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Objectives

A 33-year-old woman presented with a slow growing palatal gingival mass. The clinical differential diagnosis included benign tumors and tumor-like lesions, including the pyogenic granuloma, peripheral giant cell granuloma, peripheral ossifying fibroma, giant cell fibroma, peripheral odontogenic tumors, and oral focal mucinosis.

Study design

The lesion was excised and histopathological examination followed by immunohistochemical staining was carried out.

Results

The microscopic findings and the immunohistochemical reactivity was diagnostic for a nerve sheath myxoma.

Conclusions

The clinical features, microscopic findings, immunohistochemistry, and the differential diagnosis including the relationship to the neurothekeoma are discussed.

A 33-year-old woman presented with a few months' history of a slowly enlarging mass “behind the upper front teeth on the right side.” There were no symptoms associated with the growth. The woman was in the third trimester of pregnancy and was in good health. Intraoral examination revealed an approximately 2.5 × 1.5-cm, lobulated, pinkish-red mass covered with intact mucosa originating from the gingival tissue palatal to the right maxillary canine and first premolar teeth (Figure 1). On palpation, the nontender mass felt firm and appeared broad bodied but pedunculated at its base. A routine periapical radiograph showed no bone involvement.

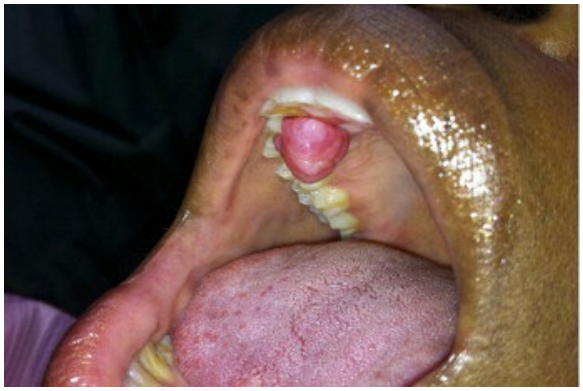

Figure 1. The pinkish-red, lobulated, palatal gingival mass.

Differential Diagnosis

The clinical differential diagnosis of this slow-growing, lobulated, smooth-surfaced mass consisted of a number of benign tumors and tumor-like lesions, including pyogenic granuloma, peripheral giant cell granuloma, peripheral ossifying fibroma, giant cell fibroma, and peripheral odontogenic tumors, including the peripheral odontogenic fibroma and oral focal mucinosis.

The pyogenic granuloma is a common, benign, tumor-like growth frequently localized to the gingiva. This painless, lobulated, soft, pinkish-red, frequently ulcerated growth may be caused by irritants, such as calculus or prosthetic appliance extensions or restoration margins. Other oral sites may be infrequently affected also. The pyogenic granuloma is most commonly encountered in children and young adults and shows a female predilection. Hormonal changes associated with pregnancy lead to an increased incidence of pyogenic granulomas. In this setting, the pyogenic granuloma is often referred to as a pregnancy tumor or granuloma gravidarum.[1, 2] The location, clinical appearance, and the

patient's pregnancy made pyogenic granuloma the most probable among the likely lesions in the differential diagnosis.

The peripheral giant cell granuloma (PGCG) is another intraoral, benign, tumor-like growth. Unlike the pyogenic granuloma that may potentially occur anywhere in the oral cavity, the PGCG is exclusive to the gingiva. The PGCG appears as a dark red to purple nodular mass localized to the attached and marginal gingiva. It is usually asymptomatic, nontender, and soft to touch. Although more common in adults, it may be encountered at any age. PGCGs are more common in females and a slight predilection for the mandibular gingiva is observed.[1, 2]

The peripheral ossifying fibroma (POF) is a tumorlike reactive mass also limited to the gingiva. This asymptomatic, well-circumscribed, pale pink, nodular growth is nontender and firm to hard in consistency. The pale pink color and hardness are attributable to the density of collagen and the variable presence of immature bone within the lesion. The POF is seen more commonly in the second decade of life and is more common in women than in men. Unlike the PGCG, the POF has a slight predilection for the maxillary gingiva.[1, 2]

The giant cell fibroma is a benign neoplasm with characteristic microscopic findings. Clinically, this asymptomatic lesion may appear papillary or dome shaped. It is mostly seen in the first 3 decades of life and about half the cases occur on the gingiva followed by the tongue and the palate. Mandibular gingival involvement is twice as common as maxillary gingival involvement. Presence of numerous large, frequently multinucleated, stellate-shaped fibroblasts in the connective tissue is the diagnostic hallmark of this lesion.[2]

Although peripheral odontogenic tumors are rare when compared with their intraosseous counterparts, a differential diagnosis of a localized gingival mass would be incomplete without their inclusion. Several varieties of these tumors have been reported in the literature, with the most common being the peripheral odontogenic fibroma and the peripheral ameloblastoma. Peripheral odontogenic tumors present as slow-growing, pink to red, sessile or broad-bodied pedunculated, firm, well-defined, asymptomatic nodules of the attached gingiva. This clinical presentation simulates the more common reactive gingival lesions, such as the POF and localized fibrous hyperplasia. An accurate diagnosis of these lesions is solely dependent on microscopic examination of the excised gingival mass.[2, 3]

Oral focal mucinosis is a tumor-like mass that has a predilection for the gingiva. It is twice as common in women and is most often seen in patients during the fourth decade of life.[4] Oral focal mucinosis may present as a sessile or broad-bodied but pedunculated, dome-shaped nodule with a smooth surface. The slow-growing, asymptomatic, pale pink nodule is nontender and firm in consistency. Patients are usually aware of the nodular mass for many months to a year or more.[2, 4]

Radiographically, all gingival soft tissue masses may show no changes or they may exert pressure over the cortical plate to produce a characteristic saucerization or cupping resorption of bone that may register as a unilocular radiolucency on a 2-dimensional film. Peripheral odontogenic tumors will most often exhibit this radiographic appearance with no true central or intraosseous component. Rarely, lesions, such as the POF, peripheral calcifying epithelial odontogenic tumor, peripheral adenomatoid

odontogenic tumor, peripheral calcifying odontogenic cyst, and peripheral odontomas/odontogenic hamartomas may exhibit intralesional calcification on radiographs.[2, 3]

Diagnosis and Management

The palatal gingival mass was excised, placed in 10% neutral buffered formalin, and submitted for histopathological examination. Routinely processed, hematoxylin and eosin stained sections were examined under a microscope. The tissue appeared to be lobulated and covered by variably thick but intact surface epithelium. The bulk of the mass consisted of hypocellular, myxoid nodules of varying shape and size. These myxomatous nodules were separated by dense collagenous septa (Figure 2). The loosely textured nodules consisted of cells with long, eosinophilic, filamentous cytoplasmic processes that streamed almost parallel to each other, producing a linear and somewhat lamellated arrangement (Figure 3, *A*). Stellate cells, with processes that produced a loose reticular pattern, were also seen. These stellate cells were more likely to exhibit multinucleation within a larger cell body (Figure 3, *B*). Some cells also appeared vacuolated, with the nucleus imparting a ringlike shape to the cell (Figure 3, *B*). The nuclei in all cell types were bland. Some myxomatous nodules exhibited clusters of large, multinucleated epithelioid cells (Figure 4). Where the myxoid nodules were not separated by collagenous septa, they were surrounded by highly cellular tissue bearing morphologic resemblance to a neurofibroma or the Antoni type A tissue of a schwannoma but without the nuclear palisading (Figure 5). This neural-type tissue constituted the remainder of the lesion's bulk (Figure 6). Antibody to S-100 protein clearly defined the nodules as they were separated by the collagenous septa (Figure 7, *A*). S-100 decorated the cells in the myxoid nodules as well as those in the adjoining hypercellular areas (Figure 7, *B*). Based on these microscopic findings, a diagnosis of a nerve sheath myxoma was made. This benign, pedunculated mass was excised and no further intervention was necessary.

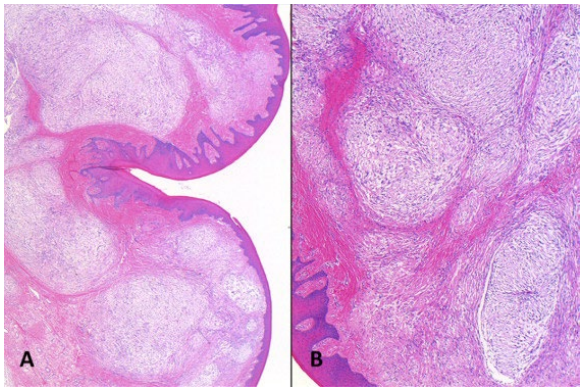

Figure 2. Myxoid nodules are separated by collagenous septa (hematoxylin and eosin stain [H&E]. A, magnification ×20 magnification; B, magnification ×40).

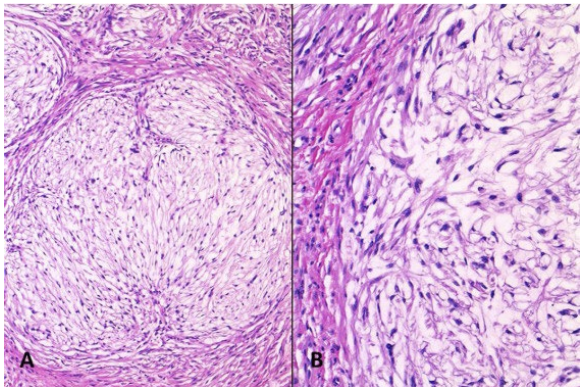

Figure 3. A, Cytoplasmic processes produce a linear and somewhat lamellated arrangement (H&E, magnification ×100). B, Processes of stellate cells produce a loose reticular pattern. Some stellate cells also exhibit multinucleation. Vacuolated cells appear ringlike or lipomatous in the presence of a peripherally placed nucleus in the lower right field of the figure (H&E, magnification ×200).

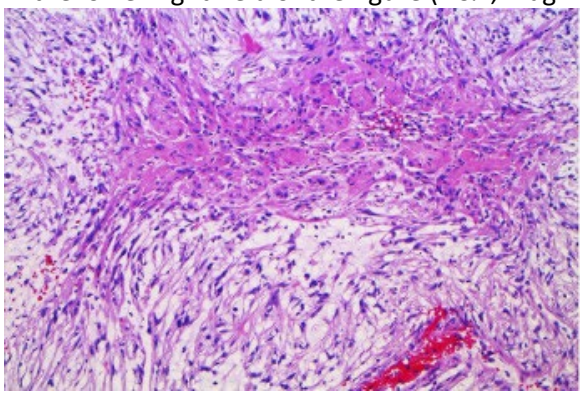
Figure 4. Some myxoid nodules also exhibit large, multinucleated epithelioid cells (H&E, magnification ×200).

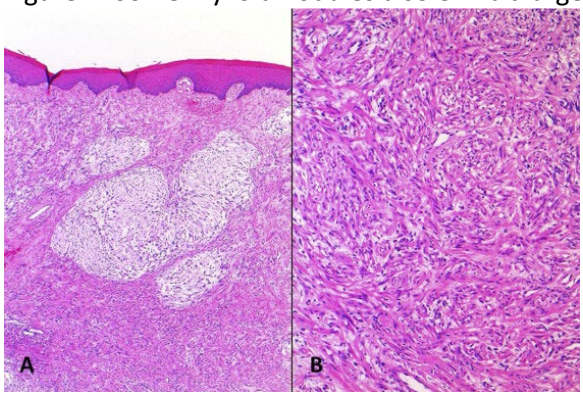

Figure 5. “Neural-type” hypercellular areas in association with the myxoid nodules (H&E. A, magnification ×40; B, magnification ×100).

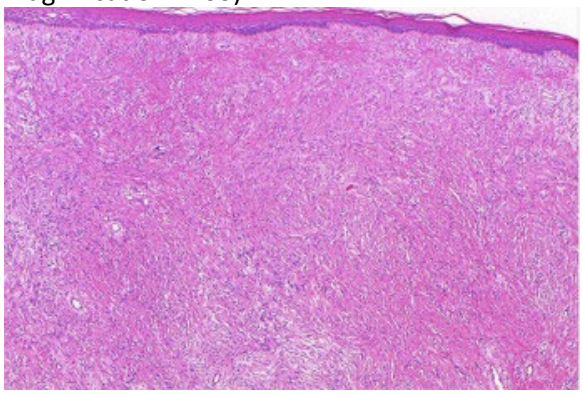
Figure 6. The “neural-type” tissue constitutes the rest of the bulk of the lesion (H&E, magnification ×40).

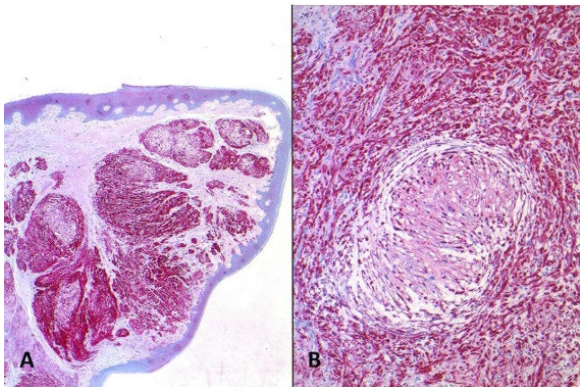

Figure 7. A, S-100 protein reactivity highlights the nodular architecture. B, Cells of the myxoid nodules and of the hypercellular areas are reactive to S-100 protein antibody (streptavidin-biotin with 3-amino-9-ethylcarbazole chromogen, counterstained with hematoxylin. A, magnification ×20; B, magnification ×40).

Discussion

The nerve sheath myxoma (NSM) is a benign tumor of perineural or Schwann cell origin. It arises in relation to small peripheral nerves and is diagnosed most frequently as a dermal proliferation of the lower extremities.[5, 6] It is diagnosed in a wide age range, from newborns[7] to 69 years[6]; however, most cases cluster in the third and fourth decades of life.[5, 6] There is no particular gender predilection, and dermal tumors present as solitary, superficial, slow-growing masses no larger than 2.5 cm.[5, 6] Because of the uncommon nature of this neoplasm, dermal tumors are diagnosed clinically as cysts of various types, lipoma, traumatic neuroma, neurofibroma, dermatofibroma, pyogenic granuloma, or as nevi.[5, 6]

Oral mucosal involvement is rare and tumors have been described on the tongue,[7] buccal mucosa and lip,[8] gingiva,5, 9 vestibule,[9] and palate.[10] The largest oral tumor described has spanned 4 cm in size.[8] The clinical diagnosis of oral tumors has included lesions such as fibrous hyperplasia, fibroma, pyogenic granuloma, peripheral ossifying fibroma, peripheral giant cell lesion, epulis, benign tumor, and pleomorphic adenoma.[7, 8, 9, 10] As can be ascertained from this list, the clinical diagnosis is influenced largely by the oral site of occurrence in each case.

A diagnosis of nerve sheath myxoma is established only on microscopic examination of the biopsied tissue. The nerve sheath myxoma is characterized by an abundance of myxoid matrix that is arranged into nodules of varying size and shape. The myxomatous nodules are separated by septa of dense collagen. The nodules are typically hypocellular,[5, 6] with an abundance of alcian blue–positive ground substance.[7, 10] The cell bodies are mostly small but cytoplasmic filaments extend and impart an overall lamellated or whorled appearance to the nodules. Occasionally, the cells may also be vacuolated and look ring-like in the presence of a nucleus arranged at the periphery along the cytoplasmic membrane. If this appearance predominates, an erroneous impression of a lipomatous neoplasm may be made.[5] This unusual feature was noted in the current case (Figure 3, *B*, lower right field). Occasional cells may appear larger and stellate in outline, and may exhibit multinucleation. In any case, the nuclei are morphologically small, round to oval, and bland.[5, 6]

Occasionally, myxoid nodules may also show corded or nested aggregates of larger epithelioid cells.[5] This feature was easily recognizable in our case (Figure 4). Nuclear palisading, Verocay body–like forms, and cystic change resembling a schwannoma have also been described.[5, 6] Elongated spindled cells

arranged in short irregular fascicles resembling Antoni type A tissue without nuclear palisading have been described in one tumor.[6] We document these areas extensively in our case (Figure 5, Figure 6).

The cells of the nerve sheath myxoma express moderate to strong nuclear and cytoplasmic reactivity to S-100 protein antibodies.[5, 6, 7, 8, 9, 10] This reactivity clearly highlighted the nodular architecture in our case (Figure 7, *A*). Also, S-100 reactivity was intense among the cells in the myxoid nodules and among the elongated spindled cells of the Antoni type A–like tissue (Figure 7, *B*), confirming their perineural/schwann cell origin.

The nerve sheath myxoma also expresses strong and diffuse cytoplasmic and membranous reactivity to nerve growth factor receptor (NGFR)[6, 8] and moderate to variable immunoreactivity to glial fibrillary acidic protein (GFAP),[5, 6] neuron-specific enolase (NSE),[8] and CD57 (Leu-7).[5, 6]

The immunohistochemistry profile of the NSM parallels the schwannoma. As described earlier, in rare instances, the NSM may demonstrate Verocay body–like structures and even S-100–positive hypercellular areas resembling Antoni type A tissue without nuclear palisading, as shown in the current case (Figure 5, Figure 6, Figure 7). Also, cystic changes, hemorrhage, and epithelioid morphology of S-100–positive cells may all resemble an ancient schwannoma. These features are an exception, however, and unlike schwannomas, the NSMs are not encapsulated.

An unencapsulated "neural-looking" tumor requires differentiation from a solitary neurofibroma. Much variation in the degree of myxoid change may be encountered in myxoid neurofibromas but well-defined myxomatous nodules separated by collagenous septa are not the norm. The S-100 protein reactivity in a neurofibroma is selective and many cells in the tumor are nonreactive,[11] whereas the staining in the NSM is uniform and pronounced, as noted in Figure 7.

The histopathological appearance of oral focal mucinosis may bear a superficial resemblance to the NSM but lacks the multinodularity that is characteristic of the NSM. In addition, the sparse population of cells in oral focal mucinosis is nonreactive to S-100 protein.[4]

In 1980, Gallager and Helwig[12] described 53 cases of a tumor supposedly of nerve sheath origin. The tumor cells were described as being large and arranged in nests and cords over a variably mucinous matrix. The cells also exhibited nuclear atypia and a variable degree of mitotic activity. Because the tumors were biologically benign, and in several instances small nerves were identified in the proximity of the tumor cells, the tumors were named neurothekeomas (nerve sheath tumors). These tumors are distinctly unique from the original description of the NSM by Harkin and Reed in 1969.[13] The nomenclature of neurothekeoma has since resulted in much confusion and controversy, and frequently the terms NSM and neurothekeoma have been erroneously used synonymously. See Table I for a comparison of the clinical, microscopic, and immunohistochemical features of NSM and neurothekeoma (cellular neurothekeoma).

Table I. Comparison of the clinical, microscopic, and immunohistochemical features of the NSM with those of the neurothekeoma (cellular neurothekeoma)

Empty Cell	***NSM***	***Neurothekeoma (cellular neurothekeoma)***

Age	Most cases in third and fourth decades of life	First 2 decades of life
Gender	No gender predilection	Female predominance
Site	Skin over lower extremities	Skin over mid face, arms, and shoulder
Tumor periphery	Unencapsulated, fairly well circumscribed	Unencapsulated, poorly circumscribed
Overall architecture	Large, variably sized, hypocellular, myxoid nodules separated by dense collagenous septa	Lobulated, multinodular appearance owing to smaller, somewhat uniformly sized cell nests separated by collagenous septa.
Ground substance	Abundance of alcian blue–positive ground substance	Occasionally, nodules or stroma may be myxoid and resemble an NSM
Tumor cells	Small cell body with elongated cytoplasmic filaments; occasionally larger stellate, epithelioid, vacuolated, or multinucleated cells	Cells may be epithelioid or spindled with relatively abundant eosinophilic and granular to slightly foamy cytoplasm
Tumor cell nuclei	Nuclei are small, round to oval, and bland	Oval nuclei and prominent nucleoli; cells may exhibit atypia and mitotic activity
Tumor cell arrangement	Cells and cytoplasmic filaments may show a lamellated or whorled appearance	Cells packed in whorls.
Histopathological variation	Occasionally Verocay body–like tissue and Antoni type A–like tissue without the nuclear palisading	Occasionally sheet-like or plexiform arrangement of cells
Immunohistochemistry profile	S-100+, NGFR+, S-100A6(calcyclin)+, variable reactivity to GFAP, NSE, and CD57 (Leu-7)	S-100–, S-100A6(calcyclin)+
Purported cell of origin	Perineural/schwann cell origin	Closer resemblance to fibrous histiocytoma

NSM, nerve sheath myxoma; NGFR, nerve growth factor receptor; GFAP, glial fibrillary acidic protein; NSE, neuron specific enolase.

To provide some semblance of differentiation between the 2 types of tumors, neurothekeomas are now referred to as cellular neurothekeomas.[9, 14, 15, 16, 17, 18] In the 2 largest reported series of cellular neurothekeomas, consisting of 133 cases[15] and 178 cases,[19] there was a female predominance, tumors were diagnosed in young adults, and the face and upper extremities were most frequently affected.

The cellular neurothekeoma is nonencapsulated and exhibits a lobulated or multinodular appearance. Unlike the NSM, in which the lesional nodules are large and variably sized, the nodules in the cellular neurothekeoma are small to medium and are somewhat matched in size with each other, resembling cell nests separated by bands of collagen. The individual cells may be epithelioid or spindled with relatively abundant, eosinophilic, somewhat granular cytoplasm. Often the cells are packed in whorls.

Some degree of atypia and mitotic activity is also noted in these tumors.[15, 19] In a variable proportion of cases, the nodules or the supporting stroma may exhibit a myxoid background mimicking an NSM; such tumors have been referred to as mixed-type or intermediate neurothekeomas.[6, 19]

Several studies in characterizing the immunohistochemical profile of the cellular neurothekeoma concluded that the lesional cells are nonreactive to S-100 protein[6, 14, 15, 16, 19]; however, both the NSM and the cellular neurothekeoma are reactive to S-100A6 protein (calcyclin). Therefore, in the context of nested spindled or epithelioid cells, the reactivity of lesional cells to S-100A6 protein in the absence of labeling with S-100 protein provides a useful panel to differentiate the cellular and mixed/intermediate neurothekeoma from the NSM.[16, 17, 18] The NSM and the cellular neurothekeoma appear to be distinctly unique neoplasms based on the differences in their demographic, clinical, and immunohistochemical profiles. The differences in these 2 tumors have been further highlighted recently using microarray-based gene expression profiling of these entities. The study demonstrated that the NSM shows a molecular genetic structure similar to the schwannoma, whereas the cellular/mixed/intermediate neurothekeoma bears a closer resemblance to the fibrous histiocytoma.[20]

Ease of access and small tumor size of the NSM permits an excisional biopsy in most cases. The prognosis is excellent. Recurrence is attributed to incomplete removal of tumor.[5]

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