



SEARCH FOR UNKNOWN PRIMARY: HOW MUCH IS REALLY NECESSARY?

Oral Medicine

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ABSTRACT

Cancer of unknown primary (CUP) is defined as a heterogeneous group of malignancies presenting as lymph node or distant metastases, for which a workup fails to identify the site of origin. This is a diagnostic and therapeutic dilemma to the clinician. The work up has to be done by a careful stepwise protocol. It is source of severe mental and the physical anguish to the patient and the economic impact is high. Thereby arises the need for oral oncologist to reflect upon how much of investigation is necessary to detect the elusive primary. We report a case of a 67 year old male patient with cervical node metastases from an unknown primary with a discussion on the necessary workup to detect the unknown primary.

KEYWORDS:

Introduction:

Cancer of unknown primary (CUP) is defined as a heterogeneous group of malignancies presenting as lymph node or distant metastases, for which a workup fails to identify the site of origin. CUP can be of various types .60% is adenocarcinoma, 30% poorly differentiated adenocarcinoma, 5% squamous carcinoma and 5% poorly differentiated malignant neoplasm. Metastases in these cases can fall into two possible sub-groups: Those with metastatic involvement to lymph nodes only and those with visceral involvement. The most common sites for such metastasis are usually lung, bone, or liver^{2,3,4}. About 2 to 4% of patients with head and neck squamous cell carcinoma (HNSCC) are estimated to have Cancer of unknown primary (CUP) and the most common manifestation is metastatic cervical lymphadenopathy⁵. Hence, we may say that they are systemic manifestations of a malignant disease of epithelial origin without a primary source.^{6,7} The inability to detect the primary tumour has two schools of thought. The first hypothesis is that the primary has involuted and is not detectable even after metastasis, and although not a common occurrence, spontaneous tumor regression has often been reported. The latter explanation is that the primary tumour's carcinogenic phenotype and genotype favour the chances of metastasis over local tumour proliferation⁸.

When a routine case history protocol followed by a diagnostic workup is not sufficient to identify the primary tumour site a diagnosis of CUP must be entertained and requires a focused search for the primary. To say that CUP is a diagnostic dilemma would be an understatement. Patients, who are affected, have to routinely undergo a volley of diagnostic and imaging investigations in the search for the unknown primary. This leads to severe economic, physical and mental anguish to the patient. It requires documentation for perusal by the specialist oral oncologist and dental practitioners to reflect on how difficult it is to detect the unknown primary.

This case report details the diagnostic work up in such a patient who presented with a metastatic lymph node involvement with unknown primary.

Case report

A 67 year old male patient reported with the chief complaint of swelling in the right side of the neck for a period of eight months. History revealed that the swelling was small in size initially and progressively increased in size over a period of eight months. He gave

a history of mild intermittent pain in the swelling since 2 months .A moderate loss of weight had been noted by the patient in the past 6 months. He had the habit of chewing betel quid for past 40 yrs 1-2 times /day.

On examination the patient appeared moderately nourished and healthy.

A solitary ovoid swelling was noted in the right submandibular region. (Fig 1) Skin over the swelling appeared normal and the surrounding areas were normal. On palpation the swelling was non tender, firm in consistency and freely mobile over the underlying structures .The swelling was not bimanually palpable. The right submandibular nodes were enlarged, non tender; hard in consistency and mobile .On intraoral examination his oral hygiene was noted to be very poor. Generalized gingival recession was noted. No other abnormalities were present.

A clinical diagnosis of submandibular lymphadenopathy due to periodontal infection was made.

Investigations showed that his blood parameters were within normal limits.

Panoramic radiograph showed extensive alveolar bone loss suggestive of periodontitis. (Fig 2) No other changes were noted. On ultrasonographic examination of the neck using a linear transducer probe at 11MHz, it was noted that the right submandibular and the jugulodi gastric nodes were enlarged. (Fig 3) FNAC of the nodes showed the presence of dysplastic epithelial cells (fig 4). A biopsy was carried out and the histopathology of the enlarged nodes was suggestive of metastatic deposits of well-differentiated squamous cell carcinoma in lymph node. (fig5)

A complete oral, ear, nose, throat clinical examination was carried out, but a primary could not be identified. To search for the primary further investigations were done. Contrast enhanced CT scan (PNS protocol) of the Head and neck region was suggestive of a soft tissue density lesion in the right submandibular region with no bony involvement. (Fig 6, 7)

Nasal endoscopy, Direct laryngoscopy, Upper GI scopy were performed and no abnormal lesions were identified. Radionuclide scanning also did not show any abnormal findings (fig 8). As the

primary lesion could not be identified with any of these investigations multiple blind biopsies from the suspected sites were suggested but the patient refused to undergo further investigations .As the investigations were being done the patient's condition deteriorated rapidly and the patient expired due to respiratory failure 2 months later.

Discussion

Cervical node metastases from an unknown primary lesion account for about 3% of head and neck cancers and the primary tumors in these cases are eventually identified in only 22%–44% of cases. Patients with lymphadenopathy primarily in the upper neck (levels 2 and 3) have a good prognosis after treatment, whereas those with a low-neck presentation (levels 4 and/or supraclavicular fossa) commonly arise from a primary sit below the clavicles and have a poor prognosis 9, 10. Our patient had only level 2 and 3 node metastases and the prognosis was considered to be good.

The need to identify the nodal metastasis with various diagnostic modalities is very important because the prognosis is better with the appropriate targeted therapy. The first step is the histopathologic assessment of the nodes. Once it is established as a squamous cell carcinoma it is essential to conduct a consistent, stepwise (fig 9) and thorough diagnostic evaluation to determine the primary ¹¹. The most probable sites for a primary squamous cell carcinoma are base of the tongue, nasopharynx, oropharynx, supraglottic larynx, and hypopharynx.¹². When a diligent search does not reveal the primary it has been suggested that a tonsillectomy should be performed ipsilateral to the presenting cervical metastasis as the tonsils can harbor occult primaries ^{11,12}.

Histopathologic assessment of the cervical nodes showed well differentiated squamous cell carcinoma and the prognosis was considered to be good in our patient. So a stepwise search for the primary was carried out, but the primary could not be identified despite having conducted a radionuclide imaging study.

The repeated examination and emotional trauma he was subjected to and financial constraints led to frustration in the patient and he refused any further investigations. The inability to detect the primary tumour is a source of anxiety for the patient and the clinician in CUP cases, mainly because the prognosis is grim for patients if the source of primary is not found. The delay in diagnosis leads to the creation of an atmosphere of distrust and skepticism on the patient's part which eventually manifests as a denial as was seen in our case. Such patients have to be carefully counseled and advised regarding the need for patience. They have to be gently coaxed into a state of acceptance and endurance to tide over the situation.

The management of patients with SCC of the head and neck from an unknown primary site is controversial, and varies from treatment of the neck alone to elective radiotherapy (RT) to the potential mucosal primary sites and both sides of the neck. The 5-year survival rates range from 35 to 50% for groups with good prognosis ^{13,14,15}.

Conclusion

But the main question remains as to how much work up is really necessary for each patient, the economic viability and the emotional impact that living with such a condition will have for the patient. Is it really necessary to rummage around the whole haystack in search for the needle? That is a question only time and money can answer, both of which are of diminutive proportions in a developing country like ours. But, it becomes a catch-22 situation for the clinician when the patient refuses treatment and it is our moral obligation to discover the occult primary.

Fig 1: Frontal profile view.



Fig 2: Orthopantomographic examination.

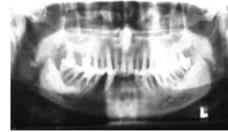


Fig 3: Ultrasonographic examination.

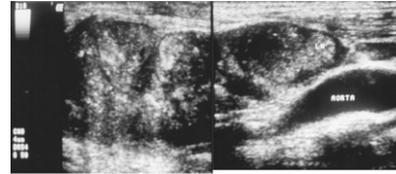


Fig 4: Fine Needle aspiration cytology.

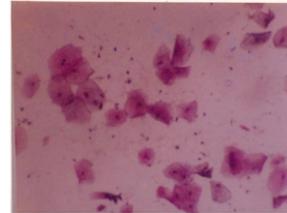


Fig 5: Photomicrograph of Well differentiated SCC.

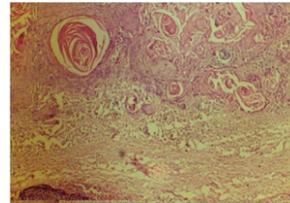


Fig 6: Contrast enhanced CT (Axial) showing soft tissue density lesion.

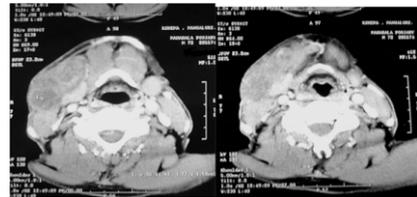


Fig 7: Contrast enhanced CT (Coronal) showing soft tissue density lesion.

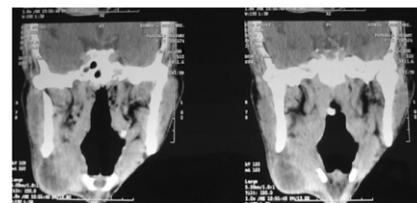


Fig 8: Radionuclide scan.

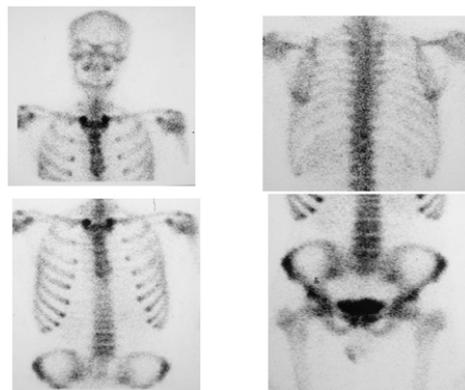
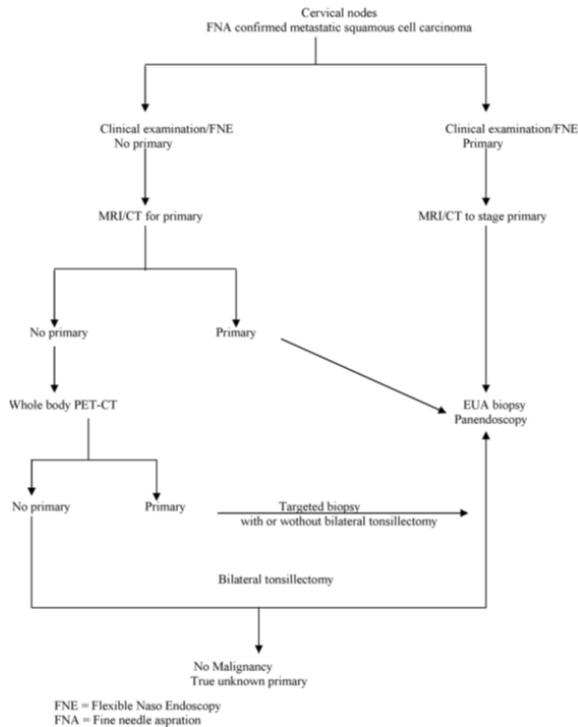


Fig 9: Flow chart showing investigative pathway for an unknown primary with cervical node metastases



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