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Metachronous Lower GI Malignancies in Head and Neck Squamous Cell Carcinoma: A Case Report and Literature Review

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Abstract: ***Second primary gastrointestinal (GI) adenocarcinoma is rare in a previously treated or untreated primary head and neck squamous cell carcinoma (HNSCC). We present a case of metachronous colon adenocarcinoma in a primary oropharyngeal squamous cell carcinoma (SCC) post-treatment. An elderly patient with stage IVA primary SCC involving the base of the tongue and adjacent tonsil has been successfully treated with definitive concurrent chemoradiotherapy using weekly cisplatin in our tertiary care center. Approximately, 3 years post-treatment, she has been diagnosed with second primary adenocarcinoma involving the right-sided colon. This metachronous malignancy has been treated by surgery followed by adjuvant chemotherapy. After our case presentation, we reviewed the literature onmetachronous malignancies in primary HNSCC and also about colorectal cancers as a second primary malignancy with their impact on survival.***

Keywords: metachronous adenocarcinoma, colon, second primary malignancy, colorectal cancer

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the most common primary cancer in India with an incidence of 17% as per the GLOBOCON 2018 report (Bray et al., 2018). The worldwide incidence is around 4.6% which clearly demonstrates the greater relative incidence of head and neck cancer in India. The mortality rate of head and neck cancer, in India, amounts to 15% as compared to 4.5% across the globe (Bray et al., 2018).

Second primary malignancy (SPM) represents one of the important long-term causes of mortality in patients with head and neck squamous cell carcinoma (HNSCC) (Jung et al., 2015; Vikram, 1984). Even from the earlier studies, approximately one-third of HNSCC deaths are attributable to SPMs (León et al., 1999)SPMs after HNSCC illustrate concepts of field cancerization (Gabusi et al., 2017; Slaughter et al., 1953),in which environmental carcinogens, such as tobacco and alcohol, may give rise to premalignant disease in the mucosa and may increase epithelial cancer risk throughout the upper aero-digestive tract. The frequently recognized sites of elevated SPM risk after an index HNSCC are the head and neck, lung, and esophagus (Morris et al., 2011).

Colon adenocarcinomas rarely occur as SPMs with the primary malignancy being a squamous cell carcinoma (SCC) reported to date in literature. Colon cancer as SPM was around 0.4% with thyroid as primary as reported in one study in the Turkish population (Karaköse et al., 2019).

Here, we present a rare case of a primary oropharyngeal SCC, who, after successful treatment developed second primary colon adenocarcinoma treated in our institute.

Case report

A 64 years female patient with hypertension and hypothyroidism as co-morbidities presented with the complaints of odynophagia and a mass on the left side of the neck from 3-4 months. Fine needle aspiration and cytology (FNAC) from neck swelling were suggestive of poorly differentiated metastatic carcinoma. She, then, underwent direct laryngoscopy (Figure 1 A-B) and a contrast-enhanced computed tomography (CECT) face and neck which revealed a large 38 × 28 mm lesion in the left tonsillar fossa, left postero-lateral border of tongue, and whole base of tongue with few bilateral level I, II, III lymph nodes, largest measuring 16mm in left level II. Biopsy from tongue lesion was a moderately differentiated, large cell keratinizing type, invasive squamous cell carcinoma. The patient was clinically staged as $cT_2N_{2c}M_0$ in accordance with AJCC 7th edition (Edge & Compton, 2010).

Then she was treated with concurrent chemo-radiotherapy. Radiotherapy doses were 7000 cGy in 35 fractions by conventional fractionation with weekly cisplatin of 40 mg/m^2. The patient tolerated treatment well after which she was on regular follow-up and was disease-free for over 33 months.

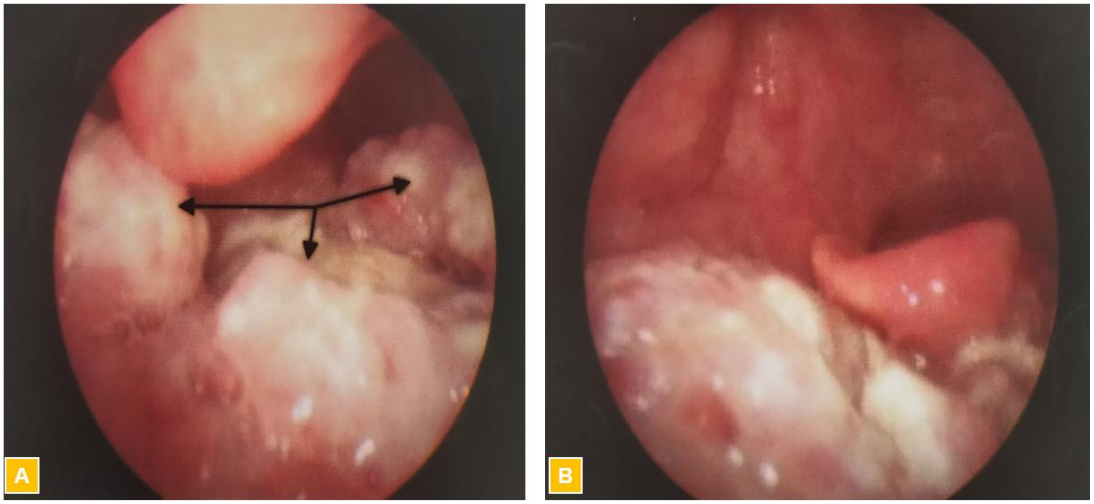

Figure 1 (A-B): Direct Laryngoscopy showing ulcero-proliferative growth in oropharynx

Then she had non-specific complaints of altered bowel habits with an increase in frequency of episodes of loose stools for over 3-4 months. Subsequently, she developed episodes of recurrent pain abdomen, nausea, and general weakness lasting for around 3-4 weeks. A routinehemogram showed a decrease in hemoglobin to 6 g/dl and the rest of the blood parameters were normal. The diagnostic CECT abdomen was done as advised by a surgical gastroenterologist which showed an ileocolic intussusception with 8 cm of terminal ileum telescoping into the caecum and ascending colon with no significant lymphadenopathy or any other abnormality (Fig 2 a-c).

She underwent right hemi-colectomy. Per-operative findings were suggestive of undisseminatedcaecal growth. Post-operative histopathological examination revealed poorly differentiated adenocarcinoma reaching beyond the muscularispropria into pericolic adipose tissue with free resected margins (Fig 3 a-c). Lymphovascular invasion and perineural invasion were not evident. All lymph nodes were free but only four were dissected. Immunohistochemistry (IHC) revealed PanCK positive, CK-20 and CDX-2 were focal positive but negative for CK-7 and p40.

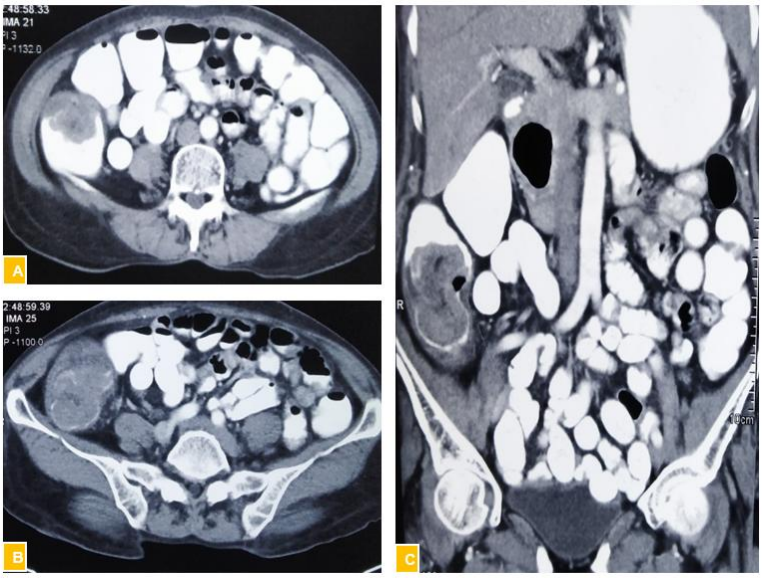

Figure 2 (A-C): Contrast enhancing CT abdomen showing mass involving caecum and ascending colon

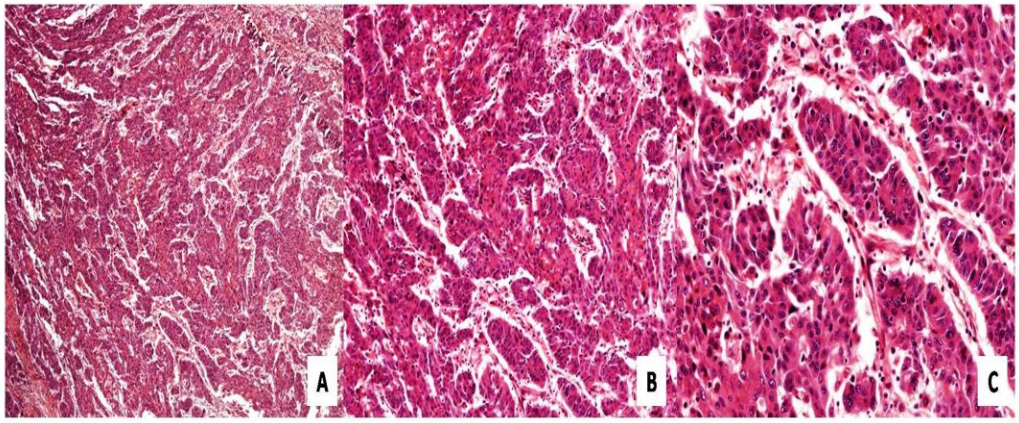

Figure 3 (A-C): Righthemicolectomy: Histopathology sections show a tumor disposed in nests, acini and sheets

Pathological stage was pT_3N_0 as per AJCC 7th edition. No evidence of any distant metastasis. Her post-operative serum carcino-embryogenic antigen (CEA) levels were 1.57 ng/ml which was normal. Then patient underwent direct laryngoscopy for assessment of primary disease which showed no locally recurrent disease and clinically neck was negative. She was then planned for 8 cycles of adjuvant chemotherapy (oral capecitabine plus intravenous oxaliplatin to doses of 1000 mg/m^2 BD for 14 days and 130 mg/m^2 on day 1respectively). Currently, she is on follow-up and clinically normal.

2. Discussion

SPM is defined as a metachronous invasive solid cancer developing $\geq$ 6 months after an index HNSCC, under the criteria of Warren and Gates (WARREN, 1932)as modified by the National Cancer Institute (Supramaniam, 2008).If the second cancer was SCC and developed in the same region as primary cancer, it would be named SPM if greater than 60 months had passed since the index diagnosis.

Second primary malignancies have gained significant importance in these last few years owing to an overall relative increase in the cancer survivorship as a direct consequence of an improvement in cancer management strategies with the incorporation of various new technologies, better understanding of the biology of cancer and the multi-disciplinary approach in the cancer field.

The burden of SPM is high in patients with HNSCC, with 1.68% excess second solid tumors developing per year (Morris et al., 2011).

Many studies demonstrated that SPMs had negatively impact survival in patients with HNSCC.

A systematic review of risk of second primary tumors (SPT's) in head and neck cancer(Coca-Pelaz et al., 2020)published in year 2020 found a mean rate of SPTs of 13.2% in patients treated for HNC, with a great discrepancy between studies. This review consists of patients from bothretrospective (98.3%) and prospective studies (1.7%). Despite wide variations among studies, the rate of SPTs in HNC patients is high. Among many studies included in this review, metachronous malignancies are found in aero-digestive tract itself and are associated with decreased overall survival (Argiris et al., 2004; Nikolaou et al., 2000; Rafferty & O'Dwyer, 2001).

On the other-hand, second primary colorectal cancer (pCRC) is rare in the clinical setting, and the 5-year cumulative incidence of second pCRC is 2.1% (Phipps et al., 2013; Ringland et al., 2009).

One study showed that 68% of patients with the second pCRC were diagnosed at the ages of 70–89 years, demonstrating that patients with the second pCRC were in older age groups at diagnosis. The cancer-specific survival rate of patients with initial pCRC was significantly higher than that of patients with the second pCRC. Patients with the second pCRC have a worse prognosis than those with initial pCRC primarily because of older age in the former group (Chen et al., 2018).

In a study by Iwatsubo T et al (Iwatsubo et al., 2019),it has been reported that colorectal cancers were around 1.79% among the patients with primary HNSCC. In this study, the incidence of second primary cancer (SPC) was associated with the histological type (SCC) and location (hypopharynx and larynx) of the primary, but not with age. Also, it proposes that excessive drinking and smoking in patients with hypopharyngeal and laryngeal cancer might also be the risk factors for cancer development in other organs and likely the cause of increased SPC risk in these patients.

Apart from genetic factors (including hereditary syndromes), factors shown to increase the risk of developing CRC include the following: increasing age (major risk factor), male sex, family history of CRC, inflammatory bowel disease, excessive alcohol intake, and smoking; and low folate consumption, etc. Incidence rates increase dramatically between the ages 40 and 50 years and each subsequent decade thereafter (Chan & Giovannucci, 2010; Ekbom et al., 1990; Wei et al., 2004).

In our case, we didn't find any established environmental risk factor that could lead to SPM but probably might have some genetic component.

Also, we need to remember that to current date there are no established tools or treatments that can prevent or decrease the incidence of SPMs. Though some studies demonstrate that isotretinoin (13-Cis retinoic acid) may reduce the SPM

rates, but a phase III randomized controlled trial (RCT) (Khuri et al., 2006) published in 2006 and another recently published phase III RCT by ECOG-ACRIN cancer research group (Bhatia et al., 2017) in 2017 concluded that treatment with low-dose 13-Cis retinoic acid (13-CRA) neither decreased the incidence of SPM nor improved the time to SPM development. Hence, there is no alternate way except early diagnosis and treatment of SPM's by careful follow-up of these patients.

In conclusion from our case report and literature review, we would like to emphasize that metachronous adenocarcinoma after a primary SCC does occur in the large bowel, although at lower rates of incidence. And these SPM's needs early diagnosis and treatment as it has a significant impact on the quality of life and survival of the patient. We hope that studies in the future might establish high-risk factors predictive of developing SPM's and categorize patients accordingly as not all the patients would require routine screening for various SPM's, owing to their lower incidence rates. Meanwhile, a treating physician shall be cautious enough in the follow-up of a treated cancer case especially if the patient had a history of established risk factors that may lead to synchronous and/or metachronous malignancies, and perform surveillance accordingly aiming atthe betterment of survival of the patient.

References

[1] Argiris, A., Brockstein, B. E., Haraf, D. J., Stenson, K. M., Mittal, B. B., Kies, M. S., Rosen, F. R., Jovanovic, B., & Vokes, E. E. (2004). Competing Causes of Death and Second Primary Tumors in Patients with Locoregionally Advanced Head and Neck Cancer Treated with Chemoradiotherapy. *Clinical Cancer Research*, *10*(6), 1956–1962. https://doi.org/10.1158/1078-0432.CCR-03-1077

[2] Bhatia, A. K., Lee, J. W., Pinto, H. A., Jacobs, C. D., Limburg, P. J., Rubin, P., Arusell, R. M., Dunphy, E. P., Khandekar, J. D., Reiner, S. A., Baez-Diaz, L., Celano, P., Li, S., Li, Y., Burtness, B. A., Adams, G. L., & Pandya, K. J. (2017). Double-blind, randomized phase 3 trial of low-dose 13-cis retinoic acid in the prevention of second primaries in head and neck cancer: Long-term follow-up of a trial of the Eastern Cooperative Oncology Group-ACRIN Cancer Research Group (C0590). *Cancer*. https://doi.org/10.1002/cncr.30920

[3] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. https://doi.org/10.3322/caac.21492

[4] Chan, A. T., & Giovannucci, E. L. (2010). Primary Prevention of Colorectal Cancer. *Gastroenterology*, *138*(6), 2029-2043.e10. https://doi.org/10.1053/j.gastro.2010.01.057

[5] Chen, Q., Zhao, S., Song, Y., Gao, P., Sun, J., Chen, X., Sun, Y., & Wang, Z. (2018). Do Patients with Second Primary Colorectal Cancer Hold the Similar Prognosis and Therapeutic Benefits as Those with Initial Primary Colorectal Cancer? *BioMed Research International*, *2018*, 9–11. https://doi.org/10.1155/2018/6172670

[6] Coca-Pelaz, A., Rodrigo, J. P., Suárez, C., Nixon, I. J., Mäkitie, A., Sanabria, A., Quer, M., Strojan, P., Bradford, C. R., Kowalski, L. P., Shaha, A. R., de Bree, R., Hartl, D. M., Rinaldo, A., Takes, R. P., & Ferlito, A. (2020). The risk of second primary tumors in head and neck cancer: A systematic review. *Head and Neck*, *42*(3), 456–466. https://doi.org/10.1002/hed.26016

[7] Edge, S. B., & Compton, C. C. (2010). The american joint committee on cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of Surgical Oncology*, *17*(6), 1471–1474. https://doi.org/10.1245/s10434-010-0985-4

[8] Ekbom, A., Helmick, C., Zack, M., & Adami, H. O. (1990). Ulcerative colitis and colorectal cancer: A Population-Based Study. *New England Journal of Medicine*. https://doi.org/10.1056/NEJM199011013231802

[9] Gabusi, A., Morandi, L., Asioli, S., & Foschini, M. P. (2017). Oral field cancerization: History and future perspectives. In *Pathologica*.

[10] Iwatsubo, T., Ishihara, R., Morishima, T., Maekawa, A., Nakagawa, K., Arao, M., Ohmori, M., Iwagami, H., Matsuno, K., Inoue, S., Nakahira, H., Matsuura, N., Shichijo, S., Kanesaka, T., Yamamoto, S., Takeuchi, Y., Higashino, K., Uedo, N., Miyashiro, I., … Fujii, T. (2019). Impact of age at diagnosis of head and neck cancer on incidence of metachronous cancer. *BMC Cancer*, *19*(1), 1–6. https://doi.org/10.1186/s12885-018-5231-7

[11] Jung, Y. S., Lim, J., Jung, K. W., Ryu, J., & Won, Y. J. (2015). Metachronous second primary malignancies after head and neck cancer in a Korean Cohort (1993-2010). *PLoS ONE*, *10*(7), 1–11. https://doi.org/10.1371/journal.pone.0134160

[12] Karaköse, M., Çordan, İ., Can, M., Kocabaş, M., Kulaksizoğlu, M., & Karakurt, F. (2019). Incidence of second primary malignancies in patients with thyroid cancer in the turkish population. *Turkish Journal of Medical Sciences*. https://doi.org/10.3906/sag-1903-104

[13] Khuri, F. R., Lee, J. J., Lippman, S. M., Kim, E. S., Cooper, J. S., Benner, S. E., Winn, R., Pajak, T. F., Williams, B., Shenouda, G., Hodson, I., Fu, K., Shin, D. M., Vokes, E. E., Feng, L., Goepfert, H., & Hong, W. K. (2006). Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. *Journal of the National Cancer Institute*. https://doi.org/10.1093/jnci/djj091

[14] León, X., Quer, M., Diez, S., Orús, C., López-Pousa, A., & Burgués, J. (1999). Second neoplasm in patients with head and neck cancer. *Head and Neck*, *21*(3), 204–210. https://doi.org/10.1002/(SICI)1097-0347(199905)21:3<204::AID-HED4>3.0.CO;2-7

[15] Mitani, S., Kadowaki, S., Oze, I., Masuishi, T., Narita, Y., Bando, H., Oonishi, S., Hirayama, Y., Tanaka, T., Tajika, M., Koide, Y., Kodaira, T., Abe, T., & Muro, K. (2020). Risk of second primary malignancies after definitive treatment for esophageal cancer: A competing risk analysis. *Cancer Medicine*,

9(1), 394–400. https://doi.org/10.1002/cam4.2688

[16] Morris, L. G. T., Sikora, A. G., Patel, S. G., Hayes, R. B., & Ganly, I. (2011). Second primary cancers after an index head and neck cancer: Subsite-specific trends in the era of human papillomavirus - Associated oropharyngeal cancer. *Journal of Clinical Oncology*, *29*(6), 739–746. https://doi.org/10.1200/JCO.2010.31.8311

[17] Nikolaou, A. C., Markou, C. D., Petridis, D. G., & Daniilidis, I. C. (2000). Second primary neoplasms in patients with laryngeal carcinoma. *Laryngoscope*. https://doi.org/10.1097/00005537-200001000-00012

[18] Phipps, A. I., Chan, A. T., & Ogino, S. (2013). Anatomic subsite of primary colorectal cancer and subsequent risk and distribution of second cancers. *Cancer*, *119*(17), 3140–3147. https://doi.org/10.1002/cncr.28076

[19] Rafferty, M. A., & O'Dwyer, T. P. (2001). Secondary primary malignancies in head and neck squamous cell carcinoma. *Journal of Laryngology and Otology*, *115*(12), 988–991. https://doi.org/10.1258/0022215011909567

[20] Ringland, C. L., Arkenau, H. T., O'Connell, D. L., & Ward, R. L. (2009). Second primary colorectal cancers (SPCRCs): Experiences from a large Australian cancer registry. *Annals of Oncology*, *21*(1), 92–97. https://doi.org/10.1093/annonc/mdp288

[21] Slaughter, D. P., Southwick, H. W., & Smejkal, W. (1953). "Field cancerization" in oral stratified squamous epithelium. Clinical implications of multicentric origin. *Cancer*, *6*(5), 963–968. https://doi.org/10.1002/1097-0142(195309)6:5<963::AID-CNCR2820060515>3.0.CO;2-Q

[22] Supramaniam, R. (2008). New malignancies among cancer survivors: SEER cancer registries, 1973-2000. *Journal of Epidemiology & Community Health*. https://doi.org/10.1136/jech.2007.063560

[23] Vikram, B. (1984). Changing Patterns of Failure in Advanced Head and Neck Cancer. *Archives of Otolaryngology*. https://doi.org/10.1001/archotol.1984.00800350006003

[24] WARREN, S. (1932). Multiple primary malignant tumors. A survey of the literature and a statistical study. *Am J Cancer*, *16*, 1358–1414. http://ci.nii.ac.jp/naid/10005037946/en/

[25] Wei, E. K., Giovannucci, E., Wu, K., Rosner, B., Fuchs, C. S., Willett, W. C., & Colditz, G. A. (2004). Comparison of risk factors for colon and rectal cancer. *International Journal of Cancer*, *108*(3), 433–442. https://doi.org/10.1002/ijc.11540