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ORIGINAL ARTICLE

Salivary gland papillary adenocarcinoma with intestinal-like features: Clinicopathologic, immunohistochemical, and genetic study of six cases

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Abstract

Background: Salivary gland tumors with papillary architecture and intestinal-like mucinous cytologic features are rare. Their clinicopathologic and genetic features are not fully understood, and whether they represent one separate entity remains unclear.

Methods: Six salivary adenocarcinomas with papillary architecture and intestinal-like mucinous cytologic features were reported. Immunostaining was done for CK7, CK20, CDX2, SOX10, S100, MUC1, MUC2, and MUC5AC. Tumor DNA samples were extracted for Sanger sequencing. Previously reported morphology-analogous cases were reviewed.

Results: Six cases involved the palate (2), retromolar region (1), submandibular region (1), tongue (1), and mandible (1). Five cases were followed up, with one case of recurrence 1 year after surgery, one death from cerebral infarction 7 days after surgery, and three cases without signs of recurrence or metastasis over 5 years. All cases had abundant mucinous production and presented a typical immunophenotype common to salivary primaries, CK7 & MUC1 positive, CK20 & CDX2 negative. Sanger sequencing demonstrated recurrent *AKT1 E17K* mutations in four cases (4/6, 66.7%). A review of reported salivary intestinal-like tumors revealed 3 out of 13 cases presented with papillary morphology and CDX2 negative. Some salivary papillary neoplasms with mucinous cytologic features termed as intraductal papillary neoplasms or mucinous adenocarcinomas were also reported with *AKT1 E17K* mutations.

Conclusion: We describe 6 cases of salivary gland papillary adenocarcinoma with intestinal-like mucinous cytologic features, which are different from conventional intestinal-type adenocarcinoma, presenting a consistent immunophenotype of CK7 & MUC1 positive, CK20 & CDX2 negative and exhibiting recurrent *AKT1 E17K* mutations.

KEYWORDS
AKT1 E17K mutation, immunohistochemistry, intestinal-like, mucinous, salivary papillary adenocarcinoma

1 | INTRODUCTION

Salivary gland tumors with papillary architecture and mucinous cytologic features are extremely rare. These papillary mucinous neoplasms are morphologically similar to gastrointestinal carcinoma or reminiscent of gastrointestinal epithelium. Owing to the rarity of this neoplastic lesion, its clinicopathologic and genetic features are not fully understood. Whether this pattern of salivary adenocarcinomas represent one separate entity or variant of other well-established tumors remains unclear.

Few tumors manifested morphologic and immunophenotypic mimicry with sinonasal intestinal-type adenocarcinoma and were named intestinal-type adenocarcinoma, as a type of adenocarcinoma, not otherwise specified (NOS).[1] Together, thirteen cases with intestinal-like morphologic appearance involving oral cavity have been reported in English literature.[2-12] Most of these cases expressed markers of intestinal differentiation, while 3 out of 13 cases exhibited papillary morphology and CDX2 negative.

Recently, Agaimy et al. [13] reported 3 cases of intraductal papillary mucinous neoplasms of minor salivary glands with variable cytologic and architectural atypia from papillary adenoma to low-grade carcinoma. All the 3 papillary neoplasms showed uniform mucinous-like cytologic features reminiscent of gastrointestinal epithelium, which positively expressed CK7 and MUC1, and have an identical *AKT1 E17K* mutation. Rooper et al.[14] proposed a distinct entity of mucinous adenocarcinomas, including all mucin-producing salivary adenocarcinomas. Papillary cystadenocarcinoma, mucinous adenocarcinoma, and signet-ring carcinoma were grouped into this novel mucinous adenocarcinoma. All eight cases performing next-generation sequencing, revealed *AKT1 E17K* mutations.

Furthermore, oral metastatic gastrointestinal adenocarcinoma is extremely rare and frequently involves bony structures, such as the jaws.[15,16] Several oral metastases have been found to be the first indication of undiscovered malignancies at a distant site, with poor prognosis.[16-19] Accordingly, it is imperative to completely exclude a metastatic tumor when encountering such unexpected histology.

Herein, we described six primary salivary gland adenocarcinomas with papillary architecture and intestinal-like mucinous cytologic features and two morphology-overlapping metastatic tumors with their clinicopathologic features, immunophenotypes, and *AKT1* mutational status, and reviewed the literature of previously reported morphology-analogous cases to comprehensively describe the peculiar features of this rare malignancy and define its differential diagnosis and classification.

2 | MATERIAL AND METHODS

2.1 | Case selection

Data on cases diagnosed as cystadenocarcinoma, mucinous adenocarcinoma, adenocarcinoma (NOS), and metastatic adenocarcinoma between 2000 and 2019 were retrieved from files in the Department of Oral Pathology, Peking University School and Hospital of Stomatology. Standard hematoxylin- and eosin-stained slides were reviewed for all the cases. For inclusion in this study, we identified a tumor as (1) obviously invasive growth and (2) a papillary mucinous epithelium with gastrointestinal-like morphologic appearance, showing tall columnar epithelial cells with modest amounts of apical intracytoplasmic mucus. Six primary cases that met the inclusion criteria were selected. Two metastatic gastrointestinal adenocarcinomas (case #M1 and #M2) were also included as control.

Clinical data and follow-up information were obtained by consulting individual medical reports and pathology files. In addition, each patient or their close relative was contacted and asked about the patient's current condition. Paraffin-embedded tumor tissues were available for all eight cases. This study was approved by the Peking University Institutional Ethics Committee.

2.2 | Immunohistochemistry

Four-micrometer-thick serial sections were cut, mounted on poly-L-lysine-coated slides, deparaffinized in xylene, and sequentially rehydrated using a graded ethanol series. Endogenous peroxidase activity was quenched by incubation with fresh 3% hydrogen peroxide (H_2O_2) for 10 min at room temperature, and antigen retrieval was subsequently performed with 10% ethylenediaminetetraacetic acid buffer (pH 8.0). Immunostaining was performed by incubating the tissue sections with antibodies specific for CK7, CK20, CDX2, SOX10, S100, MUC1, MUC2, and MUC5AC proteins (ready-to-use reagents; ZSGD-BIO) overnight at 4°C, followed by a 30-min incubation with secondary antibodies. The immunocomplexes were visualized using a liquid 3,3'-diaminobenzidine–substrate–chromogen system (Dako), and slides were lightly counterstained with hematoxylin. The immunohistochemistry results were analyzed by two independent pathologists who were blinded to each patient's information.

2.3 | Mutation analysis

The QIAamp DNA formalin-fixed paraffin-embedded (FFPE) Tissue Kit (Qiagen) was used for genomic DNA extraction from FFPE samples according to the manufacturer's protocol. Polymerase chain reaction (PCR) was performed using two primer pairs covering *AKT1* exon2 (forward 5'-AGGCACATCTGTCCTGGCAC-3'; reverse 5'-AAATCTGAATCCCGAGAGGCC-3') and *K-ras* exon2 (forward 5'-GGTGAGTTTGTATTAAAAGGTACTGG'; reverse 5'-TCCTGCACCAGTAATATGCA-3'). Amplicons were subjected to Sanger sequencing (Beijing Genomics Institute). Detected mutations were confirmed by reverse sequencing and at least two independent PCRs from the same samples.

3 | RESULTS

The detailed clinicopathologic features of the 13 reported cases and the present series are summarized in Table 1.

3.1 | Clinical findings

The six primary cases included four men and two women, whose ages at the time of initial diagnosis ranged from 35 to 84 years (median age: 61.5 years). Two cases involved the palate and the other four the retromolar region, submandibular region, tongue, and mandible, respectively. All cases presented with a painless mass, and two were accompanied by ulcers. Two cases of metastatic gastrointestinal adenocarcinoma (#M1 and #M2) in the infratemporal fossa and tongue were included as controls.

Radiographically, the primary tumors were poorly marginated, heterogeneous, round, or irregular lesions with invasion of adjacent tissues (Figure 1A). The metastatic case exhibited a ragged radiolucent area with ill-defined margins and patchy sclerosis (Figure 1B). Four of the six primary tumors exhibited obvious bone destruction. The metastatic tumor was more vascularized than the primary tumor on contrast-enhanced computed tomography imaging.

In total, five out of six primary cases were reportedly excised completely, and Case #6 underwent tumor biopsy due to their general condition. Follow-up data were available in five primary cases, among which three cases demonstrated no recurrence or metastasis at 8, 11, and 16 years after surgery. Case #4 was noted to experience multiple relapses after the third surgery. Moreover, the lesion was initially treated in another hospital 5 years earlier under a working diagnosis of "papillary cystadenocarcinoma in the left mandible." The tumor recurred three times at 1-year intervals. The last time, the patient presented with swelling in the right mandible, and the lesion was excised with a wide margin. No recurrence or metastasis was detected 2 years after the surgery. Case #5 died recorded due to cerebral infarction 7 days after the surgery.

3.2 | Pathologic findings

Microscopic examination of all primary tumors revealed a characteristic histologic pattern of infiltration with multi-cystic papillary structures containing abundant mucin. Representative histologic images are shown in Figures 2 and 3. These tumors grew as predominant papillary structures, whereas tubular and glandular structures were occasionally seen. Abundant extracellular mucus was present with mucus lake formation or homogeneous secretions in the papillary cystic space. (Figure 2) Papillae and tubules were lined with single-layer or pseudostratified, tall, columnar epithelial cells with modest amounts of apical intracytoplasmic mucus (Figure 3A,B). The tumor cells had either elongated (cigar-shaped) hyperchromatic nuclei (Figure 3A) or round nuclei (Figure 3B) with mild-to-intermediate tufting and polarity loss, accompanied by an inconspicuous nucleolus and homogenous chromatin. Tumor cells floating individually or in clusters displayed eosinophilic cytoplasm, round or oval nuclei, a fine chromatin pattern and conspicuous nucleoli (Figure 3C,D). Cell atypia, pleomorphism, and occasional pathologic mitoses were observed, but no definite areas of perineural invasion, necrosis, or angiolymphatic invasion were identified in the examined specimens. There were no significant histomorphologic differences between primary cases and metastatic gastrointestinal adenocarcinomas.

3.3 | Immunohistochemical findings

Detailed immunohistochemical features are shown in Table, Figure 4, and Figure S1. Tumor cells revealed diffuse and strongly positive immunostaining for CK7 in all primary cases, whereas the intestinal adenocarcinoma immune markers CK20 and CDX2 were completely negative (Figure 4A–C). Only one primary case exhibited intense reactivity for SOX10 (Case #1; Figure 4E). S100 was absent in all primary cases (Figure 4D). In contrast, the metastatic tumor showed an almost identical immunophenotype to their primary site counterparts with positive reactivity for CK20 and CDX2 and negative reactivity for SOX10 and S100, whereas #M2 was positive for CK7 (Figure 4F–J). The mucin profile was detected in six primary cases, which all exhibited MUC1 positivity and MUC2 negativity (Figure S1). MUC5AC was found to be positive in two cases (Figure S1).

3.4 | Molecular findings

Sanger sequencing analysis revealed *AKT1 E17K* hotspot mutations in four out of six primary cases (66.7%), including Cases #1, #2, #5, and #6 (Figure 5). Additional *KRAS* hotspot mutations were not detected in six cases.

4 | DISCUSSION

Six salivary gland tumors with papillary architecture and mucinous cytologic features are reported here, morphologically reminiscent of gastrointestinal epithelium. In addition, we also reviewed the literature of previously reported morphology-analogous cases to comprehensively describe the peculiar features of this rare malignancy. There were 4 men and 2 women in the present series with a median age at first diagnosis of 61.5 years. All the cases in this study demonstrated comparatively favorable prognosis based on a minimum follow-up of 5 years, and three of the cases experienced no recurrence or metastasis 8, 11, and 16 years after surgery. The only recurrent tumor was originally treated in another hospital, and the extent of the surgery had not been determined.

Salivary adenocarcinoma morphologically resemble sinonasal intestinal-type adenocarcinoma was classified as a type of the adenocarcinoma (NOS) in the *2017 World Health Organization Classification of Head and Neck Tumours*.[1] Thirteen cases of the oral cavity have been documented in the literature (Table). Seven cases were described as having obvious extracellular or intracellular mucin.[3,4,6,9,11,12] Of the 13 patients reported, their ages ranged from 40 to 87 years (median: 58 years), among whom 12 patients were male and one was female. Intestinal-type adenocarcinoma in the sinonasal tract or lung always express immunohistologic markers of

TABLE 1 Salivary gland adenocarcinoma with morphologically resemblance to intestine carcinoma

Reference	Age/sex	Location	Mucinous content	Growth pattern	Treatment	Immunostaining	Metastatic workup
Agaimy A[2]	41/M	Mouth floor	Not known	Papillary	Surgery/14 months, NER	CK7 (-), CK20 (+)	No
Volchok J[10]	61/M	Mouth floor	Not known	Tubulo-glandular	Surgery, chemo-radiotherapy/24 months, NER	NA	No
Bell D[3]	58/M	Tongue	Not known	Tubulo-glandular	Chemotherapy, surgery/ 13 months, NER	CK7 (-), CK20 (+), CDX2 (+)	LN
Bell D[3]	58/M	Tongue	Abundant mucin containing	Tubulo-glandular	Chemotherapy, surgery/ 11 months, NER	CK7 (+/-), CK20 (+), CDX2 (+)	LN
Gillenwater A[5]	61/M	Submandibular gland	Not known	Papillary	Surgery/ 12 months, NER	CK7 (+), CK20 (-), CDX2 (-) MUC1 (+), MUC2 (-)	No
Gillenwater A[5]	80/M	Sublingual gland	Not known	Papillary	Radiotherapy/ 70 months, NER	CK7 (+), CK20 (-), CDX2 (-) MUC1 (+), MUC2 (-)	No
Slova D[4]	49/M	Tongue	Variably sized mucin lakes	Tubulo-glandular	Surgery/ Not known, NER	CK7 (+/-), CK20 (+), CDX2 (+) Villin (+)	LN
McDaniel A[6]	60/M	Tongue	Substantial mucin containing	Tubulo-glandular	Surgery/ Not known	CK7 (+), CK20 (+), CDX2 (+),	No
Rahimi S[7]	54/M	Tongue	Not known	Tubulo-glandular	Chemo-radiotherapy/3.5 years, NER	CK7 (+), CK20 (focal, +), CDX2 (+)	Lung Metastasis
Smith S[11]	53/F	Tongue	Intra- and extracellular mucin containing	Tubulo-glandular	Surgery, radiotherapy/ 12 months, NER	CK7 (-), CK20 (+), CDX2 (+) MUC2 (+), MUC5AC (+)	No
Guo C[12]	59/M	Tongue	Mucin lakes	Tubulo-glandular	Surgery, chemo-radiotherapy/8 months, NER	CK7 (-), CK20 (+)	No
Kikuchi K[9]	87/M	Buccal	Abundant extracellular mucin	Papillary	Surgery/ 6 months, NER	CK7 (+), CK20 (+, focal), CDX2 (-)	No
Berg J[8]	40/M	Tongue	Mucin containing <10%	Tubulo-glandular	Surgery, radiotherapy/13 months, NER	CK7 (-), CK20 (+), CDX2 (+)	LN
The present series							
Case #1	35/M	Palate, L&R	Abundant mucin	Papillary	Surgery/16 years, NER	CK7 (+), CK20 (-), CDX2 (-) SOX10 (+), S100 (-), MUC1 (+), MUC2 (-), MUC5AC (focal, +)	No
Case #2	68/F	Mandible, R	Abundant mucin	Papillary	Surgery /11 years, NER	CK7 (+), CK20 (-), CDX2 (-) SOX10 (-), S100 (-), MUC1 (+), MUC2 (-), MUC5AC (-)	No
Case #3	63/M	Submandibular region, R	Abundant mucin	Papillary	Surgery/5 years, NER	CK7 (+), CK20 (+/-), CDX2 (-) SOX10 (-), S100 (-), MUC1 (+), MUC2 (-), MUC5AC (+)	No
Case #4	60/M	Retromolar region, R	Abundant mucin	Papillary	Surgery/1 year, Rec	CK7 (+), CK20 (-), CDX2 (-) SOX10 (-), S100 (-), MUC1 (+), MUC2 (-), MUC5AC (-)	No
Case #5	59/F	Tongue, R	Abundant mucin	Papillary	Surgery/7 days, Died	CK7 (+), CK20 (-), CDX2 (-) SOX10 (-), S100 (-), MUC1 (+), MUC2 (-)	No
Case #6	84/M	Palate, L	Abundant mucin	Tubulo-glandular	Biopsy/NA	CK7 (+), CK20 (-), CDX2 (-) SOX10 (-), S100 (-), MUC1 (+), MUC2 (-), MUC5AC (+)	NA

Abbreviations: (-), negative; (+), positive; Dur: duration; F: female; L, left; LN, lymph node metastasis; M: male; NA, not available; NER, no evidence for recurrence; R, right; Rec, recurrence.

intestinal differentiation, such as CK20, CDX2, and MUC2.[20,21] The immunophenotypes of the previously reported 13 cases involving the salivary gland were variable. The majority of patients (10/13, 76.9%) expressed markers of intestinal differentiation; however, three cases with papillary architecture and mucinous cytologic features presented an immunophenotype of CK7 positive and CDX2 & MUC2 negative. Interestingly, all the six primary cases in this series demonstrated a consistent CK7+/CK20−/CDX2−/MUC2− immunophenotype. In addition, our cases revealed a diffuse strong expression of MUC1, which has been detected positive in several salivary gland tumors.[22] Given that, several articles have revealed a high incidence of *KRAS* mutation in pulmonary enteric adenocarcinoma,[23,24] we also detected *KRAS* mutations in our cases, and all cases were wide-type. Therefore, we suppose primary salivary adenocarcinomas with papillary architecture and mucinous cytologic features histologically mimicking gastrointestinal epithelium yet lacking the immunophenotype for intestinal differentiation should be one separate entity rather than conventional intestinal-type adenocarcinoma.

Recently, a unified mucinous adenocarcinoma category was proposed by Rooper et al., with abundant mucin production and subdivided into papillary, colloid, signet ring, and mixed subtypes. Papillary architecture with intracellular mucin was the most common pattern (15/17, 88.2%) in their cohort, which demonstrated a consistent CK7+/CK20−/CDX2− immunophenotype and recurrent *AKT1 E17K* mutations.[14] *AKT1 E17K* mutations have frequently been described in breast cancers, with reference to the substitution of glutamate acid with lysine at the seventeenth amino acid, thus altering the pleckstrin homology domain and forming new hydrogen bonds. Altered AKT1 E17K is located in the plasma membrane, leading to constitutive activation of the PI3K downstream pathway, which is essential for cancer progression.[25] Agaimy et al.[13] described 3 cases of papillary mucinous neoplasms of minor salivary glands with variable cytologic and architectural atypia from papillary adenoma to low-grade carcinoma, and all the 3 papillary neoplasms showed uniform mucinous-like cytologic features reminiscent of gastrointestinal epithelium, which positively expressed CK7 and MUC1 and had an identical *AKT1 E17K*

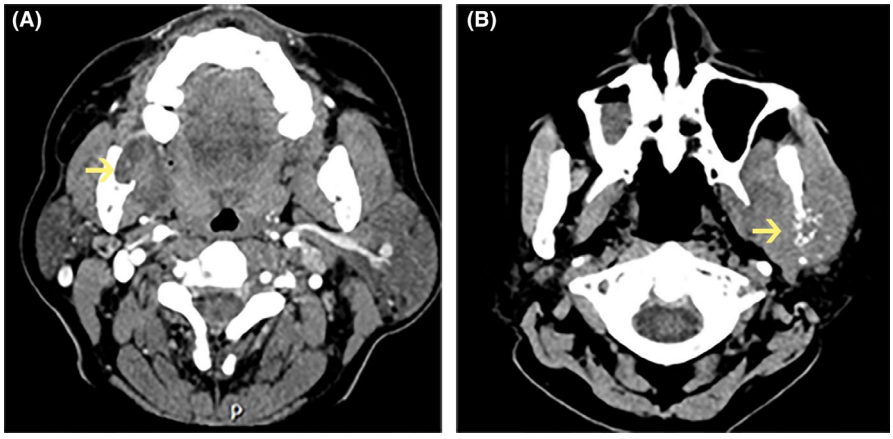

FIGURE 1 Contrast-enhanced CT images showed a heterogeneous, round, or irregular lesion with invasion into adjacent tissues of the primary case (A, Case #4) and an ill-defined ragged radiolucent with patchy sclerosis of the metastatic tumor from gastrointestinal adenocarcinoma (B, Case #M1)

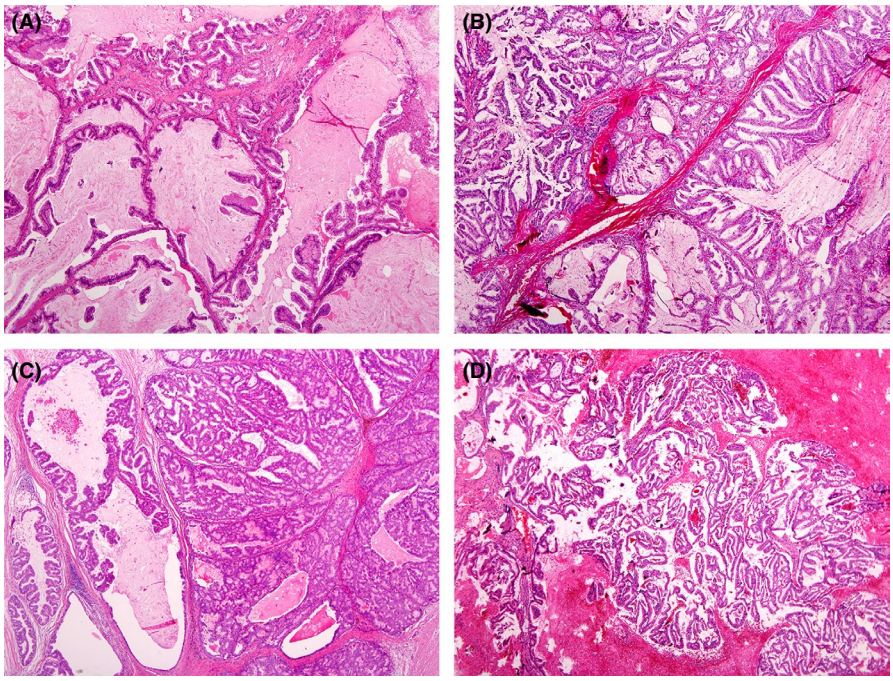

FIGURE 2 Each salivary gland adenocarcinoma with intestinal-like features demonstrated similar histologic feature, a characteristic histologic pattern of infiltration associated with gastrointestinal adenocarcinoma with multi-cystic papillary structures containing abundant mucin. (A-D, Case #1-#4) Abundant extracellular mucus was occasionally present with mucus lake formation or homogeneous secretions in the papillary cystic space. (Hematoxylin and eosin, 40×)

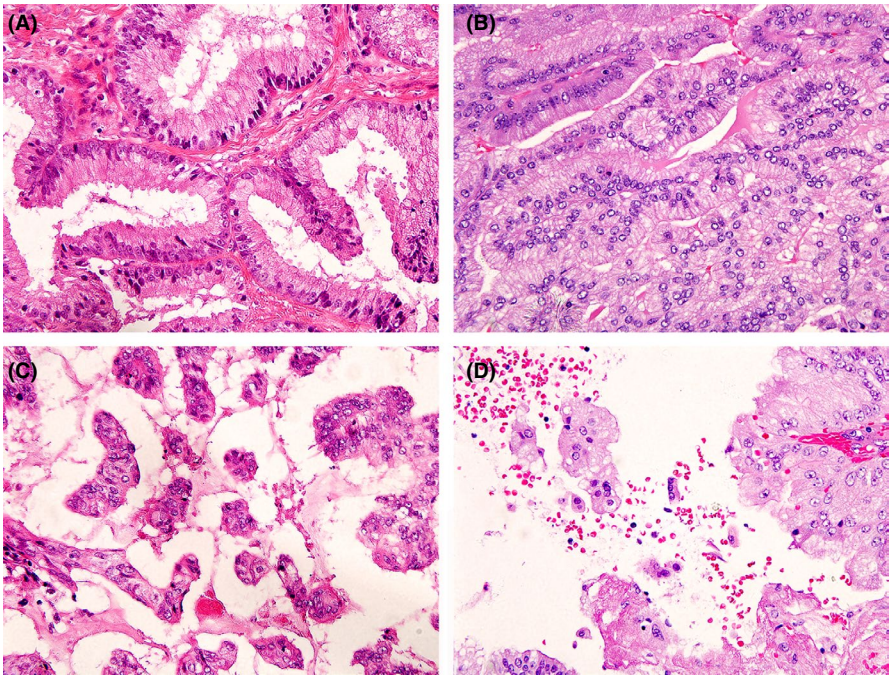

FIGURE 3 High-power view (hematoxylin and eosin, 400×) revealed the tumor cells were elongated (cigar-shaped) hyperchromatic nuclei (A) or round nuclei with mild-to-intermediate tufting and polarity loss, accompanied by an inconspicuous nucleolus and homogenous chromatin (B). Tumor cells floating individually or in clusters displayed eosinophilic cytoplasm, round or oval nuclei, a fine chromatin pattern and conspicuous nucleoli (C & D)

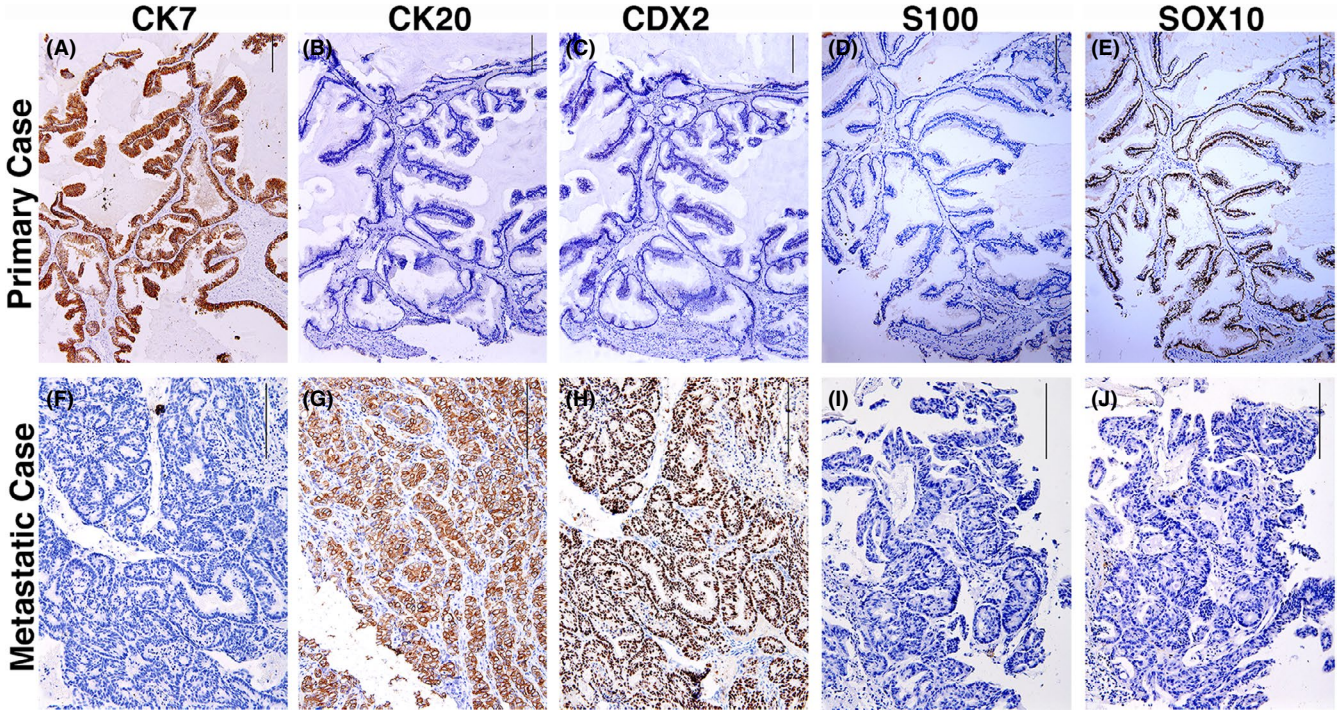

FIGURE 4 Immunohistochemistry revealed primary cases expressing CK7 (A) were negative for CK20 (B), CDX2 (C), and S100 (D), and Case #1 expressed SOX10 (E). Metastatic tumors exhibited a negative expression of CK7 (F), diffuse positive staining for CK20 (G) and CDX2 (H), and negative expression of S100 (I) and SOX10 (J). The magnification of images A–E is x100, and the magnification of images F-J is x200. (Scale bar: 200 μm)

mutation. Since then, eleven similar papillary mucinous neoplasms sequenced have activating *AKT1 E17K* mutations.[26] In the present study, four cases (4/6) exhibited the recurrent presence of *AKT1 E17K* mutation based on Sanger sequencing. Given the similar morphologic and immunohistochemical features, we suggest this papillary mucinous neoplasm might be a molecular entity with recurrent *AKT1 E17K* mutation status. Furthermore, we also favor it should be removed from the adenocarcinoma (NOS) and reclassified as a distinct entity to better explore the nature of these tumors and improve the precision of the current classification schemes.

In addition, the prognosis of metastatic colorectal tumors is poor,[27] and metastatic tumors in the oral cavity mainly involve

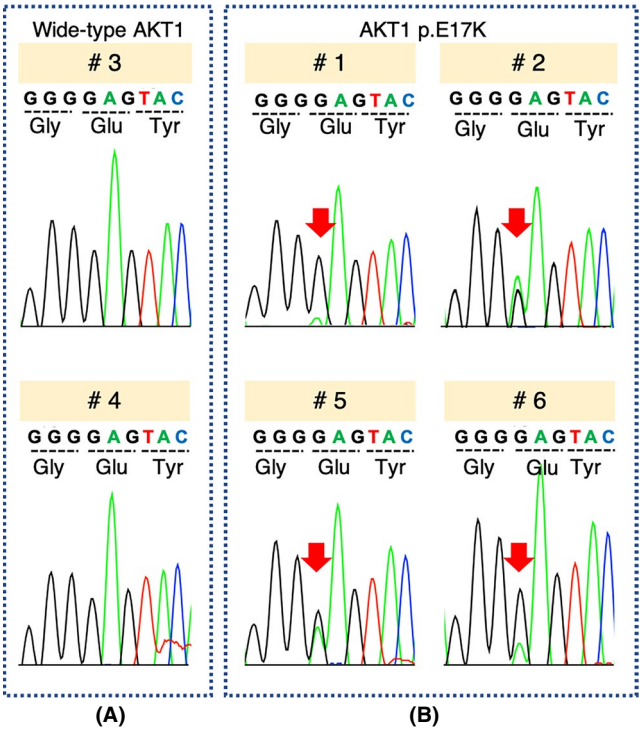

FIGURE 5 Sanger sequencing analysis revealed AKT1 E17K mutations in four out of six cases (66.7%). Cases #1 and #5 exhibited wide-type mutations. (A) Cases #2–4 and #6 displayed a G-to-A missense mutation in codon 49 (B)

the bony structure[15]; therefore, it is imperative to exclude the possibility of metastatic adenocarcinoma. Immunohistochemistry analysis revealed intense and diffuse CK7-positive staining as well as CK20- and CDX2-negative staining in all six primary cases in the present study, but the two metastatic cancers were both positive for CK20 and CDX2. In addition to immunostaining, extensive examination was performed, revealing no evidence of a primary tumor in other areas, including the gastrointestinal tract. Radiographically, the metastatic case exhibited a ragged radiolucent area with ill-defined margins and patchy sclerosis, and contrast-enhanced computed tomography imaging revealed that the metastatic tumor was more vascularized than the primary tumor, although both primary and metastatic tumors may show bone destruction. Taken together, extensive examination and $CK7^+/CK20^-/CDX2^-$ immunophenotype contribute to exclude the possibility of metastatic adenocarcinoma.

In summary, we reported six salivary gland adenocarcinomas with papillary architecture and intestinal-like mucinous cytologic features and compared them with previously reported morphology-analogous cases based on their clinicopathologic, immunohistochemical, and genetic features. Our study indicates these papillary adenocarcinomas with mucinous cytologic features are different from conventional intestinal-type adenocarcinoma. Typical morphologic information, a classical $CK7^+/CK20^-/CDX2^-$ immunophenotype, and recurrent *AKT1 E17K* mutation may define it.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

AUTHOR CONTRIBUTION

Xiaoxiao Liu: Conceptualization; Data curation; Investigation; Validation; Visualization; Writing – original draft. **Ye Zhang:** Investigation; Validation. **Chuanxiang Zhou:** Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Supervision; Validation; Writing – review & editing. **Tie-jun Li:** Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Validation; Writing – review & editing.

PEER REVIEW

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