Connective tissue lesions

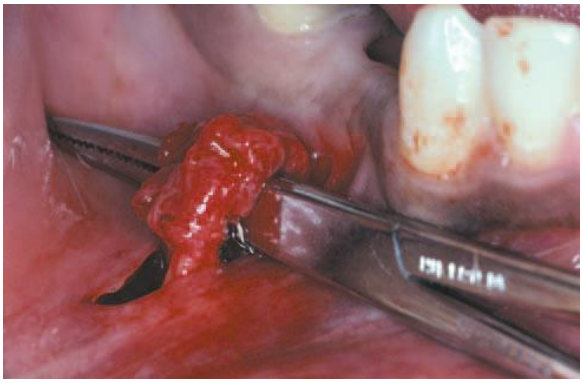
Neural lesions

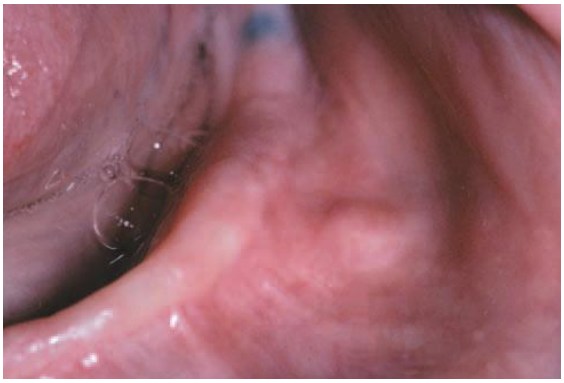
Traumatic neuroma (amputation neuroma)

The traumatic neuroma is not a true neoplasm but a reactive proliferation of neural tissue after transection or other damage of a nerve bundle. After a nerve has been damaged or severed, the proximal portion attempts to regenerate and reestablish innervation of the distal segment by the growth of axons through tubes of proliferating Schwann cells. If these regenerating elements encounter scar tissue or otherwise cannot reestablish innervation, then a tumorlike mass may develop at the site of injury.

Clinical features

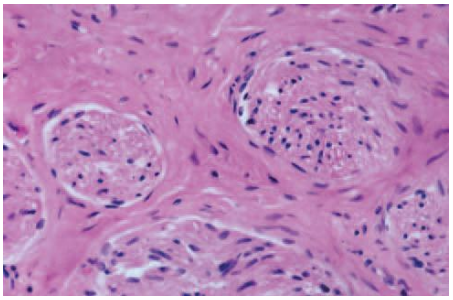
Traumatic neuromas are typically smooth-surfaced, nonulcerated nodules at any location (most common in the mental foramen area, tongue, and lower lip). Some lesions arise subsequent to tooth extraction or other surgical procedures. Intraosseous traumatic neuromas may demonstrate a radiolucent defect on oral radiographs. Traumatic neuromas are diagnosed most often in middle-aged adults. Many traumatic neuromas are associated with altered nerve sensations that can range from anesthesia to dysesthesia to overt pain (This pain can be intermittent or constant and ranges from mild tenderness or burning to severe radiating pain). Neuromas of the mental nerve are frequently painful, especially when impinged on by a denture or palpated.





Histopathological features

Microscopic examination of traumatic neuromas shows a haphazard proliferation of mature, myelinated and unmyelinated nerve bundles within a fibrous connective tissue stroma that ranges from densely collagenized to myxomatous in nature.

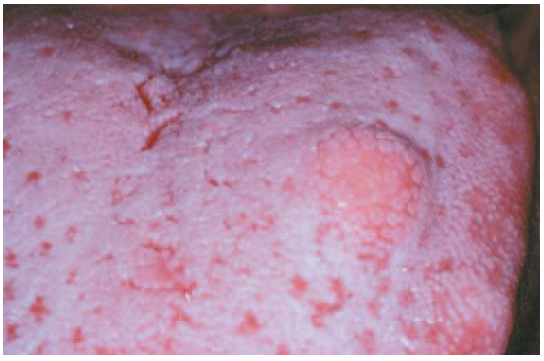


Granular cell tumor

The granular cell tumor is an uncommon benign soft tissue neoplasm that shows a predilection for the oral cavity which may be derived from Schwann cells (granular cell schwannoma) or neuroendocrine cells.

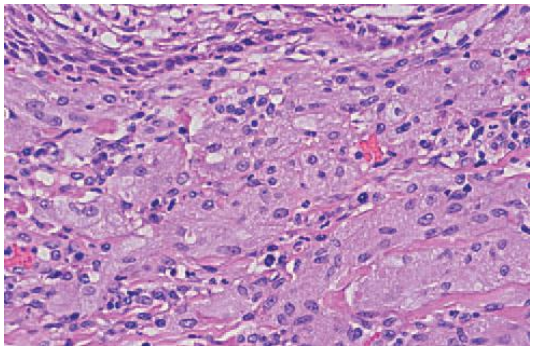
Clinical features

Granular cell tumors are most common in the oral cavity and on the skin. The single most common site is the tongue (on the dorsal surface of the tongue). The buccal mucosa is the second most common intraoral location. The granular cell tumor is typically an asymptomatic sessile pink or yellow nodule that is usually 2 cm or less in size. The granular cell tumor is usually solitary lesion.



Histopathological features

The granular cell tumor is composed of large, polygonal cells (arranged in sheets, cords, or nests) with abundant pale eosinophilic granular cytoplasm and small vesicular nuclei. The cell borders often are indistinct, which results in a syncytial appearance. The lesion is not encapsulated and sometimes appears to infiltrate the adjacent connective tissues. Immunohistochemical analysis reveals positivity for S-100 protein within the cells a finding that is supportive, but not diagnostic, of neural origin. An unusual and significant microscopic finding is the presence of acanthosis or pseudo-epitheliomatous (pseudo-carcinomatous) hyperplasia of the overlying epithelium (results in a mistaken diagnosis of squamous cell carcinoma and subsequent unnecessary cancer surgery).



Treatment

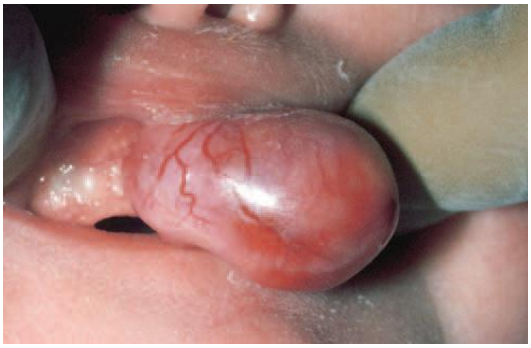
The granular cell tumor is best treated by conservative local excision, and recurrence is uncommon.

Congenital epulis

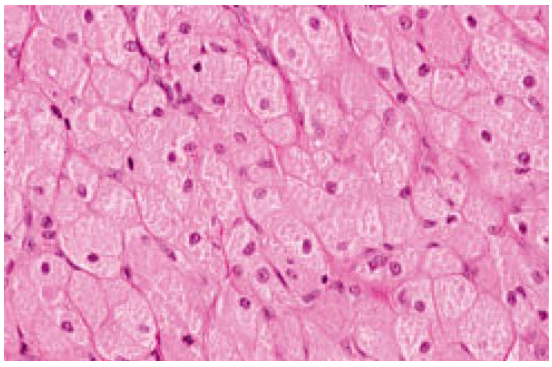
The congenital epulis is an uncommon soft tissue tumor that occurs almost exclusively on the alveolar ridges of newborns (congenital epulis of the newborn)

Clinical features: The congenital epulis typically appears as a pink smooth-surfaced, polypoid mass on the alveolar ridge of a newborn 2 cm or less in size. Multiple tumors develop in 10% of cases. The tumor is two to three times more common on the maxillary

ridge than on the mandibular ridge. It most frequently occurs lateral to the midline in the area of the developing lateral incisor and canine teeth. The congenital epulis shows a striking predilection for females, which suggests a hormonal influence in its development



Histopathological features: The congenital epulis is characterized by large, rounded cells with abundant granular, eosinophilic cytoplasm and round to oval, lightly basophilic nuclei. In older tumors, these cells may become elongated and separated by fibrous connective tissue. In contrast to the granular cell tumor, the overlying epithelium never shows pseudo-epitheliomatous hyperplasia but typically demonstrates atrophy of the rete ridges. In addition, in contradistinction to the granular cell tumor, immunohistochemical analysis shows the tumor cells to be negative for S-100 protein.

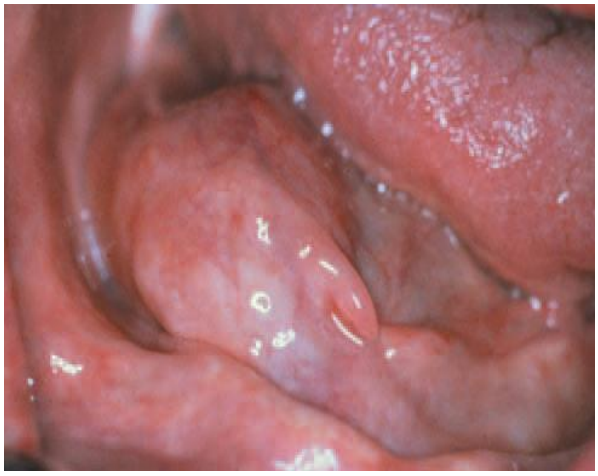


Treatment: The congenital epulis is usually treated by surgical excision. The lesion never has been reported to recur, even with incomplete removal.

Schwannoma (neurilemmoma)

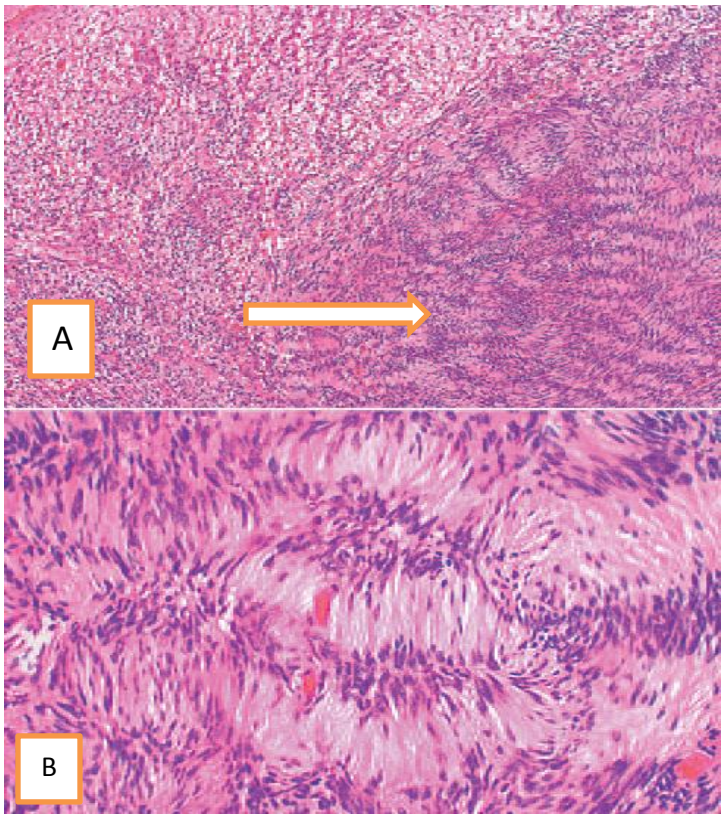
The neurilemoma is un common benign neural neoplasm of Schwann cell origin. Bilateral neurilemomas of the auditory vestibular nerve are a characteristic feature of the hereditary condition, neurofibromatosis type II (NF2).

Clinical features: The solitary neurilemoma is a slow-growing, encapsulated tumor that typically arises in association with a nerve trunk. As it grows, it pushes the nerve aside. Usually, the mass is asymptomatic, although tenderness or pain may occur in some instances. The tongue is the most common location for oral neurilemomas. On occasion, the tumor arises centrally within bone and may produce bony expansion. Intraosseous examples are most common in the posterior mandible and usually appear as either unilocular or multilocular radiolucencies on radiographs. Pain and paresthesia are not unusual for intrabony tumors. NF2 is an autosomal dominant condition caused by a mutation of a tumor suppressor gene on chromosome 22, which codes for a protein known as merlin. In addition to bilateral neurilemomas ("acoustic neuromas") of the vestibular nerve, patients also develop neurilemomas of peripheral nerves, plus meningiomas and ependymomas of the central nervous system (CNS). Characteristic symptoms include progressive sensorineural deafness, dizziness, and tinnitus.



Neurilemoma. Nodular mass in the floor of the mouth

Histopathological features: The neurilemoma is usually an encapsulated tumor that demonstrates two microscopic patterns in varying amounts: (1) Antoni A and (2) Antoni B. Streaming fascicles of spindle-shaped Schwann cells characterize Antoni A tissue. These cells often form a palisaded arrangement around central acellular, eosinophilic areas known as Verocay bodies. These Verocay bodies consist of reduplicated basement membrane and cytoplasmic processes. Antoni B tissue is less cellular and less organized; the spindle cells are randomly arranged within a loose, myxomatous stroma. The tumor cells will show a diffuse, positive immunohistochemical reaction for S-100 protein. Degenerative changes (hemorrhage, hemosiderin deposits, inflammation, fibrosis, and nuclear atypia) can be seen in some older tumors (ancient neurilemomas). However, these tumors are still benign, and the pathologist must be careful not to mistake these alterations for evidence of a sarcoma.



Low-power view showing well-organized Antoni A tissue (arrow) with adjacent myxoid and less organized Antoni B tissue (left). B, The Schwann cells of the Antoni A tissue form a palisaded arrangement around acellular zones known as Verocay bodies.

Treatment: The solitary neurilemoma is treated by surgical excision, and the lesion should not recur. Vestibular schwannomas in patients with NF2 are difficult to manage. Surgical removal is indicated for large symptomatic tumors, but this almost always results in total deafness and risks facial nerve damage

Neurofibroma

The neurofibroma is the most common type of peripheral nerve neoplasm. It arises from a mixture of cell types, including Schwann cells and perineural fibroblasts.

Clinical features

Neurofibromas can arise as solitary tumors or be a component of neurofibromatosis. Solitary tumors are most common in young adults and present as slow-growing, soft, painless lesions that vary in size from small nodules to larger masses. The skin is the most frequent location for neurofibromas. In the oral cavity, the tongue and buccal mucosa are the most common sites. Rarely, the tumor can arise centrally within bone, where it may produce a well-demarcated or poorly defined unilocular or multilocular radiolucency.

Histopathological features:

The solitary neurofibroma often is well circumscribed tumor composed of interlacing bundles of spindle-shaped cells that often exhibit wavy nuclei. These cells are associated with delicate collagen bundles and variable amounts of myxoid matrix. Mast cells tend to be numerous and can be a helpful diagnostic feature. Immunohistochemically, the tumor cells show a scattered, positive reaction for S-100 protein.

Treatment: The treatment for solitary neurofibromas is local surgical excision, and recurrence is rare.

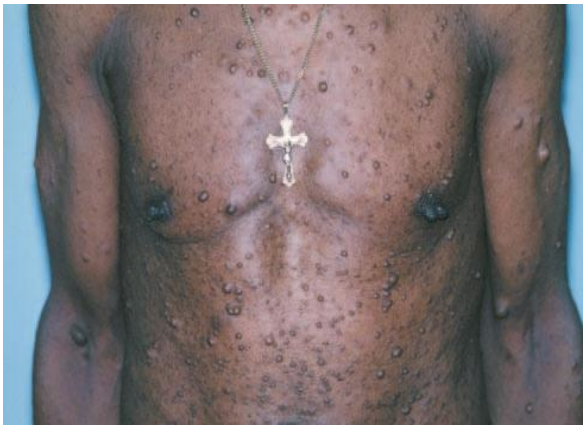
Neurofibromatosis

Neurofibromatosis is a relatively common hereditary condition. At least eight forms of neurofibromatosis have been recognized, but the most common form is neurofibromatosis type I (NF1). This form of the disease, also known as **von Recklinghausen's disease of the skin**, accounts for 85% to 97% of cases and is inherited as an autosomal dominant trait. It is caused by a variety of mutations of the NF1gene, which is located on chromosome 17 and is responsible for a tumor suppressor protein product known as neurofibromin. The diagnostic criteria for NF1 are met if a patient has two or more of the following features:

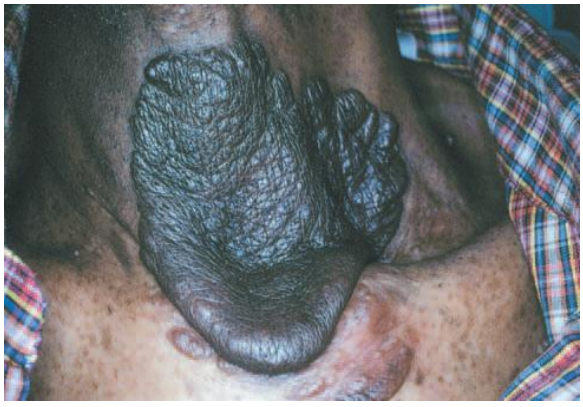
1. Six or more café au lait macules more than 5 mm in greatest diameter in prepubertal persons and more than 15 mm in greatest diameter in post-pubertal persons.
2. Two or more neurofibromas of any type or one plexiform neurofibroma.
3. Freckling in the axillary or inguinal regions.
4. Optic glioma.
5. Two or more Lisch nodules (iris hamartomas)
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis.
7. A first-degree relative (parent, sibling, or offspring) with NF1, based on the previously mentioned criteria.

The clinical appearance of neurofibroma can vary from small papules to larger soft nodules to massive baggy, pendulous masses (elephantiasis neuromatosa) on the skin. The plexiform variant of neurofibroma, which feels like a "bag of worms," is considered pathognomonic for NF1. The neurofibroma may be present at birth, but they often begin to appear during puberty and may continue to develop slowly throughout adulthood. There is a wide variability in the expression of the disease. Some patients have only a few neurofibromas; others have literally hundreds or thousands of tumors. Axillary freckling

(Crowe's sign) is also a highly suggestive sign. Lisch nodules (translucent brown-pigmented spots on the iris) are found in nearly all affected individuals. The most common general medical problem is hypertension. Other possible abnormalities include CNS tumors, macrocephaly, mental deficiency, seizures, short stature, and scoliosis. Several patients with NF1 have been described with associated Noonan syndrome or with central giant cell granulomas of the jaw



Neurofibromatosis type I. Multiple tumors of the trunk and arms.



Neurofibromatosis type I. Baggy, pendulous neurofibroma of the lower neck.

Treatment: There is no specific therapy for NF1, and treatment often is directed toward prevention or management of complications. One of the most feared complications is the development of cancer, most often a **malignant peripheral nerve sheath tumor**

(neurofibrosarcoma; malignant schwannoma), which has been reported to occur in about 5% of cases.

Muscle lesions

Rhabdomyoma

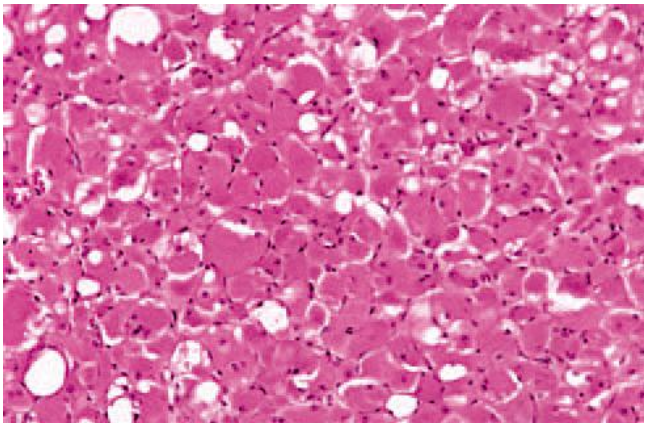
Rhabdomyomas are benign neoplasms of skeletal muscle. The same term is also used to describe a hamartomatous lesion of the heart that often is associated with tuberous sclerosis. Despite the great amount of skeletal muscle throughout the body, benign skeletal muscle tumors are extremely rare. However, these extracardiac rhabdomyomas show a striking predilection for the head and neck. Rhabdomyomas of the head and neck can be subclassified into two major categories: (1) adult rhabdomyomas and (2) fetal rhabdomyomas.

Adult rhabdomyomas of the head and neck occur primarily in middle-aged and older patients. The most frequent sites are the pharynx, oral cavity (floor of the mouth, soft palate and base of tongue), and larynx. The tumor appears as a nodule or mass that can grow to many centimeters before discovery. **Fetal rhabdomyomas** usually occur in young children. The most common locations are the face and periauricular region.

Histopathological features

The adult rhabdomyoma is composed of well-circumscribed lobules of large, polygonal cells, which exhibit abundant granular, eosinophilic cytoplasm. These cells often demonstrate peripheral vacuolization that results in a “spider web” appearance of the cytoplasm. Focal cells with cross striations can be identified in most cases. Although necessary for the diagnosis, immunohistochemical examination will show the tumor cells to be positive for myoglobin, desmin, and muscle-specific actin. The fetal rhabdomyoma has a less mature appearance and consists of a haphazard arrangement of spindle shaped

muscle cells that sometimes are found within a myxoid stroma. Some tumors may show considerable cellularity and mild pleomorphism, which makes them easily mistaken for rhabdomyosarcomas.



Adult rhabdomyoma. Medium-power view showing a uniform tumor composed of rounded and polygonal cells

Treatment: The treatment of both variants of rhabdomyoma consists of local surgical excision. Recurrence is uncommon but has been reported in a few cases.

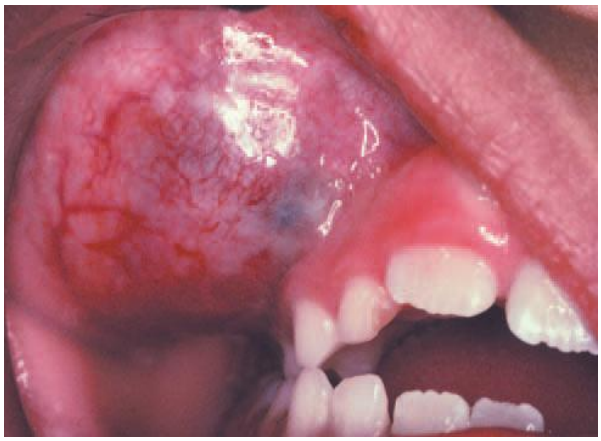
Rhabdomyosarcoma

Rhabdomyosarcoma is a malignant neoplasm that is characterized by skeletal muscle differentiation. These tumors are much more common in young children, accounting for 60% of soft tissue sarcomas in childhood. In contrast, rhabdomyosarcoma comprises only 2% to 5% of soft tissue sarcomas in adults. The most frequent site is the head and neck, which accounts for 35% of all cases.

Clinical features:

Rhabdomyosarcoma primarily occurs during the first decade of life. Several microscopic pattern are recognized for pediatric rhabdomyosarcoma but the most common are embryonal and alveolar subtypes. Embryonal rhabdomyosarcomas are most common in

the first 10 years of life and account for about 60% of all cases. Alveolar rhabdomyosarcomas occur most often in persons between 10 and 25 years of age; they account for 20% to 30% of all tumors. Pleomorphic rhabdomyosarcomas represent less than 5% of all cases and show a peak prevalence in patients older than 40 years of age. Most head and neck lesions are embryonal or alveolar types; pleomorphic rhabdomyosarcomas primarily occur on the extremities. The tumor is most often a painless, infiltrative mass that may grow rapidly. In the head and neck region, the face and orbit are the most frequent locations, followed by the nasal cavity. The palate is the most frequent intraoral site, and some lesions may appear to arise in the maxillary sinus and break through into the oral cavity. Some embryonal rhabdomyosarcomas that arise within a cavity, such as oropharynx, demonstrate an exophytic, polypoid growth pattern that resembles a cluster of grapes. The term botryoid (grapelike) rhabdomyosarcoma has been used for these lesions.



Embryonal rhabdomyosarcoma. Young child with a mass of the right maxilla.

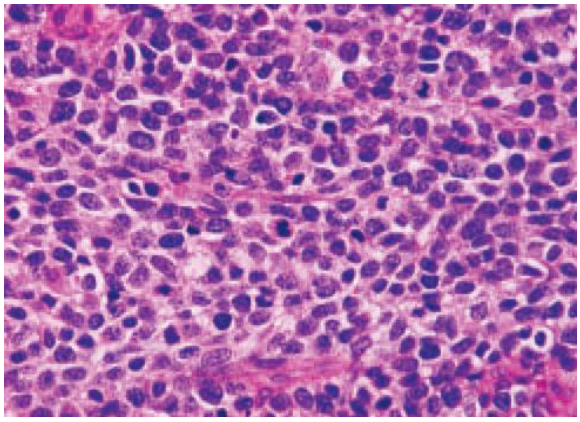
Histopathological features:

Embryonal type: The embryonal rhabdomyosarcoma resembles various stages in the embryogenesis of skeletal muscle. Poorly differentiated examples may be difficult to diagnose and consist of small round or oval cells with hyperchromatic nuclei and indistinct

cytoplasm. Alternating hypercellular and myxoid zones may be seen. Better-differentiated lesions show round to ovoid rhabdomyoblasts with distinctly eosinophilic cytoplasm and fibrillar material around the nucleus. Cross striations are rarely found. Some tumors show better-differentiated, elongated, strap-shaped rhabdomyoblasts. The botryoid subtype of embryonal rhabdomyosarcoma is sparsely cellular and has a pronounced myxoid stroma. Increased cellularity, or a so-called cambium layer, is usually seen just beneath the mucosal surface. Immunohistochemical analysis for the presence of desmin, myogenin, and muscle-specific actin can be helpful in supporting the muscular nature of the tumor.

Alveolar rhabdomyosarcoma:

Both classic and solid variants of alveolar rhabdomyosarcoma are recognized. The classic pattern is characterized by aggregates of poorly differentiated round to oval cells separated by fibrous septa. These cells demonstrate a central loss of cohesiveness, which results in an alveolar pattern. The peripheral cells of these aggregates adhere to the septal walls in a single layer. The central cells appear to float freely within the alveolar spaces. Mitoses are common, and multinucleated giant cells also may be seen. In contrast, solid alveolar rhabdomyosarcoma demonstrates cellular fields of small round basophilic cells without fibro-vascular septa. Cytogenetic and molecular studies play an important role in the diagnosis of rhabdomyosarcoma. Two distinct translocations have been identified in alveolar rhabdomyosarcoma (PAX3-FKHR and PAX7-FKHR).



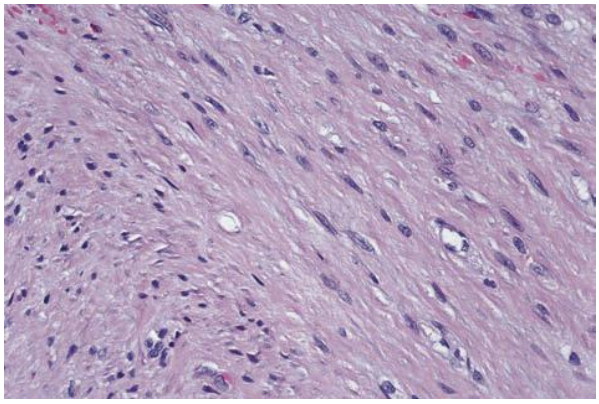
Embryonal rhabdomyosarcoma. Medium power view showing a sheet of small, round cells with hyperchromatic nuclei.

Treatment: Treatment typically consists of local surgical excision followed by multiagent chemotherapy. Postoperative radiation therapy also is used, except for localized tumors that have been completely resected at initial surgery.

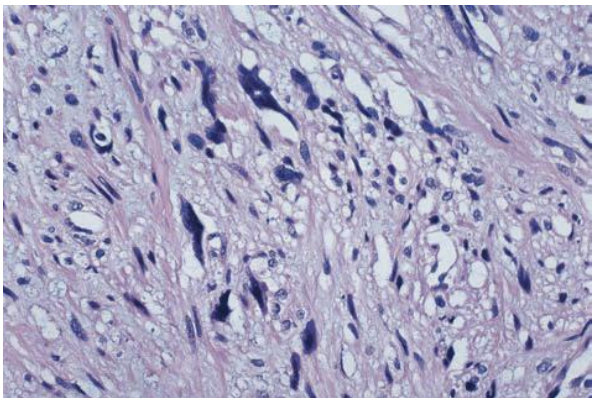
Leiomyoma and leiomyosarcoma

Leiomyoma and leiomyosarcoma are rare in the oral cavity. **Oral leiomyomas** present as slow-growing, asymptomatic submucosal masses, usually in the tongue, hard palate, or buccal mucosa. They may be seen at any age and usually are discovered when they are 1 to 2 cm in diameter. Microscopic diagnosis may occasionally be difficult because the spindle cell proliferation shares many similarities with neurofibroma, schwannoma, fibromatosis, and myofibroma. Special stains that identify collagen may be helpful in distinguishing these lesions. Immunohistochemical demonstration of actins can confirm the diagnosis. A microscopic subtype known as vascular leiomyoma (angioleiomyoma) has numerous thick-walled vessels associated with well-differentiated smooth muscle cells. Leiomyomas are surgically excised, and recurrence is unexpected.

Oral leiomyosarcomas have been reported in all age groups and in most intraoral regions. Microscopic diagnosis is a considerable challenge because of similarities to other spindle cell sarcomas. As with benign neoplasms, immunohistochemistry can be a valuable diagnostic tool to demonstrate the expression of actin proteins. (Actin is a small cytoplasmic filament, approximately 5 nm in diameter that has contractile properties). Leiomyosarcomas are usually treated with wide surgical excision. Metastasis to lymph nodes or lung is not uncommon.



Leiomyoma composed of bland spindle



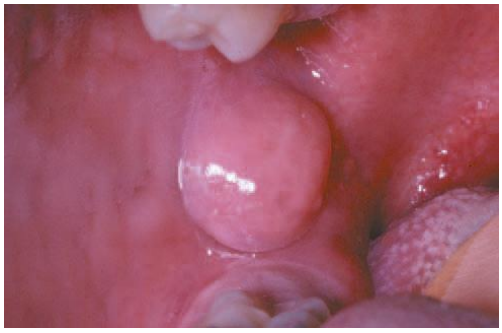
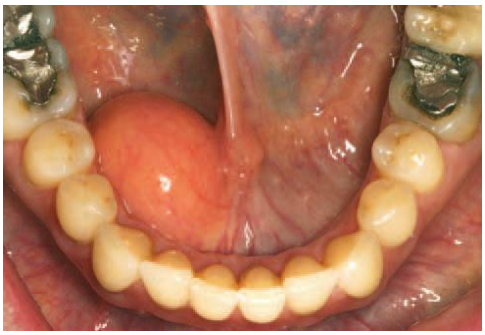
Leiomyosarcoma, high grade composed of spindle cells with atypical nuclei

Fat lesions

Lipoma

The lipoma is a benign tumor of fat. Lipomas of the oral and maxillofacial region are much less frequent than lipomas of extremities and trunk. The metabolism of lipomas is completely independent of the normal body fat. If the caloric intake is reduced, then lipomas do not decrease in size.

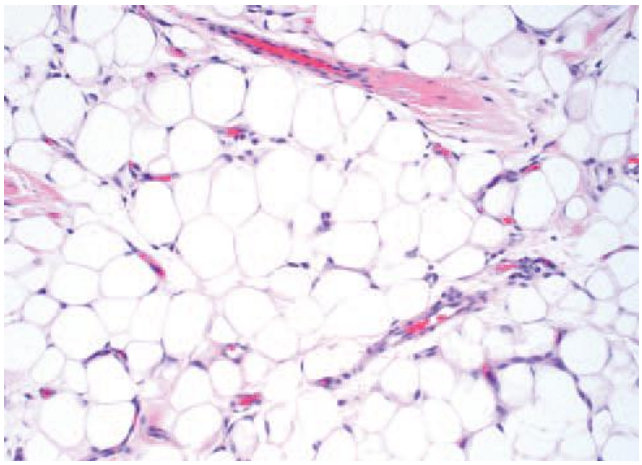
Clinical features: Oral lipomas are usually soft, smooth-surfaced nodular masses that can be sessile or pedunculated. Typically, the tumor is asymptomatic and often has been noted for many months or years before diagnosis. Most are less than 3 cm in size. A yellow hue often is detected clinically, deeper examples may appear pink. The buccal mucosa and buccal vestibule are the most common intraoral sites and account for 50% of all cases. Less common sites include the tongue, floor of the mouth, and lips. Most patients are 40 years of age or older; lipomas are uncommon in children.

Histopathological features:

Most oral lipomas are composed of mature fat cells that differ little in microscopic appearance from the surrounding normal fat. The tumor is usually well circumscribed and may demonstrate a thin fibrous capsule. A distinct lobular arrangement of the cells often is seen. On rare occasions, central cartilaginous or osseous metaplasia may occur within an otherwise typical lipoma. A number of microscopic variants have been described.

1. **Fibrolipoma:** the most common. Characterized by a significant fibrous component intermixed with the lobules of fat cells.
2. **The angiolipoma** consists of an admixture of mature fat and numerous small blood vessels.
3. **The spindle cell lipoma** demonstrates variable amounts of uniform- appearing spindle cells in conjunction with a more typical lipomatous component. Some spindle cell lipomas exhibit a mucoid background (myxoid lipoma) and may be confused with myxoid liposarcomas.
4. **Pleomorphic lipomas** are characterized by the presence of spindle cells plus bizarre, hyperchromatic giant cells; they can be difficult to distinguish from a pleomorphic liposarcoma.
5. **Intramuscular (infiltrating) lipomas** often are more deeply situated and have an infiltrative growth pattern that extends between skeletal muscle bundles.



Treatment: Lipomas are treated by conservative local excision, and recurrence is rare. Most microscopic variants do not affect the prognosis. Intramuscular lipomas have a higher recurrence rate because of their infiltrative growth pattern, but this variant is rare in the oral and maxillofacial region.

Liposarcoma

The liposarcoma is a malignant neoplasm of fatty origin. It is the most common soft tissue sarcoma and accounts for 20% of all soft tissue malignancies in adults. The most common sites are the thigh, retroperitoneum, and inguinal region. Liposarcomas of the head and neck are rare.

Clinical features:

Liposarcomas are primarily seen in adults, with peak prevalence between the ages of 40 and 60. The tumor is typically a soft, slow-growing, ill-defined mass that may appear normal in color or yellow. Pain or tenderness is uncommon; when present, it is usually a late feature. The neck is the most common site for liposarcomas of the head and neck region. The most frequent oral locations are the tongue and cheek.

Histopathological features:

Most liposarcomas can be divided into three major categories:

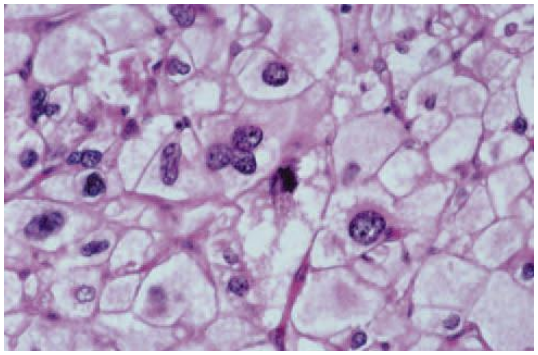
1. **Well-differentiated liposarcoma/atypical lipomatous tumor**
2. **Myxoid/round cell liposarcoma**
3. **Pleomorphic liposarcoma**
4. **Dedifferentiated liposarcoma**

The most common of these variants in the oral cavity is the **well-differentiated liposarcoma**, which accounts for 55% to 90% of all cases. These tumors resemble benign lipomas but demonstrate scattered lipoblasts and atypical hyperchromatic stromal cells

Myxoid liposarcomas demonstrate proliferating lipoblasts within a myxoid stroma that contains a rich capillary network. The round cell liposarcoma is a more aggressive form of myxoid liposarcoma with less differentiated, rounded cells.

Pleomorphic liposarcomas exhibit extreme cellular pleomorphism and bizarre giant cells.

Dedifferentiated liposarcomas are characterized by the combination of well-differentiated liposarcoma with poorly differentiated, non-lipogenic sarcomatous changes. These features may coexist in the same neoplasm, or the dedifferentiated changes may develop in a recurrent tumor or metastatic deposits.



Liposarcoma. High-power view showing vacuolated lipoblasts with pleomorphic nuclei.

Treatment

Radical excision is the treatment of choice for most liposarcomas throughout the body. In spite of this, around 50% of all tumors recur. The overall 5-yearsurvival rate ranges from 59% to 70%. The histopathologic subtype is extremely important in predicting the prognosis; the outlook for pleomorphic liposarcomas is much worse than for myxoid and well-differentiated tumors. In contrast, the prognosis for oral liposarcoma is more favorable because of the predominance of well-differentiated subtypes and because most tumors are small when diagnosed. Local recurrence has been reported in 15% to 20% of cases, but metastasis and death as a result of tumor is rare.