REVIEW ARTICLE

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Synchronous occurrence of oral squamous cell carcinoma and Warthin's tumor: systematic review and case report

Gibum Shin[1], Hyounmin Kim[1], Mikyung Gong[1], Seung-Yong Han[2], Eunae Sandra Cho[2,3,4], Hyung Jun Kim[1]

Departments of [1]Oral and Maxillofacial Surgery and [2]Oral Pathology, Yonsei University College of Dentistry, [3]BK21 FOUR Project, Yonsei University College of Dentistry, Seoul, [4]Center for Genome Engineering, Institute for Basic Science, Daejeon, Korea

Abstract (J Korean Assoc Oral Maxillofac Surg 2024;50:134-139)

We systematically reviewed the literature on the co-occurrence of squamous cell carcinoma (SCC) and Warthin's tumor (WT), thought to be quite rare, to help reduce misdiagnosis and improve treatment planning. For this systematic review, we searched for articles in the Web of Science and PubMed databases, analyzed relevant studies for forward and backward citations, and identified only articles reporting on the "co-occurrence" of WT and SCC. Of the 237 studies identified, 12 comprising 18 patients met the inclusion criteria, to which we added one study from our institution. Most WTs were associated with SCC in the parotid gland or cervical lymph nodes. Most patients (89.5%) underwent selective or radical neck dissection due to identification of lesions separate from the primary SCC. Despite its frequent co-occurrence with other neoplasms, WT in the parotid or cervical lymph nodes tends to be misdiagnosed as a metastatic node when SCC is observed as the primary tumor. Factors to consider in diagnosis and neck management include identification of an association other than growth or development by lymphangiogenesis and whether the patient is a smoker, a strong risk factor.

Key words: Warthin tumor, Oral squamous cell carcinoma

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I. Introduction

Squamous cell carcinoma (SCC) is the most common malignant oral pathology, accounting for more than 90% of the malignant lesions in the oral cavity and oropharynx[1]. Warthin's tumor (WT) is the second most common benign neoplasm of the salivary gland. This tumor mostly occurs in the parotid but is occasionally observed outside of the parotid, synchronously, unifocally, or multifocally[2,3]. Co-occurrence of WT and other neoplasms has been observed[4], but synchronous occurrence of WT and SCC is thought to be extremely rare[5-7]. For this reason, WT is often misdiagnosed as nodal metastasis of SCC when it occurs in the cervical lymph nodes or in the parotid tail in close proximity to cervical lymph nodes, leading to overall misdirection of treatment for the latter[3]. This study presents a case of synchronous occurrence of WT and oral SCC (oSCC) at our institution with a systematic literature review of similarly reported cases. Until now, only case reports have documented this phenomenon. To our knowledge, this is the first systematic review of documented co-occurrences and was performed to help reduce misdiagnosis and provide assistance in appropriate treatment planning.

II. Materials and Methods

A literature review without language restrictions was performed to support a case of synchronous WT in the parotid with SCC on the floor of the mouth (FOM) in our institution. PubMed (up to March 2023) and Web of Science (up to March 2023) were searched using the following strategies: [(adenolymphoma OR lymphomatous cystadenoma OR cystadenolymphoma OR papillary cystadenoma lymphomatosum OR Warthin) AND (oral squamous carcinoma)]. All the identified relevant articles were examined independently by two investigators. Upon encountering discrepancies, the two reviewers engaged in a collaborative discussion and analyzed the data together, leading to amicable resolution of any dif-

Hyung Jun Kim
Department of Oral and Maxillofacial Surgery, Yonsei University College of Dentistry, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
TEL: +82-2-2228-3138
E-mail: KIMOMS@yuhs.ac
ORCID: https://orcid.org/0000-0001-8247-4004

Table 1. Results of a literature review of all cases of synchronous occurrence of oral SCC and WT

Study	Age (yr)/sex	Initial symptom	Site of SCC	Site of WT (ipsilateral/ contralateral/bilateral)	Alcohol history	Smoking history	Other metastases	TNM stage	Treatment	Survival
Sato et al.[7] (1998)	72/M	Sore throat	RMT, oropharynx	Parotid, ipsilateral cervical lymph node, ipsilateral	NR	Yes (2 packs/day, 50 years)	None	T2N0M0	Neoadjuvant RTx SND (level I-III) Partial parotidectomy	DFS 7 years
	60/M	Ulcer	Buccal mucosa	Parotid, ipsilateral cervical lymph node, ipsilateral	NR	Yes (0.5 packs/day, 35 years)	None	NR	Wide excision Lymph node excision Partial parotidectomy	DFS 1.5 years
Maiorano et al.[6] (2002)	NR	NR	Larynx	Parotid, ipsilateral	NR	NR	NR	NR	Wide excision Partial parotidectomy	NR
	NR	NR	Larynx	Parotid, ipsilateral	NR	NR	NR	NR	Wide excision Partial parotidectomy	NR
Sheahan et al.[5] (2005)	55/M	NR	RMT	Cervical lymph node, ipsilateral	NR	NR	None	TxN1M0	Wide excision mRND	DFS 2 years
Schwarz et al.[8] (2009)	42/M	Tongue pain	Tongue	Cervical lymph node, ipsilateral	NR	Yes	None	T2N0M0	Wide excision SND (level I-III, bilateral)	NR
Enomoto et al.[9] (2011)	67/M	Cheek swelling	Mandible	Parotid, ipsilateral	NR	NR	None	T4aN0M0	Wide excision SND (level I-III)	NR
Iwai et al.[10] (2012)	77/F	Tongue pain	Tongue	Paraparotid node, ipsilateral	NR	Yes	None	T2N0M0	Wide excision Partial parotidectomy	NR
Bhatlawande et al.[4] (2020)	51/M	Gingival pain	Lower gingiva	Cervical lymph node, ipsilateral	Yes (20 years)	Yes (5-6 pack/day, 20 years)	None	TxN0M0	Wide excision SND (level I-IV)	NR
Sato et al.[11] (2020)	56/M	Gingival pain	Buccal mucosa, upper gingiva	Cervical lymph node, ipsilateral	NR	Yes (1.5 pack/day, 23 years)	None	T4aN0M0	Neoadjuvant CCRTx RND	DFS 8 years
Kumar et al.[12] (2020)	52/M	Voice problem	Larynx, bilateral	Submandibular gland, unilateral	Yes (200 mL/day for the last 30 years)	Yes (2 pack/day, 30 years)	None	T3N0M0	Wide excision SND (level I-IV), bilateral	NR
Yang et al.[13] (2021)	65/M	Mouth floor ulcer	FOM	Submandibular gland, ipsilateral	NR	Yes (30 years)	None	T2N1M0	Wide excision mRND & SND (level I-III)	DFS 3 years
Goh et al.[14] (2022)	63/F	Cheek mass	Buccal mucosa	Parotid, ipsilateral	NR	Yes	None	T2N1M0	Wide excision mRND	DFS 4 months
	69/M	Tongue ulcer	Tongue	Parotid, ipsilateral	NR	Yes (40 years)	None	T1N0M0	Wide excision SND (level I-III) Partial parotidectomy	DFS 7 years
Gontarz et al.[15] (2022)	86/F	NR	Buccal mucosa	Cervical lymph node, ipsilateral	NR	NR	None	T3N2bM0	Wide excision SND (level I-III)	DFS 1.5 years
	67/F		Tongue	Cervical lymph node, ipsilateral			None	T2N0M0	Wide excision mRND	DFS 2 years 11 months
	65/F		Lower gingiva	Cervical lymph node, ipsilateral			None	T2N0M0	Wide excision SND (level I-III)	DFS 2 years 4 months
	54/M		FOM	Cervical lymph node, ipsilateral			None	T3N1M0	Wide excision SND (level I-III)	DFS 3 years 10 months
Present case	64/M	FOM ulcer	FOM	Parotid, unilateral	Yes (40 years)	Yes (1 pack/day, 40 years)	None	T2N0M0	Wide excision SND (level I-III), bilateral Partial parotidectomy	DFS 8 months

(SCC: squamous cell carcinoma, WT: Warthin's tumor, M: male, F: female, RMT: retromolar triagone, NR: not reported, RTx: radiotherapy, SND: selective neck dissection, DFS: disease-free survival, CCRTx: concurrent chemo-radiotherapy, RND: radical neck dissection, FOM: floor of mouth, mRND: modified radical neck dissection)

ferences and a unanimous consensus. The references within the included studies were verified to avoid any omissions. Studies that were duplicated or not in full text were excluded. Articles that did not fit the topic were excluded.

Since all the articles were case reports, a risk bias assessment tool was not necessary.

Twelve eligible articles were identified with 18 cases of synchronous occurrence of oSCC and WT in the head and neck, and the following information was extracted and summarized in Table 1[4-15]: first author, publication year, demographic information, alcohol and smoking history, tumor sites, treatment, and survival. Our case was added for analysis.

III. Results

1. Literature review

Reviewing previous reports of similar cases and summarizing their features, the authors identified 114 articles from PubMed and 123 from Web of Science that mentioned oSCC and WT. Of these, 200 were obtained from the main database, excluding duplicate results. The articles that mentioned only 1 of the 2 tumors or types of carcinoma other than SCC were considered irrelevant and excluded. Among the 18 eligible papers that mentioned both SCC and WT, 9 that reported malignant transformation of WT rather than synchronous occurrence were excluded. Of the 7 case reports found through citations, we excluded 4 for which no full text was available, resulting in a total of 12 articles plus the 1 case at our institution for a total of 19 patients analyzed. The detailed flow chart for the systemic search is shown in Fig. 1.

Of the 19 patients, the male/female ratio was 12:5, with the exception of 2 patients whose sexes were not reported. With the exception of the 2 people whose ages were not reported, 16 of the 17 (94.1%) were older than 50 years. WT occurred primarily in the parotid or cervical lymph nodes, with 8 sites (42.1%) in the parotid and 10 cases (52.6%) in the lymph nodes; 3 cases involved the submandibular gland or paraparotid nodes. Excluding the 8 individuals who did not smoke or perform any carcinogenic habits, 11 exhibited a history of smoking, 5 of whom were heavy smokers. Of the 11 smokers, only 3 had a history of alcohol consumption, and there was no mention of any other medical history related to alco-

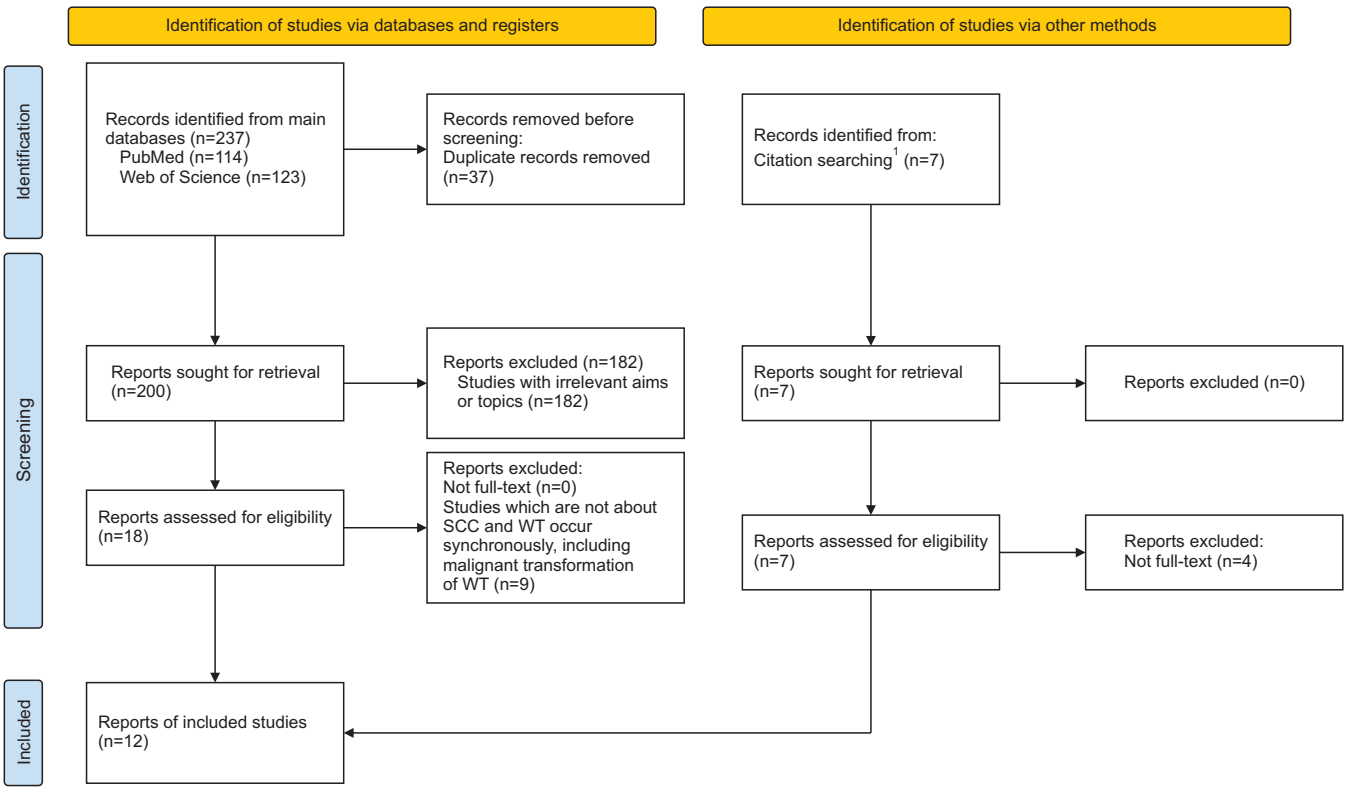

Fig. 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram for systematic reviews. [1]Citation searching refers to searching for reports referenced by the main database.

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hol except for 1 person with hepatitis C. Of the 19 patients, 17 underwent selective neck dissection (SND) or radical neck dissection (RND), except 1 for whose treatment was not reported and 1 who underwent simple excision.

2. Case report

A 64-year-old male patient presented to the clinic with an ulcer-like lesion on the FOM. The patient indicated a history of smoking 1 pack a day for more than 40 years. Likewise, he had maintained a steady drinking habit for the past 40 years and had a body mass index (BMI) of 23.4 kg/m^2, falling within the overweight range by the World Health Organization Asian BMI classification[16]. A 1.3 cm erosive lesion on the FOM was observed with no other significant findings in the parotid or cervical lymph nodes. PET-CT (positron emission tomography-computed tomography) imaging for oral cancer additionally revealed a 1 cm×1 cm mass in the deep lobe of the left parotid gland and another mass of similar size in the tail of the same side. Both parotid masses exhibited multiple cystic components with low signal on T1 clustering and with a distinct border, resembling benign tumors. Wide excision and neck dissection were performed for the FOM lesion, and partial parotidectomy was performed for the 2 parotid lesions. (Fig. 2)

Upon pathologic examination with H&E staining, the FOM lesion was diagnosed as SCC, while the lesion in the deep lobe and tail of the parotid exhibited lymphoid stroma and eosinophilic internal material with cystic growth, diagnosed as WT.(Fig. 3) No metastatic lymph nodes were observed in the neck specimens.

The resection margin was free of tumor with no adverse features. The patient did not undergo adjuvant therapy, and there was no evidence of recurrence of either type of tumor and no metastasis at the 6-month follow-up.

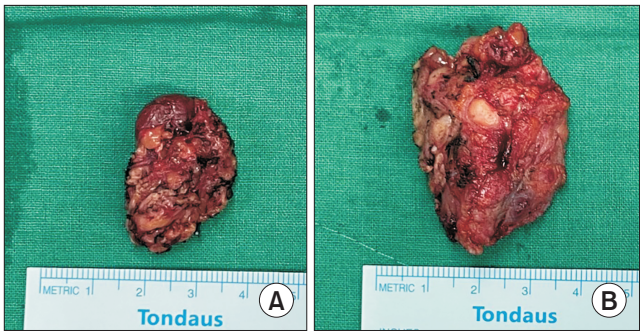

Fig. 2. Two separate encapsulated parotid masses in the deep lobe (A) and parotid tail (B).
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IV. Discussion

WT can occur simultaneously or metachronously with other neoplasms and is multifocal in approximately one-third of patients who develop this disease[17]. Nevertheless, such a "neoplasm" is rarely considered as a second primary tumor

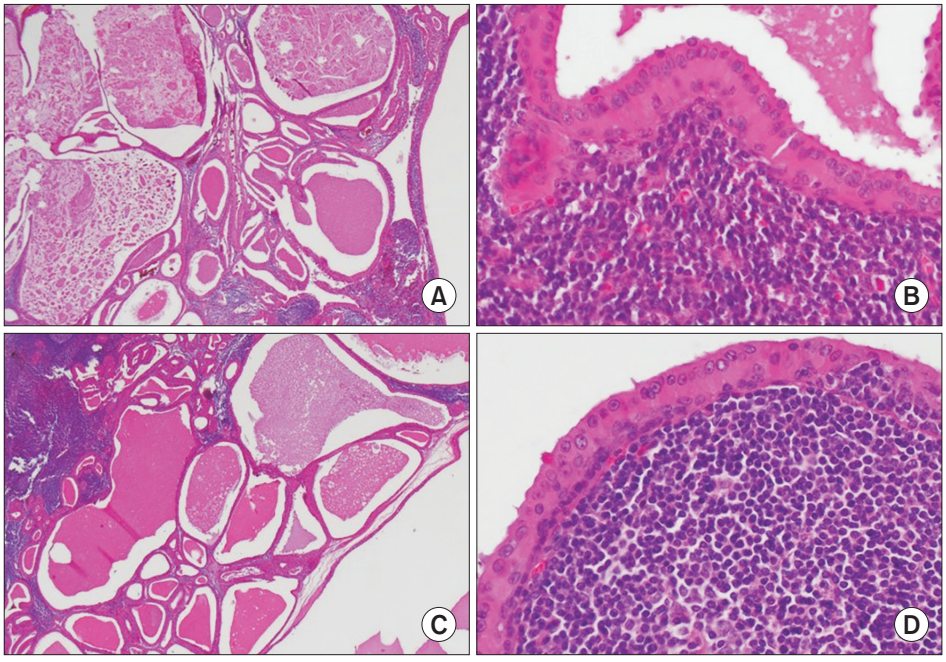

Fig. 3. Histopathologic examinations of the biopsy specimens from the deep lobe (A, B) and tail (C, D) with H&E staining (A: ×12.5, B: ×200, C: ×12.5, D: ×200).
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rather than metastasis.

This lack of consideration may be due to the difficulty in distinguishing nodal metastasis and WT in images. Though not common, enlarged lymph nodes are easily observed on magnetic resonance imaging (MRI). However, it is difficult to distinguish whether they are reactively enlarged or transformed to a malignant lesion[18]. PET-CT, a type of metabolic imaging, is used to compensate for such strictly morphological imagery, but can be misleading when a WT appears as a hot spot in nuclear imaging[8].

Due to these limitations, fine needle aspiration biopsy (FNAB) was recommended by three authors of the articles we reviewed[6,8,15] and was performed before surgery in one reported study[6]. FNAB is widely used as a diagnostic method for differential diagnosis of head and neck tumors due to its simplicity, safety, and cost-effectiveness[19]. However, due to the wide range of accuracy[20], the utility of FNAB in diagnosing parotid gland tumors remains controversial. Particularly in the case of WT, which presents with cystic features, accurate diagnosis by FNAB is challenging, and collection of an adequate number of cells can be difficult[21]. Moreover, due to the characteristic requirement of including "both epithelial and lymphatic components" in the diagnostic criteria for WT, diagnosis tends to be relatively challenging[11]. Therefore, even when FNAB is performed in cases where it is difficult to distinguish between nodal metastasis and WT on imaging, certainty in diagnosis cannot be guaranteed, and controversy remains on the performance of FNAB. In our case, FNAB was not performed as the MRI images revealed multiple cystic components with low signal on T1 clustering with a distinct border, suggestive of a benign tumor.

WT often arises with other tumors, including malignancies such as mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, clear cell carcinoma, transitional cell carcinoma, ductal carcinoma, basal cell carcinoma, secretory carcinoma, acinic cell carcinoma, lymphoma, and oSCC[6]. Among these, oSCC was reported to occur most frequently with WT, with research results on co-occurrence with other malignancies excluded as not relevant to the topic of our study. Smoking is a well-known risk factor for WT, as supported by reviewed reports. However, other information, such as drinking habits or body mass index, was rarely provided. There does not appear to be a clear link between the two diseases other than the risk factor of tobacco abuse and the high frequency among oral tumors[13-15]. In our study, 11 of 19 patients were smokers, but there was no clear evidence that this caused the co-occurrence of the two diseases.

Of the 19 patients, WT in 6 mimicked metastatic nodes where the patients underwent ipsilateral modified RND or SND that extended beyond level I-III. However, pathological examination determined no nodal metastasis, indicating that the extended neck dissection had been unnecessary[4,11,15]. For example, in Sato et al.[11], a patient exhibited nodal swelling suggestive of metastasis from maxillary cancer, but the swelling did not subside after radiotherapy. Though a radical neck dissection was planned[11], no nodal metastasis was noted after pathological examination.

Despite the difficulty of differentiation in diagnostic modalities such as PET-CT and FNAB, highly skilled surgeons can rely solely on a tumor's clinical characteristics for intraoperative decisions. Nevertheless, this series of cases underscores the importance of considering co-occurrence of two distinct diseases and highlights the necessity for additional research into genetic or molecular connections between these two conditions.

ORCID

Gibum Shin, *https://orcid.org/0009-0008-0316-4787*
Hyounmin Kim, *https://orcid.org/0000-0002-1900-4744*
Mikyung Gong, *https://orcid.org/0000-0002-9891-8711*
Seung-Yong Han, *https://orcid.org/0000-0002-9558-5384*
Eunae Sandra Cho, *https://orcid.org/0000-0002-0820-3019*
Hyung Jun Kim, *https://orcid.org/0000-0001-8247-4004*

Authors' Contributions

G.S. participated in original draft preparation and writing the manuscript. H.K. and H.J.K. participated in conceptualization and reviewing and editing the manuscript. M.G., S.Y.H., and E.S.C. participated in data curation and investigation. All authors read and approved the final manuscript.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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