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DELAYED EMERGENCE OF CONTRALATERAL BUCCAL MUCOSA SQUAMOUS CELL CARCINOMA FOLLOWING TREATMENT OF CERVICAL METASTATIC SQUAMOUS CELL CARCINOMA OF UNKNOWN PRIMARY: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Head and neck carcinoma of unknown primary (HNCUP) represents approximately two to five percent of all head and neck squamous cell carcinomas. Despite advances in fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT), panendoscopy, and directed biopsies, the primary lesion remains occult in a subset of patients. We report a rare case of cervical metastatic squamous cell carcinoma with occult primary in which contralateral buccal mucosal squamous cell carcinoma emerged shortly after completion of definitive chemoradiotherapy despite initially benign biopsy findings.

KEYWORDS

INTRODUCTION

Head and neck carcinoma of unknown primary (HNCUP), also referred to as mucosal unknown primary (MUO), represents a distinct clinical entity characterized by metastatic cervical lymphadenopathy without detectable primary tumor despite comprehensive diagnostic evaluation [1,2]. PET-CT, panendoscopy, and directed biopsies improve detection; however, false-negative investigations continue to pose a challenge. Leukoplakia is considered a potentially malignant oral disorder with variable malignant transformation risk [3].

Case presentation

A 58-year-old female presented with left-sided neck swelling of three months duration. She had a history of chronic betel nut and lime chewing for approximately 20 years. Clinical examination demonstrated a firm left level II cervical lymph node measuring approximately 3 × 3 cm. Oral cavity examination revealed leukoplakia involving the right lower buccal mucosa measuring approximately 1 × 1 cm (as shown in Figure 1).

Fine needle aspiration cytology and histopathological review demonstrated metastatic squamous cell carcinoma. PET-CT, panendoscopy, tonsillectomy, Base of the tongue mucosectomy, and directed biopsies failed to identify a primary lesion. Histopathology from the buccal leukoplakic lesion demonstrated inflammatory changes without dysplasia or invasive malignancy.

The patient underwent radical neck dissection, left tonsillectomy, tongue-base mucosectomy, and local excision of the buccal lesion. Final histopathology demonstrated metastatic squamous cell carcinoma involving three of 17 lymph nodes with extranodal extension. Tonsillar and tongue-base specimens were negative for malignancy.

The patient subsequently underwent adjuvant concurrent chemoradiotherapy using intensity-modulated radiotherapy (IMRT) with concurrent weekly cisplatin. Approximately five months following treatment completion, she developed pain and ulceration involving the previously biopsied buccal mucosal site. Repeat biopsy demonstrated moderately differentiated Squamous cell carcinoma. Patient underwent wide local excision and right supra-omohyoid neck dissection and final histopathology showed pT1N0M0. Patient has completed one year post RT and 3 months post recent surgery follow up, she is stable and free of disease. Timeline of clinical events are summarized in Table 1.

DISCUSSION

This case highlights the biological significance of field cancerization, false-negative biopsy, and limitations of PET-CT in occult mucosal disease [2,3]. Persistent leukoplakic lesions in patients with HNCUP require vigilant surveillance and repeat biopsy if clinically suspicious. The concept of field cancerization originally proposed by Slaughter et al. explains the development of multifocal mucosal malignancies in carcinogen-exposed epithelium [3].

False-negative mucosal biopsy remains a clinically important limitation in oral potentially malignant disorders because of lesion heterogeneity and superficial sampling. Mild FDG uptake in suspicious mucosal fields should not be dismissed solely on the basis of benign initial histopathology. In the present case, PET-CT demonstrated focal uptake in the gingivobuccal sulcus; however, histopathology was initially negative, likely representing either sampling error or occult premalignant transformation.

Several previously published studies have described delayed emergence of mucosal primaries following treatment for cervical metastatic SCC of unknown primary. Rusthoven et al. reported that PET-CT improves primary tumor detection but does not eliminate the possibility of occult disease [2]. Waltonen et al. described cases where initially benign mucosal findings subsequently progressed to oral cavity squamous cell carcinoma because of false-negative biopsy interpretation [6]. Strojan et al. emphasized the importance of long-term surveillance in HNCUP because delayed mucosal primary tumors may appear months after definitive treatment [1]. Similar published cases and their clinical implications are summarized in Table 2.

From a radiation oncology perspective, this case emphasizes the need for multidisciplinary surveillance, careful mucosal evaluation during follow-up, and low threshold for repeat biopsy in persistent leukoplakic lesions. The rarity of contralateral buccal mucosal SCC emerging shortly after chemoradiotherapy despite an initially benign biopsy supports the biological plausibility of aggressive field carcinogenesis and occult synchronous disease.

Unlike previously reported HNCUP cases where delayed primary tumors were predominantly identified in the oropharynx or ipsilateral mucosal sites, our patient developed contralateral buccal mucosal squamous cell carcinoma arising from an initially biopsy-negative leukoplakic lesion within a short interval following definitive chemoradiotherapy, highlighting a rare and clinically significant manifestation of field cancerization and occult mucosal transformation.

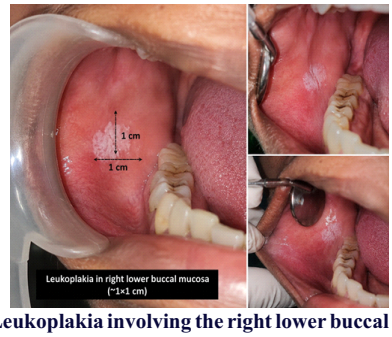


Figure 1. Leukoplakia involving the right lower buccal mucosa (~1 × 1 cm) identified during initial clinical evaluation.

Table 1. Timeline of clinical events

Timeline	Clinical Event
May 2025	Presentation with left cervical swelling
May 2025	FNAC/biopsy confirmed metastatic SCC
June 2025	PET-CT and panendoscopy negative for primary
June 2025	Buccal leukoplakia biopsy showed inflammatory changes
July 2025	Radical neck dissection + tonsillectomy + BOT mucosectomy
August- September 2025	Adjuvant chemoradiotherapy completed
~5 months post-RT	Development of buccal ulcerative lesion
Follow-up biopsy	Confirmed squamous cell carcinoma of buccal mucosa
February 2026	wide local excision and right supra-omohyoid neck dissection
March- May 2026	On Follow-up – no adverse events

Table 2. Review of literature and previously published similar cases [1,2,6]

Author	Presentation	Subsequent primary	Key message
Rusthoven et al.[2]	Cervical SCC CUP	Oropharyngeal SCC	PET improves but does not eliminate occult disease
Waltonen et al.[6]	Cervical metastasis	Oral cavity SCC	False-negative biopsy possible
Strojan et al.[1]	HNCUP	Delayed mucosal SCC	Surveillance critical
Present case	Level II metastatic SCC	Contralateral buccal SCC	Rare emergence after chemoradiation

CONCLUSIONS

Persistent leukoplakic lesions in patients with cervical metastatic squamous cell carcinoma of unknown primary should not be considered entirely benign despite negative biopsy findings. This case underscores the importance of multidisciplinary surveillance, awareness of field cancerization, and repeat evaluation of suspicious mucosal lesions after definitive treatment [1-4].

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