Four Synchronous Primary Malignancies of the Breast, Lung, Colon and Esophagus

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Abstract. *The literature contains few reports of patients with four more or more synchronous primary malignancies. We report the case of a 74-year-old woman who presented with synchronous primary malignant neoplasms of the breast (metaplastic carcinoma), lung (squamous cell carcinoma), esophagus (adenocarcinoma), and colon (adenocarcinoma). She was treated with multimodality therapy and demonstrated a favorable response at early follow-up. To our knowledge, this combination of synchronous primary malignancies has not been previously reported. The management of patients with multiple synchronous primary malignancies introduces a number of unique challenges which necessitate highly individualized treatment plans that may not strictly adhere to standard practices in the setting of a single malignancy.*

Multiple primary malignant neoplasms, defined as distinct malignant lesions which are not themselves metastases, have been documented in fewer than 1%-16% of patients with a history of cancer (1-6). Among all patients with multiple primaries, between 1.5% and 11.8% have been reported to have more than two malignancies (1-3). Multiple synchronous primary malignant neoplasms, defined as malignancies diagnosed simultaneously or within 6 months of each other, are less common than metachronous lesions, particularly as the number of malignancies increases. The English literature contains few reports of four or more synchronous primary malignancies occurring in separate organs (7-9). Herein, we describe the clinical management of the first reported case of quadruple synchronous primary malignancies of the breast, lung, colon, and esophagus.

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Case Report

A 74-year-old female with a past medical history of hypothyroidism, hyperlipidemia, and basal cell carcinoma initially presented in February 2014 for surgical evaluation of a lesion of the right breast discovered on routine screening mammogram. Physical examination was significant for a 2-cm palpable mass in the upper outer quadrant of her right breast and no palpable axillary lymphadenopathy. Her family history was notable for a sister who died of breast cancer at the age of 35 years and a father who died of lung cancer at age 76 years. The patient had a 40 pack-year history of smoking, having stopped 17 years prior.

Core biopsy of the breast mass revealed a grade 3 invasive ductal carcinoma, which was estrogen receptor (ER)-, progesterone receptor (PR)-, and HER2-negative (triple-negative). Staging chest x-ray was performed that revealed a lung nodule; therefore, computed tomographic (CT) scans of the chest, abdomen and pelvis was pursued. This revealed a 2.2 cm nodule of the left upper pulmonary lobe, diffuse distal esophageal wall thickening, and a segment of sigmoid colon with luminal narrowing. Upper endoscopy revealed a tumor from 32 cm to 37 cm from the incisors and a 5 cm hiatal hernia; biopsy of the esophageal tumor demonstrated a moderately differentiated adenocarcinoma. Colonoscopy identified a focal stricture 60 cm from the anal verge beyond which the endoscope could not be advanced; biopsies of the stricture revealed moderately differentiated adenocarcinoma, morphologically distinct from that of the esophageal cancer. Positron-emission tomography (PET)-CT scan was performed, which revealed foci of hypermetabolism in the right breast and axillary lymph nodes, left upper lobe of the lung, distal esophagus, and sigmoid colon (Figure 1).

The patient underwent staging mediastinoscopy, that was negative for metastatic disease, and thoracoscopic wide wedge resection of the left lung lesion with mediastinal lymphadenectomy, that revealed a pT1bN0 moderately differentiated primary squamous cell lung carcinoma (Figure 2B). Simultaneously, she underwent a right breast lumpectomy,

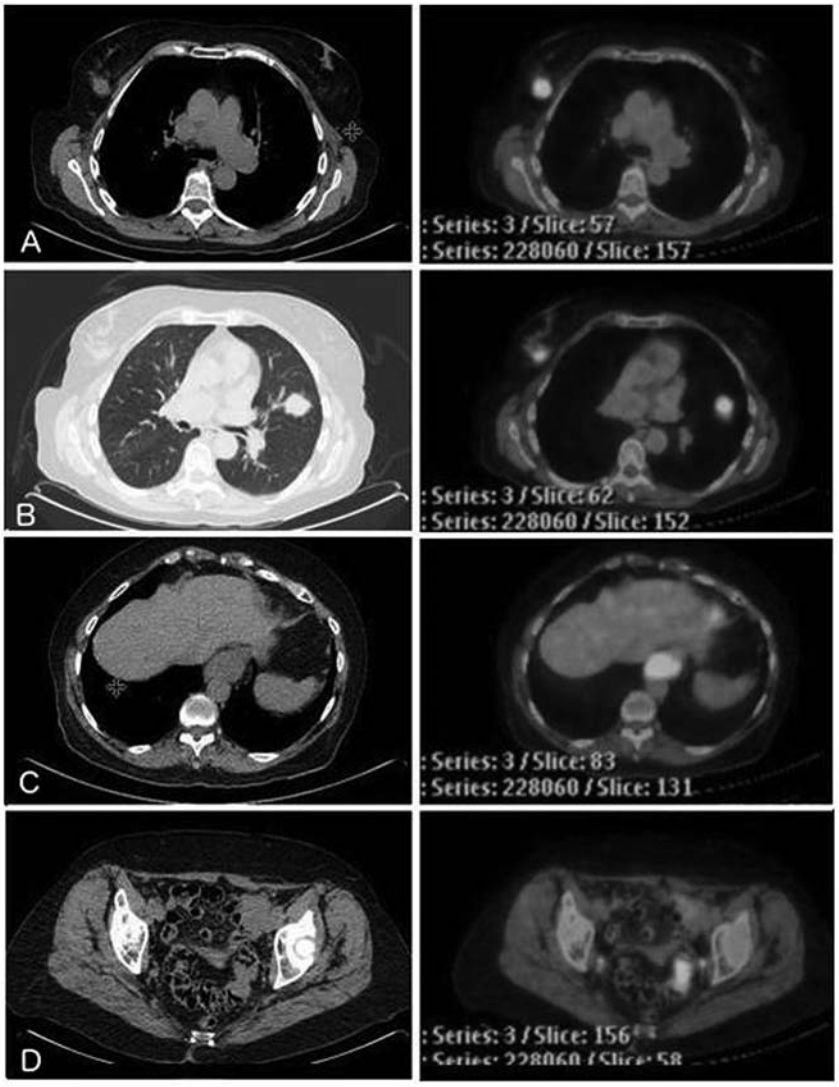

Figure 1. *Fluorine-18-fluorodeoxyglucose positron-emission tomography with computed tomography. A: Right breast mass, maximal standardized uptake value (SUV) of 14.5. B: Spiculated left upper lobe mass, maximal standardized uptake value (SUV) of 7.4. C: Distal esophageal wall thickening, maximal standardized uptake value (SUV) of 16.2. D: Segment of sigmoid wall thickening, maximal standardized uptake value (SUV) of 12.0.*

which revealed a 3.1-cm triple-negative, high-grade metaplastic carcinoma (Figure 2A). Sentinel lymph node biopsy was not performed as axillary staging would not change her adjuvant therapy. Three weeks later, sigmoidectomy was performed, revealing a pT3N0 adenocarcinoma of the colon with perineural invasion (Figure 2C).

The plan was to proceed with induction chemoradiotherapy for the patient's endoscopic ultrasound-staged T3N1 esophageal adenocarcinoma, but she developed newly-palpable right axillary lymphadenopathy. She was, therefore, administered one cycle of adriamycin and cyclophosphamide, followed by three cycles of epirubicin and cyclophosphamide for breast cancer. Adriamycin was changed to epirubicin because epirubicin may have some activity against esophageal cancer (10). This was followed by three cycles of carboplatin and paclitaxel, that was stopped due to neuropathy. Re-staging PET-CT scan demonstrated a complete resolution of her axillary lymphadenopathy and a new focus of hypermetabolism in the right hepatic lobe. CT-guided percutaneous needle biopsy revealed the hepatic lesion to be metastatic adenocarcinoma, consistent with the colonic primary. Based on the complexity of the patient's clinical picture, the presence of a solitary hepatic metastasis and the prior administration of a platinum-based chemotherapy, the decision was made to forego neoadjuvant radiotherapy for esophageal cancer and proceed with combined esophagectomy

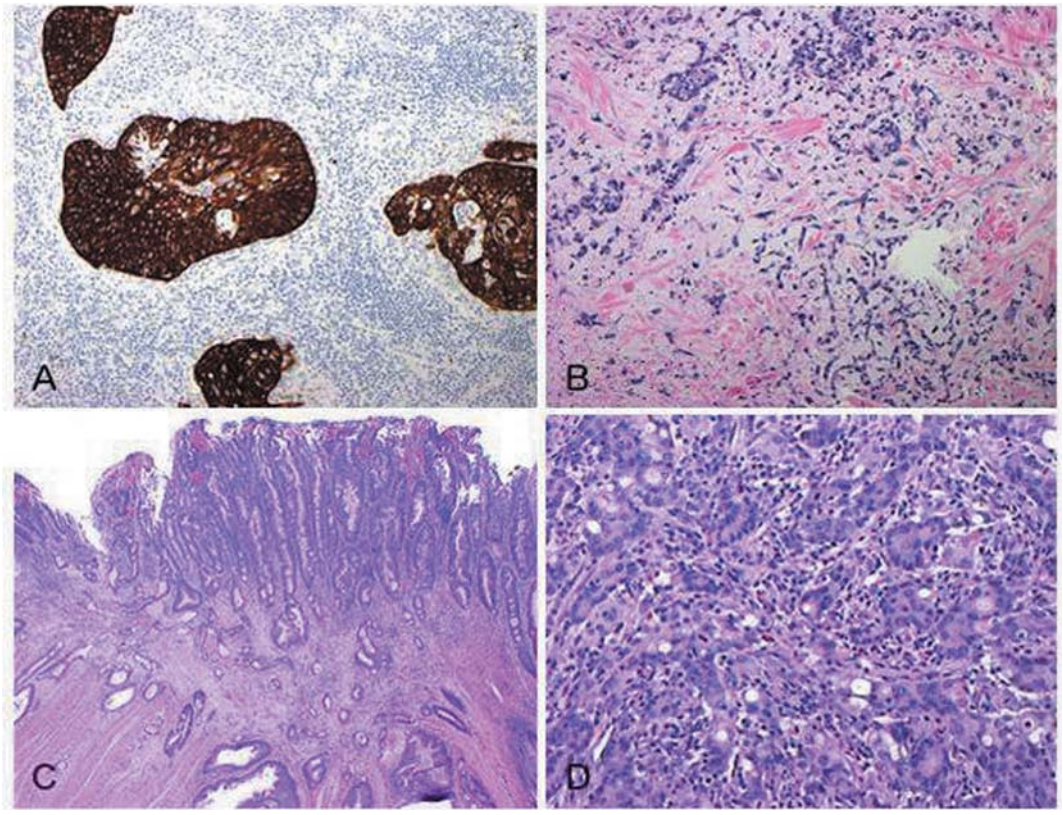

Figure 2. *A: Metaplastic breast carcinoma with small clusters and individual tumor cells within myxoid stroma (×100). B: Pulmonary squamous cell carcinoma, strongly CK5 positive (×100). C: Moderately differentiated colonic adenocarcinoma with tumor extension into muscularis propria (×20). D: Moderately to poorly differentiated adenocarcinoma of esophageal submucosa (×200).*

and hepatic metastasectomy. The patient underwent an uncomplicated Ivor-Lewis esophagectomy which revealed a pT3N1 moderately-to-poorly differentiated invasive adenocarcinoma of the gastroesophageal junction (Figure 2D) and an R0 hepatic wedge resection of the metastatic colonic adenocarcinoma. She tolerated the procedure well and was subsequently treated with seven cycles of leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX), with no evidence of disease on post-treatment restaging PET-CT scan in May 2015. Treatment was discontinued earlier than planned due to toxicity and negative PET-CT. The patient remains clinically disease-free 18 months after initial diagnosis.

Discussion

To our knowledge, this is the first reported case of four synchronous primary malignancies involving the breast, lung, colon, and esophagus. Of note, the patient had a lifetime history of five primary metachronous neoplasms, having had a basal cell carcinoma excised 20 years prior. Despite her advanced age, she tolerated resection of all four tumors and multiple cycles of chemotherapy with a favorable early response, emphasizing that age alone should not be a contraindication to aggressive management in patients with otherwise acceptable performance status.

Several notable risk factors may be implicated in the development of our patient's multiple malignancies, including her 40 pack-year smoking history, strong family history of cancer, and advanced age (1, 11). The occurrence of multiple primary malignancies raises suspicion for the presence of an underlying genetic predisposition. While there are a number of well-described hereditary cancer syndromes, these tend to emerge much earlier in life, and none is consistent with our patient's combination of malignancies. At the time of diagnosis, the patient was screened for 32 different genes associated with cancer predisposition (CancerNext panel; Ambry Genetics, Aliso Viejo, CA, USA), none of which she harbored. The identification of novel mutations associated with increased cancer risk remains an area of ongoing study.

There exist no definitive guidelines for the management of multiple synchronous primary tumors involving separate organs. The current case does, however, illustrate several important principles. Sequencing of surgical interventions should initially aim to exclude the presence of metastatic

disease. Our patient underwent pulmonary resection to confirm that the nodule represented a primary lung cancer, rather than metastasis from one of the other primary tumors. When possible, combined operations, such as single-stage thoracoscopic wide wedge resection and lumpectomy, can shorten the overall duration of therapy. Consideration must also be given to the timely resection of tumors that pose a risk of acute complications, such as malignant bowel obstruction, which in the current case was imminent with the nearly completely obstructing sigmoid adenocarcinoma.

Importantly, a balance must be met between providing effective treatment while preserving quality of life and minimizing the morbidity of what is often a highly complex, protracted, and toxic treatment course. Thoracoscopic wide-wedge resection with mediastinal lymphadenectomy was performed instead of lobectomy to treat this patient's clinical stage I lung cancer, in order to minimize morbidity while providing potentially curative therapy (12). When possible, chemotherapy regimens should be tailored to target multiple malignancies. Epirubicin, carboplatin, and paclitaxel were administered as adjuvant therapy for her metaplastic breast carcinoma (13) and also served as induction therapy for the esophageal adenocarcinoma (10, 14). Additionally, FOLFOX, administered for this patient's metastatic colon cancer, has proven activity against esophageal cancer (15).

In summary, this is the first documented case of quadruple synchronous primary malignancies of the breast, lung, colon, and esophagus. The management of patients with multiple synchronous primary malignancies introduces a number of unique challenges which necessitate highly individualized treatment plans that may not always strictly adhere to standard practices in the setting of a single malignancy. These complex treatment decisions are best made in a multidisciplinary fashion with the careful input of surgeons, medical oncologists, radiation oncologists, radiologists, pathologists, and the patient.

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