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Ectomesenchymal Chondromyxoid Tumor of the Anterior Tongue

Nineteen Cases of a New Clinicopathologic Entity

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We present 19 cases of a previously undescribed myxoid tumor of the anterior tongue. These lesions occurred in nine women and 10 men aged 9 to 78 years (median, 32 years). Most tumors were seen as slow growing, painless nodules in the anterior dorsal tongue. The duration of growth ranged from a few months to 10 years. All tumors were treated by surgical excision, and two recurred. Microscopically, they exhibited a lobular proliferation of ovoid and fusiform cells, which often had multilobated nuclei and occasional foci of atypia, in a chondromyxoid background. Some tumors entrapped muscle or nerve fibers and had a tendency for blunt infiltration of adjacent tissue. The cells were diffusely and intensely immunoreactive for glial fibrillary acidic protein (GFAP) and cytokeratin but were decorated less frequently with antibodies for smooth muscle actin and S-100 protein. Reactivity for epithelial membrane antigen and desmin was not found. We believe these tumors fail to meet established clinicopathologic criteria for any existing myxoid neoplasms of the tongue, including nerve sheath myxoma, myoepithelioma, benign mixed tumor, ossifying fibromyxoid tumor of soft parts, extraskeletal myxoid chondrosarcoma, and glial and chondroid choristomas or heterotopias. Although the histogenesis of this neoplasm is unclear, we suspect that a cell of undifferentiated ectomesenchyme is the progenitor and suggest the descriptive term *ectomesenchymal chondromyxoid tumor* (ECT) of the anterior tongue be adopted.

Key Words: Myxoid—Chondroid—Ectomesenchymal—Neural—Myoepithelial—Tongue.

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Soft-tissue chondro myxoid lesions of the oral cavity are a heterogeneous group of uncommon but well-documented entities whose clinical, light microscopic, ultrastructural, and immunohistochemical features have been reported (21,38,43). Oral focal mucinosis, myxoma, nerve sheath myxoma, ossifying fibromyxoid tumor, chondroid choristoma, benign mixed tumor, and myoepithelioma are among the differential diagnoses. Other mesenchymal lesions that may have a prominent myxoid component, such as neurofibroma and various sarcomas, may be included as well. Occasionally, we have reviewed unusual chondromyxoid tumors of the tongue that failed to meet the established clinicopathologic criteria of previously described entities. We report 19 such tumors. They exhibit a lobular proliferation of ovoid and fusiform cells, which often have multilobated nuclei and occasional foci of atypia, in a chondromyxoid background. The cells are diffusely and intensely immunoreactive for glial fibrillary acidic protein (GFAP) and are generally immunoreactive for cytokeratins. Staining is variable for smooth muscle actin (SMA) and S-100 protein but is negative for desmin and epithelial membrane antigen (EMA). We suggest the descriptive name *ectomesenchymal chondromyxoid tumor* (*ECT*) of the anterior tongue be adopted for these rare lesions until their histogenesis is more fully clarified.

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The opinions and assertions expressed herein are those of the authors and are not to be construed as official or representing the views of the Department of the Army, the Department of Veterans Affairs, or the Department of Defense.

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MATERIALS AND METHODS

All chondroid, myxoid, and myoepithelial lesions of the tongue listed in the Registry of Oral Pathology (ROP) at the Armed Forces Institute of Pathology (AFIP) from 1970 to 1994 were reviewed. These cases were submitted for consultation by both government and nongovernment medical facilities. Nineteen cases that shared similar but unusual histologic features were identified for further study. The submitting pathologists had offered a variety of diagnoses that included benign mixed tumor, neural nevus, hemangiopericytoma, mucocele, hemangioendothelioma, neurogenic sarcoma, and other less specific designations of mesenchymal lesions. All cases had sufficient hematoxylin and eosin (H&E)-stained slides for histologic evaluation. Additional sections were prepared in selected cases for alcian blue at pH 0.4 and 2.5, aldehyde fuchsin at pH 1.0 and 1.7, Safranin O, mucicarmine, and Masson's trichrome staining methods. Immunohistochemistry for GFAP, cytokeratins (AE1/AE3 and CK1 monoclonal antibody cocktail), S-100 protein, SMA, CD-57 (Leu-7), EMA, and desmin was performed on all cases in which appropriate material was available (Table 1). One case with formalin-fixed, paraffin-embedded tissue was selected for electron microscopic study. The block was deparaffinized in xylene, hydrated with graded alcohols, postfixed in 1% osmium tetroxide, dehydrated in graded alcohols, cleared in propylene oxide, and embedded in ethyl-epoxy (Ernest Fullam Laboratory). Thin sections were stained with uranyl acetate and lead citrate and were examined with a transmission electron microscope (Zeiss 109). Follow-up information was obtained from the patients' records, attending physicians, patients, or patients' family members.

RESULTS

Clinical Features

Table 2 summarizes the clinical features of the individual patients. Patients' ages ranged from 9 to 78 years with mean and median ages of 39 and 32 years, respectively. There was no sex predilection, as the lesions occurred in nine female and 10 male patients. In the 12 cases in which race had been recorded, nine patients were white and three were black.

All lesions occurred in the anterior dorsum of the tongue. Most patients described the lesions as slow-growing nodules without significant pain or discomfort. The tumors ranged in clinical size from 0.3 to 2.0 cm. Duration of the lesions varied considerably. Some patients stated that a lump arose in their tongue within a few months, whereas others recalled its presence for 8 to 10 years. Follow-up information was available for 11 patients, and the interval ranged from 2 months to 19 years (mean, 57 months). One patient (case 4) experienced a recurrence 3 months after the initial excision. In another case (case 1), the tumor was excised from the same site that the patient reported as the site of an excision 20 years previously. Both of these patients subsequently had a third excision, but no residual or recurrent tumor was found in either. A dorsal-through-ventral surgical procedure was performed in at least one patient (case 4 recurrence), and both dorsal and ventral mucosa were visible on the tissue sections. A third patient (case 14) was treated with a sclerosing agent for a "hemangioma" of the anterior dorsal tongue 10 years before the excision. The diagnosis of hemangioma had been based solely on the clinical impression.

Pathologic Features

Gross

Most specimens were elliptical or wedge-shaped portions of tongue that varied from 0.5 to 3.0 cm in greatest dimension. The tumors were most often described as submucosal, pale grey to tan to yellow, small, rubbery nodules. On cut surface, they frequently had a gelatinous consistency and occasional foci of hemorrhage. Most specimens were bisected along their long axes and submitted in toto.

TABLE 1. *Antibodies used for immunohistochemical studies*

Antibodies	Clone	Dilution	Source
Glial fibrillary acidic protein[a]	Rabbit poly	1:500	Dako, Carpinteria, CA, U.S.A.
Glial fibrillary acidic protein (mono)	Mouse mono	1:100	Dako
Cytokeratin cocktail[a]			
(AE1/AE3)	Mouse mono	1:200	Boehringer Mannheim, Indianapolis, IN, U.S.A.
(CK1)	Mouse mono	1:50	Dako
S-100 protein	Rabbit poly	1:800	Dako
Smooth-muscle actin	Mouse mono	1:4000	Sigma, St. Louis, MO, U.S.A.
CD-57 (Leu-7)	Mouse mono	1:40	Becton Dickinson, Mountain View, CA, U.S.A.
Epithelial membrane antigen[a]	Mouse mono	1:200	Dako
Desmin[a]	Mouse mono	1:40	Accurate, Westbury, NY, U.S.A.

[a] Predigestion of tissue with Protease type VIII (Sigma) for 3 min before incubation with primary antibody.

TABLE 2. *Clinical features of ectomesenchymal chondromyxoid tumor of the tongue*

No.	Age[a]/race/sex	Symptoms/duration	Contributor diagnosis	Follow-up
1.	47/W/F	Soft cystic swelling of left dorsal anterior 2/3 of tongue extending to midline, slow growing for past 10 years, tumor of same location and unknown diagnosis removed 20 years ago.	Not given	Rebiopsy of same site 6 mos after second surgery resulted in a diagnosis of benign reactive process
2.	47/F	Lesion of dorsal tongue	Neurogenic sarcoma	Lost to follow-up
3.	49/F	2-cm firm cystic painless mass of dorsal right anterior 1/3 tongue, unchanging for over 5 years, gradual enlargement in recent months	Rhabdomyoma vs. mesenchymoma vs. atypical salivary tumor	No recurrence at 19 years
4.	48/M	Unchanging anterior dorsal tongue mass for 4 to 5 years, 2 cm from tip, left of midline, rapid enlargement over 1 month	Cellular hemangioma vs. mixed tumor	Recurred 3 mos later, wide excision, neuroma and scar excised 9 mos after second surgery
5.	78/W/M	Slowly enlarging, painless, nonulcerated lesion of left lateral border of tongue for 3 years (1.0 × 1.5 cm at presentation)	Pleomorphic adenoma	Died without disease 4 yrs, 2 mos later
6.	24/B/M	Small, firm, raised lesion right dorsal tongue at junction of mid/anterior 1/3, painless, duration unknown	Benign mixed tumor	Lost to follow-up
7.	30/W/M	0.5-cm nodule middorsum of tongue for 2 mos	Neural nevus	Lost to follow-up
8.	23/W/F	0.7 × 0.6 × 0.4 raised firm lesion of the anterior dorsal tongue, painless for unknown duration	Not given	Lost to follow-up
9.	9/M	0.8 × 0.6 × 0.4 cm cyst-like mass of anterior dorsal midline tongue for 7 months	Spindle cell neoplasm	No evidence of disease at 3 yrs, 6 mos
10.	31/M	2.0-cm submucosal firm cyst of anterior tongue for 8 years with intermittent drainage	Mesenchymal neoplasm of uncertain histogenesis	Lost to follow-up
11.	25/b/F	Anterior tongue lesion, "popped out" on excision	Hemangiopericytoma	Lost to follow-up
12.	57/F	0.3-cm nodular lesion dorsolateral tongue	Mucocele	Free of disease at 4 yrs, 3 mos
13.	36/W/F	Painless 1.5 × 1.5 cm nodule of anterior 1/3 dorsal tongue for 2 mos	Epithelioid hemangioendothelioma vs. unusual salivary tumor	Lost to follow-up
14.	60/M	Firm 1.0 × 0.6 × 0.5 cm swelling right anterior tongue	Neural nevus	Recurred at 19 mos
15.	32/B/M	1.0-cm mass of midline dorsal tongue for many years	Benign fibromyxoid lesion with neural differentiation	Free of disease at 14 mos
16.	27/W/F	0.7-cm "bump" of anterior dorsal tongue for 1 mo	Chondromyxoid process	Free of disease at 8 mos
17.	24/W/F	2.0-cm enlarging lump of right dorsal tongue for 5 mos	Epithelioid leiomyoma	Free of disease at 16 yrs, 2 mos
18.	53/W/M	Small nodule on right middorsal tongue, incisional biopsy followed by excision 1 mo later	Cellular neoplasm vs. adenocystic carcinoma	Lost to follow-up
19.	32/W/M	Small nodule on anterior ("tip") dorsal tongue, present for years	Mixed tumor vs. glomus tumor vs. chondroid metaplasia	Free of disease at 2 mos

M, male; F, female; B, black; W, white.
[a] Age is in years.

Light Microscopy

The tumors were generally well-circumscribed, lobulated nodules within the superficial musculature of the tongue (Fig. 1). The lobules were separated by fibrous septa. Connective tissue and neurovascular structures were usually compressed along the lesion's periphery and created the impression of encapsulation in some cases. Although most tumors were well demarcated, it was not unusual to find muscle fibers and an occasional nerve branch entrapped within the tumor (Fig. 2). Large tumors, case 1 in particular, had lobular extensions into muscle and fat.

The tumors were composed of round, cup-shaped, fusiform, or polygonal cells with uniform small nuclei and moderate amounts of faintly basophilic cytoplasm. The cells were arranged in cords, strands, and net-like sheets in a myxoid background with frequent chondroid and hyalinized foci (Figs. 3 and 4). Some tumors had focal cytologic atypia with nuclear pleomorphism, hyperchromatism, and multinucleation (Figs. 5 and 6). The atypical areas were generally more cellular and confined within one area or lobule. Mitotic figures were scarce, and atypical mitoses were not seen. A single, small, inconspicuous nucleolus was observed in about half of the nuclei. The cell borders were indistinct except in areas of cartilaginous differentiation, where they were well delineated and resembled lacunae (Fig. 7). Some cells had peculiar cup-shaped nuclei associated with small amounts of eosinophilic fibrillary material along their concave surfaces. Nuclear pseudoinclusions or binucleated cells were common (Fig. 8). The mucinous stroma varied from densely basophilic and vacuolated to loosely myxoid and clear. Multiple or single clefts or pseudocystic spaces were found in 11 tumors (58%) (Fig. 9). Rounded aggregates of tumor cells were frequently seen within these spaces, suggestive of a papillary growth pattern.

Small capillaries were scattered throughout the tumors. Some vascular channels were quite dilated, and abundant extravasated red cells were noted focally. Hemosiderin was found in close association with smaller vessels within and around the tumors. Inflammatory cell infiltrates were minimal and usually consisted of small patches of lymphocytes at the tumor–muscle interface.

The tumors extended superiorly into the lamina propria and caused flattening of the overlying epithelial rete ridges (Fig. 1a). In most cases, the tumors were separated from the epithelium by a band of vascularized fibrous connective tissue (Fig. 1b). However, in cases 7, 14, and 18, the tumors abutted on the basal layer of epithelium, and focal ulceration was present. In case 17, focal mucosal ulceration was noted in the absence of direct tumor involvement. Minor salivary glands were not observed in any tissue specimen except case 1, and in that case, the tissue section that contained salivary glands did not contain tumor.

Histochemistry

Aldehyde fuchsin stains of the tumor at both pH 1.0 and 1.7 were positive, indicating the presence of highly acidic sulfated mucosubstances, probably chondroitin sulfates. Similar results were obtained with alcian blue stains at pH 0.4 and 2.5. The positive stains for acidic mucosubstances were resistant to bovine testicular hyaluronidase digestion and most intense in the chondroid areas. Masson's

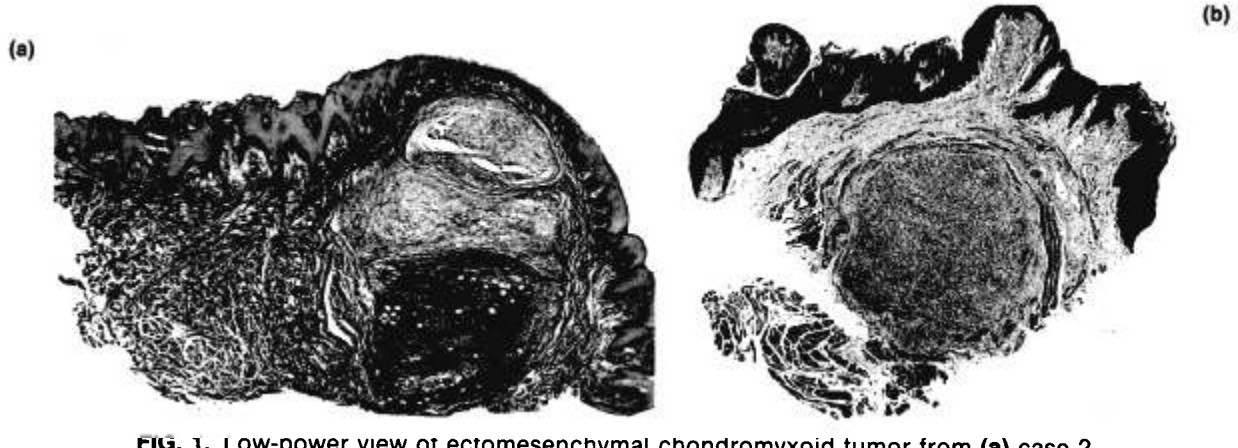

FIG. 1. Low-power view of ectomesenchymal chondromyxoid tumor from **(a)** case 2 and **(b)** case 16, showing a generally circumscribed, lobular, submucosal tumor nodule, distinct from the overlying epithelium, yet frequently causing compression of rete ridges.

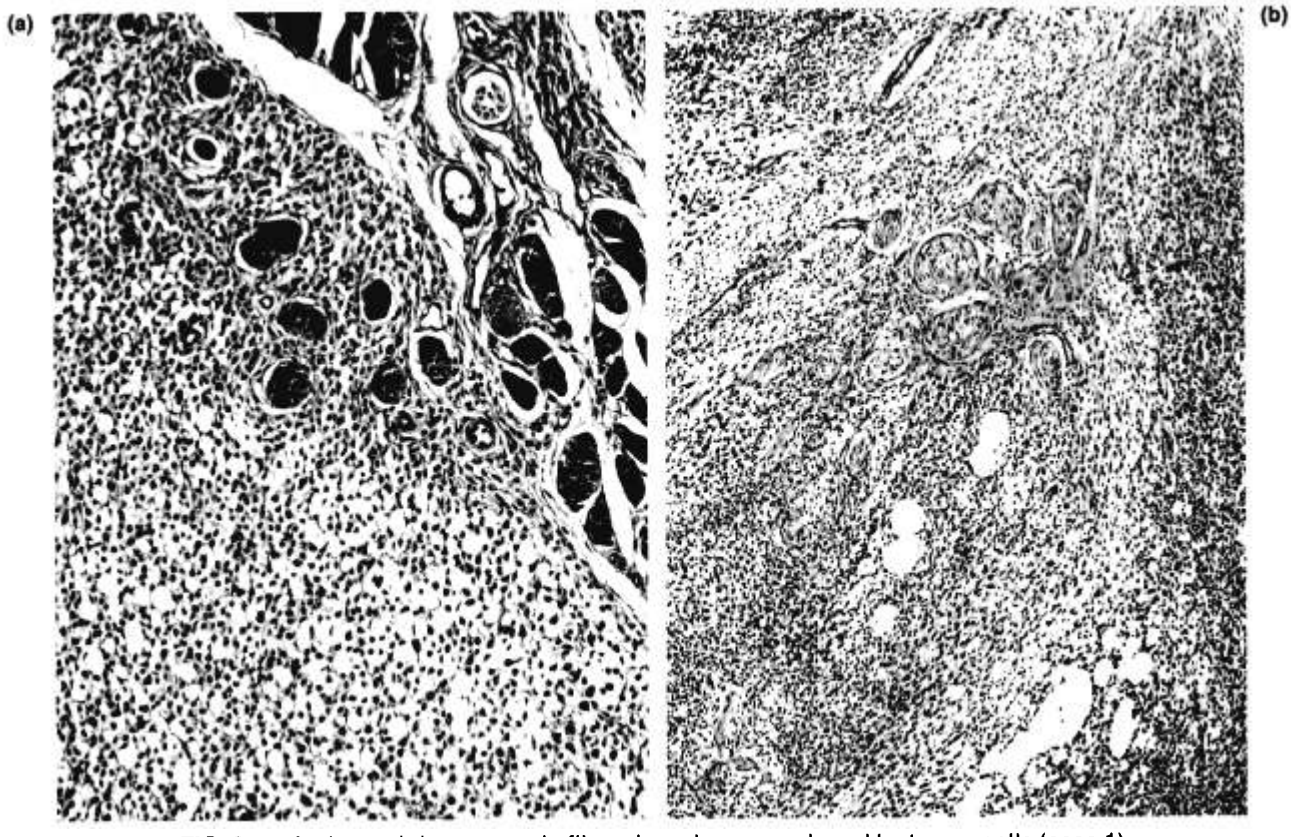

FIG. 2. a: At the periphery, muscle fibers have been enveloped by tumor cells (case 1). **b:** Nerve branches were occasionally found within the tumor (case 2).

trichrome highlighted compressed collagen at the periphery of the tumors and demonstrated a mild to moderate degree of focal collagen production within the tumors. The hyalinized areas and fibrous septa were reactive with the trichrome stain. One very cellular lesion without chondroid features (case 17) did not show any staining of collagen. The mucicarmine stain was faintly positive in the extracellular matrix and served to accentuate the chondroid areas. Tumor cells failed to stain with the periodic acid–Schiff (PAS) technique.

Immunohistochemistry

Table 3 summarizes the immunohistochemical staining results in 16 cases. Tissue blocks or unstained slides were unavailable in cases 3 and 4. Limited material was available on cases 1 and 10, and a modified battery of immunostains was performed for these cases. A monoclonal antibody for GFAP was used when material was not suitable for tissue digestion, as required for polyclonal GFAP antibodies. Reactivity with polyclonal anti-GFAP was intense in 13 of 13 (100%) tumors examined and varied from focal to widespread. The monoclonal GFAP antibody reacted in 8 of 11 (73%) tumors. The anti-cytokeratin monoclonal antibody cocktail was reactive in 12 of 13 (92%) tumors but was slightly less intense than that seen with polyclonal anti-GFAP (Fig. 10). At least focal reactivity for S-100 protein was observed in 9 of 15 (60%) tumors, and variable staining for CD57 was seen in 8 of 9 (89%) tumors. Both S-100 protein and CD57 were detected in small peripheral nerves around the tumor and demonstrated a nerve bundle within the tumor of case 2. Smooth muscle actin was found in scattered tumor cells in 7 of 13 (54%) tumors and was strongly reactive in the walls of blood vessels. None of the three tumors studied for desmin or the five tumors tested for EMA was reactive.

Ultrastructure

The tissue we examined with transmission electron microscopy displayed fixation artifact that varied from moderate to extensive. Most fields, however, showed bilobated and concave nuclei with a homogeneous chromatin distribution (Fig. 11). Nucleoli were small and one to two in number. A partial basal lamina was noted around some cells. Features of myoepithelial cells such as desmosomes and condensations of thin filaments were not seen.

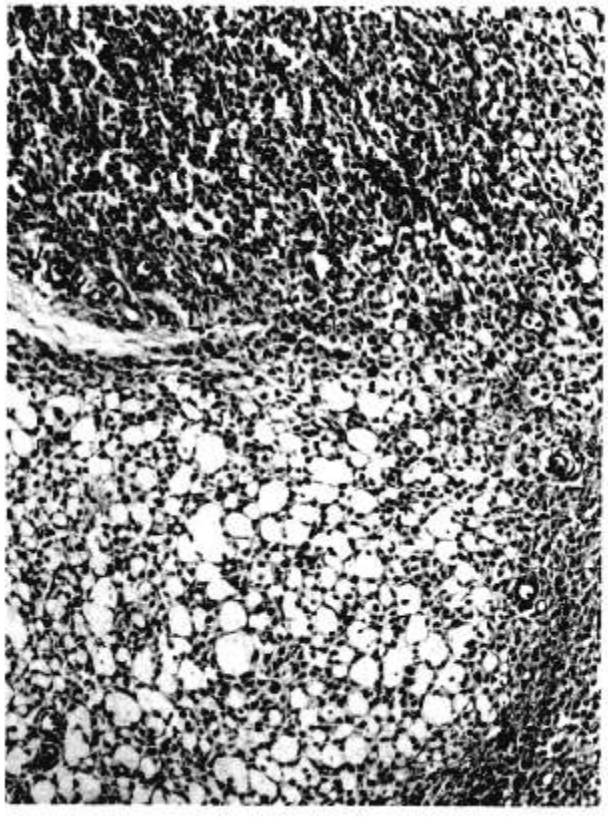

FIG. 3. Below a "net-like" pattern is seen that was common to most tumors. Focal nuclear pleomorphism and hyperchromaticity is seen above (case 1).

DISCUSSION

ECT is a unique chondromyxoid proliferation occurring in the anterior tongue. Its immunohistochemical profile suggests both neural and epithelial cell features. Its differential diagnosis is broad. In an effort to exclude myxoid variants of other lesions of the head and neck, we reviewed all chondroid, myxoid, and myoepithelial proliferations of the tongue that were accessioned to the ROP at the AFIP between 1970 and 1994.

Reactive myxoid lesions have been previously reported in the tongue and include oral focal mucinosis (5,43) and mucocele (37). The oral mucous escape reaction (MER) or mucocele is a granulation tissue–lined pseudocyst that results from spillage of salivary mucin into connective tissue from a traumatically severed minor salivary gland excretory duct. In the tongue, it arises from the glands of Blandin–Nuhn on the ventral surface (37). This ventral location contrasts with ECT, which consistently occurred on the anterior dorsal surface of the tongue, a region that is normally devoid of salivary gland ducts. Oral focal mucinosis (OFM) is the oral counterpart of cutaneous focal mucinosis. At least two cases of OFM have been reported in the tongue (5,43). It is characterized by an accumulation of hyaluronic acid in the connective tissue that results in wide separation of stellate fibroblasts and capillaries. Focal mucinosis does not have the lobular architecture, histochemical, or immunohistochemical profile of ECT.

Intraoral soft-tissue myxomas are rare, and their existence has been debated (5,41,43). The soft-tissue myxoma is a neoplasm composed of fibroblast-like cells in an abundant myxoid, hypocellular matrix. It is reported to stain only for vimentin, in contrast to ECT. Moreover, myxoma does not demonstrate chondroid features (stainable mucins after treatment with hyaluronidase) (16), whereas ECT does.

The ossifying fibromyxoid tumor of soft parts (OFT) was first described in 1989 (17). Our search of the literature failed to reveal reports of OFT specifically arising in the tongue, but the lesion has been documented in other areas of the head and neck (47). This tumor is characterized by a lobular proliferation of small round cells arranged in a trabecular or nest-like pattern. The nuclei are generally cytologically bland and uniform with inconspicuous nucleoli and may be surrounded by lacuna-like spaces (14,32). Most tumors in the original report (80%) exhibited an incomplete shell of bone in the surrounding capsule. Immunohistochemical studies of OFT showed reactivity for S-100 protein in approximately two thirds of the original 59 cases, but the intensity was less than that normally seen in schwannomas (17). Studies for GFAP, Leu-7, and muscle markers have met with conflicting results, but the overall immunohistochemical and electron microscopic results favor a Schwann cell origin (13, 17,31,39,47). Weak reactivity to low-molecular-weight cytokeratins was found in scattered tumor cells of only one case (39). Other lesions of uncertain histogenesis have been reported that show some overlapping features of OFT. However, in the face of consistent cytokeratin immunoreactivity and total absence of bone formation, it seems unreasonable that ECT should be categorized as a variant of OFT (14,32,36).

We considered that ECT may represent one of several rare extraskeletal chondroid tumors. Extraskeletal myxoid chondrosarcoma (EMC) is extremely rare in the head and neck but has been reported in the base of the skull, maxillary sinus, chin, temporal bone, epiglottis, and arytenoid cartilage (4,8,24,28,34,46). Some cases originally reported as chordoid sarcoma are now thought to represent EMC that may express epithelial antigens (45). Extraskeletal myxoid chondrosarcoma has generally been reactive for S-100 protein and vimentin (16). A recent study of 120 EMCs by one of us (J.M.M.)

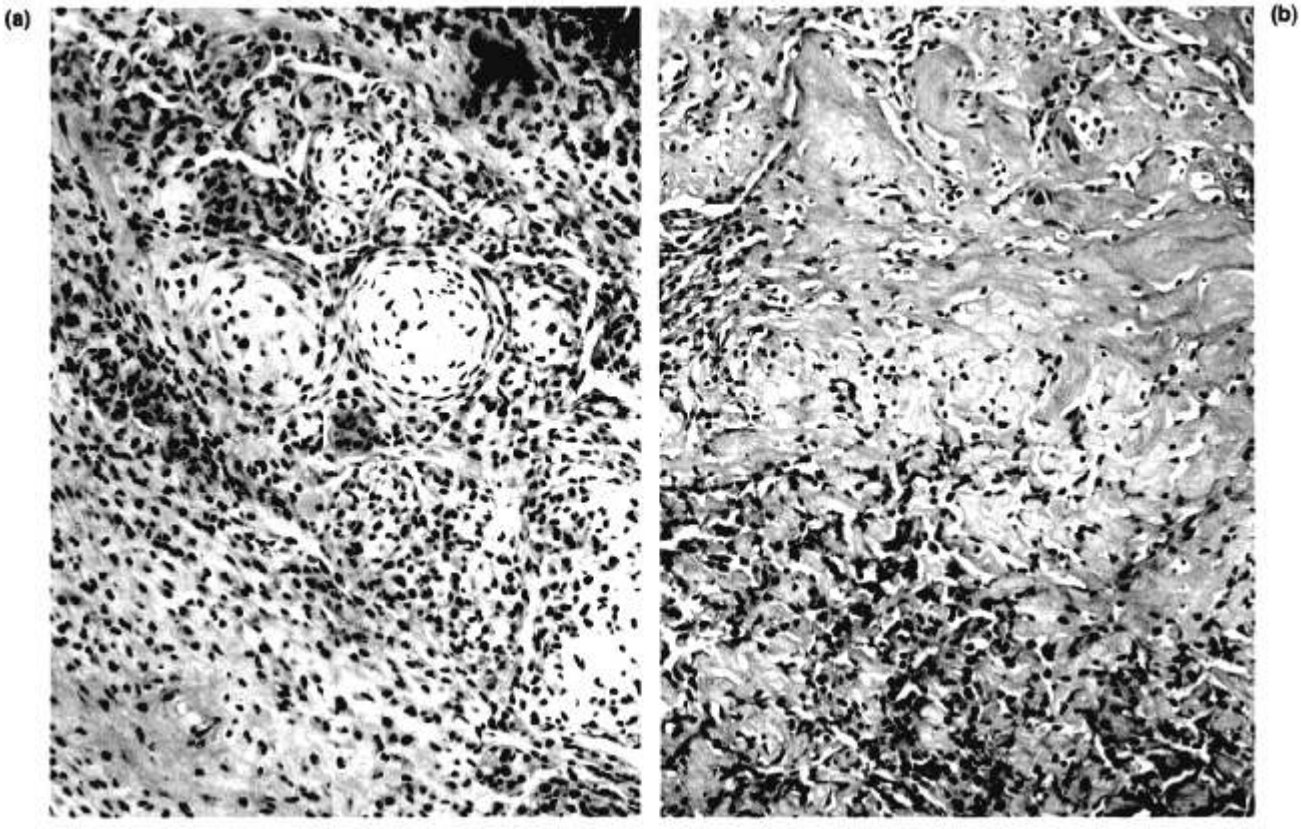

FIG. 4. a: Swirling formations suggested neural differentiation, whereas perinuclear clearing similar to an early chondrocyte lacuna may be seen in the lower left corner (case 5). **b:** Some areas of the tumor showed stromal hyalinization instead of the more common myxoid background (case 5).

found reactivity for S-100 in 27% of 26 cases, EMA in 26%, and keratin in only 9% (30). We distinguish ECT from EMC on the basis of immunoreactivity for cytokeratins and GFAP, lack of PAS staining, and clinical features. A review of the files in the department of oral pathology at the AFIP revealed only one case of lingual EMC. This lesion occurred in the right base of tongue of a 67-year-old woman.

Heterotopic glial tissue or glial choristomas rarely occur in the oral cavity (9). Thirteen cases have been reported, and two were seen as submucosal masses in the anterior third of the tongue (26,27). Glial choristomas are encapsulated aggregates of mature central nervous tissue in a variable amount of connective tissue. Astrocytes, ependymal cells, oligodendrocytes, and ganglion cells have all been identified in these lesions (9). These microscopic findings are not compatible with ECT.

It is known that chondroid choristomas of the oral cavity have a propensity for the tongue (extraskeletal chondromas) (9). These lesions are composed of well-differentiated hyaline cartilage that may be surrounded by perichondrium-like connective tissue. The maturity of the cartilage and lack of cellular atypia and multinucleate cells separate this choristoma from ECT. The presence of well-differentiated lamellar bone within the osseous choristoma of the tongue likewise precludes it from serious consideration in the differential diagnosis (9).

Nerve sheath myxoma (NSM) was originally described in 1969 as a cutaneous lesion that was characterized by a lobular proliferation of myxomatous tissue separated by fibrous septa (23). The degree of cellularity varied, but spindled or stellate cells formed syncytia or net-like patterns (2). Neurothekeoma was subsequently reported in 1980 and shared histologic features with the nerve sheath myxoma (19). Most investigators now accept these two lesions as synonymous (15,29). To date, nine cases of intraoral NSM or neurothekeoma have been well documented, and three of these have occurred in the tongue (33,43,48,49). Unlike that in ECT, alcian blue staining is hyaluronidase sensitive in neurothekeoma (2). A consistent immunohistochemical profile for neurothekeoma has not been established, but reactivity for S-100 protein and GFAP are frequent findings, whereas immunoreactivity for cytokeratins is not (3,21,38). For purposes of compar-

FIG. 5. A focus of pleomorphic spindled cells was observed in case 2, but mitoses were not evident.

FIG. 6. An area of case 1 shows cells with perinuclear clearing and scattered enlarged, hyperchromatic nuclei.

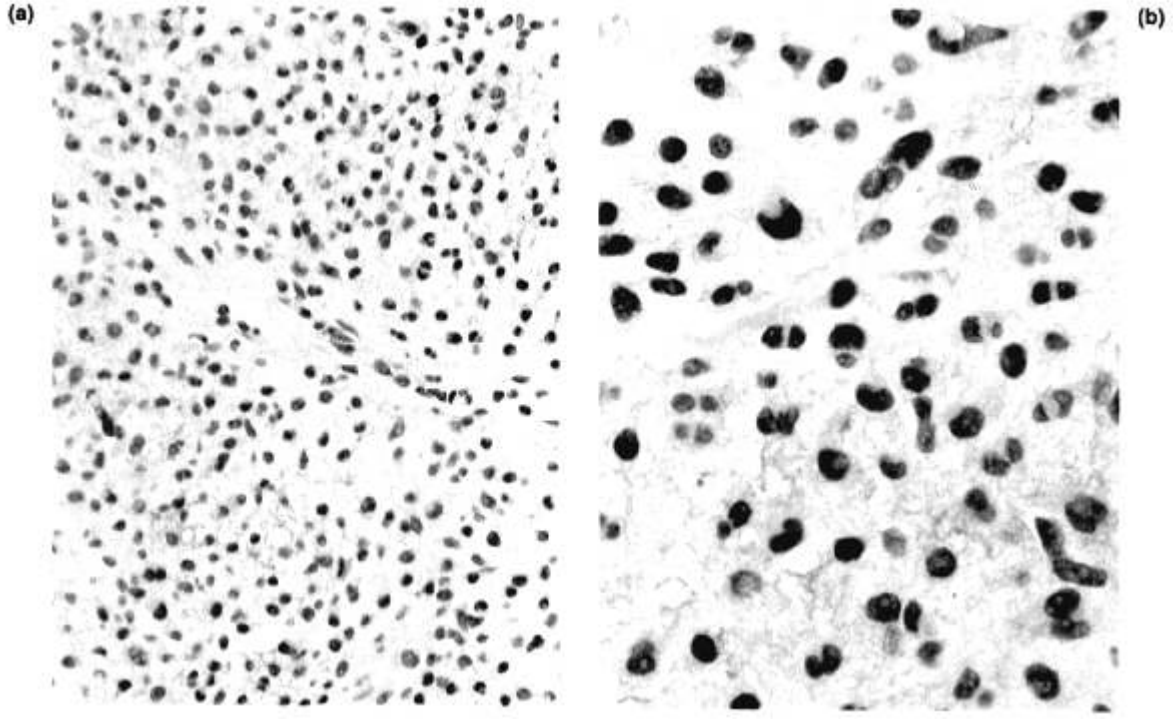

FIG. 7. a: A chondroid area from case 8 with early lacuna formation. **b:** Higher power of same area showing cells with bland cytomorphology and nuclear pseudoinclusions.

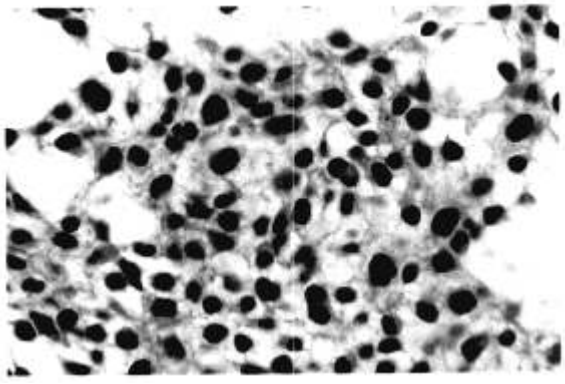

FIG. 8. An area in case 2 showing binucleated cells and cells with indented kidney-shaped nuclei (case 2).

ison, we studied a case of neurothekeoma that occurred in the tongue of a 46-year-old white man. In contrast to that in ECT, this lingual neurothekeoma demonstrated intense reactivity for S-100 and was negative for Leu-7, cytokeratins, SMA, and GFAP.

Finally, we considered that ECT may represent a variant of pleomorphic adenoma or myoepithelioma arising from minor salivary glands. Only 2% of all benign tumors of minor salivary glands are reported in the tongue (20). Salivary glands are absent in the anterior one third of the tongue, with the exception of the glands of Blandin–Nuhn, which are near the tip and exit to the ventral surface. The glands of von Ebner are in the posterior one third of the tongue,

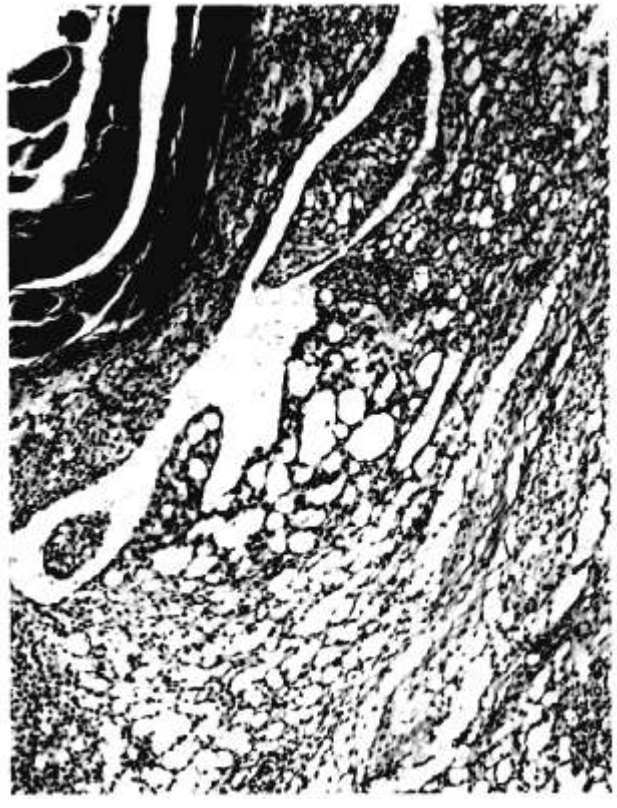

FIG. 9. The tumor from case 6 shows intratumoral clefting.

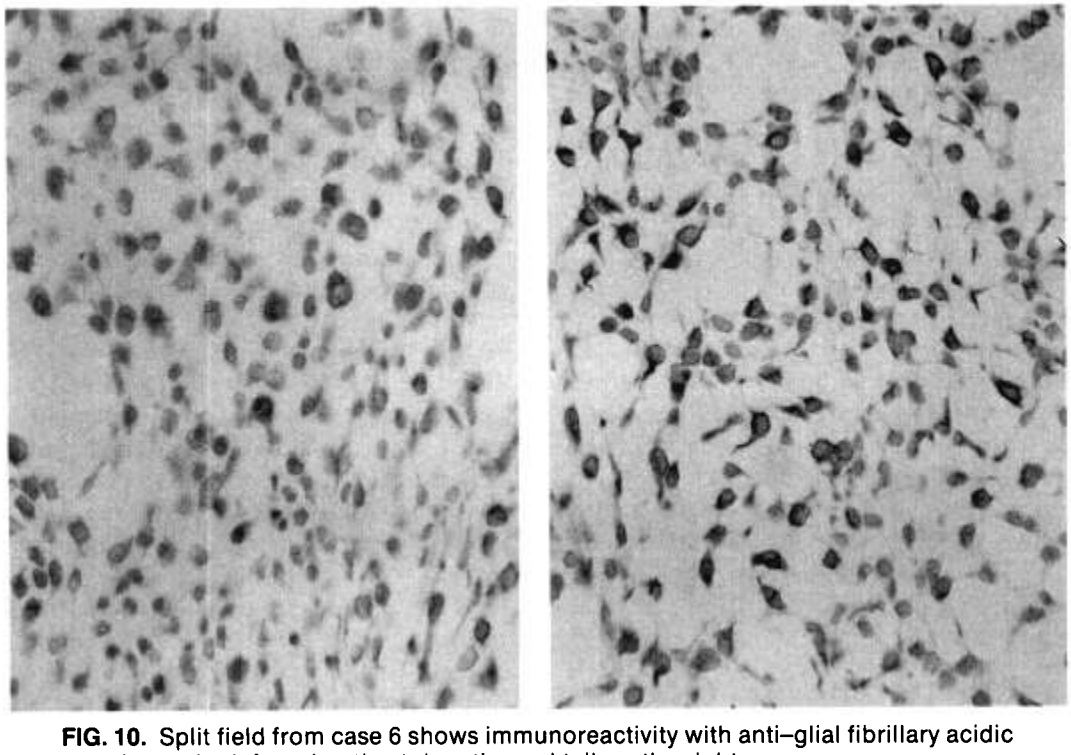

FIG. 10. Split field from case 6 shows immunoreactivity with anti–glial fibrillary acidic protein on the left and anti-cytokeratin cocktail on the right.

TABLE 3. *Immunohistochemistry of ectomesenchymal chondromyxoid tumor of the tongue*

Case no.	GFAP	Cytokeratins	S-100	SMA	Leu-7	Desmin	EMA
1.	2 m	—	—	—	—	—	—
2.	2/0 m	1	1	0	—	0	—
5.	3 m	—	3	1	2	—	—
6.	3/2 m	3	1	0	3	0	0
7.	3/0 m	3	0	1	—	—	—
8.	3/1 m	3	2	—	—	—	
9.	3/1 m	2	1	0	—	—	—
10.	0 m	—	0	—	—	—	—
11.	3/2 m	2	0	2	—	—	0
12.	3/1 m	1		2	1	—	—
13.	3	3	1	2	1	0	0
14.	3	2	3	0	—	—	—
15.	3	2	0	0	2	—	0
16.	3	1	2	0	1	—	0
17.	3 m	—	0	2	2	—	—
18.	3	2	0	—	0	—	—
19.	3	0	2	1	1	—	—

0, nonreactive; 1, faintly reactive; 2, moderately reactive; 3, intensely reactive; m, monoclonal antibody; GFAP, glial fibrillary acidic protein; SMA, smooth muscle actin; EMA, epithelial membrane antigen.

lateral to and behind the vallate papillae. The neoplastic myoepithelial cell can show reactivity for GFAP, cytokeratins, SMA, and S-100 protein. These findings are particularly well documented in the context of pleomorphic adenoma and myoepithelioma of salivary gland origin (10,12,42). The cells within the myxoid/chondroid foci of pleomorphic adenoma are consistent in their reactivity for GFAP (1,7,35). Whether a tumor can be nonreactive for SMA yet be considered "myoepithelial" remains controversial, but the immunohistochemical profile of these tumors does parallel that of ECT (11,18). The light microscopic features bear some similarity. The typical pleomorphic adenoma exhibits morphologic diversity that includes duct formation, eosinophilic hyaline foci, and squamous cysts, in addition to myxoid and chondroid areas. Tumors called myoepithelioma consist of a predominance of either spindle or plasmacytoid cells. The spindle cells are arranged in sheets or fascicles of variable density in a minimal stroma. The plasmacytoid cells form closely packed collections of round cells with eccentric nuclei and hyaline-like cytoplasm in a myxoid background (44). Five cases of lingual myoepithelioma or mixed tumor were reported by Goldblatt and Ellis (20) in a study of salivary neoplasia of the tongue accessioned at the AFIP prior to 1987. These five cases were reviewed by us, and three were reclassified as ECT (cases 5, 6, and 17). Plasmacytoid cells and ducts are not observed in ECT, and only case 17 showed any minor salivary tissue, which was in a section of tissue without tumor. Furthermore, salivary adenomas usually do not incorporate muscle fibers into the tumor, as we have observed in ECT.

In our series, ECT occurred only within the body of the tongue and, in all cases, was on the dorsal surface of the anterior one third. The taste apparatus is a tissue structure unique to this location. With that in mind, we performed immunohistochemical studies on paraffin-embedded tissue from specimens of three normal tongues. There was no immunophenotypic correlation between cells of the taste buds or their neural elements and ECT. Neural markers highlighted the plexus of nerves below the buds, and cytokeratins were found within the taste and supporting cells. Expression of GFAP or S-100 protein, however, was not found within the cytokeratin-positive cells. The consistent submucosal location of ECT, with only rare involvement of the overlying epithelium, does not support direct origin from the taste apparatus.

The anterior tongue contains components common to all areas of the oral mucosa, including vessels, smooth and skeletal muscle, and peripheral nerve. Again, the immunohistochemical and light microscopic findings fail to confirm an obvious correlation between ECT and the expected character of differentiated cells from those supporting structures. The immunoreactivity of nerve sheath components offers some similarities, but the frequent cytokeratin positivity does not support origin from fibroblasts, perineurial cells, or Schwann cells. Conventional tumors of cartilaginous differentiation have some similar microscopic features but do not account for all immunohistochemical findings of ECT. Budka (6) demonstrated reactivity for GFAP and cytokeratins in papillary meningioma, but where differentiation occurs in ECT, it is chondroid rather than meningeal.

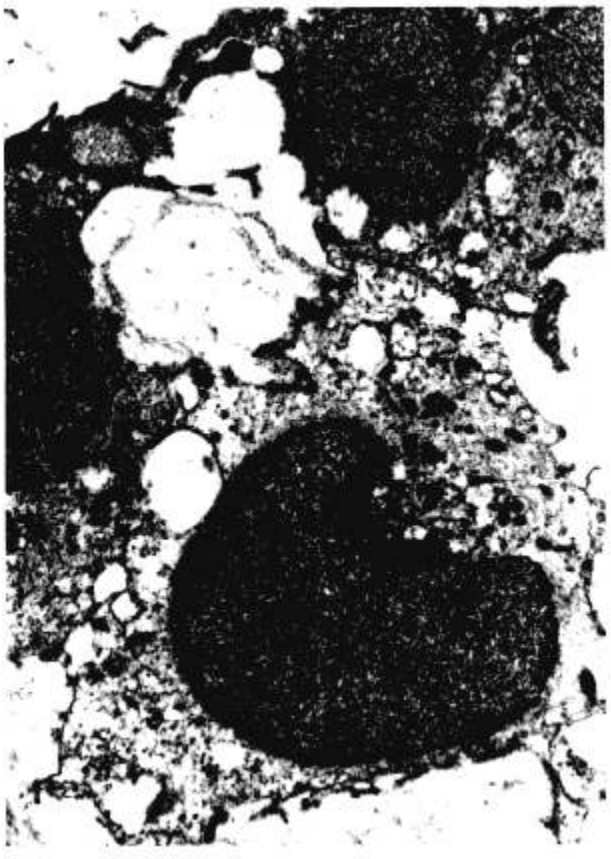

FIG. 11. Electron micrograph of paraffin-embedded tissue (case 16) shows multilobated nuclei with homogeneous chromatin and small nucleoli.

We propose two possible histogenetic origins for ECT. The first consideration for ECT is that it does indeed arise from minor salivary gland cells. The histology is not particularly suggestive of an epithelial neoplasm, and it does not conform to the morphologic criteria for any known salivary tumors (40). However, consistent reactivity for GFAP and cytokeratins, combined with the variable positivity for S-100 and SMA, correlate with the immunohistochemical profile for neoplastic myoepithelial cells (22,42). Because minor salivary glands of the anterior tongue send excretory ducts to the ventral surface, salivary tumors arising from the glands would be expected to be seen as ventral tongue rather than dorsal tongue masses, but the gland parenchyma is actually embedded in the body of the tongue musculature. It is conceivable that tumors derived from these glands might extend to the upper surface as a dorsal swelling as opposed to a ventral mass. We cannot explain why a tumor of salivary gland cells in the tongue would produce a tumor not seen elsewhere in gland-bearing mucosa.

The second histogenetic consideration is that ECT arises from uncommitted ectomysenchymal cells that have migrated from the neural crest. These crest cells ultimately form all nonepithelial components of the facial region except certain elements of skeletal muscle and endothelial cells. GFAP reactivity has been documented in cells of neural crest and ectodermal origin (6). As multipotential cells, ectomysenchyme may differentiate into cartilaginous structures (Meckel's cartilage, malleus, incus), as well as peripheral nerve (25). The anterior tongue arises from crest mesenchyme of the first branchial arch by way of the lateral lingual swellings. The tongue musculature is thought to form from migratory occipital somites accompanied by the hypoglossal nerve (cranial nerve XII). ECT does not show immunohistochemical evidence of myogenous differentiation; however, there is immunohistochemical reactivity and light microscopic morphology suggestive of both neural and chondroid differentiation. Why a nodule of undifferentiated ectomesenchyme should preferentially manifest in the tongue as a neoplastic entity is unclear. We do note, however, that the tongue may have myriad heterotopias and choristomas. In fact, of the ~155 cases of oral choristoma reviewed by Chou et al. (9), nearly 120 (77%) appeared in the tongue.

Further investigation is necessary before the histogenesis of this unusual tumor can be clarified. Although ECT displays overlapping features with other lesions, the combination of predilection for the tongue, unusual histology, and immunohistochemical profile seems to make it a unique tumor. Until the histogenesis is clarified, we prefer the descriptive name ectomesenchymal chondromyxoid tumor of the anterior tongue. This nomenclature acknowledges the chondroid and neural features observed by light microscopy as well as the results of the histochemical and immunohistochemical studies. Our clinical follow-up is limited but confirms the potential for recurrence, sometimes long after initial therapy. Therefore, we cannot completely exclude malignant behavior but believe the clinical behavior is essentially that of a benign neoplasm. □

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