Mixed adenoneuroendocrine carcinoma (MANEC) of the tongue arising within a congenital enteric cyst

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Running title

Primary MANEC of the tongue

KEYWORDS

Mixed adenoneuroendocrine carcinoma, tongue, congenital enteric cyst, primary tongue adenocarcinoma, histogenesis

Abstract

Background: Primary intestinal-type adenocarcinoma of the tongue is rare. This represents the first case of a primary mixed adenoneuroendocrine carcinoma (MANEC) of the tongue arising within a congenital enteric cyst reported.

Methods: A 52-year-old male presented with a midline tongue mass which was connected to the mucosal surface with an epithelial-lined sinus tract. Morphological examination, and immunohistochemical profiling of the neoplasm was performed.

Results: Histopathological evaluation showed a primary MANEC arising within a pre-existing congenital enteric cyst, comprising both adenocarcinoma and neuroendocrine components. The adenocarcinoma had a colonic-type morphology and co-expressed CK 7, CK 20 and CDX2. Imaging and colonoscopy excluded a distant primary colorectal neoplasm.

Conclusion: The association of primary MANEC of the tongue with a gastrointestinal heterotopic cyst supports an origin from entrapped endodermal elements as opposed to salivary duct origin. This case raises the awareness of a rare yet prognostically important complication of a gastrointestinal heterotropic cyst.

INTRODUCTION

Mixed adenoneuroendocrine carcinoma (MANEC) was designated a distinct tumour entity by the World Health Organization (WHO) in 2010.[1] These rare tumours of the gastrointestinal tract consist of both exocrine and neuroendocrine components with the arbitary requirement that each component should be more than one third of the tumour volume.[1] They have been reported at several sites in the gastrointesstinal tract (GIT) sites and comprises of a spectrum of low-grade to high-grade lesions. The neuroendocrine component may be well-differentiated to poorly differentiated whilst the exocrine components represent adenomas at one end and invasive adenocarcinomas at the opposite.

Primary adenocarcinoma of the tongue represents a small proportion of all head and neck neoplasms, the majority of which are salivary gland in origin.[2, 3] Primary lingual adenocarcinoma exhibiting a colonic phenotype has been documented in small series of published cases as colonic-type adenocarcinoma of the tongue and shares features with sinonasal intestinal-type adenocarcinoma.[4]

Congenital enteric cysts are heterotopic dysembryonic abnormalities which may arise from endodermally derived cell rests located at this site owing to the close proximity of the foetal foregut and the developing tongue.[5] These cysts are most often diagnosed and surgically excised by the age of two years but may remain undetected and asymptomatic, persisting well into adulthood. Heterotopic elements at any site represent an important potential source of malignancy.[6] This case report described a primary MANEC of the tongue with evidence of origin from foregut duplication cyst which to the best of our knowledge is the first report of its kind.

CASE REPORT

A 52-year-old male presented with an asymptomatic submucosal mass in the midline of the tongue located slightly anterior to the foramen caecum. Clinical examination showed a draining sinus tract in association with the lesion, the orifice of which appeared as a pinpoint punctum closer to the tongue tip. The patient did not report a history of occupational exposure to known carcinogenic agents including tobacco use or alcohol consumption. Pre-operative computerised tomographic (CT) imaging confirmed a hypodense lesion with surrounding rim enhancement measuring 15x6mm in diameter and infiltrating to a depth of 9mm. There was no radiological evidence of vascular invasion or of cervical lymphadenopathy. An incision biopsy showed colonic-type adenocarcinoma of the tongue pending exclusion of a metastatic lesion. A colonoscopy was performed and no abnormalities were detected.

The patient subsequently underwent a wide excision of the tongue tumour. On gross examination, the specimen measured 60 X 20 X 25 mm. A healed, linear surgical scar measuring 20mm in length was identified on the mucosal surface in keeping with site of the previous incisional biopsy. On section, a mixed solid and cystic lesion was identified within the submucosa which extended into the adjacent skeletal muscle. The tumour measured 15x10x10mm and continuity with the sinus tract was macroscopically noted.

Histological examination showed a cystic lesion lined by variable stratified squamous non-keratinising to pseudostratified ciliated columnar respiratory epithelium with interspersed foci of immature squamous metaplasia (Figure 1A). Surrounding the cyst were slivers of smooth muscle with bundles of skeletal muscle being present at the lateral and deep surgical aspects. The microscopic features of the cyst were diagnostic of a lingual foregut / enteric cyst. An exophytic, polypoid tubuloglandular mass with a sessile base protruded into the lumen of the cyst (Figure 1). The polyp showed papillary and villous projections surfaced by colonic / intestinal type epithelium. The cells were columnar with basally orientated

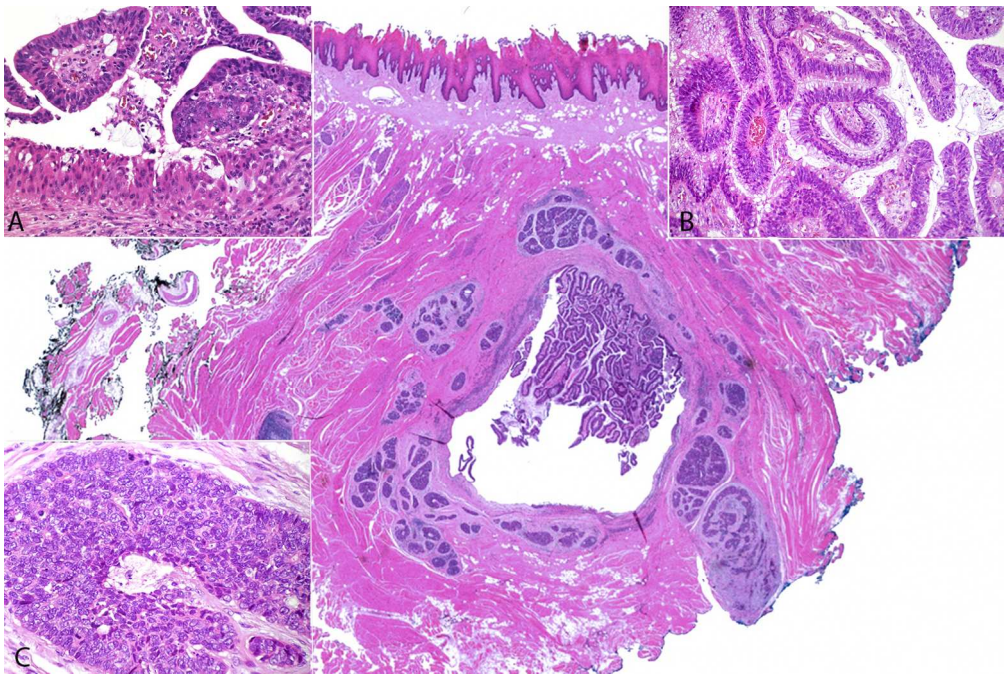

FIGURE 1. Low power photomicrograph showed a submucosal congenital enteric cyst from which a colonic type adenocarcinoma was protruding into the cyst lumen with infiltration into the cyst wall. A distinct neuroendocrine carcinoma was present as islands within the cyst wall with extension into deeper submucosal tissue, being present at a deep surgical margin. The cyst lining showed areas of stratified squamous epithelium, pseudostratified respiratory epithelium as well as interspersed areas of immature squamous metaplasia (A). The tubuloglandular morphology of the colonic type adenocarcinoma showed features of dysplasia and pleomorphism (B). The neuroendocrine carcinoma component showed nuclear granularity with areas of necrosis present (C).

185x123mm (240 x 240 DPI)

nuclei in which conspicuous features of dysplasia were noted. The nuclei showed overlapping, nuclear hyperchromasia, loss of polarity, increased nuclear to cytoplasmic ratios and stratification with prominent nucleoli (Figure 1B). The luminal cells were predominantly mucous producing with a distinct goblet cell morphology in regions. The dysplastic cells showed nuclear predominance with diminished apical mucous production. A malignant gland-forming neoplasm with features of a colonic / enteric type adenocarcinoma was noted to infiltrate the underlying connective tissue. The glandular lumina contained areas of necrotic cellular debri and focal apoptotic prominence was also noted.

A morphologically distinct neoplasm with organoid to nested growth, nuclear enlargement, hyperchromatism and occasional prominent nucleoli was juxtaposed to the enteric type malignancy. The nuclear chromatin showed conspicuous granularity and dispersion with nuclear moulding. A smaller population of tumour cells showed vesicular nuclei. The mitotic index exceeded 2 mitoses in 10 high power fields. Apoptotic cells with areas of spotty necrosis were identified within the centre of the islands. The second neoplasm had features of a neuroendocrine carcinoma (Figure 1C). Widespread infiltration of the adjacent connective tissue was noted at the periphery of the tumor accompanied by stromal desmoplasia and a mild lymphocytic host response. The neuroendocrine carcinoma was present at one of the deep excision margins. A subsequent wider excision was performed and no residual tumour could be demonstrated.

The developmental cystic lesion was continuous with an epithelial-lined sinus tract which opened onto the surface of the mucosa of the tongue. The overlying mucosa comprised stratified squamous parakeratinising epithelium in which acanthosis and focal hyperkeratosis were noted. There were no features of epithelial dysplasia or neoplastic origin from the surface epithelium. Lymphovascular space infiltration or perineural invasion were not identified.

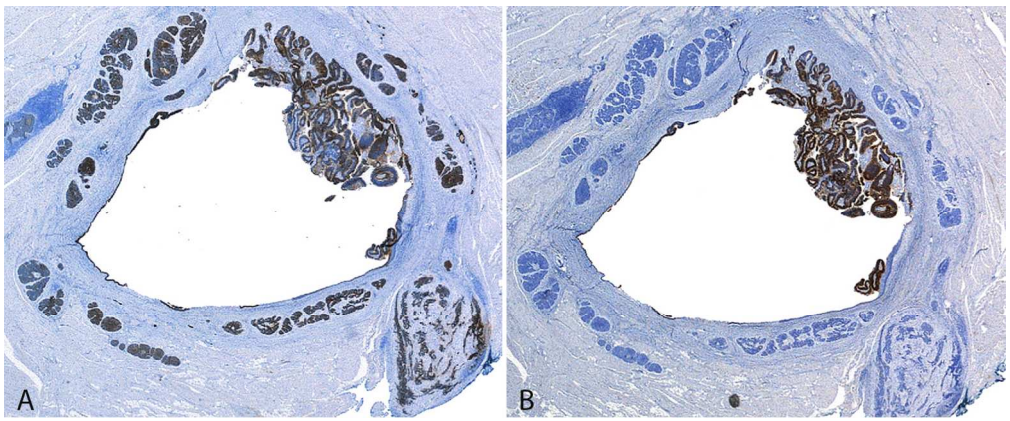

FIGURE 2. CK7 expression was present in both tumor components and the enteric cyst lining (A). CK20 expression was present in the colonic type adenocarcinoma components and enteric cyst lining but no staining was observed in the neuroendocrine carcinoma component (B).

176x72mm (240 x 240 DPI)

Examination of the immunohistochemical staining showed diffuse pancytokeratin positivity for AE1/AE3 within both tumor components. Positivity for CK 7 was detected infrequently in adjacent minor salivary gland subunits as well as in both of the neoplastic components. The lining of the enteric cyst showed focal CK 7 positivity (Figure 2A). CK 20 immunopositivity was detected in the adenocarcinoma components and cyst lining but not in the neuroendocrine carcinoma islands (Figure 2B). Markers of neuroendocrine differentiation including synatophysin, chromogranin-A and CD56 showed strong, diffuse cytoplasmic positivity within the neuroendocrine carcinoma confirming its phenotype (Figure 3). Synaptophysin staining was most predominant and diffuse, followed by less intensity of both chromogranin-A and CD56. CDX2 nuclear signalling was evident within both tumor components as well as within areas of intestinal metaplasia in the enteric cyst (Figure 4). Nuclear proliferation as detected by Ki-67 confirmed mitotically active cells in at least 60 to 90% of the tumor component (Figure 5). Polyclonal CEA staining was diffusely positive within both components. Nuclear signalling with p53 was detected within the adenocarcinoma elements as well as the adjacent areas of intestinal metaplasia from which the malignant elements were noted to arise. In contrast to this, the adjacent respiratory and squamous epithelial cyst lining were negative for p53.

Further analysis including magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning, in addition to colonoscopy, failed to identify a primary neoplasm within the abdomen. In the absence of a distant primary neoplasm following extensive clinical work-up and examination, the diagnosis of a high grade MANEC arising within an enteric cyst was made. The patient has remained free of recurrence or metastasis to the last follow-up (15 months).

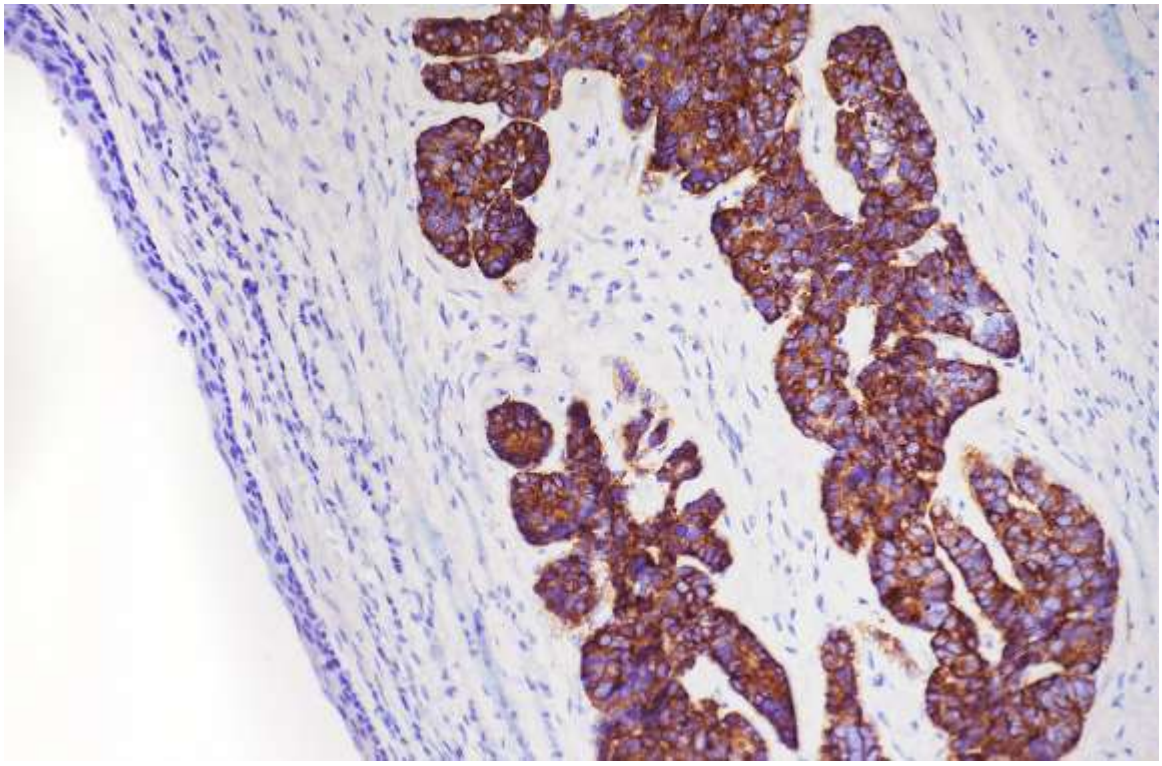

FIGURE 3. Strong synaptophysin expression in the neuroendocrine carcinoma component.

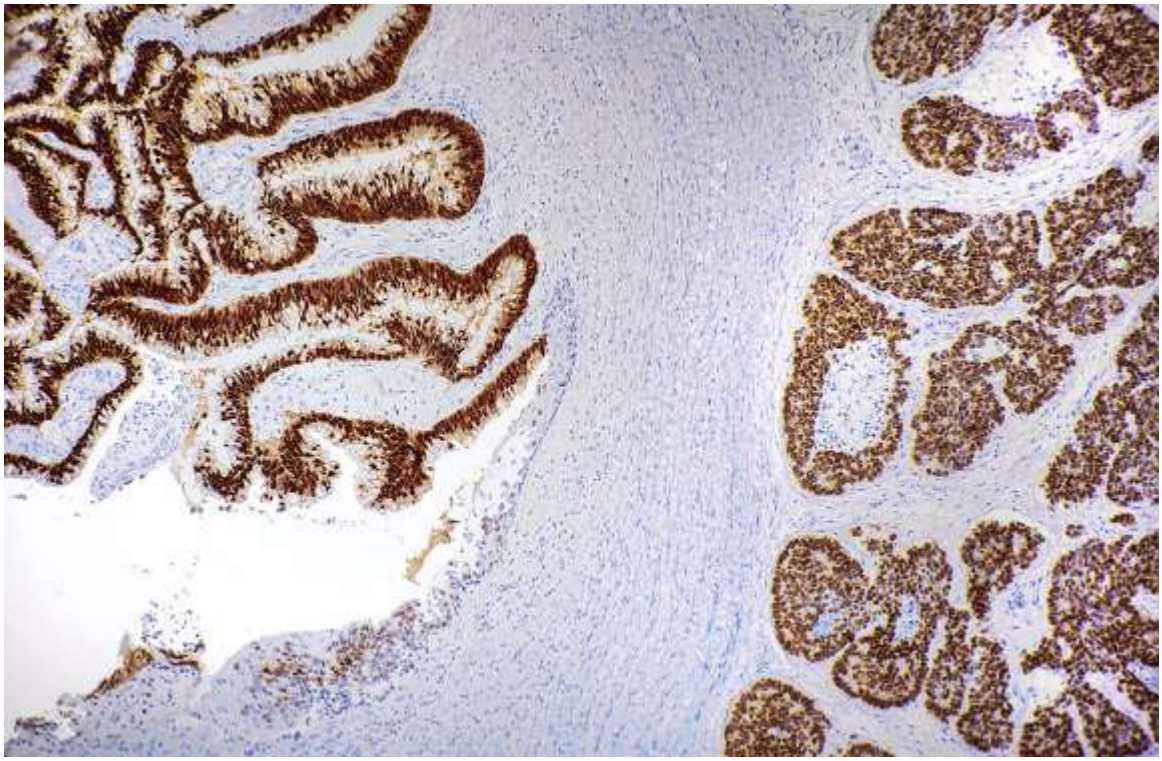

FIGURE 4. Both tumor components expressed strong nuclear expression for CDX2.

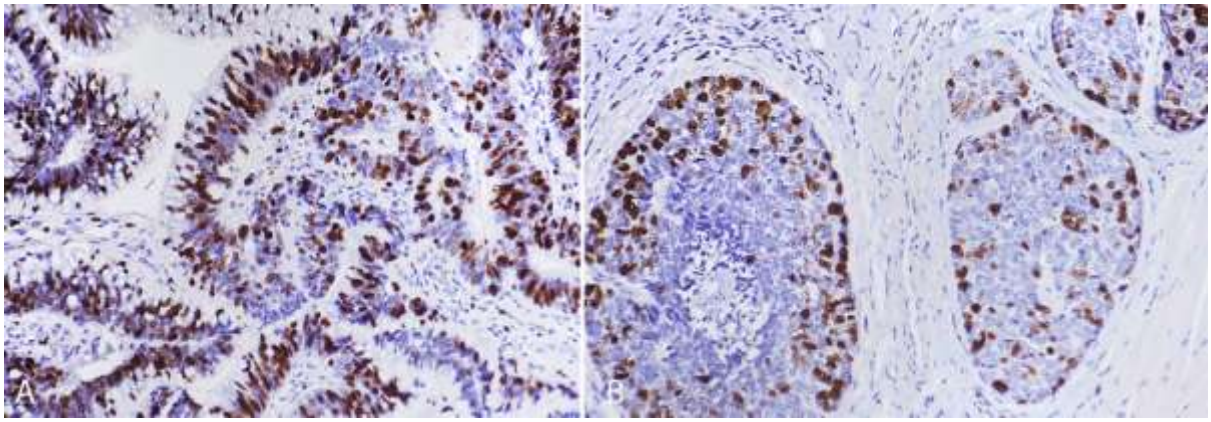

FIGURE 5. A, The Ki-67 expression in the adenocarcinoma component and B, neuroendocrine carcinoma component.

DISCUSSION

MANECs are subdivided into low, intermediate or high-grade on the basis of the tumor grade of each component.[7] Low-grade MANEC represents the classic goblet cell tumors arising within carcinoids of the appendix. High-grade MANECs at the other end of this spectrum are more aggressive entities in which an adenocarcinoma component is frequently associated with a large cell neuroendocrine carcinoma. Higher grade lesions have nuclear signalling in excess of 20% and extensive tumor associated necrosis.[8] The histogenesis of MANECs may be related to simultaneous malignant transformation of two cell types of different lineage or conversely the existence of pluripotent stem cells which under inductive influences may show divergent bidirectional differentiation.[9] A neuroendocrine cell population is not infrequent in adenocarcinomas of the GIT particularly within the colorectum, however, MANEC should be distinguished from cases of adenocarcinoma in which scattered neuroendocrine cells are present.[8]

Choristomas represent masses of heterotopic tissue comprising normal non-specialised tissue which is ectopic for the site at which it occurs. A congenital lingual enteric cyst, also known as lingual foregut cyst or lingual alimentary cyst, is a choristoma with cystic morphology representing a developmental abnormality of endodermal origin. The cyst is lined by variable GIT mucosa and often epithelium which is not characteristically found at the site at which the cyst occurs. Lesions involving the oral cavity are located in the anterior two thirds of the tongue or floor of mouth.[10] Lingual enteric cysts are of primitive foregut origin; typically present shortly after birth and are removed by surgical excision. It may cause respiratory obstruction or interfere with speech and deglutition if sufficiently large. A small number of lesions may persist undetected into adulthood where the risk of malignant transformation occurring within the lining remains a possibility.[5, 10, 11]

Evidence corroborating the most likely origin of MANEC within the pre-existing enteric cyst lining is the demonstration of malignancy arising within overlying dysplastic and metaplastic epithelium and in which both the neoplastic cells and dysplastic cyst lining express similar immunohistochemical markers which are absent within the adjacent normal epithelium. The focal CK 7 staining in the cyst lining was in keeping with its congenital foregut origin.[12] The co-expression by tumor cells of CK 7, CK 20 and CDX2 confirmed the intestinal phenotype. CK 7 expression is not usually present in primary colorectal adenocarcinoma whilst simultaneous expression of CK 7 and CK 20 within the GIT signified upper GIT origin.[6, 13]

Primary adenocarcinomas of the tongue are a diverse and scarce group of lesions most often of minor salivary gland origin. The histopathological features of these lingual lesions are the same as for salivary adenocarcinoma at any other site. Immunopositivity for CK 7 is typically seen in neoplasms of salivary origin.[14, 15] Salivary neoplasms most often originating in the tongue include mucoepidermoid carcinoma, papillary cystadenocarcinoma, adenocarcinoma NOS and clear cell carcinoma. Cribriform adenocarcinoma of the tongue and minor salivary glands, a recently described variant of polymorphous adenocarcinoma, is distinctive enough to be separated from colonic-type adenocarcinoma of the tongue.[14, 16] Adenocarcinoma with colonic / intestinal-type morphology represents an emerging entity at this site. It shares almost identical histological features with intestinal-type adenocarcinoma of sinonasal origin which also overlap with those of primary colorectal / intestinal type adenocarcinoma.[3, 4, 17] Colonic-type adenocarcinoma of the tongue with conspicuous mucinous features reminiscent of colloid adenocarcinoma of the bowel has also been described.[3] This lesion shows areas with similar extracellular mucin lakes. Colorectal adenocarcinoma consistently expresses both CK 20 and CDX2. The concomitant expression

of CK 7 as in our case is suggestive of derivation from the upper GIT, thus necessitating separation from primary and metastatic disease at this site.[3, 4, 15, 18]

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