Cytological Diagnosis of a Rare Case of Buccal Mucosa Squamous Cell Carcinoma with Malignant Pleural Effusion and Review of Literature

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Abstract: Oral squamous cell carcinoma (OSCC) is a major global health concern, especially in India, where it is one of the primary causes of cancer-related fatalities. OSCC is notorious for its propensity to spread to distal sites such as the lungs, bones, and liver, but malignant pleural effusions resulting from OSCC are extremely uncommon. This case report details an unusual presentation of OSCC in a 61-year-old male presenting with bilateral malignant pleural effusion from a primary buccal mucosa squamous cell carcinoma with no lung involvement. Through cytological analysis and immunocytochemistry, we confirm the diagnosis of metastatic squamous cell carcinoma, highlighting the significance of comprehensive diagnostic approaches.

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Introduction

Oral squamous cell carcinoma (OSCC), which accounts for more than 90 percent of all oral cavity malignant neoplasms, is the seventeenth most common cancer worldwide. It ranks third among the numerous cancer types that cause mortality in India, is the most prevalent cancer in men, and is the third most frequent cancer overall (Nethan et al., 2022). It is the most prevalent malignancy in developing nations, and its incidence is rising. In southeast Asia, the oral cavity is the most prevalent site for head and neck squamous cell carcinoma (SCC). The population's pervasive use of smokeless tobacco products, such as pan and supari, is the primary cause of such a high incidence. Oral cavity carcinomas rarely metastasize to distal organs (Singh and Sharma, 2017).

The lung is the most common distant location for metastasis, followed by the liver (Betka, 2001; Paul et al., 2023). However, pleural involvement by OSCC is extremely infrequent. Malignant effusions are often a symptom of disseminated malignancy and indicate the terminal phase of the disease. Serous effusions by OSCC are rare (Huang and Michael, 2014). There are extremely few accounts documenting pleural effusion brought on by metastasis from oral cavity cancer (Betka, 2001). The management and prognosis of oral cancer patients are greatly influenced by distant metastasis (Irani, 2016). Detection of metastatic cancer is crucial for staging and management of the patient as individuals exhibiting metastatic disease or advanced local recurrence have a dismal prognosis. No cytotoxic chemotherapy regimens have been found to enhance the longevity of the patients in the long haul (Shao and Hong, 2010). We report such an unusual case of distant metastasis of OSCC (buccal mucosa) presenting as a malignant pleural effusion diagnosed primarily on cytology.

Case report

A 61-year-old male, presented to emergency with history of cough, chest pain for two months along with acute onset of rapidly progressing shortness of breath for 1 week. On history, patient was found to be a diagnosed case of OSCC, buccal cavity five months back on punch biopsy. He was on palliation therapy due to its locally advanced disease. On general examination, patient was tachypneic (26–28 breaths/minute) with diminished breath sounds. Local examination revealed an ulceroproliferative lesion in the right buccal cavity involving the overlying skin (Figure 1A). Radiological investigations revealed bilateral pleural effusion. Pleural fluid was aspirated and sent for cytological examination. Grossly, the pleural fluid sample was hemorrhagic. Two air dried and two alcohol fixed

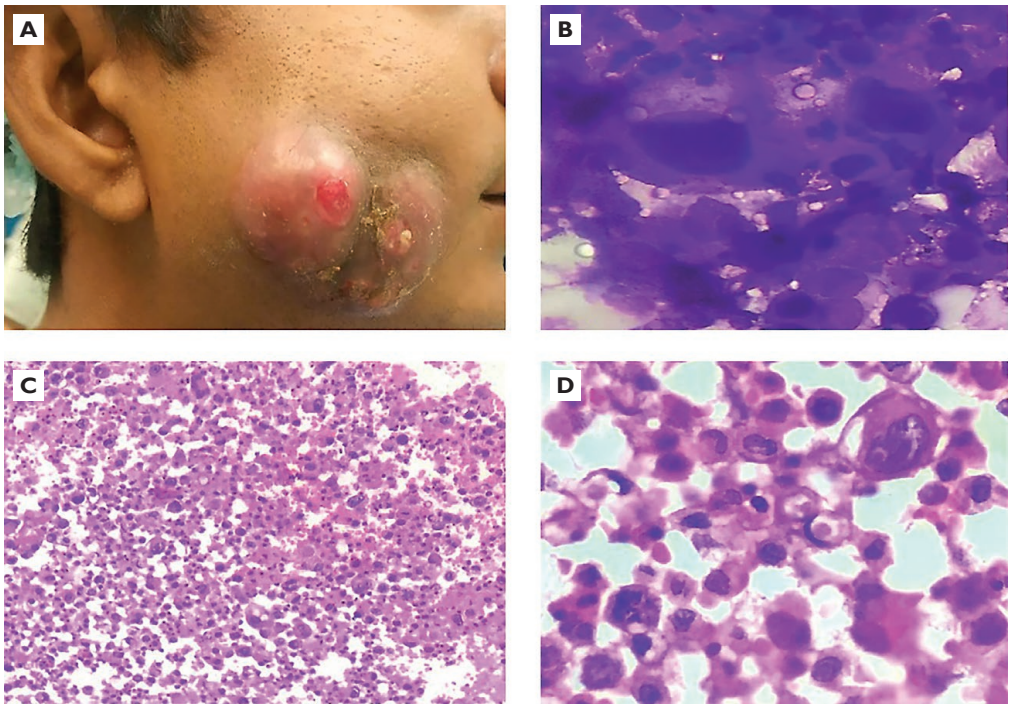

Figure 1: A) Clinical photograph of the patient with an ulceroproliferative lesion of the right buccal mucosa and extending to the right cheek. B) Cytospin smears from pleural fluid show scattered atypical cells among inflammatory cells (Giemsa, 400×). C) Cell block preparation showing discohesive tumour cells (haematoxylin and eosin [H and E], 200×). D) Atypical cells with bizarre nuclei on cell block (H and E, 400×).

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Papanicolaou smears were prepared from the cytospin deposits. Cell block preparation was also made from the aspirated material using 10% formalin as fixative and routine haematoxylin and eosin (H and E) stained sections were prepared from the paraffin embedded material.

The Giemsa stained smears were evaluated and showed presence of scattered single atypical cells amongst reactive mesothelial and inflammatory cells (Figure 1B). These atypical cells had high N:C ratio with large hyperchromatic nuclei, irregular nuclear membranes and moderate amount of cytoplasm. There were no three-dimensional cell clusters, signet ring cells, cytoplasmic vacuolations, "windows" between the cells, polygonal cells, anucleate cells, tadpole or fibre cells, squamous pearls were seen.

Cell block preparation showed discohesive singly lying tumour cells with moderate cytoplasm, pleomorphic and hyperchromatic nuclei amidst dense inflammatory background. Atypical cells with bizarre nuclei were also seen (Figure 1C and D). As the tumour cells were poorly differentiated, an initial immunocytochemistry panel of p63 and MUC5AC was done to rule out SCC, and adenocarcinoma respectively on cell block. In addition, Napsin A and TTF-1 was done to exclude any primary from the lung as the immunocytochemistry for MUC5AC was non-contributory. On immunocytochemistry, the tumour cells showed strong nuclear positivity for p63 and were negative for Napsin A and TTF-1 (Figure 2). Hence, on the basis of the patient's clinical history, morphological findings and immunocytochemistry, we conclusively determined that the patient had a metastatic SCC. Regrettably, the patient declined treatment after being informed of the dismal prognosis and was subsequently discharged. Unfortunately, he was lost to subsequent contact.

Discussion

The analysis of serous effusions, which are frequent specimens in cytopathology practice, provides a quick and precise way to identify metastatic illness (LePhong et al., 2017). Adenocarcinoma is the most prevalent malignant neoplasm found in serous effusions, followed by small cell carcinomas (14%), malignant mesotheliomas (8%), lymphoproliferative diseases (3.5%), and SCC (0.5–2.7%) (Cakir et al., 2011; Huang and Michael, 2014). The primary causes of malignant pleural effusions, which account for over 75% of cases, include lung, breast, ovary, and lymphoma malignancies. Even though SCC of the buccal cavity is common, malignant pleural effusions occur infrequently (Huang and Michael, 2014). It typically metastasizes to the lungs, bones, and liver after a protracted period of dormancy (Zbären and Lehmann, 1987).

Oral cancer with distant metastasis, which is uncommon, coincides with advanced stages of the disease, and is typically discovered after an interim dormant period (Betka, 2001).

The yield of exfoliative cytology from pleural effusion was greater than that of a biopsy, providing a diagnostic advantage over a biopsy (Paul et al., 2023). The most challenging aspect of assessing serous effusions is the extensive cytologic overlap between benign and reactive processes, as well as malignancies of diverse origins. Identification of metastatic SCC in pleural effusion is otherwise not difficult in patients who have a previous documented history of malignancy, in which the malignant effusion signifies disease progression (LePhong et al., 2017). However, when SCC is less distinct, the diagnosis might be difficult and error-prone. Due to its resemblance to other pathological effusions,

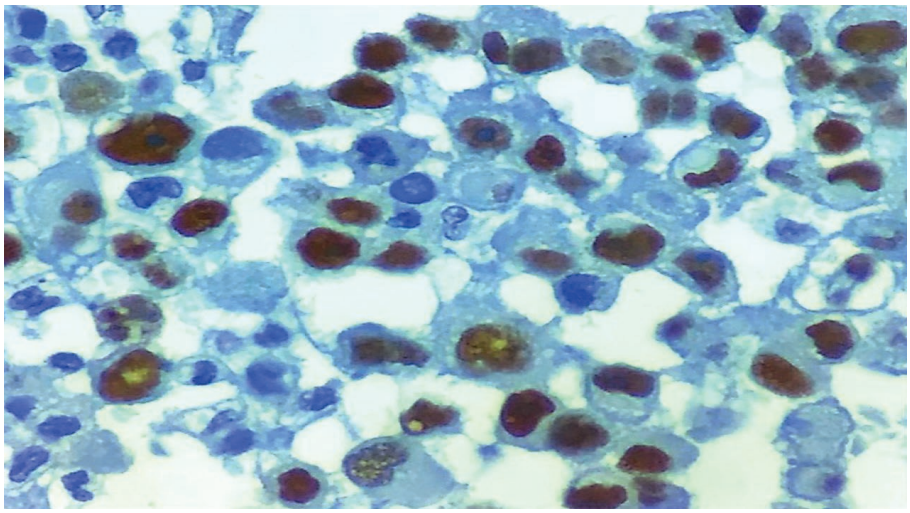

Figure 2: Immunocytochemistry on cell block showing strong nuclear positivity for p63 (400×).

the detection of metastatic moderately or poorly differentiated SCC in serous effusions offer a diagnostic difficulty (Huang and Michael, 2014). In serous effusions, adenocarcinoma and malignant mesothelioma are two frequent differential diagnoses for SCC (Huang and Michael, 2014; LePhong et al., 2017). Metastatic adenocarcinoma is the commonest imitator of poorly differentiated SCC due to the fact that both malignancies exhibit cell clusters and high nuclear atypia. However, morphologically poorly differentiated SCC cell clusters are two dimensional, more variable in size and have irregular borders, unlike the typical three-dimensional clusters with cytoplasmic vacuolations and signet ring cells in adenocarcinoma. In contrast to SCC, malignant mesothelioma cellular clusters show intercellular windows between the tumour cells and fuzzy borders attributable to the microvilli along with a low N/C ratio, relatively smooth nuclear contours and lesser nuclear hyperchromasia. Another diagnostic pitfall of SCC in pleural effusion is its coexistence with other primary malignancies like adenocarcinoma or urothelial carcinoma, the incidence of which is extremely low (Huang and Michael, 2014).

Table 1: Summary of previously reported cases of pleural metastasis from oral cavity SCC

Author	Age/ sex	Site of SCC	Radiological findings	Other metastasis	Cyto-morphology	Histomorphology	Follow-up
Ziaullah et al.[13] (2023)	61 Y/M	Left side buccal mucosa SCC	PET scan revealed a fluorodeoxy-glucose (FDG) avid uptake along the left pleura with a SUV max of 5.06 and massive pleural effusion.	Mediastinal lymphadeno-pathy. Thoracoscopy showed pleural deposits.	Negative for malignant cells	Frozen section from thoracoscopic pleural biopsy revealed infiltrating tumour cells arranged in nests with occasional keratin pearl formation suggestive of metastatic SCC deposits. Histo-pathology confirmed the diagnosis of metastatic SCC.	Expired four months later
Paul et al.[3] (2023)	54 Y/M	Right side buccal mucosa SCC extending into the left alveolus, gingivo-buccal sulcus and retromolar trigone	CT scan showed bilateral pleural effusion with no distinct mass or thickening was identified in the pleura and lung.	Absent	Metastatic squamous cell carcinoma (p40 positive cells)	Not performed	Not available
Wang et al.[14] (2017)	68 Y/F	Tongue SCC	Metastatic lesions were confirmed by neck or chest CT.	Neck and mediastinal lymph nodes, bone	NA	NA	Expired
	86 Y/F	Tongue SCC		Mediastinal lymph nodes			Expired
	67 Y/M	Tongue SCC		Lung			Expired
	68 Y/F	Floor of mouth SCC		Tiny lung nodules			Not expired
	64 Y/M	Tongue SCC		Lung nodules			Not expired
Ishikawa et al.[15] (1999)	74 Y/M	Right lower gingiva SCC	Presence of the pleural effusion and a well-circumscribed mass in the right hemithorax.	Absent	Not performed	On percutaneous biopsy found to have SCC of similar morphology.	Not available
Present case	61 Y/M	Right buccal mucosa	Bilateral pleural effusion	Absent	Metastatic SCC (p63 positive cells)	Not performed	Not available

The superscript numericals [13,3,14,15] are indexing mentioned in the references. Y – year; M – male; F – female; PET – positron emission tomography; SUV max – maximum standardized uptake value; NA – not available; SCC – squamous cell carcinoma; CT – computed tomography

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Immunocytochemical stains play a crucial role in distinguishing such differential diagnoses and establishing the diagnosis in such difficult cases as ours, in which the morphology is not particularly definitive.

In this case, immunocytochemical markers p63, Napsin A and TTF-1 were utilized to rule out alternative diagnoses. The tumour cells exhibited robust nuclear positivity for p63 but were negative for all other markers. This finding is in concordance with the previous literature, which showed that p63 is a potent nuclear stain that is expressed in 80–100% of SCC whereas it is scarcely expressed in adenocarcinoma or malignant mesothelioma making it a very useful confirmatory positive marker for diagnosing SCC (Huang and Michael, 2014; LePhong et al., 2017).

With negative expression of TTF-1 and Napsin A, metastatic adenocarcinoma from lung was also ruled out. In our case, we were aware of the history of a OSCC along with negative positron emission tomography (PET) scan for lung lesion. Therefore, the diagnosis necessitated the integration of the patient's clinical history, radiological findings, precise sample collection, and microscopic evaluation of cytology specimens. This comprehensive approach also involved utilizing immunocytochemistry on a cell block preparation to confirm the diagnosis. The patient declined treatment due to the dismal prognosis explained to him. Unfortunately, he was lost to follow up.

Pleural metastasis can be in the form of pleural effusion, pleural nodules, or nodular thickening of the pleura with enhancement, which can be seen on contrast computed tomography (Wang et al., 2017).

Pleural involvement is considered to be an extremely poor prognostic marker for survival and it does not always present with distant metastasis (Asciak and Rahman, 2018). Only a few cases have been reported in the literature (Table 1).

Conclusion

The rare occurrence of pleural involvement in metastatic OSCC is associated with a poorer prognosis. No cytotoxic chemotherapy regimen has been found to enhance the longevity of patients in such conditions. Identification of metastatic OSCC in pleural effusion is otherwise not difficult in patients with a documented history of malignancy, in which the malignant effusion signifies the progression of the disease.

In light of this, it is significantly more important for the pathologist to identify these uncommon cancers. In OSCC, malignant pleural effusion can be accurately detected using exfoliative cytology in conjunction with clinical information, imaging results, and cell block immunocytochemistry. To guarantee an accurate diagnosis, it is essential to integrate the clinical history with cytomorphological characteristics and an adequate immunocytochemistry panel.

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