Neural Tumours of Oral and Para Oral Region
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Abstract
A spectrum of benign and malignant neural tumors can occur in oral and perioral region. The growth pattern and subsequent clinical behavior of the neuroogenous tumors differs in different sites and pose significant diagnostic and therapeutic problems. This paper reviews the neural tumours of oral & paraoral region.

Key Words: Neural Tumors; Nerve Cell Tumor; Nerve Sheath Tumor.

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Introduction
The nervous system consists of two principle type of cells i.e. the nerve cell and their supporting cells. The structural and functional unit of the nervous system is the nerve cell or neuron, which possesses the delicate cytoplasmic processes called the nerve fibers. Neuralgial cells of central nervous system, the Schwann cells and the satellite cells of ganglia of the peripheral nervous system are the supporting cells.

Tumors of neural tissue arise in connection with the sheath of peripheral nerves, the neuroglia and the immature nerve cells themselves. These neoplasms of neurogenic origin arise from the cells of neuroectodermal origin. The majority of tumors in the peripheral nervous system are derived from Schwann cells and their peripheral nerve elements. They arise mainly from cranial and spinal nerves and their roots, but similar tumors also occur in the peripheral autonomic nervous system, adrenal medulla and other sites in chromaffin system. In the oral region, neural tumors occur both in the soft tissues and in jaw bones. They occur as painless, smooth surface swelling in the soft tissues of the mouth, with tongue being the most common site. Within the jaw bones they exhibit a slow rate of growth and mild expansion of the cortical plates. It’s found that vast majority of neurogenous tumors arising in the head and neck are benign and that the malignant neoplasms generally have a propensity for local invasion rather than regional or distant metastasis. This paper gives a review on the neurogenic sarcomas and olfactory neuroblastomas.

Classification of neural tumours (WHO-1992)

Benign Tumours:
1. Traumatic Neuroma: Amputation Neuroma, Post Traumatic Neuroma
2. Morton’s Neuroma: Perineural Fibrosis
3. Neuromuscular Hamartoma
4. Nerve Sheath Ganglion
5. Schwannoma: Neurilemmoma, Perineural

Malignant Tumours:
6. Plexiform Schwannoma
7. Cellular Schwannoma
8. Degenerated Schwannoma: Ancient Schwannoma, Ancient Neurilemmoma
10. Diffuse Neurofibroma
11. Pacinian Neurofibroma
12. Epitheloid Neurofibroma
13. Granular Cell Tumor
14. Melanocytic Schwannoma: Pigmented Schwannoma
15. Neurothecoma: Nerve Sheath Myxoma
17. Ganglioneuroma
18. Pigmented Neuroectodermal Tumor of Infancy: Retinal Anlage Tumor, Melanotic or Melanocytic Neuroectodermal Tumour, Melanotic Prognoma

Malignant Tumours:
1. Malignant peripheral nerve sheath tumors (MPNST).
2. Malignant Schwannoma
3. Neurofibrosarcoma
4. Malignant peripheral nerve sheath tumor with Rhabdomyosarcoma: Malignant Triton tumor
5. Malignant peripheral sheath tumor with glandular differentiation
6. Epitheloid MPNST
7. Malignant granular cell tumor
8. cellular cell sarcomas: Malignant melanoma of soft parts
10. Neuroblastoma
11. Ganglioneuroblastoma
12. Neuropithelioma: Peripheral neuroectodermal tumour, Peripheral neuroblastoma

Description of Neural Tumours

Traumatic Neuroma: Clinically traumatic neuroma occurs at the site of previous injuries, chronic irritation or surgical procedures.
in the form of extraction of the tooth. A landmark study of traumatic neuromas was that of Hubner and Lewis.(1) Who developed an animal model to investigate the causative factors in the development of the lesion. They reported that the peripheral nerve section resulted in the formation of an expanded connective tissue cap at the end of the proximal segment. Nerve fibers attempting to re-establish continuity with the distal segment penetrated into and beyond the cap, becoming tangled and entrapped in the soft tissue. Cahn L(2) was the first to report traumatic neuroma of the mental foramen. The oral traumatic neuroma typically occurs near the mental foramen, on the alveolar ridge in the edentulous area or on the lips or tongue. Reflex neuralgia with distant pain associated with face, eye and head has been reported.(3) The clinical diagnosis of traumatic neuroma may be difficult if the patient presents with atypical pain. Hence traumatic neuroma is included in the clinical differential diagnosis of any small mass that is spontaneously painful when compressed. The histopathological appearance of traumatic neuroma is characteristic and consists mass of irregular and often interlacing neurofibrils and Schwann cells situated in the connective tissue stroma of either scanty or of plentiful proportions. The connective is probably the derivative of perineurium. The proliferating nerve fibers themselves may occur in discrete bundles or spread out diffusely throughout the tissue.(3) The tri-chrome stains like Mallory’s or Masson’s may be useful in identifying collagen. Alcian blue stain is helpful in staining perineural mucin which is not present in scar tissue. The electron microscopic features like multiple nerve fascicles ensheathed by multiple laminae of perineural cells in the collagenous stroma are suggestive of traumatic neuroma.(4) S-100 protein and epithelial membrane antigen (EMA) positive staining is seen in the tumors that appear to have perineural components i.e. tumors like traumatic neuroma.

Palisaded Encapsulated Neuroma: The palisaded encapsulated neuroma is a benign neural tumor with distinctive histopathologic features.(5) This tumor was classified as a true neuroma because of the proportion of axons to the Schwann cells is approximately 1:1. Palisaded encapsulated neuroma of the mucocutaneous junction of the lower lip and additional series of cases of palisaded encapsulated neuromas were also reported.

It has a striking predilection for the face, especially the nose, upper eye lid, cheek, chin and lips. The lesion is most frequently diagnosed between fifth and seventh decade of life. Though its occurrence in the oral cavity is rare, the preferred site of occurrence is the palate and upper lip followed by the tongue.(5) Palisaded encapsulated neuroma is a well circumscribed encapsulated mass and some lesions have lobulated appearances. The tumor consists of moderately cellular, interlacing fascicles of spindle cells that are consistent with Schwann cells, with little or no pleomorphism or mitotic activity of cells. The more definite palisading and Vero cay bodies typical of the Antoni-A tissue of a neurilemoma are usually not observed. Special staining with Schofield method, a modification of the Bielschowsky silver method which uses ammoniacal silver to stain the peripheral nerve axons results in dark brown to black colored stained axons and reveal the presence of numerous axons within the tumor. The histopathologic differential diagnosis of palisaded encapsulated neuroma includes other benign neural tumors like traumatic neuroma, which differ in the absence of either scarring or inflammatory cells and the presence of the capsule. They differ from schwannoma by their superficial location, absence of Antoni type tissues, and presences of relatively numerous axons and myelin sheaths. Palisaded encapsulated neuroma differs from neurofibromas in having a capsule and broader fascicles with more axons and myelin sheath and lacking of significant mucopolysaccharide ground substance and mast cell. The presence of axons and myelin remnants distinguishes these lesions from non-neural spindle cell tumors such as leiomyoma.(6)

Although palisaded encapsulated neuroma can be diagnosed confidently on the basis of H and E stained sections alone, confusion with Schwannoma and neurofibroma may occur at times. Strong S-100 protein staining is observed within the cytoplasm of spindle cells. The positive immunostaining for Neural Filament (NF) in intraoral palisaded encapsulated neuroma proves that it contains axons. The positivity for EMA in palisaded encapsulated neuroma is a new finding which separates it from diffuse neurofibroma.

Schwannoma: It is a tumor of nerve sheath origin and is derived from the Schwann cells surrounding the tissue. It may occur at any age and in connection with both intracranial and the peripheral nerves, usually as a solitary tumor. Tumors of the peripheral nerves can present anywhere, but head and neck area is frequently
affected i.e. 25 to 48%. Uncommonly neurilemmomas may be present as a multiple lesions, as a feature of neurofibromatosis.(5)

In the oral region these tumors occur in the both soft tissue and in the maxilla and mandible. The neurilemmomas usually presents as a slowly growing encapsulated tumor that typically arises in association with a nerve trunk and as it grows it pushes the nerve aside with accompanied symptoms likes tenderness or pain.(5) Sometimes they present as firm fibrous growth or cause expansion of the jaw. The tongue is the most common location of oral neurilemmomas.(3)

The Schwannoma is usually encapsulated tumor that demonstrates a characteristic microscopic picture that can be seldom confused with that of other lesions. The tumour is classically described as being composed of two type of tissue, Antoni type-A and Antoni-B. Antoni type-A tissue is made of cells with elongated or spindle shaped nuclei which are aligned to form a characteristic palisading pattern, while the intercellular fibers are arranged in parallel fashion between rows of nuclei. These fibers in some planes will give the impression of occurring in whorls or swirls. Antoni type-B tissue does not exhibit this characteristic palisading, but rather a disorderly arrangement of cells and fibers with areas of appear to be edema fluid with formation of micro cysts. A micro cyst in Schwannoma is accounted due to degeneration of Antoni type –B tissue.(7) Verocay bodies, small hyaline structures, are also characteristically present in Schwannoma.

No distinctive features of Schwannoma allows its identification on clinical grounds alone, however intraoral differential diagnosis for Schwannoma includes benign mesenchymal neoplasms, salivary gland tumors and traumatic fibromas.(8) Yen-Chen and Miller,(7) studied extensively the ultra-structural features of Schwannoma and confirmed the general architecture of the tumor as seen with light microscope. Schwannoma cells express S-100 protein, when immunohistochemically stained, but not EMA. Perineural cells express epithelial EMA but not S-100 protein. The staining of S-100 protein is strong in the Antoni type A areas, much less in Antoni type-B areas. In contrast, in neurofibromas, S-100 antigen is variably expressed, which is reflection of mixtures of cells within the tumour.(9)

Ancient Schwanna: Ancient Schwannoma is a histological variant of Schwannoma. It was described in 1951 by Ackerman and Taylor(10), among the among the forty eight neurogenous tumors in the thorax, of which ten lesions microscopically showed features similar to those seen in typical neurilemmomas but were distinctive, because significant portions of the tumours were composed of sparsely arranged cells within a hyalinized matrix. In their original description of these lesions, they proposed the ancient neurilemmomas to begin as a cellular overgrowth with increased vascularity, followed by decreased vascularity with resulting hyalinization. They also interpreted the presence of hemorrhage, hemosiderin, inflammation, fibrosis and atypia of cells as degenerative changes indicative of long standing duration and thus designated the tumors as ancient neurilemmoma.(11) Ancient Schwannoma have been reported in various anatomic sites like the neck and the Oral cavity.(12) The third case of intra oral Schwannoma was unique in that, in addition to the usual findings associated with ancient neurilemmomas, it contained spicules of bone and starch granules.(11) A cases of intraoral ancient neurilemmoma was reported with histopathologic and electron microscopic study by Michael McCoy.(13) They also mentioned the Pseudosarcomatous change to be an outstanding feature of ancient Schwannoma, which was previously not noted by other workers.(13) The lesion is usually encapsulated and may contain both Antoni type A and Antoni type B tissue. Inflammatory cells, fibrous areas, thick blood vessels are usually present. Areas of hemorrhages, hemosiderin and many areas with large atypical and pleomorphic nuclei, some of which may be hyper chromatic were observed. Collagen fibers and reticulin fibers were also reported to be present by Picrosirus polarization method.(13) The method involved differential staining of collagen types i.e., Type I, II, and III by Sirius Red and polarization microscopy. Thus it was demonstrated that the tumor collagen was predominantly type III, while that of the capsule was type I. The only electron microscopic study of ancient Schwannoma was done by Michael McCoy et al.(13)

Neurofibroma: It is a non-encapsulated tumor of Schwann cells differing from a Schwannoma in its structure and clinical behavior. Neurofibroma is a tumor of nerve tissue origin, although the specific cell type involved is still a matter of controversy. The most widely accepted view according to Holt. J F.(14) is based on electron microscopic and autoradiographic studies, is that it arises from
Schwann cells, and perineural fibroblasts with intermingling neurites or axons. However other investigators believe that neurofibroma originates from perineural cells and does not involve Schwann cells.

Neurofibroma occurs in two forms. First the circumscribed solitary neurofibroma, which are not associated with neurofibromatosis and the second, which comprises all the various forms seen in neurofibromatosis. The distinction basically is a clinical one, because, histopathologically it is often difficult to differentiate a solitary neurofibroma from that of neurofibromatosis.

Solitary neurofibroma: The solitary neurofibroma is a slow growing, relatively circumscribed but non-encapsulated neoplasm, originating in a nerve and consisting of Schwann cells, perineural cells and varying amounts of collagen. The pathogenesis of neurofibroma is thought due to localized increase in the endoneurial matrix, which spreads the Schwann cells apart, at the same time, the Schwann cell cylinders elongate, become tortuous, and increase in numbers.

Presumably, perineural cells and cells with fibrogenic potential are involved. Shklar and Meyer,(15) reviewed 16 oral neurofibromas, of which 11 were solitary, 5 cases were oral manifestation of neurofibromatosis. It is observed about sixty percent of the solitary lesion are associated with Von Recklinghausen’s disease of skin. Thus it implies that between 20 to 60 % of introral neurofibromas may be associated with neurofibromatosis. It may occur at any age. The tongue, buccal mucosa, and vestibular areas are the most common sites. Ellis Abrahams and Melrose(16) reviewed 27 intrasosseous neurofibromas, including 7 cases of their own files. The solitary neurofibroma is a well demarcated lesion. This is in contrast to many neurofibromas of neurofibromatosis.

The tumour cells are elongated, fusiform, and often have comma shaped nuclei. They are set in a myxomatous, micro vacuolated matrix of wavy collagen fibers. Mast cells are said to be more numerous than in Antoni type B tissues of Schwannoma and are a common finding and may constitute as a useful diagnostic pointer. Blood vessels are often thickened. Intermingling of collagen fibers and axons in haphazardous arrangement is commonly observed.(3) The ultra-structure study reported, revealed that neurofibroma seemed to contain more collagen than Schwannomas.

Neurofibromatosis

Von Recklinghausen’s Disease of Skin: It is an autosomal dominant condition consisting of neurofibromas, skin pigmentation, and bony abnormalities and with a predilection to develop neurofibrosarcoma in about 5 to 16% of all cases. It’s frequency of occurrence is 1 in 3000 births approximately in general population. It involves other central nervous system changes and other stigmata.(5) The presence of six or more café au lait macules, greater than 1.5cms in diameter is generally regarded as being indicative of neurofibromatosis until otherwise proven.(16)

Axillary freckling (Crowe sign), Iris freckling (Lisch spots) are also commonly seen pigmentary abnormalities. Bony changes may be seen in 50% of the cases.(16) In the mandible, the lesions most commonly arise from the mandibular nerve with accompanying pain and par aesthesia. In such cases the radiograph shows flaring of mandibular foramen, the so called “blunderbuss’ foramen or fusiform enlargement of the mandibular canal’. Oral lesions occur in patients with Von Recklinghausen’s disease of skin. Recently, two subtype of this have been defined, Type 1 and Type 2. Type 1 is associated gene mutations of the tumour suppressor genes coding for neurofibromin on chromosome 17q11.2 and Type 2 is associated with gene mutations of the tumour suppressor genes coding for Schwannomin on chromosome 22q12.1.(3)

The incidence of the oral neurofibromas is reported between 4 to 7%. (12) The mucosal lesion may be solitary or multiple. Unilateral oral involvement seems to be more usual presentation and tongue is more commonly involved. Macroglossia due to diffuse involvement of the tongue is well recognized and reviewed. However it is reported to occur on the buccal mucosa, palate, alveolar ridge and vestibule of the oral cavity.(3) Histopathologically the lesions show same features as solitary neurofibroma, except that usually, no distinct margin is found between the neurofibroma and the surrounding tissue. The lesion may be plexiform type, where distorted masses of myxomatous peripheral nerves still contained within perineurium surrounded by neurofibroma.(3)

Harkin(17) suggest that the plexiform neurofibroma seems to occur only in neurofibromatosis. Indeed they state that “The patients who have plexiform neurofibroma are considered to have neurofibromatosis even, if it is the sole manifestation of the disease”. The electron microscopic observation of
neurofibromas of the oral cavity was done by Yen-Chen and Miller.(7) A solitary nodular neurofibroma is to be considered in clinical differential diagnosis with other sub mucosal lumps of connective tissue origin such as traumatic neuroma, granular cell tumor and lipoma. A diffuse neurofibroma resulting in macroglossia may have to be differentiated from lymphangioma and amyloidosis.(16) The treatment of neurofibroma is mainly symptomatic, consisting of surgical removal of lesions for functional or cosmetic reasons. Carbon dioxide laser and derma abrasion also have been successfully employed for extensive lesion.(5) The prognosis for neurofibrosarcoma associated with neurofibromatosis is poor with five year survival rate of 15%.

Nerve Sheath Myxoma: Nerve sheath myxoma was described by Harkin,(17) as benign cutaneous tumour arising in the endoneurium of peripheral nerves and characterized by stellate cells in an abundant mucoid matrix. The first intraoral case of nerve sheath myxoma was reported by Mincer and Spears, on the dorsum of the tongue.(18) The reviewed data of the reported cases reveal that the nerve sheath myxomas to occur in varied age group from 15 to 71 years. The tumor affected women more often than men. Tumor size varied from 0.5cms to 1cms.(18)

The duration of the lesion at these sites varied from two months to 1 year. The histopathology of nerve sheath myxoma revealed well defined lobules of myxomatous tissue separated by fibrous septa. The cellularity varies, but stellate or hyper chromatic bipolar cells are present. Multinucleated cells appear as syncytium. Palisading of nuclei and structure resembling pressure receptors are also observed. These tumours stain intensely with Alcian blue. The ultra-structural study of nerve sheath myxoma revealed the tumor to consist of three types of cells, discernible within a sparse collagenous stroma.

Type I cells characterized by fusiform shape and cytoplasm densely populated by dilated rough endoplasmic reticulum, free ribosomes numerous fine filaments. The nucleus was frequently lobulated. Basement membrane material was present but incomplete. The second cell type II resembled type I but had no basement membrane. The third type cell was found at the periphery of the lesion. Its cytoplasm contained numerous fine filaments, some mitochondria, only a moderate amount of granular endoplasmic reticulum. The nucleus was lobulated and contained much euchromatin. Basement membrane completely surrounded this cell type and was frequently arranged in multiple layers. Axons were associated with type III cells. The differential diagnosis for nerve sheath myxoma includes focal mucinosis, myxoid neurofibroma, perineurinoma and some soft tissue sarcomas with myxomatous area. Mucinosis is not circumscribed, lobulated or as cellular as neurothekeoma. Intra lesional neuritis and wire like collagen bundles found in neurofibromas distinguish them from neurothekeoma. The perineurinoma is epithelial membrane antigen immunoreactive and S-100 antigen negative. Since it is composed almost exclusively of perineural cells, the tumor also lacks the distinctive lobulated structure of neurothekeoma. Oral myxomas also do not have a lobulated pattern, and are invariably un-reactive with antibodies against S-100 antigen. Sarcomas with myxoid areas are deeply located and exhibit distinct pleomorphic, Anaplastic and mitotic features. Nerve sheath myxomas possess a number of similar histopathologic, ultra structural and immunohistochemical features with Schwannoma. Both arise from nerve sheath and may stain for S-100 protein. However, Schwannoma are rarely myxoid in appearance and they contain areas of increased cellularity (Antoni A tissue) with formation of Vero cay bodies. Although nerve sheath myxomas possess areas of increased cellularity. Vero cay body formation is not observed.

Neuroblastoma: Neuroblastomas occur primarily in the sympathetic nervous system. Fifty percent of the cases are reported to have occurred from the adrenal gland or the celiac, mesenteric or abdominal ganglia and the few from sympathetic chains and rarely from peripheral ganglia in the viscera or perivascular plexus.(19) In 50% of the reported cases the age of the patients were less than four years. The mature type of tumor (sympatheticoblastoma) occurs later in childhood or in young adults. The tumour size varied from less than 1x1cms to a massive growth which occupies most of the abdominal cavity.(19)

Typical histopathological appearance are seen in majority of the tumors grouped together as Sympatheticotonia, are characterized by the presence of Homer-Wright rosettes. In large tumors extensive areas of necrosis and scattered foci of calcification is observed. In more differentiated tumors, the cells have more cytoplasm and the short processes of the unipolar and bipolar tumor cells, which can be
demonstrated by silver impregnation techniques. The electron microscopic examination of the neuroblastoma revealed three major histopathologic patterns (type A, B, C). In undifferentiated tumors, only type A areas are found.

The more mature tumors contain all the three types of ultra-structural patterns. In type A pattern, the tumor cells are loosely attached to one another and the cell interfaces are relatively smooth, with fine undulating surfaces devoid of interdigitations, A few desmosomes however are apparent. The nuclei are round, elliptical or polygonal and occasionally have cytoplasmic invaginations. In type B areas the tumor cells are separated by numerous islands of cytoplasm which are actually tangential sections of cytoplasmic processes. Occasionally, several neoplastic cells arranged in rosette-like pattern with cytoplasmic processes of varying sizes in the center are observed. The nuclei of the tumour cells are smaller than type A areas and are more irregular, with occasional cytoplasmic invaginations and deep clefs of the nuclear membrane. Golgi zones are better developed in the type B cells. The cells of type C areas have polymorphic nuclei with prominent nucleoli. More cytoplasm is associated with these cells than the type A and type B areas.

Numerous nerve fiber processes are seen in section of type C tissue, and in some areas these nerve fibers are arranged in broad bundles.(19) Synapse like structures in neuroblastomas have been described. Neuroblastoma is often mistaken for lymphosarcomas. An important characteristic in the differential diagnosis is the distribution of reticulo endothelial cells in sympathetico-blastomas and Sympatheticictonia. These cells are scattered throughout the tumor, where as in lymphosarcomas, they are always grouped in nests. Rosette like patterns in Wilms’ tumor may cause difficulties in its differentiation from neurofibromatosis. The frequent calcification in neuroblastomas is an important characteristic for differentiation, as this feature is always lacking in Wilms tumors. Another source of confusion is Ewing’s sarcomas. They may actually have metastasized from neuroblastomas; rosette pattern however never occur in Ewing’s sarcoma.

The possibility of maturation of a neuroblastoma into a ganglioneuroma is one of the most debated and most intriguing features of the tumor. The actual number of cases in which this transformation has occurred is reported to be small. Systematic studies have shown that, among all the malignant tumors, neuroblastomas have the highest rate of cure. Maturation within these tumors has been ascribed to the changes in the concentration of nerve growth factor in the serum or to the immunological processes.(5) Ganglioneuroma: Ganglioneuromas usually originate from the ganglion cells of the sympathetic nervous system. Such tumor may also probably occur from sympathetic nerves as well as other peripheral nerves. Cases of multiple ganglioneuromas have been described and are thought to represent an unusual variant of Von Recklinghausen’s disease. This view is supported by the presence of cafe au lait spots, skin involvement and familial in some patients.(19) The lesions generally occur in children and young adults and are slow growing. They are thought to arise by the differentiation of immature neuroblasts. However lesions which histopathologically resemble ganglion neurofibromas are also found in the mouth and in the neck region. In the neck, these lesions possibly represent non-neoplastic sympathetic ganglia or perhaps involvement of the sympathetic ganglion by neurofibromatosis.(3)

In the mouth, the parasympathetic ganglia may be involved. An interesting case of unusual variety with numerous ganglion cells arising centrally within the mandible following avulsion of the mandibular nerve was reported by Rajendran et. al.(3) and Neville et. al.(5) The ganglioneuroma grow less rapidly than the neuroblastoma, and when fully differentiated are benign in nature. The ganglioneuromas and maturing neuroblastomas are derived from mature ganglion cells which, either maintain their maturity or differentiate. The ganglion cell is the hallmark of this tumor, varying in numbers and is scattered singly or arranged in clumps. Some cells show evidence of degeneration. Multinucleated cells are commonly found in the tumor. These multinucleated cells may be three to four times the normal cell size and often contain clusters of finely granular lipofuscin in their cytoplasm.

Sometimes evidence of calcification of individual or group of cells was seen. Prominent lymphoid aggregates occur in the ganglioneuromas either forming islands of cells or distributed as bands of small lymphocytes and sometimes around blood vessels. Giant cell astrocytoma, non-neoplastic ganglion, or ganglion involvement by neurofibroma are to be considered for the differential diagnosis of ganglioneurofibroma. Binucleate ganglion cells
are quite common in ganglioneurofibroma, but are extremely rare in the other two entities. In addition, ganglion like cells may be seen in ancient Schwannoma as well.

Multiple Endocrine Neoplasia Syndrome III: This group of syndromes is characterized by tumors of various endocrine organs occurring in association with a variety of other pathologic features which are so manifold, that the full range probably still remains to be delineated.(3) Steiner and associates, proposed a classification dividing these syndromes into multiple endocrine neoplasia syndrome type I (MEN I) and multiple endocrine neoplasia syndrome type II (MEN II), a type III.(20) Multiple endocrine neoplasia syndrome (MEN III), is described by Khairi and his co-workers, (21) but Chong et. al., divided MEN type II into MEN 2a and MEN 2b. (22) The patients in MEN 2a were patients with medullary carcinoma, Pheochromocytoma and parathyroid disease, which is synonymous with original type-II. Multiple endocrine neoplasia type-2b patients were described as having an abnormal phenotype characterized by a marfanoid habitus, neuromas on the tongue or lips and prominent corneal nerves. Pheochromocytomas are often seen, but no parathyroid disease noted. The age at diagnosis of MEN type III patients is variable. The oral and facial features are often the first features to be expressed. MEN type III is inherited as an autosomal dominant disorder with a high degree of penetrance. Current data suggests that MEN 2a, MEN 2b and familial medullary thyroid carcinoma are allelic variations in the same gene. Available evidence suggests that the gene locus for MEN type III is on the chromosome 10 near Centro mere but gene itself not yet clearly defined. (23) Thus the biochemical defect in MEN type III remains unknown.

However the newly described ‘ret’ oncogene is likely to be close to the locus. It is an oncogene first isolated from a neuroblastoma cell line. Whether this gene is abnormal in MEN type III and causes neural overgrowth remains to be determined. The most constant component of MEN type III is the presence of neuromas, particularly the oral ones that principally affect the lips and anterior tongue but are also seen on the buccal mucosa, gingiva, palate and pharynx. Bilateral neuromas of the commissural mucosa are highly characteristic. (3, 23) Radiographs of the patients with MEN type III reveal enlarged and bifurcated appearance of the inferior alveolar nerves. It also shows the shortened roots of the lower incisor teeth and spacing of the anterior teeth. (23)

Histopathology of the oral neuromas appears to contain tortuous mass of nerve fibers surrounded by a thickened perineurium, bear striking resemblance to traumatic neuroma. However these oral neuromas may represent hamartomatous growth rather than true neuromas. (3) Ultra structural studies suggested that these lesions represent hypertrophy of axons similar to that noted in the amputation neuromas. The soft tissue masses of mucosal neuromas may share clinical features with neurofibromatosis or multiple papillomas’. They may also share some similarity to the mucosal presentation seen in amyloidosis and hyalinosis cutis et mucosa (lipid proteinosis). Because of the endocrine neoplasm associated with this syndrome, it often manifests, very early in life. Serum and urinary levels of calcitonin are elevated in patients with medullary carcinoma of thyroid. Calcitonin level is also monitored to detect local recurrences or metastases after treatment. Pheochromocytomas may result in increased levels of Vanillylmandelic Acid (VAM) and altered epinephrine and nor- epinephrine ratio. (5) The five year survival rate of the malignancy is about 50%. (16)

Olfactory Neuroblastoma: It is defined as a rare malignant neoplasm arising from the olfactory epithelium and comprises of undifferentiated neuroectodermal tissue i.e neuroblasts. The most commonly occurring site is nasal cavity and nasopharynx. (3) It was first described by Berger et al. (24) Because of rarity, it has been difficult to recognize and diagnose pathologically this tumor. Further the cellular origin, histopathologic classification, clinical staging and treatment of Esthesioneuroblastoma (ENB) are all subjected to controversy.

Only sporadic cases reported until 1966, when Skolnik reviewed world literature (25). Chaudhry et al. (24) reported 2 cases and studied their light and ultra-structural characteristics. They were of the opinion that on the basis of biochemical, histopathological and ultra-structural characteristics, olfactory neuroblastomas to be similar to neuroblastoma arising from the adrenal or sympathetic nervous system. The incidence of olfactory neuroblastoma as reported is between 1 to 5% of all the malignant tumors occurring within the nasal cavity. The most common clinical symptoms are nasal obstruction, epistaxis and pain. The olfactory neuroblastoma is thought to arise from the basal cells of olfactory
neuroepithelium, which in turn is derived from olfactory placode.(3)

It consists of densely packed masses of small darkly staining cells, each with a poorly defined cytoplasm and regular round vesicular nucleus, sometimes with stipulated chromatin. Rosette formation is common. This is a pseudo glandular structure lined by a single layer of non-ciliated columnar cells with a basal nucleus and cuticular borders at the apex of the cells. These resemble the sustentacular and olfactory cells of the olfactory mucosa. Eosinophilic neurofibrils extend into the lumen from the cell borders. Mitotic figures are often present, but fewer in numbers. The stroma has a fibrillar neurofibril pattern. Catecholamine granules are present, both adrenaline, and nor adrenaline, but not to the extent as in sympathetic neuroblastoma. The presence of catecholamine within these tumors can be demonstrated histochemically. Combined with information provided by electron microscopy, which shows membrane bound dense granules of 100 nm to 150 nm in diameter, it is possible to establish accurate diagnosis in difficult cases.(25) A group of antibodies, such as general neuroendocrine markers such as NSE (neuron specific enolase) and PGP 9.5 are usually positive. Synaptophysin and chromogranin are also reliable markers of neuroendocrine differentiation, although not always positive in olfactory neuroblastoma. Positive staining for S-100 protein is frequently found within cells at the periphery of the lobules of paragangliomas and phaeochromocytomas. In the former, these cells also stain with GFAP but not in olfactory neuroblastoma. The differential diagnosis of neuroblastoma includes undifferentiated adenocarcinoma, adenocarcinoma, lymphoma, malignant melanoma, transitional cell carcinoma, anaplastic carcinoma, plasmacytoma, rhabdomyosarcoma and neuroendocrine carcinoma. However, the lengthy survival period and relatively slow growth of rate of olfactory neuroblastoma is unusual in other nasal malignancies.(25)

Melanotic Neuroectodermal Tumour Of Infancy: This is a benign neuroectodermally derived tumor with a predilection for the anterior maxilla in young infants.(26) The lesion occurs mainly in infants under 12 months of age, the usual presentation being between 1 and 3 months. However, growth is rapid, with the lesion extending into the adjoining alveolar buccal sulcus, which may seriously affect baby feeding. Invasion into cancellous bone with expansion of the cortical plates may occur with displacement of the partially formed deciduous teeth. This tumor varies in size from about 0.5cms to more than 3cms in diameter.(26)

The tumor is usually encapsulated and the cut surface of the tumor has a characteristic slate blue to grayish-black appearance. The histopathologic appearance of this tumor is characteristic. It is most of the times non encapsulated with the infiltrating tumor cells, many a times containing melanin pigment. The central portions of the alveolar spaces contain many small, round neuroblast like cells which show little cytoplasm and exhibit a round deeply staining nucleus.(3) The electron microscopic study of MNTI showed two types of cells. The larger cell type contained melanosomes and the smaller cell type displayed neurotubules.(26)

Two separate cell lines have also been grown in a tissue culture studies. The immunohistochemical studies about MNTI indicate that it is a primitive retinal anlage like neuroectodermal tumor with differentiation along neural, melanogenic and epithelial cell line.(26) There are occasional glial and myogenic features in MNTI, but no photoreceptors differentiation observed. However with immunohistochemical analysis, neoplastic cells have not exactly reproduced all the immunohistochemical features of mature normal cell type, there by complicating specific tissue comparison.

The high urinary excretion of VAM is reported to be strongly associated with MNTI and supports its neural crest origin. Since this is a recognized property of neuroblastoma, ganglioneuroblastoma and Pheochromocytoma and all the neural crest derivatives.(3) These levels may return to normal once the tumor is operated. Melanotic neuroectodermal tumor of infancy has to be differentiated on clinical, radiological, histopathological and biological behavior. Despite their rapid growth and potential to destroy bone, most neuroectodermal tumors of infancy are benign. The recurrence of the tumor has been reported in about 15% of the cases. In addition, about 6% of the reported cases, there is malignant transformation, resulting in metastasis and death.(5)

Neurogenic sarcoma: Malignant neoplasms arising from nerve tissue, especially from nerve sheath cells are extremely rare in and around the oral cavity(3) and they have been are observed much less frequently than their benign counter parts. Wright and Jackson,(27) categorized neurogenic sarcomas broadly into two types (i) malignant change in the lesion of
neurofibromatosis designated by Harkin, (17) as neurosarcoma (ii) Malignant tumour diagnosed in the absence of neurofibromatosis. Sordillo et al., (28) found 40% of the case to have occurred in patients with neurofibromatosis. Various different studies indicate 4 to 29% patients with neurofibromatosis develop malignant Schwannoma at some time in their lives. The de-novo sarcomas are more apt to develop later in life than those originating in neurofibromatosis.

The majority of the reported cases of malignant Schwannoma have occurred in third to sixth decade of life, with no sex predilection. Malignant Schwannoma arising in soft tissues in the oral region are commonly seen in the lips, gingiva, palate and buccal mucosa, where as in the central tumors, mandible is the more frequently involved. (3) The histopathologic features of malignant Schwannoma are nearly identical to microscopic appearance with fibro sarcoma. If, palisading arrangement present, its aids in diagnosis of the lesion, as do plump, spindle cells arranged in streams and cords with tandem nuclei. (3) However it is the contention of the most pathologist, that unless the neoplasm can actually be demonstrated microscopically arising from the nerve bundle, a neurogenic origin cannot be established. In addition to streaming fascicles, less cellular myxoid areas may also be present. With some neurofibrosarcomas, heterologous elements which include skeletal muscle differentiation (Malignant triton tumor), cartilage, bone or glandular structures are present. (5) Sordillo and his associates, (28) reported that the sarcomas arising in neurofibromatosis tend to be more collagenous and better differentiated than those arising in solitary neurofibromatosis, which tend to be highly cellular and undifferentiated, a paradox in view of the more aggressive behavior of the former lesion. One histopathologic type of malignant tumor shows round to polygonal cells which are sometimes arranged similar to that in melanoma. This pattern has collectively classified as malignant epithelioid Schwannoma.

Summary

Neural tumours arising from the peripheral nerve sheaths in the oral and paraoral tissues are relatively less common. The neural tumors occurring commonly in the head and neck region are neurilemmoma, ancient neurilemmoma (a histologic variant of neurilemmoma), neurofibroma (a solitary form or as a manifestation of Von Recklinghausen’s disease of the skin). The rarely occurring neural tumors in the head and neck region are palisaded encapsulated neuroma, nerve sheath myxoma, olfactory neuroblastoma and ganglioneuroma. Hereditary conditions like Multiple Endocrine Neoplasia syndrome III and Primitive neuroectodermal tumor of infancy, also manifests in the oral cavity. Neural tumors that occur in the jaws show enlargement of mandibular nerve canal. Radiographs are also useful in assessing the extent of damage caused by these lesions. Electron microscopy is a diagnostic technique / method of establishing the definitive diagnosis at sub-cellular level, like finding of cells with numerous processes and membrane bound granules of catecholamine, which are characteristic of cells of nervous system and of neural origin. Immunohistochemistry has proved to be a very valuable tool in the diagnosis of neurological tumors. Polyclonal or monoclonal antibodies like S-100, EMA, GFAP, Snaptophsin and Leu-7 are helpful as diagnostic markers for neural tumours.

Conclusion

The peripheral nerve is the source of wide array of tumours, both non-neoplastic and neoplastic. During the last three decades, this area has undergone an extensive re-appraisal with re-evaluation of old entities, describing new ones and clarifying the relationship between benign and malignant tumors.

Neoplasms of the peripheral nerve sheaths occupy a unique place among soft tissue tumors. First, instead of derivation from a mesenchymal cell, most peripheral nerve neoplasms are assumed to arise from cells of neuroectodermal origin. Second, the majority of the malignant nerve sheath tumors arise from antecedent benign tumours. Because of the tendency for malignant transformation an ability to distinguish between several types of benign peripheral nerve neoplasms is vitally important.

The rising trends in the study of neoplasms with monoclonal or polyclonal antibodies like S-100 proteins, NF (neural filaments), EMA (epithelial membrane antigen), etc., against tumour specific cells would help in a better understanding of, and differentiating the tumors in difficult circumstances.

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