International Journal Dental and Medical Sciences Research
Volume 5, Issue 2, Mar - Apr 2023 pp 179-187 www.ijdmsrjournal.com ISSN: 2582-6018

Spindle Cell Neoplasms of Oral Cavity – An Overview

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Date of Submission: 09-03-2023 Date of Acceptance: 18-03-2023

ABSTRACT
According to histology, neoplasms with spindle-shaped cells are known as spindle cell neoplasms. Histologically, a spindle cell tumor is identified by a mixture of fat cells and spindle cells that resemble fibroblasts inside a collagen and mucoid matrix(1). The oral cavity may be impacted by spindle cell neoplasms. It is possible to pinpoint the epithelial, mesenchymal, and odontogenic origins of spindle cell neoplasms in the oral cavity. Reviewing oral spindle cell neoplasms with an emphasis on histology is the goal of this study.
Key Words – Spindle cell, neural, myofibroblastic, muscular, vascular, epithelial, odontogenic

I. INTRODUCTION

The term "head and neck spindle cell lesions" refers to a variety of clinically and biologically diverse lesions. They may be cancerous or benign. It is frequently challenging for oral pathologists to distinguish them from other microscopic findings that are comparable (2). A working type classification for the spindle cell neoplasms of the oral cavity was recently proposed by author Shamim T. A. This categorization was created using the preponderance of spindle cells found in the histology of the lesions of the oral cavity (3). Reviewing oral spindle cell neoplasms with an emphasis on histology is the goal of this study. tumors of the neural, myofibroblastic, muscular, vascular, epithelial, odontogenic, and other forms are covered in this article.

NEURAL TUMORS

The axons, endoneurium, perineurium, and epineurium, which are identifiable compartments of peripheral nerves, are the genesis of oral neural tumors, which may be reactive or malignant in nature (4)(5)(6).

Traumatic neuroma (amputation neuroma), Neurofibroma, Neurilemmoma (schwannoma), Palisaded Encapsulated Neuroma, and Malignant Peripheral Nerve Sheath Tumor are all included in this group.

- **Traumatic Neuroma**

A nonneoplastic, excessive expansion of a nerve that develops in reaction to an operation or an injury is known as a traumatic neuroma.A neuroma develops as a result of uncontrolled proliferation of the proximal nerve if the close apposition of a nerve's ends is not maintained or if there is no distal stump (7). Histologically, a traumatic neuroma is made up of a poorly defined and disordered expansion of all the typical cells seen in a nerve fascicle, including fibroblasts, Schwann cells, perineurial cells, and a large number of tiny nerve fibres(8). Immunohistochemically, axon filaments will have silver stains (9).

- **Neurofibroma**

A benign peripheral nerve tumor known as a neurofibroma is made up of fibroblasts, Schwann cells, and cells that resemble perineurial cells as well as cells that have characteristics in between these cell types.Histologically, the majority of neurofibromas are confined, non-encapsulated tumors made up of evenly spaced, spindle-shaped cells with elongated, thin nuclei and little cytoplasm that are encased in a collagenous matrix that is located in the myxoid stroma (10). S-100 protein immunohistochemistry reveals that the tumor cells are generated from neural crest tissue because it produces sporadic positive reactions in the tumor cells (11).

International Journal Dental and Medical Sciences Research
Volume 5, Issue 2, Mar - Apr 2023 pp 179-187 www.ijdmsrjournal.com ISSN: 2582-6018

- **Neurilemmoma (Schwannoma)**

Schwannoma, also known as neurilemmoma, is a rare, benign tumor of the neural sheath that is encapsulated and of neuroectodermal origin. (12) According to histology, it consists of Verocay bodies, Antoni A and B areas, nuclear palisading, whorling of cells, and Antoni A and B regions (13). In terms of immunohistochemistry, the tumor cells exhibit a dispersed, positive response to the S 100 protein. (14).

- **Palisaded Encapsulated Neuroma**

Mostly affecting middle-aged adults' facial skin, palisaded encapsulated neuromas are benign neural tumors that are more common in the masticatory mucosa of the oral cavity (15). The tumor's histopathological features include areas of nuclear palisading and whorling of cells, as well as a moderately cellular, fascicular proliferation of spindle cells (16). Immunohistochemical stains will show Schwann cells that are positive for the S-100 protein, and peripheral nerve axons will exhibit positive neurofilament staining (16). For epithelial membrane antigen, the fibrous capsule of the lesions will stain positively, indicating perineurium (16).

- **Malignant Peripheral Nerve Sheath Tumor**

Any spindle cell sarcomas originating from peripheral nerves, neurofibromas, or tumors displaying differentiation of the nerve sheath are collectively referred to as "malignant peripheral nerve sheath tumors" (17). According to histopathology, the tumor is made up of hyperchromatic spindle cells that are expanding in a fascicular manner, alternately displaying hypocellular and hypercellular regions, exhibiting elevated mitotic activity (18). Neuron-specific enolase immunohistochemically confirms the neurogenic origin of this tumor (18).

MYOFIBROBLASTIC TUMORS

Tumors of myofibroblasts are included in myofibroblastic tumors (i.e., cells with both smooth muscle and fibroblastic features). Myofibroma, inflammatory myofibroblastic tumor, and low-grade myofibrosarcoma all fall under this group.

- **Inflammatory Myofibroblastic Tumor**

Inflammatory myofibroblastic tumor (IMT) is an unusual low grade tumor made up of myofibroblastic cells that are proliferating along with a varied admixture of inflammatory cells such as plasma cells, mature lymphocytes, macrophages, and eosinophils mixed throughout collagen fibres (19). IMT is made up of a submucosal proliferation of spindled to stellate cells grouped in storiform or poorly formed fascicles. The cytoplasmic extensions of the cells can be extremely lengthy and have been described as "spider-like" (19).Additional characteristics, such as the presence of ganglion-like cells, atypia, p53 expression, and aneuploidy, may help distinguish between patients with IMT and those who are at an elevated risk for malignancy (14) The tumor spindle cells frequently exhibit myofibroblastic character and are reactive to vimentin (99%), SMA (92%), muscle specific actin (89%), and desmin (69%), among other markers. Spindle cells may be focally positive for epithelial markers such as cytokeratin, EMA (36%), and CD68 (25%)(20).

- **Low Grade Myofibrosarcoma**

Histologically, LGMS consists of fascicles that are interlaced with slender spindle cells. The eosinophilic or amphophilic cytoplasm in the tumor cells is sparse to moderate, and they contain fusiform nuclei with a minimal level of nuclear pleomorphism (21). Myofibroblastic sarcoma has immunohistochemical markers for vimentin, SMA, muscle-specific actin, calponin, and fibronectin immunopositivity, desmin immunopositivity infrequently, and immunonegativeity for laminin and type IV collagen. Moreover, LGMS do not exhibit immunoreactivity for s-100, EMA, cytokeratin, or CD34 (14).

- **Myofibroma**

A rare spindle cell neoplasm called a myofibroma is only sometimes discovered in the oral cavity. Elongated spindle cells with eosinophilic cytoplasm in the edges and palisading polygonal cells with hyperchromatic nuclei in the central portions are seen under a microscope as a typical biphasic pattern (22). Myofibromas exhibits more collagenous stroma mixed in with spindle cells and large fibrous bundles with random, irregularly crossing angles when stained with a specific dye like Masson trichrome (23). Vimentin and actine smooth muscle antibodies will bind to the tumor cells immunohistochemically, while keratin, S-100, and EMA (Epithelial Membrane Antigen) antibodies will not (24).

MUSCLE TUMORS

Muscle tumour: an abnormal growth of tissue that originates in or is found in muscle tissue. Leiomyoma, vascular leiomyoma, leiomyosarcoma, rhabdomyoma, and rhabdomyosarcoma are all included in this group.

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- **Leiomyoma**

Leiomyoma is a benign smooth muscle tumor. The source of smooth muscle in the oral cavity is either the arterial tunica media as suggested by Stout,(25)orthe ductus lingualis and the circumvallate papillae as proposed by Glass (26)or heterotopic embryonal tissue (27). Leiomyomas can be classified histologically into three different groups: solid leiomyomas, vascular leiomyomas, and the extremely rare epitheloid leiomyomas known as leioblastomas (28). According to histology, solid leiomyoma is made up of interlacing bundles of smooth muscle cells with stellate or spindle shapes and elongated, blunt-ended nuclei that are pale in colour (29). Van Gieson's and Masson trichrome stains are specific for muscle cells and collagen fibres, while Mallory's phosphotungstic acid haematoxylin could help distinguish leiomyoma from other spindle cell cancers (14).

- **Rhabdomyosarcoma**

Rhabdomyosarcoma (RMS) is a tumor with skeletal muscle origin. The histological studies have revealed four main subtypes of RMS: botryoid and spindle cell RMS, embryonal RMS, alveolar RMS, and undifferentiated RMS. (30,31). Histopathologically, the tumor cells exhibit strong nuclear and cellular pleomorphism, nuclear hyperchromatism, conspicuous nucleoli, lack of cell cohesion, a profusion of aberrant mitotic figures, and sporadic spindle cell shape (32). Myoglobin, desmin, and specific muscle actin immunohistochemically confirm the presence of tumor cells (14).

- **Vascular Leiomyoma**

A rare benign smooth muscle tumor called a vascular leiomyoma (Angiomyoma) is made up of many blood vessels and spindle-shaped smooth muscle cells (33). A well-defined proliferation of mesenchymal tapering cells with eosinophilic cytoplasm and elongated basophilic nuclei (cigar-shaped nuclei) distinguishes the vascular leiomyoma histologically (33). The tumor cells will have positive immunohistochemical staining for actin and vimentin and negative staining for S-100 protein and CD34 (34).

- **Leiomyosarcoma**

The malignant lesion leiomyosarcoma exhibits smooth muscle differentiation and develops from pluripotent undifferentiated mesenchymal cells (35). The tumor's histopathology is characterized by palisade-like sheets of sweeping, alternating bundles and fascicles of densely packed spindle cells with a profusion of fibrillar eosinophilic cytoplasm and ambiguous cytoplasmic boundaries (35). The nuclei of the Tumor cells will be irregularly shaped, big, hyperchromatic, and bizarre. Smooth muscle actin, muscle specific actin, and vimentin will all be present in Tumor cells upon immunohistochemistry, while S-100 protein, cytokeratin, and desmin will not (36).

- **Rhabdomyoma**

A benign tumor that develops from striated muscle cells is called a rhabdomyoma. Depending on the age, rhabdomyoma can be divided into adult and foetal types. The tumor exhibits round and polygonal cells with an abundance of granular eosinophilic cytoplasm, which has the appearance of a spider web according to histopathology (37). Spindle-shaped muscle cells with noticeable cellularity and minor pleomorphism in a myxoid stroma will be seen in the foetal group (38). The tumor cells will exhibit immunohistochemically positive desmin, myoglobin, and alpha-smooth muscle actin and negative vimentin (39).

FIBROBLASTIC TUMORS

Fibroblastic tumors include tumors of fibroblasts. Solitary fibrous tumour, fibromatoses, nodular fasciitis, desmoplastic fibroma, and fibrosarcoma fall under this category.

- **Solitary Fibrous Tumor**

An SFT is made up of blood arteries with a distinctive staghorn shape intermingled among spindle- or ovoid-shaped cells that are randomly arranged within a collagenous stroma. If we may be so bold, the intercellular collagen bands could be considered to resemble Van Gogh lines due to the arrangement of cellular and stromal components in SFT, which is referred to as a "pattern less pattern"(40). Round to ovoid or bland spindle cells with vesicular nuclei and scant cytoplasm are interspersed between tumor cells, showing a patternless pattern with alternating hypo and hypercellular patches histopathologically (13). It reacts with CD99, CD34, bcl-2, and vimentin. In contrast to keratin, EMA, S-100, desmin, SMA, and muscle-specific actin, CD34 is the sole consistently expressed and sensitive marker (14).

- **Fibrosarcoma**

The World Health Organization describes adult fibrosarcoma (FS) as a "malignant neoplasm composed of fibroblasts with variable collagen synthesis and, in classical examples, a

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"herringbone" architecture" (41). Low-grade fibrosarcoma exhibits spindle cells arranged in fascicles with low to moderate cellularity and a herringbone appearance (42). There is a collagenous stroma, infrequent mitosis, and a modest degree of nuclear pleomorphism (42). Vimentin immunostaining is positive, while the following immunomarkers are negative: human osteoblasts (osteocalcin), macrophages (CD-68), leukocyte common antigen, neural tissue (S-100, neuron specific enolase), melanoma (HMB-45), neutrophils (CD-31), hematopoietic cells (CD-34), cytokeratin, EMA, and CD-99. These findings aid in the diagnosis (14).

- **Fibromatosis**

High-differentiated proliferation of fibrous tissue are known as fibromatosis (43). Fibromatosis is showing up as an aggressive kind in the oral cavity. Connective tissue may become affected by these benign fibrous tumors (44). Desmoid tumors or aggressive fibromatosis are rare diseases caused by fibroblasts that do not spread (45). According to histopathology, the lesion is distinguished by cellular proliferation of streaming fascicles of spindle-shaped cells that exhibit moderate anisonucleosis and varying amounts of collagen (43).

- **Oral Nodular Fasciitis**

A separate, benign condition known as oral nodular fasciitis is defined by the development of fibroblasts and myofibroblasts. Histologically, NF is often nonencapsulated, well defined, and composed of fibroblasts with big nuclei, frequent profuse mitosis, and no cellular atypia. A dense reticulin meshwork surrounds the fascicle-like arrangements of fibroblasts, which are frequently grouped in irregular bundles. The presence of a lot of ground material with a loose, feathery texture is one of the most crucial NF diagnostic indicators (46). According to immunohistochemical examination, the spindle cells are positive for antibodies against SMA and muscle specific actin (HHF 35), but negative for desmin and cytokeratin, suggesting that myofibroblasts are the source of the cells (14).

- **Desmoplastic Fibroma**

The unusual fibrous soft tissue tumor known as desmoplastic fibroblastoma is remarkable (47). The Tumor is made up of stellate or spindle-shaped cells that are lodged in a hypovascular fibrous stroma with a focus of fat entrapment (47). The cells don't display tumor necrosis or mitotic figures (47). The tumor cells exhibit immunohistochemical vimentin and alpha-smooth muscle actin positivity (47).

VASCULAR TUMORS

Vascular tumors include tumors of vascular tissue origin. Hemangiopericytoma, Kaposi sarcoma, and spindle cell haemangioma are all included in this category.

- **Hemangiopericytoma**

An extremely uncommon tumor with unknown malignant potential is the hemangiopericytoma/solitary fibrous tumor (48). It is thought that pericytes, or cells whose processes wrap capillary endothelial cells, are the source of the uncommon tumor known as hemangiopericytoma (14). The tumor's histology will show staghorn-like vasculature (13). It possesses localised muscle specific actin (65%), vimentin (100%) and CD34 immunoreactivity (14).

- **Spindle Cell Haemangioma**

This disorder has a unique variety known as a spindle cell haemangioma, which is either a vascular malformation or a benign process superimposed over a malformation (49). SCH appears biphasic under a microscope and has cells without nuclear atypia. There are nests of polygonal epithelioid cells with intracytoplasmic vacuolization, fronds of spindled cells made up of endothelial cells and fibroblasts in variable proportions, and irregular cavernous areas lined by a single layer of endothelial cells (49). Only the epithelioid cells and the cells lining the vascular spaces exhibit endothelial marker staining (CD31 and CD34). Only vimentin and a lower percentage of actin/desmin are stained by the majority of spindle cells. (14).

- **Kaposi Sarcoma**

Angio proliferative tumor known as Kaposi's sarcoma is infrequently detected in the oral cavity (50). The tumor can be seen under a microscope to have spindle cells, poorly defined vascular slits, dispersed hemosiderin, and red blood cell extravasation (50).

EPITHELIAL TUMORS

Epithelial tumors include tumors of epithelial tissue origin. Spindle cell carcinoma, pleomorphic adenoma, and malignant melanoma fall within this category.

- **Spindle Cell Carcinoma**

A squamous cell carcinoma variant known as SpCC has spindled or pleomorphic tumor cells

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Volume 5, Issue 2, Mar - Apr 2023 pp 179-187 www.ijdmsrjournal.com ISSN: 2582-6018

that resemble real sarcomas but are epithelial in origin. SpCC tumors are made up of bothtypical squamous cell carcinoma and a spindle cell or pleomorphic component (2). Keratin (AE1/AE3) and EMA are the most sensitive and reliable epithelial markers to be employed for the demonstration of the epithelial phenotype in spindle cell cancer (14).

- **Pleomorphic Adenoma**

The most frequent salivary gland tumor, pleomorphic adenoma, is also known as benign mixed tumors (BMTs) due to its dual origin from epithelium and myoepithelial parts (51). Myoepithelial and ductal epithelial cell growth will be visible through histology. Furthermore, stromal components have significantly increased. Usually, the tumor is not completely encapsulated (51). The tumor expresses Wilms tumor 1, calponin, p63, S100, CEA, SMA, CK7, CK14, GFAP, SMA, MSA, and SMMHC. Calponin is currently the most reliable indicator of neoplastic myoepithelium.

- **Malignant Melanoma**

0.2–8% of all melanomas are oral malignant melanoma, an uncommon and severe melanocytic tumor (52). The diagnosis of oral malignant melanoma is confirmed microscopically by the presence of atypical melanocytes with varying degrees of nuclear pleomorphism, hyperchromatism, large nucleoli, and copious cytoplasm with brown pigment (52). The tumor cells have positive immunohistochemical staining for the proteins HMB-45, S-100, and vimentin (52).

ODONTOGNEIC TUMORS

Odontogenic tumors include tumors of odontogenic origin. This group contains desmoplastic ameloblastoma, central odontogenic fibroma, ameloblastic fibroma, and ameloblastic fibrosarcoma.

- **Ameloblastic Fibroma**

Ameloblastic fibroma is a rare type of odontogenic tumor made up of malignant mesenchymal and epithelial cells. Either the mandible or the maxilla may be affected(53). Microscopically, an ameloblastic fibroma is made up of a connective tissue background that resembles stellate reticulum and appears to recapitulate dental papilla. Due to the tissue's spindled and angular cells and lack of collagen, it has a myxomatous appearance (54). Antibody KL 1 detects the presence of cytokeratin in all odontogenic epithelial cells. Proliferating indices, such as AgNOR, proliferating cell nuclear antigen, and Ki-67 can be used to suggest the malignant development (14).

- **Central Odontogenic Fibroma**

When enucleated, central odontogenic fibromas appear as solid, rather than cystic, unilocular radiolucencies. They typically appear as a tiny, well-circumscribed radiolucency anterior to the molars(55). According to histopathology, an odontogenic fibroma is a mass of cellular fibrous or fibro myxoid tissue that is not encapsulated and contains a variable amount of odontogenic epithelium. There is no organising into palisading columnar cells, and stellate reticula are uncommon even in epithelium-rich variations (55). Connective tissue cells with a stellate or spindle form exhibit immunoreactivity for vimentin. The epithelial islands are positive for CK, AE1/AE3, CK5, CK14, CK19, and 34BE12 (14).

- **Ameloblastic Fibrosarcoma**

A benign epithelial component within a malignant fibrous stroma characterises the uncommon malignant odontogenic tumor known as ameloblastic fibrosarcoma (56). According to histology, the tumor's mesenchymal part is highly cellular, exhibits hyperchromatism, pleomorphism, and obvious mitoses (56). In contrast to the ameloblastic fibroma's negativity, the sarcomatous mesenchymal component of the tumor is positive for Ki67, PCNA, and p53 (56).

- **Desmoplastic Ameloblastoma**

A rare kind of ameloblastoma is called desmoplastic ameloblastoma (57). The tumor's histology reveals many desmoplasia and distributed epithelial odontogenic nests, as well as a hypercellular centre made up of spindle- or polygon-shaped epithelial cells (57). The tumor cell’s immunohistochemical expression of the S-100 protein and desmin is varied, and the connective tissue stroma will strongly react positively to collagen type VI (57).

MISCELLANEOUS TUMORS

Unclassified category tumours fall under the umbrella of miscellaneous tumours. This group contains blue nevus, giant cell angiofibroma, ossifying fibro myxoid tumour, benign fibrous histiocytoma, and malignant fibrous histiocytoma, synovial sarcoma.

- **Synovial Sarcoma**

Synovial sarcoma is a soft tissue tumor. It demonstrates mesenchymal and epithelial differentiation. Based on the disease's morphology,

immunohistochemical markers, and chromosomal type t(X;18) translocation, the diagnosis should be made. The three forms of synovial tumor histology are described as monophasic, which has a predominance of spindle cells, biphasic, which has both spindle and epithelial cells, and poorly differentiated, which is characterised by necrosis, odd mitoses, high cellularity, nucleolar atypia, and proliferation of small round cells (58). Pathognomic translocation between chromosomes X and 18, or t(X;18), which results in SS18: SSX fusion proteins, is a defining feature of SS. (59). Spindle cells are positive for vimentin in immunohistochemistry, while epithelial and spindle cells are positive for cytokeratin and epithelial membrane antigen (60).

- **Benign Fibrous Histiocytoma**

One of the most prevalent tumors of the superficial and deep soft tissues is the benign fibrous histiocytoma, which is composed of both fibroblastic and histiocytic cells (61). Histologically, the tumor is distinguished by xanthomatous cells, multinucleated giant cells, lymphocytes, and deposits of hemosiderin dispersed throughout the whorled or storiform pattern of homogeneous spindle-shaped cells (61). The tumor cells have positive immunohistochemical staining for vimentin and CD68 and negative staining for S100, factor XIIIa, CD34, and SMA (62).

- **Malignant Fibrous Histiocytoma**

Malignant fibrous histiocytoma is an uncommon head and neck tumor of mesenchymal origin (63). According to the predominating cellular components, the tumor can be classified histopathologically into four morphologic subtypes: storiform or pleomorphic, myxoid, giant cell, and inflammatory (63). Vimentin is detected immunohistochemically in the tumor cells and giant cells.

- Ossifying Fibromyxoid Tumor

The tumor's histopathology is marked by the growth of round to spindle-shaped cells grouped in cords and nests embedded in a fibromyxoid matrix, with an incomplete shell of bone trabeculae at the tumor's periphery beneath the fibrous pseudo capsule (64). Vimentin and S-100 protein will be detected positively by immunohistochemical examination, while smooth muscle actin, muscle-specific actin, and glial fibrillary acidic protein will be detected negatively (64).

- **Giant Cell Angiofibroma**

There have only been three reports of giant cell angiofibroma (GCA), a unique ocular tumor that presents as a painless solitary lump in the buccal mucosa (65). Histopathologically, the tumor is distinguished by a pattern less proliferation of spindle cells within a stroma that is primarily myxoid and has regions of perivascular sclerosis with a large number of multinucleated giant cells (66). tumor cells and multinucleated giant cells will exhibit positive CD34 immunohistochemical results (66).

- **Blue Nevus**

A blue nevus is a benign acquired melanocytic lesion that often manifests as an asymptomatic, smooth-surfaced macule or papule that is smaller than 6 mm in diameter and slate blue or blue-black (67). Blue nevus can be divided into cellular and common subtypes histopathologically. The intramucosal proliferation of elongated, bipolar, spindle-shaped melanocytes, which are frequently organised in short fascicles parallel to the overlaying epithelium, is the primary characteristic of the common blue nevus (67). The cellular blue nevus is characterised by an intramucosal, nodular proliferation of bigger, oval-to-round, pale-cytoplasmed melanocytes with little to no melanin and dendritic spindle-shaped, pigmented dendritic aggregates (67). The spindle-shaped cells of blue nevi will express both S-100 and HMB-45 according to immunohistochemistry (68).

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