

# Carcinoma Unknown Primary with Neck Secondaries and Concurrent Granulomata – A Case Report

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## Abstract

**Background:** Association of granulomatous inflammation along with malignancy in the histopathological evaluation of surgical specimens is a known entity. In developing countries like India, where Tuberculosis (TB) is prevalent, one has to consider the possibility of concomitant TB and malignancy.

**Case Report:** A 49 year old man presented with multiple unilateral cervical lymph node enlargement, on evaluation was found to have metastasis of squamous cell carcinoma in nodes with unknown primary tumor. He underwent a comprehensive, functional neck dissection. On histopathology examination (HPE) the levels IIa and IIb nodes showed deposits of squamous cell cancer, levels IV and V nodes showed caseous necrosis, granuloma formation and acid-fast bacilli (AFB) on Zeil Nielsen staining. After surgery he was started on anti-tubercular treatment, underwent external beam radiotherapy and is currently disease free and on follow up.

**Discussion:** The formation of stromal granuloma in lymph nodes represents a T-cell mediated immune response to surface antigens of a cell. The tumor cell surface antigens may be identified as the culprits for such a granulomatous reaction once other causes like TB, are ruled out. In the HPE slides a Zeil Nielsen staining should be performed to identify any AFB and confirm the diagnosis of TB. In this case of squamous cell carcinoma metastatic squamous cell carcinoma co-existed with TB and both were treated successfully.

**Conclusion:** Carcinoma of unknown primary with neck secondaries is, in itself, an elusive disease and needs extensive work up and careful management. In endemic countries, co-existing caseous granulomatous necrosis should warrant confirmatory diagnosis of TB and treatment of both.

**Keywords:** Inflammation; X-ray; Carcinoma; Granulomatous Disease

**Abbreviations:** TB: Tuberculosis; HPE: Histopathology Examination; AFB: Acid-Fast Bacilli; FDG: Fluorodeoxyglucose; CECT: Contrast Enhanced Computed Tomography; CUPS: Carcinoma of Unknown Primary with Secondaries; CT: Chemotherapy; PET: Positron Emission Tomography; FNAC: Fine Needle Aspiration Cytology; MRND: Modified Radical Neck Dissection.

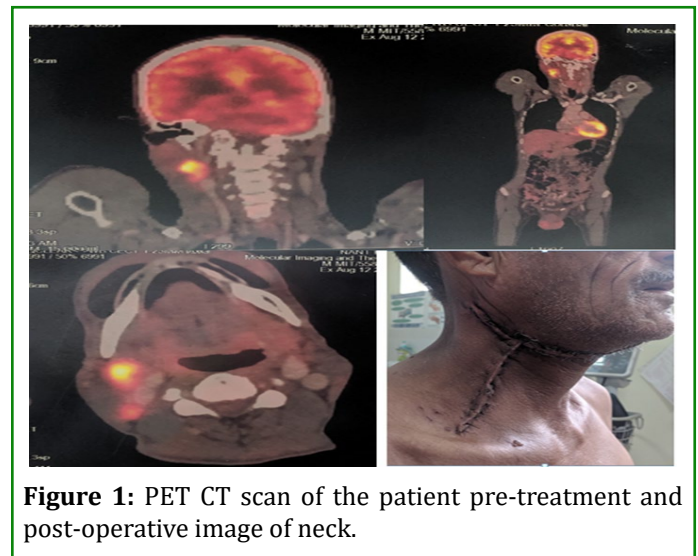
## Introduction

Tuberculosis (TB) along with carcinoma is a rare entity. It is often a dilemma to differentiate whether the granulomatous response is an immunologic reaction to tumour antigens or there is a coexistence of carcinoma and tuberculosis. Granulomatous inflammation is usually an immune response to non-neoplastic conditions and chronic infections like TB and sarcoidosis. Various theories have been suggested to answer the debate about the etiological relationship between TB and carcinoma; a simple co-existence of the two is a possibility especially in areas with a high incidence and prevalence of TB, as in India. The global TB report 2017 found an estimated incidence of approximately 28,00,000 in India; which accounted for about one quarter of the world's TB cases. A possibility of the reactivation of an old tubercular focus in the advent of immunosuppression due to malignancy should be considered [1-5]. In this article, we present the case of a male with metastatic carcinoma identified in cervical lymph nodes with an unknown primary along with caseating granulomatous inflammation and acid fast bacilli in few dissected lymph nodes.

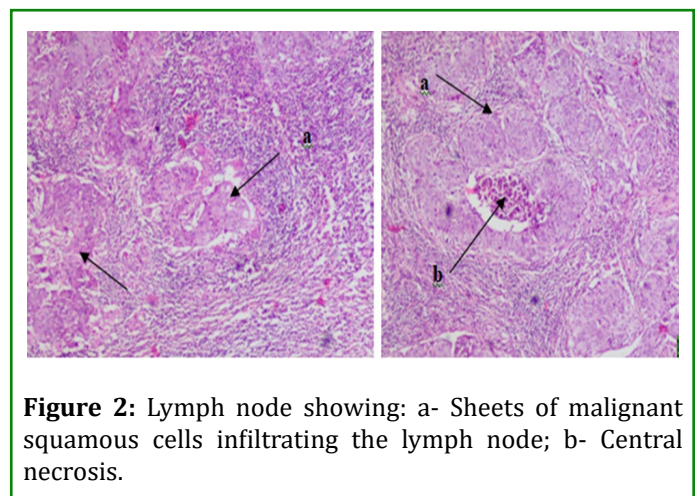
## Case Report

A 49-year-old male presented to Cancer Research Institute, Himalayan Institute of Medical Sciences, Dehradun. His only complaint was presence of multiple lumps over the right side of neck. On examination enlarged right cervical lymph nodes were identified at levels – Ia, Ib, II, III, IV and V, largest at level II (3x3cm). The nodes were not fixed, firm to hard in consistency and were not matted or tender. Oral cavity and systemic examination were unremarkable. No other lymphadenopathy was identified. FNAC from a level II right cervical lymph node showed evidence of metastatic deposits of squamous cell carcinoma with a few large bizarre and tumour giant cells. Naso-pharyngo-laryngoscopy, Bronchoscopy and Oesophagoscopy did not reveal any primary lesion. CECT of face and neck confirmed enlarged right cervical lymph nodes with areas of central necrosis. FDG-PET/CT scan (Figure 1) was done for the identification of an occult primary, but only demonstrated metabolically active lesions in the cervical nodes; no other metabolically active site was identified. With a diagnosis of neck nodal metastasis with unknown primary, patient underwent modified radical

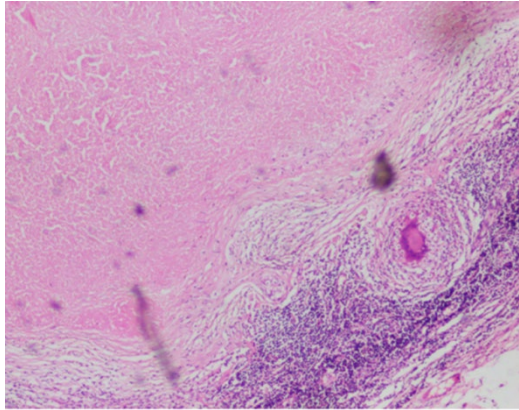
neck dissection (MRND). The histopathology reported a total of 44 nodes in the specimen. On detailed assessment of lymph nodes; nodes from level Ia, Ib and III showed reactive hyperplasia. Level IIa and IIb showed tumour metastasis of poorly differentiated squamous cell carcinoma (Figure 2) with perinodal extension. Level IV and V nodes showed evidence of chronic granulomatous inflammation with central caseating necrosis (Figures 3 & 4); suggestive of tuberculosis, but no tumour metastases. Z/N staining of the specimen did not reveal acid fast bacilli. The slides and blocks of the specimen were then sent to a prestigious institute in India for second opinion. They also reported the same findings, with Z/N staining positive for acid fast bacilli. The chest X-ray was normal and sputum AFB was negative. The patient was started on anti-tubercular treatment and given adjuvant external beam radiation therapy. After completing oncological treatment, at 1 year patient was disease free.



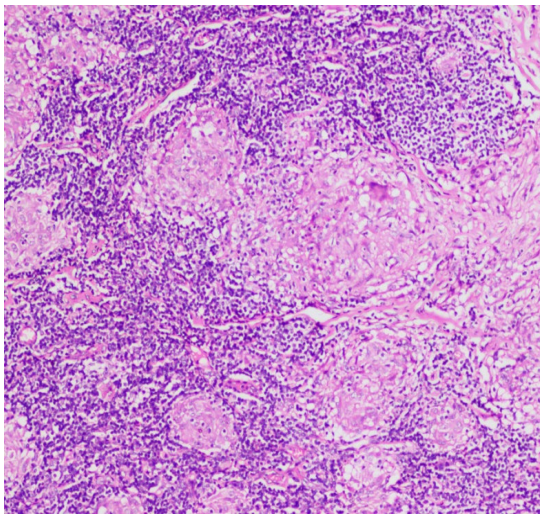
**Figure 1:** PET CT scan of the patient pre-treatment and post-operative image of neck.



**Figure 2:** Lymph node showing: a- Sheets of malignant squamous cells infiltrating the lymph node; b- Central necrosis.



**Figure 3:** Lymph node showing: a- Granuloma with giant cell; b- Caseous necrosis.



**Figure 4:** Multiple granulomas in lymph node.

## Discussion

Our case report is unique in its presentation since the only clinical finding was that of unilateral cervical metastatic poorly differentiated squamous cell carcinoma with an unknown primary cancer; even on FDG-PET/CT. The cervical lymphadenopathy revealed caseating granulomatous inflammation in nodes at levels IV and V, separate from the nodes with metastatic deposits- levels IIa and IIb. Z/N staining revealed acid fast bacilli. A retrospective analysis of 11 cases by Chhabra et al included 7 cases of epithelioid cell granulomas with caseating necrosis within the tumour and in contiguous draining lymph nodes [2]. The associated tumours studied included adenocarcinoma of colon, bronchial carcinoid tumour, Hodgkin's lymphoma and periampullary carcinoma, infiltrating breast carcinoma and mucinous cystadenoma ovary. No case with an occult primary was reported; as was

seen in our report. Only 3 out of these 7 tumours showed acid fast bacilli on Z/N staining. The formation of stromal granulomata represents a T-cell mediated immune response to surface antigens of a cell. These antigens may be identified as the culprits for such a granulomatous reaction once other causes, especially tuberculosis, are ruled out. It has been seen that, if soluble tumour-related antigens are able to reach the lymph nodes draining the tumour, they may be able to incite a granulomatous reaction in these nodes even without the presence of concurrent metastatic deposits. The prognostic significance of granulomatous reactions in malignant neoplasms is still undefined.

The FNAC of right cervical node in our study showed evidence of metastatic deposits of squamous cell carcinoma along with few tumour giant cells. For screening of malignancy FNAC has been recommended as a first line investigation tool and any presence of granulomata may be a pointer for a neoplastic process. Using FNAC, making a definitive diagnosis of malignancy in a scenario where it occurs in association with or mimics granulomata is difficult. Lymph nodes with metastatic carcinoma showing features of granulomata as in our report have also been noted in the past. These were described in patients with seminoma, nasopharyngeal carcinoma and malignant melanoma. Cancerous lesions can also occur along with sarcoid-like reactions and are seen in approximately 4.4% of patients [6-10]. These reactions may be a marker of the anti-tumour response of macrophages activated by T-lymphocytes hence leading to the formation of non-caseating epithelioid cell granulomas. These sarcoid-like reactions can occasionally become so extensive that they elude the underlying malignancy and cause complications in diagnosis and management. Parra et al recommended that the best method to make a distinction between metastatic and benign lymphadenopathy is to perform biopsies and histopathological tests. A contradictory study by Bekki, et al. indicted that biopsies could lead to confusing results and that response monitoring to chemotherapy using FDG-PET/CT proved useful in differentiating metastatic from benign lesions in patients with concurrent malignancy and lymphadenopathy. Carcinoma of unknown primary with secondaries (CUPS) by definition is a biopsy-proven malignancy with an unidentified anatomical organ of origin despite detailed diagnostic evaluation [11-13]. CUPS is one of the top 10 most commonly occurring cancers in the world (2.3-4.2%) and the fourth commonest cause of cancer-related deaths. The combination of FDG-PET and CT scan is a useful detector of primary malignancy, nodal status and distant metastases in cases presenting as CUPS. The exclusive point in our report is that a definitive primary source of malignancy could not be identified even on endoscopic imaging and FDG-PET/CT. The cervical lymph node biopsy was positive for metastatic poorly differentiated squamous cell carcinoma. This qualifies our case under the category of

CUPS. No case of CUPS along with concurrent AFB positive caseating granulomatous disease has been reported yet.

## Conclusion

Carcinoma of unknown primary with secondaries is in itself an elusive disease and needs extensive work up and careful management. Its association with a systemic or local granulomatous disease makes the diagnosis even more difficult. This may also indicate that the patient's immune system is suppressed due to the malignancy. The uniqueness of this case lies in the concurrence of CUPS and AFB positive granulomatous disease which has not yet been reported in literature.

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