

Case Series

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Diagnostic value of tonsillectomy in positron emission tomography and computerised tomography negative carcinoma of unknown primary

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ABSTRACT

Carcinoma of unknown primary (CUP) represents a heterogeneous group of malignancy metastasis unique biology of which remains poorly understood. Even after a complete diagnostic workup including positron emission tomography and computerised tomography (PET-CT) scans the primary site of origin may remain unclear. This case series analysed the diagnostic value of bilateral palatine tonsillectomy in evaluating PET-CT negative head and neck squamous cell CUP. From retrospective analysis of cluster of 68 cases with metastatic cervical nodes with no obvious primary referred for ENT evaluation during a period of 20 months, we identified 5 cases where pan endoscopy and radiological evaluation including PET-CT were negative in detecting the primary. All 5 patients underwent bilateral palatine tonsillectomy along with biopsies from base of tongue and nasopharynx as a part of completion of diagnostic work-up. Tonsillar squamous cell carcinoma was revealed by subsequent histopathology examination in 4 out of 5 patients despite negative PET-CT evaluation. Blind biopsies from other sites like nasopharynx and base of tongue were unfruitful. Our experience strongly emphasises the fact that bilateral palatine tonsillectomy has a high yield in detecting primary even in PET negative CUP, though it needs a larger evidence base.

Keywords: Carcinoma of unknown primary, Head and neck, PET-CT, Tonsillectomy

INTRODUCTION

Head and neck carcinoma presenting as CUP represents a diagnostic dilemma for the practising clinician. The term CUP represents a heterogeneous disease entity characterised by the presence of clinically overt metastatic disease in the absence of clinically or radiologically obvious primary tumour. It constitutes up to 5% of head and neck cancers.¹

The diagnostic protocol in head and neck CUP (HNCUP) includes complete clinical otorhinolaryngological evaluation, endoscopy of upper aerodigestive tract, appropriate head and neck radiology, additional imaging of chest and/or abdomen and fine-needle aspiration of the enlarged lymph node. Unfortunately, even such an extensive process does not guarantee success;

conventional imaging modalities like MRI or CT, detect approximately only 10-35% of primary neoplasms in CUP patients.²

18F-fluorodeoxyglucose (18F-FDG) PET-CT is very helpful in localization of primary tumour. Its detection rate of the primary in patients with tumour metastasis in the head and neck as well as in other body regions range between 24% and 53%.³ It allows targeted biopsies from the oropharynx and nasopharynx (which includes palatine tonsillectomy) as part of diagnostic work-up of CUP.^{4,5} However, 18F-FDG accumulation is not specific and can also occur at any site of increased glucose metabolism, like inflammation, infection, or other benign processes, resulting in false-positive results.^{6,7} More importantly a negative PET-CT evaluation cannot conclusively rule out presence of a head and neck primary emphasizing the

importance of targeted biopsy. Our case series emphasised the role of bilateral palatine tonsillectomy in evaluation of PET-CT negative HNCUP.

CASE SERIES

This study was undertaken in the department of ENT Government medical college Kottayam, Kerala, India. We retrospectively analysed 68 patients who had presented with metastatic cervical nodes with no obvious primary referred for ENT evaluation during a period of 30 months between 2017 to 2020. Of these, 5 patients were identified in whom clinical evaluation, pan-endoscopy and radiological evaluation including PET-CT were negative in detecting the primary. P16 immunohistochemistry (IHC) from the lymph node aspirate/biopsy and serology for Epstein Barr virus (EBV) were done in all patients. All patients were subsequently subjected to bilateral palatine tonsillectomy and targeted biopsies of the tongue base and lateral recess of nasopharynx. Histopathology results obtained were analysed.

Case 1

65 year old, chronic smoker with 4 months history of (L) neck swelling. There was a 6 cm, hard, mobile, level II cervical lymph node and all other areas normal clinically and by pan-endoscopy. FNAC from the cervical node was positive for metastasis from poorly differentiated squamous cell carcinoma and confirmed by the excision biopsy of the lymph node and histopathological examination. The IHC was negative for P16; EBV serology was negative. The CECT (base of skull to upper thorax) showed enlarged homogenously enhancing (L) level-2 lymph nodes. We further evaluated the patient with PET-CT, which confirmed metabolically active lymph nodes, but nothing suggestive of any primary lesion in the head and neck. The patient had undergone Bilateral tonsillectomy with blind biopsies from tongue base and nasopharynx. Subsequent histopathology revealed moderately differentiated squamous cell carcinoma in the (L) tonsillectomy specimen.

Case 2

70 year old man, chronic smoker, presented with 3 months history of (R) sided neck swelling, which was 4 cm, hard, level II cervical lymph node. Rest of the otolaryngologic examination and pan-endoscopy was normal. FNAC from the lymph node was found to be metastasis from squamous cell carcinoma. IHC of the excised lymph node revealed positivity for P16. CECT confirmed the presence of enlarged (R) level 2 cervical lymph node and PET-CT did not show any uptake in the areas other than the cervical lymph node. Here also we proceeded with bilateral tonsillectomy and blind biopsies from tongue base and nasopharynx. The primary was detected to be well differentiated squamous cell

carcinoma of right tonsil through histopathological examination.

Case 3

39 year old male, non-smoker presented with 4 months history of (R) neck swelling. The examination was normal except for the large 15×10 cm cystic swelling involving (R) level II, III and IV and an indurated 1 cm lesion over R lateral border of tongue. The tru-cut biopsy of the swelling was found to be metastatic well differentiated SCC; but biopsy from the tongue lesion was negative for malignancy. Serous fluid aspirate from the swelling revealed inflammatory cells and was negative for P16 and EBV. Further evaluation with PET-CT only showed necrotic (R) level 2,3,4 lymph nodes with moderate uptake. We proceeded with bilateral tonsillectomy along with biopsies from base of tongue and nasopharynx and the histopathology proved right tonsillar primary of moderately differentiated SCC.

Case 4

49 year old female, non-smoker, presented with left sided 4.5 cm level 2 neck node of 5 months duration; ENT evaluation and pan endoscopy was normal. FNAC suggestive of metastasis from squamous cell carcinoma with P16 positivity. However, PET-CT revealed no primary in the head and neck. Bilateral tonsillectomy and base of tongue biopsy was undertaken. Left tonsil histopathology was reported as well differentiated squamous cell carcinoma.

Case 5

61 year old male smoker reported with a neck swelling detected accidentally on routine health check-up. On examination he had a left sided firm 2.5 cm level 2 cervical lymph node; ENT evaluation was normal. Aspiration cytology was suggestive of metastasis from well differentiated squamous cell carcinoma; P 16 and EBV serology was negative. PET-CT failed to reveal any primary in the head and neck. Pan endoscopy and biopsies from tongue base and nasopharynx was undertaken along with bilateral tonsillectomy. Histopathology however did not reveal primary from any of the targeted biopsy sites. Relevant details of each patient are summarised in Table 1.

Four out of five patients (cases 1-4) had advanced (N2 and N3) neck disease and neck swelling was the presenting symptom. One patient (case 5) had N1 neck node which was accidentally detected on a routine health check-up. Nodes in all 5 patients were located at level II in the neck; case 2 had a very large node, 12 cm spanning levels II, III and IV which had undergone cystic degeneration as well.

Clinical, endoscopic and radiological (CT/MRI scans) evaluation of ENT areas was normal in all these patients.

Table 1: Relevant details of patients identified as PET-CT negative CUP.

Cases	Patients	History	Examination	FNAC/ Biopsy	Investigations	PET-CT
1	Male; 65 years; smoker	Neck swelling 4 months	Level II CLN, 6 cm, hard	FNAC-mets from poorly differentiated Ca (P16 and EBV -ve)	Pan-endoscopy, CT neck WNL	No primary
2	Male; 70 years; smoker	Neck swelling 3 months	Level II CLN, 4 cm, hard	FNAC-mets from SCC (P16 +ve)	Pan endoscopy, CT neck WNL	No primary
3	Male; 39 years; non-smoker	Neck swelling 4 months	Large cystic node, 12×10 cm level II, III and IV	FNAC-inflammatory cells (P16 and EBV -ve) Tru-cut biopsy-mets from SCC	Pan endoscopy, CT neck WNL	No primary
4	Female; 49 years; non-smoker	Neck swelling 5 months	Level II CLN, 4.5 cm, firm	FNAC-mets from SCC (P16+ EBV-ve)	Pan-endoscopy, CT neck WNL	No primary
5	Male; 61 years; smoker	Neck swelling detected on recent health check-up	Level II CLN, 2.5 cm, firm	FNAC-mets from well differentiated SCC (P16 and EBV -ve)	Pan-endoscopy, CT neck WNL	No primary

PET-CT evaluation revealed only metabolically active lymph nodes but was negative for detection of the primary site in all cases. P 16 positivity on IHC was obtained in two patients (cases 2 and 4). It was from excision biopsy of the lymph node in case 2 and from aspiration cytology of the lymph node in case 4. EBV serology was negative in all patients.

Out of five patients undergoing bilateral tonsillectomy, four were found to harbour malignancy in the ipsilateral tonsil. Moderately differentiated squamous cell carcinoma was reported for cases 1 and 3 and well differentiated squamous cell carcinoma for cases 2 and 4. Tonsillectomy biopsy was negative for case 5. None of the patients had malignancy in the contralateral tonsil. Targeted biopsies of the tongue base and nasopharynx was negative for malignancy in all patients.

DISCUSSION

In patients presenting with a secondary cervical node with no other clinical manifestations it was prudent to embark on a meticulous search for a possible primary in the head and neck. Identifying the primary tumour involves several advantages elaborated as follows.

Targeted therapeutic approach possible, reduces the irradiation field (exclusion of parotid gland, eye, spine and brain possible); less radiotherapy-related side effects such as xerostomia, mucositis and late toxicities; leaves the opportunity to irradiate a possible metachronous tumour in the future; reduces the risk of post-treatment manifestation of the primary, which is associated with

poor prognosis;^{8,9} facilitates follow-up to focus on a specific anatomical region and confers benefits in terms of better cause-specific and disease-free survival for patients in whom the occult tumour was identified.¹⁰⁻¹²

When encountered, the initial step in the work-up of HNCUP was clinical evaluation involving a full history and physical examination, including flexible fibre optic laryngoscopy and imaging modalities mainly CT scan and MRI. PET-CT offered high lesion-to-background contrast, making it a potentially more sensitive imaging modality for the detection of these lesions and carried a diagnostic rate of 7-38%.^{13,14} Once imaging was complete, pan-endoscopy with tumour mapping was performed, followed by targeted biopsies. Reported diagnostic rates of tumour mapping are approximately 20-50% when biopsies can be targeted with PET-CT which markedly decreased to 9-29% when PET-CT was negative.¹⁵⁻¹⁸

PET-CT has limitations in not identifying carcinoma in-situ or early mucosal primaries; oropharynx, especially the tonsil and base of tongue are frequent anatomical sites harbouring the primary tumour (incidence varies from 74% to 89%).^{20,21} Several meta-analyses have assessed the diagnostic performance of FDG PET in CUP and report primary tumour detection rates of 24-43%.²²⁻²⁵ However, the major limitation of PET-CT was that tumours less than 1 cm in diameter were not reliably detected. In a study of 111 identified unknown primary tumours, the average diameter was 1.15 cm and 57% of tumours were less than 1 cm in diameter, emphasising more than half of unknown primary tumours may be

below PET-CT detection level.²⁶ Therefore PET-CT should always be followed by targeted biopsies and palatine tonsillectomy to have a histological corroboration.

Only less than 20% of patients with CUP have a primary site identified due to spontaneous regression or immune-mediated destruction of the primary tumour or inherent small size of the primary tumour favouring metastatic spread above local tumour growth.²⁷ 68 cases of HNCUP were evaluated for primary site identification by us over period of 30 months. All had clinically normal-looking tonsils with normal endoscopy and radiological imaging; PET-CT could not identify obvious primary in any of the cases.

Targeted biopsy or tonsillectomy?

In cases with positive PET-CT, confirmatory biopsy was still necessary because of the risk of false-positive results due to the hypermetabolic activity of normal lymphoid tissues of Waldeyer's ring; highest (39.3%) being in the palatine tonsils. When PET-CT was able to provide targeted biopsies, diagnostic rates of tumour mapping ranged from 20-50%. However, when physical examination and PET-CT were negative, diagnostic rates decreased to a range of 9-29%.²⁸⁻³³ Even if PET-CT findings were negative, further effort should be made to identify the primary tumour because of the chance of false-negative results. Palatine tonsillectomy can be done in concurrence with the institutional protocol and has detection rates superior to biopsy of tonsillar tissue alone.^{34,35}

Tonsillectomy-ipsilateral or bilateral?

When pathology was consistent with p16 positive squamous cell carcinoma (SCC), the oropharynx is the most likely source of origin. Representing 2-5% of all new head and neck malignancies, the primary site was eventually isolated to the palatine or lingual tonsils in 80-90% of patients. Palatine tonsillectomy has increased the primary detection rates to 94% along with 100% 5-year disease free survival rates.³⁶

Considering that tonsil cancers can be located in the submucosa or arise deeply in the tonsillar crypts, there was high probability of having a false-negative result by sampling the tonsil via biopsy. The NCCN guidelines do not make specific recommendations regarding on which side to perform a palatine tonsillectomy. The oncological rationale of bilateral tonsillectomy was based on the detection of possible cases of a bilateral/contralateral tumour and the additional advantage of creating an anatomical symmetry of the palatine arches, avoiding confusion during subsequent follow-up after treatment.³⁷ There was evidence that primary resides in contralateral tonsil in 10%, providing further basis for a bilateral tonsillectomy.

Guntinas-Lichius et al have showed substantial survival improvement after bilateral tonsillectomy, with a 5-year survival rate of 57% versus 42% in patients with and without tonsillectomy, respectively.³⁸ In another review by Roeser et al 14 (10%) synchronous bilateral and 2 (1%) contralateral tumours were identified on 140 occult tonsillar malignancies.³⁹ Bilateral tonsillar resection was further supported by this review, mainly for oncological reasons. It seemed clear that the advantage of finding the primary tumour largely outweighed the minimal risks associated with the bilateral tonsillectomy procedure.

Furthermore, patients who underwent tonsillectomy during childhood may present with an occult tumour arising from the tonsil fossa. In fact, SCC of the tonsil remnant, although rare, had been reported and has similar characteristics to tonsillar ones.⁴⁰ These findings appeared to justify the excision of any tonsillar remnant despite a normal appearance. The results of this systematic review and meta-analysis suggest that palatine tonsillectomy has a high overall detection rate of subclinical primary tumours.

On retrospectively analysing, though in 4 out of 5 cases the primary was revealed by bilateral tonsillectomy, this may be insufficient to draw a generalisation. The relevance may be questionable, but the value of bilateral tonsillectomy over blind biopsies should be appreciated and hence the purpose of this study.

CONCLUSION

In cases of CUP head and neck, PET-CT should preferably be corroborated by tonsillectomy. Performing blind biopsies on the tonsils, instead of tonsillectomy, appears unreasonable and unjustified. Considering the significant bilateral/contralateral occult tonsillar tumours and the low morbidity of tonsillectomy, reported in the literature, it is prudent to include bilateral tonsillectomy in the diagnostic work up of CUP.

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