CASE REPORT

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Synchronous Warthin tumor and papillary oncocytic cystadenoma in the ipsilateral parotid gland: an unreported association

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Abstract

The occurrence of ipsilateral, synchronous, primary salivary gland tumors of different histological type is rare. In this report, we present the case of a 52-year-old male, established smoker, who showed simultaneously two different benign tumors in the right parotid gland. The patient complained of swelling below the angle of the mandible. Ultrasonography and computed tomography imaging revealed one mass of about 2.8 cm in the right gland. Besides, one small nodule in the left parotid gland was observed. The cytological diagnosis of the right gland was benign tumor, type IVa of the Milan system, consistent with Warthin tumor (WT). The clinical diagnosis was bilateral parotid WT. The histopathological (HP) study of the surgical specimen revealed a WT in combination with a papillary oncocytic cystadenoma (POC) in the right parotid. To our knowledge, this combination of tumors has not been previously reported. In our case, the association of tumors was not detected by imaging or fine-needle aspiration cytology (FNAC). WT and POC are difficult to distinguish by FNAC because their epithelial component is very similar. POC can resemble WT without lymphoid stroma, but the totality of HP features allows the differentiation of both processes. These tumors can be related to a common causal determinant and should not be considered as a result of chance. Both tumors follow favorable courses and are curable by surgical resection.

Keywords: salivary gland, synchronous neoplasms, ipsilateral tumors, Warthin tumor, papillary oncocytic cystadenoma, tumor association.

Introduction

Salivary gland tumors are relatively uncommon and represent less than 2% of all tumors in humans [1]. These tumors are usually solitary. Multiple, discrete separate tumors arising in the major salivary glands are very unusual. The terminology for multiple, primary salivary gland tumors is based on five factors [2, 3]: number of glands involved, distribution (unilateral or bilateral), number of foci within a gland, and sequence of tumor development (synchronous or metachronous). Tumors that involve a single gland at the same time and comprise more than one histological type are classified as either hybrid or synchronous. Hybrid tumors show a biphasic histological appearance in spite of their clonal origin [4]. In contrast, synchronous tumors represent the development of at least two neoplasms originating at independent sites in the gland. Most cases of synchronous ipsilateral major salivary gland tumors reported in the literature have been observed in the parotid gland. The synchronous development of primary tumors with different histological types is very uncommon and when it occurs, the most frequent combination is Warthin tumor (WT) and pleomorphic adenoma [5].

To the best of our knowledge, the synchronous and ipsilateral coexistence of WT and papillary oncocytic cystadenoma (POC) has not been reported. This paper describes for the first time a case of this combination of neoplasms.

Case presentation

A 52-year-old male was referred to as the Service of Otorhinolaryngology. He consulted for a right neck painless swelling below the angle of the mandible. The lump had been discovered by self-checking five months ago. The patient had a history of tobacco abuse and his smoking index was 30 pack-year (one pack/day for 30 years). In the past, he underwent a left eye enucleation because of traumatic injuries. No trismus, facial nerve palsy, or pharyngolaryngeal symptoms were noticed. Physical examination revealed a right well-delimitated mobile lump measuring about 3 cm. The mass was not tender and the skin covering the lesion appeared normal. Ultrasonography revealed a solid, well-defined, hypoechoic nodule with cystic and minimally vascularized areas in the right parotid gland (Figure 1A). The nodule measured 2.8 cm in the largest diameter (Figure 1B). A computed tomography (CT) scan demonstrated a solid heterogeneous nodule, contrast enhancer, with hypodense areas within it probably cystic. Its limits were well defined. It involved the tail of the right gland (Figure 1C). The size of the lesion was 2.2×2×2.4 cm on the axial, coronal, and sagittal

planes, respectively. The parotid showed abundant fatty infiltration. A similar well-delimited, solid, predominant hyperdense nodule with a hypodense zone was detected on the left parotid gland (Figure 1D). This lesion measured 1.3 cm in the largest diameter.

Fine-needle aspiration cytology (FNAC) of the right gland showed clusters of oncocytic epithelial cells, as well as scattered individual cells. These cells had distinct borders, abundant finely granular cytoplasm, and uniform, round nuclei with small, centrally placed nucleoli. The background was composed of abundant mature lymphocytes and some foamy macrophages. Cytological diagnosis was benign tumor, type IVa of the Milan system, compatible with WT. Bilateral WT was the clinical diagnosis.

A right superficial conservative parotidectomy was proposed. However, the patient preferred to wait and see. Consequently, yearly ultrasonography was performed. After four years, the lesions were stable and the patient accepted the surgical treatment. The postoperative period was uneventful. The patient suffered temporary marginal nerve paresis with complete recovery in the third month. No recurrence was observed after six months of follow-up.

The surgical specimen was sent for histopathological (HP) examination.

Pathological findings

The parotidectomy specimen weighed 20 g and measured 5 cm in maximum diameter. The cut surface showed a single mass comprising of two closely adjoining nodules measuring 4.2×2.8 cm in its longest dimension. Both nodules were well defined, spherical to ovoid (Figure 2A). One was solid and the other one cystic. The solid nodule measured 2.2×1 cm was light brown and showed some slit-like spaces. The cystic nodule was tan, incomplete bilocular and had a proliferation of papillary appearance inside. It measured 2×1.8 cm. Both lesions seemingly respected the resection edges of the surgical specimen.

The entire surgical specimen was fixed in 10% buffered formalin. Representative tissue samples were embedded in paraffin. For routine microscopy, 4-µm-thick sections were stained with Hematoxylin and Eosin (HE) and Alcian Blue–Periodic Acid–Schiff (PAS), pH 2.5. Immunohistochemical (IHC) staining was performed using the EnVision FLEX+ Visualization System (Dako, Agilent Technologies, SL, Las Rozas, Madrid, Spain). The IHC reaction was performed using appropriate tissue controls for the antibodies utilized. Automatic staining was performed on a Dako Omnis stainer (Agilent Technologies, SL). Antibodies used are detailed in Table 1.

The microscopic study disclosed two distinct neoplasms: a WT and a POC (Figure 2B). The neoplasms were separated from each other by a thick fibrous band. The WT tumor showed a thin fibrous capsule and was constituted by numerous, irregular cystic spaces lined by a bilayered oncocytic epithelium whose supporting stroma was composed of abundant lymphoid tissue (Figure 3A). The lumens contained secretions and cellular debris. The luminal epithelium consisted of tall columnar cells showing palisading of their regular ovoid nuclei located in the centers of the cells. The cytoplasm was eosinophilic and finely granular with apocrine-like secretion and cilia. Beneath the columnar cells smaller, triangular, eosinophilic, basaloid cells provided with granular cytoplasm and round nuclei with small nucleoli were present. This epithelium formed variable shaped, simple papillary projections in the cystic spaces (Figure 3B). The lesion revealed a predominance of lymphoid stroma in some areas and a paucity in other zones (Figure 3C). Very occasional Alcian Blue-positive mucocytes were present (Figure 3D). Cellular atypia, mitoses, or focal squamous metaplasia were not seen. The lymphoid stroma showed occasional germinal centers and formed about 40% of the tumor.

Table 1 – ***Immunohistochemical antibodies used in this study***

Antibody	Source	Clone	Dilution	Retrieval solution pH (Dako)
AMA	BioGenex	113-1	1:400	High
CK7	Dako	OVTL 12/30	FLEX RTU	High
MUC4	Santa Cruz Biotechnology	8G7	1:50	High
p63	Dako	DAK-p63	FLEX RTU	High
DOG1	Leica Biosystems	K9	1:100	High
S100 protein	Abcam	Ab55787	1:100	High
SOX10	Biocare Medical	BC34	1:100	High
ER	Dako	Alpha EP1	FLEX RTU	High
PR	Dako	636	FLEX RTU	High
Mammaglobin	Dako	304-1A5	FLEX RTU	High

AMA: Anti-mitochondrial antibody; CK7: Cytokeratin 7; MUC4: Mucin 4; DOG1: Discovered on gastrointestinal stromal tumors protein 1; SOX10: SRY-box transcription factor 10; ER: Estrogen receptor; PR: Progesterone receptor; BioGenex (Izasa, SA, Barcelona, Spain); Dako (Agilent Technologies, SL, Las Rozas, Madrid, Spain); Santa Cruz Biotechnology, Inc. (Quimigen, SL, Madrid, Spain); Leica Biosystems, Barcelona, Spain; Abcam, Cambridge, UK; Biocare Medical, SL, Alcalá de Henares, Madrid, Spain; RTU: Ready-to-use.

The POC was incomplete bilocular and delimited by a thick fibrous capsule. The cyst showed two groups of papillary projections in the lumen with supporting connective tissue (Figure 4A). Small and scant collections of lymphocytes were observed in the stroma. The epithelial lining of the papillary fronds was composed of one or two layers of columnar to cuboidal oncocytic cells with eosinophilic granular cytoplasm admixed with a significant number of mucocytes (Figure 4B). The oncocytic cells displayed round to oval nuclei with finely dispersed chromatin and small definite nucleoli. This epithelium formed microcystic spaces containing pink secretory material (Figure 4C). Intracystic secretion and mucocytes were strongly reactive for Alcian Blue (Figure 4D). Solid epithelial growth, cytological atypia, necrosis, squamous epithelium, or mitotic figures were not present. The cyst wall was lined by oncocytic cuboidal cells. The uninvolved parotid gland showed no significant abnormalities.

The IHC panel revealed in the epithelium of both neoplasms intense reactivity for anti-mitochondrial antibody (AMA), cytokeratin 7 (CK7), and mucin 4 (MUC4). Besides, the basal cell layer showed strong nuclear positivity for p63 (Figures 5 and 6). There was negativity for discovered on gastrointestinal stromal tumors protein 1 (DOG1), S100 protein, SRY-box transcription factor 10 (SOX10), estrogen receptor (ER), progesterone receptor (PR), and mammaglobin in cells of both tumors.

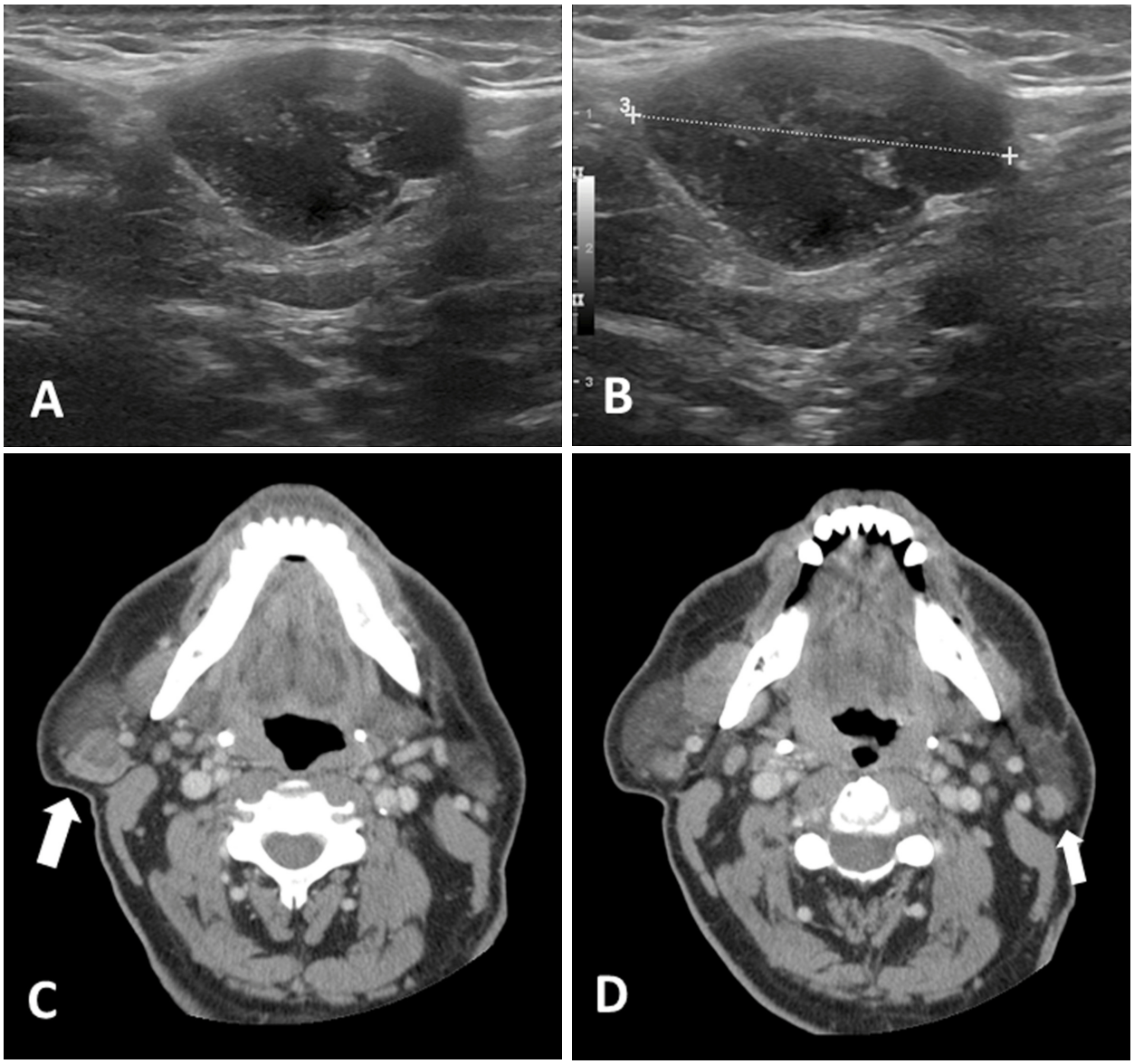

Figure 1 – ***Imagistic study, ultrasonography and computed tomography (CT) scan: (A) Solid, hypoechoic lesion with well-defined borders on the right parotid gland; (B) The nodule measures 2.8 cm in its major axis; (C) Solid, sharply defined, heterogeneous nodule, contrast enhancer in the tail of the right parotid gland (arrow); (D) Hyperdense, well-delimited nodule in the tail of left parotid gland (arrow).***

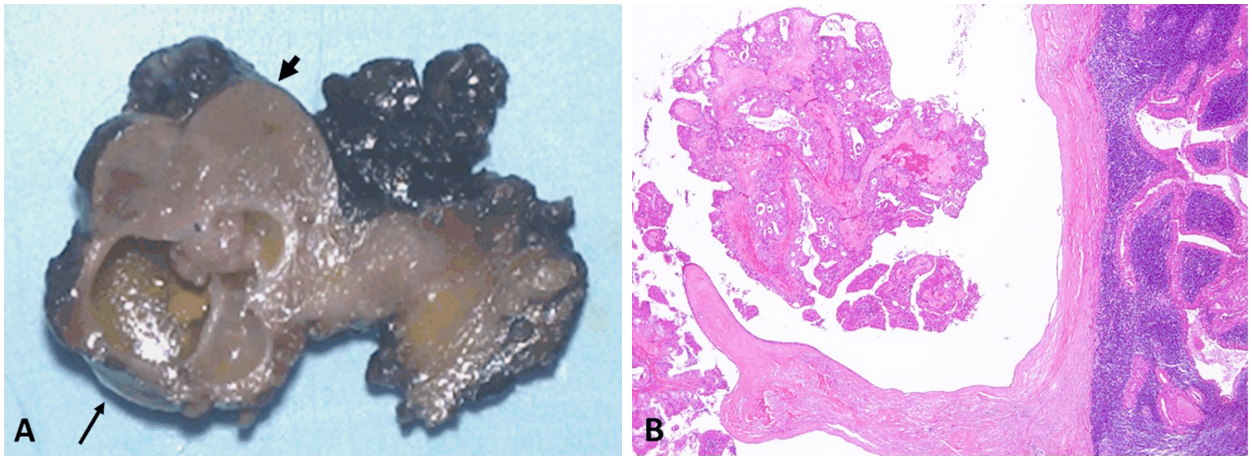

Figure 2 – ***Presence of two tumors in the parotid gland: (A) Macroscopic aspect of the bisected surgical specimen – solid nodule with light brown coloration (short arrow) and pink, cystic nodule with limited intraluminal growth (long arrow); (B) Microscopic panoramic vision of both nodules – Warthin tumor (right side) and papillary oncocytic cystadenoma (left side). Hematoxylin–Eosin (HE) staining: (B) ×40.***

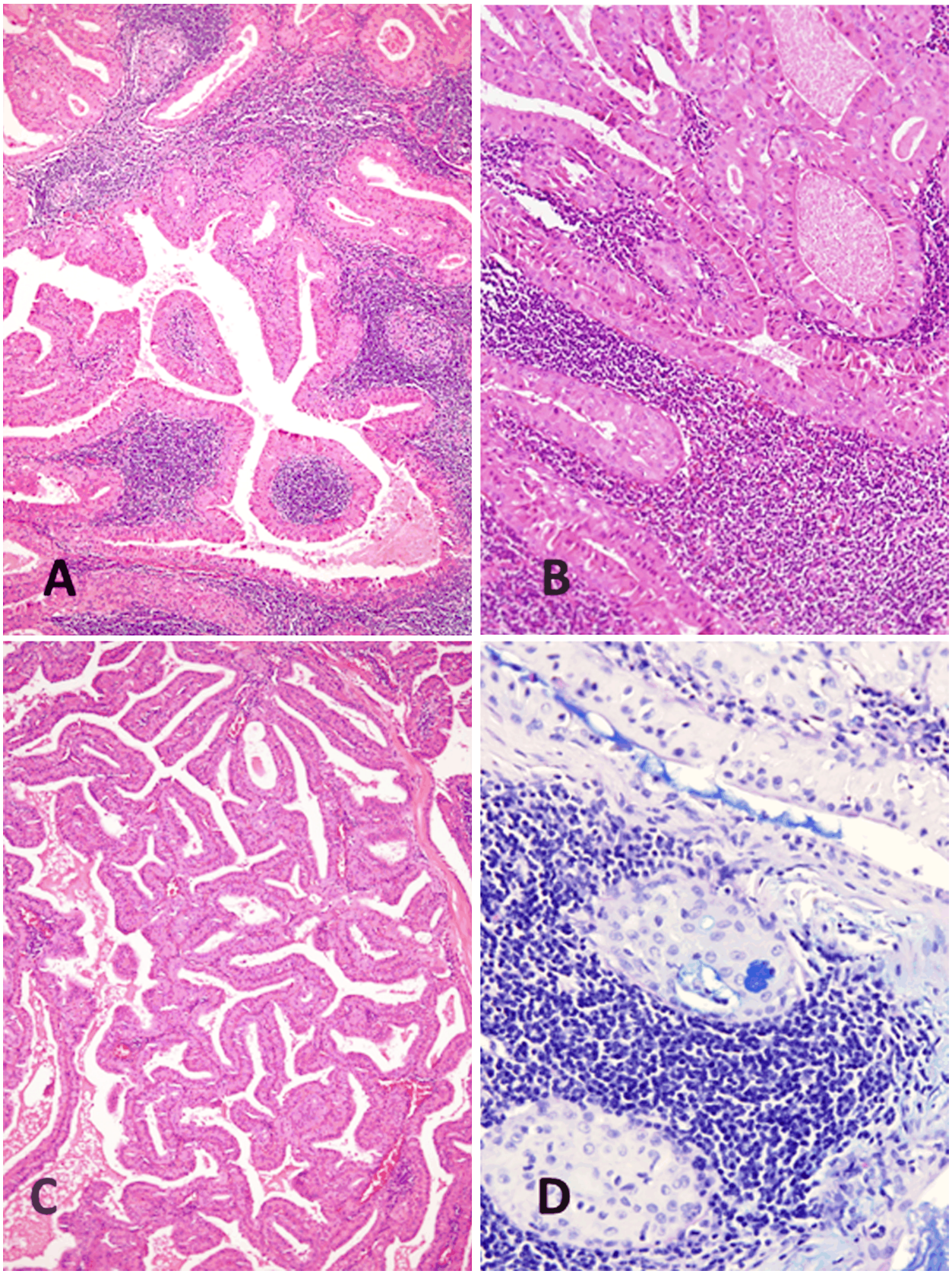

Figure 3 – ***Histopathology of the Warthin tumor: (A) The oncocytic epithelium lines cystic spaces and is closely associated with lymphoid stroma; (B) The luminal columnar cells have palisaded and hyperchromatic nuclei – the basal cells have round nuclei with small nucleoli; (C) Area of predominance of epithelial tissue; (D) Occasional presence of mucocytes. Hematoxylin–Eosin (HE) staining: (A and C) ×100; (B) ×200. Alcian Blue–Periodic Acid–Schiff (PAS) staining: (D) ×400.***

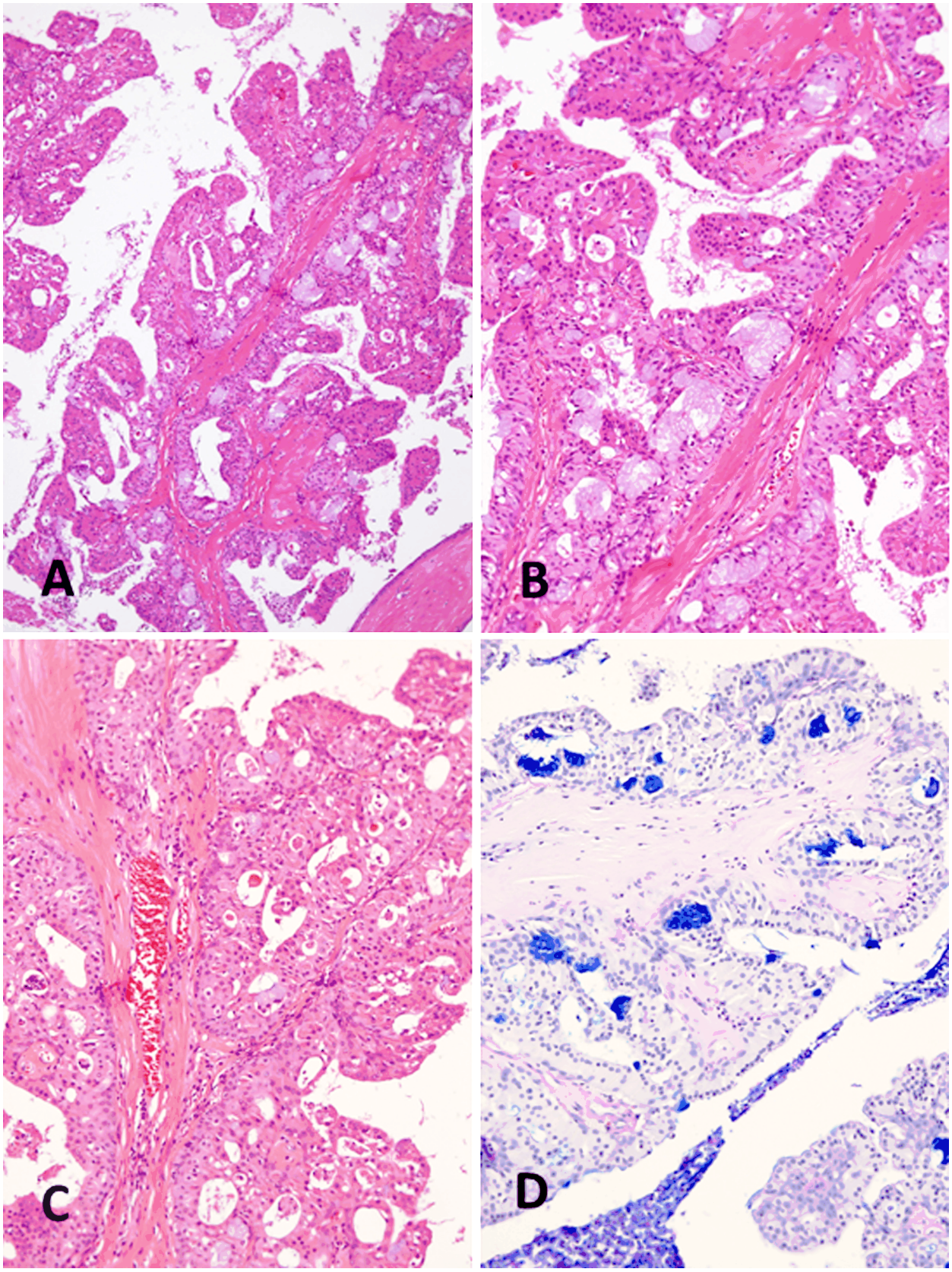

Figure 4 – ***Histopathology of the papillary oncocytic cystadenoma: (A) Papillary proliferation of the lining epithelium showing oncocytic cells and mucocytes; (B) Oncocytes are forming one or two layers – mucocytes are prominent; (C) Microcysts containing pink secretory material; (D) Abundant mucocytes showing secretion of acid mucin. Hematoxylin–Eosin (HE) staining: (A) ×100; (B and C) ×200. Alcian Blue–Periodic Acid–Schiff (PAS) staining: (D) ×200.***

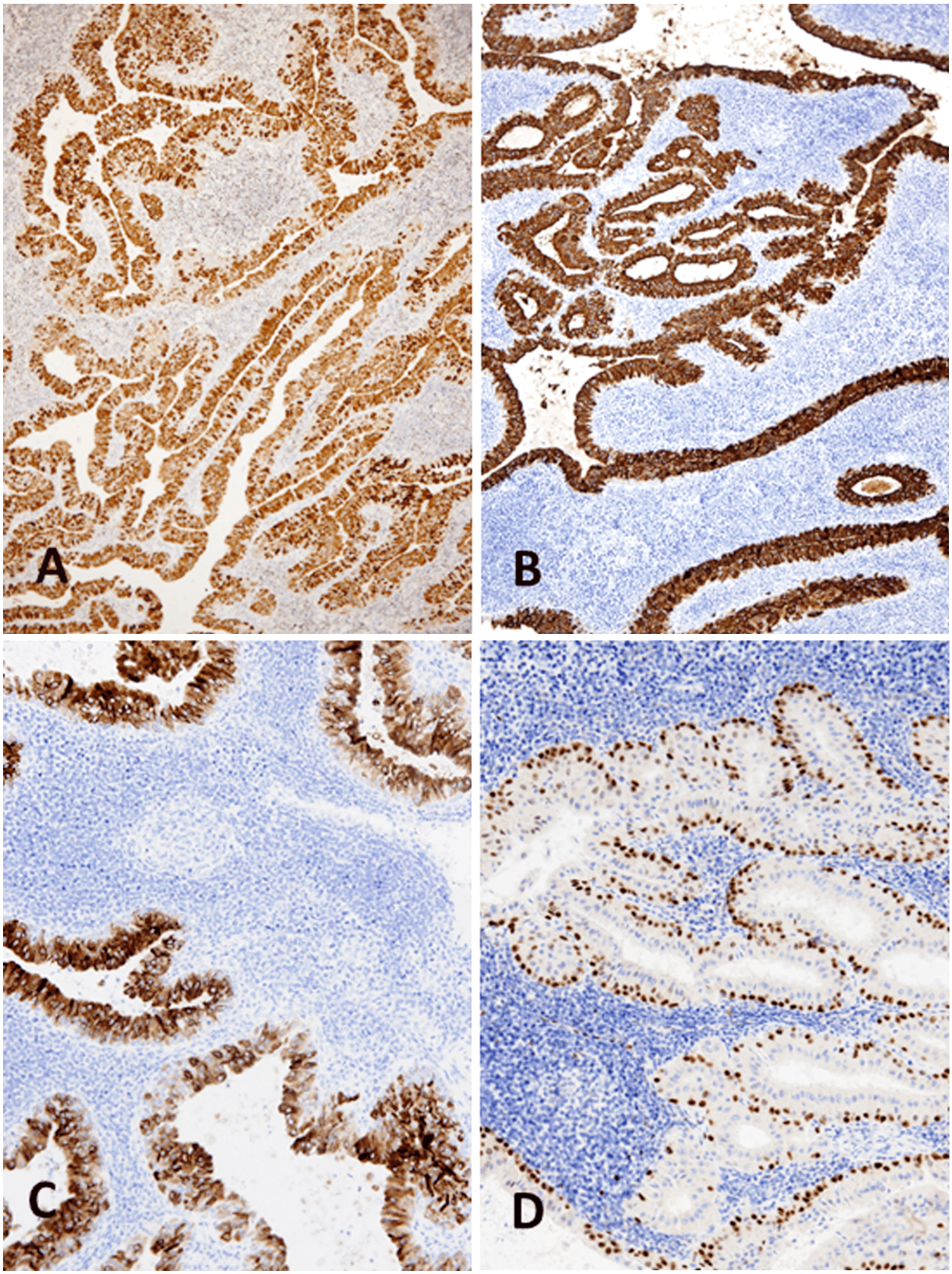

Figure 5 – ***Immunohistochemical study of Warthin tumor. Epithelial cells are reactive for: (A) AMA (×100); (B) CK7 (×100); (C) MUC4 (×200); (D) p63 (×200). AMA: Anti-mitochondrial antibody; CK7: Cytokeratin 7; MUC4: Mucin 4.***

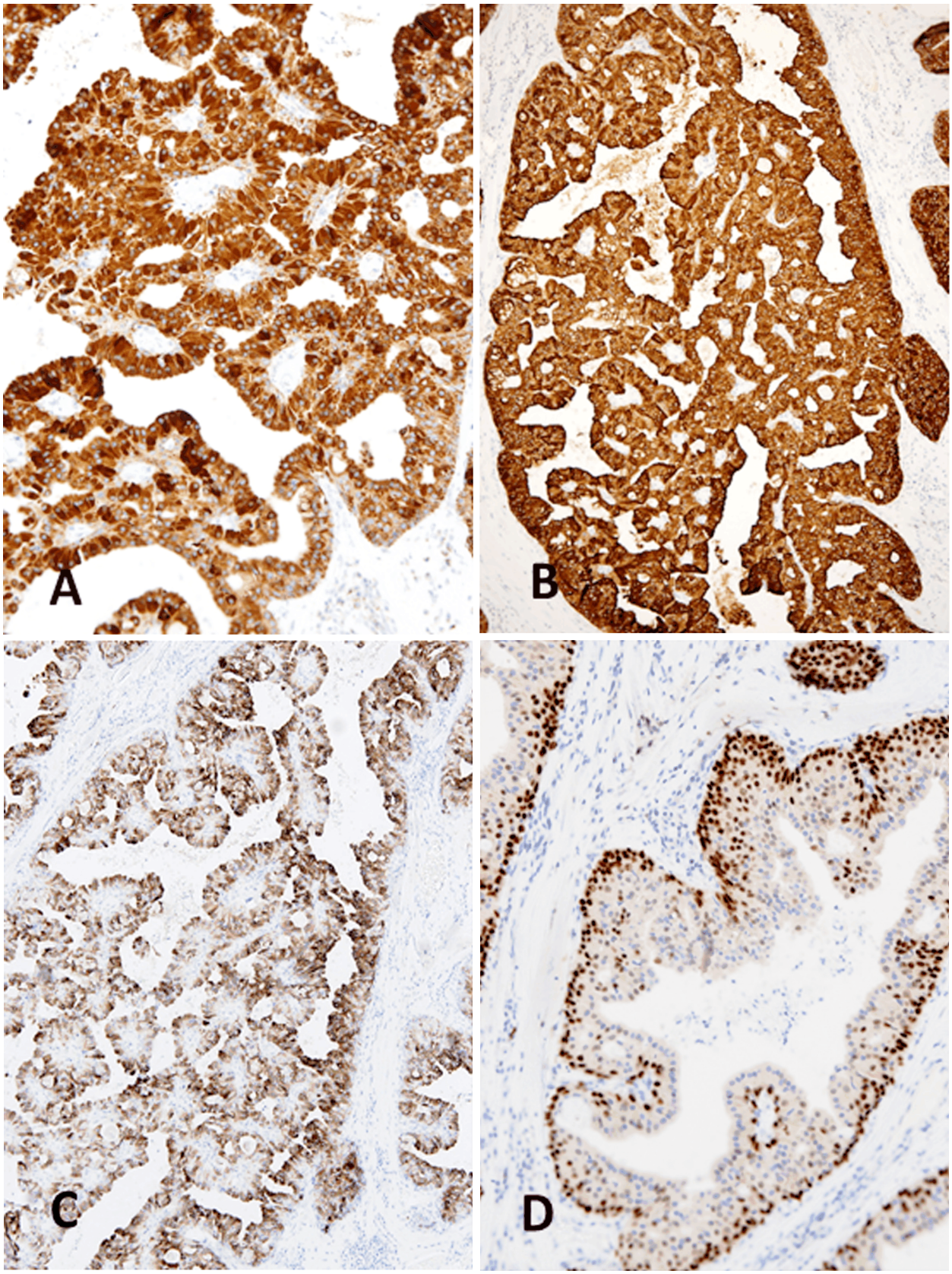

Figure 6 – ***Immunohistochemical study of papillary oncocytic cystadenoma. Epithelial cells are reactive for: (A) AMA (×100); (B) CK7 (×100); (C) MUC4 (×100); (D) p63 (×200). AMA: Anti-mitochondrial antibody; CK7: Cytokeratin 7; MUC4: Mucin 4.***

Discussions

The coincidence of unilateral, primary salivary gland tumors of different histological types is very uncommon and encompasses less than 1% of salivary gland tumors (range 0.1–0.7%) [5–8]. In the series described, the most frequent combination was WT and pleomorphic adenoma. This combination represents 45.6% of the ipsilateral, synchronous tumors of different histological type. The mean age at the identification of two distinct synchronous lesions was 63.2 years [standard deviation (SD) 9.96, range 44–85 years], the median of 61.5 years, and the male:female ratio 3.2:1 [5, 6, 8].

Reported primary, salivary gland tumors associated with WT include pleomorphic adenoma [5, 9], atypical monomorphic adenoma [5], basal cell adenoma [5, 10], oncocytoma [5, 11, 12], myoepithelioma [13], sebaceous lymphadenoma and sclerosing polycystic adenosis tumor [14], benign lymphoepithelial lesion [5], mucoepidermoid carcinoma [2, 5, 15], acinic cell carcinoma [5], ductal adenocarcinoma [5], adenocarcinoma not otherwise specified [16], adenoid cystic carcinoma [5], epithelial–myoepithelial carcinoma [17], squamous cell carcinoma [5], malignant mixed tumor [6], carcinoma in pleomorphic adenoma [6], Merkel cell carcinoma [18], Langerhans cell histiocytosis [19] and lymphoma [12, 20].

This paper describes the unreported, rare situation in which an encapsulated POC was found to occur synchronously, ipsilaterally, and adjacently to a WT. Clinically, the WT was bilateral. The patient, a 58-year-old man, was an established smoker. The imaging study detected a single mass in the right parotid gland. This fact has been previously reported. Thus, Janecka *et al.* [8] observed a clinically solitary mass in six of seven cases of simultaneous parotid tumors of different histological types. In addition, in our case, FNAC identified only one of the components, the WT. This can be explained taking into account that WT and POC are difficult to distinguish because the epithelial component of these tumors is almost the same.

Synchronous, ipsilateral combination of two benign tumors in a major salivary gland represents 65.2% of synchronous ipsilateral tumors. The mean age at the identification of both tumors was 62.1 years (SD 8.44, range 44–85 years), the median of 61 years, and the male:female ratio 6.5:1 [5, 6, 8].

WT is a lymphoepithelial cystadenoma in which the bilayered oncocytic epithelium forms multiple cysts with papillae whose supporting stroma is composed largely of lymphoid tissue with germinal centers. The tumor was considered the second most common salivary gland neoplasm and arises almost exclusively in the parotid gland [21]. However, some authors consider that at present WT is the most common tumor type of the parotid gland [22]. It occurs more commonly in males than in females, usually in the sixth to seventh decades of life (mean age of 62 years, range 29–88 years) [21]. The tumor has been associated with smoking [21, 23]. Moreover, is the most common salivary gland neoplasm to present synchronously or metachronously with multifocality and unilateral or bilateral location [5, 17, 24]. Thus, the tumor is multifocal in 20.5% of the cases of which 14% are monolateral and 6.5% are bilateral [17]. The term papillary *cystadenoma lymphomatosum* accurately describes the features of the tumor. However, there is a wide variation in the proportion of the lymphoid stroma throughout the neoplasm. Some authors consider that WTs develop from heterotopic glandular duct epithelium in intraparotid lymph nodes during embryogenesis [21]. Therefore, an intranodal location of the tumor does not necessarily indicate a diagnosis of malignancy. WT must be differentiated from other salivary gland tumors that may show tumor-associated lymphoid proliferation, such as oncocytoma, acinic cell carcinoma, cystadenocarcinoma, or mucoepidermoid carcinoma [25].

Cystadenoma of the salivary glands can be subdivided into mucinous and papillary types [21]. POC is an infrequent and benign neoplasm with prominent oncocytic epithelium predominance, which usually occurs in the minor salivary glands [24], and it is rare in the major salivary glands [26–28]. The parotid gland is the major salivary gland most commonly involved. However, until 2018, only seven cases of POC had been described in this location [29]. The tumor presents a clear predominance in women [21, 30]. The mean age at the time of diagnosis was 57 years (range 12–89 years) [21]. Most tumors are multicystic, but 20% can be unicystic, and 25% show a well-defined fibrous capsule [30]. They tend to be relatively small lesions. The epithelium lining papillary structures is oncocytic, but mucous cells can be focally present. This epithelium can be bilayered resembling the epithelium of WT [21]. On the other hand, a prominent mucinous differentiation in a POC of the parotid gland has been observed [31]. Apocrine differentiation and squamous epithelium may be focally present. The neoplasm does not show a diffuse, dense and well-organized lymphoid stroma with germinal centers. However, a rare case of cystadenoma showed a dense follicle-containing lymphoid stroma but lacked the oncocytic epithelium [32]. It was proposed that POC represents WT without lymphoid stroma, but the whole of HP characteristics does not support this concept [21].

The two associated tumors that we are describing showed an oncocytic epithelium with presence of mucocytes, therefore the antibody panel showed a similar reactivity for AMA, CK7, MUC4, and p63. IHC study can assist the final diagnosis enhancing the accuracy, but HE staining is still the gold standard method for the HP diagnosis of salivary gland tumors. Regarding the differential diagnosis, intraductal papilloma (IDP) shares some features with POC, but the IDP is unicystic and the papillary fronds are more abundant and complex [21, 33]. Besides, the cells lining the duct do not show epithelial proliferation [21]. Low-grade intraductal carcinoma with prominent oncocytic change shows a solid, cribriform, fenestrated, or low papillary growth arising from the cyst wall. The cells show nuclear atypia and relatively high (3.8–15%) Ki-67 labeling index [34]. Cystic change may be present in oncocytoma, but the papillary pattern, typical of POC, is not a feature of oncocytoma [27]. On the other hand, the difference between low-grade cystadenocarcinoma with oncocytic epithelial lining and POC is based on the identification of genuine invasion of salivary gland parenchyma by the cystadenocarcinoma [35]. Cytological

atypia, mitoses or invasive growth pattern are not features of the POC. Conservative local excision is the appropriate treatment. Recurrences are exceptional [21].

The combination of tumors we are reporting could suggest that several tumor-initiating cells appear in a small amount of time in at least two locations owing to a systemic stimulus of the type of a blood-borne mutagen including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons associated with tobacco use [36]. Therefore, the two tumors can be related to a common causal factor and should not be considered as a result of chance.

Conclusions

Synchronous WT and POC in the ipsilateral parotid gland are reported as the first case in the world literature. Preoperative diagnosis based on imaging was difficult to suspect. Due to the unifocal image and the cytological similarity of the epithelial component, the POC in our case was not detected by FNAC. POC can resemble WT without lymphoid stroma, but the whole of HP features differentiates both processes. The coincidental tumors can be related to a common causal determinant and should not be considered as a product of chance. They follow favorable courses and are curable by surgical resection.

Conflict of interests

The authors declare that they have no conflict of interests.

Compliance with ethical standards

No Ethics Committee approval is required at our institution for a case report involving a single patient.

Consent

Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

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