

## Case Report

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# Synchronous HPV positive bilateral palatine tonsillar squamous cell carcinoma – Brief review of current literature on the role of magnetic resonance imaging

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### Abstract

Synchronous bilateral palatine tonsillar Squamous Cell Carcinoma (SCC) is a rare presentation and less than 10 cases of Human Papillomavirus (HPV) mediated synchronous bilateral palatine tonsillar SCC has been reported. We report case of a patient who presents with a painless left sided neck swelling and was subsequently diagnosed by imaging and histopathology with bilateral Squamous Cell Carcinoma (SCC) of the palatine tonsil and cervical nodal metastasis. Due to its excellent soft tissue/tumor contrast resolution, Magnetic Resonance Imaging (MRI) is the preferred imaging modality for initial staging. Improved sensitivity for the detection of synchronous tumors can be achieved by Positron Emission Tomography (PET)/ Computed Tomography (CT) examination. Due to the rare nature of this pathology, no specific treatment guideline has been provided by National Comprehensive Cancer Network (NCCN). Treatment options available include bilateral Transoral Robotic Surgery (TORS) radical tonsillectomy combined with bilateral neck dissection with adjuvant radiotherapy or chemoradiotherapy and/or upfront concurrent chemoradiotherapy.

### Background

Palatine tonsils are the most common site of oropharyngeal malignancy followed by the base of tongue and the soft palate [1]. The incidence of oropharyngeal malignancy associated with Human Papillomavirus Infection (HPV) has increased in the recent years, with approximately 40-80 percent of cases attributed to HPV [2,3].

Synchronous Head and Neck Squamous Cell Carcinoma (HN-SCC) is defined as two foci of SCC, separated by a wide zone of uninvolved tissue, diagnosed concomitantly or within the first

6 months of each other. The term “Metachronous” is used for malignant tumors diagnosed between 6 months and 5 years after the diagnosis of the initial primary malignancy [3-5]. The estimated overall incidence of synchronous and metachronous HN-SCC malignancy is 1-8 percent and 17-30 percent, respectively. However, synchronous bilateral palatine tonsillar SCC is more unusual with less than 40 cases reported in the literature, with the first case reported in 1971 [6]. Moreover, less than 10 cases of HPV mediated synchronous bilateral palatine tonsillar SCC have been reported [7].

The role of imaging in palatine tonsil carcinoma is to radiologically stage the lesion based on its size and locoregional spread and to define the extent of the nodal spread. Although both contrast enhanced CT and MRI are routinely used for the staging of this cancer, MRI is the preferred modality due to its superior soft tissue/contrast resolution. PET-CT is a useful adjunct, although tonsil tissue is normally FDG avid.

We present case of synchronous HPV mediated bilateral palatine tonsillar SCC and review the role of MR imaging in this diagnosis and its treatment.

### Case report

A man in his early seventies presents with an insidious and painless left sided neck swelling. Patient reports no pain, dysphagia, odynophagia, hemoptysis, and denies any systemic complaints such as fever, fatigue, chills, nausea or weight loss. He has not noticed any new oral cavity ulcers/lesions.

His social history is remarkable for no history of smoking or prior tobacco exposure. He has no prior medical history and no prior history of radiation.

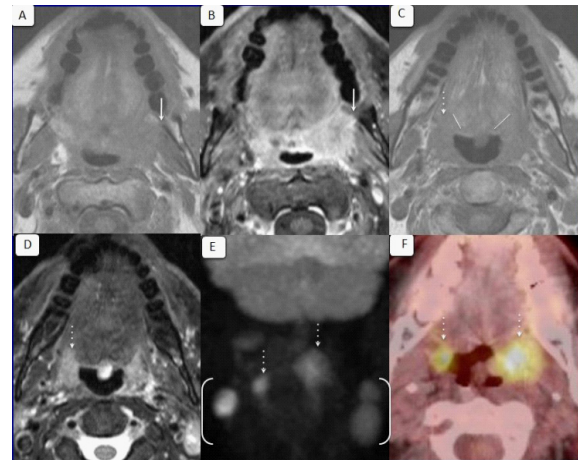
### Investigations

On physical examination, enlarged nodes are palpable on the left side of his neck. Additionally, a heterogeneous mass is noted in the left palatine tonsil. The right palatine tonsil appears normal. A biopsy of the left palatine tonsil reveals HPV mediated p16+ fragments of squamous cell carcinoma, moderately to poorly differentiated, non-keratinizing in background of tonsillar tissue. The patient is counselled regarding the results and is scheduled for an MRI and a PET/CT exam. The patient is also advised to undergo a direct laryngoscopy under general anesthesia for further characterization and surgical planning.

MRI reveals a heterogeneously enhancing mass centered in the left palatine tonsil, measuring 3.1 cm in its maximum dimension. The lesion extends laterally into the parapharyngeal fat and invades the left medial pterygoid muscle (arrow, figure 1a & 1b). An abnormal bulge in the anterior right palatine tonsil (dashed arrow, figure 1 c & 1d) effaces the right glossotonsillar sulcus and flattens the fat planes in the right aspect of the base of the tongue. The subsequent PET /CT shows abnormal radiotracer uptake in the bilateral palatine tonsils (dashed arrows in figure 1e & 1f) and several pathologically enlarged bilateral cervical lymph nodes, with the largest node measuring upto 2.4 cm, (brackets in figure 1e). The standardized uptake values (SUV) of the left and right palatine tonsils measuring 12.2 and 12.0, respectively. Multiple bilateral cervical lymph nodes also demonstrate abnormal SUV, ranging from 6.3 to 18.9. No additional foci of malignancy are identified below the neck on the PET-CT study.

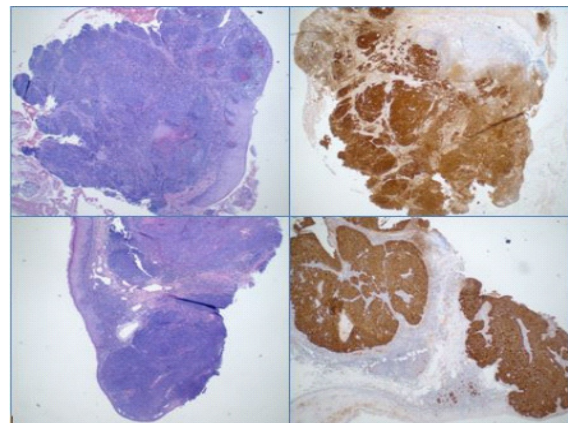
Additional biopsies of the tonsils under general anesthesia reveals HPV mediated p16+ fragments of squamous cell carcinoma in both tonsils (Figure 2).

Therefore a final diagnosis of bilateral synchronous palatine tonsillar carcinoma (cT4aN2M0 on left side and cT1N2M0 on right side). Both lesions were HPV mediated - p16 positive on immunostaining. N2 bilateral cervical nodal disease is also pathologically confirmed.



**Figure 1:** Synchronous squamous cell carcinoma in the bilateral palatine tonsils.

Axial T1 weighted (A&C), axial T1 post contrast (B) and axial T2 weighted (D) images at the level of the oropharynx show an aggressive enhancing mass centered in the left palatine tonsil that invades the left lateral pterygoid muscle (solid arrow). In addition, the right glossotonsillar sulcus is effaced by the abnormal fullness of the anterior right palatine tonsil (dashed arrow), suggestive of a synchronous tonsillar tumor. As a result, the right aspect of the base of the tongue is deformed. The straight lines drawn parallel to the normally seen fat planes at the base of the tongue highlight the flattening of the fat planes in the right base of the tongue as compared to the normal left side (C). The maximum intensity projections (MIP) (E) and fused axial CT/PET (F) exam show abnormal radiotracer uptake in the bilateral palatine tonsils as well as in multiple bilateral cervical lymph nodes (brackets).



**Figure 2:** Right tonsil squamous cell carcinoma (Top left, H&E stain 2x; Top right p16 immunostain is brightly positive 2x). Left tonsil squamous cell carcinoma (Bottom left, H&E stain 2x; Bottom right p16 positive 2x).

### Differential diagnosis

The differential diagnosis of bilateral palatine tonsil lesions on imaging includes tonsillitis +/- abscess which is usually seen in young adults and associated with fever. There is also an associated intra-peri tonsillar rim enhancing fluid collection. This was highly unlikely in our case. Non Hodgkin's lymphoma (NHL) which is usually submucosal and bilateral is another differential in our case. However, in NHL non-necrotic cervical nodes are seen and additional nodes may be present elsewhere with presence of systemic symptoms.

## Treatment

Upon the completion of the clinical, radiological and pathological staging, the patient is presented and discussed in the multidisciplinary HN tumor board. The final consensus is to proceed with definitive chemoradiation that includes radiation to a dose of 70 Gy in 35 fractions delivered to the bilateral palatine tonsils and any sites of PET positive nodes over approximately 7 weeks and weekly Cisplatin in a dose of 40 mg/m<sup>2</sup> as the chemotherapeutic agent.

The patient underwent chemoradiation treatment for 7 weeks.

## Discussion

Synchronous bilateral palatine tonsillar SCC is a rare presentation with less than 40 cases described in the English literature, with the first report published in 1971 [6]. Moreover, less than 10 cases of HPV mediated synchronous bilateral palatine tonsillar carcinoma have been reported [7].

Smoking, alcohol and Human Papillomavirus (HPV) infection are known major risk factors implicated in tonsillar carcinoma. However, there is an increasing association between HPV overexpression and synchronous bilateral tonsillar carcinoma. In a review by Joseph AW et al., three models/mechanisms of pathogenesis were described. This included the theory of 'Field Cancerization' in which a persistent HPV infection may cause synchronous carcinomas at different anatomical sites, a second mechanism that multiple independent infections from several HPV types infect different areas of squamous epithelium resulting in carcinoma at different sites and a third postulated mechanism that primary HPV-induced tonsillar carcinoma subsequently generated a monoclonal second primary carcinoma in the contralateral tonsil by migration of HPV-infected cells [8,9].

The role of imaging is to provide accurate radiological staging. Several changes have been made to the oropharyngeal cancer staging in the recently released 2018 AJCC Cancer Staging Manual. The most important of which is that the staging of the palatine tonsillar cancers is now dependent on the HPV status of the cancer. This is based on extensive data showing improved outcome in HPV + patients and the need for de-escalation of treatment for these patients [10]. Understanding the key distinctive features involved in the different T and N stages can hone the radiologist's evaluation of the tumor and its locoregional extent.

MRI is the preferred imaging modality due to its superior soft tissue/tumor contrast [11,12].

Also, in comparison to CT, MR images are less degraded by dental amalgam. This tissue contrast is highlighted by the visualization of the tumor with multiple sequences including T1-weighted (T1), fat-suppressed T2W (T2FS) and post-contrast fat-suppressed (T1+C) images in axial, coronal and sagittal planes. In addition, Diffusion-Weighted (DWI) imaging can be added to further increase the accuracy of lesion characterization. This latter sequence is also useful in the early determination of tumor response to chemotherapy [13]. In cases of tonsillar cancer, the borders of the tumor should be delineated with respect to tonsillar pillars, glossotonsillar sulcus, base of tongue, and the superior constrictor muscle. Invasion of deep/extrinsic muscles of tongue, medial-lateral pterygoid muscles, pre-epiglottic fat, larynx, arterial encasement and prevertebral fascia should be assessed, which are important factors for tumor resectability [14].

Bony invasion (e.g. of mandible, pterygoid plates, hard palate or skull base) can be sought out. Lastly, perineural spread can be suspected with enlargement and abnormal enhancement of the nerves within greater and lesser palatine canal, the pterygopalatine fossa, foramen rotundum, infraorbital fissure/canal, as well as foramen ovale [14,15].

The limitations of MRI include difficulty in visualization of small mucosal & submucosal lesions. The appearance of palatine tonsils is also variable and at times asymmetrical, thus further making the diagnosis of synchronous malignancy challenging. PET-CT is an important adjuvant modality, reinforcing the MR findings with abnormal increased radiotracer uptake in bilateral tonsils.

NCCN guidelines provide no clear recommendation on the treatment of bilateral palatine tonsillar SCC. In a recent report by Christine M Kim et al. they stressed that the contralateral tonsil should routinely be removed in the setting of a known unilateral HPV positive palatine tonsillar SCC since missing a occult contralateral malignancy has grave prognostic implications [9]. Rokkjaer et al. concluded that bilateral tonsillectomy should be recommended in all patients with suspected or biopsy-proven palatine tonsillar SCC (unilateral or bilateral) and in those with carcinoma of unknown primary. However, there is no clear consensus whether bilateral tonsillectomy should be considered as a standard procedure [6,9,16]. Definitive chemoradiation is an acceptable alternate therapy. In these cases, the radiation field must include both tonsils/primary site as well as any sites of positive regional nodes.

Recognition of synchronous malignancy therefore in the contralateral tonsil is essential in minimizing the chance of early recurrence, decreasing morbidity and improving the five year survival rate.

## Learning points/take home messages

1. Synchronous bilateral palatine tonsillar SCC is a rare presentation. HPV mediated (p16 positive) synchronous bilateral TC cases are even less commonly reported in the literature.
2. MRI is integral in imaging work up of these patients and is indispensable for evaluation and radiological staging. A systematic MR protocol and review of images is essential. When combined with PET-CT, the diagnostic accuracy can further improve.
3. Possibility of a synchronous PCT should be entertained with equivocal imaging or clinically findings of the contralateral tonsil, especially in those with HPV positive SCC. Biopsy of the contralateral tonsil can confirm the diagnosis and decrease the possibility of early recurrence.

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