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Research Article

TUMORS OF ADIPOCYTES IN ORAL CAVITY

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ABSTRACT

Adipose tissue tumors are uncommon. The most prevalent benign tumors are lipomas. Their presence in the oral cavity is, nevertheless, irregular. The prevalence of the different histopathological variations is even rarer. Amongst malignant variants, the liposarcoma is common but is rarely presented in oral cavity. The WHO 2022 classification has tried to add new entities along with their molecular alterations and immunohistochemical markers. The present review is gives a brief note about the different tumors of adipocytes associated with oral cavity.

INTRODUCTION

Adipose tissue, body fat or simply fat is a loose connective tissue composed mostly of adipocytes. Its main role is to store energy in the form of lipids, although it also cushions and insulates the body. It is a major endocrine organ in human body as it produces hormones. (1) Tumors such as lipomas are very commonly seen amongst other tumors of adipose tissue.Connective tissue containing adipocytes and fat cell compose the adipose tissue in human body. Properties of triglycerides which make the adipose tissue as a preferred form of energy are as follows: fat are insoluble in water and caloric density of triglycerides is twice that of proteins and carbohydrates. Adipocytes specialized in concentrating triglycerides as lipid droplets.

The development of adipose tissue has been linked to embryonic stem cells. These cells following compartmentalization into mesenchymal stem cells gives rise to myogenic factor 5 (Myf5) positive and negative cells. Brown adipocytes and myocytes develop from Myf5 positive cells whereas white and plaucilocular intermediate adipocytes develop from Myf5 negative cells. Various transcription factors play an important role in the development and lineage commitment of different types of cells. (2)

Two functionally different types of adipose tissues are classically described in mammals, which differ in several important properties: BAT (brown adipose tissue) and WAT (white adipose tissue).

Table 1 Important features of WAT and BAT are as follows

White adipose tissue (WAT)	Brown adipose tissue (BAT)
Each cell 50-150 um	2% to 5% of the newborn body weight
Presence of single huge droplet of lipid that fills almost the entire cell	Greatly reduced during childhood and adolescence
Unilocular hence triglycerides are stored in single large droplet	Color of brown fat is brown due to very abundant mitochondria (containing cytochrome pigment) and large number of blood capillaries
During the process of tissue processing there is removal of lipid content by xylene	Adipocytes of brown fat contain many small lipid inclusions hence it is multilocular
It usually has a signet ring appearance	Its main function is thermogenesis

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Classification of tumors of adipocytes WHO classification – February 2013 (3)

I. Benign

1. Lipoma
2. Lipomatosis
3. Lipomatosis of nerve
4. Lipoblastoma/ Lipoblastomata
5. Angiolipoma
6. Myolipoma of soft tissue
7. Chondroidlipoma
8. Extra-renal angiolipoma
9. Extra-adrenal myolipoma
10. Spindle cell/pleomorphic lipoma
11. Hibernoma

II. Intermediate (locally aggressive)

Atypical lipomatous tumors /well –differentiated liposarcoma (ALT/WDLS)

1. Adipocytic
2. Sclerosing
3. Inflammatory

III. Malignant

1. Dedifferentiated liposarcoma
2. Myxoid liposarcoma
3. Pleomorphic liposarcoma
4. Liposarcoma, not otherwise specified

WHO- 2022 (4)

1. Lipoma
2. Angiolipoma
3. Spindle cell/pleomorphic lipoma
4. Atypical spindle cell/pleomorphic lipomatous tumor
5. Atypical lipomatous tumor/well-differentiated liposarcoma
6. Dedifferentiated liposarcoma
7. Myxoid liposarcoma
8. Myxoid pleomorphic liposarcoma
9. Atypical spindle cell lipomatous tumor/atypical pleomorphiclipomatous tumor (ASLT/APLT)
10. Myxoid pleomorphic liposarcoma

The two new entities introduced in the WHO 2022 classification are atypical spindle cell lipomatous tumor/atypical pleomorphic lipomatous tumor (ASLT/APLT) and myxoid pleomorphic liposarcoma.(4)

Benign neoplasms

1. Lipoma

Definition: Benign slow growing neoplasm composed of mature fat cells (Shafer, 7th edition) Hamartomatous proliferation of mature fat cells. (WHO) Lipoma can occur anywhereon the human body thus it is termed as "universal tumor"or "ubiquitous tumor.(5) In 1848 Roux first described oral lipoma as a slow growing, soft doughy and yellow in color hence termed it as yellow epulis.It is also known as universal tumor or ubiquitous tumor.

It is seen 15%- 20 % in head and neck region. But its prevalence rate in oral cavity is about 1%-4 %.(6) Lipoma cells are metabolically different from normal fat cells even though they are histopathologically similar. Fatty acid precursors incorporated at more rapid rate into lipoma fat then into normal fat. In lipoma fat lipoprotein lipase activity is reduced.

Two types of lipomas are

1. Subcutaneous (Superficial) lipomas

Commonly localized in upper back and neck, shoulder and abdomen and not encounted in face, hands, lower legs / feet

2. Deep lipomas are larger in size

It is localized in head especially in forehead and scalp and in trunk especially in thorax, mediastinum, chest wall and pleura.

Classification of intraoral lipoma

Rajendra and Shiva Pathasundharam described three types of lipomas. Depending on their morphology they are divided as follows:

1. Diffuse form affecting deeper tissues
2. Superficial form
3. Encapsulated form

Etiology: (7)

1. Hypertrophic theory – Inadevert growth of adipose tissue and obesity are cause of these lesions. But the limitations of this theory are (a) Theory does not explain lesions occurring in areas devoid of preexisting adipose tissue. (b) Lesions were not used up in usual metabolism during starvation like normal tissue.
2. Metaplasia theory-Lipomatous growth occurs due to aberrant differentiation of in situ mesenchymal cells into lipoblast, since fat cells almost anywhere in the body.
3. J J Lin et al – Congenital lesions arising from multipotent cells of an embryo which is remaining clinically dormant until they differentiate into fat cells under hormonal influence during adulthood.
4. In 1996 Suzuki et al suggested that mitochondrial diabetes caused by t RNA mutation. But following follow up over period of 12 yrs it lead to two important observations
    1. Lower limp paresthesia manifesting even with mild hyperglycemia
    2. Lipoma (round 10mm diameter) – manifesting at age 44 over the left breast

Hence another researcher named Holme et al suggested that mitochondrial DNA mutations may be either a direct or indirect cause of perturbation of maturation process of adipocytes.

5. Other triggering factors include trauma and chronic irritation that leads to proliferation of fatty tissue into benign neoplasm.

Clinical features

- Age – 40- 60 years
- Gender- Males> Females (In head and neck region)
- Site–a) In oral cavity Buccal mucosa (37%) > tongue (24.4 %) > lip (10.5%) > palate (7.4%)

  b) In head and neck region most commonly seen in Parotid gland

  The buccal mucosa has abundant fatty tissue and thus is the most common site of intraoral lesions. (8, 9)
- Progress of the lesion – Slow grossing , round / discoid mass , soft / doughy consistency

- Color – Yellowish coloration (10)

Signs of lipoma

On inspection it is a well contoured margin withround to large lobulated mass having smooth surface with thin epithelium making the superficial blood vessels visible. On palpation it is a fluctuant lesion which is not freely movable, non-tender, soft and cheesy consistency. Slip sign is positive. Palpation of edge of lipoma with a finger makes the finger slip under the swelling. Specimen of lipoma after resection usually floats in formalin due to low density. This is known as floating phenomenon.

Macroscopic features of lipoma

Subcutaneous lipoma is soft, well circumscribed, thinly encapsulated and rounded mass.
The cut surface shows pale yellow to orange with uniform greasy surface and irregular lobular pattern. In cases of lipomas of deeper structures they are usually delineated from surrounding tissues by thin capsule.

Microscopic features of lipoma

It is made up of mature fat cells mimicking normal adipocytes. But they differ in size. Usually the normal adipocytes are 100 um. But the lipoma adipocytes are 200 um.The adipocytes have a round, vacuolated clear cytoplasm with nuclei eccentrically placed. Lobules of fat cells separated by fibrous septa.Soap bubble appearance of vacuoles within cytoplasm and multinucleated cells with nuclei arranged in 'Floret pattern'. (11)

Ultrastructure

Mature adipocytes are centrally positioned with large lipid vacuole and peripherally placed nucleus and cytoplasm. Cytoplasm consists of smooth membrane bound vesicles, mitochondria, rough endoplasmic reticulum, Golgi apparatus. Nuclei showperipheral condensation of chromatin and prominent nucleoli.

Differential diagnosis

Oral lymphoepithelial cysts, epidermoid and oral dermoid cysts. Unlike oral lipomas, lymphoepithelial cysts are found in the floor of the mouth, soft palate and mucosa of the pharyngeal tonsil. Although oral dermoid and epidermoidcysts can occur in other sites of the oral mucosa,they typically occur on the midline of the floor of the mouth. (12)

Cytogenetic related to Lipomas

Cytogenetic studies by Bassett et al. have concluded that intramuscular lipomas unveiled simple translocations or loss ofchromosomal material involving the q14-15 region on chromosome12, paracentric or pericentric inversions of chromosome 12q14-15, aberrations involving 6p21-22, or loss of material from the q12-14 orq22 region of chromosome 13. The rearrangements involving 12q14-15 and 6p21-22 lead to over expression of HMGIC and HMGIY, respectively. (13)
Lipomas are frequently characterized by aberrations of the 12q13-q15chromosomal region and often by rearrangements of the HMGA2 gene. Other studies showed abnormalities involving chromosome region 12q13-15 specifically translocations with 3q27-28, 1p32-34, 21q21-22, 2p21-23, and other non-recurrent rearrangements. Abnormalities not involving 12q13-15 include lipomas with deletion 13q, ring chromosomes, and rearrangements of 6p21-23, 11q13, 1p36, and 13q12-q22. (14)

The recent WHO 2022 article has added a new molecular alteration i.e. HMGA rearrangement the histopathological variants of lipoma are as follows: (15) (Table 2)

Table 2 Histopathological variants of Lipoma

Variants of Lipoma	Distinct features
Fibrolipoma	Most commonly is seen on cheek. It shows female predominance.
	Histopathological features are similar to simple lipoma with broad bands of dense connective tissue are interspersed between fat cells.
	Simple lipoma and fibro lipoma are both usually well circumscribed and thinly encapsulated
Osteolipoma	It has origin directly from multipotent cells, which differentiate into lipoblasts, chondroblasts, osteoblasts or fibroblasts, characterising a ''mesenchymoma'' orarise after repetitive trauma, metabolic changes, or possibly ischaemia that leads to metaplasia of existing elements.
	Cartilaginous or osseous metaplasia in lipoma is characterized by mature, benign cartilage or bone formation within the neoplastic fatty tissue. It is commonly seen in parotid region, the tongue as well as the hard and soft palate.
	On histopathologylipomatous proliferation of mature non-atypical adipocytes with metaplastic ossification foci in the center is seen. Trabeculae of vital lamellated bone scattered among adipocytes.
Chondrolipoma	It is a benign lipoma variant that can simulate liposarcoma and myxoidchondrosarcoma.
	It is usually seen in younger adults. It has a female predeliction.
	Following histopathological analysis chondroid lipomas may be confused with chondrosarcomas due to the scattered nests of lipoblast-like cells and myxochondroid matrix
Infiltrating lipoma	Intramuscular lipoma (when it arises within skeletal muscle) or intermuscular lipoma (when it arises between skeletal muscles).
	It shows the presence of fat

	cells, which are separated by a scant fibrous stroma containing small numbers of blood vessels and by strands and groups of striated muscle fibres. It is usually seen in deeper tissues (tongue muscles)
Angiolipoma	Common and usually appear in the late teens or early twenties. It shows male predominance. Mucolabial fold along with buccal mucosa are the common associated intraoral sites. On histopathological evaluation mature adipocytes and thin-walled capillary-sized vessels, which often contain fibrin thrombi are seen.
	WHO 2022 classification have made a mention about PRKD2 mutation as molecular alterations associated with angiolipoma. (4)
Myxolipoma	Admixed with abundant mucoid substances and it is considered to be a lipoma with a high degree of myxoid change. It is seen between the age group of 30 to 70 years. Tongue, buccal mucosa and lower lipappears to be the most common intraoral sites.
Angiomyxolipoma	Proliferation of adipose tissue associated with a myxoidstroma and multiple vascular channels. On histopathological analysis combination of mature adipocytes and bland spindle cells scattered within a myxoid stromal background containing abundant small to medium-sized vascular channels.
Sialolipoma	Intraglandularlipoma contains atrophic salivary gland acini and dilated ducts. It has been proposed that lipomas growing close to salivary glands can induce marked changes in their acini and ducts.
Intraosseouslipoma	Incidence is very low -0.1% and infrequently seen in the maxillofacial region. 3 stages – based on degree of involution Stage 1 – Lesions with no secondary necrosis Stage 2– Lesions with partial necrosis Stage 3 – Lesions with complete secondary necrosis

2. **Spindle cell lipoma/Pleomorphic lipoma(16, 17)**

Spindle cell lipoma and pleomorphic lipoma represent the two extremes of a morphological continuum. It was first described by Enzinger and Harvey (1975). There are two cell types in these lesions: spindle-shaped mesenchymal cells with features of fibroblast and differentiated fat cells in almost equal proportions.Grows as solitary, painless subcutaneous mass located in the upper back or the posterior aspect of the neck. It shows a male predominance (M: F=10:1). It is commonly seen in fourth and the fifth decade of life.

Microscopic examination

It shows a mixture of spindle cells and mature adipocytes. Spindle cells are uniform with single elongated nucleus with bipolar cytoplasm arranged in short parallel bundles or fascicles resembling "school of fish" appearance. The stroma consists of a fibromyxoid matrix mixed with variable amounts of brightly eosinophilic, ropy collagen fibers.

Pleomorphic lipoma shows presence of scattered, hyperchromatic pleomorphic cells and bizarre giant cells - concentric floret-like arrangement. Myxoidstroma can be prominent resulting in angiectoid spaces with a pseudoangiomatous growth pattern WHO 2022 have made a distinct mention about molecular alterations of 13q14 (RB1 locus) deletion and RB1 as an IHC marker for spindle cell/pleomorphic lipoma. (4) Conditions associated with multiple lipomas: (18) (Table 3)

Table 3 Conditions associated with multiple lipomas

Condition	Prominent features
Bannayan-Zonana syndrome	Rare hamartomatous disorder, characterized by macrocephaly, multiple lipomas and hemangiomas
Cowden syndrome	It is a genetic disorder characterized by multiple noncancerous, tumor-like growths called hamartomas and an increased risk of developing certain cancers
Frohlich syndrome/ Prune- belly syndrome	Rare congenital disorder characterized by triad of deficient abdominal musculature, cryptorchidism and urinary abnormalities
Proteus syndrome	Genetic condition associated with overgrowth of bones, skin and other tissues
Gardner's syndrome	Genetic condition is characterized by numerous adenomatous polyps lining the intestinal mucosal surface with a high potential for malignancy
Pai syndrome	Rare idiopathic developmental condition characterized by midline craniofacial abnormalities
Dercum's syndrome	A rare genetic condition associated with generalized overweight or obesity in combination with painful adipose

	tissue

Investigations for lipoma

Lipoma has a characteristic radiographic appearance. Computed tomography scan it shows a high densityfrom 83 to 143 Hamsfield units with well or poorly defined margins depending on the capsule. (19) Ultrasonography shows a lesion which is round or elliptical in shape with intact or mostly intact capsule . Most lipomas arehypoechoic with ecogenic lines or spots. (20)

Treatment

Lipomas are treated with excision of lesion. It has very low recurrence rate 3%- 62.5%. In the modern world diode lasers can be also used. Its advantages include bloodless surgery, instant disinfection of surgical wound. The wavelength used includes 810nm, 940nm and 980nm Also intralesional steroid injection of triamcinolone acetonide can be used.

Malignant neoplasms

1. **Liposarcoma**

It is a rare, malignant neoplasm of oral cavity composed of wide spectrum of histologic patterns of fat cells. It represents around 20% soft tissue malignancies. It is more commonly seen in extremities such as thighs, retro peritoneum and inguinal region. (21)Liposarcoma first described by Virchow in 1857.

Etiology

Its etiology is usually unknown. But it may be linked to trauma or it may arise de novo.
Most commonly seen deep seated in the connective tissue stroma rather than submucosal or subcutaneous fat. (22)

Clinical features

It compromises about 3% in head and neck region. The peak incidence of all liposarcomas occurs between 40 and 60 years of age, with men more frequently affected than women. (23) The most common intraoral sites include tongue, submandibular area, cheek, floor of mouth and soft palate. It usually presents as a slow growing, painless, non-ulceratedsubmucosal mass.

Macroscopic examination

It is well circumscribed, encapsulated, or both, usually showing a multilobular pattern with occasional satellite nodules. The tumor may appear mucinous, gelatinous, or more fibrous,
soft or firm in consistency. The color is pale yellow. Areas of necrosis or hemorrhage may be present, either superficially or at a depth, and are frequent in deep soft tissue.(22)

Histopathology

WHO 2002 classification- 5 categories

a. Atypical ipomatous tumor/well‑differentiated liposarcoma
    I. (ALT/WDL)
b. Dedifferentiated
c. Myxoid
d. Round cell-term eliminated - high grade of myxoid variant
e. Pleomorphic

The description about each variant is tabulated as follows: (Table 4)

Table 4 Histopathological variants of liposarcoma

Variant	Histopathology
Atypical lipomatoustumor/well−differentiated liposarcoma (ALT/WDL)	Adipocytic, sclerosing and inflammatory types. Presence of variation in adipocyte size, atypical and enlarged adipocyte nuclei with hyperchromatic and bizarre stromal cells in fibrous septa. Lipoblasts -large cells with a hyperchromaticnuclei.Presenceof dense chronic inflammatory infiltrate with lymphoid follicles which can obscure the adipocytic nature of the tumor in the inflammatory type
Dedifferentiated liposarcoma	Combination of well differentiated liposarcoma with poorly differentiated , nonlipogenicsarcomatous changes
Myxoid liposarcoma Low-grade Myxoid liposarcoma	Presence of delicate plexiform representing chicken wire pattern of capillary network associated with primitive mesenchyme like cells (spindle cells) and lipoblasts Stroma is myxoid ground substance with microcyst formation
High grade Myxoid liposarcoma	Characteristic myxoid matrix with plexiform capillary networks are diminished by tightly packed tumor cells Tumor cells with increased nuclear size, frequent mitotic activity, and nuclear overlapping

The prognosis of liposarcoma is influenced by several factors: histopathological variant, location, tumor size, adequacy of surgical treatment and distant metastases.(24)

The cytogenetic feature of ALT/WD and dedifferentiated liposarcoma has been revealed in the form of supernumerary ring or giant marker chromosomes with 12q13-15 amplification.(25)

WHO 2022 have made a distinct mention about molecular alterations of 12q13-15 (MDM2) amplification and MDM2, CDK4 as an IHC marker for atypical lipomatous tumor/well-differentiated liposarcoma and also in case of dedifferentiated liposarcoma(4)

In case of Myxoid liposarcoma WHO 2022 have made a mention about molecular alterations of FUS-DDIT3 (rarely EWSR1-DDIT3) and DDIT3as an IHC marker. (4)

Myxoid pleomorphic liposarcoma is associated with large deletions of RB1 and RB1 is assigned as the IHC marker. (4)

Treatment

Wide local excision followed by radiotherapy. The 5 year survival rate – 59%- 70% and 10 yr survival rate – 50 %.In oral cavity it has a favorable prognosis. The local recurrence is rare and it is about 15-20%. Metastasis is rare but if present it may be there to lungs, bone and brain.

Recently Described Adipocytic Tumors

1. Anisometric Cell Lipoma (Dysplastic Lipoma)

It was first described in literature by Evans in 2015 as subcutaneous minimally atypical lipomatous tumor with various fat cell sizes. It was misdiagnosed as ALT/WDL Later Michal et al described IHC and genetic features and coined the term "dysplastic lipoma'' It shows a male predominance. Most commonly seen in middle aged people. It presents as a subcutaneous mass on the posterior neck, upper back, or shoulders.(26)

Histopathology

Highly variable adipocyte size and shape. One of the important characteristic features includes Lochkern change. Lockhern change is said to be seen classically in normal adipocytes and lipogenic tumors. The cause of these nuclear vacuolization was investigated by many authors and pathologists including Unna, Sack, Winkler, Rable and Plaut. There are two schools of thoughts for the nuclear vacuolization. The first as proposed by Unna, Sack and Winkler who believed that Lochkern change was due to truehole formation in the nucleus. The second school of thought was as proposed by Rable and Plaut that subsequently got confirmed by the ultra‑structural work of Ghadially. They proposed that Lochkern change was due to nuclear invagination by cytoplasm. Both true lipoid inclusions and pseudo‑inclusions could occur within the nucleus.

There are three types as given by Winckler (27)

2. Lochkern cells-nucleus with one or multiple holes
3. Ringkern‑nucleus with a big central hole producing ring‑like appearance
4. Kerbenkern -notched

2. Atypical Spindle Cell/Pleomorphic Lipomatous Tumor

WHO Classification of Tumors of Soft Tissue and Bone of 2013 has classified spindle cell liposarcoma as merely a variant of well-differentiated liposarcoma. Marino-Enriquez et al - "atypical spindle cell/ pleomorphic lipomatous tumor" to describe a large series of atypical low-grade adipocytic neoplasms. It is very rare in head and neck region.(26)

Histopathology

Tumor is composed of scattered adipocytes and mildly atypical spindle cells in a myxoid stroma. Tumor exhibits an infiltrative growth pattern.

WHO 2022 have made a distinct mention about molecular alterations ofdeletions of RB1 and flanking genes and RB1 as an IHC marker for atypical spindle cell/pleomorphic lipomatous tumor. (4)

Lipoblastoma

It is believed not to be a true neoplasm but rather continuation of normal process of fetal fat development carried into postnatal life. It is commonly seen in infants. The most common sites include limbs, trunk, retroperitoneum and lastly head and neck. Diffuse lipoblastoma involving deeper soft tissue is called lipoblastomatosis. Histopathologically only loose myxoid stroma with numerous spindled cells and mature adipocytes are seen. Admix of mature adipocytes and focal lipoblasts in a myxoid stroma is also seen. (28)

Hibernoma

It is a rare neoplasm of adults that account for ~1.6% of benign lipomatous tumors. It usually contains multi- vacuolated fat that analogues to brown fat of hibernating animal. Histopathologically admixture of palely staining uni vacuolated fat cells and multi vacuolated eosinophilic cells with deeply eosinophilic granular cytoplasm. (29)

CONCLUSION

Tumors of adipocytes very rare in oral cavity.Lipoma is the most common in oral cavity rarely recurs one's it has been excised. Liposarcoma rare in oral cavity but if it occurs it is seen on tongue and submandibular gland. Proper histopathological analysis in most of the cases helps to support the clinical diagnosis.

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