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A Tale of Two Malignancies: Navigating the Grey Zone between Metastatic and Second Primary

Abstract – Nasopharyngeal carcinoma (NPC) is a common malignancy in Southeast Asia, often presenting with advanced locoregional disease or distant metastasis. Diagnostic challenges arise when new lesions develop post-treatment, particularly when histopathological features overlap with the primary tumour. We present a rare case of bilateral tonsillar squamous cell carcinoma in a previously treated NPC patient, highlighting the diagnostic dilemma between metastasis, second primary, or synchronous tumour

Keywords – Nasopharyngeal carcinoma, bilateral tonsillar mass, metastasis, second primary, synchronous tumour

1 INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one of the common malignancies in Southeast Asia which present with advanced locoregional disease and distant metastasis [1]. Its commonly associated with Epstein – Barr virus (EBV) infections. Post-treatment surveillance is crucial, as recurrence or new malignancy can mimic the original disease, making distinction between recurrence, metastasis, and second primary tumour particularly challenging especially the histopathological features overlap with primary tumour [2]. It's more complicated when the new lesion is at bilateral tonsillar region which is rare metastatic region of NPC and prevalence of bilateral tonsillar carcinoma itself is <10% [3]. Differentiating between these possibilities has significant therapeutic and prognostic implications

2 CASE PRESENTATION

A case of 52 years old Malay gentleman with underlying dyslipidemia, was diagnosed with non-keratinizing nasopharyngeal carcinoma (T4n2M0) in July 2024. He initially presented with right diplopia with bilateral cervical lymphadenopathy and constitutional symptoms. On examination noted to have right abducent nerve palsy and during Naso endoscopic examination reveals mass at bilateral fossa of Rosen muller. Biopsy confirmed non keratinizing NPC. Subsequently he underwent four cycles of chemotherapy and 35 fraction of radiotherapy which he completed on march 2025.

Initial surveillance which is two months post CCRT noted progressive left neck swelling started three weeks post completion of treatment with compressive and constitutional symptoms. Physical examination revealed increasing of left cervical swelling with no oropharynx mass. subsequently on next surveillance which is three month post treatment noted to have bilateral oropharynx mass with worsening of obstructive symptoms.

Scope finding no mass at nasopharynx, bilateral tonsillar mass extending up to epiglottis level. Biopsy of bilateral tonsillar mass came back as Squamous cell carcinoma, poorly differentiated P-16 negative. Computed tomography imaging showed reduction of the primary nasopharyngeal lesion but new extensive bilateral cervical lymphadenopathy with lung, liver and bony lesions.

3 DISCUSSION

This case presents a significant diagnostic dilemma, whether the bilateral oropharyngeal squamous cell carcinomas represent metastatic transformation of the original nasopharyngeal carcinoma (NPC), a radiation-induced second primary tumour, or synchronous primary malignancies [1,2].

In patients with a prior history of cancer, the appearance of any new lesion warrants biopsy to establish a definitive diagnosis. Immunohistochemical (IHC) profiling, including EBV, HPV, and p16 testing, provides valuable information to differentiate between these possibilities especially in head and neck malignancies [2]. Additionally, PET-CT imaging helps to identify the extent of disease, detect occult metastases, and identify additional primary tumours.

In this case, the original NPC was non-keratinizing, likely EBV-related, whereas the

bilateral tonsillar masses were poorly differentiated squamous cell carcinomas, p16-negative (non-HPV related), yet sharing similar histological morphology. Histologically, non-keratinizing NPC and poorly differentiated squamous cell carcinoma can appear similar. Thus, immunohistochemical markers become essential for accurate distinction. EBER positivity supports NPC origin, while p16 or HPV positivity suggests a de novo oropharyngeal primary. Negative results for both may indicate a radiation-induced malignancy or field cancerization effect.

Although NPC metastasis to the tonsil is rare, it remains possible. Furthermore, bilateral tonsillar involvement is uncommon, occurring in fewer than 10% of documented cases [3]. According to the Modified Cahan classification, radiation-induced malignancies typically demonstrate a latency period of more than 3 years.

The Modified Cahan criteria define a radiation-induced tumour as one that meets the following conditions:

1. The new tumour arises within the previously irradiated field.
2. There is a sufficient latency period between radiation exposure and the appearance of the new tumour (commonly >4 years).
3. The treated tumour and the alleged induced tumour must have been biopsied and the two tumour must be different histologically
4. The tissue in which the alleged induced tumour arose must been metabolically and genetically normal before radiotherapy exposure

In the present case, while the lesions developed within the irradiated field and after an latency interval less than 4 years, the shared squamous histology between the tonsillar lesions and the original NPC argues against a classic radiation-induced malignancy.

The concept of field cancerization must also be considered. Prior exposure to carcinogens such as chemoradiotherapy or smoking can cause widespread mucosal genetic alterations, predisposing to multiple independent neoplasms. This mechanism may account for synchronous or metachronous tumours within the head and neck region. Synchronous tumors are defined as two or more primary cancers that occur at the same time or within six months of each other, while metachronous tumors develop more than six months apart. This mechanism may explain the occurrence of multiple tumors within the head and neck area in this patient.

Although EBER testing in oropharyngeal carcinoma is not routinely performed, it could be valuable in differentiating metastatic NPC from a second primary tumour , an area that warrants further research.

From a therapeutic perspective, distinguishing between metastatic disease and a second primary tumour is crucial, as management strategies and prognoses differ substantially. Recurrent or metastatic NPC may be best managed with systemic chemotherapy or immunotherapy, while a second primary tumour could warrant locoregional treatment. Additionally, the patient's post-CCRT condition must be carefully considered, as prior radiotherapy may limit tissue healing and tolerance to further treatment. p16-negative oropharyngeal cancers are usually less sensitive to radiation, which can make their treatment more challenging and the outcome guarded.

This case highlights the need for a team approach, involving radiologists, pathologists, and oncologists, to ensure accurate diagnosis and proper individualized treatment planning. Although this case does not fully meet the formal criteria for a radiation-induced malignancy, a high index of suspicion should always be maintained. Radiotherapy exposure itself may contribute to a field cancerization effect, predisposing to multiple independent primaries and complicating diagnostic and therapeutic decision-making.

4 CONCLUSION

It's important to differentiate for diagnostic and management of the patient but challenging when clinical, radiological and pathological finding overlap. Overlap in histological subtype further complicates interpretations. Conclusion, we need a multidisciplinary team approach of patient and proper surveillance for patient with new head and neck lesion post treatment. A high index of suspicion for radiation induced malignancy should be maintained. Field cancerization and differentiation should be considered [3].

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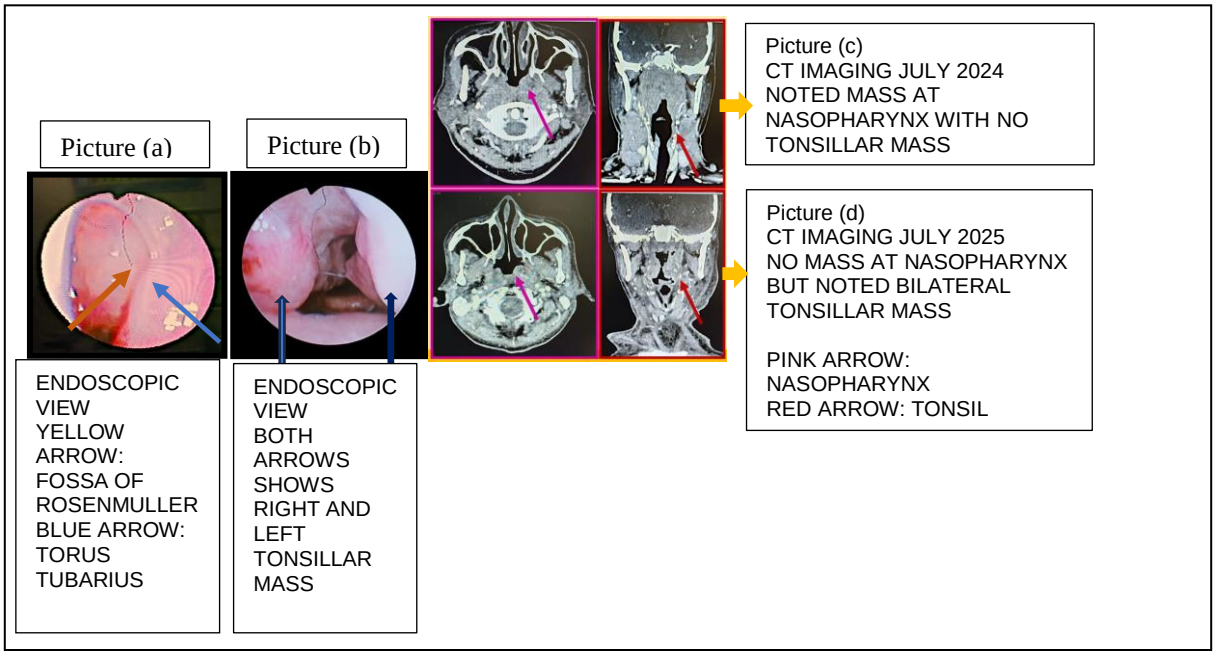

Figure 1. Endoscopic view and CT Imaging presentation