[4]

If myelin sheath got affected, it leads to loss of nerve conduction impulse and cause sclerosis of nerve; if it occurs in Schwann cells, it leads to schwannomatosis and failure of impulses conduction and insulating power to myelin sheath. If perineurium, endoneurium, epineurium affected, it causes neurofibromatosis and traumatic neuroma. In case of perineurium affected, perineurioma occurs.

PATHOGENESIS IN NERVE TUMOR FORMATION

Nerve sheath tumors consists of a mixture of nonneoplastic components of nerve including axons, perineural cells, fibroblasts and inflammatory elements such as mast cells and lymphocytes along with neoplastic proliferation of Schwann cell differentiation,[15] which are the primary neoplastic cell component of nerve sheath. Schwann cells are characterized cytologically by wavy nuclear contours and S-100 protein expression mostly seen in immunohistochemistry.[15]

PREDISPOSING FACTOR

About 70% of nerve tumor occurrence is sporadic, but people with an inherited condition such as neurofibromatosis 1 and 2 and schwannomatosis (20%) have an increased risk of developing nerve sheath tumors. Similarly, subsequent to radiation therapy for any cancer type, a year later tend to develop nerve sheath tumor (10%).[8,15]

Neurofibromin 1 (NF1) is a gene located cytologically on the long (q) arm of chromosome 17 at band 11.2 (17q11.2) representing 220 KDa cytoplasmic protein with regions

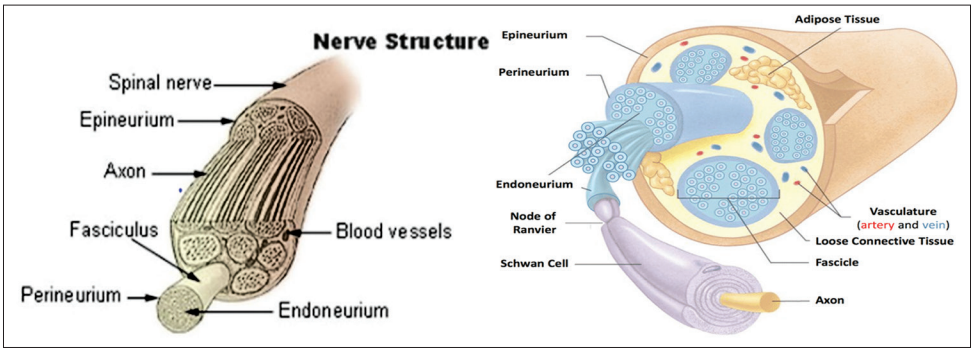

Figure 1: Anatomy and physiology of nerve. Source: Lumen-anatomy and physiology - module 12

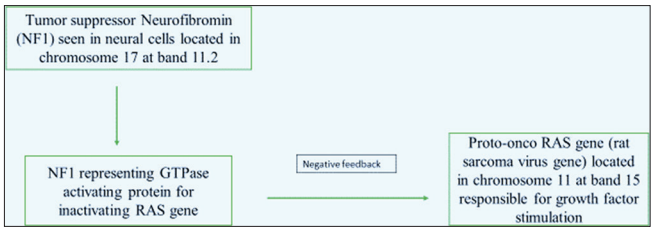

Figure 2: Normal homeostasis of nerve cell growth

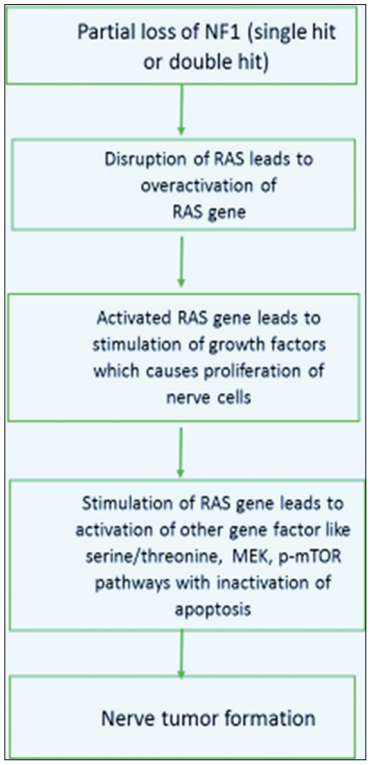

Figure 3: Pathological pathway for nerve cell growth

similar to GTPase activating protein (GAPs).[10] NF has been identified as a GAP for the Rat sarcoma virus (RAS) family of proto-oncogenes and acts as negative feedback mechanism for RAS that control the activity of RAS proto-oncogenes. This is by catalyzing the active ras-GTP to its inactive GDP-bound conformation.[8,10,20] Thus, disruption of NF 1 gene leads to hyperactivation of RAS gene signaling (RAS) which is present in major organs and nerve cells.[8,10,20]

In normal homeostasis: (A)

Algorithm (A): Normal mechanism of nerve cell growth in which NF gene which acts as negative feedback for RAS gene present in chromosome 17 [Figure 2].

In case of inherited or *de novo* mutation: (B)

Pathogenesis (B): In case of inherited or *de novo* mutation, biallelic loss of neurofibromatosis type I (NF1) which makes RAS gene overexpression responsible for growth factor stimulation. RAS activation stimulates other pathway like MEK/extracellular signal-regulated kinase (ERK), mouse strain AK thymoma (AKT) mammalian target of rapamycin (mTOR), tp53 causes over proliferation of nerve cells leads to neurofibroma formation [Figure 3].

RAS gene promotes cell growth in which the GTP bound causes RAS domination which leads to multiple downstream survival and proliferation pathways, including the serine/threonine protein kinase RAF to activate MEK and ERK (extracellular signal-regulation kinase). RAS leads to downstream regulation of other gene level such as PI3K/AKT/mTOR (phosphatidyl inositol 3, AK thymoma, mTOR) which causes cell growth, survival and proliferation.[8,10,20]

Bispecific allelic loss of NF (one hit from the germline and other acquired somatically) resulting in RAS activation is directly assumed to responsible for development of neuro-fibromas. Yet understanding of pathogenesis of nerve tumorigenesis is bit more complex; however, it is possible to understand if proper knowledge about nerve sheath layer and pathways of nerve conduction were known.[8,10,20]

Neurofibroma occurs due to nonmyelinating p75+ Schwann cell progenitors which are the major cell for NF 1 loss. Schwannomas represent more homogenous proliferation of mature Schwann cells.[20]

Multiplex pathways which are involved are explained as follows

Rat sarcoma virus pathway

The RAS/RAF genes are the proto-oncogenes characterized by signal transduction in cell biology. The main function of these pathway is to transduce signals from extracellular structure (cell surface receptor) into intrinsic nucleus of cell that drives broad spectrum of physiological and pathological cellular processes such as growth, proliferation, differentiation, migration and apoptosis. Proper activation of these gene level helps in cell growth with appropriate apoptosis and it also able to stimulate the angiogenesis for formation of new blood vessels. But overactivation of RAS due to genetic or somatic mutation of NF1 leads to activation of various pathway such as serine/threonine, ERK1, ERK2 phosphorylate and MEK pathway and stimulate downstream effectors and regulate different transcription factors like neurotropic factor (NT3, Ciliary neurotrophic factor and leukemia inhibitory factor) leads to expression of gene that stimulate proliferation. Thus, the initial formation of tumor growth occurs but activation of these pathway alone will not lead to malignant progression.[10,20]

MEK/extracellular signal-regulated kinase pathways

ERK belongs to the mitogen-activated protein

kinase (MAPK) family which also named as MEK, which plays a vital role in signaling cascades and transmits extracellular signals to intracellular cells. Therefore, MAPK cascades are central signaling elements that regulate basic processes in the cells like cell proliferation, differentiation and stress responses. MEK/ERK, a type of serine/threonine protein kinase, is a signal transduction protein that transmits mitogen signals (induces mitosis). ERK is generally located in the cytoplasm; upon activation, ERK enters the nucleus and regulates transcription factor activity and gene expression. RAS activation leads to continues activation of ERK/MAPK pathways promotes the transformation of normal cells into tumor cells; it also has disorderly anti-apoptotic properties so leads to formation of cells without apoptotic properties cause nerve tumor formation.[10,20]

TRANSMISSION TO MALIGNANT TUMORS

For malignant progression, additional pathways gets activated due to heterogenicity loss of NF1 locus which are SCF, PI3K/mTOR, P-TEN and MAPK pathways. These eventually lead to disorder of epigenetic regulation, mitosis and angiogenesis causing aggressive growth of tumor cells. Abbreviation: RAF: Rapidly accelerating fibrosarcoma, MEK: Mitogen activating protein kinase, AKT: Mouse strain AK thymoma, mTOR: Mammalian target of rapamycin IAP: Inhibitor of apoptotic proteins, ERK: Extracellular signal regulated kinase, SCF: Stem cell factor, NF1: Neurofibromin 1, PTEN: Phosphatase and tensin homolog [Figure 4].

NF 1 inactivation and loss of NF expression characterize majority of malignant transformation but bi-allelic NF 1 loss is insufficient for malignant transformation. Generally, conditional NF1 gene inactivation in Schwann cell will result in plexiform development of neurofibroma based on this concept. Initially it started in mouse studies and was noticed heterozygosity loss at the NF 1 locus is permissive to neurofibroma formation. Murine studies also revealed the importance of insufficient NF1 mast cells leading to proliferation of nerve cells. So, based on these various authors maturation, proliferation and recruitment of mast cells which is been mediated by SCF, the ligand for KIT receptor tyrosine kinase (RTK) suggesting SCF/KIT dependent tumorigenic tumor-stromal interactions in plexiform neurofibroma, in addition to RAS activation. There also mutation or alteration in gene such asTP53, CDKN2A, SUZ12 and tyrosine kinase amplification epidermal growth factor receptor (EGFR) reported as secondary coordinating mutations facilitating malignant progression.[8,10,20]

Receptor tyrosine activating signaling pathways

RTKs are a family of cell surface receptors for wide array of growth factors, hormones, cytokines, neurotrophic factors and other extracellular signaling molecules. Multiple soluble or membrane-bound growth factors bind and activate RTKs including vascular epithelial growth factor, EGFR, fibroblast growth factor receptor, mitogen-activated protein kinase (MEK), nerve growth factor receptor, platelet derived growth factor and the proto-oncogene c-KIT. These growth factors are key regulators of normal cellular processes including the survival, proliferation, differentiation and migration.[20]

Aberrant change in pathways due to genetic or epigenetic alteration is a common cause of cell transformation, cancer

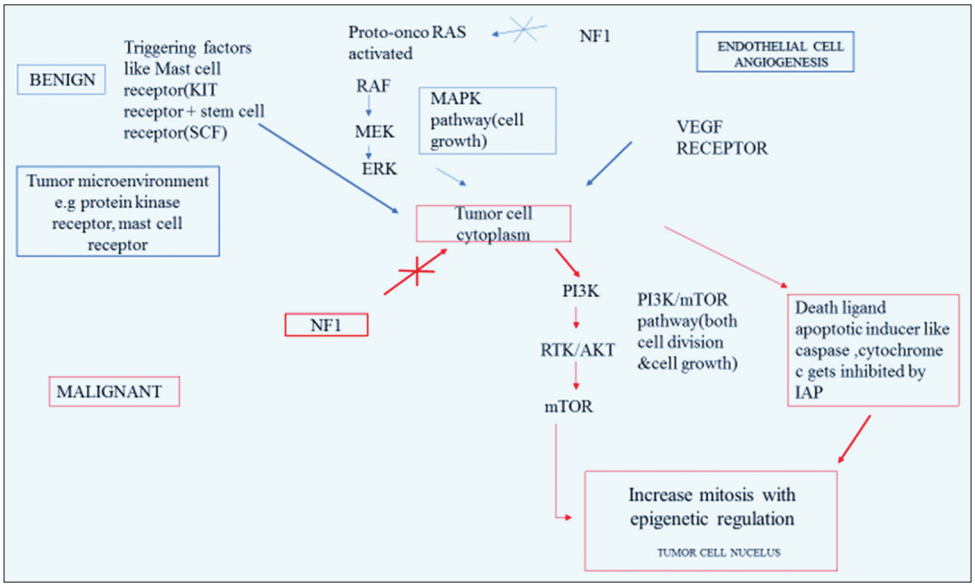

Figure 4: Benign to malignant pathway

development and metastasis, and RTKs play critical roles in development/regulation stemness and proliferation. Genetic alteration that activates RTKs or component of downstream pathway such as MAPK, PI3K/AKT and JAK/STAT have been identified in progression to malignant nerve sheath tumor.[20]

PI3K/mouse strain AK thymoma/mammalian target of rapamycin pathway

The AKT/mTOR pathways play important roles in modulating cellular functions in response to extracellular signals, such as growth factors and cytokines. mTOR acts as downstream targets of AKT and plays a key role in the AKT/mTOR pathway. mTOR activates p70S6 kinase, directly or indirectly activates S6 ribosomal protein (S6RP) and inhibits 4E-binding protein 1. mTOR activation causes protein synthesis, which induces cell proliferation, survival, motility, invasion and differentiation, and finally it can lead to cancer initiation and progression Activation of mTOR is more common activated pathway in MPNST and plays key role in pathogenesis of tumor. Alteration in expression or activity of any of the following phosphatase and tensin homolog, phosphatase mouse strain AK thymoma, (phosphatase mTOR) and p-S6RP lead to poor prognosis of malignant sheath tumor. For identifying proper mechanism of these pathways, various studies are conducted. One of such studies results shows dual inhibition of mTOR pathways negate the tumor cells to survive proteolytic stress and also abrogate the cell death and tumor suppression.[20]

WnT signaling

WnT pathway is a major developmental pathway involved in maintenance of normal cells and altered in several human cancers. WnT signaling is a complex process that requires interplay of many different proteins. WnT ligands may activate 3 different pathways: (i) the canonical pathway, involving β-catenin and LEF/TCF transcription factor; (ii) the planar cell polarity pathway; and (iii) the Wnt/calcium pathway. WnT signaling pathway orchestrates highly complex molecular events. Aberrant activation of WnT pathway could trigger cell malignant transformation. In the last 20 years, involvement of the WnT pathway has mainly been revealed in human epithelial malignancies. However, the WnT pathway may also play a role in tumors of mesenchymal origin. Mesenchymal stem cells could differentiate into Schwann cell–like cells. WnT pathway is tightly implicated in the myelination process elicited by Schwann cells. Key role for WnT/β-catenin signaling in the initiation of myelination and in myelin sheath compaction in the central and peripheral nervous systems. Inhibition of WnT/β-catenin signaling resulted in hypomyelination and oligodendrocytes generation or axonal integrity. Thus, the dysregulation of this pathway could lead to either developmental defects or tumorigenesis. In recent studies done by Largaespada and his colleagues made contribution in pathogenesis of MPNST using *in vivo* genetics screen which was done in mice. They identified WnT signaling pathway genes are potential drivers of benign neurofibromas and MPNST evidence also suggested that canonical WnT signaling pathways cross-talks with other pathways to drive benign into malignant transformation but detail explained for involvement of these pathway is still ongoing.[20]

CLASSIFICATION

WHO classification - 2013

Based on nerve of origin and histopathological variants

- Schwannoma
  - Conventional schwannoma
  - Cellular schwannoma
  - Plexiform schwannoma
  - Melanotic schwannoma
  - Microcystic/reticular schwannoma
- Neurofibroma
  - Circumscribed neurofibroma (dermal/soft tissue/intraneural)
  - Diffuse and massive soft tissue neurofibroma
  - Plexiform neurofibroma[3,15]
- Perineurioma
  - Intraneural perineurioma
  - Soft tissue perineurioma
  - Sclerosing perineurioma[3,15]
- Granular cell tumor
  - Benign granular cell tumor
  - Malignant granular cell tumor[3,15]
- Miscellaneous benign nerve sheath tumors
  - Palisaded encapsulated neuroma
  - Nerve sheath myxoma[3,15]
- Benign hybrid tumors
  - Hybrid neurofibroma/schwannoma ("neurofibroma with Schwannian nodules")
  - Hybrid schwannoma/perineurioma
  - Hybrid benign nerve sheath tumors NOS[3,15]
- Malignant peripheral nerve sheath tumor
  - Low-grade MPNST
  - High-grade MPNST
  - Epithelioid MPNST
  - MPNST with divergent differentiation (triton tumor, MPNST with
  - Glandular differentiation)
  - MPNST ex schwannoma
  - Malignant melanotic schwannoma

  - Perineurial MPNST
- Miscellaneous malignant intraneural neoplasms
  - Synovial sarcoma of nerve.[3,15]

Based on causes

- Nonneoplastic
  - Traumatic neuroma

- Neoplastic
- Benign
  - Neurofibroma
  - Schwannomas
  - Hybrid tumors
  - Granular cell tumor
- Malignant
  - Malignant nerve sheath tumors.

Even though nerve sheath tumors are classified based on origin, only some tumors have oral manifestation which are explained below.

NEUROFIBROMA

Neurofibroma is the most common type of PNSTs. It is well-defined benign tumors either appears in intraneural or extra neural sites of nerve sheath. Neurofibromas are mostly solitary arise from small peripheral nerves of skin and subcutaneous tissues; neurofibromas rarely involves central sites like spinal nerve roots and cranial nerve has not been described so far. Cells of origin for neurofibroma are nerve endoneurium and a feature of mixture of Schwann cells, nerve axons, fibroblastic cells, perineurial-like cells as well as inflammatory cells including mast cells and lymphocytes. Lesions can present at any age, i.e., both male and female are equally affected and are more common in superficial cutaneous sites, where they present as localized, pedunculated growths.[5,15]

The majority of neurofibromas (90%) are sporadic and are caused by biallelic (double hit) inactivation of NF 1 gene on chromosomes 17q11.2. The minor of 10% are nonsporadic neurofibromas which are caused by NF1 or von Recklinghausen disease.[4,15]

NF1 is an autosomal dominant multisystem disorder caused by heterozygous mutations in the NF gene on chromosome 17q11.2. Most common arise in soft tissue less common in oral cavity (palate, gingiva and tongue). Clinically seen as solitary lesion and are less frequently seen as multiple asymptomatic small sessile nodules covered by normal mucosa[4,5,10,15]

Diagnostic criteria for neurofibromin 1

1. Six or more *café-au-lait* macules (with a greatest diameter of >5 mm in prepubertal subjects, or <15 mm in postpubertal subjects)
2. Two or more NFs of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal region
4. Optic glioma
5. Two or more Lisch nodules (IRIS hamartomas)
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
7. A first-degree relative with NF1.[7,13,15]

Neurofibroma variants

Multiple subtypes of neurofibroma are recognized based on macroscopic and/or histologic pattern of involvement, architectural growth patterns includes localized, diffuse and plexiform and some uncommon subtypes are cellular, glandular.[7,13-15]

Localized

Most common subtypes which present in skin as painless nodule or a polyploid/pedunculated mass lesion. They may be further subdivided into cutaneous or intraneural types. Localized cutaneous occurs sporadically in the majority of cases, it involves a major nerve and has an indistinct outer margin because of that, it is so difficult to determine exactly where the lesion ends. In intraneural subtypes, the lesion expands in a single nerve which are surrounded by a thin rim of fibroconnective tissue. Histologically both are well-demarcated but lack a well-defined capsule.[10,5,15]

Diffuse

Second common subtype characterized as plaque with associated skin thickening. It is more common arise in head and neck region and are larger than localized forms and may be cosmetically disfigured. Histologically diffuse neurofibroma is less described than localized forms. Both localized and diffuse neurofibroma grow around adnexal structures; however, neurofibroma also infiltrate fat which is not seen in localized forms.[5,15]

Plexiform

Rarest form, mostly seen in major nerve trunk and the massive soft tissue. Plexiform neurofibroma is defined by the involvement of numerous successive nerve fascicles or a nerve plexus. Most commonly involves head and neck region nerves i.e., trigeminal nerve particularly ophthalmic and maxillary divisions. Microscopically, seen as an admixture of areas which resembling both of other types. Plexiform neurofibroma has a potential for malignant degeneration and are majorly recognized precursor for MPNST in NF1 patients.[5,15]

Pathological findings

The major finding is that of spindle-shaped cells arranged haphazardly in a fibromyxoid matrix. A diagnostic feature is the presence of loose collagen fibers in the matrix, characteristically described as a "shredded carrot" pattern which lacks hyalinized vessels. The fibro myxoid matrix may become fibrous ("collagenous neurofibroma") or myxoid ("myxoid neurofibroma") predominantly. Nerve fibers seen on routine histology, especially in the localized intraneural subtype are most often located in the middle of the lesion. Inflammatory cells including mast cells and lymphocytes are dispersed. A classic feature of diffuse subtype is the presence of Schwann cells with meissnerian differentiation ("Meissner-like corpuscles") which is capable of producing inflammatory cells.[5,15]

Cytologically, the spindled cells have wavy nuclei with tapered ends and poor cell borders. Increased nucleoli and mitotic activity are not observed. Degenerative atypia such as hyperchromasia and nuclear pleomorphism can be seen but atypia presented only focally. In the absence of diffuse atypia, increased mitotic activity or increased cellularity, focal atypia alone does not alter prognosis and these cases are named as "ancient neurofibroma"[5,15]

Immunohistochemistry

Classic diagnostic features in nerve sheath tumors shows strongly positive of S-100 for neurofibroma in some (40%–50%) but not all cells. Basement membrane markers (collagen IV and laminin) are less consonant for schwannoma. CD34 is positive for fibroblastic-like cells. The myxoid background material is Alcian blue positive. Neurofilament highlights nerve axons within the lesion. Epithelial membrane antigen (EMA) is focally positive in entrapped perineurial-like cells but lacks the diffuse staining pattern which is most commonly seen in perineuroma. Glial fibrillary acidic protein (GFAP) can be weakly positive in some cases.[2,5,10,15]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for neurofibromas is ample mostly influenced by the site of occurrence (intra vs. extraneural) includes both neoplastic and nonneoplastic conditions.

Neoplastic condition includes schwannoma, nerve sheath myxoma, neurothekeoma, as well as a variety of nonnerve sheath tumors, in particular dermatofibrosarcoma protuberans and desmoplastic malignant melanoma.

Nonneoplastic condition like traumatic neuroma and ganglioneuroma which infiltrate dorsal root or sympathetic ganglia, represent the main entities in the differential diagnosis.[5,15]

The atypical differential diagnosis for neurofibromas is desmoplastic malignant melanoma composed of deceptively bland cells with wavy nuclei, closely mimicking neurofibroma.

Important point to differentiate melanoma from neurofibroma include the presence of significant sun damage, atypical junctional melanocytic hyperplasia or melanoma *in situ*, the presence of very long, hyperchromatic cells, a "packeted" pattern of growth, dense fibrosis and deep nodular lymphoid aggregates.

Immunohistochemistry are not helpful in differential diagnosis, as both express S100 protein, and more specific melanocytic markers (e.g., HMB45, Melan-A, tyrosinase) are essentially never positive in desmoplastic melanoma. A recent report shows that CD34 immunoreactivity in a "fingerprint" pattern is more typical of neurofibroma than desmoplastic melanoma.[5,15]

SCHWANNOMAS/NEURILEMMOMA

Schwannoma is a benign, encapsulated PNST of neuroectodermal origin composed purely of Schwann cells. Most common is in 4th–6th decade of life and there is no predilection for male or female. The tumor cells are always found at the outside zone of the nerve involved. So, it pushes the nerve aside. Schwannoma occurs in numerous body sites includes skin and subcutaneous tissues, especially the head and neck and flexor surfaces of the extremities. In addition to the skin/subcutaneous tissues, peripheral schwannomas are also seen in the gastrointestinal tract. Schwannomas involving the central nervous system are less common than those of the peripheral nervous system and may be either intracranial or intraspinal. Intracranially involves eight cranial nerve particularly of vestibular branch. Intraspinal tumors involve the sensory (dorsal) nerve roots with sparing of the motor (ventral) nerve roots. The majority of schwannomas (90%) are sporadic and are associated with two-hit loss of function mutations in the neurofibromatosis 2 gene (NF2) located at 22q12.2. NF2 is a proto-oncogene which encodes the Merlin protein product, a tumor suppressor protein involved in various cytoskeletal functions.

The minority of 10% are associated with germline mutations and about half of these are found in association with neurofibromatosis 2 (NF2) and the other half in association with schwannomatosis.[5,15]

Diagnostic criteria for NF 2

1. Bilateral acoustic neuroma/family history of NF2+ unilateral acoustic neuroma/any 2 of meningioma, neurofibroma, schwannoma, corneal opacities
2. Unilateral acoustic neuroma + any 2 of meningioma, neurofibroma, schwannoma, corneal opacities
3. 2 or more meningiomas + unilateral acoustic neuroma/any 2 of glioma, schwannoma or cataract
4. 1st degree relative with NF2 and any 1 of the above criteria.[7,14,15]

CLINICAL PRESENTATION

Tumors of peripheral nerve are usually asymptomatic clinically seen as a slow-growing solitary masses covered by normal appearing mucosa that measure a few millimeters to many centimeters in diameter. Most common in head and neck region particularly of lips mostly lower lip. Other presentation which is noticed so far in schwannoma patients includes are difficulty in swallowing, speaking or breathing, macroglossia, loss of sensation and taste.[4,7,14,15]

Schwannoma variants

Various subtypes are noticed so far based on morphological, pathological findings and cytological findings which are of cellular, plexiform, melanotic schwannoma.

Cellular

Benign neoplasm and important variant of schwannoma because of its high cellularity, growth pattern and destructive in nature. But it not metastasized easily. Cellular schwannoma is defined as a schwannoma consists mostly of a compact, fascicular proliferation of well differentiated, cytologically bland Schwann cells, lacking Verocay bodies.[5,15]

Morphologically, it lacks the biphasic pattern of conventional type and resembles mostly like gastrointestinal stromal tumor (GISTs), solitary fibrous tumors, monophasic synovial sacroma and MPNST but only classic differences in cellular variants, it does not metastasis easily and most common occur in paraspinal region of pelvis, retroperitoneum and mediastinum.

Cellular schwannomas have local recurrence which is variable and higher than conventional schwannomas. Histologically, presence of foamy histiocyte aggregates, well formed capsule containing lymphoid aggregates and diffuse strong S100 protein, pericellular collagen IV expression with increased mitotic activity. These are important clues for diagnostic cellular variants. Because of increased mitotic activity it leads to misdiagnosing of MPNSTs but strong S100 rises the possibility to cellular type.

Cytologically, lack of expression of smooth muscle actin, desmin, CD117 and DOG1 (discovered on GIST/anoctamin-1) which is recently described as membrane protein expressed in tumor.[5,15]

Plexiform schwannomas

Distinct subtypes of schwannomas which is defined by intraneural-nodular pattern of growth occurs in superficial (cutaneous or subcutaneous) locations seen as a multiple mass involving nerve fibers. They may associate with schwannoma predisposing syndromes such as NF 2 and schwannomatosis but associated is so weak (approx. 5%).

Microscopically, seen often as uniformly hypercellular and lack hypocellular (Antoni B) regions. Unlike plexiform neurofibroma, the lesion is overall relatively hypercellular and lacks the fibrillary "shredded carrot" background of neurofibroma.[5,7,14,15]

Immunohistochemical staining pattern, especially S100 (diffuse in schwannoma, patchy in neurofibroma) is helpful in distinguishing these two.

Melanotic schwannomas

Rare, distinct subtypes, potentially malignant neoplasm characterized by epithelioid cells with variably sized nuclei and marked accumulation of melanin in neoplastic cells and associated melanocytes. About one half of melanotic schwannomas contain psammoma bodies and are known as "psammatous melanotic schwannoma" and is associated with approximately half the cases with carney complex, an autosomal dominant disorder characterized by cutaneous, soft tissue and cardiac myxomas, pigmented skin lesions, endocrine dysfunction. Melanotic schwannoma occurs around a decade earlier than conventional schwannoma. Most commonly found in the cervical and thoracic spine (approximately 50% of cases), paraspinal ganglia and autonomic nerves of the gastrointestinal tract.[5,15]

Pathological findings

Grossly, diffuse brown to black pigmentation can be identified. Microscopically, the lesion is circumscribed, hypercellular, without distinct Antoni A and Antoni B regions or Verocay bodies.[5,15]

The cells are epithelioid and spindled in appearance with abundant cytoplasmic melanin pigment with cytologic atypia in the form of macronucleoli and hyperchromasia.

Tumor cells are diffusely positive for S100 as well as positive for HMB45 and Melan-A (melanocytic markers). Staining for basement membrane markers (collagen IV, laminin) highlights groups and nests of cells as opposed to the characteristic pericellular pattern seen in conventional schwannoma. Intracytoplasmic melanin pigment can be stained by Fontana Masson stain. Melanosomes are evident on ultrastructural analysis.[5,15]

Differential diagnosis

The differential diagnosis includes:

- Melanoma
- Meningeal melanocytoma
- Pigmented neurofibroma.

A thorough skin exam for atypical pigmented lesions should be performed to definitively rule out the chances of metastatic melanoma. Features for diagnosis of melanotic schwannoma include characteristic location (spinal nerves and paraspinal ganglia), spindled morphology, low mitotic rate and (in a subset of cases) psammomatous calcifications.[15]

Meningeal melanocytomas immunohistochemical features are similar with melanotic schwannoma and are differentiated based on their characteristic location within the meninges (which would be an unusual location for a schwannoma). Pigmented neurofibroma more commonly involves peripheral nerves in the skin and soft tissues includes head and neck, lower legs, buttocks and uncommon in central sites such as spinal nerves and paraspinal ganglia. As with melanotic schwannoma, pigmented neurofibroma is positive for melanocytic markers and therefore morphologic features should be used to distinguish.[15]

HYBRID NERVE SHEATH TUMORS

Most peripheral tumors occur as moral lesions exhibit distinct morphological and immunophenotypic features but tumors with histologic features of more than one PNST have been increasingly recognized and are named as "HYBRID NERVE SHEATH TUMORS" which is combination of tumors with overlapping of clinical, histological features.[9,15]

The most common hybrid tumors: Schwannoma/perineurioma; Neurofibroma/schwannoma which are predominantly sporadic lesion but, in many cases, associated with syndrome NF1 or NF2. They are usually encountered in the dermis or subcutaneous tissue, with no predilection for a particular anatomic site. Tumors occur at any age and there is an equal male to female ratio for all subtypes.[9,15]

Clinical appearances

It usually present with painless nodules or masses, which are relatively small in size (usually <5 cm) and most commonly benign tumors and rarely metastasis or transformation into MPNST.[9,15]

Variants

Schwannoma/perineurioma

Though it is combination of tumors it shows histological and cytomorphological features with any one of variants like the classic histologic finding in

schwannoma/perineurioma is that of a circumscribed or unencapsulated mass with architectural features of perineurioma but cytomorphologic features more suggestive of Schwannian-type differentiation. Specifically, the architectural pattern is predominately storiform or less commonly whorled or lamellar; distinct hypercellular/hypocellular (Antoni A and B) regions, palisading and Verocay bodies are absent. Hyalinized vessels are also not observed.[9,15]

Cytomorphologically, the majority of cells are plump spindle cells with tapered ends and eosinophilic cytoplasm. Relatively slenderer, less plump spindle cells are also observed but are present in fewer numbers. Mitoses are absent to rare.

The plump spindle cells stain positive for S-100 and more slender spindle cells are EMA positive and correspond to the perineurial component. Although it is difficult to enumerate the exact proportion of Schwannian to perineurial-type cells on morphology alone, immunohistochemistry demonstrates a ratio as approximately 2:1 Schwannian to perineurial-type cells. Significantly, co-expression of S-100 and EMA is not observed on the same cell when tissue sections are stained with dual chromogenic markers. GFAP is positive in most lesions, a feature which is not seen in either pure schwannoma or pure perineurioma. Neurofilament is entirely negative or less common.[9,15]

Neurofibroma/schwannoma

Biphasic tumors with nodules of hypercellular Antoni A appearing Schwannian cells within histological features of neurofibroma or else it is typical-appearing neurofibroma. The neurofibromatous component mostly form majority of the lesion and has a plexiform growth pattern. The Schwannian nodules are predominately hypercellular and have both palisading and classic Verocay bodies.

Hypocellular Antoni B regions and hyalinized vessels are not seen, so differential staining pattern is helpful in making the diagnosis, as Schwannian nodules will demonstrate diffuse S-100 positivity while the neurofibroma component will show a more focal and heterogeneous staining pattern.[9,15]

MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

Malignant nerve sheath tumor are malignant spindle cell tumors arising from peripheral nerve or in extra neural soft tissues or from neurofibroma, neurilemmoma. It previously known as neurosarcomas, neurogenic sarcomas, neurofibrosarcomas and malignant schwannomas. The world health organization determined the term "MALIGNANT PERIPHERAL NERVE SHEATH TUMORS" for tumors of neurogenic origin with aggressive in origin. MPNSTs are uncommon tumors that can cause significant diagnostic challenges, but if it occurs in setting of hereditary syndrome like NF1, NF2 (approx. 50%) it can diagnose through criteria and presence of malignant features in immunohistochemical or cytogenic markers.[1,10,8,15]

Clinical features

MPNSTs are usually present in second to sixth decade of life with no sex predilection. It most commonly occurs in lower extremities, retroperitoneum and back are common sites. About 8%–16% of cases are presenting in head and neck region. In head and neck, the nasopharynx and nasal cavity and oral cavity (approx. 10%).[15,19]

The common appearance is painless swelling that becomes symptomatic when the lesion applies pressure on the surrounding structures. Sudden pain and an increase in size of neurofibroma suggestive of malignant transformation. In oral cavity, it presents as a bosselated, sessile, circumscribed, submucosal mass associated with pain/paresthesia and muscle weakness/atrophy.

PATHOLOGICAL FINDINGS

MPNSTs are aggressive sarcoma of neural origin that may arises spontaneously or in association with syndrome (5%–42%), they spread by direct extension to surrounding tissues and rarely by hematogenous or perineural route.[1,10,8,16,17-19,15]

Microscopically, tumors are usually cellular with a variable herring bone (fibrosarcoma-like) to fascicular architecture and infiltrative growth. Characteristically, the tumors exhibit alternating loose and cellular regions with perivascular accentuation. Some arise in the postirradiation setting. Most MPNSTs are high grade with >75% exhibiting brisk mitotic activity (>4 mitoses per high-power field) and areas of tumor necrosis. Tumors often show a hemangiopericytomatous vascular pattern.[15,20]

Magnetic resonance imaging is the most useful imaging modality for characterizing the anatomical extent of the tumor for surgical planning. Fluorodeoxyglucose-positron emission tomography helps in differentiating benign neurofibromas from MPNST in patients with NF1.[6,15]

There is no pathognomonic molecular or immunohistochemical study for MPNST.[21,22] S100 protein is not strongly differentiated; strong diffuse staining nearly excludes a diagnosis of MPNST. Thus, in the absence of a history Of NF1 or gross or microscopic evidence of association of tumor with nerve sheath or neurofibroma, the most reliable method of diagnosis remains electron microscopy, which can identify ultrastructural features of Schwann cells.[1,8,15]

GRADING OF MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

French system (FNCLCC) for grading soft tissue sarcomas.

Tumor differentiation.

Depends on histologic type/degree of differentiation ranging from well-differentiated tumors similar to mature counterparts:

- Score = 1, well-differentiated MPNST arising in transition from neurofibroma
- Score = 2, conventional, monomorphous spindle cell MPNST
- Score = 3 highly pleomorphic MPNSTs (often arising in NF1 syndrome), as well as MPNST with divergent differentiation (triton tumor, glandular, osteosarcomatous, chondorsarcomatous and angiosarcomatous).

Mitotic count:

- Score 1: Between 0 and 9 mitoses per 10 high-power fields (0.1734 mm2)
- Score 2: Between 10 and 19 mitoses per 10 high-power fields
- Score 3: >20 mitoses per 10 high-power fields.

Tumor necrosis

- Score 0: Necrosis absent
- Score 1: <50% necrosis
- Score 2: >50% necrosis.

Grading:

- Grade 1 (score 2–3)
- Grade 2 (score 4–5)
- Grade 3 (score 6–8).[15]

DIFFERENTIAL DIAGNOSIS

Most commonly encountered is that of monophasic synovial sarcoma, synovial sarcoma has been reported in an intraneural location and has considerable morphologic overlap with MPNST.[11,12]

A strong diagnosis of MPNST is the presence of pleomorphic cells, a finding that is very unusual in synovial sarcoma. In difficult cases, evaluating for the synovial sarcoma specific translocation t (X; 18) may be necessary. Cytogenetic analysis of MPNST generally shows a complex karyotype without cytogenetic abnormalities.

OTHER DIFFERENTIAL DIAGNOSIS

- Melanoma
- Clear cell sarcoma
- Epithelioid sarcoma and carcinoma.

Lack of expression of Melan-A, HMB45, MITF is very helpful in the distinction of epithelioid MPNST from melanoma and clear cell sarcoma and absence of cytokeratin expression distinguishes them from carcinoma and epithelioid sarcoma. Both epithelioid MPNST and epithelioid sarcoma may show loss of SMARCB1/INI1/BAF47 protein expression, a potential diagnostic pitfall in the differential diagnosis with malignant rhabdoid tumor.[10,15]

CONCLUSION

PNSTs are dynamic, evolving area of surgical pathology with increasing multiteam collaboration.[5,15] Most of lesion are not radiosensitive and can be removed by surgically or can be treated by agents targeting at molecular level such growth factor inhibitors such as cetuximab, transuzumab, etc., various newer modalities are been forming for managing the PNSTs.[20] The recognition of tumors based on clinical, histological and cytological studies not only helps in diagnosis of tumors but also helps in management of tumors. Greater availability of molecular techniques also helps in morphologic diagnoses and is likely to play an increasing important role in the immediate future.[15,20]

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Conflicts of interest

There are no conflicts of interest.

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