

Management of multiple primary cancers: Priorities and treatment strategies?

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Case Report

Abstract

Multiple primary cancers are known entity due to the propensity of cancer survivors to develop additional malignancies both from genetic predisposition and exogenous influences. However, the development of triple or quadruple primary cancers, especially presenting simultaneously, presents challenging diagnostic and treatment dilemmas. We report here a patient who presented initially with neurological symptoms. Extensive evaluation and pathologic workup revealed that the patient actually has an intra-medullary vascular neoplasm at the level of upper thoracic spine, mucinous adenocarcinoma of the right lower lobe, poorly differentiated adenocarcinoma of the stomach near the gastro-esophageal (GE) junction, and conventional type adenocarcinoma of the hepatic flexure of the colon. The patient underwent neoadjuvant chemo-radiation for the GE junction carcinoma followed by surgical resection of the three different adenocarcinomas simultaneously as definitive management. This case illustrates the utility of immuno-histochemistry in delineating the site of origin for primary tumors, and the challenges posed when dealing with multiple primary neoplasms concurrently.

Keywords: Multiple Primaries, Lynch Syndrome, Colon Cancer, Lung Cancer, Hemangioblastoma, Gastroesophageal Cancer.

1. Introduction

Historically, multiple primary malignant cancers were known to occur with a higher incidence than statistical chance.¹⁻³ The earliest comprehensive descriptions by Warren and Gates led to the conclusion that certain populations are at risk for development of secondary neoplasms.⁴ Patients who present simultaneously with multiple neoplasms present a diagnostic and therapeutic challenge due to the limitations in addressing each malignancy with available resources and potential for detrimental side effects to the patient. The role of immunohistochemistry in the current era has helped to decipher cells of origin and rendered what would have traditionally been mistakenly deemed an incurable stage IV disease into a potentially treatable scenario with multiple synchronous primaries. Here we present an

interesting case of a patient who presented with four solid organ neoplasms simultaneously. We discuss the rationale for his management as well as the approach utilized to maximize effectiveness in his treatment.

2. Case Presentation

Our patient is a 58 year old African American male smoker, with past medical history significant for insulin dependent diabetes, hepatitis C, hypertension, and upper gastrointestinal bleeding 4 years prior from NSAID use, who initially presented with numbness of his bilateral lower extremities. His family history was significant for multiple cancers including colon, upper aero-digestive tract, and cutaneous malignancies.

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Evaluation of this patient including MRI of the spine showed a syrinx in the intra-medullary region of his thoracic spine. (Figure 1 - MRI of spine) The patient then had a CT scan of the chest demonstrating the presence of a slowly enlarging right lower lobe nodule measuring about 2.8 x 2.4 cm in comparison to previous CT scans. Because of the possibility of metastatic lung cancer, he then underwent a PET CT for further evaluation. Unfortunately, he was found to have activity in the right lower lobe with maximum Standard Uptake Values (SUV) of 4.6, activity at the GE junction with maximum SUV of 16.0, and activity at transverse colon with a SUV of 15.9. A percutaneous biopsy of the lung nodule showed it to be a moderately differentiated right lower lobe adenocarcinoma. (Figure 2A) The patient then had

an upper endoscopy and lower colonoscopy confirming a gastric cancer near the GE junction, and another primary colon cancer. (Figure 2B & 2C) Further staging of the GE junction tumor with endoscopic ultrasound showed the tumor to be T3N1 with two abnormal lymph nodes in the lower esophageal area. These lesions were individually verified in terms of their sites of origin based on immuno-histochemistry. As treatment for his multiple tumors, he needed confirmation that the spinal lesion was unrelated. Therefore, the patient underwent a surgical excisional biopsy of the T2 / T3 spinal lesion to assess for metastatic disease. The results fortunately revealed a low grade vascular neoplasm, best categorized as a hemangioblastoma. (Figure 2D)



Figure 1: An MRI sagittal image of the patient's thoracic image is depicted. There is a tumor extending from lower cervical region to T2/T3 level of the thoracic spine.

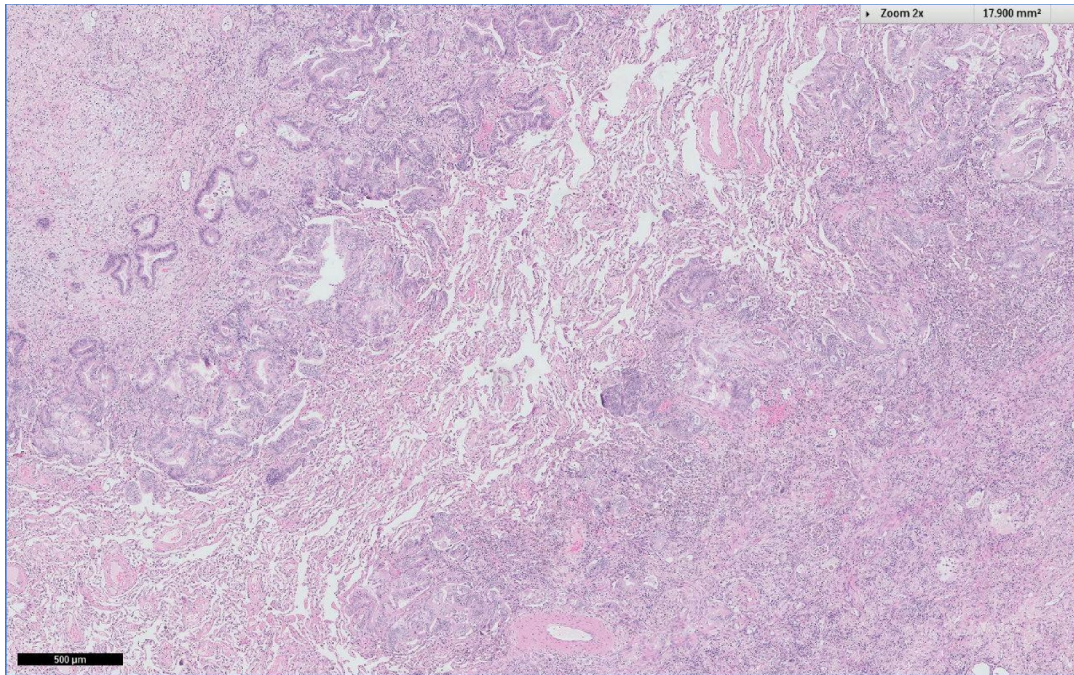


Figure 2 : The hematoxylin and eosin (H&E) stains of the four types of tumor are displayed.

Figure 2A: H&E image of the lung cancer. Immunostains showed that the tumor is positive for CK7 and CK20 but negative for TTF-1.

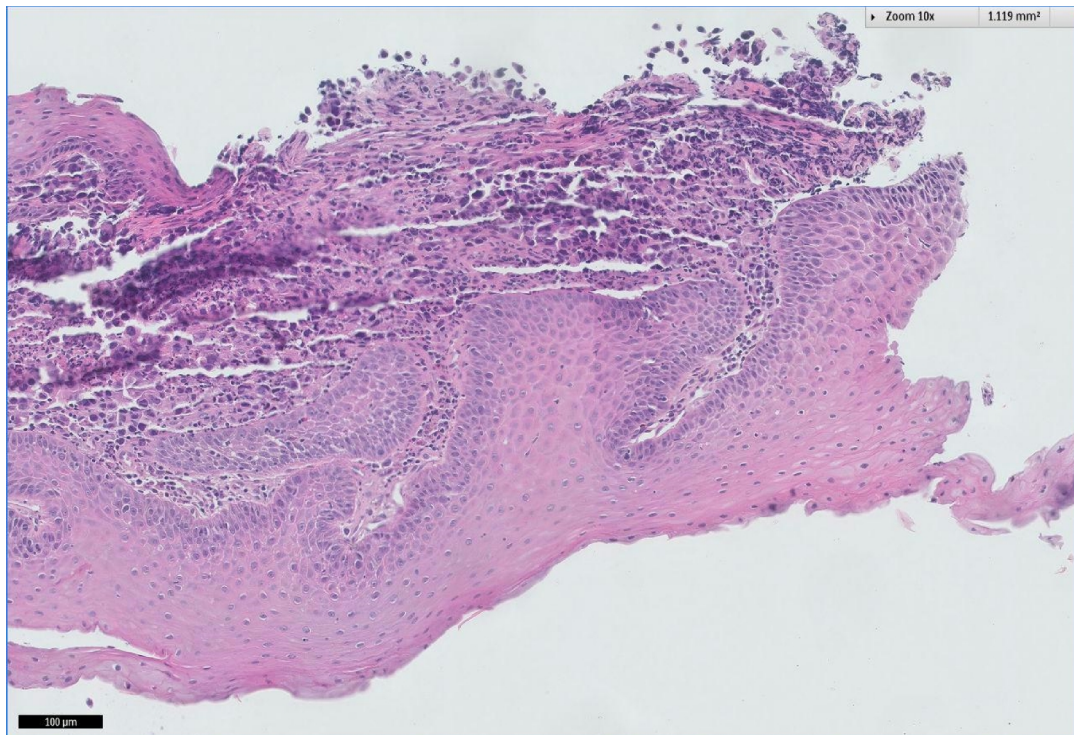


Figure 2B: H&E image of the gastric cancer. Immunostains showed that the tumor is positive for CK7 and negative for CK20 and TTF-1.

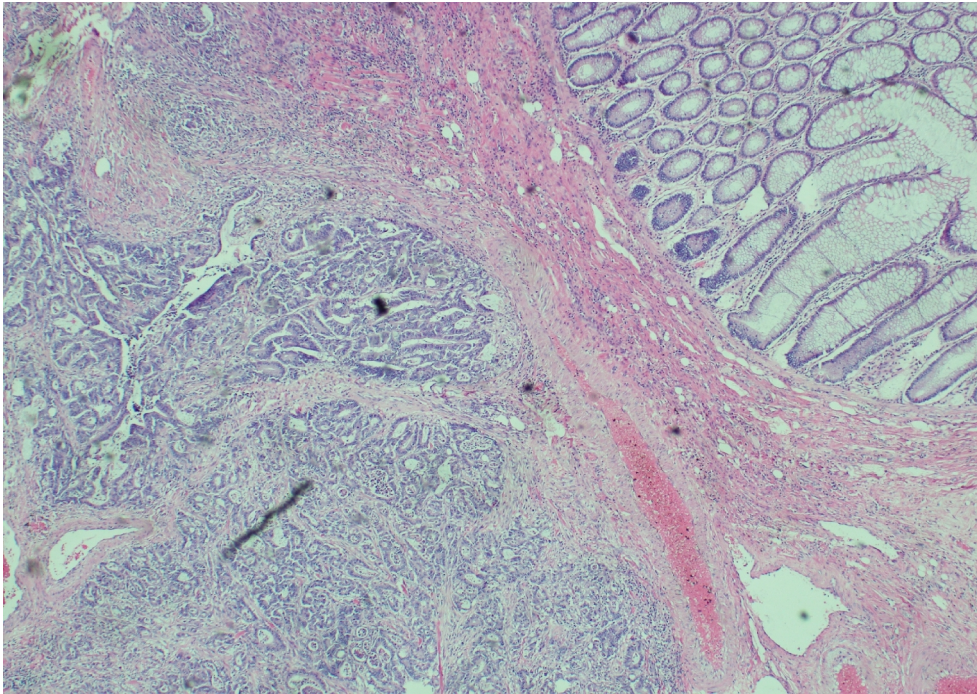


Figure 2C: H&E image of the colon cancer. Immunostains showed that the tumor is positive for CDX2, rarely positive for CK20 and negative for CK7.

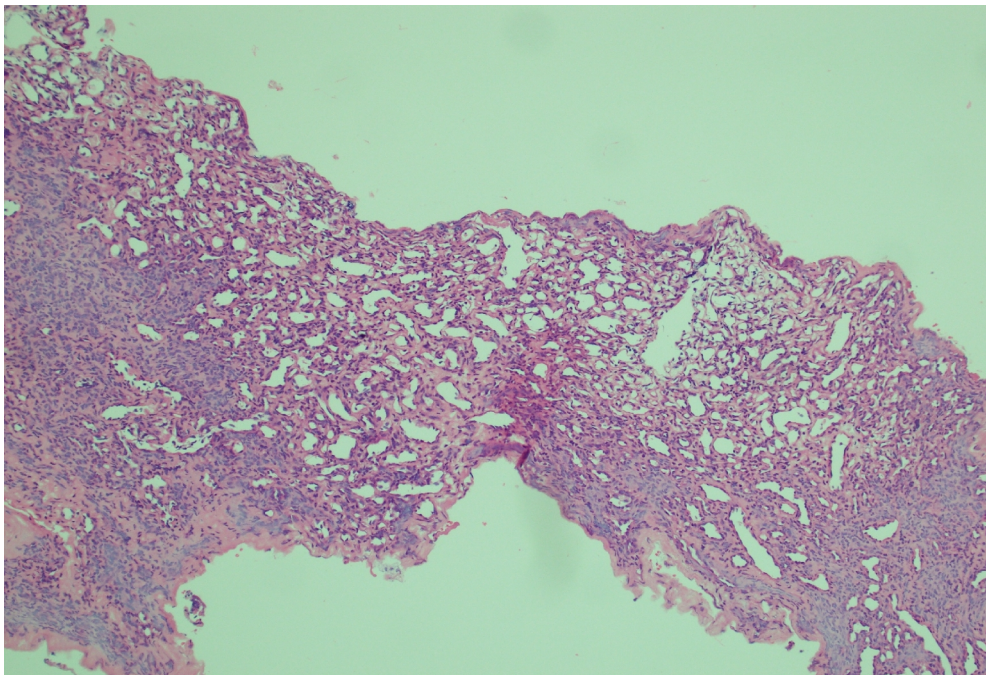


Figure 2D: H&E image of the spinal hemangioblastoma, WHO grade 1. Immunostains were focally positive for inhibin and NSE.

Because of the multiple primary cancers identified, we elected to treat the patient concurrently with combination chemotherapy and radiation therapy followed with surgical therapy. The patient received 5040 cGy of radiation to the GE junction in combination with 5-Fluorouracil (5-FU)/cisplatin initially. The radiation was delivered in 28 fractions via intensity

modulated radiation therapy (IMRT). The regimen of continuous infusional 5-FU/cisplatin was chosen, in part, due to the fact that cisplatin could also be expected to be active against his lung cancer, and 5-FU against both his colon and GE junction cancers. Following neoadjuvant chemo-radiation, subsequent repeat endoscopy revealed that the lesion in the GE junction

completely disappeared. However, the colonic lesion enlarged in the intervening 3 months leading to a circumferential nearly obstructing colon cancer. The patient was then advised on surgery consisting of an Ivor-Lewis esophago-gastrectomy along with right lower lobectomy using the chest incision and extended right colectomy using the abdominal incision. The patient tolerated the surgery well and was discharged in 15 days tolerating a regular diet. His final lung cancer stage was a pathologic stage IA (T1bN0M0). His colonic lesion was a pathologic stage II (T3N0M0) colon cancer. His GE junction cancer was ultimately a clinical stage IB gastric cancer. Screening for Lynch syndrome detected absence of MSH-6 protein during immunohistochemical analysis, suggesting Lynch as a possibility in this patient.

Postoperatively, our patient initially had plans for surgical intervention for his intra-medullary lesion in the spine due to the neurological deficits caused by the compressive nature of the lesion. Unfortunately, the patient developed recurrent metastatic colon cancer to the liver 7 months after his surgery. He is currently undergoing treatment again with chemotherapy with plans for surgical resection of the liver metastases in the near future.

3. Discussion

Multiple primary malignant tumors were first described by Billroth in 1889 as a type of medical curiosity.⁵ This gained traction after extensive and detailed studies by Warren and Gates in 1932.⁴ Incidence of multiple primary malignant tumors are now estimated to be around 1% based on autopsy findings in patients with other malignancies.⁶ The frequent presentation in patients with pre-existing malignancies are thought to be related to their genetic pre-disposition, environmental factors and behavioral influences.⁷ As such, the known risk of subsequent malignancies should trigger caution in follow-up of patients with prior malignancies and to advise changes in their lifestyles to mitigate their risks.^{7,8}

The incidence of metachronous primary tumors in excess of three primaries occurs in less than 0.1 % of patient with cancer.⁹⁻¹⁴ Based on the early descriptions of Moertel *et al*, patients who present with multiple primary tumors within six months of the initial presentation are classified as having synchronous tumors.² Furthermore, he divided the classification of multiple primary malignant neoplasms to neoplasms of multicentric origin within the same tissue or organ, versus those of different tissues or organs, or a mixture of both.³ This classification has stood the test of time since his early descriptions. As in the case of our patient, he presented with four primaries of different organs and several histologies. Clinical and pathological correlation as well as immunohistochemical methods excludes him as having systemic metastases from one primary tumor.

One of the largest series of patients with either synchronous or metachronous tumors with respect to gastric cancer published in the literature came from the Yonsei University Health System in Korea.⁹ Patients with synchronous multiple primary cancers with at least one site consisting of gastric cancer comprised less than 0.04 % of the total number of patients presenting with any type of malignancies.⁹ However, those with head and neck, esophagus, lung and kidney types of cancer presented more commonly as the synchronous variety rather than the metachronous presentation. The most common sites for metachronous tumors including the stomach were colon, thyroid, lung, kidney and breast. Other authors have also noted the correlation between presence of lung cancer and that of upper aero-digestive tract malignancies as in the case of our patient.⁷ Patients who presented with metachronous lesions fared much better compared with those presenting with synchronous lesions with overall 10 year survival at 80.7 % compared with 48.2 %.⁹

Genetic predisposition such as Lynch syndrome may contribute to a subset of patients with multiple primary malignancies.¹⁵ Lynch syndrome is an autosomal dominant genetic condition that predisposes to the development of colon cancers as well other malignancies including stomach, small intestine, endometrial, hepatobiliary, upper urinary tract, brain and skin cancers.¹⁵ The etiology of Lynch syndrome is a defective DNA mismatch repair system which leads to microsatellite instability.¹⁶ Specifically, Lynch *et al*. reported that there is a 21.5 % incidence of multiple cancers in patients with the syndrome named after him.¹⁵ Our patient had confirmation of MSI deficiency in his colonic specimen thereby leading to the distinct possibility that he has Lynch Syndrome, and is therefore predisposed to the development of multiple tumors. Testing for Lynch syndrome on this patient included the following: a screen for loss of DNA mismatch repair proteins by immunohistochemistry and confirmation of microsatellite instability within the tumor by PCR analysis of tumor DNA. In this patient, MSH-6 protein was determined to be absent during immunohistochemical analysis. Microsatellite regions of DNA, in some literature referred to as 'short tandem repeats', are not translated into proteins and are generally quite stable. The 5 mononucleotide repeat markers (BAT25, BAT26, Mono27, NR24, and NR21) examined in this patient's colon cancer were all unstable by PCR analysis. The instability of these microsatellite areas of DNA is diagnostic of a tumor with defective mismatch repair proteins.

In the case of synchronous primary tumors, the immediate difficulty is more than the increased subsequent cancer risk. The problem is complicated by the necessity to manage multiple primary tumors simultaneously using cytotoxic agents, radiation or surgical intervention. Frequently, each modality carries

a certain detrimental impact on the patient necessitating alterations to the standard regimen. In the case of our patient, treatment algorithm had to be tailored to the severity of the disease. Therefore, neoadjuvant chemo-radiation for the GE junction gastric cancer was chosen as the first management modality. In addition, the regimen of 5-FU / cisplatin could be expected to have activity against all three of his adenocarcinomas. Following neoadjuvant chemoradiation, he underwent surgical treatment to address 3 cancers simultaneously - namely lung, colon and GE junction. The surgical approach was also modified slightly in order to accommodate the treatment since an Ivor-Lewis incision would be perfectly suited to surgically remove all 3 sites of cancer. Since the spinal lesion is low grade, it was postponed until a later date for definitive surgery. Although there are reports of synchronous and metachronous multiple primaries cancers in the literature, our patient likely represented a unique management approach in terms of surgical treatment to resect 3 solid organ malignancies simultaneously.

4. Conclusion

In summary, we present here a case of multiple primary neoplasms in a patient with likely Lynch syndrome, supported by molecular testing. His presentation demonstrated the utility of immunohistochemistry to decipher the cancers of origin from multiple sites. PET/CT was also helpful to assess for other sites of diseases prior to definitive management. His treatment algorithm illustrates the importance of multi-disciplinary management of patients with cancer.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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