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Review Article

Dentistry Section

Spindle Cell Tumours of the Head and Neck- A Taxonomic Review

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ABSTRACT

Spindle cell neoplasms of the head and neck region are relatively rare, yet there importance cannot be doubted. Spindle cells are of mesenchymal origin and constitute a part of the body's connective tissue. Soft tissue spindle cell neoplasms may range from reactive lesions to benign and malignant tumours. This heterogenous group of lesions include those of neural, fibroblastic, myofibroblastic, myogenic and epithelial tumours. As the spindle cells contain both benign and malignant mimics, misclassification has the potential to result in either under or over treatment of the patient. The aim of this review is to evaluate available data on spindle cell neoplasms, to gain more insight into the molecular pathogenesis and immunohistochemistry of these lesions, and to integrate recent knowledge on spindle cell neoplasms and their emerging concepts for future prospects. An effort has also been made to add a few relevant neoplasms to the present working classification.

Keywords: Head and neck, Neoplasms, Spindle cells, Tumours

INTRODUCTION

The head and neck region is a fascinating and complex area of cytopathology. It exhibits a diverse collection of spindle cell lesions that can be challenging in any site due to the variety of structures from which they can arise [1]. Thus, the diagnostic and therapeutic decisions related to these lesions are more difficult and vexatious [2].

Spindle cells are of mesenchymal origin and constitute a part of the body's connective tissue. On cytologic examination these cells appear elongated with a fusiform or ovoid nucleus [3,4]. The tissue of origin can be determined based on evidence of collagen, cartilage, bone, fat or myxomatous material formed by the tumour cells [3]. Epithelial-Mesenchymal Transition (EMT) and lack of expression of cell adhesion molecules like cadherins is a primary process describing the pathogenetic mechanisms [5,6]. EMT has been postulated as a versatile mechanism that facilitates cellular reconstitution during embryonic development and when incited later in life, contributes to various pathologic processes [7].

Soft tissue spindle cell neoplasms may range from reactive lesions to benign and malignant tumours [8,9]. This heterogenous group of lesions includes those of neural, fibroblastic, myofibroblastic, myogenic, epithelial and vascular [10] tumours. They are quite rare in the oral cavity [9] and account for less than 1% of all the tumours of oral origin and 3% of the salivary gland tumours [1].

The vast appearances and architectural patterns of the spindle cell tumours make the distinction from similar microscopic lesions quite enigmatic [11]. As the spindle cells contain both benign and malignant mimics, misclassification has the potential to result in either under or over treatment of the patient [12]. The tissue of origin can determine the biologic potential of the lesions [13]. Thus, the use of one or more ancillary techniques like immunohistochemistry, and molecular pathology can be quite beneficial. Electron microscopy also plays an important role in evaluation of soft tissue tumours [14].

The aim of this review is to evaluate available data on spindle cell neoplasms, to gain more insight into the molecular pathogenesis and immunohistochemistry of these lesions, and to integrate recent updates on spindle cell neoplasms and their emerging concepts for future prospects. An effort has also been made to add a few relevant neoplasms to the present working classification.

Classification

Over the years many efforts have been made by several authors to enumerate and classify spindle cell neoplasms of the head and neck. Few noteworthy mentions are:

William CF et al.,; Åkerman M et al.,; Jordan RC, et al.,; Chan JKC,; Al-Nafussi A; Anderson CE et al.,; Shamim T [1,4,9,10,15-17].

Neural Tumours

Neurofibroma: Neurofibroma is associated with a germline mutation in the NF1 gene, which is a tumour suppressor gene mapped at 17q11.2 chromosome. It encodes for neurofibromin, a protein functioning as neural cell signalling molecule [18]. Immunohistochemical studies have demonstrated the tumour cells to be weakly positive for GLUT-1, Collagen IV, Ki-67 and p53 [19]. Histochemical stains that detect acid mucopolysaccharide rich myxoid matrix in neurofibroma, which is absent in neurilemmoma, may be of diagnostic help [20]. Intraoral ultrasonography (IOUS) and Doppler mode were used by Sugawara as a diagnostic adjunct [21]. In a recent study, Schwann cells differentiation was observed on induction, Plexiform neurofibroma (PNF)-derived immortalized Pluripotent Stem Cells (iPSCs). These cells inhold the naturally occurring constitutional and somatic NF1 mutations and are perceived to be of great clinical relevance [22].

Neurilemmoma (Schwannoma): The pathogenesis of Schwannoma could be traced to inactivation of Merlin (schwannomin), the protein product of NF2, by mutations, methylation or LOH and a loss of chromosome 22 or 22q. Merlin bewields intracellular signaling pathways, thus its loss activates Rac1 and Ras, and the PAK1, mTORC1, EGFR-Ras-ERK, PI3K-Akt, WNT and Hippo pathways, and receptor tyrosine kinases [23]. Verocay bodies are epithet of the tumour along with a distinct capsule and hyalinised vessels with microcyst changes, which are frequently encountered [20,24]. Patil SB et al., utilised special stains like Perl's Prussian blue and toulidine blue to assess supplemental features like mast cells [25]. Additional immunomarkers found to be positive are podoplanin, calretinin and SOX10 [24]. Pseudosarcomatous change has been mentioned in ancient schwannoma [26]. Recent studies have shown that radiosurgery demonstrates high rates of local control and facial nerve preservation, as compared to microsurgery [27].

Palisaded encapsulated neuroma (PEN): The pathogenesis of PEN is controversial as some authors consider them a forme fruste manifestation of MEN2B syndrome and others are of the view that they represent a simple hyperplasitic reaction of otherwise normal nerves. Negative GFAP staining is a distinctive aid to differentiate it from schwannoma or neurofibroma [28]. Argenyi ZB studied the immunohistochemical profile of 11 cases of PEN and concluded that Schofield method, a modification of the Bielschowsky silver method remains a felicitous method for the axon-like structures, the ratio of axons to Schwann cells is generally less than 1:1; and regardless of the present definition of PEN, they are occasionally not entirely encapsulated as observed by Col IV and EMA strains [29].

Traumatic neuroma (Amputation neuroma): It is a reactive proliferation of nerve tissue involving the peripheral nerve [30] in response to chronic irritation, mechanical destruction, complicated wound healing or irregular scar tissue development. Motor nerve does not exhibit the development of traumatic neuroma due of minimal regenerative potential. Interleukins and transforming growth factor-β1 play a conducive role in the proliferation of Schwann cells [31]. Researchers have demonstrated that inhibiting Nerve Growth Factor (NGF) after nerve injury, impaires formation of neuroma and neurological pain in rats [32]. Mallory's or Masson's trichome can be used to identifying collagen, alcian blue to stain perineural mucin which is absent in scar tissue; and S-100 and EMA for tumour cells. Electron microscopic features like multiple nerve fascicles ensheathed by multiple laminae of perineural cells in the collagenous stroma are suggestive of traumatic neuroma [26]. Recenty, soft tissues and conduits have expanded the horizon for the treatment modalities of traumatic neuropathic pain [33].

Malignant peripheral nerve sheath tumour (MPNST): Biologically, MPNSTs present a conundrum, although the loss of SMARCB1 protein expression and a simple genetic aberration such as the loss of p53 on chromosome 17p have been implicated in the pathogenesis of MPNST arising in schwannoma [34,35]. Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) has been studied to assess the differentiation of MPNST in NF1 patients from benign neurofibromas [35]. Few cases of MPNST may lack S100 expression, and demonstrate whorls of EMA expression suggestive of perineurial differentiation [24].

Myofibroblastic Tumours

Myofibroma: Myofibroma is one of the most common fibrous proliferation in childhood showing a predilection for the soft tissues in the head and neck region [36]. The 2013 WHO classification, moved myofibroma to the group of perivascular tumours, due to "morphologic continuum" between it and myopericytoma [37]. Recenly, activating germline PDGFRB mutations have been associated with familial infantile myofibroma [38]. Immnunohistochemically, the characteristic biphasic myofibroma cells express alpha-smooth muscle actin, muscle-specific actin and vimentin, and immunonegative for desmin, S-100 protein and CD34 [36]. Newaz ZA et al., highlighted the role of CT and MRI in the differential diagnosis of the tumour [37].

Inflammatory myofibroblastic tumour (IMT): Cytogenetic studies on IMT have demonstrated clonal gene rearrangements of the short arm of chromosome 2, and subsequently ALK gene (anaplastic lymphoma kinase) translocation at chromosome 2p23 and involving tropomyosin; which are uncommon in adults over 40 years of age with IMT [39,40]. The World Health Organisation categorised IMT under tumours of intermediate biological potential owing to its tendency for local recurrence and rarely distant metastasis [39]. Alaggio R et al., from their study on Inflammatory Myofibroblastic tumours in childhood, concluded that, IMTs are locally aggressive lesions, with a local recurrence rate of 23%, and 5-year and 10-year event-free survival rates of 87.4% and 72.8%, respectively [41].

Low-grade myofibrosarcoma: After the diagnostic criteria were established by Mentzel T et al., low-grade myofibrosarcoma was reclassified as a separate entity by WHO classification of soft tissue tumours. The cell of origin is proximal resident mesenchymal cells or they are believed to have been recruited from bone marrow-derived circulating fibrocytes often undergoing epithelial-mesenchymal transformation. Calponin is diffusely positive, while h-Caldemon is usually negative. It can display fibronectin but not collagen IV and laminin [42].

Fibroblastic Tumours

Solitary fibrous tumour (SFT): The recently updated World Health Organisation (WHO) classification of tumours of the Central Nervous System (CNS), restructured Solitary Fibrous Tumour (SFT) and Haemangiopericytoma (HPC) into one combined entity [43]. The histogenesis of SFT is controversial, whether it is of mesothelial origin or an undifferentiated mesenchymal cell. Chan suggested a diagnostic criteria for SFT. Bcl-2 negativity may be helpful in differentiating it from mesothelioma. 70% cases exhibit CD99 immunopositivity [44].

Fibromatosis: Type 1 Gingival Fibromatosis (GF) is associated with the mutation of SOS-1 (Sun of sevenless-1) gene on 2p21-p22 chromosome, whereas type 2 inherited GF is associated with mutation of chromosome 5 called GINGF2 [45]. The Wnt (β-catenin) pathway plays a pivotal role in the pathogenesis of aggressive fibromatosis or desmoids type fibromatosis [46]. Excessive accumulation of Extracellular Matrix (ECM) components seems to contribute to the pathologic manifestation of GF [47].

Nodular fasciitis (NF): NF was originally described by Konwaller et al. It exhibits propensity for the head and neck region [48]. Studies on reciprocal translocation involving chromosome 15 categorised this lesion as a true neoplasm. Immunonegativity for CD34, cytokeratins, desmin and S-100 protein was demonstrated [49]. Fluoroscent In Situ Hybridisation (FISH) evaluation of FNA material for USP6 rearrangements may aid in accurate pre-operative diagnosis [48].

Desmoplastic fibroma (DF): DF is believed to have originated from fibroblastic and myofibroblastic cells. It was first described by Evans in 1995. Recent studies have revealed a FOSL1 gene overexpression in DF due to chromosomal aberrations [50]. Aetiology of DF can be associated with chromosomal rearrangement, trauma, endocrine disorders, or multifactorial. Radiographically, internal pseudo-trabeculation was observed in many cases. Negative labeling to β-catenin was noteworthy [51].

Fibrosarcoma: Radiotherapy to the local site is considered to be a prime predisposing factor for fibrosarcoma. Immunohistochemically, spindle cells show positive immunoreactivity for vimentin, smooth muscle actin, and 30-40% immunopositivity for MIB-1, show immunonegativity for desmin, S-100, CD34. The American Joint Committee on Cancer devised the most acceptable staging system for fibrosarcomas all over the body [52]. New markers such as miRNA expression profiles can be an additional supportive diagnostic step in the recognition of fibrosarcoma [53].

Muscle Tumours

Leiomyoma: The source of smooth muscle in oral leiomyoma is either the arterial tunica media which was suggested by Stout, or the ductus lingualis and the circumvallate papillae as suggested by Glass, or heterotopic embryonal tissue. Mason's trichrome, Van Geison's stain or Mallory's phosphotungstic acid (PTAH) can be utilised to specifically stain muscle cells and collagen fibers. Immunohistochemically, the tumour cells express vimentin, smooth Muscle Actin (SMA), desmin and are negative for cytokeratin and S-100 [54,55]. Molecular markers such as PCNA, bcl-2, CDK4, p53 and MDM2, may be useful in differentiating benign from malignant tumours [55].

Vascular leiomyoma (VL): Smooth muscle present in the tunica media of the blood vessels are considered to be the most probable histogenesis of VL [56]. Vascular endothelium stains like CD31 and factor VIII, aid in the differential diagnosis. Smooth muscle identification using h-caldesmon is more significant than α-SMA and desmin to avoid a malignancy misdiagnosis. Molecular markers, such as proliferating cell nuclear antigen, p53, B-cell lymphoma 2, mouse double minute 2 homolog, and cyclin-dependent kinase 4, are also of great relevance in identifying malignancy. CT could be of significance in cases of clinical suspicion of VL, showing an intense enhanced submucosal mass [57].

Leiomyosarcoma: Oral leiomyosarcomas may present as a primary tumour, radiation-induced tumour or metastasis. The oral cavity is an extremely uncommon site as the mouth is a smooth muscle deficit tissue; thus, before considering the oral cavity as the primary site, a thorough medical evaluation and detection for extraoral leiomyosarcomas should be carried out to exclude metastatic disease. Intraorally, the tissue of origin is the vasculature wall, embedded neuromuscular bundle, circumvallated papillae of the tongue, myoepithelial cell, or pluripotential mesenchymal cell. Overexpression of p-53 is commonly observed [58].

Rhabdomyoma: The histogenesis of the tumour is traced to the muscle component of the third and fourth brachial arches. Its cellular genesis is presumably from primitive mesenchymal stem cells that undergo striated muscle differentiation [59]. Adult rhabdomyoma presents typical radiological features such as a homogenous lesion with elevated FDG-uptake in F-FDG PET/CT that is isointense or slightly hyperintense on T1 and T2-weighted MRI and slightly hyperdense on CT [60]. PAS staining with diastase digestion demonstrates large numbers of glycogen rich tumour cells, that depicts the degree of maturation of the tumour cells, thus can differentiate between adult and fetal forms [61]. Definitive diagnosis demands fine needle aspiration cytology or biopsy and requires immunohistochemical stains [60]. HHF35 is a specific and sensitive marker for tumours of muscle origin. Transmission electron microscope examination demonstrated thin and thick myofilaments in differing proportions, among numerous mitochondria, interspersed with glycogen inclusions [61].

Rhabdomyosarcoma: Rhabdomyosarcoma is postulated to be derived from primitive mesenchymal stem cells directed towards myogenesis. It can be present as a primary malignancy or as a component of a heterogeneous malignancy [62]. Adult rhabdomyosarcoma is concomitant with fusion products, while Embryonal rhabdomyosarcoma have allelic loss at chromosome 11p15.5. The p53 and RB pathways are common targets involved in both types. Amplication of genes MDM2 and CDK4, occur frequently in adult type but rarely in embryonal [63]. The pleomorphic variant is associated with the worst prognosis in adult patients. Rhabdomyosarcoma expresses a higher level of V-ATPase as compared to other sarcomas, thus making it susceptible to esomeprazole treatment; this can be a promising selective target for treatment [62].

Vascular Tumours

Hemagiopericytoma: Soft tissue hemangiopericytoma is a controvertible pathologic entity [64]. Its aetiology is obscure, and has been linked to trauma, hypertension, hormonal imbalance. Angiography can be a guiding factor for diagnosis, demonstrates hypervascularity, radially arranged branching vessels around and inside the tumour, and longstanding, well-demarcated tumour stains [65]. Among the hemangiopericytomas in adults, sinonasal hemangiopericytoma is the only one that exhibits convincing pericytic differentiation. According to the review of Watanabe K et al., on sinonasal hemangiopericytomas, atleast 3 histologic subtypes have been identified. Electron microscopic studies showed well-developed myofilaments with dense bodies. Intimate relationships between solitary fibrous tumour and hemangiopericytoma have been reported where CD34 can be useful [66].

Spindle cell haemangioma or haemangioendothelioma (SCH): Weiss and Enzinger (1986) described a unique low to intermediate grade vascular tumour as haemangioendothelioma with biologic behaviour common to both a cavernous haemangioma and an angiosarcoma. The term SCH was proposed by Perkins and Weiss describing solitary lesions, and "spindle cell haemangiomatosis" was reserved for multifocal lesions. A 10% of cases were found to be associated with various developmental anomalies [67]. Spindle cells are negative for endothelial markers and react for vimentin, and at times for actin, desmin, Lysoszyme, factor XIIIa, HAM-56, alpha-1-antithrypsine, MAC387 [68].

Kaposi Sarcoma (KS): The pathogenesis of KS remains ambiguous, whether it involves transformation and proliferation of a unique HHV-8 somatic cell rendering them immortal (monoclonal), or a non-neoplasic elaboration of infected cells (oligoclonal) [69]. Early KS showing sparse spindle cell component can be confused with bacillary angiomatosis (BA). Warthin-Starry silver stain can help in exclusion. Identification of KSHV DNA by polymerase chain reaction or detection of KSHV latency-associated nuclear antigen (LANA) and immunohistochemistry, can aid in differentiation from clinically similar lesions [70]. In recent times, novel therapeutic strategies targetting specific molecules involved in KS oncogenesis, such as vGPCR, have provided promising results [69].

Lipomatous Tumours

SCL: The histogenesis of spindle cells are traced to non-lipoblastic stellate mesenchymal cells of the primitive fat lobules which have lost their capacity to differentiate to lipocytes yet they are capable of collagen synthesis. Histologically, SCL is composed of mature fat cells, collagen-forming CD34-positive spindle cells, and sparse mast cells [71]. CD34 can aid in differentiating SCL from spindle cell liposarcoma which is rarely positive for CD34. Its desmin negative behaviour can differentiate it from other similar lesions [72].

Epithelial Tumours

Pleomorphic adenoma (PA): PA invariably shows chromosomal rearrangements leading to an increased expression of pleomorphic adenoma gene 1 (PLAG1 zinc finger) gene, because its transcriptional regulation is placed under the control of the constitutively active gene promoter, b-catenin CTNNB1. Another commonly encountered chromosomal rearrangement in PA is t(5;8)(p11;q12), which causes expression of PLAG1 under the regulatory elements of the Leukaemia Inhibitory Factor Receptor-A (LIFR) gene on chromosome 5. Recent studies have shown that PLAG1 IHC is more sensitive than FISH for the diagnosis of PA. Less commonly HMGA2 (previously HMGIC) gene rearrangements or amplifications are also seen in PA and carcinoma ex-PA but are not yet suitable for testing in a clinical setting [73]. A recent investigation suggested that WT1 cells in PA undergo EMT [74].

Spindle cell myoepithelioma: The World Health Organisation (WHO), recognised myoepitheliomas as a distinct entity in 1991 [1]. Of all its subtypes, spindle cell type is most common accounting for 65% of the cases [75]. The myoepithelial cells in this variant, are elongated with uniform, ovoid to fusiform nuclei having round ends. The chromatin is evenly dispersed with indistinct nucleoli. Mitotic activity is quite rare. In Papanicolaou stained preparations, subtle nuclear grooves can often be found. Myoepitheliomas can be differentiated from pleomorphic adenomas by the absence of ducts and lack of a chondriod stromal component [1]. Malignant transformation has been associated to the overexpression of c-kit receptors and p53 mutations [75].

Spindle cell carcinoma (SpCC): The prime pathogenetic hypothesis proposed for SpCC are that it represents a "collision tumour" (carcinosarcoma), or it is a squamous cell carcinoma with an atypical reactive stroma (pseudosarcoma), or it has an epithelial origin, with "dedifferentiation" or transformation to a spindle cell morphology (sarcomatoid carcinoma). Recently, the third hypothesis has been supported by various studies [76]. A dysfunctional intercellular adhesion complex cadherin catenin is believed to cause the morphological shift of cells from squamoid to a spindled type, thus, permiting a more infiltrative and diffuse growth pattern. The p53 gene mutations is believed to be the most common gene mutation identified [77]. The transitory cells expressing dual antigen-positivity of epithelial and mesenchymal markers, suggest that SpCC may be a sarcomatous metaplasia of squamous cell carcinoma [78]. Diffuse Ki-67 reactivity was also seen in spindle cell regions [77].

Malignant melanoma (MM): Melanocytes are derived from the neural crest during embryonal development. The HMB-45 antigen is more specific than S-100, as it is localised in the premelanosomes and melanosomes of normal and malignant melanocytes. The gene for HMB-45 antigen (gplOO) and for melanocyte specific antibodies, HMB-50 and NKI-beteb, has been identified as the Pmel 17 gene, which encodes a melanosomal enzyme that converts dihydroxyindole carboxylic acid form (DHICA) into melanin. Tyrosinase, a product of the c-locus, acts as a regulatory protein by controlling intracellular levels of L-dopa. Serum tyrosinase activity and protein levels progressively increase in advanced melanotic melanoma, thus it is considered to be a better marker than HMB-45 [79].

Odontogenic Tumours

Ameloblastic fibroma (AF): AF is considered a true neoplasm with an indolent course as shown by the immunoexpression of Ki-67, MMP-9 and e-cad. AF is characterised by low Ki-67 expression associated with limited growth, low values of MMP-9 expression associated with low matrix break down, and strictly membranous high e-cad expression [80]. Odontogenic epithelial cells in AF are positive for cytokeratin as detected by antibody KL-1, while only immature dental papilla-like mesenchymal tissues are positive for tenascin. Basement membrane and dental papilla-like cells are positive for vimentin. These findings indicate that ameloblastic fibroma had developed at the early stage of tooth formation. Proliferating cell nuclear antigen (PCNA) positive cells are rarely encountered in AF, which indicates its slow growing nature [81]. The PRKAR1A gene encodes the regulatory subunit of protein kinase A (PKA), which is an important mediator in eukaryotic cells, involved in proliferation, differentiation and apoptosis of cells. Thus, PRKAR1A is a promising gene in the clarification of AF pathogenesis [82].

Ameloblastic fibrosarcoma (AFS): AFS has been a controversial odontogenic entity, with many hypothesis put forward regarding its nomenclature. Huguet P et al., proposed that the behaviour of AFS is benign, with absence of metastatis, and good prognosis [83]. Altini N et al., supported the concept that the dental matrix material does not alter the basic biologic characteristics of AFS, thus these malignant tumours should be designated as ameloblastic sarcomas [84]. Perin J et al., were of the opinion that, AFS is a semi-malignant tumour, thus "proliferating ameloblastic fibroma" is a more appropriate designation [85]. Chomette G et al., indicated that the epithelial component, being unable to assume its functions of organisation, may initiate the malignant transformation of its odontogenic mesenchyme. Histoenzymologically, AFS is always associated with a high level of alkaline phosphatase and ATPase activity, a feature not present in common fibrosarcomas [86]. Ultrastructually, these tumours exhibit features of fibroblasts [87].

Central odontogenic fibroma (COF): The World Health Organisation (WHO) Classification of Head and Neck Tumours (4th edition) was published in January 2017. The subtypes, epithelium rich and epithelium poor types were excluded due to poorly defined [88]. The pathogenesis of COF has been ambiguous due to its rarity. Various theories proposed implicate the role of neural crest cells (Dunlap), aberration in C-kit (Chandrashekhar) conferring immortality to tumour cells. Subsequent role of Ras was also reported [89].

Desmoplastic ameloblastoma (DA): Histological subtypes are, simple accounting for 88% of cases, and DA with osteoplasia constituting 12% of the group. The lower expression of PCNA and Ki-67 makes DA a slow growing tumour as compared with conventional ameloblastoma [90]. Presence of oxytalan fibres in the stromal tissue suggest that the tumour might have been derived from the epithelial rest of Malassez of a neighbouring tooth [91]. SMO gene mutation is believed to be associated with higher recurrence of ameloblastoma which led to the hypothesis that BRAF and other non-SMO genetic mutations possibly confer better prognosis [92]. The higher MIB-1 index and microsattelite alterations have been associated with shorter disease-free survival. Alteration of ameloblastin is a key point in ameloblastoma pathogenesis and its activity requires the heparin binding domains. MMP-2 may be associated with local invasiveness [93].

Miscellaneous Tumours

Benign fibrous histiocytoma: The World Health Organisation (WHO) denoted the term "fibrohistiocytic" to a lesion composed of cells resembling round histiocytic and spindle fibroblastic morphology. Vimentin and CD68 positivity reflect its fibroblastic and histiocytic heritage [94].

Malignant fibrous histiocytoma: Tumour cells are strongly immunopositive for vimentin, has variable positivity for muscle-specific actin, CD68, and focally expressive for desmin. Ki67 expression ranges from 10% to 100% [95].

Synovial sarcoma: It is positive for immunostain pattern of EMA, CD99, and Bcl-2, and negative for CD34. The monophasic variant is less positive (50%-80%) for cytokeratins than its biphasic counterpart. Transducin-like enhancer of split 1 (TLE1) is a new marker showing 85% to 97% positivity [96].

Ossifying fibromyxoid tumour (OFT): S100 expression is the most consistent immunohistochemical marker with PHF1 gene rearrangement seems as the most significant genetic event associated with OFT [97].

Giant cell angiofibroma (GCA): WHO's reclassification in 2013, considered GCA as a synonym for extrapleural SFT rather than being a separate entity. Immunohistochemically, GCA is positive for CD34, CD99, vimentin, variable bcl2 and negative for CD31, CD68, c-kit/CD117, muscle specific actin, S100, desmin [98].

Blue nevus (BN): Immunohistochemically, the dendritic melanocytes of sclerosing, hypomelanotic, epithelioid, amelanotic, atypical variants of BN stain positively with S100, HMB-45, MART-1, factor XIIIa. Celullar variant is additionally positive for CD34 [99].

Atypical fibroxanthoma (AFX): CD10 has been reported as a useful marker for AFX, exhibiting positivity rate of (95%-100%, while CD99or p30/32 shows 35-73% positivity [100].

Dermatofibroma protuberans (DP): DP exhibits a loss of CD34 expression, while maintaining the signature COLIA1-PDGFB (platelet-derived growth factor, b polypeptide) fusion gene [96].

A brief tabulation of the diagnostic aspect, pathogenesis, diagnostic histopathological features and prognosis of spindle cell tumors of head and neck are enlisted in [Table/Fig-1].

CONCLUSION

Spindle cell neoplasms of the head and neck region are relatively rare, yet there importance cannot be doubted. Most of the lesions exhibit a histologic overlap that can perplex the diagnostician. In such cases, the diagnostic and therapeutic decisions are more complex, and demand exhaustive investigation of the diagnostic features [115].

Tumours	Diagnostics	Pathogenesis	Histopathology	Prognosis
Neural tumours				
Neurofibroma	CD34, S-100 and EMA [19] IOUS and Doppler mode [21].	NF1 mutation [18] PNF-derived iPSCs have shown promising results [22].	Schwann cells with wavy nuclei in a serpentine configuration, characteristic "shredded carrot pattern" [18].	Malignant transformation rate is around 5% to 16% [18].
Neurilemmoma	Perl's Prussian, Toulidine blue. 25S100, GFAP, col IV [24].	NF2 mutation, loss of heterozygosity or methylation [23].	Composed of Antoni type-A and Antoni-B. Verocay bodies are Characteristic [26].	Malignant transformation is exceedingly rare [20].
Palisaded Encapsulated Neuroma	S-100 protein, collagen IV [28] and Schofield Method [29].	Hamartomatous or forme fruste manifestations of MEN2B [28].	Axons to Schwann cells <1:1. Schwann cells in a sinuous configuration with tapered nuclei and "Lochkerne" [28].	Recurrent PEN are extremely rare [28].
Traumatic Neuroma	S-100, EMA [101] Mallory's or Masson's trichome, Alcian blue [26].	Enhanced levels of dephosphorylated NFATc4 [32].	Interlacing neurofibrils and Schwann cells situated in the connective tissue stroma of variable proportions [26].	Diathermy minimise the development of TN to 35% [30].
Malignant Peripheral Nerve Sheath Nerve	FDG-PET [35] S100, EMA [24].	Loss of SMARCB1 or INI1, TOR and hsp90 pathways [34,35].	High cellularity, pleomorphism, mitotic activity and an organised cellular growth pattern, with less extracellular matrix material [36].	Triton tumour-poor Prognosis [35].
Myofibroblastic tumours				
Myofibroma	α-SMA, actin, Vimentin [36] CT, MRI [37].	PDGRRB mutation [38].	Biphasic pattern: peripheral eosinophilic spindle cells, and central more primitive spindle cells in a vascular pattern [36].	Local recurrence rate is 7% to 31% [36].
Inflammatory Myofibroblastic tumour	Actin, vimentin, desmin, SMA, ALK-1 [39,40].	IgG4-related autoimmune disease, ALK Translocation [39,40].	Fascicles of spindle cells interspersed with inflammatory cells, and aprominent vascular component [39].	Tumours of intermediate biological Potential [39].
Low-grade Myofibrosarcoma	Vimentin, SMA, desmin, Calponin [102].	Synergistic effect of mechanical tension, TGF-β and fibronectin [42].	Fascicles of spindle cells with wavy nuclei and fibronexus [42].	Recurrence rate was 38.2% [102].
Fibroblastic tumours				
Solitary Fibrous tumour	CD34, CD99. Bcl-2 –ve [44].	NAB2-STAT6 fusion gene due to paracentric inversion on chromosome 12q13 [103].	Chan's criteria-spindle cells with scanty cytoplasm, ropey collagen, alternate hypercellular and hypocellular foci, few mitotic Figures [44].	Has a benign non-recurring course [44].
Fibromatosis	Vimentin, collagen I, α-SMA [45].	Mutation of SOS-1 and GINGF2 [45].	Epithelial acanthosis, excessive accumulation of extracellular Matrix [47].	Recurrence-months to years post surgery [47].
Nodular Fasciitis	Vimentin, α-SMA, muscle specific actin [49] FISH [48].	Fusion of MYH9 with USP6 [48].	Myofibroblastic cells in a storiform pattern, juxtaposed to hypocellular myxoid areas with extravasated RBCs [48].	Recurrence rate of 1-2%; for parotid gland lesions 6-7% [48].
Desmoplastic Fibroma	Vimentin, HHF [35], factor XIIIa, α-SMA [50] FISH [51].	11q12 breakpoint mutation, non random chromosomal aberrations at trisomy 8 or 20 [50].	Uniform stellate fibroblasts with myofibroblasts scattered in an abundant hypocellular dense collagen in a myxoid stroma [50].	Recurrence rates: after excision 20-40%, and curettage 70% [51].
Fibrosarcoma	Vimentin, SMA, MIB-1, [52] miRNA expression Profile [53].	Chromosomal translocation at t(12;15)(p13;q25) with respect to gene ETV6-NTRK3 [104].	Spindle cells with oval to fusiform nuclei, uni- or bipolar cytoplasm and lance shaped, tapered cells, in a herringbone pattern [53].	5-year survival rate is 40-60%. 10 year survival rate: 30% (for high) -60% (low) [53].
Muscle tumours				
Leiomyoma	Mason's trichrome, Van Geison's, PTAH. SMA, vimentin, desmin [54,55].	Approximately 2.3 chromosomal gains and 6.5 chromosomal losses were found [105].	WHO described histologic variants-leiomyoma (solid), angiomyoma (vascular leiomyoma), and epitheloid leiomyoma (leioblastoma) [55].	Recurrence rate is extremely low following complete Resection [54].
Vascular leiomyoma	Actin, CD31, myosin, desmin, factor VIII, h-caldsmon. CT [57].	On an average, 3.3 foci of chromosomal gains and 5 losses were observed [105].	Blood vessels surrounded by smooth muscle bundles, with collagen fibers in an interlacing or swirling arrangement [56].	Excellent prognosis following surgical Excision [56].
Leiomyosarcoma	HHF-35, α-SMA, h-caldesmon, desmin, p-53 [58].	Chromosomal loss-1p, 3p21-23, 8p21-pter, 13q12-13, 13q32-qter, gain-1q12-31 [106].	Interlacing fascicles of spindle cells in an angulated form, with perinuclear vacuolization, "cigar-shaped" nuclei [58].	5-year survival rate is as 60% [58].
Rhabdomyoma	F-FDG PET/CT [60] PAS. S-100 Vimentin, HHF 35 [61].	Adult rhabdomyomas-true neoplasms, cardiac form-Hamartomas [60].	Large polygonal vacuolated cells with a granular cytoplasm and abundant glycogen [59].	Recurrence rate of 16%-42% following incomplete removal [59].
Rhabdomyosarcoma	Myoglobin, desmin, muscle-specific actin, MyoD, myogenin [107].	chromosomal translocations at 2;13 or 1;13, with PAX3-FKHR and PAX7-FKHR fusion Products [63].	Zones of loose and dense cellularity, remarkably recapitulate normal embryonal myogenesis [107].	It is an aggressive tumour with a high recurrence rate [107].

Vascular tumours				
Haemangiopericytoma	Angiography. CD34, desmin, muscle actin, factor XIIIa, CD-34 [64].	Are near-diploid, with breakpoints in 12q13, 12q24 and 19q13 and t(12;19) (q13;q13) Translocations [64].	Tightly packed cells around ramifying thin-walled and endothelial lined small capillary-sized vessels to large gaping sinusoidal Spaces [64].	Prognosis is worse for adult type with 10-year survival rate of 70% [64].
Spindle cell Haemangioma	Vimentin, CD31, CD34, HAM-56, factor VIII, Ulex lectin [68].	Arteriovenous shunt, thrombus organisation with new vascular Proliferation [67].	Irregular cavernous spaces with RBCs, lined by endothelial cells, and solid areas spindle cell proliferation [67].	Spontaneous regression has been Reported [67].
Kaposi Sarcoma	Warthin-Starry silver stain, PCR. LYVE-1, VEGFR-2,3, angiopoietin-2, D2-40 [69,70].	Monoclonal HHV-8 transformation, oroligoclonal non-neoplasic Proliferation [69].	Patch stage-small, irregular, blood vessels. Plaque stage-exaggerated features. Nodular stage-intersecting sheets and fascicles of spindle cells [69].	5-year survival rate of 74% has been Reported [69].
Lipomatous tumours				
Spindle cell lipoma	CD-34 +ve, desmin –ve [72].	Multiple involvement in BSL or Madelung's disease) [71].	Admixture of mature fat cells and well-aligned uniform spindle cells, and wiry collagen bundles [71].	Solitary SCL shows no features of local Recurrence [71].
Epithelial tumours				
Pleomorphic adenoma	Luminal cells-CK, S-100. ME cells-α-SMA or calponin, Vimentin [108].	Chromosomal rearrangements at 8q12 as t(3;8)(p21;q12), t(5;8)(p11;q12),73 WT1 cells EMT [74].	Foote and Frazell classified PA according to its cellular: stromal components ratio. Seifert added the principal stromal component [74].	Even though PA is benign, it has a high rate of Implantability [108].
Spindle cell Myoepithelioma	S-100, CK 7&14, p63, GFAP, actin, calponin, Myosin [75].	Cytogenic abnormality is seen on chromosome 12q [75].	Interlacing fascicles or nests of neoplastic myoepithelial cells with a stroma like appearance, separated by collagen Stroma [75].	Recurrence rate 15-18%. Malignant transformation in recurring disease [75].
Spindle cell carcinoma	Cytokeratin, vimentin, SMA, muscle actin, Desmin [78].	A dysfunctional intercellular adhesion complex cadherin Catenin [77].	Monophasic or biphasic pattern with fascicles of anaplastic spindle cells interspersed with mitotic figures [76].	Recurrence rate of 73.3% and metastasis rate of 33.3% [76].
Malignant Melanoma	HMB-45, S-100, serum Tyrosinase [79].	NRAS (15%), BRAF (50%), CKIT (2%), GNAQ/GNA11 Mutations [109].	Subtypes are superficial spreading, lentigo maligna, nodular, acral lentiginous, mucosal, desmoplastic and naevoid melanoma [109].	5-year survival rate for stage IA is 97%, and for stage IV is 15-20% [110].
Odontogenic tumours				
Ameloblastic Fibroma	Ki-67, MMP-9, e-cad, cytokeratin, tenascin, Vimentin [80,81].	LOH at the genetic locus 17p13, The PRKAR1A gene mutation [82].	Epithelial component-peripheral columnar cells and central stellate reticulum like area. CT component-more cellular, mimic dental papilla, with little collagen [81].	Metastasis is uncommon, fatal cases associated with uncontrollable local infiltration [81].
Ameloblastic Fibrosarcoma	Alkaline phosphatase and ATPase. P53, PCNA, c-KIT, Ki-67 [86,87].	LOH of 17p13.1 loci involving p53 and CHRNB1 genes. 62% for p53, 55% for CHRNB1 [111].	The bland epithelial component is present in a branching cord pattern with a hypercellular malignant mesenchymal or fibroblastic Component [87].	Distant metastasis-4.5%, overall mortality rate of 25.4% [87].
Central Odontogenic Fibroma	Vimentin, α-smooth muscle actin, Cytokeratin AE1/AE3 [112].	Aberration in C-kit causing unchecked signal transduction pathways of tyrosine kinase [89].	A variably cellular fibroblastic stroma with; some matrix resembling bone and some resembling cementum [88].	Recurrences are infrequent following postsurgical follow-up [89].
Desmoplastic Ameloblastoma	S-100, Fas, desmin, p63, TGF-β, caspase-3, collagen I&VI, Fibronectin [91].	SMO gene mutation [92], microsattelite alterations, alteration of Ameloblastin [93].	Tumour cells can induce stromal desmoplasia which often compresses the neoplastic cells, resulting in loss of diagnostic peripheral Palisading [88].	Recurrence rate of 21.4% compared to other types (10.1%) of Ameloblastoma [113].
Miscellaneous tumours				
Benign Fibrous Histiocytoma	Vimentin, CD68, factor XIIIa [94].	Fibroblastic differentiation without any relationship to true histiocytes [94].	Biphasic cell population of histiocytes and fibroblasts with vesicular nucleus arranged in a storiform pattern [94].	Prognosis is good and without recurrence [94].
Malignant Fibrous Histiocytoma	Vimentin, muscle-specific actin, CD68, desmin, Ki67 [95].	In 2002, the WHO renamed it as an undifferentiated pleomorphic sarcoma, NOS [114].	Enzinger and Weiss in 1995 defined 5 subtypes: Storiform-pleomorphic, Myxoid, Giant cell, Inflammatory, Angiomatoid Types [114].	Metastasis rate: lung (90%), bone (8%) and liver (1%) [114].
Synovial Sarcoma	EMA, CD99, Bcl-2, TLE1, FISH [96].	SYT gene rearrangement, Wnt/b-catenin pathway [96].	SFT-like appearance with haemangiopericytoma-like vessels [96].	The tumour is Chemosensitive [96].
Ossifying Fibromyxoid Tumour (OFT)	Lack of epithelial markers and strong S100 expression [97].	PHF1 gene rearrangement, mosaic pattern of loss of INI1/ SMARCB1 [97].	3 microscopic subtypes: typical, atypical, and malignant, based on cellularity, nuclear grade, and mitotic activity [97].	Mortality rate of 10% in cases of Metastatsis [97].
Giant Cell Angiofibroma	CD34, CD99, vimentin, variable bcl2 [98].	Mutations on chromosome 6q13 and translocation at t(12;17) [98].	Homogenous irregularly organised proliferating cells in a collagenized or myxoid, richly vascularized stroma [98].	Non-invasive yet recurrence rate is Controversial [98].

Blue Nevus (BN)	S100, HMB-45, MART-1 [99].	Activating mutations in Gnaq and Gna11 gene [99].	A pigmented dendritic melanocyte with a small, elongated, hyperchromatic nuclei [99].	Malignant blue nevus has an aggressive Course [99].
Atypical Fibroxanthoma (AFX)	Vimentin, desmin, procollagen-1, CD10, CD99, CD68, SMA [100].	UV radiation induced mutation of C-T transitions and CC-TT double transitions in p53 [100].	Composed of spindle, plump, epithelioid and bizarre cells, in haphazard, vaguely fascicular or storiform patterns [100].	Recurence rate: 5-10%, Metastasis: 1% of cases [100].
Dermatofibroma Protuberans (DP)	Loss of CD34 Expression [96].	COLIA1-PDGFB fusion Gene [96].	Monotonous and bland spindle-shaped tumour cells infiltrating fat lobules with a collagenous stroma [96].	Fibrosarcomatous changes in 10-15% of Cases [96].

[Table/Fig-1]: Brief tabulation of the diagnostic aspect, pathogenesis, diagnostic histopathological features and prognosis of spindle cell tumours of head and neck.

Among the malignancies, Kaposi's Sarcoma was the most common tumour and among the benign lesions, tumours of neural origin predominated [116]. Over the course of time, few uncommon or previously unrecognised entities have been reported which have caught the attention of the clinical diagnosticians. These soft tissue tumours such as deep benign fibrous histiocytoma, hemosiderotic fibrolipomatous tumour, spindle cell liposarcoma, spindle cells in myoepithelioma; demand a better appreciation of the biologic behaviour and rational classification schemes [117,118].

This review summarises the molecular concepts and immunohistochemical features of individual spindle cell neoplasms. IHC elucidates the histogenesis of the cells which can aid in differentials while the molecular pathogenesis provides an insight into the biology of these varied neoplasms which can form basis for future treatment and research proposals. At present there is no consensually accepted classification for spindle cell neoplasms of maxillofacial region. Shamin T [17] proposed a working type classification for spindle cell neoplasms of the oral cavity. Here, an attempt has been made to gather the various classifications and enumerations that have been documented through the years, and few tumours like spindle cell lipoma, spindle cell myoepithelioma, atypical fibroxanthoma and dermatofibroma protuberans, are proposed to be added to the working type classification.

Given the anatomic location of these tumours in the head and neck region, sampling is difficult; thus a more extensive and detailed study with large sample size can throw light on the unexplored and unknown aspects of these neoplasms.

REFERENCES

[1] William CF, Celeste P. Salivary Gland Cytopathology. Chapter 11-Spindle Cell Tumors: Spindled Myoepithelioma, Myoepithelial-Predominant Pleomorphic Adenoma and Schwannoma. 2008.
[2] Batsakis JG, Rice DH, Howard DR. The pathology of head and neck tumors: spindle cell lesions (sarcomatoid carcinomas, nodular fasciitis, and fibrosarcoma) of the aerodigestive tracts, Part 14. Head Neck Surg. 1982;4(6):499-513.
[3] Wikivet. Spindle Cell Tumours. Available from: https://en.wikivet.net/Spindle_Cell_Tumours. [Accessed on 1st september 2018]
[4] Åkerman M, Domanski HA. Monographs in Clinical Cytology. The Cytology of Soft Tissue Tumours. Basel: Karger, 2003;16:103-06.
[5] Prakash N, Kumar HMS, Sharada P, Pradeep GL. Spindle Cell Carcinoma of the Oral Cavity: A Case Report of a Rare Entity and Review of Literature. World Journal of Dentistry 2010;1(1):55-58.
[6] Zidar N, Boštjancic E, Gale N, Kojc N, Poljak M, Glavač D, et al. Down-regulation of microRNAs of the miR-200 family and miR-205, and an altered expression of classic and desmosomal cadherins in spindle cell carcinoma of the head and neck-hallmark of epithelial-mesenchymal transition. Hum Pathol. 2011;42(2):482-88.
[7] Gale N, Poljak M, Zidar N. Update from the 4th edition of the World Health Organization classification of head and neck tumors: what is new in the 2017 WHO blue book for tumors of the hypopharynx, larynx, trachea and parapharyngeal space. Head and Neck Pathol. 2017;11:23-32.
[8] Lewis JS Jr. Spindle cell lesions-neoplastic or non-neoplastic?: spindle cell carcinoma and other atypical spindle cell lesions of the head and neck. Head Neck Pathol. 2008;2(2):103-10.
[9] Jordan RC, Regezi JA. Oral spindle cell neoplasms: a review of 307 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95(6):717-24.
[10] Chan JKC. Vascular tumours with a prominent spindle cell component. Current Diagnostic Pathology. 1997;4:76-90.
[11] Shamim T. The spindle cell neoplasms of the oral cavity. Iran J Pathol. 2015;10(3):175-84.
[12] Dickson BC. An update on mesenchymal tumors of the head and neck. Diagnostic Histopathology. 2014;20(8):308-15.
[13] Huether MJ, Zitelli JA, Brodland DG. Mohs micrographic surgery for the treatment of spindle cell tumors of the skin. J Am Acad Dermatol 2001;44(4):256-59.
[14] Erlandson RA, Woodruff JM. Role of electron microscopy in the evaluation of soft tissue neoplasms, with emphasis on spindle cell and pleomorphic tumors. Hum Pathol. 1998;29(12):1372-81.
[15] Al-Nafussi A. Practical morphological approach to the diagnosis and differential diagnosis of soft tissue sarcomas. Current Diagnostic Pathology. 2002;8:395-411.
[16] Anderson CE, Al-Nafussi A. Spindle cell lesions of the head and neck: an overview and diagnostic approach. Diagnostic Histopathology 2009;15(5):264-72.
[17] Shamim T. A simple working type classification proposed for the spindle cell neoplasms of the oral cavity. J Cytol. 2013;30(1): 85.
[18] Narang BR, Palaskar SJ, Bartake AR, Pawar RB, Rongte S. Intraosseous neurofibroma of the mandible: a case report and review of literature. J Clin Diagn Res. 2017;11(2):ZD06-ZD08.
[19] Campos MS, Fontes A, Marocchio LS, Nunes FD, de Sousa SC. Clinicopathologic and immunohistochemical features of oral neurofibroma. Acta Odontol Scand. 2012;70(6):577-82.
[20] Barnes L. Tumors of the nervous system. In: Surgical Pathology of The Head and Neck. 2nd ed, vol 2. New York: Marcel Dekker, Inc 2001.
[21] Sugwara C, Takahashi A, Kawano F, Kudo Y, Ishimaru N, Miyamoto Y. Intraoral ultrasonography of tongue mass lesions. Dentomaxillofacial Radiology. 2016;45:20150362.
[22] 2017 NF Conference update: Stem cell technology for Neurofibromatosis. Available from: http://www.ctf.org/news/2017-nf-conference-update-stem-cell-technology-for-neurofibromatosis. [Accessed on 24th August 2018]
[23] Brodhun M, Stahn V, Harder A. Pathogenesis and molecular pathology of vestibular schwannoma. HNO. 2017;65(5):362-72.
[24] Rodriguez FJ, Folpe AL, Giannini C, Perry A. Pathology of peripheral nerve sheath tumors: Diagnostic overview and update on selected diagnostic problems. Acta Neuropathol. 2012;123(3):295-319.
[25] Patil SB, Chatura KR. Schwannoma and its unusual variants-A histopathological study. Indian Journal of Pathology and Oncology. 2016;3(4):727-31.
[26] Basnaker M, Kumar GS. Neural tumors of oral and paraoral region. International Journal of Dental Clinics. 2011;3(1):34-43.
[27] Chun LK, Nguyen TP, Sheppard JP, Lagman C, Tenn S, Lee P, et al. A systematic review of radiosurgery versus surgery for Neurofibromatosis type 2 vestibular schwannoma. World Neurosurg. 2018;109:47-58.
[28] Koutlas IG, Scheithauer BW. Palisaded encapsulated ("solitary circumscribed") neuroma of the oral cavity: a review of 55 cases. Head and Neck Pathol. 2010;4:15-26.
[29] Argenyi ZB. Immunohistochemical characterization of palisaded, encapsulated neuroma. J Cutan Pathol. 1990;17(6):329-35.
[30] Yang J-R, Wang C-J, Kao W-B, Wang Y-L. Traumatic neuroma of bilateral mental nerve: a case report with literature review. Taiwan J Oral Maxillofac Surg. 2010;21:251-60.
[31] Ananthaneni A, Srilekha N, Guduru VS, Kiresur MA. Rare case report of Traumatic neuroma of anterior superior alveolar nerve associated with high frenal attachment. Asian J Neurosurg. 2015;10:169-71.
[32] Oliveira KMC, Pindur L, Han Z, Bhavsar MB, Barker JH, Leppik L. Time course of traumatic neuroma development. PLoS ONE. 2018;13(7):e0200548.
[33] Yao C, Zhou X, Zhao B, Sun C, Poonit K, Yan H. Treatments of traumatic neuropathic pain: a systematic review. Oncotarget. 2017;8(34):57670-79.
[34] Endo M, Yamamoto H, Hariyama K, Kohashi K, Ishii T, Setsu N, et al. Conventional spindle cell-type malignant peripheral nerve sheath tumor arising in a sporadic schwannoma. Human Pathology. 2013;44:2845-48.
[35] Farid M, Demicco EG, Garcia R, Ahn L, Merola PR, Cioffi A, et al. Maignant peripheral nerve sheath tumors. Oncologist. 2014;19(2):193-201.
[36] Narayen V, Ahmed SA, Suri C, Tanveer S. Myofibroma of the gingival: a rare case report and literature review. Hindawi Publishing Corporation. Case Reports in Dentistry. 2015;2015:243894.
[37] Newaz ZA, Pannu V, Kennedy J, Barghan S, Kashtwari DN, Nair MK. Imaging features of intraosseous myofibroma of the jaws: a case report and literature review. J Adv Radiol Med Image. 2016;1(1):102.
[38] Agaimy A, Bieg M, Michal M, Geddert H, Markl B, Seitz J, et al. Recurrent somatic PDGFRB mutations in sporadic infantile/solitary adult myofibromas but not in angioleiomyomas and myopericytomas. Am J Surg Pathol. 2017;41(2):195-203.
[39] Binmadi NO, Packmanb H, Papadimitriouc JC, Scheper M. Oral inflammatory myofibroblastic tumor: case report and review of literature. The Open Dentistry Journal. 2011;5:66-70.

[40] Lourenço SV, Boggio P, Nico MMS. Inflammatory myofibroblastic tumor of the tongue: report of an unusual case in a teenage patient. Dermatology Online Journal. 2012;18(5):6-13.
[41] Alaggio R, Cecchetto G, Bisogno G, Gambini C, Clabro ML, Inserra A, et al. Inflammatory myofibroblastic tumors in childhood: a report from the Italian Cooperative Group studies. Cancer. 2010;116(1):216-26.
[42] Qiu JY, Liu P, Shi C, Han B. Low-grade myofibroblastic sarcomas of the maxilla. Oncol Lett. 2015;9(2):619-25.
[43] Kinslow CJ, Bruce SS, Rae AI, Sheth SA, McKhann GM, Sisti MB, et al. Solitary-fibrous tumors/hemangiopericytoma of the central nervous system: a population-based study. J Neurooncol. 2018;138(1):173-82.
[44] O'Regan EM, Vanguri V, Allen CM, Eversole LR, Wright JM, Woo S-B. Solitary fibrous tumor of the oral cavity: clinicopathologic and immunohistochemical study of 21 cases. Head and Neck Pathol. 2009;3:106-15.
[45] Pascu EI, Pisoschi CG, Andrei A-M, Munteanu MC, Rauten A-M, Scrieciu M, et al. Heterogeneity of collagen secreting cells in gingival fibrosis-an immunohistochemical assessment and a review of the literature. Rom J Morphol Embryol. 2015;56(1):49-61.
[46] Skubitz KM. Biology and treatment of aggressive fibromatosis or desmoids tumor. Mayo Clin Proc. 2017;91(6):947-64.
[47] Gawron K, Łazarz-Bartyzel K, Potempa J, Chomyszyn-Gajewska M. Gingival fibromatosis: clinical, molecular and therapeutic issues. Gawron et al. Orphanet Journal of Rare Diseases. 2016;11:9.
[48] Gibson TC, Bishop JA, Thompson LDR. Parotid gland nodular fasciitis: a clinicopathologic series of 12 cases with a review of 18 cases from the literature. Head and Neck Pathol. 2015;9:334-44.
[49] Souza AA, Neto EGC, de Araújo VC, Passador-Santos F, de Seixas Alves MT, Soares AB. Description of a rare case of nodular fasciitis of the apical aspect of the upper buccal sulcus. Hindawi Publishing Corporation. Case Reports in Dentistry. 2016;2016:4231683.
[50] Pereira TSF, de Lacerda JCT, Porto-Matias MD, de Jesus AO, Gomez RS, Mesquita RA. Desmoplastic fibroblastoma (collagenous fibroma) of the oral cavity. J Clin Exp Dent. 2016;8(1):e89-92.
[51] Woods TR, Cohen DM, Islam MN, Rawal Y, Bhattacharyya I. Desmoplastic fibroma of the mandible: a series of three cases and review of literature. Head and Neck Pathol. 2015;9:196-204.
[52] Wadhwan V, Chaudhary MS, Gawande M. Fibrosarcoma of the oral cavity. Indian J Dent Res. 2010;21(2):295-98.
[53] Augsburger D, Nelson PJ, Kalinski T, Udelnow A, Knösel T, Hofstetter M, et al. Current diagnostics and treatment of fibrosarcoma-perspectives for future therapeutic targets and strategies. Oncotarget. 2017;8(61):104638-53.
[54] Kaur G, Gondal R. Oral leiomyoma. J Oral Maxillofac Pathol. 2011;15(3):361-67.
[55] Nguyen AP, Frydrych A. Oral leiomyoma in an adult male: a case report. The Open Dentistry Journal. 2017;11:520-26.
[56] Matiakis A, Karakostas P, Pavlou AM, Anagnostou E, Poulopoulos A. Angioleiomyoma of the oral cavity: a case report and brief review of the literature. J Korean Assoc Oral Maxillofac Surg. 2018;44(3):136-39.
[57] Yoon TM, Yang HC, Choi YD, Lee DH, Lee JK, Lim SC. Vascular leiomyoma in the head and neck region: 11 years ecperience in one institution. Clin Exp Otorhinolaryngol. 2013;6(3):171-75.
[58] Azevedo RS, Pires FR, Gouvêa AF, Lopes MA, Jorge J. Leiomyosarcoma of the oral cavity: report of a radiation-associated and a metastatic case. Oral Maxillofac Surg. 2012;16(2):227-32.
[59] Andrade NN, Gandhewar T, Aggarwal N, Mathai P. Adult rhabdomyoma of the tongue in a child: Report of a case and a literature appraisal. Contemp Clin Dent. 2018;9:2-4.
[60] de Trey LA, Schmid S, Huber GF. Multifocal adult rhabdomyoma of the head and neck: manifestation in 7 Locations and review of the literature. Hindawi Publishing Corporation Case Reports in Otolaryngology. 2013;2013:758416.
[61] Souza AA, de Araújo VC, Santos FP, Martinez EF, de Menezes Filho JF, de Araujo NS, et al. Intraoral adult rhabdomyoma: a case report. Hindawi Publishing Corporation Case Reports in Dentistry. 2013;2013:741548.
[62] Sun X, Guo W, Shen JK, Mankin HJ, Hornicek FJ, Duan Z. Rhabdomyomasarcoma: Advances in molecular and cellular biology. Hindawi Publishing Corporation. Sarcoma. 2015;2015:232010.
[63] Xia SJ, Pressey JG, Barr FG. Molecular pathogenesis of rhabdomyosarcoma. Cancer Biol Ther. 2002;1(2):97-104.
[64] Marec-Bérard P. Malignant hemangiopericytoma. Orphanet Encyclopedia. 2004:1-4.
[65] Fareed MM, Al Amro ASM, Akasha R, Al Assiry M, Al Asiri M, Tonio M, et al. Parapharyngeal space hemangiopericytoma treated with surgery and postoperative radiation case report. Head & Neck Oncology. 2012;4:10.
[66] Watanabe K, Saito A, Suzuki M, Yamanobe S, Suzuki T. True hemagiopericytoma of the nasal cavity: Immunohistochemical and electron microscopic study of 2 cases and a review of the literature on sinonasal hemangiopericytomas. Arch Pathol Lab Med. 2001;125:686-90.
[67] Murakami K, Yamamoto K, Sugiura T, Kirita T. Spindle cell hemangioma in the mucosa of the upper Lip: a case report and review of the literature. Hindawi Case Reports in Dentistry. 2018;2018:1370701.
[68] Tosios KI, Gouveris I, Sklavounou A, Koutlas IG. Spindle cell hemangioma (hemangioendothelioma) of the head and neck: case report of an unusual (or underdiagnosed) tumor. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105:216-21.
[69] Ramírez-Amador V, Anaya-Saavedra G, Martínez-Mata G. Kaposi's sarcoma of the head and neck: a review. Oral Oncology. 2010;46:135-45.
[70] Fatahzadeh M. Kaposi sarcoma: review and medical management update. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(1):2-16.
[71] Imai T, Michizawa M, Shimizu H, Imai T, Yamamoto N, Yura Y, et al. Bilateral multiple spindle cell lipomas of the tongue. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106:264-69.
[72] Comunoglu N, Comunoglu C, Ekici AI, Ozkan F, Dervisoglu S. Spindle cell lipoma. Pol J Pathol. 2007;58(1):711.
[73] Griffith CC, Schmitt AC, Little JL, Magliocca KR. New developments in salivary gland pathology: Clinically useful ancillary testing and new potentially targetable molecular alterations. Arch Pathol Lab Med. 2017;141(3):381-95.
[74] Triantafyllou A, Thompson LD, Devaney KO, Bell D, Hunt JL, Rinaldo A, et al. Functional histology of salivary gland pleomorphic adenoma: An appraisal. Head Neck Pathol. 2015;9(3):387-404.
[75] Weltzel M, Cohn JE, Spector H. Myoepithelioma of the parotid gland: a case report with review of the literature and classic histopathology. Hindawi Case Reports in Otolaryngology. 2017;2017:6036179.
[76] Sarma A, Das R, Sharma JD, Kataki AC. Spindle cell carcinoma of the head and neck: a clinicopathological and immunohistochemical study of 40 cases. Journal of Cancer Therapy. 2012;3:1055-59.
[77] Rizzardi C, Frezzini C, Maglione M, Tirelli G, Melato M. A look at the biology of spindle cell squamous carcinoma of the oral cavity: report of a case. J Oral Maxillofac Surg. 2003;61:264-68.
[78] Hunt JL. Immunohistochemistry of head and neck neoplasms. In: Diagnostic Immunohistochemistry: Therapeutic and genomic applications. Philadelphia: WB Saunders; 2010.
[79] Slominsky A, Wortsman J, Nickloff B, McClatchey K, Mihm MC, Ross JS. Molecular pathology of malignant melanoma. Am J Clin Pathol. 1998;110:788-94.
[80] Waguih HM, Salem M, Dahmoush HM, ElShafei MM. Immunohistochemical assessment of the potential behaviour of ameloblastic fibroma using Ki-67, MMP-9 and E-Cadherin. EDJ. 2015;61(4):1-14.
[81] Takeda Y. Ameloblastic fibroma and related lesions: current pathologic concept. Oral Oncology. 1999;35:535-40.
[82] Bernardes VF, Gomes CC, Gomez RS. Molecular investigation of ameloblastic fibroma: how far have we gone? Head Neck Oncol. 2012;9(4):45.
[83] Huguet P, Castellvi J, Avila M, Autonell F, Basas C, Bescos MS. Ameloblastic fibrosarcoma: report of a case. Immunohistochemical study and review of literature. Medicina Bucal. 2001;6(3):173-79.
[84] Altini M, Thompson SH, Lownie JF, Berezowski BB. Ameloblastic sarcoma of the mandible. J Oral Maxillofac Surg. 1985;43(10):789-94.
[85] Prein J, Remagen W, Spiessl B, Schafroth U. Ameloblastic fibroma and its sarcomatous transformation. Pathol Res Pract. 1979;166(1):123-30.
[86] Chomette G, Auriol M, Guilbert F, Delcourt A. Ameloblastic fibrosarcoma of the jaws-report of three cases. Clinico-pathologic, histoenzymological and ultrastructural study. Pathol Res Pract. 1983;178(1):40-47.
[87] Gilani SM, Raza A, Al-Khafaji BM. Ameloblastic fibrosarcoma: a rare malignant odontogenic tumor. Eur Ann Otorhinolaryngol Head Neck Dis. 2014;131(1):53-56.
[88] Soluk-Tekkesin M, Wright JM. The World Health Organization Classification of Odontogenic Lesions: A summary of the changes of the 2017 (4th) edition. Turk Patholoji Derg. 2018;34(1).
[89] Chandrashekar C, Sen S, Narayanaswamy V, Radhakrishnan R. A curious case of central odontogenic fibroma: A novel perspective. J Oral Maxillofac Pathol. 2018;22(S1):16-19.
[90] Lee SK, Kim YS. Current concepts and occurrence of epithelial odontogenic tumors: I. Ameloblastoma and adenomatoid odontogenic tumor. Korean J Pathol. 2013;47(3):191-202.
[91] Sivapathasundharam B, Einstein A, Syed RI. Desmoplastic ameloblastoma in Indians: report of five cases and review of literature. Indian J Dent Res. 2007;18(4):218-21.
[92] Effiom OA, Ogundana OM, Akinshipo AO, Akintoye SO. Ameloblastoma: current etiopathological concepts and management. Oral Diseases. 2018;24:307-16.
[93] Gomes CC, Duarte AP, Diniz MG, Comex RS. Current concepts of ameloblastoma pathgenesis. J Oral Pathol Med. 2010;39:585-91.
[94] George A, Pynadath MK, Jayapalan CS, Noufal A, Manjunath GA, et al. Benign fibrous histiocytoma of maxillary gingival. Dentistry. 2014;4:227.
[95] Guo H, Xiong Y, Nong L, Zhang S, Li T. Reassessment of the pathological diagnosis in 33 cases of malignant fibrous histiocytoma. Beijing Da Xue Xue Bao Yi Xue Ban. 2008;40(4):374-79.
[96] Wei S, Henderson-Jackson E, Qian X, Bui MM. Soft tissue tumor immunohistochemistry update. Arch Pathol Lab Med. 2017;141:1072-91.
[97] Bakiratharajan D, Rekhi B. Ossifying fibromyxoid tumor. Arch Pathol Lab Med. 2016;140:371-75.
[98] He Y, Zhang C, Liu G, Tian Z, Wang L, Kalfarentzos E. Giant cell angiofibroma misdiagnosed as a vascular malformation and treated with absolute alcohol for one year: a case report and review of the literature. World J Surg Oncol. 2014;12:117.
[99] Zembowicz A. Blue nevi and variants: an update. Arch Pathol Lab Med. 2011;135:327-36.
[100] Sakamoto A. Atypical fibroxanthoma. Clinical Medicine: Oncology. 2008;2:117-27.
[101] Manchanda AS, Narang RS, Puri G. Palisaded encapsulated neuroma. J Orofac Sci. 2015;7:136-39.
[102] Yamada T, Yoshimura T, Kitamura N, Sasabe E, Ohno S, Yamamoto T. Low-grade myofibroblastic sarcoma of the palate. International Journal of Oral Science. 2012;4:170-73.
[103] Ronchi A, Cozzolino I, Zito Marino F, Accardo M, Montella M, Panarese I, et al. Extrapleural solitary fibrous tumor: a distinct entity from pleural solitary fibrous

tumor. An update on clinical, molecular and diagnostic features. Ann Diagn Pathol. 2018;34:142-50.
[104] Sandberg AA. Translocations in malignant tumors. Am J Pathol. 2001;159(6):1979-80.
[105] Mittal KR, Chen F, Wei JJ, Rijhvani K, Kurvathi R, Streck D, et al. Molecular and immunohistochemical evidence for the origin of uterine leiomyosarcomas from associated leiomyoma and symplastic leiomyoma-like areas. Mod Pathol. 2009;22(10):1303-11.
[106] Rubin BP, Lazar AJF, Oliveira AM. Molecular pathology of bone and soft tissue tumors. In: Cell and tissue based molecular pathology. Churchill Livingstone 2009.
[107] Sahni P, Singhvi A, Nayak MT, Deora SS. Gingival rhabdomyosarcoma in an adult: a unique entity. Turk Patoloji Derg. 2015;31:153-57.
[108] Lotufo MA, Júnior CA, de Mattos J, França CM. Pleomorphic adenoma of the upper lip in a child. Journal of Oral Science. 2008;50(2):225-28.
[109] Scoyler RA, Long GV, Thompson JF. Evolving concepts in melanoma classification and their relevance to multidisciplinary melanoma patient care. Mol Oncol. 2011;5(2):124-36.
[110] Malek H, Wilson A, Raizer J. Neurological complications of malignant melanoma. In: Schiff D, Arrillaga I, Yen PY. Cancer neurology in clinical practice. 3rd ed. Switzerland: Springer international publishing AG; 2018.
[111] Bilodeau EA, Prasad JL, Alawi F, Seethala RR. Molecular and genetic asects of odontogenic lesions. Head Neck Pathol. 2014;8(4):400-10.
[112] Iordanidis S, Poulopoulos A, Epivatianos A, Zouloumis L. Central odontogenic fibroma: Report of case with immunohistochemical study. Indian J Dent Res. 2013;24:753-55.
[113] Sheikh S, Pallagatti S, Singla I, Kalucha A. Desmoplastic ameloblastoma: a case report. J Dent Res Dent Clin Dent Prospects. 2011;5(1):27-32.
[114] Bali A, Singh MP, Padmavathi, Khorate M, Ahmed J. Malignant fibrous histiocytoma-an unusual transformation from benign to malignant. J Cancer Sci Ther. 2010;2:053-57.
[115] Neville BW, Damm DD, Allen CM, Bouquot JE. Epithelial pathology. In: Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. Philadelphia: WB Saunders; 2004.
[116] Brasileiro BF, Martins-Filho PRS, Piva MR, da Silva LCF, Nonaka CFW, Miguel MCC. Myofibroma of the oral cavity. A rare spindle cell neoplasm. Med Oral Patol Oral Cir Bucal. 2010;15(4):e596-600.
[117] Fletcher CDM. Recently characterized soft tissue tumors that bring biologic insight. Modern Pathology. 2014;27:S98-S112.
[118] Liyanage RLPR, Wadusinghearachchi NS, Siriwardena BSMS, Jayasooriya PR, Tilakaratne WM. Pigmented mucoepidermoid carcinoma with spindle cell differentiation. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;117(6):e449-51.

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