Head and Neck Pathology (2019) 13:131–139
https://doi.org/10.1007/s12105-018-0916-4

ORIGINAL PAPER

Palatal Polymorphous Adenocarcinoma with High-Grade Transformation: A Case Report and Literature Review

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Received: 26 January 2018 / Accepted: 26 March 2018 / Published online: 29 March 2018

Abstract
Polymorphous adenocarcinoma (PAC) is the second most common intraoral malignant neoplasm of the minor salivary glands. However, it is very rare for PAC to show high-grade transformation (HGT) and to our knowledge, the English literature only seven reported cases. HGT tends to be observed when PAC recurs, and it is extremely rare to be seen at initial presentation. Here we report a 43-year-old Japanese male patient with PAC of the right palate showing HGT at initial presentation. Histopathologically, the tumor was characterized by a prominent solid and papillary-cystic growth pattern, with nuclear atypia and necrosis in area of HGT. The immunohistochemical staining pattern was consistent with PAC, as the tumor cells showed diffuse positivity for cytokeratin, vimentin and S-100, and focal positivity for bcl-2, α-SMA and EMA. The tumor cells in HGT areas were markedly positive for AR and Ki-67 (about 40%/HPF), and also focally positive for cyclin D1 and p53, whereas HER2/neu, ER, PgR, p63, D2-40, GCDFP-15, and mitochondria were negative. Here we present a very rare case of palatal PAC with HGT at initial presentation.

Keywords Polymorphous adenocarcinoma (PAC) · High-grade transformation (HGT) · Minor salivary gland · Palate

Introduction

The concept of dedifferentiation/high-grade transformation (HGT) was first proposed by Dahlin and Beabout in 1971, when they described dedifferentiated chondrosarcoma as a distinct clinicopathologic entity characterized by low-grade chondrosarcoma juxtaposed to a histologically different high-grade sarcoma [1]. HGT is defined as the histological progression of a low-grade to a high-grade malignant neoplasm [2]. It can occur at the time of initial presentation or at recurrence. The first reported case of a salivary gland tumor showing HGT was an acinic cell carcinoma

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Table 1 Summary of clinicopathological findings of dedifferentiation/HGT derived from PAC cases in head and neck

Case No.	Aurhor [Ref.]	Age	Sex	Sites	Size	Treatment (times)	Histological growth patterns			Metastasis		Outcome ⟨month⟩
							LG area (con-PAC)	HG area (transformation)	LG/HG area (demarcate)	Cervical lymph nodes	Distant organs	
⟨HGT in recurrence cases⟩												
1	Mills et al. [5]	48	F	Palate, R	Initial primary, 15 mm Recurrence, 35 mm	Sur (1) Rad (1) Hyp (1)	Cys, Pa, So	So, Nec	Clearly separated	Node (+), R Nodes 43 (–), L	Mandible (+)	AWD ⟨NA⟩
2	Pelky et al. [7]	38	F	Palate, L	Initial primary, NA First recurrence, NA Second recurrence, NA Third recurrence, 40 mm Fourth recurrence, 30 mm	Sur (5) Rad (2) Che (1)	Tub, Tra, Sin-F, Crib	So, Come-Nec (*) (Fourth recurrence)	NA (*)	NA	(–)	NA
3	Pelky et al. [7]	44	F	Palate	Initial primary, NA First cervical node, NA Second cervical node, NA Recurrence, NA	Sur (4) Rad (1)	Tub, Tra, Sin-F, So, Crib (*)	So, Come-Nec	NA (*)	Two times (+) (lymphadenectomy)	(–)	NA
4	Simpson et al. [8]	66	M	Palate	Initial primary, 30 mm Recurrence, 12×7 mm	Sur (2)	So, Crib, Tub, Sin-F, Pa†	So, Come-Nec††, ¶¶	NA (*)	NA	(–)	AWD ⟨156⟩
⟨HGT in initial presentation cases⟩												
5	Lloreta et al. [6]	47	M	Nasal cavity, R	Initial primary, NA	Sur (1)	So (clear), Cord, Gland-like	So, Come-Nec SDC-like Undifferentiated ACa	Cleary separated	NA	NA	DOD ⟨36⟩ Septic shock by E. coli urine infection

Table 1 (continued)

Case No.	Aurhor [Ref.]	Age	Sex	Sites	Size	Treatment (times)	Histological growth patterns			Metastasis		Outcome ⟨month⟩
							LG area (con-PAC)	HG area (transformation)	LG/HG area (demarcate)	Cervical lymph nodes	Distant organs	
6	Simpson et al. [8]	63	M	Palate, L	Initial primary, 25 mm Cervical node, 20 mm	Sur (2) Che (1)	Sin-F, Tub, Crib, So†	So, Come-Nec, SDC-like††, ¶¶	Some extent separated	First Sur (+), Multiple, L Second Sur (+), Bilateral	(−)	AWD ⟨5⟩
7	Radhakrishnan et al. [9]	73	F	Maxillary alveolous, R	Initial primary, 35 × 20 mm	Sur (1)	So, Crib, Sin-F, Tub	So Poorly differentiated ACa¶	NA (*)	One node (+), R	Abdomen (+) Lung (+)	NA
	Our present case	43	M	Palate, R	Initial primary, 25 × 20 × 18 mm	Sur (1)	Tub, Pa, So, Crib, Sin-F†	So, Come-Nec, Tra††, ¶¶	Cleary separated	(−)	(−)	AWD ⟨39⟩

M male, *F* female, *L* left, *R* right, *Sur* surgery, *Rad* radiation therapy, *Che* chemotherapy, *Hyp* hyperyhermia, *LG* low-grade, *HG* high-grade, *So* solid, *Crib* cribriform, *Sin-F* single-file (Indian-file, cord), *Tub* tubule, *Cys* cystic, *Pa* papillary (micro-, small-, or cystic-papillary), *Tra* trabecular, *Nec* necrosis, *Come-Nec* comedo-necrosis, *SDC* salivary duct carcinoma, *ACa* adenocarcinoma, *NA* not available, (*) not indicated typical histologic-image, (+) positive, (−) negative, *AWD* alive without disease, *DOD* died of disease, *[Ref.]* reference number, ⟨month⟩ —month of passage from final operation

††Positive for androgen receptor (AR)

†Focally positive for AR

¶ > 20% Ki-67 labeling index (LI)

¶¶ > 30% Ki-67 LI

in 1988 [3]. Subsequently, HGT has been recognized in a variety of salivary gland carcinomas, including acinic cell carcinoma, adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, polymorphous adenocarcinoma (PAC), myoepithelial carcinoma, low-grade mucoepidermoid carcinoma, and hyalinizing clear cell carcinoma [4]. However, PAC with HGT is very rare with only seven cases having been described in the English language literature [5–9] (Table 1). Five of the tumors arose in the palate [5, 7, 8], one in the nasal cavity [6] and one in the maxillary alveolus [9]. HGT arising from palatal PAC at initial presentation is very rare in only one case (Table 1: Case No. 6). In three recurrent cases, HGT arising from typical PAC developed after a protracted clinical course, the recurrences having been managed by excision and radiation therapy (Table 1: Case No.1, 3, 4). These tumors were composed of two distinct elements—low-grade and high-grade—that were partly admixed with each other. However, a few cases of PAC have been reported to significantly comprise a variety of morphological growth patterns, the so-called "polymorphous feature" [10–13]. In the present case, conventional PAC (con-PAC) elements exhibited a variety of growth patterns consistent with PAC, and the HGT elements exhibited comedo-like necrosis of solid growth patterns with high positivity for Ki-67, p53, cyclin D1 and androgen receptor (AR). Here we report a rare case of con-PAC with HGT arising in a minor salivary gland of the right palate at initial presentation.

Case Report

A 43-year-old Japanese man was referred to the Department of Oral and Maxillofacial Surgery, Meikai University Hospital, for a painless swelling in the right palate. On examination, the right palate showed normal coloration without ulceration (Fig. 1). Computed tomography (CT) revealed a palatine tumor (Fig. 2a) with osteolysis (Fig. 2b). Cervical lymphadenopathy was not evident, and the results of blood tests were all within the normal ranges. Both the patient and his family had an unremarkable medical history. The clinical diagnosis was a suspected malignant tumor of a minor salivary gland in the right palate. Although biopsy of the palatine tumor was performed, the pathological diagnosis was normal tissue without a tumor component. Therefore, the lesion was resected under general anesthesia. Macroscopically, the surgical specimen was a solid mass, measuring $42 \times 30 \times 24$ mm, and the cut surface revealed a circumscribed multi-lobulated solid mass, measuring $25 \times 20 \times 18$ mm, that was homogeneously light yellow to grayish-white. Microscopic low-power examination showed that the lesion was well-circumscribed (Fig. 3a), but not completely

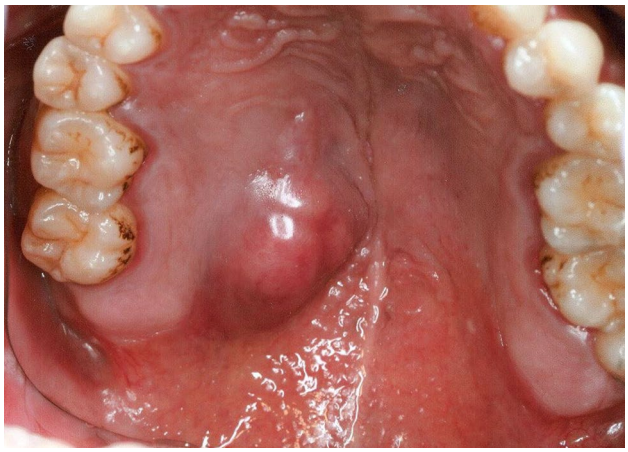

Fig. 1 Intra-oral appearance of the right palate. Swollen nodular lesion showing in the right palate without mucosal ulcer

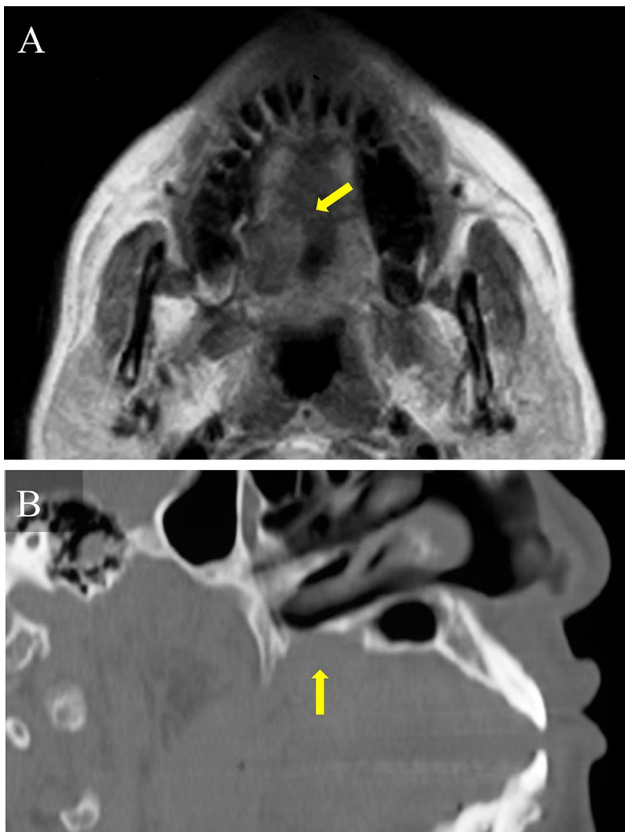

Fig. 2 Computed tomography (CT) findings. **a** CT showing undelineated mass lesion (yellow arrow) in the right palate, **b** and with cortical bone osteolysis in the hard palate (yellow arrow)

encapsulated and focally infiltrative (Fig. 3b). In many of the tumor cells, neoplastic extensions approached the overlying surface epithelium, but the tumor and surface epithelium were sharply separated from the mucosal epithelium by a narrow rim of uninvolved connective tissue

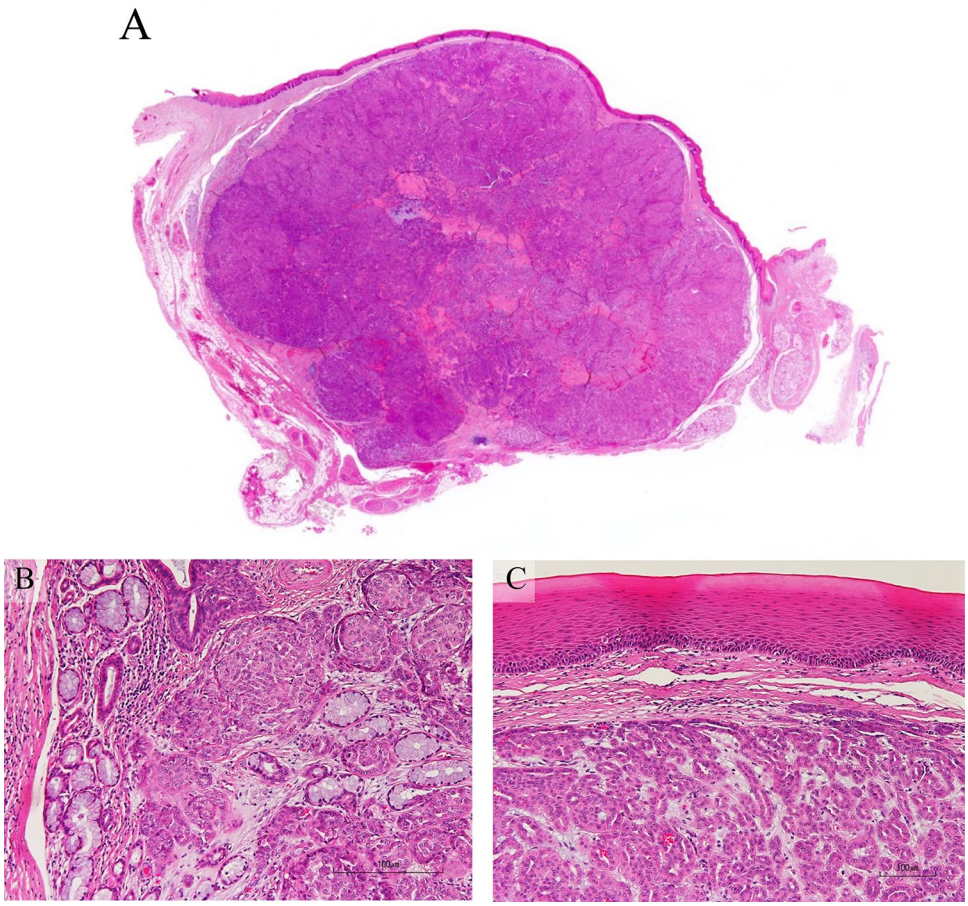

Fig. 3 Microscopic features of the surgical specimen. **a** Survey view, tumor showing well circumscribed nodule. **b** Tumor is unencapsulated, and focally infiltrative into submucosal minor salivary gland. **c** Tumor and surface epithelium are sharply separated by a narrow rim of uninvolved connective tissue. HE, original magnification × 12.5 (**a**), × 100 (**b, c**)

(Fig. 3c). The morphological growth patterns in areas of con-PAC included small tubular and papillary (Fig. 4a, b), lobulated small papillary (Fig. 4c), cystic-papillary and solid (Fig. 4d), solid with peripheral palisading (Fig. 4e), cord-like cribriform (Fig. 4f), and perineural and perivascular invasion (Fig. 4g, h). HGT areas showed mainly solid growth, with comedo-like necrosis clearly separate from con-PAC elements (Fig. 5a, b), marked mitoses with irregular nuclei (Fig. 5c), cellular and atypical trabecular arrangements (Fig. 5d), and partly atypical clear and oncocytic cells (Fig. 5e, f). Immunohistochemistry showed that tumor cells in the con-PAC and HGT areas were diffusely positive for pan-cytokeratin (CK), vimentin, and S100 protein (Fig. 6a–c), and the Ki-67 positive rate was higher in HGT areas (about 40%/HPF) than in con-PAC areas (about 4%/HPF) (Fig. 6d). HGT solid elements (with or without necrosis) were positive for AR, Ki-67, cyclin D1, and p53 (Fig. 6e–h), but negative for ER, PgR, HER2/neu, p63, D2-40, GCDFP-15, and mitochondria.

The case study protocol was reviewed and approved by the Research Ethics Committee of Meikai University School of Dentistry (A1321).

Discussion

Polymorphous low-grade adenocarcinoma (PLGA), now shortened to polymorphous adenocarcinoma (PAC), is the WHO classification term for a salivary gland tumor [12], that in some cases show more aggressive behavior and morphologic appearance as highlighted by the current case. Although described earlier as terminal duct carcinoma by Batsakis et al. [10] and lobular carcinoma by Freedman and Lumerman [13], the term PLGA was first used in 1984 by Evans and Batsakis [11] in their study of 14 cases, designating it as PLGA with low-grade behavior and diverse morphologic feature. PAC occurs most commonly in minor salivary glands of the oral cavity and oropharynx [12]. The most frequent site of presentation is the palate, accounting for about 60% of all cases, followed by the lip, buccal mucosa, and alveolar ridge [12]. It may also affect the retromolar region, floor of mouth, posterior tongue and nasal cavity [14–16]. PAC is the second most common intraoral malignant neoplasm affecting minor salivary glands [12]. However, it is very rare for PAC to show HGT: the English literature includes only five reports of seven cases [5–9],

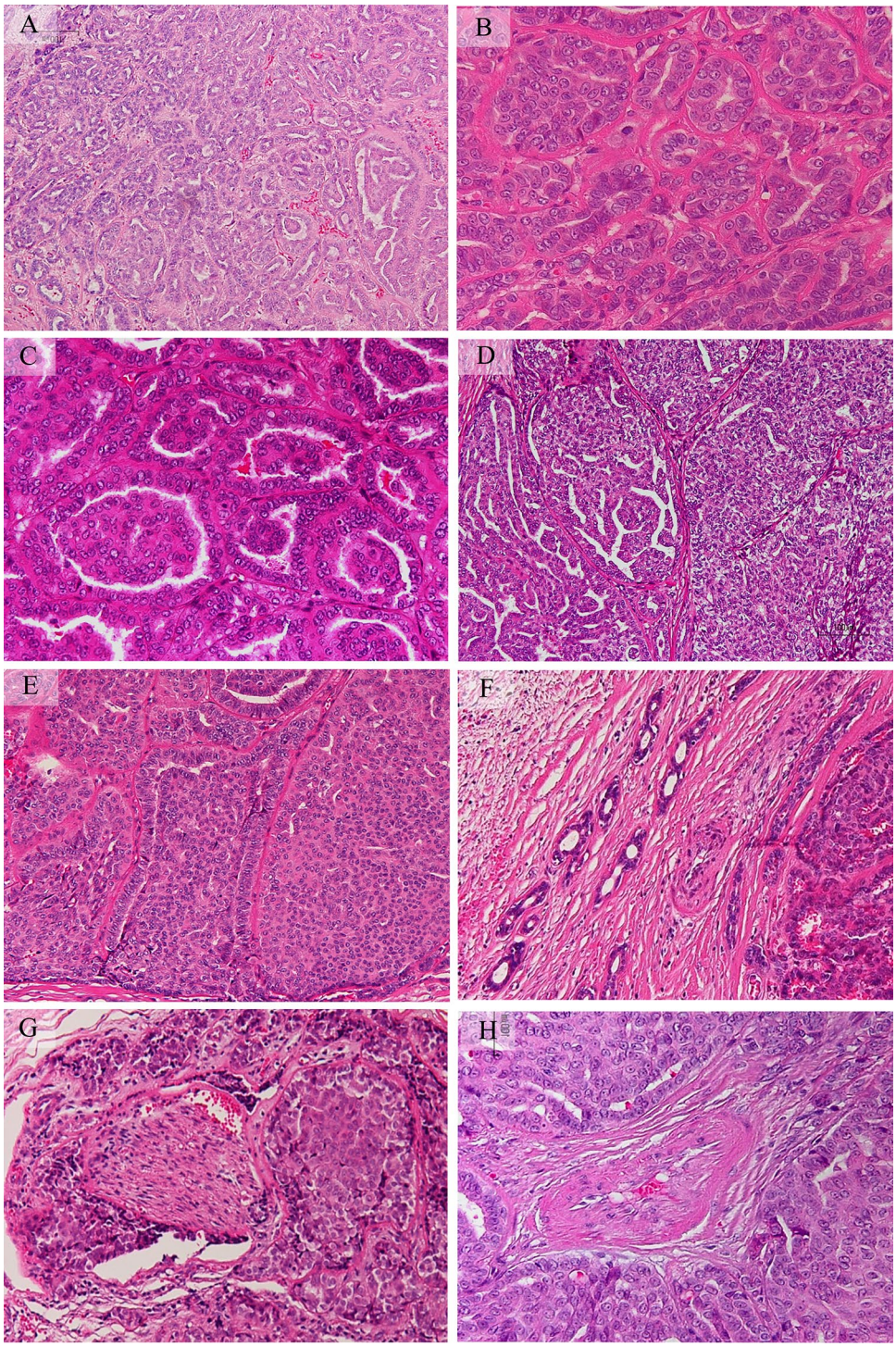

Fig. 4 Morphological growth pattern in con-PAC area. **a, b** Tumor growth showing small tubular and papillary, **c** lobulated small papillary, **d** cystic-papillary and solid, **e** solid with peripheral palisading, **f** cord-like cribriform, **g, h** perineural and perivascular invasion. HE, original magnification × 40 (**a**), × 100 (**d**), × 200 (**b, c, e, f, g, h**)

five cases in the palate [5, 7, 8], one in the nasal cavity [6] and one in the maxillary alveolus [9]. It can occur at the time of initial presentation or at recurrence (Table 1). In three recurrent cases, HGT arising from typical PAC developed after a protracted clinical course during which recurrences were managed by excision, follow up, and radiation therapy (Table 1; Case No. 1, 3, 4). One case of PAC demonstrated a variety of morphological growth patterns, such as solid, cribriform, small tubules, fascicular streams, and occasional foci of Indian filing and micropapillary structures composed of small to intermediate-sized, uniform and bland tumor cells. The other components were considered to be poorly differentiated adenocarcinoma or undifferentiated carcinoma. HGT arising from PAC at initial presentation (Table 1: Case No. 5–7), had low-grade components typical for PAC, and high-grade components considered to

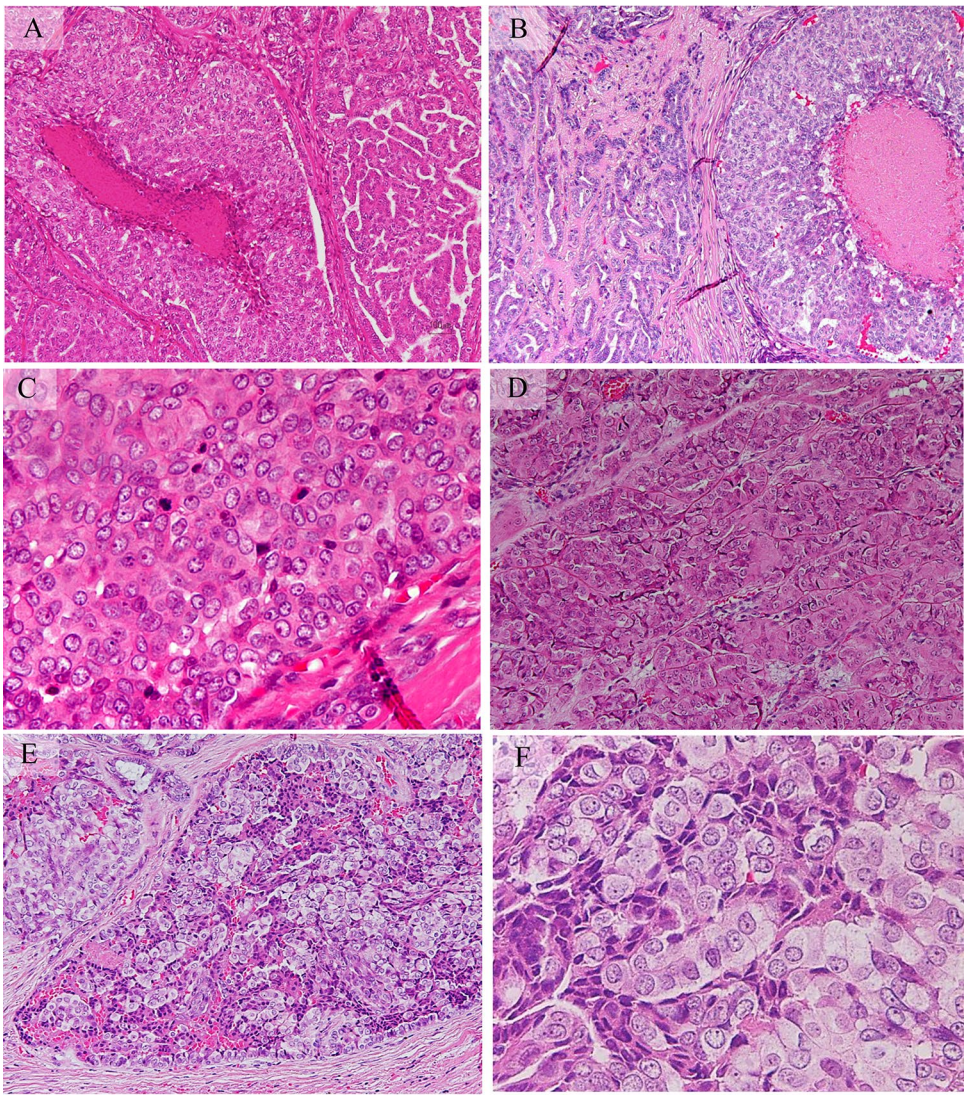

Fig. 5 Morphological growth pattern in HGT area. **a, b** HGT area showing mainly solid growth pattern with comedo-like necrosis clearly separate to con-PAC elements, **c** marked mitoses and irregular nuclei. **d** Focally, high-cellular trabecular arrangement, **e, f** and clear and oncocytic atypical cells in part. HE, original magnification × 100 (**a, b**), × 200 (**d, e**), × 400 (**c, f**)

be poorly differentiated adenocarcinoma or undifferentiated carcinoma exhibiting high-grade morphology characterized by a predominantly solid growth pattern, nuclear atypia with prominent nuclei, foci of necrosis, a high mitotic count and a high Ki-67 positivity index. In one case, the HG element displayed AR positivity (Table 1: Case No. 6), thus resembling SDC. In the present case, the HGT area morphologically resembled case of Simpson et al. [8], and the con-PAC area comprised a variety of morphologic growth patterns. Our present case is the second reported case of HGT arising from con-PAC at initial presentation.

Diagnosis of PAC is often difficult due to this morphological diversity and variable growth patterns. Histological growth patterns of PAC and adenoid cystic carcinoma (ACC) have several overlaps, such as infiltrating tubular, cribriform and solid histology, presence of cystic spaces and neurotropism [12, 17]. However, immunohistochemical staining pattern of PAC is diffusely positive for pan-CK including CK 7, vimentin and S100 protein [9, 11, 18–21], but ACC is a biphasic tumor [22, 23]. Myoepithelial markers (α-SMA and p40) are negative in PAC [18, 20, 24], but positive in ACC [22, 24]. Additionally, *PRKD1* E710D mutations are largely restricted to classic PAC [21, 25–27]. Although PAC and ACC exhibit nearly similar histological patterns, their biologic behavior is significantly different [12, 17]. Therefore, initial pathological diagnosis of PAC in minor salivary glands is very important.

HGT is composed of conventional carcinoma juxtaposed with areas of high-grade morphology, usually either poorly differentiated adenocarcinoma or undifferentiated carcinoma, and commonly the low-grade and high-grade areas can be clearly demarcated [1, 2, 4]. In the present case, the con-PAC and HGT areas were clearly demarcated (Fig. 5a, b), although they were partly admixed (transitional zone). Kusafuka et al. [28] have suggested that HGT of ACC or epithelial-myoepithelial carcinoma may be associated

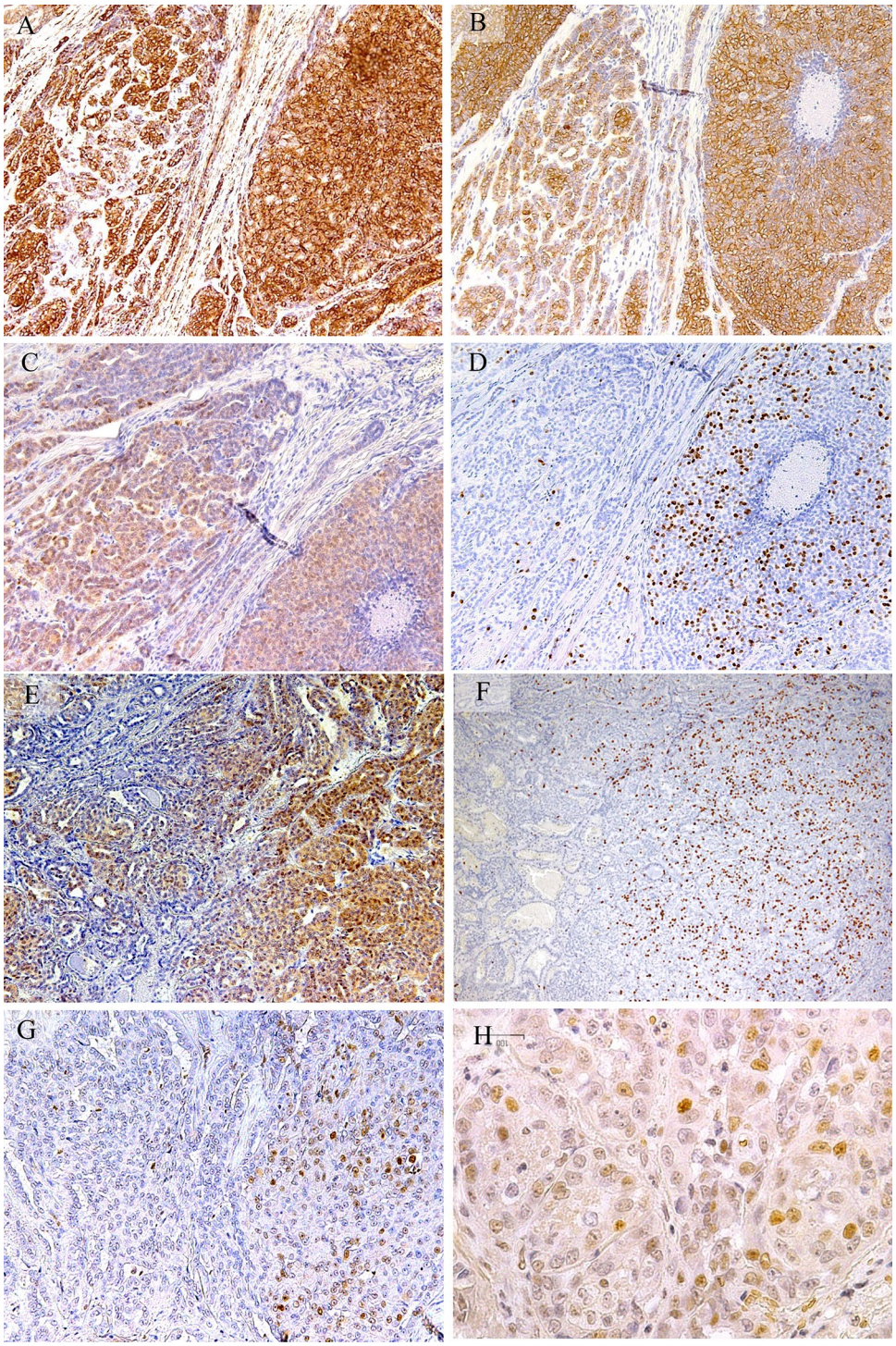

Fig. 6 Immunohistochemical features in con-PAC and HGT areas. **a, b, c** Both con-PAC and HGT areas show diffusely positive for pan-cytokeratin, vimentin and S100 protein, without biphasic positive pattern (two-cell pattern components). **d** Positive reactivity for Ki-67 is about 40% (HPF) in HGT elements, and about 4% (HPF) in con-PAC elements. **e** Positive reactivity for AR shows diffusely in solitary HGT elements and focally in con-PAC elements. **f** Ki-67 positive rates are about 40% (HPF) in the HGT area, **g, h** and also expression of cyclin D1 and p53 are higher HGT area than con-PAC area. Immunohistochemistry, original magnification × 100 (**a**–**g**), × 200 (**h**)

with *p53* gene alteration and overexpression of p53 protein and cyclin D1. Costa et al. have reported that the most useful tool for identifying the transformed component is a combination of morphological criteria along with immunohistochemistry for Ki-67 expression [8, 29]. In the present case, immunohistochemistry was able to distinguish between the low- and high-grade components. Positive reactivity for Ki-67, p53 and cyclin D1 was higher in HGT than in con-PAC areas. Therefore, the most compatible pathological diagnosis was PAC with HGT. Here we have reported an extremely rare case of HGT arising in PAC of palatal minor salivary gland at initial presentation.

Author Contributions Case study design: KK; Clinical data resources: ST, HS; Investigation of the literature: FI, ST; Immunohistochemical analysis: KK, IT; Visualization: KK, KK; Supervision: FI, TN, TJL,

KK; Writing-original draft: KK; Writing-review & editing: TN, TJL, KK; All authors gave final approval and agreed to be countable for all aspects of the work.

Compliance with Ethical Standards

Conflict of interest All authors have indicated they have no potential conflicts of interest and no financial relationships relevant to this article to disclose.

Ethical Approval This article dose not contain any studies with animals performed by any of the authors.

Ethical Standards All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent from a patient has been obtained in this case report.

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