Primary carcinoma esophagus with unusual synchronous second malignancies: A case series

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ABSTRACT

Multiple primary cancer is no longer a rarity. As life expectancy has increased, more individuals are living long enough to develop not only one but also two or more cancers. Herein, we report on three cases of synchronous malignancies associated with the primary esophagus cancer. All three patients posed a challenge for the treatment. These patients carry a dismal prognosis so early diagnosis of subsequent cancer at a curable stage by regular follow-up is encouraged. The early investigation of new symptoms and signs may help to diagnose, initiate early treatment, and reduce the number of deaths from subsequent primary cancers in patients.

Key words: Carcinoma esophagus, Early diagnosis, Synchronous malignancy

Esophageal carcinoma accounts for approximately 6% of all gastrointestinal malignancies [1]. Most cases occur in males, at a rate of 4:1 relative to females. Because the esophagus has no covering serosa, direct invasion of contiguous structures may occur early. Squamous cell carcinoma and adenocarcinoma constitute 95% of all esophageal tumors, although other rare histologic subtypes are occasionally seen. Approximately half of the patients present with unresectable or metastatic disease and less than 15% of patients are curable [2]. The incidence of synchronous second primary cancers (SPCs) in patients with squamous esophageal cancer (EC) is reported to be 5–10%. The most well-known synchronous malignancies are head and neck and lung cancers [3,4]. The association between SPCs and these cancers can be explained by a process called "field cancerization," which arises from exposure to common carcinogenic agents such as tobacco smoke [5,6]. Accurate detection of synchronous second primary cancer should be of particular concern for patients with EC, because the survival of these patients has increased significantly due to advances in multimodality therapies and surgical procedures.

The unusual site and different histopathology of the second primary tumor pose a challenge to treating physician as very limited literature is available regarding the treatment strategy and survival outcome of these patients. Here, we examined the clinical features and survival outcomes of three patients with synchronous second primary cancer associated with carcinoma esophageal at presentation.

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CASE SERIES

Case 1

A 47-year-old male presented in our outpatient department (OPD) in August 2021 with complaints of difficulty in swallowing solid food for 6 months. The patient was a gutka chewer (three gutka pouches per day) for five years. The patient's general condition was good with a Karnofsky Performance Status (KPS) of 90. His blood pressure was 122/78 mm Hg and other vitals were within normal limits.

Upper gastrointestinal endoscopy revealed a circumferential growth in the esophagus at 25–35 cm from the incisor. On histopathology, it came out to be keratinizing moderately differentiated squamous cell carcinoma. After a thorough workup, it was diagnosed as a case of locally advanced carcinoma esophagus. The patient received four cycles of neoadjuvant chemotherapy in the form of 3 weekly paclitaxel,cisplatin,5-FU regimen (PCF) regimens, which showed good symptomatic relief.

Meanwhile, in September 2021, the patient complained of a non-healing ulcer in the left upper alveolus, headache, several bouts (3–4/day) of vomiting, and backache. The clinically accessible size of the ulcer was approximately 2 × 2.5 cm. Histopathology from the alveolus ulcer revealed poorly differentiated carcinoma. Contrast-enhanced computed tomography (CECT) scan brain came out to be in favor of multiple brain secondaries. A positron emission tomography (PET-CT) scan showed metabolically

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active lesions in the maxillary alveolus, paraesophageal lymph nodes, brain, and fifth rib. The patient was given palliative brain radiotherapy (RT) (30Gy/10#) to the brain, palliative RT (30Gy/10#) to the thorax for the primary disease, and palliative RT (30Gy/10#) to the face and neck for secondary synchronous malignancy. After all these aggressive treatments, the patient was symptomatically better. As the patient was reluctant to IV chemotherapy, so was kept on oral capecitabine.

After 3 months of completion of RT, a repeat PET-CT scan was done, which showed a decrease in esophageal thickening, left maxillary alveolar lesion, and decrease in the right cerebellar lesion with complete resolution of the left occipital lesion (Fig. 1a) with comparison to the previous PET-CT scan. However, there was an increase in the number, extent, and metabolic activity of skeletal lesions and the appearance of a few abdominal lymph nodes, along with bilateral pulmonary parenchymal changes. The patient was started on palliative chemotherapy in the form of a weekly I/V PCF regimen along with inj Zoledronic acid 4mg, q-4wks. After 6 weekly cycles of chemotherapy, the patient showed good symptomatic relief but started complaining of dribbling of urine. A new PET-CT scan was advised which showed a decrease in the thickness of the esophageal lesion; however, a new focal area of increased fluorodeoxyglucose uptake was noted in the left posterolateral aspect of the prostate gland (Fig. 1b). Prostate-specific antigen was 13.13ng/ml. A transurethral prostatic biopsy was done, which came out to be adenocarcinoma (Fig. 2). The patient denied further oncological treatment and wished to be on palliative treatment only.

Case 2

A 55-year-old female presented in OPD in March 2021 with complaints of difficulty in swallowing solid food for one year. No addiction history was present. Her vitals were within normal limits with a KPS of 80. Barium swallow revealed luminal narrowing with mucosal irregularity and upholding of contrast in the distal esophagus. Upper G.I endoscopy showed an ulceroproliferative growth at 33 cm from the incisor. On histopathology, well-differentiated squamous cell carcinoma was reported (Fig. 3a). The patient received six cycles of neoadjuvant chemotherapy (NACT) followed by radical concurrent CT-RT (60Gy/30#). The patient completed treatment and was kept on follow-up.

However, within 3 months of follow-up, the patient came with complaints of mild difficulty in swallowing solid food. A CECT scan thorax was advised which showed diffuse circumferential asymmetrical thickening involving the lower one-third of the esophagus extending from the lower border of D8 involving the gastroesophageal junction (Fig. 4). Upper GI endoscopy and guided biopsy were repeated which revealed gastroesophageal reflux disease with gastric nodule and extrinsic bulge in the cardiac region with histopathology of the gastric nodule suggestive of neuroendocrine tumor (Fig. 3b). Immunohistochemistry was performed and came out to be CEA+, synaptophysin 4+, and CGA-4+. The patient was advised for salvage surgical management but she was very reluctant for the same, so she was planned for six cycles of chemotherapy (VAC). After four cycles of chemotherapy, a repeat CECT thorax was done that showed mild diffuse symmetrical thickening in the distal esophagus (reduced in comparison to the previous report) (Fig. 3b). The patient completed her six cycles of chemotherapy. PET-CT scan was in favor of residual disease, so now the patient was sent to a gastrosurgeon for surgical management.

Case 3

A 53-year-old male presented in OPD in July 2021 with complaints of difficulty swallowing solid food for 3 months. The patient was a bidi smoker (3–4 bundles/day) for over 35 years and a gutka chewer (1–2 pouches/day) for over 20 years with a family history of cancer in the first degree. The patient's general condition was average at the time of presentation with a KPS of 70. Barium swallow revealed luminal narrowing in the lower esophagus. Upper GI endoscopy showed a deep ulcer with a nodular margin extending from 37 cm to the gastroesophageal junction. On histopathology, moderately differentiated squamous cell carcinoma was reported. CECT thorax showed asymmetrical circumferential heterogeneous mural wall thickening in the lower esophagus and poorly defined nodular opacities noted in bilateral lungs (old infective lesion) (Fig. 5a).

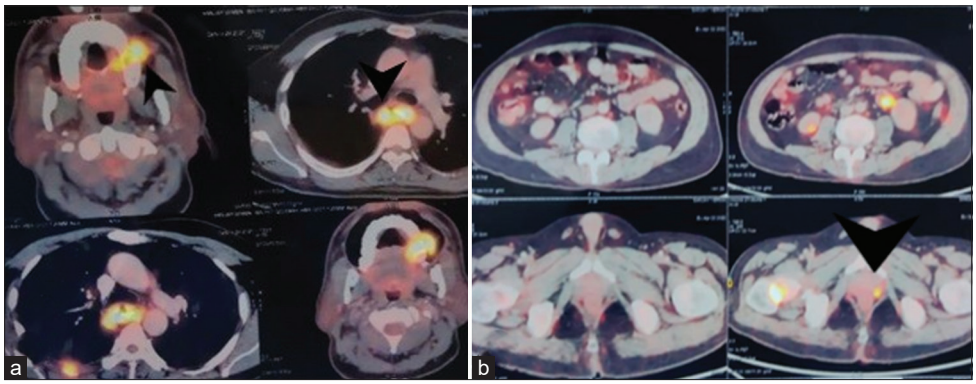

Figure 1: Whole body PET-CT scan showing (a) fluorodeoxyglucose (FDG) active lesion in esophagus, 5th rib and left upper alveolus; (b) high FDG uptake lesion in posterolateral wall of prostate with skeletal lesion (Case 1)

The patient received three cycles of NACT followed by concurrent CT-RT (60 Gy/30#). The patient completed treatment and was kept on regular follow-up. Within 3 months of completion of treatment, the patient complained of generalized body weakness and choking sensation while swallowing solid food. Barium swallow was re-advised which showed structural narrowing with an irregular margin in the lower esophagus. The patient was started on salvage chemotherapy. In the due course of treatment for recurrent primary lesion, the patient came with complaints of gross hematuria for 3 days. Ultrasound (USG) whole abdomen (Fig. 5b) revealed a hypoechoic lesion in the liver and right kidney. An USG-guided fine-needle aspiration cytology (FNAC) from the renal mass was performed which was suggestive of squamous cell carcinoma. The patient was kept on palliative chemotherapy (PCF) to which he did not respond well. The patient had complained of generalized body weakness and was reluctant to further chemotherapy. He was kept on only on conservative management in view of poor general condition. The patient expired in August 2022.

DISCUSSION

Multiple primary malignant tumors arising from other organs were defined according to the following criteria of Warren and Gates [7]: (a) the tumors must be clearly malignant on histologic examination, (b) the tumors must be separated by normal mucosa, and (c) the possibility that the second tumor represents metastasis must be excluded. In this study, all three cases were distinguished from metastatic EC by cell morphology, gland architecture, specific molecular markers (when required), and the pattern of tumor spread.

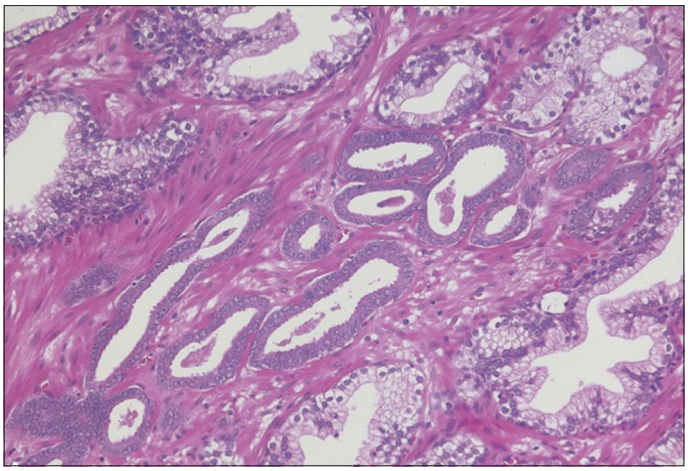

Figure 2: H&E stain slide showing adenocarcinoma (Case 1)

The most well-known sites for second primary malignancy are aerodigestive tract organs such as the oral cavity, pharynx, larynx, and lung. The previous studies suggested that gastric cancer could be another common SPC, especially in regions with a high prevalence of gastric cancer [5,6].

Koide *et al*. published a case series of 31 patients of EC and observed that 21 synchronous and ten metachronous associated cancers were found and 25 of them were resected. Early-stage EC was much more frequent in the associated cases than in the non-associated cases [4]. Lee *et al*. studied a consecutively collected database and identified a total of 317 patients diagnosed with squamous oesophageal carcinoma between June 2005 and December 2007. Of these, 21 patients had synchronous primary cancer that developed in a different organ such as head and neck cancer (18.2%), lung cancer (22.7%), gastrointestinal cancer (27.3%), pancreatic-biliary cancer (22.7%), and others (liver and thyroid-9.1%) [2]. However, in our study, sites for synchronous primary lesions were very unusual. In the first patient, one synchronous tumor was in the alveolus and another was in the prostate. In the second patient, the second tumor was in the gastric region and it was a neuroendocrine tumor. In the third case, a synchronous tumor developed in the kidney. Out of these, two patients presented with distant metastasis at the time of presentation of the second malignancy.

Given the well-known harmful effects of smoking, including increased risk of cancers such as aerodigestive tract and lung cancers, physicians should pay attention to the risk of synchronous SPC during the initial staging of patients with squamous EC [8]. In a previous study, it was found that approximately one-third of SPC were detected in the first 6 months after the diagnosis of squamous EC [5]. In our series also, two patients were having a history of tobacco consumption, and all three patients developed second malignancies within 6 months of the primary diagnosis.

PET-CT is the standard modality for EC staging and planning multimodality therapy [9]. An earlier study reported that PET-CT

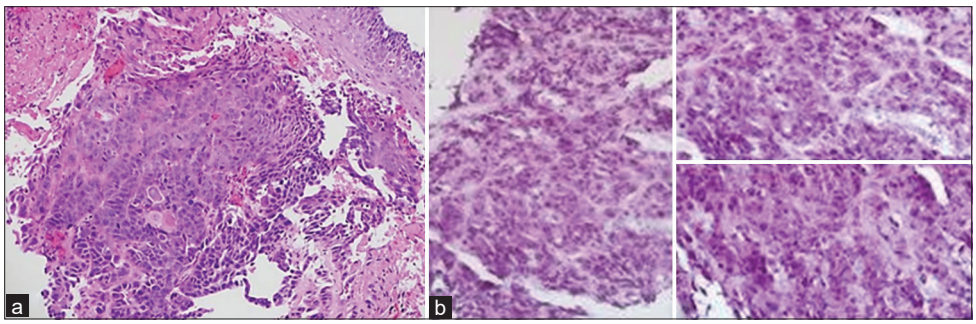

Figure 3: (a) H&E stained slide-showing well-differentiated squamous cell carcinoma; (b) H&E stained and Immunohistochemistry favor well-differentiated neuroendocrine tumor (Case 2)

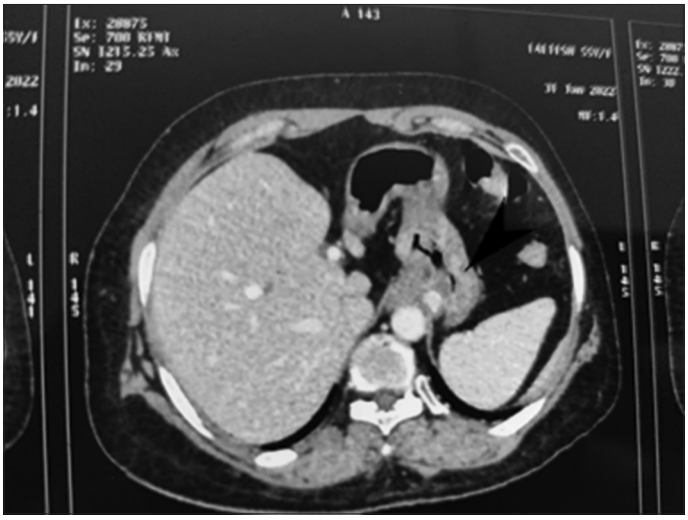

Figure 4: CECT scan abdomen showing lesion in lower esophagus (Case 2)

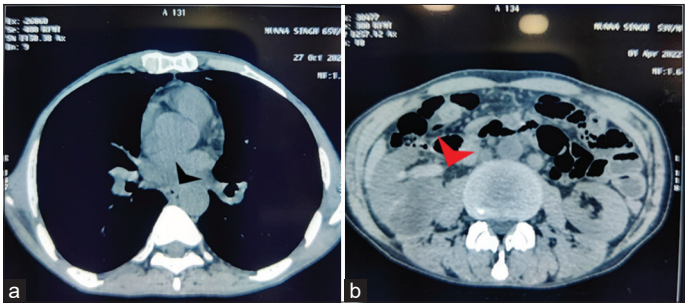

Figure 5: (a) CT scan thorax showing complete obstruction of esophageal lumen due to soft-tissue mass; (b) CT scan abdomen showing a right renal mass (Case 3)

was useful for screening SPC at the initial staging of malignancies, demonstrating 91% sensitivity and 69% positive predictive values for detecting SPC [10]. In our study, also, PET-CT scan played a useful role in the early diagnosis and disease extension.

Treatment plans for both EC and SPC may not be optimal due to the technical complexity of surgical treatment, different biological behaviors of synchronous tumors, additional costs, and increased patient anxiety. The current evidence strongly recommends a multidisciplinary approach for treating patients with EC [11]. However, the unexpected detection of SPC poses difficulties for physicians' therapeutic decision-making. These factors may lead to stage-inappropriate treatment and, thus, poor outcomes for EC patients. Similarly, in our cases, we have to face treatment challenges as very sparse literature is available for guidance. However, the prognosis of esophageal carcinoma in patients with SPC is not very clear.

CONCLUSION

The second primary cancer in the case of squamous EC patients should be looked at initial staging work-up. Complementary staging with PET-CT plays a substantial role in the detection of synchronous SPC that was missed on conventional CT. Esophageal carcinoma with SPC poses a challenge in providing stage-appropriate treatment. Hence, a vigilant close follow-up in carcinoma esophagus is required to detect synchronous malignancies in the early stage for proper management.

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