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CASE REPORT

A Report on Synchronous Polymorphous Low-grade Adenocarcinoma and Unknown Primary Squamous Cell Carcinoma

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ABSTRACT

Background: This is a case report of synchronous, noncollision head and neck malignancies, consisting of a large polymorphous low-grade adenocarcinoma (PLGA) and an unknown primary squamous cell carcinoma (SCC) that was diagnosed on final pathology.

Materials and methods: Positron emission tomography–computed tomography (CT) scan with and without contrast was obtained, which showed a large destructive soft tissue mass emanating from the right maxilla into the right maxillary sinus with invasion into the surrounding tissue and bone, compatible with an underlying primary maxillary malignancy. Increased D-18 fluorodeoxyglucose activity was also seen in the neck corresponding to numerous bilateral cervical lymph nodes. Magnetic resonance imaging showed the extent of the soft tissue mass, which expanded to the inferior aspect of the right orbital floor, with no evidence of gross invasion into the orbit.

Results: The patient underwent a subtotal maxillectomy, bilateral modified radial neck dissection, and reconstruction. Pathology revealed metastatic PLGA present in the right cervical lymph nodes. Left cervical lymph nodes, however, revealed metastatic SSC. The patient was taken back to the operating room and a panendoscopy was performed. Physical examination was benign and multiple biopsies were negative for SSC. The patient underwent radiation therapy for PLGA and unknown primary SSC antigen.

Conclusion: Synchronous tumors of the head and neck are seldom reported and they present unique treatment challenges. This case report discusses the diagnosis, management, and unique nature of two malignant synchronous noncollision tumors in the head and neck.

Keywords: Head and neck cancer, Polymorphous low-grade adenocarcinoma, Squamous cell carcinoma, Synchronous malignancies.

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INTRODUCTION

This is a case report of synchronous, noncollision head and neck malignancies, consisting of a large polymorphous low-grade adenocarcinoma (PLGA) and an unknown primary squamous cell carcinoma (SCC) that was diagnosed on final pathology. Synchronous tumors of the head and neck are seldom reported and propose unique treatment challenges. This case report discusses the diagnosis, management, and unique nature of two malignant synchronous noncollision tumors in the head and neck.

CASE REPORT

A 71-year-old male presented with a slowly expanding mass in his right palate. Medical history was significant for hypertension and adenocarcinoma of the prostate diagnosed in 2002. Radiation therapy to the pelvis was the modality of treatment. Medications included Metoprolol, Norvasc, Maxzide, and Terazosin. The patient denied any surgical history or allergies. Social history was significant for tobacco use, $^1/_2$ pack of cigarettes per day for 30 years, and moderate alcohol consumption.

On physical examination, midface asymmetry was clearly evident. The right cheek and infraorbital region were more prominent than the left. The overlying skin was not adhered to the tumor. Manual palpation of the neck yielded indurated lymph nodes in levels I and II bilaterally. Intraoral examination was significant for a 5 × 4 cm rubbery, firm mass on the right palate, extending across the midline without ulceration of the overlying mucosa. Nasal endoscopic evaluation revealed a large amount of mucous and blood with engorgement of turbinates on the right side. Laryngoscopy with a fiberoptic endoscope showed normal hypopharynx, larynx, and functioning vocal chords.

Computed tomography (CT) scan confirmed the presence of a 6.8 × 4.8 × 6.1 cm mass with bony destruction

of the right palate and anterior and lateral sinus walls (Fig. 1). Coronally, the mass extended to the orbital floor but showed no evidence of orbital invasion. Positron emission tomography (PET) showed increased D-18 fluorodeoxyglucose activity in the right maxillary sinus. The standard uptake value (SUV) in the right maxillary sinus measured 12.1. Two lymph nodes, both 2 cm in size, with increased SUV uptake, presented in levels II and III on the right side. Left-sided lymph nodes with increased SUV were confirmed in levels III and IV. The PET scan showed no evidence of distant metastasis.

Magnetic resonance imaging with and without gadolinium contrast was utilized to evaluate the soft tissue extent of the tumor into the ethmoids and to aid in surgical planning. Results showed a soft tissue mass with a well-defined mucosa lining in the right maxillary sinus eroding through the floor and walls of the maxillary sinus while the orbital floor and medial orbital wall remained intact. Magnetic resonance imaging findings showed mucosal thickening of the ethmoids without evidence of tumor invasion. The mass showed homogeneous intermediate T1 sequence and intermediate T2 signal with mild inhomogeneous enhancement. Enlarged cervical lymph nodes were consistent with those mentioned in the CT and PET findings.

Initial incisional biopsy provided no histopathologic yield secondary to difficulty achieving hemostasis. The surgical team performed a second biopsy in the operating room, where a deeper sample could be obtained in a more controlled environment. A diagnosis of PLGA was confirmed and clinically staged at T4N2cM0.

The patient was presented to a multidisciplinary head and neck tumor board and a decision was made for surgery. A tracheostomy to establish a stable airway was performed, followed by a Weber–Ferguesen approach with ethmoid extension to gain access for a class 3D maxillectomy[1] and for removal of the primary tumor (Figs 2 to 4). The resection included the orbital floor and medial orbital wall, leaving behind all orbital contents. Bilateral modified radical neck dissections were

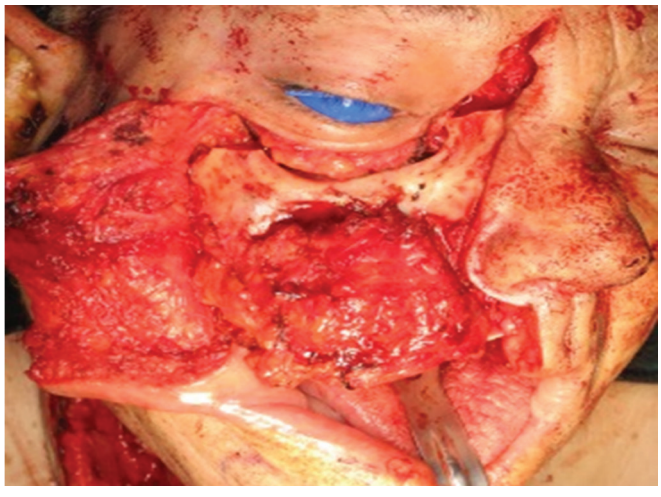

Fig. 1: Weber–Ferguson approach to access the primary PLGA

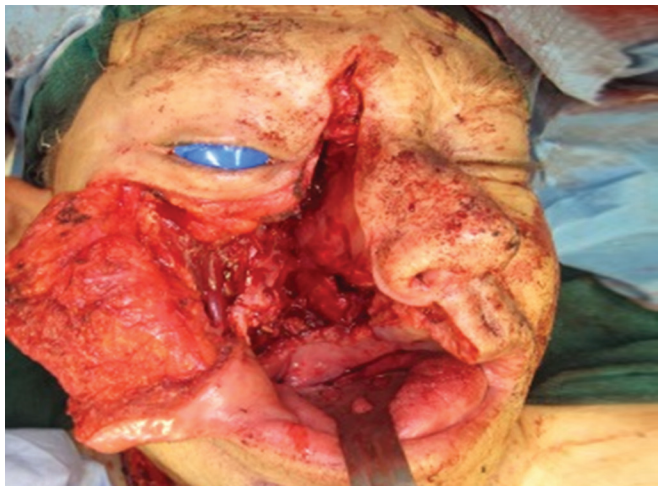

Fig. 2: Postresection defect

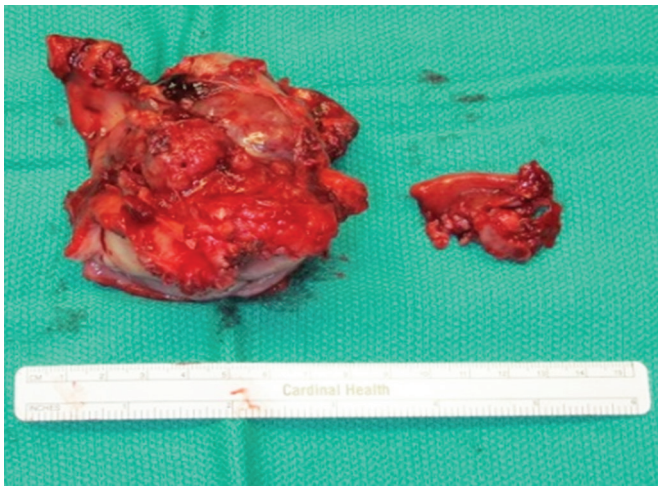

Fig. 3: Primary PLGA

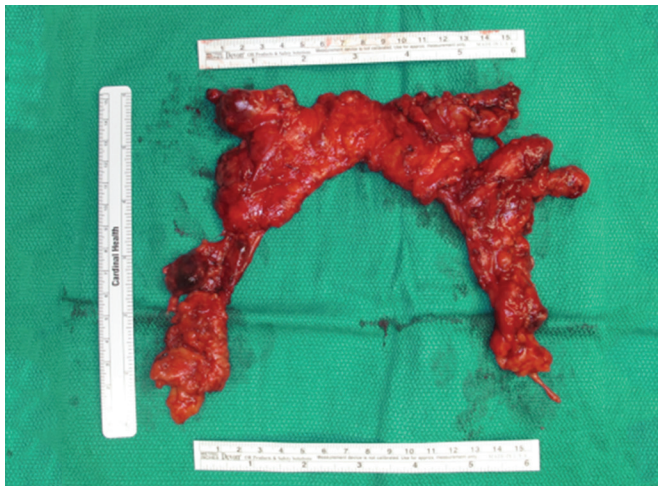

Fig. 4: Fat adipose lymphatic tissues (FALT) from bilateral neck dissections

performed in en bloc fashion (Fig. 5). Final reconstruction of the ablative site was completed using a rectus flap.

Review of surgical histopathologic report yielded a 6.0 × 5.5 × 5.2 cm primary PLGA. Extracapsular spread of the PLGA was noted in 5 of 10 lymph nodes in the right neck (Fig. 6). Surprisingly, 14 of 16 left-sided lymph nodes returned for squamous cell carcinoma antigen (SCCa) with extranodal extension (Fig. 7).

Microscopic examination of the right neck lymph nodes showed strong expression for cytokeratin 7 and P16 (Fig. 8) and focal faint expression for cytokeratin 5/6 and P63. These histologic markers highlight the positivity to luminal and nonacinar cells consistent with PLGA.[2,3] Lymph nodes in the left neck had strong expression for P63 and cytokeratin 5/6 (Figs 9 and 10). Histologic examination of the left neck showed no affinity for cytokeratin 7, cytokeratin 20, or P16. The P63 gene is typically overamplified in SCCa, thus the P63 antibody is a specific epithelial marker. Cytokeratin 5/6 highlights the basaloid layer in SCCa. These findings are consistent with SCCa.[3-5]

Prior to adjunctive therapy, consisting of radiation therapy, the patient returned to the operating room for panendoscopy to search for the unknown primary SCCa. On thorough examination, no primary site for the unknown SCCa was appreciated. All biopsies taken during this procedure returned negative.

The patient declined chemotherapy and adjunctive treatment consisted of radiation therapy to the surgical site and bilateral necks. On completion of surgical therapy, a total of 7040 cGy in 32 fractions was administered.

Six weeks after completion of radiation therapy, physical exam revealed a well-healed surgical site with no evidence of wound breakdown. The patient had limited opening to 30 mm, and remained polyethylene glycol dependent. Other complaints consisted of bilateral hearing loss, decreased taste, and thick saliva. No local or regional recurrences were noted on examination. The patient was sent for speech and swallow therapy and routine follow-up visits.

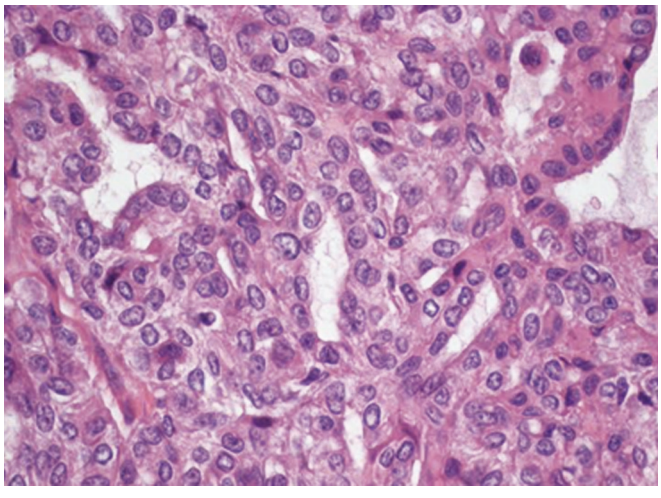

Fig. 5: Hematoxylin-eosin stain of 40× magnification of PLGA

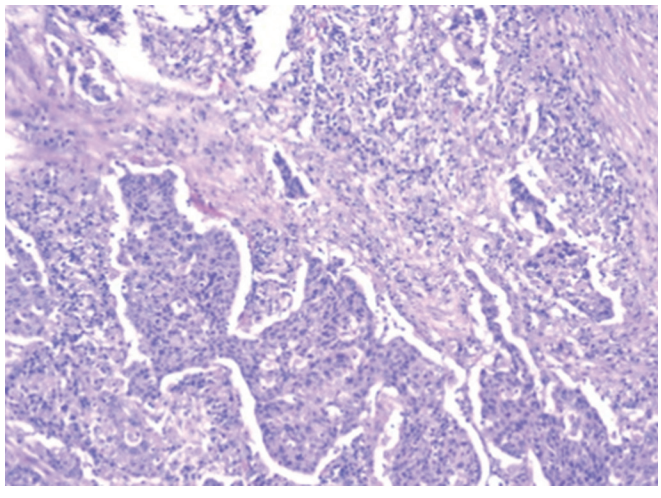

Fig. 6: Hematoxylin-eosin stain 10× magnification of squamous cell carcinoma antigen

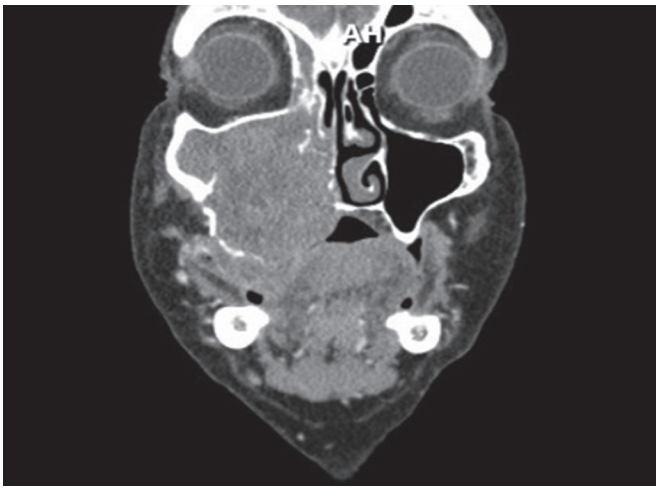

Fig. 7: Coronal view CT face with 6.8 cm mass in the right maxilla and maxillary sinus

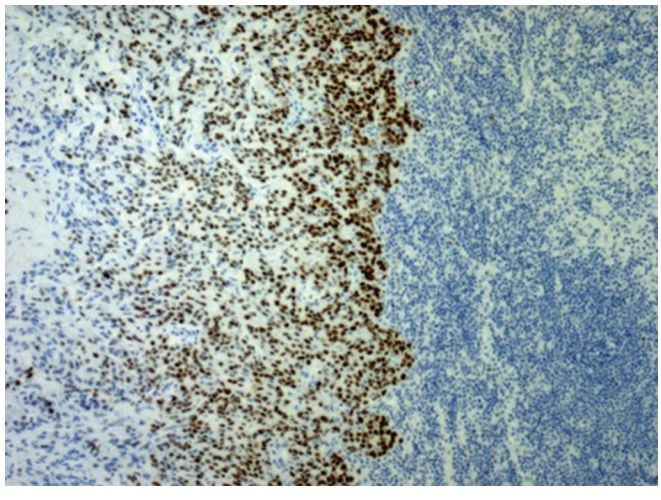

Fig. 8: p16 stain of PLGA nodes in the right neck

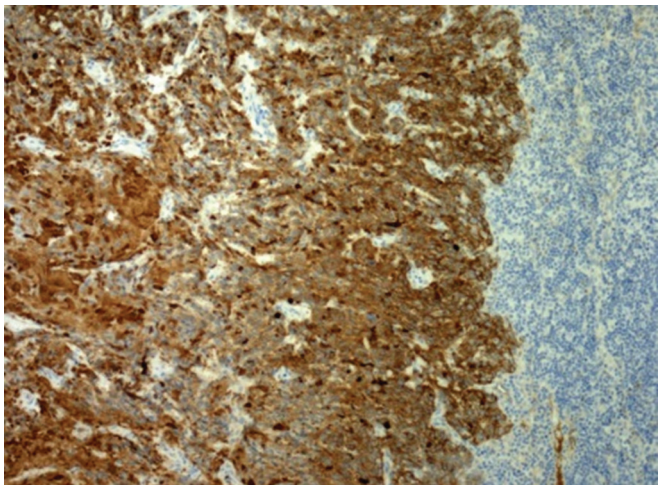

Fig. 9: p63 stain from squamous cell carcinoma antigen nodes in the left neck

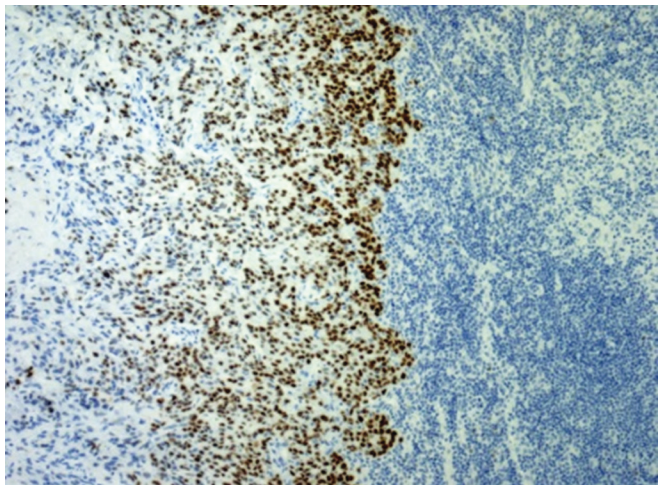

Fig. 10: Cytokeratin 5/6 stain from squamous cell carcinoma antigen nodes in the left neck

DISCUSSION

Multiple aspects of this case are distinctive. The large size and cervical metastasis were unique characteristics of this particular PLGA. The surprising diagnosis of the SCCa with an unknown primary site is a rare finding among SCCas of the head and neck. There exist two synchronous independent multifocal malignant diseases of different tissue origin, with one being discovered by the final histopathologic results.

The pathologic size of the PLGA in our case is 6.0 × 5.5 × 5.2 cm (Fig. 4). This is the third largest PLGA noted in the literature.[6,7] Most PLGAs are identified early in their development at an average size of 2.2 cm.[8] Castle et al noted that tumors of the palate typically measure 1.1 cm larger than those found in the lip. This is most likely due to the more cosmetic nature of the lips. The inconspicuous location on the palate and the patient's apathetic attitude toward medical care can account for the sizeable nature of the primary PLGA.

The majority of PLGAs show no evidence of metastasis. Vincent et al report that a regional metastasis of PLGAs occurs at a rate of 9%.[9] In a study of 40 PLGA cases, those with papillary cystic growth pattern had a higher incidence of local recurrence, uncontrolled local recurrence, and cervical lymph node metastasis.[10,11] Multiple patients have been known to have several episodes of recurrence and metastasis. Polymorphous low-grade adenocarcinoma metastasis is most common to the cervical lymph nodes followed by the lungs and in rare cases the skin and the orbit.[12]

Recurrence rates of PLGA are reported to be from 9.1 to 17%, and they occur anywhere from 2 to 14 years after initial therapy.[8,9] Castel et al demonstrated that PLGAs originating from the palate are 1.6 times as likely to recur as compared with primaries of other locations. The National Comprehensive Cancer Network recommends treatment of T3 and T4 lesions of minor salivary glands with surgical excision and considerations for radiation and chemotherapy in cases with adverse features. Based on two studies of 40 and 17 cases, adjunctive radiation therapy may not be indicated.[10] Castle et al note that of the 17 patients undergoing radiation therapy, for management of PLGA, the incidence of recurrence was greater than in the group of patients who were treated with only surgery.

Squamous cell carcinoma antigen with an unidentifiable primary site accounts for nearly 1 to 5% of all SCCa carcinomas of the head and neck. Of these, only 40% of the primary sites are deceted.[13] Treatment in these cases is still debated with no well-defined answer. Some treatment modalities call for radiation, while others call for bilateral neck dissection and radiation. Bilateral tonsillectomy has been suggested based on findings that 23% of patients with unknown primary SCCas were discovered to have invasive SCCa or carcinoma *in situ* in both tonsils.[14] There is some evidence that in patients with advanced disease, combination modalities are more effective than single-modality therapy.[15] In the case presented, the advanced nature of the SCCa required adjunctive radiation therapy. It is debatable, however, as to whether there was any benefit to radiation therapy for management of the PLGA.

The following criteria for multicentric neoplasms (multiple primary) remain defined: (1) the tumors must be clearly malignant on histological exam; (2) each tumor must be geographically separate and distinct, not connected by either submucosal or intraepithelial neoplastic changes; and (3) the possibility of the second tumor representing a metastasis must be excluded.[16] While the criteria for multiple neoplasms remain clear, the distinction among simultaneous, synchronous, and metachronous is varied in the literature. Simultaneous

and synchronous are used synonymously, with a few exceptions. According to Shikhani, the Tumor Registry defines synchronous tumors as those diagnosed within the same month,[17] while Gluckman et al describe synchronous tumors as those diagnosed within a 6-month window.[18] Tumors diagnosed beyond the 1- or 6-month period are classified as metachronous.

In the case presented, the large size indicates a long-standing PLGA. Had the PLGA been diagnosed at an earlier time, it is possible that this patient could have fallen into a metachronous diagnosis. This may be true for many patients who are unmotivated or unable to seek care with long-standing malignant disease. In patients with advanced staged malignant diseases, especially those with malignancies of less aggressive nature, it is entirely possible that a synchronous tumor diagnosis is made, though the processes may have begun at an interval greater than 1 or 6 months.

Synchronous malignancies in the head and neck are rare, occurring between 4.9 and 7% of all head and neck malignant diseases[17,19] and are noted to occur at a higher incidence in patients who smoke and drink.[20] In 1956, Slaughter presented the theory of field cancerization by which an area under the chronic stress of a carcinogen may become malignant at multiple sites.[21] In the case of synchronous head and neck malignancies, Panosetti et al demonstrated that the synchronous cancer is most likely to be found in adjacent anatomical sites.[22] This supports the field cancerization theory by which alcohol and cigarette products are the carcinogens.

In a study of 1,961 cases of head and neck cancer, primary malignancies of the salivary glands were shown to be 20 times more likely to have a secondary salivary malignancy, synchronous or metachronous, as compared with malignancy of another tissue origin.[15] In essence the co-occurrence of a primary salivary gland carcinoma and synchronous squamous cell carcinoma is extremely rare.

There are multiple cases documenting synchronous head and neck malignancies of different tissue origins. The majority of these involve a thyroid malignancy and another type of head and neck tissue malignancy.[23] Chau et al[9] report a collision tumor of a benign salivary gland tumor, pleomorphic adenoma, and SCC, but this seems to be the only case documenting a collision tumor of these two tissue origins.[24]

The overall 5-year survival rate is reported to be significantly less in cases of synchronous malignancies than in patients with single primaries or metachronous processes. For those patients with synchronous primaries diagnosed during initial treatment and those requiring interfering treatment modalities causing delayed therapy for the second primary, the 5-year survival rate drops to as low as 8%.[18,25] In patients who required no additional treatment modalities, the 5-year survival rates are reported to be as high as 28%. Watanbe et al suggest management for these synchronous malignancies by treating the disease with the poorer 5-year survival rate first, followed by adjunctive treatment for the secondary malignancy.[26]

In the case presented, there was definitive indication for adjunctive radiation therapy for treatment of the SCCa of the unknown primary. Although the radiation field was broadened to include the PLGA, this most likely had little effect on the treatment outcome. All in all, despite the unexpected SCCa, both tumors were managed simultaneously without delayed or interfering treatments.

CONCLUSION

Head and neck malignant pathologies account for less than 4% of newly diagnosed malignancies in the human body.[27] In this case report, we presented two synchronous noncollision malignant disease processes of multifocal tissue origin in the head and neck. Synchronous tumors in this region present complex diagnostic and treatment challenges. To our knowledge, this is the first case report with synchronous malignancies of salivary gland origin with SCC.

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