Asymptomatic renal metastasis from laryngeal primary: A common malignancy with uncommon pattern of relapse

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Abstract
Introduction
Loco-regional failure is the predominant pattern of failure in the patients of head and neck squamous cell carcinoma treated with chemoradiotherapy. Distant metastasis is a relatively rare phenomenon. Rare reports of head and neck malignancies with renal metastases are available in literature though none of them have carcinoma of larynx as the primary. We here in describe clinical history of a patient with locally advanced carcinoma of larynx who later developed renal metastasis.

Case report
We highlight a case of locally advanced squamous cell carcinoma of the supraglottic larynx in a 49 year old gentleman who was initially managed with induction chemotherapy followed by concurrent chemoradiation. Later the disease relapsed in the form of asymptomatic bilateral renal metastasis. He was started on targeted therapy with tablet gefitinib. However on disease progression, treatment was changed to biochemotherapy with combination of injection paclitaxel, carboplatin and cetuximab. To the best of our knowledge, this is the first reported case of asymptomatic renal metastasis from a laryngeal primary.

Conclusion
This case report underscores the importance of awareness of unusual pattern of relapse in carcinoma larynx. Patients of carcinoma larynx should be kept on periodic follow-up and appropriate investigations should be done expeditiously on suspicion of recurrence.

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Introduction
Kidney has been a frequent site of metastasis for various malignancies like lung, breast, skin (melanoma), and tumours of the genitourinary, gastrointestinal, and gynaecologic tracts, respectively but reports of head and neck squamous cell cancer metastasizing to the kidney is rare. Only three cases have been reported till date. Here we highlight a case of asymptomatic renal metastasis from a laryngeal squamous cell carcinoma in a 49 year old gentleman. He was managed initially with induction chemotherapy followed by concurrent chemo-radiation for his laryngeal primary. Later he relapsed in the form of asymptomatic renal metastasis.

Case report
A 49 year old male patient presented to our multidisciplinary head and neck cancer clinic with complaints of progressively worsening dysphagia, odynophagia and hoarseness of voice over six months. There was no history of cough, dyspnoea or haemoptysis. He was a chronic smoker for more than 20 years. Clinical examination revealed a 3x3cm tender lymph node mass in his right neck involving level II-III. Laryngeal expansion was present and laryngeal crepitus was absent. On indirect laryngoscopy, an ulceroproliferative growth was noted involving laryngeal surface of epiglottis, right aryepiglottic fold (AEF) and right false vocal cord. Right true vocal cord could not be identified separately from the growth. Right hemilarynx was completely fixed.

Direct laryngoscopy guided biopsy from the growth established a diagnosis of squamous cell carcinoma. Contrast enhanced computed tomography scan (CECT) of the face and neck revealed a heterogeneously enhancing mass involving right AEF, right pyriform sinus (PF5) with destruction of right ala of thyroid cartilage. A solitary node of 3x3 cm size was also found on the right side of the neck, level II (Figure 1). CECT of the chest and ultrasonography of his abdomen ruled out any distant metastasis. We reached a diagnosis of carcinoma supraglottic larynx (stage T4N2aM0) based on these investigations.

The various treatment options along with their associated risk and benefit were discussed with the patient. In view of his desire for voice preservation, a plan of induction chemotherapy followed by concurrent chemo-radiotherapy was made. Initially he received 3 cycles of neo-adjuvant chemotherapy (NACT) with docetaxel (75mg/m² body surface area (BSA) IV D1), cisplatin (40 mg/m² BSA IV D1-D2) and 5fluorouracil (750 mg/m² BSA IV D1-D5) every 3 weeks. After three weeks of completion of induction chemotherapy, clinical examination revealed thirty percent reduction in the size of the primary lesion and complete resolution of the nodal mass in the neck. Subsequently he underwent concurrent chemo-radiation (CRT) to a total dose of 70 Gy in 35 fractions over 7 weeks with three cycles of chemotherapy with cisplatin (40mg/m² BSA once every week). Planned concurrent chemotherapy schedule (5-7 weekly cycles of cisplatin) could not be completed due to emergence of grade 3 haematological toxicities, dysphagia and mucositis (according to RTOG acute morbidity scoring criteria).

After one month of completion of radiation therapy, direct laryngoscopy revealed no residual disease in the larynx. He was kept on follow-up with clinical and endoscopic examination every 3 months.

He was in complete clinical and radiological remission for 10 months but subsequently presented with progressively worsening hoarseness of voice again.

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voice. Direct laryngoscopy showed edematous bilateral arytenoids without any evidence of local recurrence. A contrast enhanced CT scan of face, neck, chest and abdomen showed a bulky left kidney with 4x5cm ill-defined heterogeneously enhancing lesion in the upper and mid pole with peri-nephric fat stranding. There was also a 1.5x1 cm ill-defined lesion in the anterior cortex of the mid pole of the right kidney. On whole body 18F-FDG PET-CT scan, there was increased FDG uptake (SUV max-15) in the cortical region of the bilateral kidneys (Figure 2). There was however no evidence of loco-regional recurrence on radiological and metabolic imaging. USG guided biopsy from the left renal mass revealed features of metastatic squamous cell carcinoma (Figure 3).

The histopathological characteristics were identical to the primary laryngeal squamous cell carcinoma. Kidney function test revealed no anomalies. Palliative therapy with tablet gefitinib (250 mg OD) was offered to him. After two months of gefitinib, whole body PET-CT scan revealed stable disease in the bilateral kidney with new findings of bilateral pulmonary metastases and mediastinal lymphadenopathy. Hence the treatment was changed to biochemotherapy with combination of injection paclitaxel, carboplatin and cetuximab.

**Discussion**

Head and neck cancer is the sixth most common type of cancer, representing about 6% of all cases and accounting for an estimated 650,000 new cancer cases and 350,000 cancer deaths worldwide every year\(^2\).

The median age at diagnosis is in the early 60s and there is a male preponderance, especially in laryngeal cancer. The 5-year survival for all stages combined on the basis of Surveillance Epidemiology and End Results (SEER) data is about 60% and survival is worse for specific primary sites such as the hypopharynx\(^3\).

Concurrent chemoradiation is being increasingly used for organ preservation in locally advanced SCC of head and neck. The updated MACH-NC meta-analysis showed an absolute benefit of 4.5% in a five year overall survival (OS) rate by addition of chemotherapy to radical radiation\(^4\). According to site wise analysis in MACH-NC meta-analysis addition of concomitant chemotherapy gives an OS benefit of 5.4% at five years in laryngeal primary\(^5\).

Multiple studies over the last two decades have established the importance of induction chemo-therapy in management of locally advanced head and neck carcinoma. Induction
chemotherapy with triple drug TPF regimen (taxane, cisplatin and 5FU) compared with PF regimen (cisplatin and 5FU) has shown a survival benefit of 10% at 5 years in patients with stage III and IV head and neck SCC in the Tax-324 trial\(^4\). Progression-free survival was also significantly better in patients treated with TPF regimen. The rate of treatment interruption exceeding 3 days was 33% in the chemoradiotherapy group versus 40% in the TPF plus chemo-radiotherapy group.

Our patient also could not complete the intended number of chemotherapy cycles in the concurrent setting\(^7\).

Locoregional relapse remains the predominant pattern of failure in head-and-neck squamous cell carcinoma treated with high-precision definitive radiotherapy. The majority of failures occur ‘in-field’, within the high-dose volume as evident from a tertiary cancer centre study from India\(^8\). In a retrospective analysis of 2550 patients of laryngeal and hypopharyngeal primaries, Spector G et al. found the overall incidence of distant metastases to be 8.5% with the following distribution: glottis 4.4%, supraglottis 3.6%, subglottis 14% and aryepiglottic fold 16%. Distant metastases were related to advanced local disease (T3/T4), lymph node metastases at presentation (N+), tumour location (hypopharynx) and locoregional tumour recurrence\(^9\). The presence of extracapsular extension (ECE) in metastatic lymph nodes augments the risk of distant metastasis nine fold in laryngeal carcinoma. Metastatic lymph nodes without ECE show a risk three times greater\(^9\).

Multiple molecular and genetic factors have been found to influence and predict distant metastasis in head and neck cancers. Accumulated literature reveals that receptor tyrosine kinases (RTKs), Stat3, Rho GTPases, Protein kinases (PK) like PKCs, and NF-κB play critical role to promote metastasis in HNSCC\(^10\).

Various imaging modalities have been used to detect distant metastasis in head and neck squamous cell cancers. Kubota et al. compared FDG-PET with MRI and CT for the detection of recurrence of head and neck cancer after radio-chemotherapy. The lesion-based sensitivity (visual interpretation) and negative predictive value of FDG-PET (88% and 91%, respectively) were higher than those of MRI/CT (75% and 67% respectively). The specificity, accuracy and positive predictive value of FDG-PET (78%, 81% and 70%, respectively) were significantly (P<0.05) higher than those of MRI/CT (30%, 47% and 39% respectively)\(^11\).

Abgral et al.\(^12\) proved the superiority of FDG-PET in detecting occult recurrences over clinical examination, CT or MRI. The positive predictive value of PET was 77% (30/39), the negative predictive value was 100% (52/52) while the overall accuracy was 90% (82/91). However, Fakhry N et al.\(^13\) found that positron emission tomography (PET) does not appear to offer a first-choice technique for the detection of metastases before salvage surgery as CT detected all lesions visible on positron emission tomography. Among the study population of 37 patients, nine had visceral metastasis.

The sensitivity, specificity, positive predictive value & negative predictive value for detecting metastasis or second primary were, respectively, 100%, 94%, 86% and 100% for CT and 92%, 87%, 74% and 97% for PET. CT and PET were strictly concordant in 32/37 (86%) of cases.

Palliative chemotherapy remains the standard-of-care for patients with metastatic SCC of the head and neck region. Different targeted therapies have also been found to be of worthwhile benefit in managing these cases. Cetuximab has been found to result in an improvement of median survival from 7-4 months to 10-1 months (P=0.036) when used in combination with platinum agents and 5FU\(^14\). EGFR-tyrosine kinase inhibitors, gefitinib or erlotinib, have shown modest activity when given alone, with response rates of 1–11%, disease control rates of 34–53% and median overall survival of 5-5–8-1 months in patients with recurrent or metastatic head and neck cancers (HNC)\(^14\). A phase III, placebo-controlled study, which is in progress in the USA (Eastern Cooperative Oncology Group, E1302), is comparing docetaxel with or without gefitinib as first-line or second-line chemotherapy.

Figure 3: Photomicrograph 3A shows a core of normal kidney tubules and a core of fibro-collagenous tissue infiltrated by islands of tumour tissue (H&E stain; 4X).
Metastasis to the kidney from a head and neck SCC is extremely rare. Available literature review provides only three cases of head and neck SCC metastasizing to kidney. Wada et al. described a case of renal metastasis from a hypopharyngeal primary in a 67-year-old gentleman. He presented with haematuria and left renal mass. Left nephrectomy was performed. The patient was alive, with no evidence of disease, 8 months following nephrectomy. Unni et al. described a case of renal metastasis from oropharyngeal primary in a 60-year-old man who presented with symptoms of right flank pain and intermittent haematuria for 1 month. Computerized tomography (CT) of the abdomen and pelvis revealed a large right renal mass with possible inferior vena cava thrombus. Right radical nephrectomy and caval thrombectomy were subsequently performed. Postoperatively the patient was considered for palliative chemotherapy.

In both of the above scenarios, the patient underwent salvage nephrectomy. But salvage surgery was not considered in our patient as he had bilateral renal metastasis. Option of using chemotherapy with platinum agent and methotrexate were also ruled out in view of their associated nephrotoxicity. So finally we decided to administer targeted therapy with single agent gefitinib.

Conclusion
Renal metastasis from a laryngeal SCC has not been reported in literature till date. Patients of head and neck carcinomas with renal metastasis usually present with urological symptoms like pain and haematuria. However this brief report demonstrates that these patients may be completely asymptomatic at presentation. Whole body FDG-PET scan may be useful in timely detection of such asymptomatic visceral metastasis in advanced head and neck SCC. However, routine follow-up PET-CT in head and neck SCC may not be cost-effective in developing nations like ours.

This case report also illustrates the option of managing such patients with anti-EGFR therapy when surgery or chemotherapy is ruled out.

Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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