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HPV-Related Oropharyngeal Cancer Metastatic to Small Bowel Presenting as Small Bowel Obstruction – A Case Report and Systematic Review

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Abstract Squamous cell carcinomas (SCC) account for the majority of all primary oropharyngeal carcinomas. These tumors can progress locally as well as metastasize to lymph nodes, the lung, bone, and liver. Metastases of primary laryngeal SCC to the small bowel is exceedingly rare and portends a poor prognosis as they often present with catastrophic symptoms. HPV-related head and neck SCC (HNSCC) is a peculiar subset of all HNSCC, and available data from prospective studies suggest better survival outcomes with HPV-related HNSCC compared to non-HPV-related HNSCC. In this article, we report the case of a patient who was managed at a tertiary hospital for a HPV-related laryngeal SCC with metastases to the small bowel presenting as small bowel obstruction (SBO). We also conducted a systematic review of HNSCC metastatic to small bowel with a focus on relation to HPV. We identified 13 reported cases of HNSCC metastatic to the small bowel. Of these, only 1 case was positive for p16 (a marker of HPV infection in HNSCC). We present the second case of HPV-related HNSCC with metastases to the small bowel.

Keywords: *HPV, metastatic, oropharyngeal, head and neck, cancer, small bowel, obstruction*

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1. Introduction

Primary laryngeal squamous cell carcinomas (SCC) account for approximately 99% of all laryngeal carcinomas, but only less than 5% of all malignancies worldwide [1]. Typical metastatic sites of laryngeal SCC are regional and mediastinal lymph nodes, lung, bone, and liver in descending order [2,3]. Metastatic tumors to the small bowel are commonly from primaries located in the lung, breast, uterus, ovary, testis, choriocarcinoma and malignant melanoma [4]. Metastases of a primary laryngeal SCC to the small bowel is extremely rare and usually associated with a dismal prognosis [5]. HPV-related head and neck squamous cell carcinomas (HNSCC) is a distinct type of HNSCC with a more favorable prognosis. HPV-related HNSCC with metastasis to the small bowel has been described in a single case report. We present the second case of HPV-related HNSCC metastatic to small bowel presenting as small bowel obstruction (SBO).

2. Case Presentation

A 59-year-old man with stage IV, T4N2 laryngeal SCC presented to our tertiary medical center with syncope, dysphagia, and odynophagia. He was previously treated with 35 sessions of radiation therapy and completed 2 of 3 planned concomitant cycles of platinum-based chemotherapy approximately four years ago but was lost to follow up.

His neck examination was significant for diffuse cervical lymphadenopathy, subcutaneous nodules, and erythematous fibrotic skin. Fiberoptic examination of the larynx showed post-radiation changes without any discrete mass. CT neck with and without contrast showed a 2.2cm mass in the right submandibular space extending into the inferior parotid gland. While in hospital on day 4, he developed bilious, non-bloody emesis. CT abdomen with IV contrast confirmed small bowel obstruction (SBO) by an intraluminal mass in the mid jejunum. Patient underwent emergent laparotomy. Intraoperatively, a single

palpable mass involving the mesentery was identified 40cm distal to the ligament of Treitz, and palpable lymph nodes were noted at the base of the vascular arcade. There was no evidence of carcinomatosis. A 15cm bowel segment was resected, followed by primary anastomosis. The postoperative course was unremarkable.

Pathology revealed a poorly differentiated metastatic squamous cell carcinoma involving the serosal surface, with extensive lympho-vascular invasion within the mesentery. All three excised lymph nodes were positive for metastatic carcinoma. Immunohistochemistry confirmed metastatic SCC from the patient's laryngeal primary, with p63 and p16 positivity.

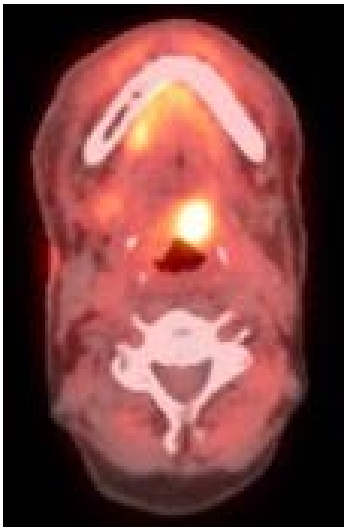

Figure 1. PET-CT: Left vocal cord, Right lingular tonsil adenopathy

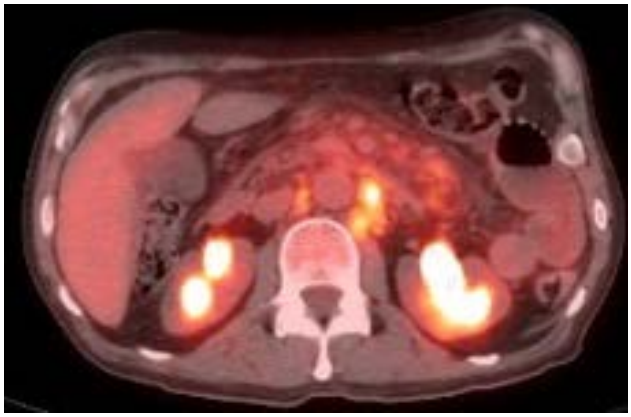

Figure 2. PET-CT. Extensive intra-abdominal lymph node involvement

Outpatient Positron emission tomography (PET) scan done 24 days after discharge demonstrated significant tracer uptake in the left vocal cord and right tonsil along with retroperitoneal and mesenteric lymphadenopathy (Figure 1, Figure 2). Palliative chemotherapy and immunotherapy were offered, but he was lost to follow-up. He presented again three months later with worsening dysphagia to solids and liquids, malnutrition, and 70-pound weight loss. Flexible laryngoscopy demonstrated a base of tongue mass encroaching the epiglottis. Vocal cords were hypomobile, but the airway was patent. CT of neck, chest, and abdomen revealed new development of irregular mass at the base of the left tongue and multiple enhancing lesions in the liver. The patient elected hospice care.

3. Systematic Review

We systematically searched PubMed with the following terms: 1) small bowel/intestine metastasis and 2) head and neck cancer. The search returned with 224 studies, of which, 13 cases were identified as HNSCC metastatic to the small bowel (Figure 3). We additionally identified 7 cases from review articles (Table 1).

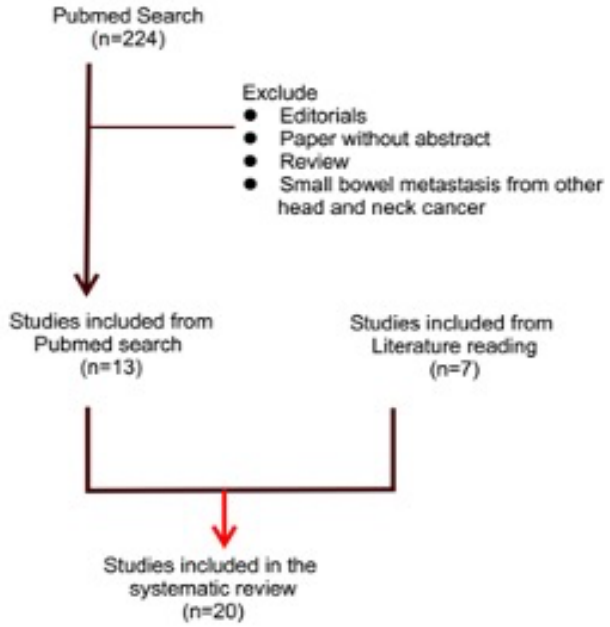

Figure 3. Systematic Review

The mean age of the patients was 66.5 years (range 48 to 90 years) and all were male. The most frequent site of the primary tumor was the supraglottic larynx (23.8%, 5 cases). For those that were reported, there was a wide variation in cancer staging at the time of diagnosis, ranging from stage I up to stage IV with both lymph node involvement and distant metastases. Radiotherapy was the most common treatment modality for the initial cancer treatment, with 87.5% of the cases having received radiotherapy. Obstruction was the most common presentation of intestinal metastases (43%), followed by perforation (28.5%). Ileum was the most common site for metastases accounting for 52.4% of the cases followed by 23.8% in the jejunum and 14.3% in the duodenum. The median time from initial diagnosis to small bowel metastases was 24 months, with a range of 0 to 56 months. The median survival time post-diagnosis of small bowel metastases was two months, with a range of 0 to 12 months. Our patient had a similar presentation to the cases we identified but differed based on a longer time from initial presentation to the diagnosis of small bowel metastases (42 months) and slightly more prolonged median survival after surgery (5 months).

Table 1. Details of All Cases with Head and Neck Squamous Cell Carcinoma Metastatic to the Small Bowel

Study (Author, Year)	Age/Sex	Site of Primary	Stage	Initial Rx	Time to primary diagnosis to intestinal metastases	Presentation of intestinal metastasis	Site of intestinal metastasis	Survival after intestinal metastases	Biomarker
Boquien et al.1961 [7]	84/M	Pyriform sinus	NR(N2)	RT	10 months	Obstruction	NR	Died 15 days, due to collapse	NR
Lesur et al. 1988 [8]	90/M	Tonsil	NR	RT	3 months	Obstruction	Ileum	Died 1 month, due to pulmonary embolism	NR
Bresler et al. 1988 [9]	70/M	Supraglottic larynx	T3N1M1	NR	2 days	Obstruction	Ileum	Died 7days, due to respiratory distress	NR
Francois et al.1989	59/M	Supraglottic larynx	T2N2Mx	Sx and PoRT	29 months	Melena	Ileum	NR	NR
Hamdan et al. 1991 [10]	68/M	Larynx	NR	RT and Sx	36 months	Perforation	Ileum	Died 3 days, due to septic shock	NR
Petiot et al. 1991 [11]	78/M	Supraglottic larynx	T1NXMX	RT	12 months	Perforation	Jejunum	Survived for 3 months	NR
Airoldi et al. 1993 [5]	54/M	Supraglottic larynx	T3N1N0	Sx	18 months	Intestinal bleeding	Ileum	Died 10 months, due to local disease progression	NR
Gonzalez et al. 1994 [12]	72/M	Vocal cord	T3N2N0	RT and Sx	NR	Perforation	Jejunum	Died 14 days, due to respiratory distress	NR
Wu et al. 1996 [13]	68/M	Hypopharynx	NR	RT and Sx	24 months	Hematemesis	Duodenum/Gastric	Died soon, due to aspiration pneumonia and multi organ failure	NR
Yoshihara et al.1997 [14]	71/M	Supraglottic larynx	T4N0	Sx and Chemo	24 months	Obstruction	Ileum	Died 6 months, due to abdominal recurrence	NR
Buyukcelik et al.2003 [15]	71/M	Vocal cord	NR	Sx and PoRT	56 months	Biliary obstruction	Duodenum (Ampulla of Vater)	Died 12 months, due to progressive disease	NR
Guillem et al.2004 [16]	63/M	Base of tongue	T4N1M1	Chemo	Initial presentation	Obstruction	Ileum	Died 8 months, due to abdominal recurrence	NR
Arulraj et al. 2005 [17]	67/M	Oropharynx	NR	Chemo and RT	9 months	Obstruction	Ileum	NR	NR
Huang et al.2010 [18]	48/M	Hypopharynx	T3N2aM0	Sx and Chemo	6 months	Melena	Duodenum	NR	NR
Aoyagi et al.2011 [19]	40/M	Tongue	T4N3cM0	Chemo and Sx	21 months	Perforation	Ileum	NR	NR
Jacques et al.2014 [20]	75/M	Oropharynx	NR	Sx and RT	24 months	Melena	Jejunum	NR	NR
Glicksman et al. 2014 [21]	58/M	Larynx	T4N2c	Chemo and Sx	5 months	Perforation	Ileum	Died 5 months, due to progressive disease	Cytokeratin, CK34BE12
Patel et al. 2016 [22]*	68/M	Oropharynx	NR	Chemo and RT	24 months	Perforation	NR	NR	p16
Dwivedi et al. 2010 [23]	65/M	Base of tongue	T4N2cM0	Chemo and IMRT	10 months	Melena	Jejunum	Died 1 month, due to chest infection	NR
Sanchez et al. 2017 [24]	61/M	Glottis	T1bN0Mx	Chemo and RT	56 months	Obstruction	Ileum	Died in a few weeks	p63
This case, 2018	60/M	Tonsil	T4N2	Chemo and RT	42 months	Obstruction	Jejunum	Survived 5 months post-operation	p16, p63

Abbreviations: NR- not reported; RT- radiotherapy; Sx- surgery; PoRT- postoperative radiotherapy; Chemo-chemotherapy; IMRT-intensity modulated radiotherapy. * The only published study reporting HPV-related HNSCC metastatic to small bowel.

4. Discussion

To the best of our knowledge, this is the second reported case of HPV-related small bowel metastasis. HPV-related HNSCC has a better survival compared to HPV-negative cancers. Better survival in HPV-related HNSCC was demonstrated in a prospective trial enrolling stage III/IV patients [6]. In this study, p16 positive cancers (a marker of HPV infection in HNSCC) had about half the risk of death as p16 negative cancers. The long interval between presentation and eventual recurrence (approaching four years) in our case report is likely associated with having HPV-related disease.

This systematic review also points towards an important finding of relatively short survival time post diagnosis of intestinal metastatic disease in patients with HNSCC. 38% of the reported cases had a survival time of approximately one month or less after diagnosis of intestinal metastases. This could in part be explained by severe complications of metastatic disease including intestinal obstruction with subsequent perforation, bleeding, shock, sepsis and multi-organ failure contributing to disease burden and morbidity. HNSCC with metastasis to the small intestine can be particularly challenging to detect early and are typically identified when they cause catastrophic symptoms such are bleeding, perforation, or as in the case of our patient SBO.

5. Conclusion

HNSCC with metastasis to the small bowel is extremely rare. HPV-related HNSCC metastatic to small bowel has only been reported in a single individual. This case report describes a second individual with HPV-related metastasis to the small bowel. Physicians should consider this potential diagnosis in a patient with HNSCC and unexplained gastrointestinal symptoms.

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Statement of Competing Interests

Disclosures for author Abhishek Kumar: stock investment in ABBV, ACADia Pharma, ADMA, Biologics, AGNEUS, AIKIDO, AMGEN, AVEO Pharma, Astrazeneca, Biotelemetry inc, Bristol Meyer, Bio Path holdings, BeyondSpring Inc, Cara Therapeutics, ChemBio Dagnostics, Contrafect Corp, Cardiff Oncology, CRISPR Therapeutics, CVS Health, Precision Biosciences, EDITAS Medicine Inc, Five Prime Therapeutics, Globus Medicine Inc, IDEXX Laboratories, Iovance Biosciences, Johnson and Johnson, ELiLilly, Northweast Bio, PFIZER, POSEIDA Therapeutics, PTC therapeutics, Spectrum Pharmaceuticals iNc, Viking Therapeutics and Vertex Pharmaceuticals. Other authors do not have any disclosures.

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