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CASE REPORT

Case series of multiple primary cancers in single individuals: diagnostic and therapeutic dilemmas

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ABSTRACT

Background and Objectives: Cancer recurrence represents treatment failure; the development of new primary tumors is suggestive of persistent exposure to etiological risk factors or genetic predisposition due to mutations in multiple cell lines.

Case presentation/Design/Methods: The first case is a 65-years-old Caucasian male who presented with esophageal and lung cancer diagnosed synchronously. Smoking was the common risk factor for both cancers, underscoring field cancerization. The diagnosis and management was a challenge and different from either cancer presenting alone. Multidisciplinary approach was used and led to good outcomes.

The second case is a 72-years-old Caucasian male presenting a rare dilemma of genetic mutation leading to multiple primary gastrointestinal cancers in a single individual. The gene explaining this group of cancers has not been diagnosed yet and the field needs to be explored further.

Conclusion: Multiple primary cancers can be secondary to a common environmental risk factor or genetic mutations.

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KEYWORDS
Multiple cancers; field cancerization; esophageal cancer; colon cancer; carcinoid tumors

1. Clinical scenario

A 38-years-old male is evaluated for a two-month history of painless bright red blood per rectum that is usually associated with defecation. His medical history is otherwise unremarkable. He does not smoke, drinks socially, is not on any medications and denies any allergies. His family history is significant for colon cancer on his paternal side. He undergoes colonoscopy and is diagnosed with colon cancer in the descending colon. He undergoes clinical staging and it is opted operable. Surgical staging mirrors clinical staging and he is discharged home with proper follow-up planned. What is another necessary step in the management of this patient?

(A) Colonoscopy in 4 weeks
(B) Endoscopy
(C) Genetic Counselling and Lynch Syndrome testing
(D) No further management needed

2. Introduction

Cancer recurrence represents treatment failure; the development of new primary tumors is suggestive of persistent exposure to etiological risk factors or genetic predisposition due to mutations in multiple cell lines. The detection of synchronous cancers stresses the importance of recognizing and eradicating the environmental risk factors like smoking and alcohol [1]. Field cancerization effect suggests that carcinogenic exposure or genetic factors affect tissues or organs, potentiating many cells in the same area to become transformed [2]. Genetic profiling helps stratify patients in high risk and helps diagnose cancer at early stages in family members.

3. Case presentation # 1

A 61-years-old Caucasian male with medical history of esophageal reflux and 45 pack-year smoking was admitted to the hospital with significant dysphagia. Vital indicators were all within normal limits. Physical examination was significant for absence of lymphadenopathy, regular cardiac rate and rhythm, and intact neurological exam. Significant laboratory tests were hemoglobin of 11 g, MCV of 74.9 fl and platelets of 424,000/μl. Endoscopy showed extrinsic compression of proximal esophagus and biopsy showed esophageal squamous cell cancer. Staging computerized tomography showed three bilateral pulmonary nodules and mediastinal lymphadenopathy. EBUS of left para-tracheal lymph node showed squamous cell cancer which was CK56 positive, p63 positive, and TTF-1 negative. Esophageal cancer was staged as TxN1M0 (stage 3).

Biopsy of the 1.9 cm pleural based right upper lobe pulmonary nodule revealed adenocarcinoma which was

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TTF-1 positive. This was staged as T1aNxMx at diagnosis. Other solid lung nodules were sub-centimeter but FDG avid on PET scan. Lung carcinoma was treated as unknown stage because other nodules were not biopsied. Magnetic resonance imaging of brain was negative for any metastatic disease. Molecular analysis was negative for EGFR, RAS, BRAF, ALK, MET, RET or ERBB2 mutations. He was initiated on concurrent chemotherapy and radiotherapy with carboplatin and paclitaxel to treat both esophageal and lung cancers.

4. Case presentation # 2

A 72-years-old Caucasian male first presented in 2008 with gastric and ileal carcinoid. He underwent video laparoscopy, exploratory celiotomy, adhesiolysis, hemigastrectomy, omentectomy with Roux-en-Y gastrojejunostomy, and mid-ileal resection with radical lymphadenectomy for carcinoid peritoneal washings. He then presented in 2012 with colon adenocarcinoma diagnosed on colonoscopy. He underwent right hemicolectomy and segmental sigmoid resection due to stage T2N0 colon adenocarcinoma with 15 negative lymph nodes. He later presented in February 2013 with hepatocellular carcinoma (HCC) and underwent segmental hepatectomy (segment 8) and cholecystectomy for 2-cm poorly differentiated HCC and negative margins with background cirrhotic liver stage 2. All cancers were diagnosed at early stages due to routine surveillance, and were resected and cured. This patient was not a smoker, was a social drinker and did not have any other identifiable environmental risk factors leading to multiple primary gastrointestinal cancers. He underwent genetic mutation testing and profiling which was negative for the common known mutations except for CDKN1B missense mutation that could explain multiple small bowel neuroendocrine tumors. Notably, he also had family history of gastric adenocarcinoma in his sister and colon adenocarcinoma in his maternal uncle. He is followed every three months for close observation.

5. Discussion

5.1. Environment

The concept of field cancerization was first explained in 1953 in the aero digestive tract. Later, a lateral cancerization concept was introduced, which basically means the normal epithelium next to the cancer cells has high tendency for dysplasia. Smoking, alcohol and certain infections are risk factors for oropharyngeal and gastrointestinal cancers and can lead to multiple primary cancers [3]. Multiple primary cancers are an uncommon occurrence and are being recognized more in the literature due to better diagnostic and surveillance techniques [4]. In our first case, smoking was the biggest risk factor leading to synchronous esophageal squamous and lung adenocarcinoma both of which have been associated with smoking [5]. Tobacco and alcohol consumption can lead to high incidence of tongue and oral mucosal cancer [6]. In some head and neck cancers, HPV infection can be a common trigger leading to multiple primary cancers. HPV-16 and HPV-18 have been recognized as the culprit in oropharyngeal, laryngeal, tonsillar, anal and cervical cancers. This infection has also been a target for developing anti-cancer vaccination [6].

5.2. Genetics

Multiple genetic mutations have been diagnosed that play a role in reproduction of cancer cells. Lynch syndrome is an inherited disorder with 85% penetrance and the mutations leading to it are mismatch repair genes like *hMSH2*, *hMLH1*, *PMS1*, *PMS2* and *hMSH6* [7]. It leads to higher incidence of colorectal cancer, endometrial cancer, gastric adenocarcinoma, and ovarian cancers [5]. Familial Adenomatous Polyposis is another inherited disorder with 100% penetrance that happens due to a mutation in the *Adenomatous Polyposis Coli* (*APC*) gene [8]. It leads to colorectal cancer and other gastrointestinal cancers [8]. Peutz-Jeghers syndrome is a syndrome due to a mutation of the *STK-11* gene that leads to colorectal, gastric, pancreatic, small intestinal, breast and ovarian cancers [9]. Hereditary diffuse gastric cancer syndrome is an uncommon disorder that occurs due to CDH-1 mutation and leads to invasive gastric and lobular breast cancer [10]. A new mutation recognized is CDKN1B, which encodes cyclin dependent kinase p27. This mutation leads to development of multiple small intestinal neuroendocrine tumors [11].

5.3. Challenges

With better diagnostic techniques and so many novel therapies for cancers, life expectancy has increased leading to diagnosis of multiple primary neoplasms in the same individuals. Multiple primary cancers are defined as the occurrence of two or more cancers diagnosed in separate organs without the possibility of metastases. These are called synchronous if diagnosed within six months of each other and asynchronous or metachronous if spaced out by more than six months [12]. Diagnosis and treatment for multiple cancers remains a challenge because the treatment guidelines have not been established yet. It should involve a multidisciplinary approach including medical oncology, surgical oncology, radiation oncology and specialists of the cancer sites. There should be a

low threshold for referring these patients to cancer centers for second opinions.

Peculiarities of our first case were that the treatment approach was different than it would be for either cancers existing alone. The idea is to treat the life-threatening cancer first [12]. A single focus of lung adenocarcinoma is normally treated with surgery if operable or radiation therapy if inoperable, with intention to cure it [13]. Lung cancer in this case was not staged as it would not have changed the management, which would not be the case if this cancer existed alone. Lymph nodes were positive for esophageal squamous cancer, which was more likely to be life threatening so treatment was directed towards it. Paclitaxel and carboplatin is the desired chemotherapy regime combined with radiotherapy for advanced non-small lung cancer which was offered to this patient [14].

Our second case is a unique presentation of four primary gastrointestinal cancers which do not usually exist in this combination and cannot be explained with any genetic mutation known to date. This patient was not a smoker, was a social drinker and did not have any other identifiable environmental risk factors leading to multiple primary gastrointestinal cancers establishing unknown genetic mutation as the etiological factor here. He underwent genetic testing for common disorders, which was negative. This finding points toward the fact that more undiagnosed predisposing mutations exist and need more research in this regard. Another interesting factor is that colorectal cancer and hepatocellular cancers were incidental findings diagnosed due to regular screening tests including computerized tomography, endoscopy, colonoscopy and tumor markers. This led to early diagnoses of these potentially fatal cancers and cure. One potential use of genomics is early detection in family members of the mutants. This cannot be applied to the general population because of risk of false-positivity and high cost [15].

6. Conclusion

Multiple primary cancers can be due to a common environmental risk factor or genetic mutations. The diagnosis and management guidelines are not well established due to rarity and should involve multiple disciplines.

Disclosure statement

No potential conflict of interest was reported by the authors.

Availability of data and material

All data generated or analyzed during this study are included in this published article. Data to compare the study were taken from PubMed.

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