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Case Report

A case of a CD56-expressing ectomesenchymal chondromyxoid tumor of the tongue: potential diagnostic usefulness of commonly available CD56 over CD57

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Abstract: Ectomesenchymal chondromyxoid tumors (ECTs) are rare. Only approximately 55 cases have been reported in the English literature. Distinguishing ECTs from soft tissue myoepithelioma (STM) is often difficult owing to morphological and immunohistochemical similarities. Here, we present a case of an ECT arising from the anterior dorsum of the tongue in a 24-year-old woman. Grossly, the tumor was soft, had a myxoid appearance, and measured 8 × 7 × 7 mm. Microscopically, it was well-demarcated, lacked a fibrous capsule, and predominantly consisted of short, spindle to ovoid cells in a myxoid background. Vimentin, glial fibrillary acidic protein (GFAP), and S-100 protein were strongly positive on immunohistochemical analysis. While CD56 was moderately immunopositive, cytokeratin (AE1/AE3) and alpha-smooth muscle actin (αSMA) showed focal weak positivity. Thus, the immunohistochemical findings suggested a diverse immunophenotype, indicating mesenchymal (vimentin and αSMA positive), neurogenic (S100, GFAP, and CD56 positive), and epithelial differentiation (cytokeratin positive). This reflected the fact that ECTs probably arise from uncommitted ectomesenchymal cells that have the potential for multilineage differentiation. The immunohistochemical staining pattern observed for ECTs slightly differs from that of STMs. Strongly positive staining for GFAP and weakly positive staining for cytokeratin are observed in ECTs, whereas the opposite is typically observed for STMs. These findings indicated that the patterns of expression on immunohistochemistry differ between ECTs and STMs, although inevitably, there was some overlap. Thus, CD56 expression in the case presented here is noteworthy, and it could potentially become an adjunct diagnostic marker for ECT instead of previously used CD57.

Keywords: Ectomesenchymal chondromyxoid tumor, tongue, multilineage, myoepithelioma, immunohistochemistry, CD56

Introduction

Ectomesenchymal chondromyxoid tumors (ECTs) are extremely rare. Only approximately 55 cases have been reported in the English literature [1-6]. The first case was reported by Smith et al. in 1995, who coined the term "ectomesenchymal chondromyxoid tumor" [7]. The disease almost exclusively occurs in the anterior dorsum of the tongue [8] and presents as slow-growing, painless, and well-circumscribed nodules ranging in size from 0.3 to 3.5 cm in patients aged 7 to 78 years, with no apparent sex predilection [3].

Histological analysis has revealed that ECT is characterized by a well-demarcated lobular growth pattern. Neoplastic cells proliferate in the form of a reticulum, cords, or sheets in a myxoid or chondromyxoid background. The constituent cells are relatively uniform, with sporadic cytological atypia and mitotic figures [7]. A definitive immunohistochemical characterization of ECT has not been possible because the immunohistochemical profiles of the published cases show some variation in expression of diverse lineage markers [3, 8]. Among immunohistochemical markers, CD57 is more frequently examined than CD56. The expression of

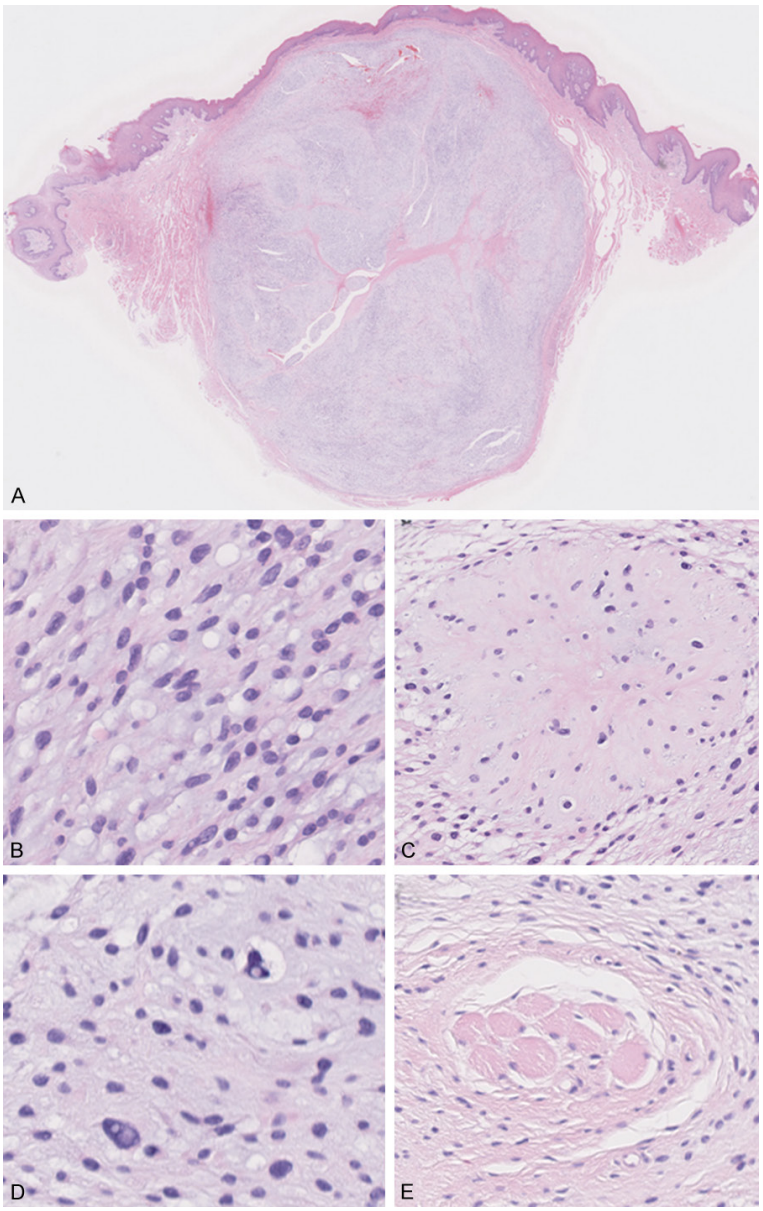

Figure 1. Morphological findings. A. A well-demarcated tumor without a fibrous capsule was present, appearing as a single nodule with mild lobulation (× 12.5). B. The tumor was mainly composed of short spindled to ovoid cells without obvious nuclear atypia in a myxoid background (× 400). C. A scattered chondroid matrix was formed and cells embedded within it were similar to chondrocytes (× 200). D. Tumor cells with enlarged atypical nuclei were occasionally present (× 400). E. The tumor entrapped skeletal muscle at the periphery (× 200).

CD57 is suggestive of a neurogenic lineage [3]. However, CD56, an additional marker suggestive of a neurogenic lineage, is a more commonly available and useful marker in pathology laboratories, compared to CD57.

Distinguishing ECT from soft tissue myoepithelioma (STM) is sometimes problematic because of the morphological and immunohistochemical similarities between the two. However, subtle differences do exist [3]. The World Health Organization recently adopted ECT as a synonym of STM in the latest edition of Classification of Tumors of Soft Tissue and Bone (4th, 2013) [9].

Here, we present a case of ECT arising in the anterior dorsum of the tongue. In this particular case, ECT could be distinguished from STM by immunohistochemistry (IHC). We discuss the features that can be used to distinguish ECT from STM in detail, provide a literature review of IHC patterns, and discuss the potential usefulness of CD56 as an adjunct diagnostic marker.

Clinical summary

A 24-year-old woman presented with a gradually growing, dome-shaped mass on the tongue. The patient first noticed the mass 1 year previously, and she was referred for excision of the tumor. The tumor was located in the anterior dorsum of the tongue and had a maximum diameter of 8 mm. On palpation, the tumor was found to be soft and non-tender. A benign lesion was suspected clinically, and local excision was performed. The surgical margin was free of tumor cells, the postoperative course was uneventful, and the patient was referred to a local physician for follow-up treatment.

Pathological findings

The surgically resected specimen consisted of an elastic soft tumor measuring 8 × 7 × 7 mm. It exhibited a myxoid appearance on the cut surface.

Histopathological analysis revealed a well-demarcated tumor without a fibrous capsule

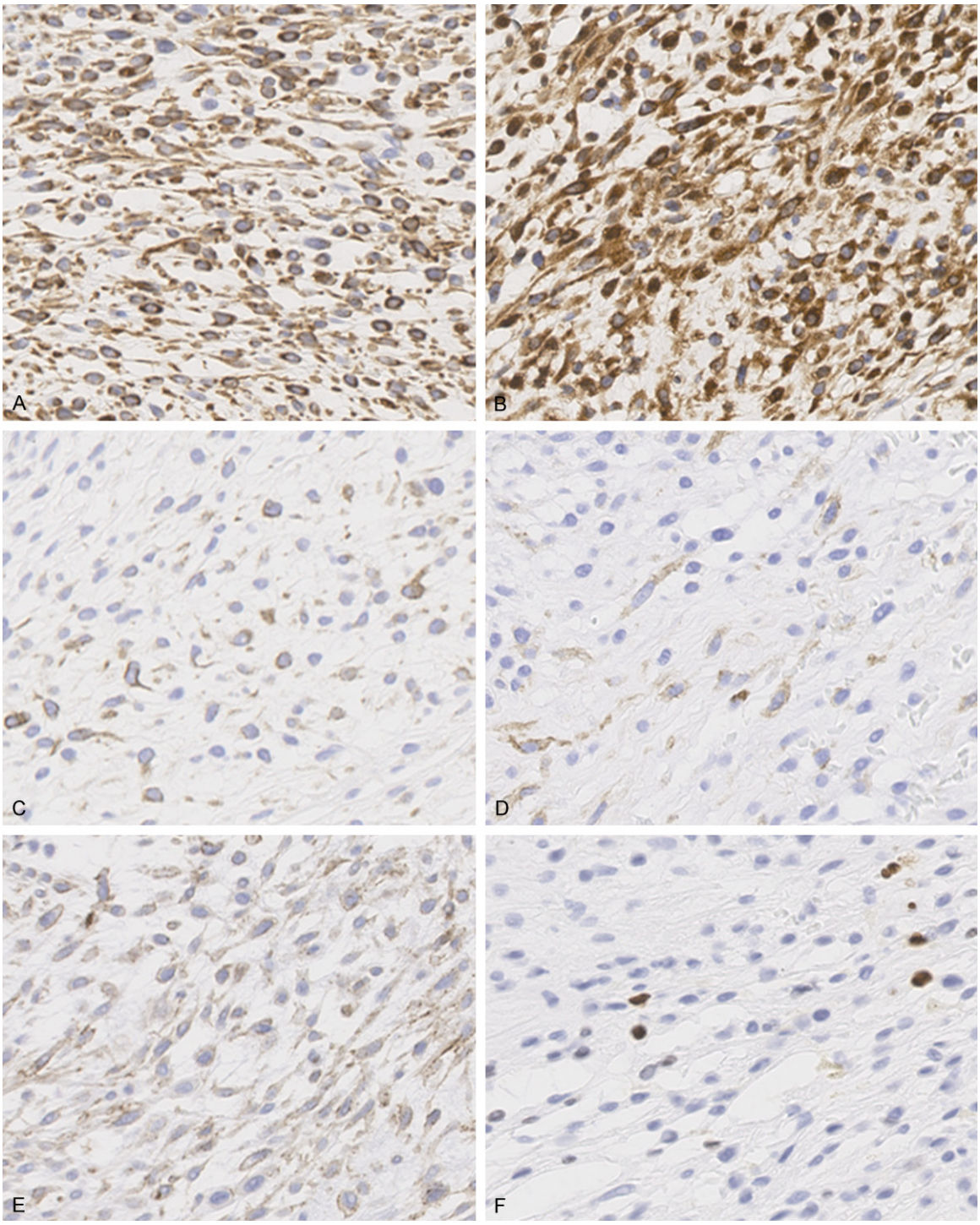

Figure 2. Immunohistochemical findings. A. Strong immunopositivity for glial fibrillary acidic protein (× 400). B. Strong immunopositivity for S100 (× 400). C. Focal and weak immunostaining for cytokeratin (AE1/AE3) (× 400). D. Focal and weak immunostaining for α-smooth muscle actin (× 400). E. Moderate immunoreactivity for CD56 (× 400). F. Low immunolabeling with Ki67 (MIB-1) (× 400).

that appeared as a single and mildly lobulated nodule (**Figure 1A**). The tumor predominantly consisted of short, spindle to ovoid cells without obvious nuclear atypia in a myxoid background (**Figure 1B**). A scattered chondroid matrix was observed, and some of the cells

embedded within the matrix appeared similar to chondrocytes (**Figure 1C**). Occasionally, tumor cells with enlarged and atypical nuclei were observed (**Figure 1D**). Mitotic figures were not apparent, and no necrosis was detected. Skeletal muscle was entrapped within the tumor at the periphery, indicating a tendency for blunt infiltration of the adjacent tissue (**Figure 1E**).

Analysis of the tumor by IHC revealed that it was strongly positive for vimentin (V9, 1:100; Dako, Glostrup, Denmark), glial fibrillary acidic protein (GFAP; polyclonal, 1:200; Dako) (**Figure 2A**), and S-100 protein (polyclonal, 1:1000; Dako) (**Figure 2B**), and showed focal but weak staining for cytokeratin (AE1/AE3, 1:100; Dako) (**Figure 2C**) and alpha-smooth muscle actin (αSMA; 1A4, 1:100; Dako) (**Figure 2D**). The tumor was also moderately immunopositive for CD56 (123C3, 1:50; Dako) (**Figure 2E**). The Ki67 (MIB-1, 1:100; Dako) labeling index was 4.2% (n = 1000 cells) (**Figure 2F**). The labeling index did not increase in areas with nuclear atypia. Epithelial membrane antigen (E29, 1:100; Dako), p63 (4A4, 1:80; Dako), desmin (D33, 1:60; Dako), CD34 (QBEnd 10, 1:40; Dako), and c-kit (polyclonal, 1:100; Dako) were immunonegative (data not shown).

A diagnosis of ECT was rendered based on the findings obtained from the histopathological and IHC analyses.

Discussion

The differential diagnosis in the case presented here could have included a variety of lesions such as STM [10], oral focal mucinosis [11], nerve sheath myxoma/neurothekeoma [12], neurofibroma [13], schwannoma [14], and cartilaginous choristoma [15]. These lesions, with the exception of STM, could be excluded based on morphological and IHC analysis, especially given the diverse set of mesenchymal (vimentin and αSMA), neurogenic (S100, GFAP, and CD56), and epithelial (cytokeratin) markers that were simultaneously expressed. Compared with STM, ECT typically exhibited stronger staining for GFAP and weaker staining for cytokeratin, and was likely to lack expression of specific markers for myoepithelial differentiation such as p63 [6], as was observed in our case. On the other hand, STM more consistently stained positive for cytokeratin and less consistently for GFAP than ECT [9]. Given the lack of expression of p63 and modest staining for cytokeratin in this case, the possibility of STM was excluded. ECT became the most appropriate diagnosis in conjunction with the strong positivity for GFAP.

Focal areas of cellular atypia were reported to consist of hyperchromatic nuclei, prominent nucleoli, nuclear pseudoinclusions, and binucleated cells [16], which were also observed in this case. Atypia is often related to secondary inflammatory stimuli or aging of the tumors [16]. Indeed, the lack of increase in the Ki67 (MIB-1) labeling index in these areas may indicate that ECT aging caused the atypia.

In the case presented here, the expression of CD56 was particularly noteworthy. In fact, 2 out of 4 cases of ECT had CD56-expression [17, 18]. Sixty percent of ECTs, including our case, were positive for CD56. We suspect that cases with CD56 expression might be encountered more frequently if IHC analysis is performed in each case. However, in most instances, spindle-shaped soft tissue tumors would not be expected to express CD56. For example, one of the CD56-expressing tumors included in the differential diagnosis of ECT was schwannoma [19, 20]. In contrast, CD57 has been more frequently evaluated in ECT. The combined data from a comprehensive review plus an additional 7 cases indicated that 75% (24 out of 32 cases) were positive for CD57 [2]. Hence, following GFAP (88%; 53 of 60 cases) and S100 (84%; 48 of 57 cases), CD57 is one of the most frequently expressed markers of ECT. In addition to CD57, αSMA is often positive (56%; 27 of 48 cases). Other markers are expressed in less than 50% of ECT cases [2]. CD56 is a more useful neurogenic marker than CD57 [21] and is shown to have a relatively high positive rate compared to other markers, though the number of tested cases is limited. Moreover, CD56 is more commonly available than CD57 in pathology laboratories. As the expression of CD56 in myoepithelioma is not well established, IHC for CD56 instead of CD57 could potentially become an adjunct diagnostic marker for ECT.

Previous reports have speculated on the histogenesis of ECT on the basis of IHC data [5, 6, 18]. ECT possesses a diverse immunophenotype, suggestive of mesenchymal, neurogenic,

and epithelial differentiation. Ectomesenchymal cells have the potential to differentiate into multiple lineages including neurogenic, chondrogenic, myogenic, adipogenic, osteogenic, odontogenic, and epithelial cells [18, 22, 23]. If ECT is presumed to originate from ectomesenchymal cells, the diversity of immunopositivity for various antibodies in ECT could be explained by their multilineage potential. Given that the anterior two-thirds of the tongue, which is derived from the first branchial arch, encompasses the usual site of occurrence of ECT, the most likely hypothesis regarding the histogenesis of ECT is that it is derived from uncommitted ectomesenchymal cells that migrate from the neural crest of the first branchial arch during embryogenesis [1].

Neurogenic differentiation, one of the features of divergent differentiation, was observed using cultured cells obtained from ECTs [1]. In addition, *Oct3/4, Sox2, and Nanog* mRNAs were expressed in ECT tissue [1]. These mRNAs are also markers for undifferentiated ES cells [24]. Hence, the cells in ECTs have characteristics that resemble those of ES cells and may have the capacity to self-renew [1].

Recurrence of ECT has been documented in only 4 cases, with intervals of 3 months to 20 years [7, 25]. The rate of recurrence is therefore low, and it is most likely that ECTs are benign tumors. Given the benign nature of ECTs, conservative surgical excision is the recommended treatment [8].

In conclusion, ECT is a rare tumor that is likely derived from uncommitted ectomesenchymal cells and harbors a multilineage immunophenotype. Although there is an overlap of morphology and immunophenotype between ECT and STM, IHC analysis revealed some expression pattern differences. Additional studies are required to validate these findings and to determine the usefulness of CD56, which has the potential to become an adjunct diagnostic marker for ECT.

Disclosure of conflict of interest

None.

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